Pharmaco-Mechanical Strategies to Optimize the Balance between Ischemia and Bleeding after Percutaneous Coronary Intervention

– *Navigating between Scylla and Charybdis* –

Evitata Charybdi in Scyllam incidi*, *"Having avoided Charybdis, I've fallen into Scylla"
(Erasmus, *Adagia* 1.5.4)

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Pharmacomechanische strategieen om de balans tussen ischemie en bloedingen te optimaliseren na percutane coronaire interventies
- Navigeren tussen Scylla en Charybdis -

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To my Father

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General Introduction:

Coronary artery disease (CAD) and relative morbidity are estimated as the primary cause of death in western countries.[1] Percutaneous coronary intervention (PCI) assumed a dominant role in this field, and the number of procedures across Europe, both for stable and unstable CAD, continued to rise in the last decade.[2] The implementation of refined treatment strategies, better devices and more efficacious pharmacological treatment to reduce the occurrence of ischemic complications early and late after PCI, reduced the burden of cardiovascular mortality. With this respect, dual antiplatelet therapy, constituted by the association of aspirin and an inhibitor of the platelet receptor P2Y12, become a pivotal pharmacological treatment after PCI, preventing both stent and non-stent related ischemic events.[3-5] Evidence from multiple trials demonstrated that the beneficial anti-ischemic effect of P2Y12-inhibitors implemented on top of aspirin is linearly related to the pharmacological potency and the overall duration of treatment.[4-7] Nevertheless, the implementation of more potent or prolonged treatments raised the issue of a proportional increase of bleeding complications.[6-8] Bleedings are far from being innocent bystanders, and such complications both during and after PCI have been shown to significantly impact mortality in a similar or even greater magnitude than coronary ischemic events.[8, 9] Like Ulysses navigating between Scylla and Charibdis, two mythological monsters inhabiting the two coasts of the strait of Messina, menacing navigators passing too close to one side or the other, clinicians should be aware of the trade-off of both bleeding and ischemia and their impact on patients' health.[10]

The use of the radial approach, as compared to the more traumatic femoral approach, has demonstrated a significant reduction of peri-procedural bleeding.[11] This holds particularly true during the acute setting, when more potent antithrombotics are used, increasing bleeding liability.[12, 13] In addition the use of radial artery might give additional benefits independently from bleeding prevention.[14] As such international guidelines now advocate radial artery as the default access site for PCI.[15, 16] On the other side, radial intervention might be complicated by radial artery occlusion, that despite not being associated with apparent clinical consequences, hamper future interventions from this route.[17] Several predictors for radial occlusion have been described, yet a deeper understanding of their mechanisms is needed.[17-19]

Stent type selection, and subsequent antiplatelet treatment, has also been considered an important factor for the ischemia/bleeding balance after PCI. Since the introduction of first-generation drug-eluting stents (DES), which were developed to reduce in-stent restenosis, concern was raised about their higher thrombogenicity, especially for late or very late events (>12 months after intervention).[20] As a reaction to this preliminary data, the community and international guidelines took position for prolonging DAPT in patients treated with DES to at least 12 months.[21] This practice, initially advocated for first generation DES, has been automatically translated also to second-generation DES despite their technical improvements (i.e. reduced strut-thickness, more biocompatible or resorbable drug carriers). Hence, since longer DAPT was recommended after DES implantation, it was common practice to use bare-metal stents in patients deemed at high bleeding risk, despite no direct comparison between these two strategies was available. Multiple studies questioned this practice, especially in light of the promising results of new generation DES. The EXAMINATION trial randomly allocated patients with ST-segment elevated myocardial infarction to a treatment with BMS or DES. The results at 5-years follow-up suggested a significant reduction of the composite ischemic endpoint of all-cause death, recurrent myocardial infarction and any revascularization mostly driven by a significant 28% relative reduction of all cause mortality.[22] On the same line, a meta-analysis including randomized studies allocating patients to BMS vs. cobalt-chromium everolimus DES consistently demonstrated an improved safety and efficacy of 2nd generation DES, with a significant 33% reduction of cardiac death, 59% reduction of definite stent thrombosis and 71% reduction of target vessel revascularization.[23] As such, if bleeding risk status should be considered a treatment modifier for stent selection deserves further clarification.

With respect to the long-term prevention of ischemic recurrences, multiple trials questioned the recommended 12 months DAPT duration endorsed by international guidelines after stent implantation or ACS.[2] Studies presented before 2014 tested both a prolonged or shortened DAPT duration in patients receiving coronary stents.[24-27] The overall interpretation of the evidence available at that time did not suggest a significant benefit from a treatment prolongation beyond 12 months, whereas a consistent reduction of bleeding complication was observed with shorter treatment courses.[28, 29] Still, due to their relatively small size, these trials were not powered to detect differences for rare events such as late stent thrombosis. Specifically designed to answer this question, the DAPT trial, a large randomized controlled trial sponsored by the Food and Drug Administration, randomly allocated 9961 patients previously treated with first and second generation DES, well tolerating and adhering to a first run-in phase of 12 months of dual antiplatelet therapy, to a strategy of DAPT interruption or continuation up to 30 months.[6] The DAPT trial demonstrated a significant 29% relative reduction of the composite ischemic endpoint and a 71% relative reduction of definite or probable stent thrombosis.[6] Still, a prolonged treatment was associated with a roughly 60% increase of moderate or severe bleeding and with a significant increase of non-cardiac and all-cause mortality.[6]

In light of the evidence produced by more than 10 randomized clinical trials, growing importance has been given to the selection of the right patient population for the decision of shortening or prolonging DAPT. As such, individualization of the treatment duration based on the single-patient risk profile appear a promising approach in order to deliver the proper treatment to the right recipient, in line with the principles of precision medicine.

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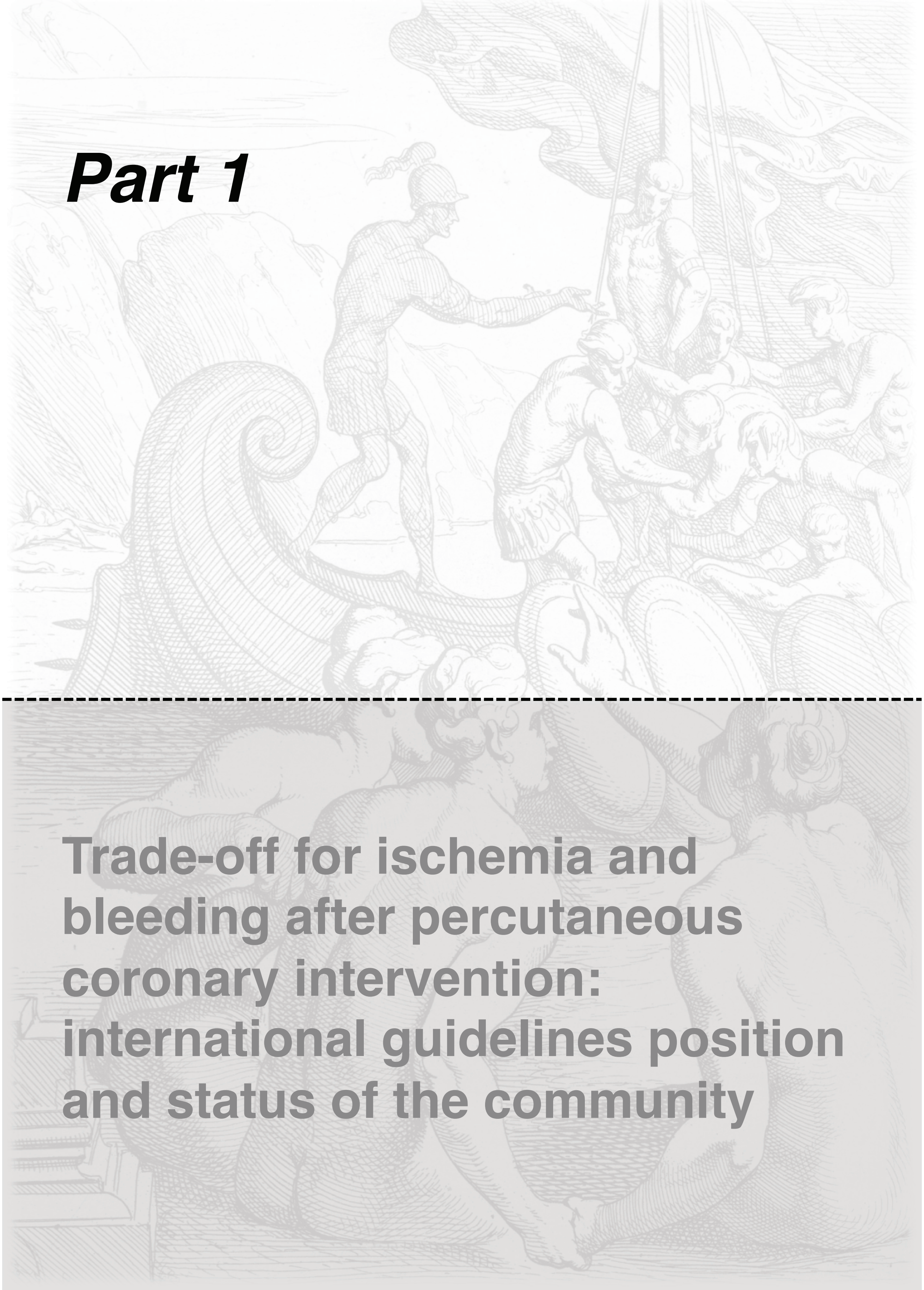
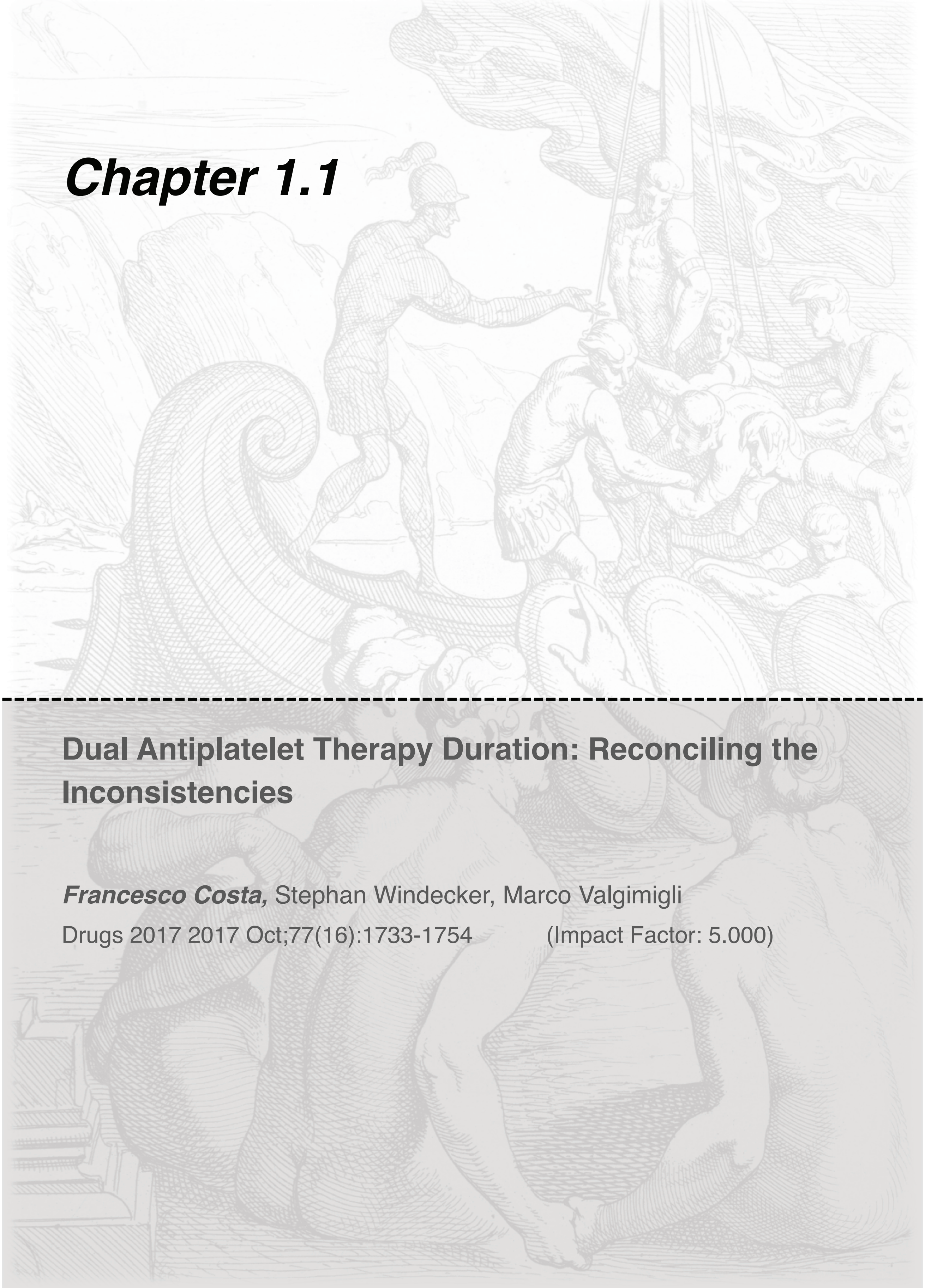


Part 1

Trade-off for ischemia and bleeding after percutaneous coronary intervention: international guidelines position and status of the community



Chapter 1.1

Dual Antiplatelet Therapy Duration: Reconciling the Inconsistencies

Francesco Costa, Stephan Windecker, Marco Valgimigli

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1

Dual Antiplatelet Therapy Duration: Reconciling the Inconsistencies

Francesco Costa[1,2] · Stephan Windecker[3] · Marco Valgimigli[2,3]

Abstract Dual antiplatelet therapy (DAPT) prevents recurrent ischemic events after an acute coronary syndrome (ACS) as well as stent thrombosis (ST) in patients with prior stent implantation. Nevertheless, these benefits are counterbalanced by a significant bleeding hazard, which is directly related to the treatment duration. Although DAPT has been extensively studied in numerous clinical trials, optimal treatment duration is still debated, mostly because of apparent inconsistencies among studies. Shortened treatment duration of 6 or 3 months was shown to mitigate bleeding risk compared with consensus-grounded 12-month standard duration, without any apparent excess of ischemic events. However, recent trials showed that a >12-month course of treatment reduces ischemic events but increases bleeding compared with 12 months. The inconsistent benefit of a longer DAPT course compared with shorter treatment durations is puzzling, and requires a careful appraisal of between-studies differences. We sought to summarize the existing evidence aiming at reconciling apparent inconsistencies among these studies, as well as thoroughly discuss the possible increased risk of fatal events associated with long-term DAPT. Benefits and risks of prolonging or shortening DAPT duration will be discussed, with a focus on treatment individualization. Finally, we will provide an outlook for possible future directions in the field.

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Key Points

Dual antiplatelet therapy is the cornerstone treatment for secondary prevention of ischemic events after acute coronary syndrome and stent implantation.

Despite apparent inconsistencies among major clinical trials, a prolonged course with dual antiplatelet therapy reduces ischemia but increase bleeding to a similar extent.

In order to maximize treatment benefits over risks, dual antiplatelet therapy duration should be individualized on a patient-by-patient basis.

1 Introduction

Dual antiplatelet therapy (DAPT) in the form of aspirin plus a $P2Y_{12}$ inhibitor is one of the most commonly prescribed treatments in cardiovascular medicine. For patients with coronary artery disease (CAD), DAPT is of paramount importance for secondary prevention after an acute coronary syndrome (ACS) and for preventing stent thrombosis in patients with previous stent implantation. Twenty years have passed since the first clinical trial testing a DAPT strategy after percutaneous coronary intervention (PCI) [1]. Thereafter, DAPT has been intensively investigated in more than 35 randomized clinical trials, which lead to a continuous refinement of treatment strategies and clinical guidelines [2–10]. The optimal duration of DAPT after coronary stent implantation has also varied during the past two decades [1, 11–15]. After an initial phase in which 1–6 months' DAPT was recommended after stent implantation [1, 11, 13, 15], the evidence of a higher thrombotic milieu with first-generation drug-eluting stents (DES) in 2006 abruptly shifted towards a more conservative position [16–18], with guidelines recommending, based on consensus, at least 12 months of DAPT [19]. In the following 8 years, the introduction of safer stent platforms [20–23], and further evidence from six randomized clinical trials supporting shorter DAPT courses with second-generation DES, moved the recommended therapy duration back to 6–12 months [6, 24]. However, in 2014 and 2015, two large clinical trials again challenged this position by showing a significant reduction of non-fatal ischemic events when prolonging treatment beyond 1 year [5, 25]. This benefit came at the cost of a significant increase in severe bleeding [5, 25]. Whether this novel evidence represents a new paradigm shift is debated. The clinical community expressed concerns over the reproducibility of such benefits in clinical practice and voiced a stance from guidelines [26]. The main challenge in interpreting current evidence arises from the difficulties in understanding the reason for the inconsistent results across studies, in terms of benefit of prolonged DAPT in some studies but lack thereof in others. In fact, clinical trials testing 3 or 6 months versus 12 months' DAPT showed no difference in ischemic events [3, 27–33], with improved safety after short-term DAPT, whereas 30 months or longer DAPT duration significantly reduced ischemic events as compared with 12 months [3, 5]. The interpretation of these results might appear puzzling, and one burning clinical question remains open: what is the 'sweet spot' of DAPT duration that maximizes the benefits and the risks of the treatment? Should DAPT duration be adapted on a patient-by-patient basis? And if so, which patient subgroup would benefit more from a longer treatment course?

In this review we will try to reconcile 20 years of apparently contrasting evidence regarding DAPT duration and to provide an outlook for future directions in the field.

2 Optimal Duration of Dual Antiplatelet Therapy (DAPT)—State of the Art

In total, 14 randomized controlled trials (RCTs) have tested different DAPT duration strategies in patients receiving coronary stent implantation (Table 1). These trials can be grouped based on three research questions:

Q1: Is a <12-month DAPT similarly effective as a 12-month DAPT regimen?

Q2: Is a >12-month DAPT similarly or more effective than 6-month DAPT regimen?

Q3: Is a >12-month DAPT more effective than a 12-month DAPT regimen?

2.1 Studies of <12 Months' DAPT Versus 12 Months' DAPT

A shorter (i.e., 3–6 months) DAPT course after coronary stent implantation has been compared with the standard of care (i.e., 12 months) in seven RCTs (Table 1) [27–33]. These studies tested the hypothesis that a shorter DAPT regimen was non-inferior to the standard of care. Patients were randomly allocated to DAPT duration at the time of stent implantation in all but one trial [29].

The EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial included 1443 patients treated with DES implantation and randomized to 6 versus 12 months' DAPT thereafter [30]. Most patients were treated with everolimus-eluting stents and roughly half presented with ACS, but only a minority (≈3%) with ST-segment elevated myocardial infarction (STEMI). Three-vessel disease was present in 20%, long lesion (i.e., >20 mm) in 40% and the vast majority of patients included were treated for a single lesion, overall determining a low-to-moderate PCI complexity. The rate of the primary endpoint, a composite of cardiac death, myocardial infarction (MI), or ischemia-driven target vessel revascularization at 12 months, was 4.8% in the 6-month DAPT group and 4.3% in the 12-month DAPT group ($p < 0.001$ for non-inferiority with a predefined non-inferiority margin of 4.0%). The rate of the safety endpoint, a composite of thrombosis in myocardial infarction (TIMI) major and minor bleeding, trended higher in the 12-month DAPT group but the difference was not statistically significant (0.6 vs 1.4%; hazard ratio [HR] 0.40; 95% CI 0.13–1.27; $p = 0.12$) [30].

The SECURITY (Second-Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial randomized 1399 patients at the time of PCI to 6 or 12 months' DAPT after DES implantation [31]. All patients were treated with second-generation DES. Only 38% of patients presented with ACS, patients with STEMI were not included, and overall PCI complexity was low. The net clinical benefit endpoint, a composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC (Bleeding Academic Research Consortium) type 3 or 5 bleeding at 12 months, was 4.5% in the 6-month DAPT group and 3.7% in the 12-month DAPT group ($p < 0.05$ for noninferiority with a predefined

Table 1 Randomized controlled trials testing dual antiplatelet therapy duration strategies after coronary stent implantation

Study	Year	No. of patients	Randomization DAPT duration (mo)	Clinical presentation (% ACS)	STEMI included	PCI complexity	Coronary stent implanted	Study hypothesis	Primary endpoint	Primary endpoint met
3–6 months vs 12 months' DAPT										
EXCELLENT [30]	2012	1443	6 vs 12	52	Y	Mod	1st gen DES 25% 2nd gen DES 75%	Non-inferiority of 6 vs 12 mo DAPT	Cardiac death, MI, TVR	Yes
RESET [28]	2012	2117	3 vs 12	54	N	Low	1st gen DES 21% 2nd gen DES 85%	Non-inferiority of 3 vs 12 mo DAPT	Cardiac death, MI, ST, TVR, TIMI major or minor bleeding	Yes
OPTIMIZE [27]	2013	3119	3 vs 12	32	N	Low	2nd gen DES 100%	Non-inferiority of 3 vs 12 mo DAPT	Death, MI, stroke, major bleeding	Yes
SECURITY [31][a]	2014	1399	6 vs 12	38	N	Low	2nd gen DES 100%	Non-inferiority of 6 vs 12 mo DAPT	Cardiac death, MI, ST, stroke, BARC 3 or 5 bleeding	Yes
ISAR SAFE [29]	2015	4000	6 vs 12	40	Y	Mod	1st gen DES 10% 2nd gen DES 89%	Non-inferiority of 6 vs 12 mo DAPT	Death, MI, ST, stroke, TIMI major bleeding	Yes
I LOVE IT 2 [32]	2016	1829	6 vs 12	82	Y	Mod	2nd gen DES 100%	Non-inferiority of 6 vs 12 mo DAPT	Cardiac death, MI, TLR	Yes
IVUS XPL [33]	2016	1400	6 vs 12	49	N	Mod–high	2nd gen DES 100%	Comparability of 6 vs 12 mo DAPT	Cardiac death, MI, stroke, TIMI major bleeding	Yes
6 months vs >12 months' DAPT										
PRODIGY [4]	2012	1970	6 vs 24	75	Y	Mod–high	BMS 25% 1st gen DES 25% 2nd gen DES 50%	Superiority of 24 mo DAPT	Death, MI, CVA	No
ITALIC [37][a]	2015	1822	6 vs 24	24	N	Mod	2nd gen DES 100%	Non-inferiority of 6 vs 24 mo DAPT	Death, MI, TVR, stroke, major bleeding	Yes
NIPPON [38]	2016	2772	6 vs 18	NA	NA	Low	2nd gen DES 100%	Non-inferiority of 6 vs 18 mo DAPT	Death, MI, CVA, major bleeding	Yes
12 months vs >12 months' DAPT										
DAPT [5]	2014	9961	12 vs 30	43	Y	Mod–low	1st gen DES 38% 2nd gen DES 60%	Superiority of >12 mo DAPT	Death, MI, stroke, and def/prob ST	Yes

Table 1 continued

Study	Year	No. of patients	Randomization DAPT duration (mo)	Clinical presentation (% ACS)	STEMI included	PCI complexity	Coronary stent implanted	Study hypothesis	Primary endpoint	Primary endpoint met
DES LATE [42]	2014	5045	12 vs 36	61	Y	Mod–low	1st gen DES 64% 2nd gen DES 30%	Superiority of >12 mo DAPT	Cardiac death, MI, stroke	No
ARCTIC INTERRUPTION [40]	2014	1259	12 vs 18–24	0	N	Low	1st gen DES 41% 2nd gen DES 63%	Superiority of >12 mo DAPT	Death, MI, ST, stroke, TVR	No
OPTIDUAL [41][a]	2016	1385	12 vs 18–48	36	Y	Low	1st gen DES 34% 2nd gen DES 59%	Superiority of >12 mo DAPT	Death, MI, stroke, ISTH major bleeding	No

ACS acute coronary syndrome, *BARC* Bleeding Academic Research Consortium, *BMS* bare-metal stent, *CVA* cerebrovascular accident, *DAPT* dual antiplatelet therapy, *DES* drug-eluting stent, *ISTH* International Society of Thrombosis and Haemostasis, *MI* myocardial infarction, *mo* months, *NA* not available, *PCI* percutaneous coronary intervention, *ST* stent thrombosis, *STEMI* ST-segment elevated myocardial infarction, *TIMI* thrombosis in myocardial infarction, *TLR* target lesion revascularization, *TVR* target vessel revascularization

[a] Prematurely stopped

noninferiority margin of 2.0%). Only 12 cases of major bleeding were observed, with no statistically significant difference in the two arms [31].

The ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months' Dual Antiplatelet Therapy After Drug-Eluting Stenting) trial randomized 4000 patients 6 months after PCI with DES implantation to DAPT interruption or continuation up to 12 months [29]. The study was terminated earlier due to slow enrollment before reaching the planned level of 6000 patients, but still appeared to reach the non-inferiority hypothesis. Almost half of enrolled patients presented with ACS, and 10% with STEMI. Three-vessel disease was present in 30%, 63% of patients were treated for a single lesion, and median overall stent length was 28 mm. The primary endpoint, a composite of death, MI, stent thrombosis, stroke, or TIMI major bleeding occurred in 1.5% of patients treated with DAPT for 6 months and in 1.6% of those treated for 12 months ($p < 0.001$ for noninferiority with a predefined noninferiority margin of 2.0%). TIMI major bleeding was rare, and similar in the two study arms [29].

More recently, the I-LOVE-IT 2 (Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization) trial randomized 1829 patients across 32 centers in China to 6 or 12 months' DAPT [32]. According to the factorial 2:2 design of the study, patients were also randomized to stent type, receiving a balanced mixture of durable-polymer or bioresorabable-polymer cobalt-chromium sirolimus-eluting stents. The majority of enrolled patients presented with ACS (82%), 58% with unstable angina and 13% with STEMI. Three-vessel disease was rare (<2%), and median SYNTAX score at baseline was 11–12. However, the median stent length per patient was 40 mm, with more than 25% of patients receiving a stent length >60 mm. The rate of the primary endpoint, a composite of cardiac death, MI and target lesion revascularization, was 6.8% in the 6-month DAPT group and 5.9% in the 12-month DAPT group ($p < 0.05$ for non-inferiority with a predefined non-inferiority margin of 3.7%). The rate of major bleeding was similar in the two groups (1.2 vs 0.7%; $p = 0.21$) [32].

Similarly, the IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions) study, used a factorial 2:2 design randomizing 1400 patients to an intravascular ultrasound guided procedure or standard of care and to 6 or 12 months' DAPT [33]. The study sample size was calculated primarily to test the superiority of intravascular ultrasound guidance versus angiographic guidance and not DAPT duration. Almost all patients included in the study presented either with stable coronary artery disease (SCAD) or with unstable angina. A second-generation everolimus-eluting stent was used in all patients. Three-vessel disease was present in 31%, and median overall stent length was 47 mm. Due to the design of the study, which specifically included patients with long coronary lesions, the overall PCI complexity in the study was at least moderate. At 12-months' follow-up, the composite of cardiac death, MI, stroke, and TIMI major bleeding was similar between patients treated for 6 months or 12 months (2.2 vs 2.1%; $p = 0.85$). Interestingly, at the subgroup analysis for the primary endpoint, patients randomly allocated to the intravascular ultrasound (IVUS) guided stent implantation benefited significantly more from a shorter DAPT treatment compared with those treated with angiographic guidance alone ($P_{\mathrm{int}} = 0.018$), in line with the hypothesis that an optimized stent implantation with IVUS guidance in patients with long lesions might reduce the burden of device-related complications and the need for a longer DAPT treatment [33].

Two additional studies tested an even shorter DAPT duration, as short as 3 months after endeavor zotarolimus-eluting stent (E-ZES) implantation [27, 28]. The RESET (Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor ZES Implantation) trial randomized 2117 patients to standard-of-care treatment with DES plus 12 months' DAPT or to a strategy including E-ZES implantation plus 3 months' DAPT [28]. Overall the study population was at low risk, with patients almost exclusively with either SCAD or unstable angina.

Three-vessel disease was present in 15%, the median stent length was 24 mm and the vast majority of patients included were treated for a single lesion. This determined an overall low PCI complexity. A strategy of E-ZES plus 3 months' DAPT was non-inferior to the standard of care of DES plus 12 months' DAPT (4.7 vs 4.7%; $p < 0.001$ for non-inferiority) for the net clinical benefit primary endpoint [28]. Similarly, the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice) trial tested the non-inferiority of 3 months compared with 12 months' DAPT in 3119 patients systematically treated with E-ZES [27]. The population included in the OPTIMIZE study was largely stable, with only 5% of patients enrolled with non-ST segment elevated MI, whereas patients with STEMI were not included. More than 80% of patients had a single lesion, with a median lesion length of 18 mm. Again, in this specific patient population, a strategy of 3-month DAPT was non-inferior to 12 months' treatment (6.0 vs 5.8%; $p = 0.002$ for non-inferiority) with respect to the net clinical benefit primary endpoint (i.e., death, MI, stroke and major bleeding) [27].

While it was claimed that a very short DAPT regimen consisting of 1-month DAPT suffices after DES based on two RCTs testing 1-month DAPT after bare-metal stent (BMS) or second-generation DES [34–36], it should be emphasized that no single DAPT study has so far tested 1-month DAPT versus a longer DAPT regimen. This study is ongoing (ClinicalTrials.gov: NCT03023020) and will inform the community on the benefits and risks of such a short-term DAPT regimen after contemporary DES implantation in high bleeding risk patients.

2.2 Studies of 6-Month Versus >12-Month DAPT

Three RCTs compared 6 months' treatment with >12 months' treatment (Table 1) [4, 37, 38].

The PRODIGY (PROlonging Dual antIplatelet treatment after Grading stent-induced intimal hYperplasia study) trial used a 4:2 factorial design to randomly allocate 2013 all-comer PCI patients to treatment with four coronary stents (i.e., BMS, paclitaxel-eluting stent, E-ZES, everolimus-eluting stent) and two DAPT duration strategies (6 vs 24 months' DAPT) [4]. The overall complexity of the PRODIGY population was high, with three-quarters of patients presenting with ACS, a mean age of ≈68 years, ≈66% with multivessel disease, and ≈40 mm of overall implanted stent length. At 24 months' follow-up, there was no difference in the primary efficacy endpoint of death, MI, and stroke between 6 and 24 months' DAPT, while there was an excess of bleeding in patients in the longer DAPT duration arm [4].

Similarly, the ITALIC (6- Versus 24-Month Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stent in Patients Nonresistant to Aspirin) study was designed to test the non-inferiority of 6 versus 24 months' DAPT [37]. The trial was stopped early after 80% of the initially planned sample size. All patients were treated with second-generation everolimus-eluting stents. Only a quarter presented with ACS at the time of stent implantation. At the end of follow-up the event rate for the primary endpoint was low, with little differences between the two study arms, and the trial appeared to meet its non-inferiority hypothesis [37].

Recently, the NIPPON (NoborI dual antiplatelet therapy as aPPrOpriate DurationN) trial tested the non-inferiority of a 6- versus 18-month randomized DAPT duration among 3775 patients treated with bioabsorbable polymer DES in Japan [38, 39]. At 18 months' follow-up, the rate of the primary endpoint of all-cause death, MI, cerebrovascular accident (CVA), and major bleeding was similar between the two study arms (1.45% for 18 months' DAPT vs 1.92% for 6 months' DAPT), meeting the prespecified non-inferiority margin. However, the results from this study should be interpreted with caution due to the early study termination and the wide non-inferiority margin selected (i.e., 2%), which exceeded the event rate of the experimental arm [38, 39].

2.3 Studies of 12-Month Versus >12-Month DAPT

Four RCTs compared the standard 12 months' DAPT with a prolonged treatment beyond 12 months, and ranging from 18 to 48 months (Table 1) [5, 40–42]. In general, this group of studies tested the hypothesis that a prolonged DAPT duration was superior to the standard treatment with respect to very late stent thrombosis and other ischemic events.

In the ARCTIC INTERRUPTION (Dual-Antiplatelet Treatment Beyond 1 Year After Drug-Eluting Stent Implantation) trial [40], which was an extension of the ARCTIC study of bedside platelet function monitoring to adjust antiplatelet therapy [43], the primary study hypothesis was the superiority of $\geq$18-month DAPT duration compared with the standard 12-month period after stent implantation [40]. The study included a highly selected patient population, comprising only patients undergoing elective stenting. Ultimately, the primary efficacy endpoint was identical between the two study arms (4% for both treatments), with a significant excess of major or minor bleeding in the prolonged DAPT arm [40].

The DES LATE (Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Events) trial conglobated the extended follow-up of 2701 patients from the REAL-LATE and ZEST-LATE trials, with an additional cohort of 2344 patients [42]. All patients free from adverse events after DES implantation and an initial phase of 12 months' DAPT were included. In DES LATE, 80% of patients received first-generation DES. The primary endpoint of cardiac death, MI, or stroke was similar in the two study arms, occurring in 2.6% of patients in the prolonged DAPT and 2.4% in the standard DAPT group [42].

In the DAPT (Dual Antiplatelet Therapy) study, 22,866 patients treated with DES implantation were screened for inclusion and received an initial 12 months' DAPT with aspirin and thienopyridines (i.e., clopidogrel or prasugrel) during the study run-in phase [5]. At 12 months, 9961 patients had no further ischemic and bleeding events, were compliant to the prescribed treatment, and were randomized to continue DAPT for up to 30 months or discontinue the treatment while continuing aspirin monotherapy. Roughly 50% of patients included were initially treated for an ACS, and importantly, $\approx$38% received a first-generation DES. In the DAPT study population, extended DAPT resulted in a 1% absolute reduction in very late stent thrombosis, a 1.6% absolute reduction of major adverse cardiovascular and cerebrovascular events (MACCE), driven by a 2% reduction of MI. However, bleeding was increased to a similar extent, with a 0.9% absolute increase in moderate or severe GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) bleeding and 2.6% increase in BARC 2, 3, or 5 bleeding. All-cause mortality at 33 months' follow-up was higher among patients randomized to an extended DAPT treatment [5]. A signal towards an increase in all-cause death after DAPT prolongation beyond 1 year was inconsistent in several meta-analyses [3, 44, 45]. In a separate analysis of the DAPT trial restricted to the subgroup of patients treated with contemporary everolimus-eluting stents, extended DAPT resulted in a 0.4% absolute reduction in stent thrombosis, a 1.1% absolute reduction in MI, and a 1.2% absolute increase in moderate/severe bleeding, with an overall 1.1% absolute risk increase of all-cause death after extended DAPT treatment [46]. The increased risk of death appeared to some extent to be associated with cancer fatalities [47], and although this signal was also observed in other studies [48], the authors interpreted this finding as due to chance in line with an internal revision from the American Food and Drug Administration (FDA) [49].

More recently, the OPTIDUAL (Optimal Dual Antiplatelet Therapy) trial tested the hypothesis that 48 months of DAPT with clopidogrel was superior to 12 months of DAPT after DES implantation [41]. The trial was stopped prematurely after enrolling 1385 of 1966 planned patients. Overall, a third of included patients received a DES during an ACS, and a third received a first-generation DES. The study ultimately failed to show superiority of an extended DAPT treatment, with a similar rate of the primary endpoint of death, MI, stroke, or major hemorrhage between the two study arms (5.8 vs 7.5%; HR 0.75; 95% CI 0.50–1.28). A substantial equipoise for the safety endpoint of moderate and severe GUSTO bleeding (1.9 vs 1.7%) and BARC 2, 3, or 5 bleeding (2.6 vs 2.9%) was also shown between the extended and the standard DAPT duration arms [41].

2.4 Other Studies of DAPT Duration in Patients with Prior Myocardial Infarction

Two RCTs included patients with high-risk or established cardiovascular disease, randomized to DAPT or aspirin monotherapy [25, 50].

The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial randomized 15,603 patients with multiple atherothrombotic risk factors or a history of vascular disease to clopidogrel on top of aspirin, or aspirin monotherapy [50]. The composite primary endpoint of death, MI, or stroke at 28 months was similar in the two study groups (6.8% in the DAPT group and 7.3% in the aspirin monotherapy group; $p = 0.22$). In addition, no significant difference for major bleeding was noted in the two study arms [50]. However, in a prespecified analysis of the CHARISMA trial where only 12,153 patients with established cardiovascular disease were considered, DAPT was associated with a 1% absolute reduction of the primary endpoint (6.9 vs 7.9%; RR 0.88; 95% CI 0.77–0.99; $p = 0.046$) [51].

Similarly, the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54) trial was designed to test the effect of a dual antiplatelet treatment with ticagrelor (90 mg twice daily [BID] or 60 mg BID) on top of aspirin compared with aspirin monotherapy in patients with high-risk features who previously had an MI 1–3 years earlier [25]. After a mean of 33 months of therapy, DAPT with aspirin and ticagrelor versus aspirin monotherapy resulted in a 1.2–1.3% absolute reduction in the primary composite endpoint of cardiovascular death, MI, or stroke and a 1.2–1.5% absolute increase in major bleeding, with no excess in fatal bleeding or intracranial hemorrhage [25].

Results from these two trials suggest that DAPT extension in patients with prior MI could be beneficial, but patients' selection is key in order to disentangle the ischemic benefit and the bleeding risk, which was indeed similar after longer treatment. However, given the specific design of these two studies, direct comparisons with all the other aforementioned DAPT duration trials are challenging. A significant proportion of patients included in these trials discontinued DAPT for several months or years after the initial qualifying ischemic event [52]. Hence, most patients restarted DAPT at the time of study inclusion after being off-treatment with DAPT. The presence of this time-gap between the initial DAPT period mandated by the index ischemic event and the reinitiation of therapy could be an important confounder, mining the comparability with the other 14 DAPT duration RCTs. Indeed, data suggest that the biggest benefit from extended DAPT duration derives from patients that do not discontinue DAPT treatment [52]. In fact, in a pre-specified subgroup analysis from the PEGASUS trial, patients who discontinued DAPT for 1 year or longer and then reinitiated DAPT did not derive any benefit from the addition of ticagrelor on top of aspirin [52].

2.5 Summary of the Available Evidence

Taken together, results from these diverse trials showed

- a reduction of major bleeding associated with shortened (3–6 months) compared with 12-month DAPT duration, with no difference in ischemic events;
- reduction of ischemic events in study arms where DAPT was prolonged to 30 months or more compared with 1-year therapy, with an associated increase of major bleeding.

Hence, while a direct correlation between DAPT duration (longer) and bleeding risk (increased) was observed across studies, a similar clear relationship was not found for ischemic events. The benefit of extending DAPT was observed only in studies where >12-month DAPT was compared with a shorter regimen, but not in those where 3–6 months' therapy was contrasted with ≥1-year treatment duration.

These apparently inconsistent results deserve a deeper reading of between-trial differences. In addition, the uncertainty regarding the net clinical benefit of longer DAPT treatment, which is based on the similar figures for ischemic risk reduction and bleeding risk increase, confirms that the 'one size fits all' theory should no longer be pursued when selecting DAPT duration. Multiple subgroup analyses from clinical trials have been proposed to inform DAPT decision making, and to find specific patient subsets in which the benefits of prolonged/shortened DAPT duration were maximized over risks.

3 DAPT Duration in 2017—Outstanding Questions, Apparent Inconsistencies and Future Directions

3.1 Why are Study Results Not Consistent with Respect to the Benefit of Prolonged DAPT for Non-Fatal Ischemic Endpoints?

It remains to be explained why the ischemic benefit of long-term DAPT is inconsistently observed across studies and only in those where a >12-month DAPT is compared with 1 year of treatment. These apparent inconsistencies might be explained by taking into account several factors.

3.1.1 Study Power

The DAPT study was the first study powered to detect a difference in hard clinical endpoints between standard 12-month DAPT and longer treatment duration up to 30 months, assuming an annual event rate in the short DAPT group of 0.5% for stent thrombosis and 2.9% for MACCE [5]. This study ultimately included 9961 patients, with an event rate of 1.4% for definite or probable stent thrombosis and 5.9% for MACCE in the short DAPT group. The contrast between study arms in terms of difference in treatment duration between the two strategies was 18 months, and 9499 patients reached the follow-up time of 30 months. Hence, the standardized sample size (i.e., number of patients included corrected by the actual treatment difference between study arms) was 14,248 patient-years in the DAPT trial, which ultimately found a statistically significant benefit from longer DAPT treatment

[5]. Seven RCTs randomized patients to 6 versus 12 months' DAPT. Taken together, these studies included a total of 15,404 patients, with an event rate of 0.55% for definite or probable stent thrombosis and 1.82% for MI in the short treatment arm [45]. In fact, in this group of studies the difference in treatment duration between the two tested pharmacological strategies was only 6 months, accounting for a total of 7702 patient-years of treatment. Moreover, the observed risk of spontaneous MI or stent thrombosis (ST) observed cumulatively in studies assessing DAPT duration of <12 months was lower than that observed in the DAPT study. As such, the apparent inconsistency of treatment benefit within the first year might be related to a lack of study power within trials testing DAPT treatment of <12 months to detect a treatment effect, which is definitively smaller than what many had anticipated.

3.1.2 Stent Type

The type of implanted stent across DAPT studies is of paramount importance to understand between-study differences (Table 1). First-generation DES, as well as BMS, are associated with a higher rate of device-related ischemic complications compared with newer-generation DES [23, 34, 53–57]. RCTs testing 12-month versus <12-month DAPT duration implemented second-generation DES exclusively, or in a vast majority of cases [27, 28, 31–33]. Contrariwise, studies testing 12-month versus >12-month DAPT duration included a significant proportion of patients treated with first-generation DES (raging from 34 to 64% of included patients) (Table 1) [5, 42]. Interestingly, this information is not available for the PEGASUS study [58]. In the PRODIGY trial, the type of stent implanted, which was randomly allocated according to the 4:2 factorial study design, was a treatment modifier for DAPT duration with respect to the primary endpoint ($P_{int} = 0.004$), and an excess of definite or probable stent thrombosis was observed among patients treated with first-generation DES allocated to a shorter DAPT treatment (HR 0.12; 95% CI 0.02–1.00; $p = 0.049$) [53]. Similarly, in the DAPT trial the benefit of longer DAPT (30 versus 12 months) was inconsistent between implanted stent types ($P_{int} = 0.048$), with a significant reduction of MACCE from longer DAPT only among patients treated with first-generation DES (absolute risk difference [ARD] for MACCE: sirolimus-eluting stents ARD = –2.6%; paclitaxel-eluting stents ARD = –3.9%) but not in those treated with second-generation DES [5].

Therefore, the trade-off between benefits and risks of a prolonged DAPT regimen may dramatically change based on type of stent implanted at the time of intervention.

In the whole DAPT study, the number needed to treat for benefit (NNTB) in terms of ischemic events (definite or probable stent thrombosis: ARD = 1%, NNTB = 100; MI: ARD = 2%, NNTB = 50) and the number needed to treat for harm (NNTH) to provoke a bleeding (ARD = 0.9%, NNTH = 111) slightly favored a longer DAPT strategy [5]. However, when the analysis is restricted to the group of patients treated with contemporary everolimus-eluting stents, the balance between ischemia and bleeding appears upturned, disfavoring longer DAPT treatment in terms of NNTB in terms of ischemic events (definite or probable stent thrombosis: ARD = 0.5%, NNTB = 200; MI: ARD = 1.1%, NNTB = 91) versus NNTH from bleeding (ARD = 1.2%, NNTH = 83), with no benefit from longer DAPT in terms of the overall MACCE rate, and an excess of non-cardiovascular death [46].

Since first-generation DES are no longer used in clinical practice, interpretation of trials largely based on the use of second-generation DES is critical in order to have a clearer understanding of the trade-off between ischemia and bleeding in contemporary practice [59].

In summary, current data suggests that the ischemic benefit of longer DAPT appears more evident among patients treated with first-generation DES, which are no longer used in clinical practice. The ischemic benefit observed among patients treated with contemporary DES is smaller, and might be outweighed by the bleeding hazard of longer treatment duration if patients are not selected to be at relatively higher ischemic but lower bleeding risk.

3.1.3 Patient Selection

Baseline and procedural characteristics might have an important influence on the impact of DAPT duration (Table 1). Intuitively, patients with a perceived higher ischemic risk at baseline or undergoing more complex procedures might derive a larger benefit from longer or more potent platelet inhibition [51, 60, 61]. Within DAPT duration trials, the type of population included was heterogeneous. The overall different risk profile among trials might be evaluated through three markers of risk: age, type of clinical presentation, and PCI complexity. The average age of patients enrolled in clinical trials for DAPT duration was highly variable, and spanned from 60.2 years in the I-LOVE-IT 2 trial to 67.9 years in the PRODIGY trial (Fig. 1). Elderly patients are often underrepresented in clinical trials, and a higher age denotes higher risk of events [62]. A treatment-by-age heterogeneity was observed for the primary endpoint in the ISAR-SAFE ($P_{int} = 0.03$) and IVUS-XPL trial ($P_{int} = 0.05$), indicating a significant interaction between age and treatment duration (i.e., 6 vs 12 months' DAPT) disfavoring longer treatment duration in elderly patients (i.e., >65 years) [29, 33]. In addition, a similar trend was shown in the

PRODIGY trial, with longer treatment showing a less favorable safety profile for older than younger patients [63].

The type of clinical presentation was also at variance across DAPT duration trials (Table 1). ACS patients were excluded from the ARCTIC interruption study, and only few ACS patients were actually included in the ITALIC, OPTIMIZE, SECURITY, and OPTIDUAL studies. STEMI patients were enrolled in half of DAPT duration trials (Table 1). Clinical presentation appeared as an important treatment modifier for DAPT duration in the DAPT trial, with a higher benefit for longer DAPT among patients presenting with MI at the time of index PCI [64]. Patients with prior MI were also associated with a significant reduction in cardiovascular mortality after longer DAPT in a subsequent meta-analysis [65]. Contrariwise, stable patients appeared to derive a smaller benefit from longer DAPT, which is largely outweighed by the increase in bleeding [66]. In the PRODIGY trial, bleeding events occurred relatively more often after longer DAPT among stable versus unstable patients at the time of presentation [67]. This was associated with a better net clinical benefit profile using shorter rather than long DAPT among stable patients [67].

PCI complexity, although difficult to categorize and compare across trials, was also heterogeneous (Fig. 2). The proportion of patients included with multivessel disease ranged from 68.5% in the IVUS-XPL study to 25% in the I-LOVE-IT 2 study [32, 33]. The mean number of lesions treated per patient at the time of index PCI ranged from 1.27 to 1.55 (Fig. 2). The number of stents implanted during the index procedure varied from 1.86 in the PRODIGY trial to 1.27 in RESET [4, 28]. Also, the mean overall stent length was variable, ranging from 47 mm in the IVUS-XPL trial to 18 mm in the OPTIDUAL trial (Fig. 2). A pooled data analysis from six RCTs demonstrated a significant benefit from a standard 12-month DAPT, compared with shorter treatment among patients with complex PCI, defined using six markers of risk (i.e., three coronary vessels treated, three or more stents implanted, three or more lesions treated, bifurcation stenting, overall stent length of >60 mm, revascularization of a chronic total occlusion) [68]. Importantly, the magnitude of the benefit from longer DAPT was directly related to the number of markers of complexity present, in line with the hypothesis that the higher the complexity of PCI, the higher the benefit from longer DAPT [68].

3.1.4 Timing of Randomization

Study design and timing of randomization varied among trials. Six trials included a run-in phase between stent implantation and randomization to DAPT duration (Fig. 3). During this initial period, patients experiencing a novel ischemic or bleeding event were excluded from randomization in the study. Hence, the type of population finally randomized in the study was at a relatively lower risk due to the exclusion of those patients having suffered events during the run-in phase. In this respect, it may be assumed that the longer the observational/run-in phase, the greater the degree of patient selection before entering the study. In the DAPT trial, among 22,866 patients receiving a DES and treated with DAPT during the run-in phase of the study, less than half were ultimately randomized in the study [5]. Similarly, in the ARCTIC interruption trial [40], only half of the initial 2440 patients included in the bedside platelet function testing phase of the trial [43] were without contraindication to prolong DAPT and were finally enrolled in the DAPT duration study. Hence, clinicians should be careful before drawing conclusions from these studies and generalizing them to an all-comer, real-world population.

3.2 In Which Patients Should We Prolong and in Which Patients Should We Shorten DAPT?

Multiple patient or procedural characteristics may be factored in when deciding upon DAPT duration (Fig. 4). Important information has been provided by subgroup analyses of DAPT duration trials [64, 66, 69, 70]. However, subgroup analysis from RCTs has to be considered hypothesis generating, and should be interpreted with caution, as it might be confounded by type I and/or II errors. In addition, the interrelations between multiple coexisting factors (e.g., clinical presentation and peripheral artery disease) are complex and have never been studied.

3.2.1 Clinical Presentation

The type of clinical presentation (i.e., SCAD, unstable angina, non-STEMI, or STEMI) at the time of PCI is a major determinant of a patient's mortality risk, which ranges between 0.36% in SCAD and 4.78% in high-risk STEMI patients, or the risk for ischemic recurrences [71]. For this reason, a more potent (i.e., use of ticagrelor or prasugrel vs clopidogrel) or prolonged regimen (i.e., 12 vs 6 months' treatment) is advocated by international guidelines among patients presenting with ACS, but not those with SCAD [6, 7]. In the PRODIGY trial, 1465 (74.3%) patients presented with ACS and 505 (25.7%) with SCAD [4]. No heterogeneity was noted with respect to the randomized DAPT duration for the primary efficacy endpoint among patients presenting with ACS or SCAD. However, there was a borderline quantitative interaction between clinical presentations and bleeding outcomes ($P_{int} = 0.056$

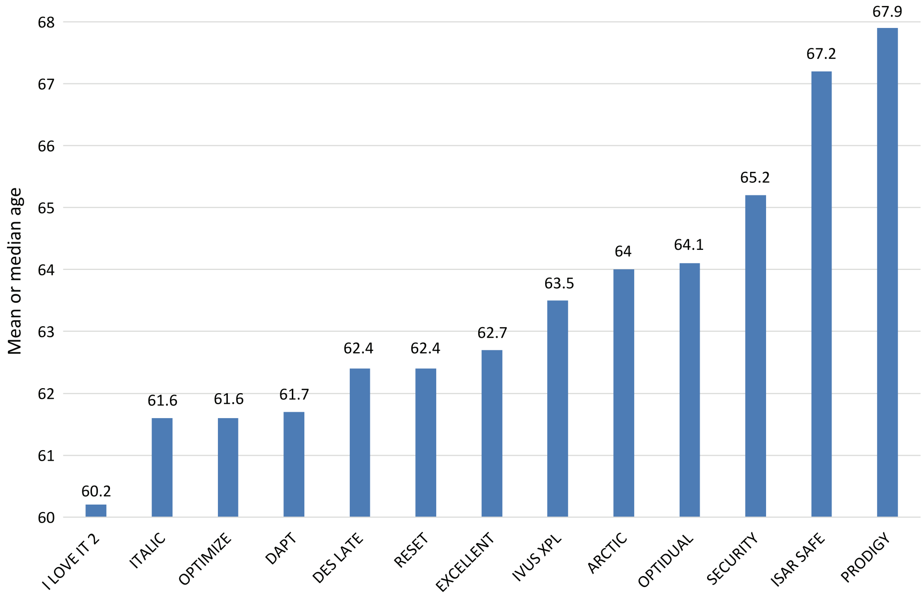

Fig. 1 Patients' age in dual antiplatelet therapy duration trials

for BARC 2, 3, or 5; $P_{int} = 0.091$ for BARC 3 or 5), suggesting a higher risk of bleeding after a longer DAPT in the SCAD patients, but not in ACS patients [67]. The analysis of net adverse clinical events (NACE) consisting of death, MI, cerebrovascular accident, or BARC 2, 3, or 5 bleeding showed significant harm from longer DAPT in SCAD patients (NACE in the 24-month vs 6-month DAPT arm: 13.3 vs 5.6%; HR 2.5; 95% CI 1.35–4.69; $p = 0.004$; NNTH = 13), and no benefit in the ACS population (16.1 vs 14.1%; HR 1.15; 95% CI 0.88–1.50; $p = 0.29$), with positive quantitative interaction testing ($P_{int} = 0.024$) [67].

In the DAPT trial, 30.7% presented with MI at the time of stent implantation [64]. Thirty-month DAPT compared with 12-month treatment significantly reduced definite or probable stent thrombosis both in patients with MI (0.5 vs 1.9%; $p < 0.001$) and without MI (0.4 vs 1.1%; $p < 0.001$) ($P_{int} = 0.69$). Yet, the reduction of MACCE from longer DAPT was bigger for patients with MI (3.9 vs 6.8%; $p < 0.001$) than patients without MI (4.4 vs 5.3%; $p = 0.08$) at the time of presentation, with a positive interaction testing ($P_{int} = 0.03$) [64]. Importantly, longer DAPT was associated with a significant increase in all-cause death among patients presenting without MI (2.1 vs 1.5%; $p = 0.04$) [64, 66], whereas no such detrimental effect was observed in patients with prior MI.

A recent individual patient data meta-analysis from six trials and 11,473 patients compared the effect of 3–6 months' DAPT with 12 months' DAPT among patients presenting with ACS or SCAD [9]. In patients with ACS ($n = 4758$), shortening DAPT to 6 months was not associated with a significant increase of MI or definite/probable stent thrombosis compared with 12 months' DAPT (HR 1.28; 95% CI 0.73–2.27). However, in the same population, shortening DAPT to 3 months was associated with a two-fold increase in the risk of MI or definite/probable stent thrombosis compared with 12 months' DAPT (HR 2.08; 95% CI 0.73–2.27). In patients with SCAD at presentation ($n = 6715$), there was no difference in the risk of MI or definite/probable stent thrombosis when shortening DAPT to 3 or 6 months compared with 12 months [9].

A second meta-analysis from six RCTs included a total of 33,435 patients with prior MI, and compared the effect of standard (12 months) versus extended (>12 months) DAPT [65]. In this high-risk patient category, extended DAPT significantly decreased the risk of the primary ischemic endpoint of cardiovascular death, MI, or stroke (6.4 vs 7.5%; ARD = 1.1%; $p = 0.001$). This benefit was consistent within each component of the primary endpoint, including a significant 15% relative reduction of cardiovascular death (RR 0.85; 95% CI 0.74–0.98). Concurrently, extended DAPT significantly increased risk of major bleeding (1.85 vs 1.09%; ARD = 0.76%; $p = 0.004$), with no excess in fatal bleeding [65]. Yet, despite in this pooled analysis no between-study heterogeneity was noted, supporting a possible class-effect benefit for different P2Y12

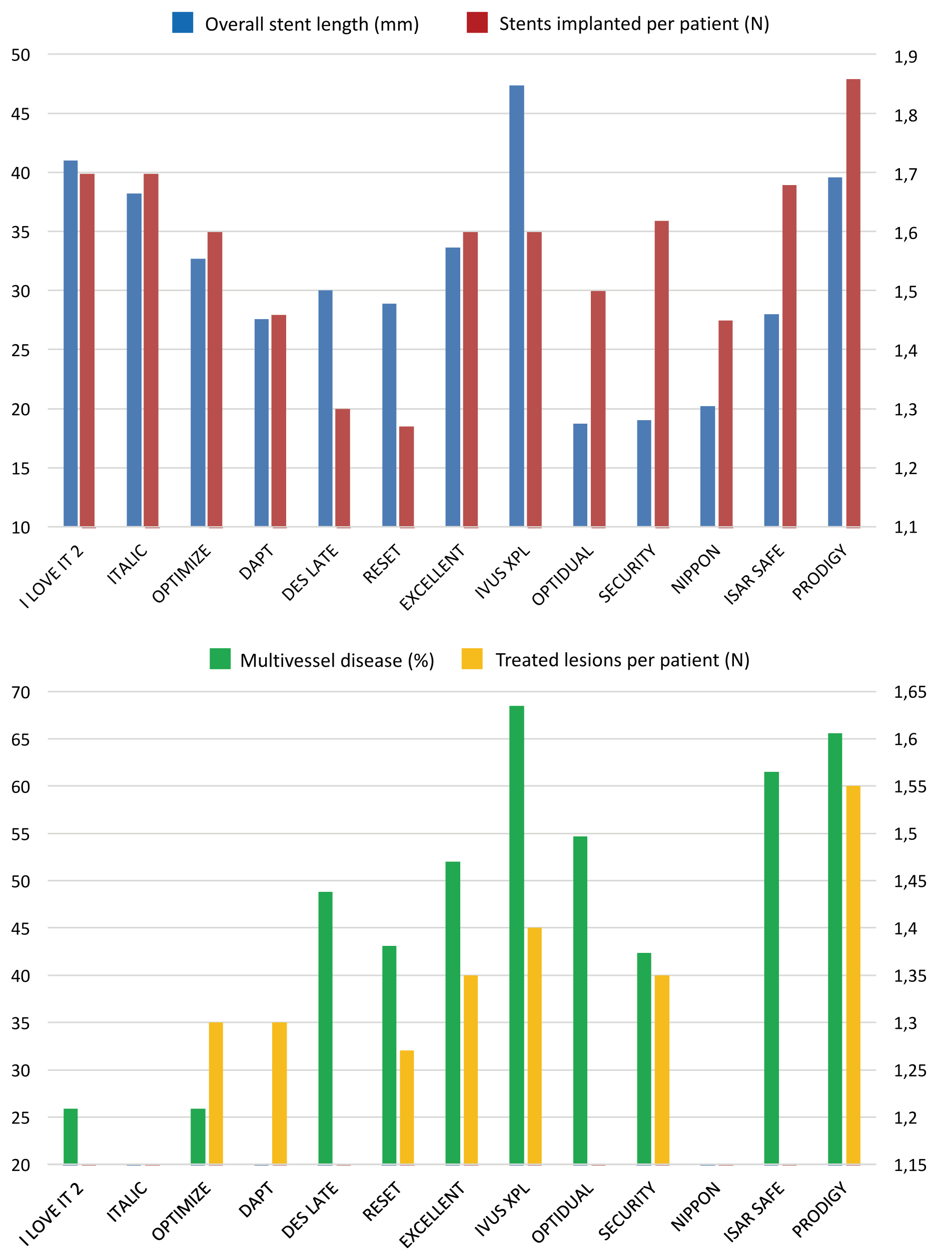

Fig. 2 Percutaneous intervention complexity in dual antiplatelet therapy duration trials taking into account overall stent length (*blue bars*), mean number of implanted stents per patient (*red bars*), proportion of patients with multivessel disease (*green bars*) and mean number of treated lesions per patient (*orange bars*)

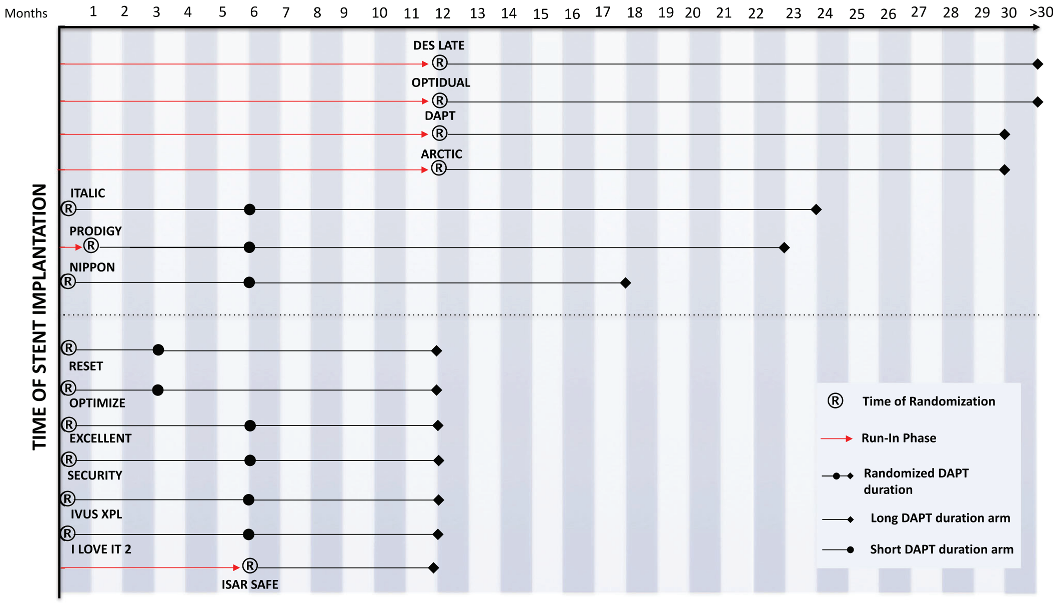

Fig. 3 Main features of trial designs in dual antiplatelet therapy duration trials. In the ITALIC trial, although patients were randomized at the time of PCI, study protocol was pre-specified to include events from the moment in which DAPT therapy started to differ between groups (i.e., at 6 months). *DAPT* dual antiplatelet therapy, *PCI* percutaneous coronary intervention

inhibitors used, a separate study suggested an advantage of extended treatment with ticagrelor versus a similar strategy with thienopyridines, since the former appeared to exert a relatively more favorable effect on all-cause mortality [72].

In summary, current evidence provides support to the concept that DAPT duration should be based on patients' clinical presentation. The trade-off between efficacy and safety of extended DAPT beyond 1 year appeared particularly beneficial in higher risk patients with prior MI. Concurrently, patients at lower risk, such as those presenting with stable angina at time of PCI, appear to be better suited to a shorter course of treatment for 3 or 6 months.

3.2.2 Complex PCI

The complexity of coronary intervention has been consistently considered an important element to be taken into account for decisions around DAPT duration [26]. A recent patient-level meta-analysis from six RCTs ($N = 9577$) investigating DAPT durations ($\geq$12 vs $\leq$6 months) after coronary stenting defined complex PCI based on six covariates, including three-vessel PCI, and/or an implantation of three or more coronary stents, and/or three or more coronary lesions, and/or bifurcation stenting (i.e., bifurcation technique using stents in both the main and the side branch), and/or a final total stent length >60 mm, and/or treatment of a chronic total occlusion [68]. Ultimately, 17.5% of patients had at least one of these characteristics and were considered to be in the complex PCI group [68]. Patients undergoing complex PCI had a higher MACCE rate (5.0 vs 2.5%; $p = 0.001$). In this group, long DAPT ($\geq$12 months) compared with short DAPT ($\leq$6 months) almost halved the adjusted MACCE rate (unadjusted event rates: 4.0 vs 6.0%; adjusted HR 0.56, 95% CI 0.35–0.89), whereas no benefit for a longer treatment was observed in the non-complex PCI group (2.5 vs 2.6%; adjusted HR 1.01; 95% CI 0.75–1.35) ($P_{int} = 0.01$). Interestingly, the magnitude of benefit in favor of long DAPT was directly and positively related to the number of complex PCI factors. Longer DAPT was associated with an increased risk of major bleeding irrespective of PCI complexity ($P_{int} = 0.15$) [68].

In summary, patients undergoing complex PCI represent a higher-risk population, which appeared to be better suited to 12 months or more of DAPT because of a significant reduction of ischemic adverse events, even if this benefit came at a consistently higher price to pay in term of bleeding.

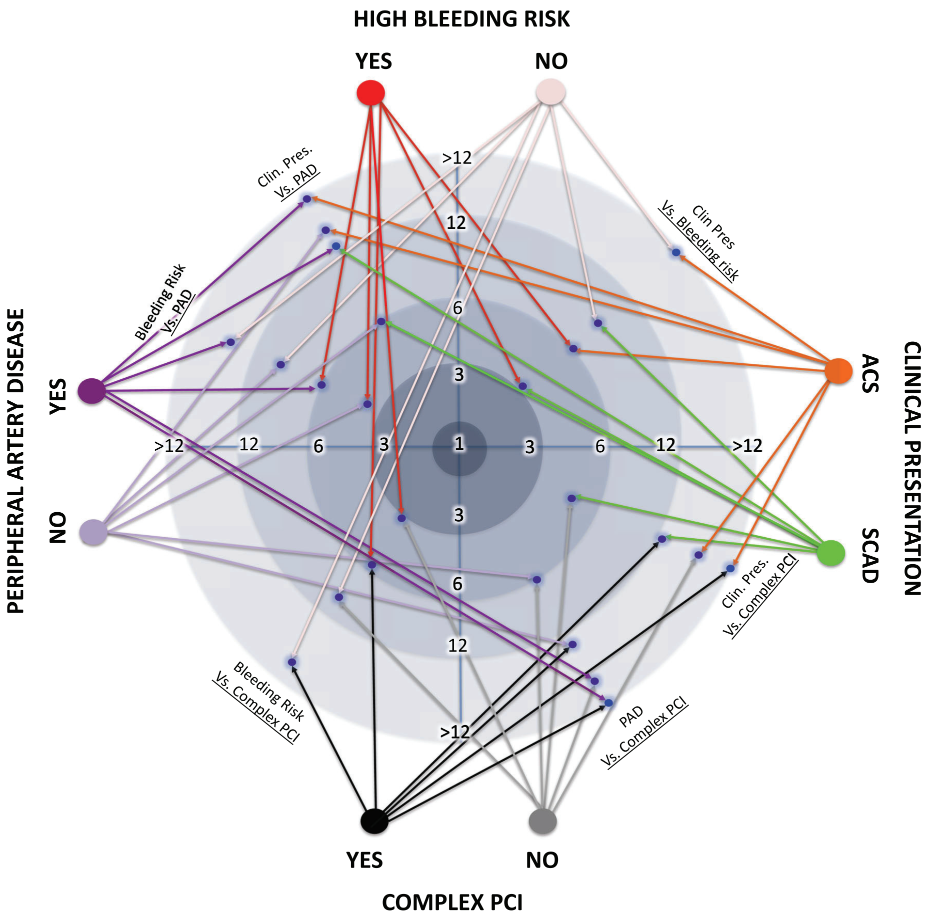

Fig. 4 The 'moving target' of dual antiplatelet therapy duration. An algorithm for the selection of dual antiplatelet therapy duration based on four interrelating factors (bleeding risk, clinical presentation, complex PCI, and peripheral artery disease) is presented in the figure. The presence or the absence of each factor, and its relation with the others, drives the suggested DAPT duration. The *concentric circles* represent DAPT duration from its inception (i.e., 1, 3, 6, 12, or >12 months from *inner* to the *outer circle*). DAPT duration is obtained from the intercept of the lines originating from each relevant factor (e.g., high bleeding risk 'yes' and complex PCI 'no'). The interrelationships between factors and the suggested DAPT duration presented in this figure should be considered as the authors' personal opinion, as no studies evaluated the interrelation between multiple subgroups. These represent an attempt to summarize the evidence and give a practical outlook for clinicians. *ACS* acute coronary syndrome, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *SCAD* stable coronary artery disease

3.2.3 Peripheral Artery Disease

The presence of concomitant peripheral artery disease (PAD) among patients with CAD has been invariably shown as an important marker of ischemic events and mortality [73, 74]. Among 3096 patients with PAD in the CHARISMA trial, DAPT compared with aspirin alone was associated with a lower rate of MI and hospitalization for ischemic events, but a higher rate of minor bleeding [75]. In the PEGASUS trial, patients with a history of PAD carried a 60% higher risk of MACCE [76]. In this higher-risk subgroup, treatment with ticagrelor 60 mg BID compared with placebo provided a robust absolute risk reduction of 5.2% at 3 years for the primary ischemic endpoint, with a significant reduction of acute limb ischemic events and a reduction of both cardiovascular and all-cause mortality [76]. In the all-comer PRODIGY trial, 12.5% of patients included had a history of symptomatic PAD [77]. Again, a history of PAD was associated with a higher risk of death and ischemic events (HR 2.80; 95% CI 2.05–3.83;

$p < 0.001$), and prolonged versus short DAPT significantly reduced the incidence of the primary efficacy endpoint in PAD patients (16.1 vs 27.3%; HR 0.54; 95% CI 0.31–0.95; $p = 0.03$) but not in patients without PAD (9.3 vs 7.4%; HR 1.28; 95% CI 0.92–1.77; $p = 0.14$), with a positive interaction testing ($p = 0.01$) [77]. Longer DAPT provided a consistent benefit in patients with PAD, also reducing definite or probable stent thrombosis and all-cause mortality [77].

In summary, there is compelling evidence that patients with a history of PAD are at higher ischemic risk, encouraging a prolonged antiplatelet therapy regimen in this subgroup.

3.2.4 Risk Scores

Clinical risk scores, which integrate risk factors to establish an individual's absolute risk of a given condition, are often used in clinical practice to estimate bleeding risks in patients with atrial fibrillation and treated with oral anticoagulants [78]. The concept of using a risk score to guide DAPT decision making for treatment duration was tested for the first time in the PRODIGY trial [79]. In this retrospective analysis, the authors used the PRODIGY dataset to bench-test three validated bleeding risk scores in patients with ACS (i.e., CRUSADE and ACUITY) [80, 81] and atrial fibrillation (i.e., HAS-BLED) [82]. The CRUSADE score showed a higher discrimination [79]. Most importantly, when patients from the PRODIGY trial were stratified according to the CRUSADE score in *high* (CRUSADE >40) versus *non-high* (CRUSADE ≤40) bleeding risk, patients at higher bleeding risk had an almost 3-fold greater rate of major bleeding when treated with 24- versus 6-month DAPT (9.7 vs 3.7%; ARD 6%; 95% CI 0.4–12.3; $p = 0.04$; NNTH = 17), whereas patients with non-high risk did not experience a significant increase in major bleeding when treated with long versus short DAPT duration (2.4 vs 1.6%; ARD 0.8%; 95% CI –0.6 to 2.2; $p = 0.25$) ($P_{\text{int}} = 0.05$) [79]. Consistently, the risk for red blood cell transfusion in the 24- versus 6-month DAPT duration arms was five times higher among patients at higher bleeding risk according to CRUSADE (8.3 vs 1.8%; ARD 6.5%; 95% CI 1.6–12.3; $p = 0.02$; NNTH = 15), but not in those without high CRUSADE score (1.7 vs 1.2%; ARD 0.5%; 95% CI –0.6 to 1.7; $p = 0.45$) ($P_{\text{int}} = 0.01$). However, no interaction between the bleeding risk status defined according to the CRUSADE score and DAPT duration was observed for the primary ischemic endpoint in the PRODIGY study ($P_{\text{int}} = 0.58$) [79]. These bleeding risk scores were not initially designed for long-term event prediction in a CAD population; in fact, CRUSADE and ACUITY were created to predict in-hospital, mostly access-site-related bleeding, whereas HAS-BLED was designed to predict long-term bleeding in patients with atrial fibrillation with an indication to oral anticoagulation [80–82].

Within the DAPT trial, the authors developed a specific tool for decision making on treatment duration so as to possibly identify patients in the DAPT trial ($N = 11{,}648$) with a net benefit for ischemia and bleeding from a treatment extension of up to 30 months compared with standard treatment of 12 months [83]. Eight factors were identified (i.e., congestive heart failure/low left ventricular ejection fraction, vein graft stenting, MI at presentation, prior MI or PCI, diabetes mellitus, stent diameter <3 mm, smoking, and paclitaxel-eluting stent) that were independently associated with ischemia but not with bleeding, and one factor (i.e., age) was identified that was independently associated with bleeding, but not with ischemia. From this model, they developed a risk score (DAPT score) ranging from −2 to +10, to predict the difference between the anticipated reduction in ischemic events and the anticipated increase in bleeding events with extended DAPT, with lower scores identifying patients at higher bleeding versus ischemic risk, and higher scores identifying patients at higher ischemic versus bleeding risk.

The DAPT score showed modest discrimination during internal validation and external validation in 8136 patients enrolled in the PROTECT (Patient-Related Outcomes with Endeavor vs Cypher Stenting) trial [83]. Importantly, patients with a high DAPT score (i.e., score ≥2) derived a larger reduction in MI and stent thrombosis after a prolonged 30-month DAPT (risk difference −3.0%; 95% CI −4.1 to −2.0; $p < 0.001$), with only a modest increase in major bleeding (risk difference 0.4%; 95% CI −0.3 to 1.0; $p = 0.26$). In turn, patients with a low DAPT score (i.e., score <2) did not derive any reduction of ischemic events from prolonging DAPT (risk difference −0.7%; 95% CI −1.4 to 0.09; $p = 0.07$), but suffered a significant increase in major bleeding (risk difference 1.5%, 95% CI 0.8–2.3, $p < 0.001$). The DAPT score appeared to significantly modulate the outcomes for DAPT duration both for ischemic ($P_{\text{int}} < 0.001$) and bleeding events ($P_{\text{int}} = 0.02$). Still, these figures were not confirmed in the everolimus-eluting stent subgroup (ischemia $P_{\text{int}} = 0.18$; bleeding $P_{\text{int}} = 0.15$) [83].

Although the DAPT score represented the first attempt to develop a specific tool to guide DAPT decision making, it suffers from several limitations due to the original trial design and population. The population of the DAPT trial was highly selected due to the initial run-in phase of the study, which excluded almost 50% of the initially screened population [5]. As per the DAPT trial design, the DAPT score is only able to inform the decision to continue or not continue DAPT beyond 12 months, whereas it cannot inform earlier DAPT suspension within the first year of treatment. Since current guidelines recommend at least 6 months of DAPT in stable patients, and most bleeding events occur early after treatment initiation, earlier treatment decision making at the time of PCI or in the first 3–6 months of treatment is advisable [6]. Hence, whether the DAPT score performance might be replicated in an external population to provide earlier decision making for DAPT duration remains to be ascertained. In a recent analysis, the DAPT score failed to demonstrate a differential treatment effect within the first year of treatment, and inform decision making for 6 versus 12 months' DAPT after implantation of predominantly second-generation DES in the ISAR-SAFE trial [84].

More recently, the PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) study group pooled data from eight RCTs and 14,963 patients with indication for DAPT who underwent elective, urgent, or emergent PCI [85]. The aim of the study was to find independent predictors at the time of PCI of long-term bleeding while on DAPT and develop a predicting tool to inform DAPT duration earlier at the time of stent implantation. In fact, the median time to a first major bleeding after DAPT initiation was $\cong 5$ months in the PRECISE-DAPT study. Ultimately, a simple five-item (age, creatinine clearance, hemoglobin, white blood cell count, prior spontaneous bleeding) prediction algorithm for the prediction of out-of-hospital bleeding in patients treated with DAPT was proposed.

The predictive performance of this novel score was assessed in the derivation cohort and validated in 8595 and 6172 patients treated with PCI from the PLATO trial and BernPCI registry, respectively [86]. The PRECISE-DAPT score showed good discrimination in both validation cohorts and appeared superior to its comparator (i.e., PARIS bleeding score [87]) in terms of integrated discrimination and net reclassification [85].

The PRECISE-DAPT score was tested in patients randomized to different DAPT durations ($N = 10{,}081$) to evaluate bleeding and ischemic events resulting from a long (12–24 months) or short (3–6 months) treatment duration in relation to the score-predicted bleeding risk [85].

It was observed that among patients deemed at high bleeding risk based on PRECISE DAPT (score ≥ 25), prolonged DAPT compared with short DAPT was associated with no ischemic benefit and a significant bleeding increase, resulting in one major bleeding incident for every 38 patients treated. On the other hand, a prolonged DAPT in patients without high bleeding risk at baseline (score <25) was not associated with a significant excess of bleeding compared with short DAPT, but provided a significant reduction of the composite ischemic endpoint of MI, definite stent thrombosis, stroke, and target vessel revascularization, preventing one ischemic event for every 65 patients treated. The favorable profile of this decision-making algorithm remained consistent when the analysis was confined to patients presenting with ACS at the time of stent implantation. Hence, addressing upfront at the time of PCI a <12-month treatment duration in patients deemed at high bleeding risk (PRECISE-DAPT score ≥ 25) may prevent exposing them to an excessive bleeding hazard. In turn, patients at non-high bleeding risk (PRECISE-DAPT score <25) might receive a standard (i.e., 12 months) or a prolonged (i.e. >12 months) course of treatment if tolerated [85].

It should be emphasized that the accuracy of these prediction tools ranged from low/moderate to good, and clinicians must remain aware that these tools cannot be a substitute for a case-by-case clinical evaluation [88]. In addition, none of these risk prediction models has been prospectively tested in the setting of prospective RCTs; hence, their value in improving patient outcomes requires further investigation.

4 Future Studies

Optimization of DAPT duration remains the subject of intense investigation. Since international guidelines entailed the possibility of a very short (i.e., 1 month) DAPT course after BMS in patients at high risk for bleeding, and several studies showed that novel DES are safer than BMS in terms of device-related adverse events during a standard [56] or abbreviated DAPT course [36], the optimal duration of DAPT in patients at high bleeding risk and treated with contemporary DES is under investigation.

The MASTER-DAPT (Management of High Bleeding Risk Patients Post-Bioresorbable Polymer Coated Stent Implantation with an Abbreviated Versus Prolonged DAPT Regimen) study (NCT03023020) will enroll patients deemed at high bleeding risk undergoing PCI with bioresorbable polymer-coated stent implantation, and will evaluate the safety of an abbreviated treatment with DAPT (i.e., 1 month) compared with the guideline-recommended standard of care (i.e., at least 3 or 6 months of DAPT in patients with or without concomitant need for oral anticoagulation). High bleeding risk inclusion criteria in the MASTER-DAPT study will include an indication for oral anticoagulants, PRECISE-DAPT score ≥ 25, the occurrence of a recent or previous bleeding event for which the underlying cause has not been definitively treated, older age, diagnosed malignancy at high bleeding risk, and other clinical factors. The study will be powered to test the non-inferiority in terms of NACE and MACCE of the

Table 2 Upcoming randomized controlled trials testing dual antiplatelet therapy duration strategies

Study	No. of patients	Population	Randomization	Stent used	Primary endpoint	Primary study hypothesis	Trial identifier no.	Expected completion year
MASTER-DAPT	4300	High bleeding risk	1 vs at least 3–6 mo DAPT	Biodegradable polymer sirolimus-eluting stent (Ultimaster®)	NACE (i.e., death, MI, stroke, and BARC 3 or 5 bleeding)	Non-inferiority of 1 mo compared with at least 3 or 6 mo DAPT	NCT03023020	2019
REDUCE	1500	ACS	3 vs 12 mo DAPT	Biodegradable polymer sirolimus-eluting dual therapy progenitor cell-capturing stent (Combo®)	NACE (i.e., death, MI, stroke, and bleeding)	Non-inferiority of 3 mo compared with 12 mo DAPT	NCT02118870	2017
SMART-DATE	2700	ACS	6 vs 12 mo DAPT	Any second-generation drug-eluting stent	MACCE (i.e., death, MI, or CVA)	Non-inferiority of 6 mo compared with 12 mo DAPT	NCT01701453	2019
Hong MK et al.	3020	SCAD undergoing PCI	1 vs 6–12 mo DAPT	Biodegradable polymer biolimus A9-eluting stent (Biomatrix Flex®) vs polymer-free biolimus A9-eluting stent (Biofreedom®)	NACE (i.e., cardiac death, MI, TVR, CVA, or major bleeding)	Evaluate patient and device-related outcome for two DAPT duration strategies	NCT02513810	2020
HOST-IDEA	2152	PCI	3 vs 12 mo DAPT	Biodegradable polymer sirolimus-eluting stent (Orsiro®) vs polymer-free sirolimus-eluting stent (Coroflex Isar®)	Target lesion failure, definite or probable stent thrombosis or major bleeding	Evaluate device-related outcome of the two randomized stents and DAPT duration strategies	NCT02601157	2022
GLOBAL LEADERS	16,000	PCI	1 mo DAPT followed by ticagrelor alone for 23 mo vs 12 mo DAPT followed by aspirin indefinitely	Biodegradable polymer biolimus A9-eluting stent	Death or MI	Superiority of 1 mo DAPT followed by ticagrelor alone compared with standard DAPT for 12 mo followed by aspirin	NCT01813435	2017
TWILIGHT	9000	PCI	3 mo DAPT followed by ticagrelor alone for 12 mo vs 15 mo DAPT with aspirin plus ticagrelor	Any locally approved drug-eluting stent	BARC 2,3, or 5 bleeding	Superiority of 3 mo DAPT followed by ticagrelor alone compared with 15 mo DAPT	NCT02270242	2019
STOPDAPT-2	3000	PCI	1 mo DAPT followed by clopidogrel alone for 59 mo vs 12 mo DAPT followed by aspirin alone for 48 mo	Cobalt-chromium everolimus-eluting stent	NACE (i.e., CV death, MI, definite stent thrombosis, stroke, or bleeding)	Non-inferiority of 1 mo compared with 12 mo DAPT	NCT02619760	2022

Table 2 continued

Study	No. of patients	Population	Randomization	Stent used	Primary endpoint	Primary study hypothesis	Trial identifier no.	Expected completion year
BVS LATE	2000	PCI patients treated with BVS	12 vs >12 mo DAPT	Bioresorbable vascular scaffold	MACCE (i.e., death, MI, or stroke)	Superiority of >12 mo compared with 12 mo DAPT	NCT02939872	2024

ACS acute coronary syndrome, *BARC* Bleeding Academic Research Consortium, *BVS* bioresorbable vascular scaffold, *CV* cardiovascular, *CVA* cerebrovascular accident, *DAPT* dual antiplatelet therapy, *MACCE* major adverse cardiovascular and cerebrovascular events, *MI* myocardial infarction, *mo* months, *NACE* net adverse clinical events, *PCI* percutaneous coronary intervention, *SCAD* stable coronary artery disease, *TVR* target vessel revascularization

abbreviated DAPT regimen compared with the standard of care, and its superiority with respect to the occurrence of major bleeding within 12 months (Table 2).

European guidelines also entail the possibility of shortening DAPT duration from 12 months down to 6 months in patients presenting with ACS and deemed at high bleeding risk [6, 7]. This treatment opportunity has been explored in sub-group analyses [64, 67, 85] and meta-analyses [9, 65], yet prospective data are lacking. The SMART-DATE (Safety of 6-Month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes) study will enroll 2700 patients treated with PCI after an ACS and evaluate whether 6 months of DAPT is non-inferior to 12 months in terms of MACCE at 18 months (NCT01701453). Similarly, the REDUCE study will evaluate the feasibility of 3 months DAPT after ACS and implantation of a novel biodegradable polymer sirolimus-eluting stent with a progenitor cell-capturing technology, which should favor early stent endothelization (NCT02118870) (Table 2). However, these trials when available have to be interpreted with caution given the non-inferiority design and the low number of patients included.

The GLOBAL LEADERS (NCT01813435), TWILIGHT (NCT02270242) and STOPDAPT-2 (NCT02619760) studies will investigate whether, at the time DAPT is stopped, continuation of treatment with a P2Y12 inhibitor monotherapy leads to more favorable outcomes compared with aspirin monotherapy (Table 2) [89, 90].

Finally, treatment duration in patients that received a bioresorbable vascular scaffold (BVS) remains an important matter of debate [91]. Current BVS technology showed a higher risk of device thrombosis, especially late after implantation, which might be related to the slow resorption process of the scaffold [92, 93]. Thus, a general recommendation regarding DAPT duration cannot be extrapolated to patients treated with the current generation of BVS, and whether these patients might benefit from longer DAPT treatment due to their higher thrombotic milieu is suggestive, but still not supported by prospective data. With this purpose in mind, the BVS LATE study will evaluate optimal DAPT duration in 2000 patients who received BVS and underwent an initial uneventful treatment with DAPT for 12–14 months (NCT02939872) (Table 2).

5 Conclusions

In August 2017, the European Society of Cardiology will publish the *Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease*, which is the first document of its kind that will maintain a specific focus on DAPT throughout the spectrum of CAD. After more than 20 years from the first appraisal of its value in preventing stent thrombosis, DAPT has been one of the most extensively investigated treatments in cardiology. This effort resulted in a significant amount of data, which have provided a solid basis for guidelines recommendations. While results of the main studies are apparently inconsistent throughout, differences in study designs, type of coronary devices, and targeted populations should be taken into account to reconcile these differences. Ultimately, current evidence is consistent with the notion that longer DAPT duration is associated with a reduction of non-fatal ischemic events, but also with an increase in major bleeding of the same/similar order of magnitude. In order to disentangle these risks and maximize treatment benefits, DAPT duration should be individualized on a single-patient basis, taking into account the baseline ischemic versus bleeding risk status.

The individualization of DAPT duration should be based on several clinical and procedural considerations, as well as dedicated, clinical risk scores that might better inform the decision making in the context of a comprehensive clinical evaluation. This should be equally based on the evaluation of patients' risks and their needs and preferences, in order to also improve quality of life and adherence. The concept of treatment individualization was beautifully described more than 2400 years ago by the father of western medicine, Hippocrates, who stated "It's more important to know what sort of person has a disease than to know what sort of disease a person has". In the time of 'precision' cardiovascular medicine, this ancient adage appears indeed extremely modern.

Compliance with ethical standards

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Chapter 1.2

Perspectives on the 2014 ESC/EACTS Guidelines on Myocardial Revascularization. Fifty years of Revascularization. Where are we? Where are we heading?

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Perspectives on the 2014 ESC/EACTS Guidelines on Myocardial Revascularization

Fifty Years of Revascularization: Where Are We and Where Are We Heading?

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Abstract The joint European Society of Cardiology and European Association of Cardio-Thoracic Surgery (ESC/EACTS) guidelines on myocardial revascularization collect and summarize the evidence regarding decision-making, diagnostics, and therapeutics in various clinical scenarios of coronary artery disease, including elective, urgent, and emergency settings. The 2014 document updates and extends the effort started in 2010, year of the first edition of these guidelines. Importantly, this latest edition provides a systematic review of all randomized clinical trials performed since 1980, comparing different strategies of myocardial revascularization, including coronary artery bypass graft (CABG), balloon angioplasty, percutaneous coronary intervention (PCI) with bare-metal stents (BMS) and first- and second-generation drug-eluting stents (DES). This review aims to highlight the most relevant novelties introduced by the 2014 edition of the ESC/EACTS myocardial revascularization guidelines as compared with the previous edition and to describe similarities and differences with the American societies' guidelines.

Keywords PCI · CABG · Guidelines · Coronary stent · DES · BMS

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Introduction

The most recent edition of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) joint guidelines on myocardial revascularization celebrates the 50th anniversary of the first coronary artery bypass graft (CABG) procedure [1, 2]. The first percutaneous coronary revascularization procedure was performed only 13 years thereafter, in 1977. Since their first introduction, revascularization techniques gained expertise and clinical relevance worldwide, becoming one of the most commonly performed interventions in modern medicine. The ESC joint guidelines inform European and non-European practitioners since the early 2000s and represent the endeavor of dozens of clinical and research professionals in the field of cardiovascular medicine. The 2014 edition of the ESC/EACTS revascularization guidelines provides a concise and updated summary of the evidence surrounding the value of revascularization in various clinical scenarios, including elective, urgent, and emergency settings. Unique to this edition, they provide a systematic review of all randomized clinical trials performed since 1980, comparing different strategies of myocardial revascularization, including CABG, balloon angioplasty, percutaneous coronary intervention (PCI) with bare-metal stents (BMS) and first- and second-generation drug-eluting stents (DES).

The following perspective paper is intended to highlight the most relevant novelties in the field of revascularization introduced in these guidelines, as compared with the previous 2010 edition [3]. In addition, similarities and differences with respect to the American societies' guidelines on myocardial revascularization are discussed whenever proper [4–9].

The Heart Team: from Inception to Mainstream

The 2010 edition of the ESC guidelines introduced and strongly empowered the concept of the Heart Team. This has been a great achievement whereby all relevant cardiac specialties and heart care providers are brought together to choose the best revascularization modality for each single patient. Current guidelines further extend the importance of the Heart Team discussion, by inciting the development of shared institutional protocols, in order to better select the patients that deserve a multidisciplinary evaluation, saving time, resources, and delays of urgent procedures, especially in centers without on-site surgery. American guidelines also advocate the institution of the Heart Team, indicating the need for multidisciplinary discussion in patients with left main coronary artery disease (CAD) or complex multivessel CAD.

Applying Risk Scores in Practice

Aiming at achieving the best revascularization modality for each individual patient, the 2014 ESC/EACTS revascularization guidelines have updated and expanded the risk score section. The Society of Thoracic Surgeons (STS) score is recognized as the appropriate, recommended tool to stratify surgical risk during CABG, whereas the role of the EuroScore has been reconsidered and its use is no longer indicated, based on the concern that it overestimates the surgical risk (Table 1). However, the newly introduced EuroScore II overcomes this limitation, and its use should be preferred over the first iteration of this surgical risk score.

Table 1 Comparison among guidelines indications for risk scoring

	ESC GL 2014		ESC GL 2010		American societies' GL
	CABG	PCI	CABG	PCI	CABG and PCI
STS score	I B	–	I B	–	• IIa B[a]
EuroScore	III B	III C	I B	IIb B	–
EuroScore II	IIa B	IIb C	–	–	–
SYNTAX	I B	I B	III B	IIa B	• IIa B[a]
SYNTAX II	IIa B	IIa B	–	–	–

ESC European Society of Cardiology, *GL* guidelines

[a] From the 2011 ACCF/AHA/SCAI PCI Guideline [4]: this document specifies that calculation of STS and SYNTAX is reasonable in patients with unprotected left main and complex CAD

The Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) score, introduced in the previous edition, is now recommended for the risk stratification of patients who undergo revascularization (CABG vs. PCI). The more recent SYNTAX II score has been introduced in this guidelines edition for the very first time (Table 1). The latter is a combination of anatomical and clinical factors that were found to be superior to the conventional SYNTAX score in guiding decision-making between CABG and PCI [10].

Among the aforementioned scores, STS and SYNTAX are also mentioned in the American guidelines as reasonable tools to guide the decision-making of the revascularization modality.

Revascularization of the Left Main Coronary Artery

There is increasing evidence that both CABG and PCI may provide effective treatment for selected patients with left main CAD, especially those with an overall low to intermediate anatomical complexity. A prespecified analysis of the SYNTAX trial evaluated a subgroup of patients with predominant distal left main disease [11]. Despite its limited statistical power, this study showed that CABG and PCI had a comparable rate of the primary endpoint—a composite of death, myocardial infarction, stroke, and repeat revascularization—in the low and intermediate SYNTAX tertile (SYNTAX score ≤22 and SYNTAX score 23–32). In contrast, it observed a numerical increase of deaths and a significant increase of repeat revascularizations in the PCI group with the highest SYNTAX tertile (SYNTAX >32). In keeping with this, the PRECOMBAT trial showed comparable outcomes at 1 and 2 years in patients with LM disease treated with CABG or PCI [12].

Based on these data, the indication for PCI of left main CAD with low anatomical complexity (SYNTAX score ≤22) has been upgraded and now equated to CABG, whereas in anatomies with intermediate (SYNTAX score 23–32) complexity, PCI should be considered, but CABG remains the preferred revascularization modality (Table 2).

Similar to the 2010 edition, the most recent revascularization guidelines reiterate the contraindication to the elective treatment of left main CAD with PCI, in case of high anatomical complexity (SYNTAX >32) in patients who have an acceptable surgical risk (Table 2). Properly powered trials evaluating the outcomes of the new-generation DES vs. CABG are still lacking. The EXCEL trial is expected to provide important insights on this matter.

At variance from the European document, the American societies' guidelines recommend CABG for the treatment of left main CAD and suggest PCI as an alternative in patients with an increased surgical risk and an amenable anatomy [4, 6, 9] (Table 2).

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Table 2 Recommendation for the type of revascularization (CABG or PCI) in patients with SCAD and left main coronary artery disease with suitable anatomy and low predicted surgical mortality

	ESC GL 2014		ESC GL 2010		American societies' GL[c]
	CABG	PCI	CABG	PCI	PCI
SYNTAX score ≤22	I B	I B	I A	IIa/b B[a]	• IIa B—if low risk of PCI complications and significantly increased surgical risk (e.g., STS ≥5 %)
SYNTAX score 23–32	I B	IIa B	I A	IIb B[b]	• IIb B—if low to intermediate risk of PCI complications and increased surgical risk (e.g., STS >2 %)
SYNTAX score >32	I B	III B	I A	III B	• III B—if unfavorable anatomy for PCI and good candidates for CABG

GL guidelines

[a] Indication IIa B for left main lesion at ostium/shaft. Indication IIb B for left main lesion at distal bifurcation

[b] Indication for left main disease associated to two- or three-vessel disease and a SYNTAX score ≤32

[c] Indication to improve survival with revascularization as compared to medical therapy

Revascularization of the Proximal Left Anterior Descending Artery

PCI indication was upgraded for the treatment of the proximal left anterior descending artery (LAD) disease (Table 3). In this regard, one study comparing PCI with DES and CABG in patients with isolated proximal LAD disease demonstrated similar outcomes over a 10-year follow-up [13]. Similarly, no survival benefit with CABG vs. PCI was observed for the treatment of two-vessel disease including proximal LAD. Accordingly, PCI is now equally recommended as CABG for the treatment of proximal LAD alone as well as in the context of a two-vessel disease. This recommendation slightly diverges from the American document, which considers CABG superior for the treatment of two-vessel disease including the proximal LAD [6, 9].

Revascularization for Three-Vessel Coronary Artery Disease

At variance with previous guidelines, PCI is now equally recommended as CABG for the treatment of three-vessel disease with a low anatomical complexity (SYNTAX score≤22) [14–16], whereas in more complex anatomies (SYNTAX score >22), PCI is still contraindicated (Table 4).

These recommendations are largely based on the results of the 5-year follow-up of the SYNTAX trial. CABG showed better outcomes in the overall three-vessel disease population, whereas PCI demonstrated to be a reasonable alternative in those with a low SYNTAX score ≤22, although at the price of an increased risk of repeat revascularization [16]. The risk of stroke in this population has been shown to be lower after PCI as compared to CABG. The SYNTAX trial tested the effect of TAXUS stent implantation, a first-generation DES. Given the overwhelming evidence showing superior outcomes when newer generation DES are compared to paclitaxel-eluting stent in patients undergoing coronary stent implantation, it remains likely that the use of newer generation DES may further improve the efficacy and safety of PCI when compared to CABG in this high-risk population. This hypothesis requires validation in prospective clinical trials.

Revascularization in Patients with Comorbidities

The 2014 edition largely focuses on revascularization modalities in patients with various comorbidities, especially diabetes mellitus and chronic kidney disease.

Table 3 Recommendation for the type of revascularization (CABG or PCI) in patients with SCAD and proximal left anterior descending coronary artery disease with suitable anatomy and low predicted surgical mortality

	ESC GL 2014		ESC GL 2010		American societies' GL[a]
	CABG	PCI	CABG	PCI	
One-vessel disease	I A	I A	I A	IIa B	• IIa B for CABG with LIMA • IIb B for PCI
Two-vessel disease	I B	I C	I A	IIa B	• I B for CABG • IIb B for PCI

GL guidelines

[a] Indication to improve survival with revascularization as compared to medical therapy

Table 4 Recommendation for the type of revascularization (CABG or PCI) in patients with SCAD and three-vessel coronary artery disease with suitable anatomy and low predicted surgical mortality

	ESC GL 2014		ESC GL 2010		American societies' GL
	CABG	PCI	CABG	PCI	
SYNTAX score ≤22	I A	I B	I A	IIa B	• IIa B—it is reasonable to choose CABG over PCI in patients with complex three-vessel disease (e.g., SYNTAX >22) who are good candidates for CABG
SYNTAX score 23–32	I A	III B	I A	III A	
SYNTAX score >32	I A	III B	I A	III A	

CABG is strongly recommended over PCI for patients with diabetes and multivessel disease, provided surgical risk is acceptable. In cases where a percutaneous treatment is indicated, new-generation DES should be preferred over bare-metal stents [15, 17]. In keeping with this, American guidelines also indicate CABG as the treatment of choice in patients with diabetes and multivessel disease [9].

These recommendations are mainly based on the results of the FREEDOM trial [15]; this study randomized diabetic patients with multivessel disease to CABG or PCI+DES and found a significantly higher rate of the primary endpoint—a composite of death, myocardial infarction, and stroke—in the PCI group. Moreover, death and myocardial infarction occurred more frequently in the PCI group, whereas stroke rate was higher after CABG. Similar results are provided by a recent meta-analysis that confirmed a survival benefit of CABG over PCI in diabetic patients with multivessel disease, irrespectively the use of DES or BMS [17].

As in diabetic patients, new guidelines recommend new-generation DES over BMS in patients with chronic kidney disease (CKD). In patients with CKD and multivessel disease, CABG is still the treatment of choice, with off-pump CABG that may be preferred over the on-pump approach [18].

The lack of properly powered randomized trials comparing different revascularization modalities is notable in this setting. In patients at risk of contrast-induced acute kidney injury, the use of short-term, high-dose statin therapy should be considered [19].

Antiplatelet Therapy and Revascularization

New guidelines no longer indicate to pretreat with clopidogrel all patients scheduled for a diagnostic coronary angiogram (Supplementary Table 1); indeed, pretreatment did not outperform no-pretreatment option in a meta-analysis of 37,814 patients, which included both prospective controlled studies and retrospective registry data [20]. Differently, it remains reasonable to pretreat patients with known coronary anatomy scheduled for PCI. Pretreatment may still be considered in cases where the probability of CAD is high and the anticipated need for urgent CABG unlikely.

The indications for dual antiplatelet therapy (DAPT) duration have been updated (Table 5). In patients with spontaneous coronary artery dissection (SCAD) receiving a DES, 6-month DAPT is now recommended. A shortened DAPT duration may be considered in case of high bleeding risk. This indication was extrapolated from several trials comparing standard or prolonged DAPT regimens with shorter courses, which eventually failed to demonstrate a benefit from a prolonged DAPT, but rather observed an increased risk of bleeding after a longer therapy [21, 22].

If the individual ischemic risk is high and bleeding risk is low, DAPT may be prolonged beyond 6 months. American guidelines (GL) recommend at least 12 months of therapy in patients with SCAD treated with DES, unless at high bleeding risk (Supplementary Table 1).

The novel $P2Y_{12}$ inhibitors, prasugrel or ticagrelor, are recommended as first-line treatment during acute coronary syndrome (ACS), whereas clopidogrel should be used only when prasugrel and ticagrelor are not available (Supplementary Table 2 and 3). American guidelines are less prescriptive and state that it is reasonable to prefer ticagrelor over clopidogrel, provided ischemic risk is high and an early invasive strategy is planned, whereas they state that prasugrel should be preferred over clopidogrel if the bleeding risk is low [8].

Importantly, after the presentation of the ACCOAST trial, the European GL now contraindicate the pretreatment with prasugrel in patients with non-ST-segment elevation-ACS (NSTE-ACS) and unknown coronary anatomy, given the increased risk of major bleeding and the lack of ischemic benefit [23]. Notably, the administration of $P2Y_{12}$ inhibitors before catheterization in ST segment elevation myocardial infarction (STEMI) is recommended, and ideally, they should be administered at the time of the first medical contact. This recommendation is in keeping with American guidelines and is supported by a small randomized study [24], two observational studies [25, 26], and one meta-analysis [20] showing a reduction of death and MACE without increase of bleeding, in STEMI patients pretreated with clopidogrel.

Table 5 Indication to antiplatelet therapy after stenting in European and American guidelines

ESC GL 2014	ESC GL 2010	American societies' GL
No-ACS patient • New DES→6 months • BMS→at least 1 month	No-ACS patient • DES→6 to 12 months • BMS→at least 1 month	No-ACS patient • DES→at least 12 months • BMS→at least 1 month
ACS patient • New DES→up to 12 months • BMS→up to 12 months	ACS patient • DES→12 months • BMS→12 months	ACS patient • DES→at least 12 months • BMS→at least 12 months
Special considerations - Shorter DAPT (<6 months) may be considered in patients with high bleeding risk. - DAPT may be used for more than 6 months in patients at high ischemic risk and low bleeding risk. - In patients with SCAD and atrial fibrillation with indication to anticoagulation and low bleeding risk, triple therapy should be considered for at least 1 month, irrespective of the stent used, followed by dual therapy with (N)OAC+ASA or clopidogrel up to 12 months. In patients with ACS and atrial fibrillation with indication to anticoagulation and low bleeding risk, triple therapy should be considered for at 6 months, irrespective of the stent used, followed by dual therapy with (N)OAC+ASA or clopidogrel up to 12 months. In case of high bleeding risk, triple therapy should be considered for 1 month, irrespective the clinical presentation and the type of stent used, followed by dual therapy with (N)OAC+ASA or clopidogrel.	Special considerations - In patients with a compelling indication for long-term anticoagulation, BMS implantation or stand-alone balloon angioplasty or CABG should be preferred over DES to restrict the duration of triple therapy to 1 month. - Triple therapy should be prescribed for the shortest necessary duration.	Special considerations - In patients receiving BMS for a non-ACS indication, at increased risk of bleeding; clopidogrel (should be given for a minimum of 2 weeks). - If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable. - Continuation of clopidogrel, prasugrel, or ticagrelor beyond 12 months may be considered in patients undergoing placement of DES.

Anticoagulant Therapy and Revascularization

The anticoagulation section has also been revised with some novelties regarding the management of bivalirudin and use of novel oral anticoagulants (NOAC).

In the previous edition of the European guidelines as well as in Americans' [7], bivalirudin had a first-class indication as recommended anticoagulant during PCI in STEMI compared to heparin plus glycoprotein IIb/IIIa inhibitors (GPI) (Supplementary Table 3). However, the recently published HEAT PPCI trial [27] did not show a reduction of bleeding in patients treated with bivalirudin as compared to heparin alone. Accordingly, the current document gives bivalirudin a second-class indication as anticoagulant in the setting of STEMI as compared to heparin without GPI. While this new indication has been largely interpreted as downgrading, it should be emphasized that previous guidelines set a recommendation of bivalirudin instead of unfractionated heparin (UFH) plus routine use of glycoprotein IIb/IIIa inhibitors, whereas the more recent availability of comparative effectiveness data of bivalirudin versus UFH alone has made possible to provide new recommendations of bivalirudin as contrasted to UFH without routine use of glycoprotein IIb/IIIa inhibitors.

In the NSTE-ACS setting, bivalirudin administered during the PCI and prolonged for up to 4 h thereafter has a class IA indication as an alternative to UFH+GPI and is recommended whenever available (Supplementary Table 2). This indication is mainly driven by the results of the ACUITY and ISAR-REACT 4 trials where bivalirudin compared to UFH+GPI showed a similar efficacy and a better bleeding profile [28, 29]. It has to be highlighted that most of the evidence in this setting comes from trials testing bivalirudin versus UFH+GPI, a combination that is no longer routinely applied; thus, confirmation of bivalirudin benefit in properly powered trials is still needed [30].

In elective patients instead, bivalirudin is recommended in case of heparin-induced thrombocytopenia (Supplementary Table 1).

In addition, a prolonged infusion of bivalirudin should now be considered for up to 4 h after PCI, based on the concern of an increased risk of acute stent thrombosis.

With respect to NOACS, these guidelines also mention the possibility of adding a third agent, namely, rivaroxaban, on top of the standard DAPT with aspirin and clopidogrel for ACS patients treated with PCI in patients at low bleeding risk. This is based on the recent ATLAS-ACS2 trial that observed a mortality benefit from a triple therapy consisting of ASA, clopidogrel, and low-dose rivaroxaban (i.e., 2.5 twice daily) in patients recently treated for ACS [31]. However, this was at an expense of an increase of severe bleeding, and no data currently exists on the value of rivaroxaban when tested in patients taking the new $P2Y_{12}$ inhibitors.

The lack of formal guidance with respect to DAPT duration in patients requiring long-term oral anticoagulation has now been overcome with this edition of the guidelines. Also in this setting, new-generation DES should be preferred over BMS, provided that the bleeding risk is low (HAS BLED ≤2).

In patients with SCAD with absolute indication to anticoagulation and low bleeding risk (HAS BLED ≤2), the duration of the triple therapy—consisting of aspirin, clopidogrel, and a (N)OAC—should be of at least 1 month and ideally continued up to 12 months, whereas in patients presenting ACS, triple therapy should be considered for 6 to 12 months, irrespective of the stent used. Importantly, for patients at high bleeding risk (HAS BLED>2), the duration of triple therapy should be of 1 month irrespective the presentation (i.e., SCAD or ACS) and the type of stent used.

Recommendations on New-Generation Drug-Eluting Stents

At variance with the previous document, which listed several relative limitations to the use of DES, in the current edition, second-generation drug-eluting stents receive an unrestricted indication of use (Table 6). To support this, a network meta-analysis recently published by Windecker et al. included more than 100 studies comparing revascularization and medical therapy in patients with stable coronary artery disease [32]. This meta-analysis showed a survival benefit for CABG as compared to medical treatment, in keeping with previous data. In addition, new-generation DES, but not balloon angioplasty, BMS, or first-generation DES, showed a survival improvement compared to medical therapy. This is the first report that demonstrates a reduction of mortality in SCAD with percutaneous revascularization. A possible biological explanation for the survival benefit of these new stents could be related to the lower risk of myocardial infarction and stent thrombosis. This is consistent with other recent studies that showed a dramatic improvement in cardiac outcomes, including cardiac survival, myocardial infarction, and stent thrombosis with cobalt-chromium everolimus-eluting stents (new-generation devices), compared with both first-generation DES and bare-metal stents [33, 32, 34].

According to this evidence, new guidelines recommend new-generation DES as default in all clinical conditions and lesion subsets. In addition, the previous concerns associated with early DAPT cessation are not confirmed by recent data, and new-generation DES are recommended over BMS also in patients who may require earlier discontinuation of antiplatelet therapy. American guidelines profoundly diverge from the current ESC position and list several, strong contraindication to DES use as the inability, or the unproven ability, to comply or tolerate a prolonged DAPT (Table 6). It is worth mentioning that American guidelines on percutaneous coronary intervention date back to 2011, so it is possible that these differences will be in part leveled with updated editions.

Table 6 Position of European and American guidelines with respect to the use of drug-eluting stents

ESC GL 2014	ESC GL 2010	American societies' GL
• Unrestricted use of new-generation DES	The use of DES is relatively contraindicated if • Clinical history difficult to obtain, especially in the setting of acute severe clinical conditions (STEMI or cardiogenic shock). • Expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy. • Non-elective surgery required in the short-term that would require interruption of DAPT. • Increased risk of bleeding. • Known allergy to ASA or clopidogrel/prasugrel/ticagrelor. • Absolute indication for long-term anticoagulation.	• Before implantation of DES, the interventional cardiologist should discuss with the patient the need for and duration of DAPT and the ability of the patient to comply with and tolerate DAPT. • Balloon angioplasty or BMS should be used in patients with high bleeding risk, inability to comply with 12 months of DAPT, or anticipated invasive or surgical procedures within the next 12 months, during which time DAPT may be interrupted. • DES should not be implanted if the patient is not likely to be able to tolerate and comply with prolonged DAPT or this cannot be determined before stent implantation. • DES should not be implanted if the patient is not likely to be able to tolerate and comply with prolonged DAPT or this cannot be determined before stent implantation.

Conclusions and Future Perspectives

The 2014 edition of the ESC/EACTS guidelines implements important novelties including the unrestricted indication to new-generation DES, the modulation of DAPT duration according to clinical presentation, and the new indications for the treatment of left main and three-vessel CAD. The value of bioresorbable polymer or no-polymer DES over more conventional durable polymer DES remains under evaluation, and whether this more sophisticated technology will translate into improved patient outcomes remains unsettled. The use of bioresorbable vascular scaffolds, instead of permanent metallic DES, while highly promising for restoring physiological vessel motion long-term after intervention remains also a matter for ongoing research. The recent DAPT and PEGASUS trials explored the effectiveness of a long-term treatment with a $P2Y_{12}$ inhibitor, clopidogrel/prasugrel for the first, ticagrelor for the latter, showing ischemic benefit for reductions of patient and device-oriented non-fatal endpoints, counterbalanced by higher bleeding rates [35, 36]. The optimal DAPT type and duration, which maximize the benefits in terms of ischemic protection and minimize the risks in terms of bleeding, will be most likely based on the individual patient's risk profile. It is probable that in the near future, strategies based on weighting patients risk by the use of clinical (i.e., risk scores), biochemical (i.e., circulating biomarkers), or genetic-based tools (i.e., gene polymorphisms) will help physicians to better individualize this treatment.

The MATRIX program is the first large multicenter study showing the superiority of the radial as compared to femoral access, for the reduction of a net clinical benefit endpoint, driven by lower major bleeding and mortality rates [30, 37–41]. Future recommendations will most likely further upgrade the use of radial over femoral route for ACS patients undergoing invasive management, which will have implications in terms of training programs as well as health care quality assessment.

The decision to revascularize a given lesion or vessel in the near future will likely depend even more on functional parameters. Some techniques have already demonstrated solid results (i.e., fractional flow reserve—FFR) whereas some more recent potentially simplified iterations look promising (i.e., instantaneous wave-free ratio—IFR). The results of future studies evaluating the incremental value of a routine functional evaluation and imaging-based stent optimization algorithm may further optimize outcomes and patient selection in revascularization procedures. The recent COSIRA study reported the efficacy of a coronary sinus reducer to relieve symptoms in patients with refractory angina not amenable for revascularization. This device may serve the growing proportion of patients that remains symptomatic despite maximal antianginal therapy [42]. However, even if the concept of a mechanical treatment of refractory angina is intriguing, more informative clinical studies are needed to confirm the role of such device in clinical practice.

Conflict of Interest The authors declare that they have no competing interest.

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Chapter 1.3

Dual antiplatelet therapy duration after coronary stenting in clinical practice: results of an EAPCI survey

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Dual antiplatelet therapy duration after coronary stenting in clinical practice: results of an EAPCI survey

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KEYWORDS

- acute coronary syndrome
- clopidogrel
- dual antiplatelet therapy (DAPT)
- drug-eluting stent
- stable coronary artery disease

Abstract

Aims: Our aim was to report on a survey initiated by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) concerning opinion on the evidence relating to dual antiplatelet therapy (DAPT) duration after coronary stenting.

Methods and results: Results from three randomised clinical trials were scheduled to be presented at the American Heart Association Scientific Sessions 2014 (AHA 2014). A web-based survey was distributed to all individuals registered in the EuroIntervention mailing list (n=15,200) both before and after AHA 2014. A total of 1,134 physicians responded to the first (i.e., before AHA 2014) and 542 to the second (i.e., after AHA 2014) survey. The majority of respondents interpreted trial results consistent with a substantial equipoise regarding the benefits and risks of an extended versus a standard DAPT strategy. Two respondents out of ten believed extended DAPT should be implemented in selected patients. After AHA 2014, 46.1% of participants expressed uncertainty about the available evidence on DAPT duration, and 40.0% the need for clinical guidance.

Conclusions: This EAPCI survey highlights considerable uncertainty within the medical community with regard to the optimal duration of DAPT after coronary stenting in the light of recent reported trial results. Updated recommendations for practising physicians to guide treatment decisions in routine clinical practice should be provided by international societies.

Introduction

The importance of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes and after coronary stent implantation has been substantiated in numerous trials[1,2] and has also been endorsed by international guidelines[3,4]. However, the optimal duration of DAPT after coronary stenting, which maximises the benefits in terms of ischaemic protection and minimises the risks in terms of bleeding, remains unclear.

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Between 2010 and 2014 results have been reported from a number of randomised clinical trials comparing different DAPT duration regimens after coronary stent implantation[5]. Data from these studies failed to show clear evidence of benefit in terms of ischaemic events, in prolonging DAPT beyond one year. Moreover, a DAPT regimen shorter than 12 months was shown to be safer than the currently recommended 12-month DAPT duration[6]. During the American Heart Association Scientific Sessions 2014 (AHA 2014), results from three additional clinical trials investigating the optimal DAPT duration after stenting in an aggregate of approximately 20,000 randomised patients – DAPT, ISAR-SAFE and ITALIC[7-9] – were reported for the first time.

In the light of the anticipated impact of the data from these three trials on clinical practice, the European Association of Percutaneous Coronary Interventions (EAPCI) sought to assess the opinions of the scientific community concerning DAPT duration both before and after AHA 2014. To do this, the association undertook a voluntary web-based survey of the community regarding opinions on DAPT duration after coronary stenting. The current manuscript is a summary of the results.

Methods

This survey initiative was designed to address three major domains concerning DAPT duration: i) clinical practice regarding DAPT duration based on the evidence available before AHA 2014; ii) the expectations of and the reactions to the results of DAPT[7], ISAR-SAFE[8] and ITALIC[9], whose primary findings were presented for the first time during AHA 2014; and iii) the anticipated impact of this new evidence on clinical practice according to the opinion of practising physicians. Accordingly, this survey was built into two sets of questions, distributed before and after the AHA 2014 congress.

The questions included were drafted by the EAPCI Scientific Document Committee and subsequently approved by the EAPCI board. The survey was undertaken using a free web-based survey tool (SurveyMonkey, Palo Alto, CA, USA) and comprised multiple choice questions, including the possibility of adding further comments if required. It was not mandatory to reply to the entire survey. The sample population comprised the mailing list of EuroIntervention – the official journal of the EAPCI. Overall, a total of 15,200 individuals were invited to participate. The invitation to the first part of the survey was sent on the 30th October 2014 and a reminder was sent on the 7th November 2014. For the second part of the survey, the invitation was sent on the 2nd February 2015 and a reminder on the 9th February 2015.

Results

RESPONDENT CHARACTERISTICS

Of the 15,200 invitations sent, a total of 1,134 (7.5%) and 542 (3.6%) physicians responded to the first and the second part of the survey, respectively. Among those, 884 (78%) for the first and 415 (76.6%) for the second part of the survey provided personal and professional information with respect to age, medical and institutional qualification, and geographic region of practice **(Online appendix)**. The characteristics of the respondents are detailed in **Table 1**. Participation in the survey was global, with the majority of respondents being European (65.1% for the first and 71.5% for the second part of the survey) **(Table 1, Online Figure 1)**. The majority of participants were interventional cardiologists at various career stages (87.4% and 90.3%, respectively), followed by cardiologists in training (5.8% and 4.6%, respectively) and non-interventional cardiologists (5.7% and 4.1%, respectively). A minority of responders declared professional qualifications other than cardiological ones (1.2% and 1%, respectively) **(Table 1)**. About half of participants worked in an academic environment, while the remaining 50% were affiliated to non-university-based centres or private institutions **(Table 1)**. The mean age of respondents was 45 years.

DECLARED CLINICAL PRACTICE OF RESPONDENTS CONCERNING DAPT DURATION BEFORE AHA 2014

The main findings of this part of the survey are shown in **Online Table 1**. The majority (53.2%) of respondents indicated a recommendation for a 12-month DAPT duration in all patients treated with drug-eluting stents (DES); one quarter (23.5%) selected

Table 1. Respondent characteristics.

	Survey before AHA (n= 884)	Survey after AHA (n=415)
Age	45.0	46.2
Country of work		
Europe	65.1%	71.5%
North America	8.0%	9.1%
South America	8.4%	8.4%
Asia	13.9%	4.9%
Africa	3.9%	4.2%
Australia	0.7%	1.9%
Professional figure		
Interventional cardiologist (>10 years of experience)	49.8%	56.6%
Interventional cardiologist (>5 years of experience)	20.7%	17.3%
Interventional cardiologist (<5 years of experience)	16.9%	16.4%
Cardiologist in training	5.8%	4.6%
Non-interventional cardiologist	5.7%	4.1%
Other	1.2%	1.0%
Type of practice		
University hospital	49.3%	53.7%
Non-academic public hospital	31.5%	29.6%
Private institution	19.3%	21.2%

a six-month regimen in patients presenting with stable disease and a 12-month regimen for ACS patients; 10.3% routinely prolonged DAPT beyond one year. Three quarters of respondents declared that they take both ischaemic and bleeding risk into consideration when prescribing DAPT. History of stent thrombosis (86%), stenting of the left main or proximal left anterior descending coronary artery (79.7%) and stable versus unstable presentation (74.8%) were the covariates most frequently used in practice to weigh the ischaemic risk **(Figure 1)**. On the other hand, previous bleeding (82.5%), age (76.4%) and renal function (65.3%) have more frequently been identified as important to forecast bleeding **(Figure 2)**. This clinical and/or angiographic set of key covariates used to predict ischaemic or bleeding risk was consistent across institution characteristics (i.e., academic or not academic) and medical qualification/experience (i.e., interventional cardiologist with more than 10 years of experience vs. others, or cardiologist in training vs. others).

With respect to changes to the initially prescribed treatment, 36% of participants reported weighing the occurrence of minor or nuisance bleeding while on DAPT in the decision making on DAPT duration after its prescription, whereas the majority declared adhering to the originally prescribed DAPT duration.

The belief that first-generation DES are more thrombogenic than newer-generation devices and as such require long-term DAPT was widely held (93.5%). However, 54.8% of participants thought that there are still insufficient data to conclude that vulnerability to short DAPT is stent-specific within the class of newer-generation DES. The majority agreed that six-month DAPT is a safe pharmacological strategy after implantation of newer-generation DES, but expressed a need for more clinical data, particularly if a duration shorter than six months is to be recommended, for example after implantation of new-generation non-polymeric DES. The majority also stated that there are insufficient data to draw conclusions on the optimal DAPT duration regimen after bioresorbable everolimus vascular scaffold implantation.

Respondents generally agreed that long-term DAPT exerts protective effects well beyond the prevention of stent-related ischaemic recurrences.

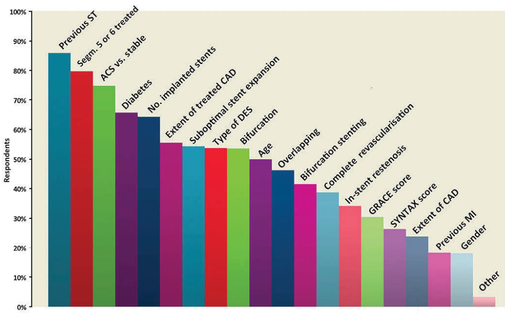

Figure 1. *Please select which of the following variables or scores you generally use to weigh the ischaemic risk after DES implantation (multiple answers allowed).*

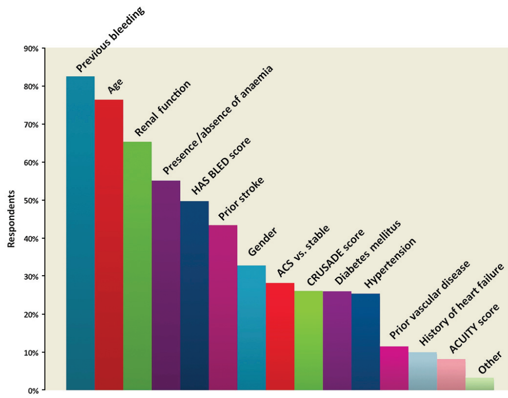

Figure 2. *Please select which of the following variables or scores you generally use to weigh the bleeding risk after DES implantation (multiple answers allowed).*

In patients deemed at high risk of bleeding, six responders out of ten (with a gradient noted across professional activity, 75% non-interventional cardiologists and 55% cardiologists in training) would prefer to implant bare metal stents followed by 30-day DAPT.

ANTICIPATION AND INTERPRETATION OF TRIAL RESULTS PRESENTED AT AHA 2014

Before AHA 2014, 41.4% of respondents believed that the evidence guiding DAPT duration in patients receiving DES was average, and 22.8% asserted that it was confusing. The expectations for the upcoming trials were aligned to the results of previous randomised studies available at that time. Indeed, 72.6% expected the DAPT trial not to show the superiority of 30-month vs. 12-month DAPT and 85% expected ISAR-SAFE to show non-inferiority of a six-month DAPT strategy as compared to a 12-month strategy **(Online Table 1)**.

In relation to the DAPT trial, following AHA 2014, 48.5% of respondents interpreted the results of the trial as showing substantial remaining equipoise between the two treatment strategies (i.e., extended duration [30 months] vs. standard duration [12 months]) in terms of efficacy and safety. Against this, 28.4% responded that a standard 12-month DAPT duration remained the preferred clinical strategy **(Figure 3)**, 23.1% reported that that they were convinced of the superiority of 30-month DAPT duration, and 6.1% believed that it should become the new standard of care. These results were consistent across geographic regions. The reasons reported for not adopting the extended duration used in the DAPT trial as a new standard of care were: concern regarding bleeding risk for 75.4% of respondents, the use of a high proportion of early-generation DES in the trial for 55.4% of respondents, concern about the higher mortality observed in the 30-month group for 41.6% of respondents, limited use of new $P2Y_{12}$ inhibitors for 29.1% of respondents, and

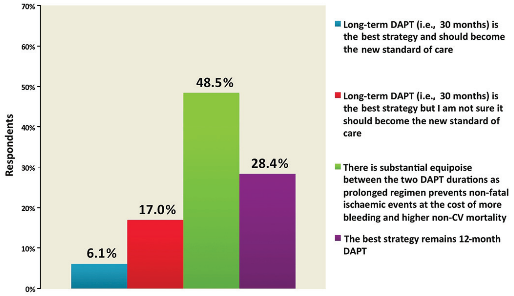

Figure 3. *What is your interpretation of the results of the DAPT trial which were presented at AHA and simultaneously published in the New England Journal of Medicine?*

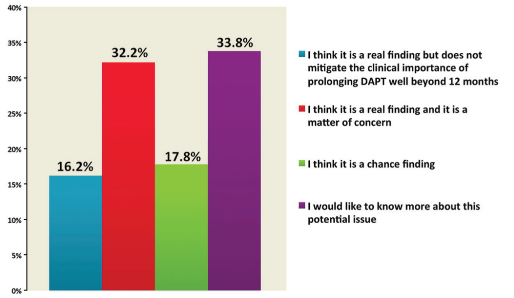

Figure 5. *What is your interpretation of the mortality findings in the DAPT trial (i.e., excess of non-cardiovascular mortality in the 30-month DAPT group)?*

the highly selected patient population for 34.2% of respondents, and/or concerns regarding the reproducibility of these results in clinical practice outside trials for 24.6% of respondents **(Figure 4)**.

The excess of non-cardiovascular mortality observed in the extended duration treatment arm of the DAPT trial was interpreted as a finding which raises concerns by 32.2% of respondents, while 33.8% would like to know more about this issue **(Figure 5)**. The benefit in terms of reduction of stent thrombosis was related to first-generation DES use in the view of 35% of the respondents, while 30.6% thought that it was not applicable to current practice with new-generation DES, whereas 23.8% thought that this benefit applied to all stent types **(Figure 6)**.

Evaluating the results of all three studies presented during AHA 2014 in aggregate, 44.4% of respondents believed that the results were compatible with both the possible benefit of long-term DAPT and also the feasibility of stopping therapy early if needed **(Figure 7)**; 22.7% of respondents did not declare a clear opinion and 20.1% found the results contradictory and/or confusing.

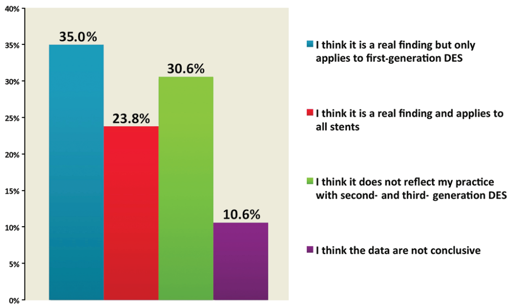

Figure 6. *What is your interpretation of the stent thrombosis findings in the DAPT trial (i.e., lower risk of ST with prolonged DAPT irrespective of stent type)?*

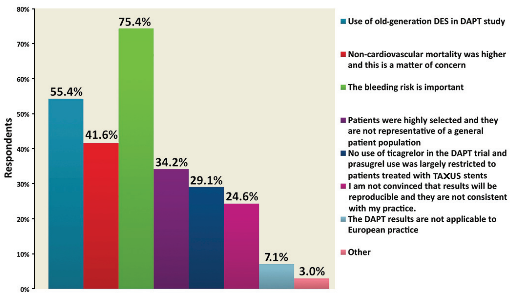

Figure 4. *What is/are the reason(s) behind your belief that 30-month DAPT should not become the new standard of care after DAPT trial (multiple answers allowed).*

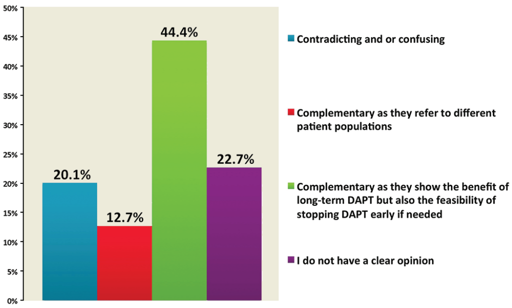

Figure 7. *How do you find the results of the DAPT trial as compared to the ISAR-SAFE and ITALIC/ITALIC+ trials?*

PRACTICE AFTER THE DAPT, ISAR-SAFE AND ITALIC TRIALS

The main findings of this part of the survey are shown in **Online Table 2**. The majority of respondents (58.1%) indicated that DAPT duration should be individualised, i.e., prolonged in selected patients and shortened in selected patients, as opposed to a 12-month DAPT regimen in all, whereas 12.5% believed that practice and recommendations should not change after the new evidence provided at AHA 2014. Forty percent of respondents believed that a prolonged therapy, beyond one year, should be limited to less than 10% of the patient population; whereas 34% of respondents would treat 10 to 30% of their patients with this strategy **(Online Table 2)**.

Comparing the answers to the parts of the survey delivered before and after AHA, a uniform 12-month DAPT duration in all patients was less frequently selected after AHA 2014 (37.3% before vs. 22.9% after).

The most frequently preferred therapeutic options were: 1) six-month DAPT in stable and 12-month DAPT in ACS patients (24.8% before AHA vs. 29.4% after AHA), 2) DAPT beyond one year in a sizeable proportion of patients (7.4% before AHA vs. 13.0% after AHA), 3) a tailored DAPT duration for individual patients based on ischaemic and/or bleeding risk (9.7% before AHA vs. 16.2% after AHA) **(Figure 8)**. After AHA 2014, the evidence that prolonged DAPT protects against non-stent-related events (64.5% before AHA vs. 71.8% after AHA) was regarded as more compelling than before **(Figure 9)**.

In contrast with the opinions expressed before AHA 2014, after the meeting the quality of evidence on DAPT duration in DES recipients was interpreted as "average" by 27.4% of the respondents (as compared to 41.4% of responders before AHA), whereas the majority regarded it as confusing (22.8% before AHA vs. 46.1% after AHA) **(Figure 10)**.

Overall, 40% of participants called for a change in the guidelines regarding DAPT duration **(Online Table 2)**: the majority of cardiologists working in an academic environment responded in support of a formal change in guidelines supporting practice around DAPT duration, whereas the opposite was voiced by the majority of non-academic cardiologists. When asked about how guidelines should change based on the new evidence, 72% of respondents thought

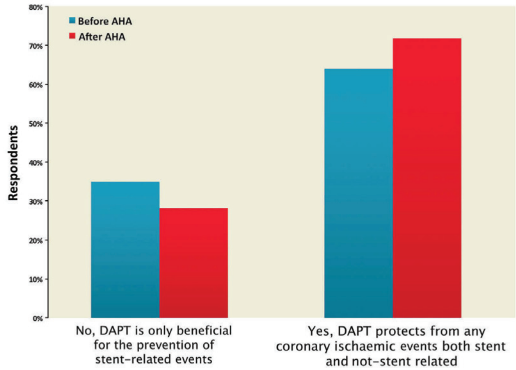

Figure 9. *Comparison of the answers to the question "Do you think prolonged DAPT is beneficial for the prevention of ischaemic events, which are not stent-related?" before and after AHA.*

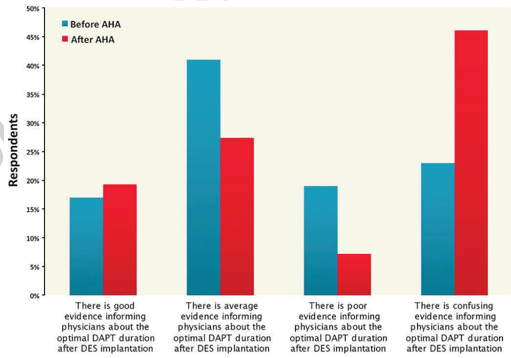

Figure 10. *Comparison of the answers to the question "How do you judge the evidence regarding DAPT duration after DES implantation?" before and after AHA.*

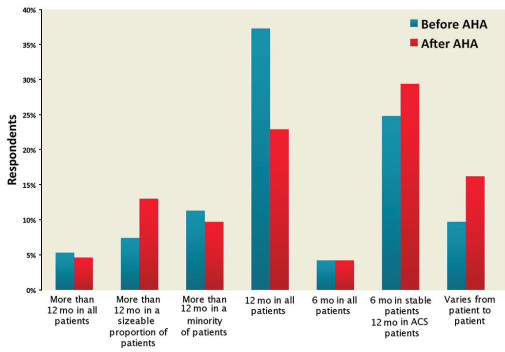

Figure 8. *Comparison of the answers to the question "For how long do you generally prescribe DAPT after DES implantation in patients not requiring oral anticoagulation?" before and after AHA.*

that guidelines should more proactively recommend an individualised therapy in different patient populations **(Online Table 2)**.

Finally, 54.7% of participants believed that new randomised trials testing individualised therapy duration based on ischaemic and bleeding risk are needed, 35.6% expressed the need for trials comparing conventional DAPT versus a $P2Y_{12}$ inhibitor alone long-term treatment strategy, whereas 34.8% solicited a consensus statement based on the evidence available **(Online Table 2)**. The "other" option was selected by a few calling for new "real-world" prospective registries (two respondents), new randomised trials including potent $P2Y_{12}$ inhibitors (two respondents), new-generation DES (one respondent) or the implementation of intravascular imaging in decision making (one respondent).

INTERPRETATION OF THE SURVEY RESULTS

The main findings of the EAPCI survey on DAPT duration can be summarised as follows:

- Before AHA 2014, the practice most commonly recommended was 12-month DAPT duration after DES implantation, whereas only one responder out of ten declared a clinical practice consistent with routine DAPT duration beyond one year after stent implantation.
- After AHA 2014, most respondents did not report extended DAPT duration of up to 30 months as representing the preferred approach in comparison with a 12-month treatment duration, and fewer than two responders out of ten believed that this should become the new standard of care.
- After AHA 2014, the evidence regarding DAPT duration was more frequently interpreted as confusing.
- The majority of respondents reported that DAPT should be prolonged or shortened in selected patients according to both ischaemic and bleeding risks and that future guidelines should more proactively recommend strategies in this direction.
- The results of the survey indicate that following the data presented at AHA 2014 considerable confusion exists regarding the optimal duration of DAPT after coronary stenting. The community needs guidance on how DAPT should be individualised and this largely reflects the lack of coordination across DAPT studies performed so far. Many meta-analyses on this topic already exist based on aggregate data, reaching inconsistent conclusions depending on different study selection and methods of analysis. Hence, a collaborative effort among all principal investigators of DAPT studies would be desirable to characterise further the included patient population in each of these and to be able to identify the patients who would most benefit from prolonged versus shortened DAPT and vice versa.

Limitations

This survey has a number of important limitations which should be carefully weighed when interpreting the results. Firstly, only a small percentage of invited practitioners took part in this survey. Therefore, the results are not necessarily representative of the opinion of the whole community. However, low participation rate is a common limitation of surveys in general, especially when the population targeted is that of professionals at an advanced career stage. Secondly, the use of multiple choice questions may lead to question bias. To reduce this effect, respondents were able to add open answers if they felt it was appropriate. In addition, respondents may have been subject to social desirability response bias: for example, this may have overestimated the percentage of those who declared weighing ischaemic and bleeding risks before selecting DAPT duration. Thirdly, the comparison of questions dispensed before and after AHA 2014 was not performed on an individual but on an aggregate basis. As such, it is not possible to evaluate if the single respondent changed his/her opinion or if a new cohort of respondents drove the change in the second part of the survey. However, in view of the relatively high number of contributors, it is likely that we have captured real changes in opinion due to the new evidence provided. Fourthly, this survey was designed and administered before the publication of the results of the PEGASUS trial[10], which explored the effects of a prolonged therapy with ticagrelor in patients with previous myocardial infarction. It is possible that the opinion of the respondents may have changed in the light of this new evidence. Finally, the focus of this survey was on duration and not on type of DAPT (i.e., based on which $P2Y_{12}$ inhibitor). A further EAPCI survey addressing the evidence provided by the PEGASUS study and whether the medical community believes duration of DAPT also to be dependent on type of $P2Y_{12}$ inhibitor is in preparation.

Conclusions

This EAPCI survey highlights considerable uncertainty within the medical community with regard to the optimal duration of DAPT after coronary stenting in the light of recently reported trial results. The medical community surveyed called for new evidence or updated guidance on how DAPT duration should be individualised for each patient.

Impact on daily practice

Against the conduct of ten dedicated randomised studies investigating various durations of dual antiplatelet therapy (DAPT) and the recent publication of the DAPT trial, which enrolled almost 9,500 patients, the optimal duration of dual antiplatelet therapy after coronary stenting remains unclear. This survey highlights uncertainties within the medical community with regard to how DAPT duration should be managed in clinical practice. A joint effort of international societies, leveraging on the contribution of each principal investigator of the available trials to provide outcomes in pre-specified patient subsets, or ideally the performance of an individual patient meta-analysis, may clarify the most suited DAPT duration for each single patient in practice in future. Providing guidance to the clinical community with respect to the individualisation of the antiplatelet therapy based on patients ischaemic and bleeding risk will be crucial to optimise benefits versus risks.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Online data supplement

Online Appendix. List of respondents.

Online Table 1. Declared clinical practice of respondents concerning DAPT duration before AHA 2014.

Online Table 2. Declared clinical practice of respondents concerning DAPT duration after AHA 2014.

Online Figure 1. Geographic region of practice of the respondents.

Part 2

Prognostic impact of bleeding and thrombosis

Chapter 2.1

Trade-off of Myocardial Infarction versus Bleeding types on Mortality after Acute Coronary Syndrome: Lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) Randomized Trial

Marco Valgimigli, ***Francesco Costa***, Yuliya Lokhnygina, Robert M. Clare, Lars Wallentin, David J. Moliterno, Paul W. Armstrong, Harvey D. White, Claes Held, Philip E. Aylward, Frans Van de Werf, Robert A. Harrington, Kenneth W. Mahaffey, Pierluigi Tricoci

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Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial

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This paper was guest edited by Anthony DeMaria.

Aims Dual antiplatelet therapy reduces non-fatal ischaemic events after acute coronary syndrome (ACS) but increases bleeding to a similar extent. We sought to determine the prognostic impact of myocardial infarction (MI) vs. bleeding during an extended follow-up period to gain insight into the trade-off between efficacy and safety among patients after ACS.

Methods and results In 12 944 patients with non-ST-segment elevation ACS from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, we investigated the relative impact of MI and bleeding occurring >30 days post-ACS and subsequent all-cause mortality. Bleeding was graded according to Bleeding Academic Research Consortium (BARC) criteria. MI was associated with a five-fold increase in mortality. BARC type 2 and 3, but not type 1, bleeding had a significant impact on mortality. MI was associated with a greater risk of mortality compared with BARC 2 [relative risk (RR) 3.5; 95% confidence interval (CI) 2.08–4.77; $P < 0.001$] and BARC 3a bleeding (RR 2.23; 95% CI 1.36–3.64; $P = 0.001$), and a risk similar to BARC 3b bleeding (RR 1.37; 95% CI 0.81–2.30; $P = 0.242$). Risk of death after MI was significantly lower than after BARC 3c bleeding (RR 0.22; 95% CI 0.13–0.36; $P < 0.001$). MI and bleeding had similar time-associations with mortality, which remained significant for several months, still being higher early after the event.

Conclusion In patients treated with antiplatelet therapy after ACS, both MI and bleeding significantly impacted mortality with similar time-dependency. Although BARC 2 and 3a bleeding were less prognostic for death than MI, the risk of mortality was equivalent between BARC 3b bleeding and MI, and was higher following BARC 3c bleeding.

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Introduction

Dual antiplatelet therapy (DAPT) reduces the occurrence of both stent-related and spontaneous myocardial infarction (MI) after acute coronary syndrome (ACS).[1–3] However, this benefit is counterbalanced by an increase in bleeding.[2–4] Bleeding, which was historically considered an acceptable price to pay for antithrombotic therapy, has been recently shown to independently impact mortality, and a causal relationship is generally accepted, although mechanisms are not fully understood.[5–8] International guidelines not only recommend at least 12 months of DAPT after ACS or coronary stent implantation, but they also encourage considering bleeding risk when selecting treatment duration.[9–12]Adequately accounting for the efficacy on coronary thrombotic events and safety in medical decision-making on type and duration of antiplatelet therapy is challenging.[13]

In light of recent clinical trial data with DAPT regimens beyond 1 year showing further reduction of ischaemic events at the price of a similar increase in bleeding, the number of patients who may qualify for longer-term DAPT is going to increase.[14,15] Therefore, it is critical to understand the prognostic implications of MI, especially spontaneous MI, relative to bleeding in order to assist clinicians in selecting patients for more potent or prolonged antiplatelet treatment. Previous studies reported on the prognostic implications of in-hospital—largely procedural—bleeding vs. ischaemic events.[16,17] However, the impact of spontaneous (i.e. non-procedural) bleeding occurring later during treatment has been less extensively investigated,[18,19] and its effect on mortality, depending on the severity and how it compares with the mortality risks following an MI, remains unclear.

In this analysis, using a large randomized clinical trial of patients with non-ST-segment elevation (NSTE) ACS with long-term follow-up, we aimed to assess the relative impact on all-cause mortality of MI and bleeding occurring late after the initial ACS presentation on all-cause mortality.

Methods

Patient population

The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial design and inclusion and exclusion criteria have been described previously.[20] In brief, TRACER was an international, prospective, randomized, double-blind trial of vorapaxar vs. placebo in patients hospitalized for NSTE ACS managed according to contemporary practice. A total of 12 944 patients from 37 countries and 818 sites were enrolled, and 12 702 who were alive and free from recurrent MI at 30 days after randomization were considered in the current analysis.

All enrolled patients had acute symptoms of coronary ischaemia within 24 h before hospital presentation and at least one of the following findings: a cardiac troponin (I or T) or creatine kinase-MB level that was higher than the upper limit of the normal range or a new ST-segment depression of >0.1 mV or transient ST-segment elevation (<30 min) of >0.1 mV in at least two contiguous leads. Also, at least two of the following criteria were required: age ≥55 years; previous MI, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG); or presence of diabetes mellitus or peripheral arterial disease.

Study procedures

Patients were randomly assigned in a 1:1 ratio to receive vorapaxar (a loading dose of 40 mg and a daily maintenance dose of 2.5 mg thereafter), which is an oral protease-activated receptor 1 antagonist, or matching placebo. Type and timing of revascularization were at the discretion of the operating physician. Concomitant antiplatelet treatments were also decided by the treating physician and according to international guidelines; >90% of patients were treated with clopidogrel during the index ACS hospitalization.

Endpoints

The endpoint of interest for this analysis was all-cause death. We aimed to assess the association of mortality with (i) any MI and (ii) bleeding that was not related to CABG. We only included MI and bleeding events that occurred at least 30 days after randomization. This time window was justified by the need to focus only on late events occurring in patients already stabilized post-ACS, excluding early events that are largely influenced by in-hospital interventional or surgical procedures. Bleeding events were graded according to the Bleeding Academic Research Consortium (BARC) criteria.[21] In brief, BARC bleeding was defined as follows: BARC type 1, any bleeding that is not actionable; type 2, any overt, actionable sign of bleeding; type 3a, overt bleeding with a haemoglobin drop of 3–5 g/dL or any transfusion; type 3b, overt bleeding with a haemoglobin drop >5 g/dL, requiring vasopressors, surgical intervention, or due to cardiac tamponade; type 3c, any intracranial or intraocular bleeding; type 4, any bleeding that was CABG-related; and finally type 5, any bleeding resulting in death. MI was classified according to the Third Universal Definition of Myocardial Infarction.[22]

An independent clinical events committee (CEC) adjudicated all events. Definitions were previously described.[20] Bleeding events were classified by the CEC according to the TIMI (Thrombolysis In Myocardial Infarction) and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) definitions. The BARC classification was derived with an algorithm on data points adjudicated by the CEC. The ethics committee or institutional review board of each participating institution approved the study protocol, and written informed consent was required prior to study inclusion. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Duke University Institutional Review Board approved the use of the TRACER database for secondary analyses.

Statistical analysis

Demographic and baseline variables were summarized by the worst BARC bleeding event experienced from 30 days postrandomization (see Supplementary material online, *Table S1*) and by whether an MI occurred during this period (see Supplementary material online, *Table S2*). Continuous variables were presented as medians (inter-quartile ranges), and categorical variables were presented as counts (proportions).

All-cause mortality risk was investigated using Cox proportional hazards models. All models described below included covariates for MI and

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Table 1 Model 1: Association between risk of mortality and BARC 1, 2, and 3 (any 3a, 3b, 3c pooled) bleeding events occurring >30 days after randomization (adjusted for known mortality risk factors)

Covariate	Definition	Death for no event	Death for event	Adjusted[a] HR (95% CI)	*P*-value for covariate risk (HR)
MI	—	3.19% (382/11 984)	16.43% (118/718)	5.36 (4.26–6.74)	<0.001
Any BARC bleeding					<0.001
Nuisance (BARC 1)	Non-actionable bleeding	3.95% (467/11 824)	3.76% (33/878)	0.89 (0.61–1.31)	0.551
Minor (BARC 2)	Any overt, actionable sign of bleeding	3.79% (455/11 990)	6.32% (45/712)	1.70 (1.23–2.36)	0.001
Major (BARC 3a–c)	Any overt, actionable bleeding associated with ≥3 g/dL hgb drop, transfusion, or more severe bleeding	3.41% (421/12 356)	22.83% (79/346)	5.73 (4.32–7.59)	<0.001

CI, confidence interval; hgb, haemoglobin; HR, hazard ratio; MI, myocardial infarction; BARC, Bleeding Academic Research Consortium.
[a]Adjustment covariates include: MI and BARC bleeding through Day 30 post-randomization, age, body mass index, female sex, Killip class ≤2 at enrolment, history of peripheral arterial disease, prior stroke, prior MI, hypertension, hyperlipidaemia, diabetes mellitus, smoker at enrolment, and systolic blood pressure at enrolment.

Table 2 Model 2: Association between risk of mortality and BARC 1, 2, 3a, 3b, and 3c bleeding events occurring more than 30 days after randomization (adjusted for known mortality risk factors)

Covariate	Definition	Death for no event	Death for event	Adjusted[a] HR (95% CI)	*P*-value for covariate risk (HR)
MI	—	3.19% (382/11 984)	16.43% (118/718)	6.15 (4.90–7.74)	<0.001
Major bleeding					
BARC 3a	Overt bleeding with hgb drop 3–5 g/dL or any transfusion	3.75% (470/12 538)	18.29% (30/164)	2.77 (1.86–4.12)	<0.001
BARC 3b	Overt bleeding with hgb drop > 5 g/dL, requiring vasopressors, surgical intervention, or due to cardiac tamponade	3.78% (475/12 577)	20.00% (25/125)	4.51 (2.86–7.10)	<0.001
BARC 3c	Intracranial or intraocular bleeding	3.76% (476/12 645)	42.11% (24/57)	28.2 (17.5–45.7)	<0.001

CI, confidence interval; hgb, haemoglobin; HR, hazard ratio; MI, myocardial infarction; BARC, Bleeding Academic Research Consortium.
[a]Adjustment covariates include: MI and BARC bleeding through Day 30 post-randomization, age, body mass index, female sex, Killip class ≤2 at enrolment, history of peripheral arterial disease, prior stroke, prior MI, hypertension, hyperlipidaemia, diabetes mellitus, smoker at enrolment, and systolic blood pressure at enrolment.

BARC bleeding during the first 30 days postrandomization, as well as age, body mass index, female sex, Killip class ≤2 at enrolment, history of peripheral arterial disease, prior stroke, prior MI, hypertension, hyperlipidaemia, diabetes mellitus, smoker at enrolment, and systolic blood pressure at enrolment. Randomized treatment was not included as a covariate in the models because of the lack of association with all-cause mortality.[20] MI and BARC bleeding events after 30 days were included as time-dependent binary indicators. Risk of recurrent events has been modelled taking into account the first occurrence of such an event, whereas in case of events of different severity (i.e. BARC 2 followed by BARC 3 bleeding), these have been considered as separate covariates. Hazard ratios (HRs) and *P*-values for the risk of all-cause death associated with post-30-day bleeding and post-30-day MI events were obtained from Model 1—BARC 3a, 3b, and 3c bleeding events were treated the same as BARC 3 bleeding events (*Table 1*)—and from Model 2, where they were evaluated separately (*Table 2*). The relative hazard of MI vs. bleeding events was estimated from the same models. Additional analyses investigated the time-dependent nature of the risk of death associated with post-30-day bleeding and MI events as a function of the time elapsed since the event. In these analyses, the natural log of the hazard of death was modelled as a function of (i) natural log, (ii) square root, (iii) quadratic, and (iv) piecewise linear function (with separate slopes for 0–30 days and after 30 days) of time elapsed since the bleeding or MI event. The best-fitting model was selected using the Akaike Information Criterion. For patients who experienced both a bleeding event and an MI, both events were counted and each was considered individually as predictors of death (i.e. the models included covariates for MI and bleeding events).

All statistical tests were performed at a significance level of 0.05. All analyses were performed at the Duke Clinical Research Institute (Durham, NC, USA) using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 3 Myocardial infarction occurring > 30 days after randomization in the TRACER trial, stratified according to the Third Universal Definition of Myocardial Infarction

Event	Definition	Frequency	Valid per cent (%)
Myocardial infarction		718	—
Type 1	Spontaneous	594	82.7
Type 2	Secondary to ischaemic imbalance	46	6.41
Type 3	Resulting in SCD	0	0.0
Type 4a	Related to PCI	34	6.69
Type 4b	Related to stent thrombosis	35	4.87
Type 5	Related to CABG	7	5.07
STEMI		77	10.75
New Q-wave		31	5.18

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SCD, sudden cardiac death; STEMI, ST-segment elevation myocardial infarction.

Results

In the TRACER trial, a total of 12 702 patients were alive and free from any recurrent MI at 30 days. A total of 718 patients (5.6%) suffered a recurrent MI 30 days after the index event, most of which were spontaneous (*Table 3*). Bleeding events occurring during study follow-up were distributed as follows: BARC 1 occurred in 878 patients (6.9%); BARC 2 occurred in 712 patients (5.6%); BARC 3 occurred in 346 patients (2.7%) (*Table 1*). More than one post-30-day MI occurred in 0.98% of patients during follow-up, whereas multiple BARC 2 or 3 bleeding events occurred in 1.39%. The proportion of patients experiencing both bleeding and MI during follow-up was 1.46%, with similar rates of patients experiencing an MI first (0.72%) or bleeding first (0.75%) (*Figure 1*). Demographic and clinical characteristics of patients experiencing bleeding and MI events are presented in the Supplementary materia online, *Tables S1 and S2*, respectively. Patients with vs. without bleeding were older; more often affected by dyslipidaemia or diabetes; and more often had a history of stroke, peripheral vascular disease, and atrial fibrillation. Patients with vs. without MI were older and more often affected by hypertension, dyslipidaemia, diabetes, and other comorbidities.

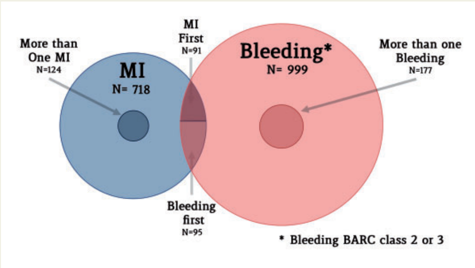

Figure 1 Distribution of minor and major bleeding and myocardial infarction in the TRACER trial. The Venn diagram shows patients experiencing minor or major bleeding (in red) and myocardial infarction (in blue). Smaller circles represent patients experiencing more than one event during follow-up. The intersection represents patients experiencing both myocardial infarction and bleeding during follow-up. MI, myocardial infarction.

Mortality following bleeding or myocardial infarction

Death occurred in 500 patients (3.9%) at the end of follow-up. *Table 1* reports the number of patients who died following MI or bleeding events. When considered as time-dependent covariates in the multivariable-adjusted model, both post-30-day bleeding and MI were associated with mortality (*Table 1*). Patients with an MI ≥30 days after randomization had a five-fold increase in the hazard of death [adjusted HR 5.36; 95% confidence interval (CI) 4.26–6.74; $P < 0.001$]. BARC 1 bleeding did not affect survival (adjusted HR 0.89; 95% CI 0.61–1.31; $P = 0.551$), whereas BARC 2 and 3 bleeding types were associated with a significant increase in the risk of mortality, with a progressive increase in risk with more severe categories of bleeding (*Table 1*). When BARC 3 major bleeding subcategories (BARC 3a, 3b, and 3c) were separately included in a second multivariate-adjusted model for mortality, a consistent risk progression among more severe bleeding events was also noted (*Table 2*). The prognostic impact was independent from the randomized treatment with vorapaxar for both MI ($P_{int} = 0.19$) and different bleeding types (BARC 1: $P_{int} = 0.61$; BARC 2: $P_{int} = 0.20$; BARC 3: $P_{int} = 0.17$).

Relative impact of bleeding vs. myocardial infarction on mortality

The relative impact on mortality of an MI vs. a bleeding event is displayed graphically in *Figure 2*. The relative hazard of death was threefold higher in patients experiencing an MI vs. a BARC 2 bleeding event [5.36 vs. 1.70; relative risk (RR) 3.15; 95% CI 2.08–4.77; $P < 0.001$], whereas no significant difference was noted for BARC 3 bleeding (5.36 vs. 5.73; RR 0.94; 95% CI 0.63–1.40; $P = 0.747$). In a second adjusted model for mortality that accounted for the BARC 3 subcategories (BARC 3a, 3b, and 3c) separately, the risk of mortality associated with MI was significantly higher than for BARC 3a bleeding (6.15 vs. 2.77; RR 2.23; 95% CI 1.36–3.64; $P = 0.001$). MI was associated with a non-significant increase in the risk of death compared with BARC 3b bleeding (6.15 vs. 4.51; RR 1.37; 95% CI 0.81–2.30; $P = 0.242$). Mortality following MI was significantly lower than following a BARC 3c bleeding event (6.15 vs. 28.2; RR 0.22; 95% CI 0.13–0.36; $P < 0.001$) (*Figure 2*).

Time relation of bleeding and myocardial infarction with hazard of mortality

The time-pattern of the associated hazard of mortality was similar between MI and bleeding events. For both MI and bleeding, the risk of death was higher early after the event; it rapidly dissipated in the subsequent days, but it still kept a significant prognostic impact for several months thereafter. The mortality risk was no longer significantly different from that in patients without an MI or bleeding event 215 days after an MI; 183 days after a BARC 2 minor bleeding event; and 538, 239, and 113 days for BARC 3a, 3b, and 3c bleeding, respectively (*Figure 3*).

Discussion

We have confirmed the prognostic significance of MI and bleeding occurring late after hospitalization, and found that the relative prognostic impact of MI compared with bleeding markedly varied based on the severity of bleeding. The risk of mortality following an MI was three-fold higher compared with that of BARC 2 bleeding, whereas it was similar to that of BARC 3 bleeding. When BARC 3 subcategories were separately appraised, MI had a higher mortality risk than BARC 3a bleeding, and was substantially equivalent to the risk of mortality following BARC 3b bleeding. Importantly, the risk of death was highest after intracranial or intraocular haemorrhages (captured in the BARC 3c category), and it was ∼4.5-fold higher than the risk of bleeding following MI.

Our analysis was based on centrally adjudicated events and analysed bleeding according to a standardized, widely accepted and reproducible bleeding definition. Prior analyses have observed a similarly increased risk of mortality between spontaneous MI and bleeding during a 4 year follow-up.[23] However, this consideration might largely depend on bleeding definition and the type of bleeding

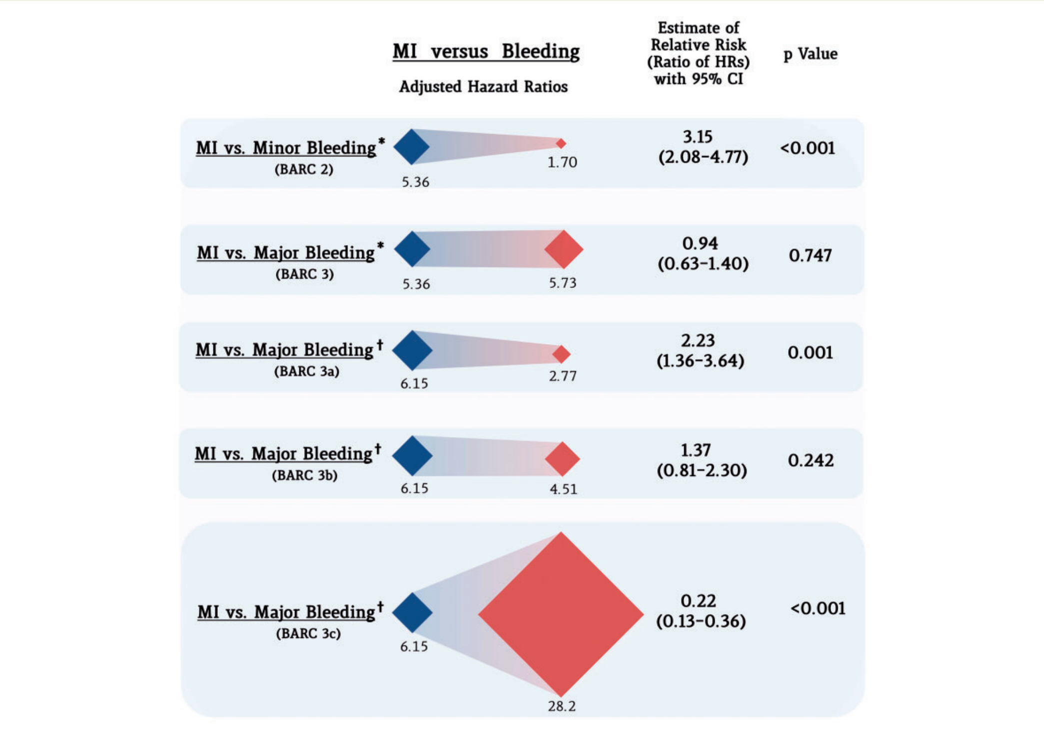

Figure 2 Differential impact of myocardial infarction vs. bleeding on mortality. Blue rhombuses represent the magnitude (adjusted hazard ratio) of the impact on mortality of late myocardial infarction, whereas red rhombuses represent that of bleeding of different severity. On the right part of the figure, the estimate of the relative risk (ratio of the hazard ratios) for each category is presented. *The estimates of the impact of events on mortality is derived from Model 1, including BARC 3 bleeding as a single category. †The estimates of the impact of events on mortality is derived from Model 2, including BARC 3 bleeding subcategories separately. MI, myocardial infarction.

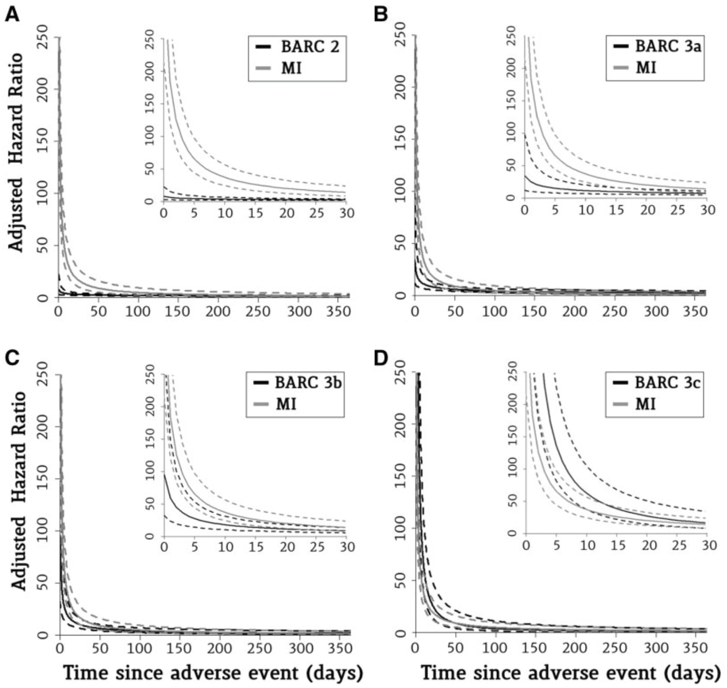

Figure 3 Evolution of the prognostic impact of minor and major bleeding vs. myocardial infarction over time. This figure shows the adjusted hazard ratio for mortality of myocardial infarction vs. minor (BARC 2) and major (BARC 3a–c) bleeding as a function of time elapsed after the event. Inside graph: The decline in hazard ratio as an exponential function of time in the first 30 days. Outside graph: The decline in hazard ratio for the first year after the event. Solid lines represent point estimates; dashed lines represent 95% confidence intervals. MI, myocardial infarction; BARC, Bleeding Academic Research Consortium.

explored.[24] In fact, accounting for bleeding severity, we found that recurrent MI had higher prognostic impact on mortality than bleeding, except for BARC 3c categories. This information is of major importance, as it indicates that it might be fair to pursue a more potent antiplatelet regimen to avoid an MI even at the expense of mild-to-moderate bleeding in patients with high ischaemic risk. In addition, our data suggest that combining all bleeding, including minor bleeds that are more frequent but less prognostically significant, into a safety endpoint or net clinical outcome including MI may pose significant challenges in interpreting the clinical benefit of drugs.

The temporal association with mortality was similar between MI and minor or major bleeding. Although the highest risk of mortality was present in the first week after the event, its magnitude rapidly decreased thereafter, despite remaining elevated for several months. Prior studies assessing the temporal association of ischaemia and bleeding with mortality have had contrasting results.[16,18] In one report based on an NSTE MI population, the impact of bleeding was sustained over time up to 1 year after the event, whereas the impact of MI rapidly dissipated and was no longer significant after 30 days.[16] In a second report focusing on ST-segment elevation MI patients, recurrent MI had a more long-lasting effect on mortality (>1 year), whereas severe bleeding did not have a significant impact on mortality as early as 30 days after the event.[18] A similar result in an all-ACS population was observed by Hochholzer *et al.*,[19] who found the risk of bleeding being no more significantly elevated 40 days after the event. Reconciling these inconsistent results is challenging as they concern different populations, different types and definitions of events, and different statistical methods. Accordingly, further studies are needed to confirm the time-association pattern between MI and bleeding with mortality.

The findings of our analysis might also help explain the efficacy/safety balance of recent clinical trials exploring newer strategies of prolonged DAPT, which have demonstrated an ischaemic benefit obtained at the expense of increased bleeding complications.[14,15,25,26] The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial tested the effect of a long course of treatment with two different doses of ticagrelor (90 and 60 mg) vs. placebo in patients with an MI that occurred 1–3 years earlier.[15] Ticagrelor reduced the primary efficacy endpoint by an absolute 1.2%, mainly by reducing MIs and stroke, but with no significant impact on mortality. Interestingly, the treatment with ticagrelor also increased major bleeding to a similar extent. The DAPT trial included patients treated with drug-eluting stents, who after a 12 month run-in phase of standard DAPT with thienopyridines were randomized to stop or continue the $P2Y_{12}$ inhibitor.[14] After 30 months, patients randomized to an extended DAPT course showed a reduction of ischaemic events at the expense of a similar increase. Taken together, these trials and our current findings strongly suggest that DAPT duration should be weighed considering the ischaemic vs. bleeding risk profile of the patient, as both complications may concur to significantly increase mortality, with comparative effects that largely depend on the bleeding severity.[14,15,27–29]

Net clinical benefit outcomes have become a popular endpoint to account for both efficacy and bleeding effect. However, there is an intrinsic risk of misinterpretation when heterogeneity among components exists with respect to either importance, number of events, or magnitude of treatment effect.[30] In this scenario, one can imagine that if the directions of minor bleeding and MI are different, but minor bleeding occurs more frequently, the net clinical benefit will be pushed towards the treatment with fewer events, irrespective of their clinical significance. To overcome this limitation of the classic time-to-event analysis, alternative statistical approaches have been proposed.[31–33] These methods rank or weigh events according to their clinical significance, minimizing imbalances from differences in direction and magnitude of single components of the endpoint. However, the evidence regarding how various bleeding types should be weighed in combined endpoints against MI is so far limited. Hence, our study could be useful, informing a more objective way to rank/weigh ischaemic and bleeding events.

The limitations of our study must be acknowledged. This is a *post hoc* analysis, and the interplay between MI, bleeding, and mortality is very complex; we could not account for all possible factors implicated in their causal relationship. Second, we did not evaluate the prognostic impact of MI subcategories; however, because we excluded events occurring during the first 30 days, PCI- and CABG-related MI were observed rarely. Finally, although bleeding events were stratified by severity, we did not have a systematic measure of infarct severity or size. For example, imaging assessing infarct size or changes in ejection fraction are typically not systematically performed in large phase 3 randomized clinical trials and were not available in TRACER. It is likely to expect a different impact on mortality of events related with larger areas of myocardium at risk and/or with proximal segments of the coronary arteries.[34,35]

Conclusions

Recurrent MI occurring 30 days after hospitalization for NSTE ACS appeared to be associated with a higher risk of mortality compared with mild-to-moderate bleeding, and had a similar prognostic implication compared with severe, non-intracranial bleeding. Intracranial and intraocular bleeding were associated with a mortality risk that was higher than for MI. These findings may help interpret the risk-and-benefit profile of antithrombotic medications.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Chapter 2.2

Anatomic Characteristics and Clinical Implications of Angiographic Coronary Thrombus: Insights From a Patient-Level Pooled Analysis of SYNTAX, RESOLUTE, and LEADERS Trials.

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Coronary Interventions

Anatomic Characteristics and Clinical Implications of Angiographic Coronary Thrombus

Insights From a Patient-Level Pooled Analysis of SYNTAX, RESOLUTE, and LEADERS Trials

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Background—The distribution of thrombus-containing lesions (TCLs) in an all-comer population admitted with a heterogeneous clinical presentation (stable, ustable angina, or an acute coronary syndrome) and treated with percutaneous coronary intervention is yet unclear, and the long-term prognostic implications are still disputed. This study sought to assess the distribution and prognostic implications of coronary thrombus, detected by coronary angiography, in a population recruited in all-comer percutaneous coronary intervention trials.

Methods and Results—Patient-level data from 3 contemporary coronary stent trials were pooled by an independent academic research organization (Cardialysis, Rotterdam, the Netherlands). Clinical outcomes in terms of major adverse cardiac events (major adverse cardiac events, a composite of death, myocardial infarction, and repeat revascularization), death, myocardial infarction, and repeated revascularization were compared between patients with and without angiographic TCL. Preprocedural TCL was present in 257 patients (5.8%) and absent in 4193 (94.2%) patients. At 3-year follow-up, there was no difference for major adverse cardiac events (25.3 versus 25.4%; P=0.683); all-cause death (7.4 versus 6.8%; P=0.683); myocardial infarction (5.8 versus 6.0%; P=0.962), and any revascularizations (17.5 versus 17.7%; P=0.822) between patients with and without TCL. The comparison of outcomes in groups weighing the jeopardized myocardial by TCL also did not show a significant difference. TCL were seen more often in the first 2 segments of the right (43.6%) and left anterior descending (36.8%) coronary arteries. The association of TCL and bifurcation lesions was present in 40.1% of the prespecified segments.

Conclusions—TCL involved mainly the proximal coronary segments and did not have any effect on clinical outcomes. A more detailed thrombus burden quantification is required to investigate its prognostic implications.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00114972, NCT01443104, NCT00617084. **(*Circ Cardiovasc Interv*. 2015;8:e002279. DOI: 10.1161/CIRCINTERVENTIONS.114.002279.)**

Key Words: drug-eluting stent ■ outcome ■ percutaneous coronary intervention ■ thrombus

Coronary thrombus has been associated with acute coronary syndromes and disease progression. The rupture of thin cap fibro-atheromas allows the blood to come in contact with the highly thrombogenic contents of the plaque (eg, necrotic core/collagen) favoring the occurrence of most of acute coronary syndromes.[1,2] In addition, invasive imaging studies have shown that coronary thrombosis can also be present in stable coronary artery disease (CAD) and has been associated with plaque progression.[3,4]

Thrombus-containing lesions (TCLs) seems to be associated with an increased risk of distal embolization and no or poor distal flow and low myocardial blush grades after percutaneous coronary intervention.[5,6] However, the prognostic relevance of coronary thrombus as assessed by angiography is still unclear, and the results presented in the literature are disputed.[7–9]

The aim of the present study is to examine the angiographic anatomic characteristics of TCL and their correlations with clinical events (all-cause death, myocardial infarction [MI], and all revascularizations) in the largest-ever pooled all-comer population enrolled in contemporary percutaneous coronary intervention trials.

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WHAT IS KNOWN

- The effect of coronary thrombus on prognosis is disputed, particularly in the era of sophisticated coronary intervention.

WHAT THE STUDY ADDS

- In a population with a broad spectrum of coronary disease, the presence of intracoronary thrombus was not associated with an increased incidence of adverse outcomes.
- Thombi were most commonly located in proximal coronary locations and at the site of coronary bifurcations.

Methods

Patient Population

We analyzed patient-level data from 3 all-comer coronary drug-eluting stent trials: LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trial, RESOLUTE (Resolute All Comers) trial, and SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery). Detailed individual study design and trial results are available elsewhere.[10–12] In brief, all studies included patients with obstructive CAD that was amendable to coronary stent implantation (Table I in the Data Supplement). These trials had an all-comers design, but in the SYNTAX trial, the enrolled patients must had complex (3-vessel or left main) CAD to be enrolled. All studies complied with the Declaration of Helsinki and were approved by the ethical review board in each institution. All patients provided written, informed consent for participation in the individual study. The angiographic images were reviwed by independent core laboratory analysts (Cardialysis, Rotterdam, The Netherlands) who identify the presence or absence of thrombus. Aiming to evaluate the clinical characteristics and prognosis, the patients were divided into 2 groups according to the presence or absence of at least one TCL as assessed by coronary angiography.

Table 1. Segment Weighing Factor

Segment No.	Right Dominance	Left Dominance
1	1	0
2	1	0
3	1	0
4	1	na
16	0.5	na
16a	0.5	na
16b	0.5	na
16c	0.5	na
5	5	6
6	3.5	3.5
7	2.5	2.5
8	1	1
9	1	1
9a	1	1
10	0.5	0.5
10a	0.5	0.5
11	1.5	2.5
12	1	1
12a	1	1
12b	1	1
13	0.5	1.5
14	0.5	1
14a	0.5	1
14b	0.5	1
15	na	1

Table 2. Baseline Clinical Characteristics

	Pts Without Thrombus Containing Lesions N=4193	Pts With Thrombus Containing Lesions N=257	*P* Values
Age	64.6±107	62.7±10.7	0.006
Male, %	3127 (74.6)	208 (80.9)	0.022
Diabetes mellitus, %	1032 (24.6)	50 (19.5)	0.061
Body mass index, kg/m^2	27.7±4.5	27.8±4.5	0.831
Hypertension, %	3061 (73.0)	150 (58.4)	<0.001
Hyperlipidemia, %	2842 (67.8)	136 (52.9)	<0.001
Current smoker, %	1279 (30.5)	132 (51.4)	<0.001
Peripheral vascular disease, %	317 (7.6)	16 (6.2)	0.446
Family history of premature CAD, %	1443 (27.3)	87 (33.9)	0.518
History of stroke/TIA, %	222 (5.3)	13 (5.1)	0.849
Creatinine >200 μmol/L	1.3	0.4	0.530
Creatinine clearance, mL/min	90.6±37.4	98.7±33.9	0.001
Previous myocardial infarction, %	1225 (29.2)	55 (21.4)	0.006
Previous PCI, %	1027 (24.5)	32 (12.5)	<0.001
Presentation			<0.001
NSTEMI, %	558 (13.3)	62 (24.1)	
Stable CAD, %	2131 (50.8)	50 (14.0)	
STEMI, %	539 (12.9)	112 (43.6)	
Unstable angina, %	965 (23.0)	33 (12.8)	
LVEF, %	56.8±11.9	54.7±11.9	0.052

CAD indicates coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; Pts, patients; STEMI, ST-segment–elevation myocardial infarction; and TIA, transient ischemic attack.

Clinical Outcomes

Major adverse cardiac events (MACE) were defined as a composite of all-cause death, MI, and any repeat revascularization. There was a wide variation in the definition of MI among studies. This is because of each study inclusion criteria, variations in study design, and the different periods during which studies were performed. Because all clinical events from each individual trial were adjudicated by independent clinical event committees, no attempt was made to readjudicate MI events in the different trials to compensate for the differences in individual definition of MI. Therefore, all MIs reported in the current study are as per individual study protocol definitions.

Table 3. Baseline Angiographic Characteristics

	Pts Without Thrombus Containing Lesions, N=4193	Pts With Thrombus Containing Lesions, N=257	*P* Values
Baseline SYNTAX score±SD	17.7±11.6	18.6±10.7	0.239
Number of total occlusions/patient±SD	0.27±0.49	0.37±0.56	0.010
Number of aorto-ostial lesions/patient±SD	0.06±0.25	0.07±0.27	0.714
Number of lesions with severe tortuosity/ patient±SD	0.81±1.09	0.73±1.07	0.265
Number of lesions with length >20 mm/ patient±SD	0.51±0.76	0.51±0.65	0.884
Number of lesions with heavy calcification/ patient±SD	0.40±0.87	0.35±0.82	0.367
Number segments with diffuse disease/ patient±SD	0.04±0.19	0.04±0.18	0.877
Lesions in left main/patient	0.10±0.31	0.07±0.26	0.086
Lesions in LAD proximal/patient	0.33±0.50	0.34±0.50	0.820
Lesions in LAD mid/patient	0.58±0.58	0.54±0.58	0.243
Lesions in LAD apical/patient	0.15±0.38	0.13±0.36	0.275
Lesions in first diagonal/patient	0.25±0.45	0.28±0.48	0.247
Lesions in second diagonal/patient	0.01±0.11	0.02±0.12	0.722
Lesions in proximal circumflex/patient	0.19±0.40	0.17±0.37	0.481
Lesions in distal circumflex/patient	0.35±0.52	0.30±0.49	0.116
Lesions in intermediate/patient	0.08±0.27	0.09±0.31	0.416
Lesions in first obtuse marginal/patient	0.13±0.34	0.13±0.34	0.686
Lesions in second obtuse marginal/patient	0.12±0.34	0.09±0.29	0.107
Lesions in RCA proximal/patient	0.27±0.45	0.33±0.47	0.045
Lesions in RCA mid/patient	0.34±0.49	0.34±0.48	0.983
Lesions in RCA distal/patient	0.25±0.46	0.27±0.48	0.447
Lesions in posterolateral/patient	0.07±0.25	0.05±0.23	0.21
Lesions in posterior descending /patient	0.01±0.09	0.00±0.00	0.17

LAD indicates left anterior descending coronary artery; Pts, patients; RCA, right coronary artery; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

Angiographic Assessment

The angiographic assessment was performed by an independent corelab (Cardialysis, Rotterdam, The Netherlands) based on the SYNTAX score concept. The SYNTAX score for each patient was calculated by scoring all coronary lesions with a diameter stenosis ≥50%, in vessels ≥1.5 mm, using the SYNTAX score algorithm, which is described in full elsewhere.[13] All angiographic variables were recorded prospectively by a team of 2 core laboratory analysts.

A bifurcation was classified by a division of a main, parent, branch into 2 daughter branches of at least 1.5 mm diameter according to the Medina classification.[14] The smaller of the 2 daughter branches was designated as the side branch. After the SYNTAX score recommendations, bifurcations were only scored for the following segment junctions: 5/6/11, 6/7/9, 7/8/10, 11/13/12a, 13/14/14a, 3/4/16, and 13/14/15. Coronary thrombus was defined according to the Academic Research Consortium definition as spheric, ovoid, or irregular intraluminal filling defect or lucency surrounded on 3 sides by contrast medium seen just distal or within the coronary stenosis in multiple projections or a visible embolization of intraluminal material downstream.[15] To further evaluate the prognostic effect of thrombus, the summation of segment weighing factors (Table 1) used in the SYNTAX score was used if TCLs were present.

Data Analysis

All patients with a calculated SYNTAX score were included in the analysis. Discrete data were summarized as percent (frequencies) and were compared using the chi-squared test. Continuous data were expressed as mean±SD and were compared using Student's *t* test or Wilcoxon rank-sum test based on their distributions. Survival curves were constructed for time-to-event variables using Kaplan–Meier estimates and compared by the log-rank test. Comparison of events rates between groups were adjusted for confounding factors in a Cox-regression model. All variables were stratified according to presence of at least one TCL using a Cox-regression model. The differences were regarded significant when $P<0.05$ (2-tailed). The Breslow-Day chi-squared test was calculated to test the statistical evidence of heterogeneity across the studies ($P<0.1$). The chi-squared test and I^2 statistic were calculated to test the statistical evidence of heterogeneity across the studies[16] (Table II and Figures I–V in the Data Supplement). SPSS version 21.0 (SPSS Inc, Chicago, IL) was used for all other statistical analyses.

Results

Baseline Characteristics

Table 2 depicts patients' baseline demographics. Preprocedural thrombus was present in 257 patients (5.8%) and absent in 4193 (94.2%). Patients with at least one TCL were younger (62.7±10.7 versus 64.6±10.7; $P=0.006$), more frequently male (80.9% versus 74.6%; $P=0.022$) and current smokers (51.4% versus 30.5%; $P<0.001$), less likely to have

Table 4. Kaplan–Meier Events Rate Comparison Between Groups

	Pts Without Thrombus Containing Lesions, N=4193	Pts With Thrombus Containing Lesions, N=257	*P* Values
30 days, n (%)			
MACE	254 (6.1)	17 (6.6)	0.714
All-cause death	47 (1.1)	3 (1.2)	0.937
All MI	163 (3.9)	9 (3.5)	0.754
All revascularization	114 (2.7)	11 (4.3)	0.131
1-year			
MACE	669 (16.0)	48 (18.7)	0.229
All-cause death	127 (3.0)	10 (3.9)	0.423
All MI	196 (4.7)	11 (4.3)	0.778
All revascularization	480 (11.5)	35 (13.7)	0.217
3-year			
MACE	1067 (25.4)	65 (25.3)	0.874
All-cause death	287 (6.8)	19 (7.4)	0.683
All MI	250 (6.0)	15 (5.8)	0.962
All revascularization	742 (17.7)	45 (17.5)	0.822

MACE indicates major adverse cardiac events (composite of all-cause death, myocardial infarction, and all revascularization); and MI, myocardial infarction.

hypertension (58.4% versus 73.0%; *P*<0.001), and hyperlipidemia (52.9 versus 67.8%; *P*<0.001). The left ventricular ejection fraction tended to be higher in patients without TCL (56.8±11.9 versus 54.7±11.9; *P*=0.052). Presence of thrombus at baseline was more frequently related with an acute presentation (*P*<0.001).

Angiographic Characteristics

Patients with and without TCL had similar angiographic characteristics (Table 3). There were differences for higher prevalence of total occlusions (0.37±0.56 versus 0.27±0.49 total oclusions/patient; *P*=0.010) and more frequent involvement of the proximal right coronary artery (0.33±0.47 versus 0.27±0.45 lesions/patient; *P*=0.045) in the thrombus group.

Clinical Outcomes

There was no difference between the groups (Table 4 and Figure 1) for any of the studied outcomes ≤3-year follow-up. MACE occurred in 1067 patients (25.4%) in the group without thrombus at baseline and 65 (25.3%) in the group with thrombus (*P*=0.874). Consistently, all-cause death (*P*=0.683), MI (*P*=0.962), and any revascularization (*P*=0.822) was not significantly different in the 2 groups.

Subgroup Analysis

In the stratified analysis, the occurrence of MACE was homogenously distributed across the clinical and angiographic covariates, with the only exception of clinical presentation (Figure 2). There was a significant interaction between the patients presenting with acute coronary syndrome (hazard ratio 0.881, confidence interval 0.65–1.19) and stable CAD (hazard ratio 1.637, 95% confidence interval 1.04–2.59) with respect to the presence of thrombus at baseline (*P*=0.028).

A more detailed analysis of the subgroup with stable CAD can be found in Table III in the Data Supplement. The thrombus at baseline was related to a higher rate of MACE (38% versus 26%, *P*=0.03) mainly because of an increased rate of repeated revascularization (30% versus 18%, *P*=0.01). However, after adjustment for confounders (ie, age, creatinine

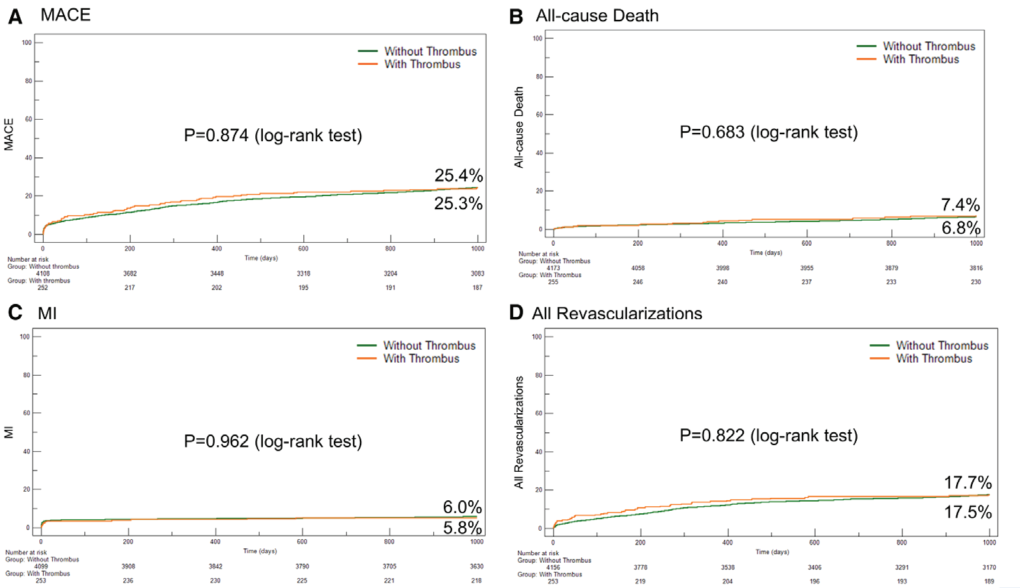


Figure 1. Kaplan–Meier cumulative curves for MACE (**A**; composite of all-cause death, myocardial infarction, and all revascularizations), all-cause death (**B**), myocardial infarction (MI; **C**), and all revascularizations (**D**). MACE indicates major adverse cardiac events; and MI, myocardial infarction.

	Patients with Thrombus	Patients without Thrombus	HR (95% CI)		P	$P_{interaction}$
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.299	(0.785 - 2.150)	0.385	0.31
Male	49/208 (23.6%)	779/3127 (24.9%)	0.962	(0.721 - 1.284)	0.791	
Female	16/49 (32.7%)	287/1066 (24.9%)	1.291	(0.780 - 2.135)	0.321	
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.087	(0.771 - 1.532)	0.635	0.691
Age<65	35/143 (24.5%)	469/2023 (23.2%)	1.088	(0.772 - 1.534)	0.631	
Age>65	30/114 (26.3%)	598/2170 (27.6%)	0.981	(0.680 - 1.416)	0.919	
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.075	(0.807 - 1.431)	0.777	0.706
DM	15/50 (30.0%)	339/1032 (32.8%)	0.961	(0.573 - 1.611)	0.879	
Non-DM	50/207 (24.2%)	728/3161 (23.0%)	1.073	(0.806 - 1.430)	0.628	
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.070	(0.736 - 1.554)	0.724	0.796
CrCl<90	36/107 (33.6%)	508/2100 (24.2%)	1.070	(0.736 - 1.554)	0.997	
CrCl>90	29/150 (19.3%)	559/2093 (26.7%)	0.999	(0.713 - 1.401)	0.724	
MACE	36/138 (26.1%)	672/2642 (25.4%)	1.060	(0.684 - 1.643)	0.793	0.824
LVEF<50	15/53 (28.3%)	235/815 (28.8%)	0.981	(0.582 - 1.653)	0.941	
LVEF≥50	21/85 (24.7%)	437/1827 (23.9%)	1.061	(0.685 - 1.644)	0.791	
MACE	65/257 (25.3%)	1067/4193 (25.4%)	2.098	(0.984 - 4.471)	0.055	0.028
ACS	46/207 (22.2%)	522/2062 (25.3%)	0.881	(0.652 - 1.191)	0.410	
Stable CAD	19/50 (38.0%)	545/2131 (25.6%)	1.637	(1.036 - 2.587)	0.035	
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.054	(0.732 - 1.517)	0.778	0.862
SS 0-11	10/61 (16.4%)	255/1412 (18.1%)	0.905	(0.481 - 1.703)	0.757	
SS 12-22	24/101 (23.8%)	367/1412 (26.0%)	0.920	(0.609 - 1.391)	0.694	
SS>22	31/95 (32.6%)	445/1369 (32.5%)	1.055	(0.733 - 1.518)	0.775	

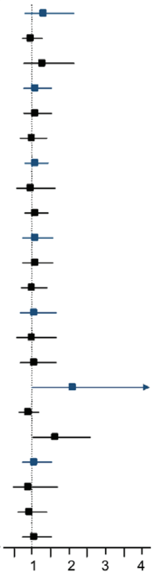


Figure 2. Stratified analysis for MACE (composite of all-cause death, all myocardial infarction, and all revascularizations according to the presence or absence of thrombus containing lesions. ACS indicates acute coronary syndromes; CAD, coronary artery disease; CI, confidence interval; CrCl, creatinine clearance; DM, diabetes mellitus; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; SS, anatomic SYNTAX score; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

clearance, previous MI, LVEF, and number of total occlusions/patient), this effect was no longer present (Figures VIA–VID and VIIA–VIID in the Data Supplement).

Anatomic Characteristics of Thrombus Containing Lesions

In the subgroup of patients with TCL (n=257), 261 lesions had angiographic thrombus. As shown in Figure 3, the presence of TCL occurred preferentially in proximal segments. More specifically, 43.6% of these complex lesions were seen in the first 2 segments of the right coronary artery and 36.8% in the first 2 segments of the left anterior descending coronary artery.

As demonstrated in Figure 4, TCLs were seen often in coronary bifurcations. The association of thrombus-containing and bifurcation lesions was present in 40.1% of the aforementioned prespecified segments. In the left anterior descending coronary artery, there was appreciable coexistence of thrombus and bifurcation lesions (45.9% of the lesions). On the other hand, the combination thrombus–bifurcation was not frequent in the distal right coronary artery (8.6% of the lesions).

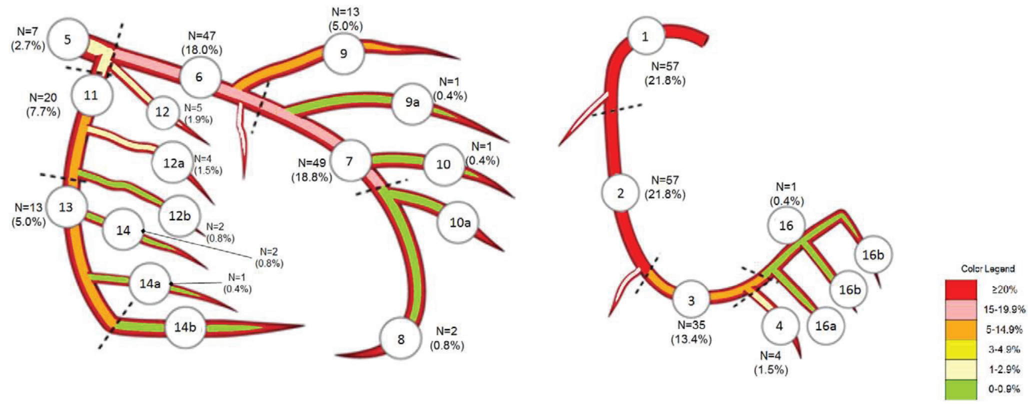
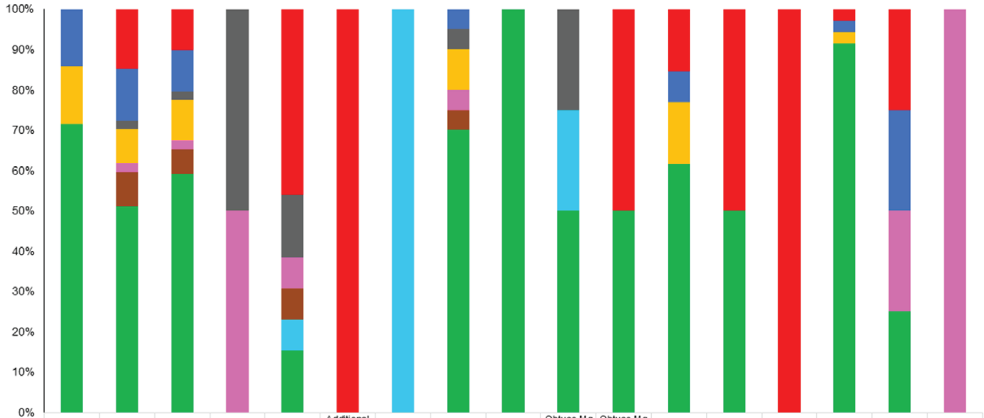


Figure 3. Distribution of angiographic thrombus containing lesions.



	LM	LAD prox	LAD mid	LAD apical	First Dg	Additional First Dg	Second Dg	Prox LCX	Intemediate	Obtuse Mg a	Obtuse Mg b	Distal LCX	Left Pl	Left Pl a	RCA dist	PD	Right PL
1,1,1	0	7	5	0	6	1	0	0	0	0	1	2	1	1	1	1	0
1,1,0	1	6	5	0	0	0	0	1	0	0	0	1	0	0	1	1	0
1,0,1	0	1	1	1	2	0	0	1	0	1	0	0	0	0	0	0	0
1,0,0	1	4	5	0	0	0	0	2	0	0	0	2	0	0	1	0	0
0,1,1	0	1	1	1	1	0	0	1	0	0	0	0	0	0	0	1	1
0,1,0	0	4	3	0	1	0	0	1	0	0	0	0	0	0	0	0	0
0,0,1	0	0	0	0	1	0	1	0	0	1	0	0	0	0	0	0	0
No bifurcation	5	24	29	0	2	0	0	14	5	2	1	8	1	0	32	1	0

No bifurcation ▪0,0,1 ▪0,1,0 ▪0,1,1 ▪1,0,0 ▪1,0,1 ▪1,1,0 ▪1,1,1

Figure 4. Per-segment association of thrombus and bifurcation lesions according to Medina[14] classification. Dg indicates diagonal branch; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; Mg, marginal; PD, Posterior descending branch; Pl, posterolateral branch; and RCA, right coronary artery.

Clinical Outcomes According to Myocardium at Risk

We divided the subgroup of patients with TCL into tertiles of the sum of segment weighing factors (Table 1). As shown in Figure 5, the weighting for myocardium at risk did not produce significant difference in outcomes (MACE, all-cause death, MI or all revascularizations) for patients with TCL.

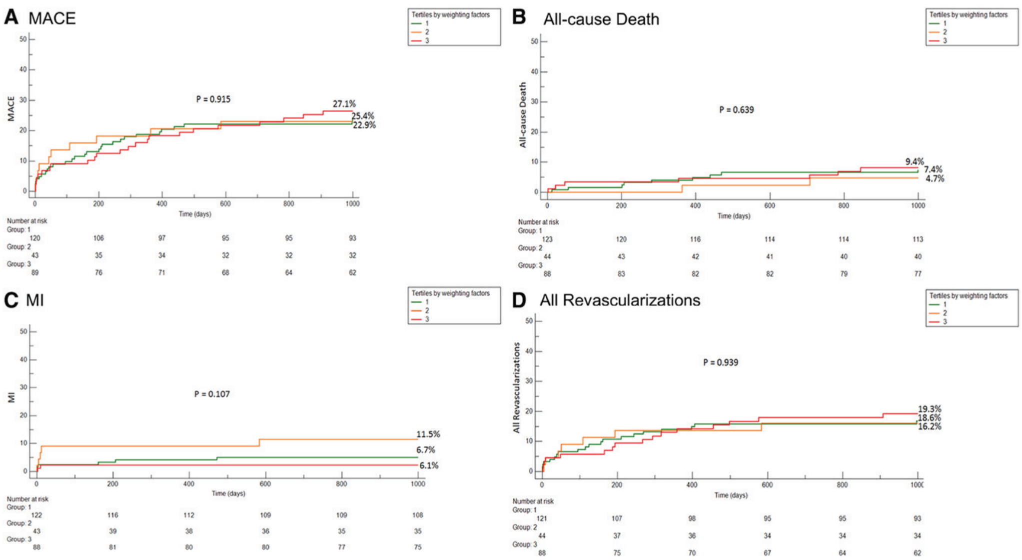


Figure 5. Kaplan–Meier cumulative curves for MACE (**A**; composite of all-cause death, myocardial infarction and all revascularizations), all-cause death (**B**), myocardial infarction (MI; **C**), and all revascularizations (**D**) according to tertiles of the sum of segment weighing factors in patients with thrombus-containing lesions.

Table 5. Distribution of Complex Coronary Lesions

	% in Proximal Segment	% in Mid Segment	% Total
Wang et al[17]			
Observation: Site of coronary occlusion distribution, %			
RCA	12.5	14.4	26.9
LAD	14.5	24.0	38.5
LCX	8.6	4.3	13.0
LM	...	...	0.5
Present study			
Observation: Thrombus containing lesions distribution, %			
RCA	21.8	21.8	43.7
LAD	18.0	18.8	36.8
LCX	7.7	5.0	12.6
LM	...	...	2.7
PROSPECT substudy[19]			
Observation: VH-TCFA–containing lesion distribution, %			
RCA	17.1	15.1	32.2
LAD	24.2	10.8	35
LCX	15.2	11.8	27
LM	...	...	n.a.
Tian et al[20]			
Observation: OCT-TCFA–containing lesion distribution, %			
RCA	n.a.	n.a.	45.0
LAD	n.a.	n.a.	35.9
LCX	n.a.	n.a.	19.1
LM	...	...	n.a.

LAD indicates left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; OCT, optical coherence tomography; RCA, right coronary artery; TCFA, thin cap fibroatheroma; and VH, virtual histology intravascular ultrasound.

Discussion

The findings of our study can be summarized as follows: (1) TCL were seen more often in the proximal segments; (2) there was a considerable coexistence of bifurcation and TCLs; (3) the presence of thrombus at baseline was not related to any additional risk of MACE, even after weighing for myocardium at risk.

Anatomy of Angiographic Coronary Thrombus

Coronary thrombus is mostly formed after rupture of atherosclerotic lesions containing a large necrotic core and a thin fibrous cap.[1,2] In the present study, we found that thrombus was angiographically detected in the proximal coronary segments and mainly in the right and left anterior descending coronary arteries. Our results are similar to those reported by Wang et al who analyzed coronary angiograms from 208 consecutive patients presented with ST-elevation MI.[17] However, in their methodology, they were evaluating the site of coronary occlusion. Although they used a slightly different coronary segmentation (BARI classification), they also have found that the 2 most proximal segments of right coronary artery and left anterior descending coronary artery were also responsible for the absolute majority (65.4%) of acute coronary occlusion.[17] In the present analysis, a 25-fold larger population was studied and included a population with a broader spectrum of the disease (also stable CAD and NSTEMI) in which the vessel occlusion was not mandatory for diagnosis of thrombus. Importantly, all angiographic assessments were performed by an experienced independent core laboratory, which has proven to have a higher consistency and better prognostic discrimination than investigator-reported angiographic findings.[18]

Interestingly, distribution of thin cap fibroatheroma, as assessed by virtual histology intravascular ultrasound (VH-IVUS) and optical coherence tomography, resembles the distribution of thrombus found in the present study; this may indicate that thin cap fibroatheromas are the underlying substrate of coronary thrombus found in this study[19,20] (Table 5). These invasive imaging findings are also in line with previous anatomopathological studies.[2,4,21]

It has to be highlighted, however, that angiography, because of its limited resolution, is far from being the gold standard tool for coronary thrombus diagnosis. For instance, in the present analysis, there was a low percentage (9.2%) of patients with acute coronary syndromes that were classified as having TCL. Similarly, Goto et al detected angiographic thrombus in only 14.6% of patients in a population of exclusively acute coronary syndromes.[7] Importantly, although Goto et al defined thrombus as "an intraluminal filling defect or an area of contrast staining noted within the target stenosis,"[7] we used the definition recommended by the Academic Research Consortium.[15]

Another interesting aspect of our findings is the relatively frequent association between thrombus and bifurcation. In the LAD, a bifurcation lesion was present in almost half of the TCL. The most plausible explanations for this association are the following: (1) the most frequent location of thin cap fibroatheromas is in bifurcation[22] and (2) the endothelial shear stress in coronary bifurcations has a particular distribution. In relatively straight segments, the endothelial shear stress is pulsatile and unidirectional.[23] Conversely, in coronary bifurcations, disturbed laminar flow occurs, and pulsatile flow generates low or oscillatory endothelial shear stress.[23] The role of endothelial shear stress in more advanced atherosclerosis was demonstrated 45 years ago[24] and have been reproduced in autopsy-based coronary models, human in vivo studies in arterial models derived from intravascular ultrasound or magnetic resonance, and in vivo animal experiments.[23,25]

Thrombus and Clinical Events

In the present study, the presence of thrombus did not have any effect on clinical events, even when it was adjusted for the amount of myocardial at risk. Corroborating our findings, Singh et al have shown that the introduction of the coronary stents and the use of more contemporary antiplatelet therapy made the presence of thrombus irrelevant for long-term death and MI.[8] On the other hand, Sianos et al have demonstrated that large thrombus burden is an independent predictor of major adverse events (defined as death, repeat MI infarct-related artery infarct-related artery) in patients treated with drug-eluting stents for STEMI.[9] Additionally, large thrombus burden has been related to larger myocardial damage as detected by contrast-enhanced cardiac magnetic resonance.[26] The aforementioned findings suggest that, for clinical prognostic discrimination, the angiographic thrombus assessment should be no longer classified as a binary variable but as a more detailed thrombotic burden quantification.

Limitations

The present study has all inherent limitations of a post hoc analysis. In addition, the number of stable patients with TCL was limited and may have hindered an accurate risk estimation in this subset. The classification of bifurcation lesions was restricted to those defined by the SYNTAX score, and we could not stablish whether TCL could be associated with smaller side branches. However, the use of the SYNTAX score concepts have demonstrated consistent prognostic effect for percutaneous coronary intervention–treated patients.[12,27–29] Information on thrombus aspiration was not available in this study. Nevertheless, the recent Thrombus Aspiration in ST-Elevation MI in Scandinavia (TASTE) trial showed that routine thrombus aspiration exclusively in a context of primary percutaneous coronary intervention did not reduce the rate of death from any cause or the composite of death from any cause, rehospitalization for MI, or stent thrombosis at 1 year.[30] Also, the Trial of Routine Aspiration Thrombectomy With Percutaneous Coronary Intervention (PCI) Versus PCI Alone in Patients With ST-Segment–Elevation Myocardial Infarction (STEMI) Undergoing Primary PCI (TOTAL) randomly assigned 10 732 patients with STEMI undergoing primary PCI to routine manual thrombectomy versus PCI alone. Manual thrombectomy did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within 180 days but was associated with an increased rate of stroke within 30 days.[31]

Conclusions

In this patient-level pooled analysis of 3 contemporary, all-comers stent trials, coronary TCL involved mainly the proximal coronary segments and frequently bifurcations. Angiographic thrombus did not have any effect on 3-year MACE, demonstrating that a more detailed thrombus burden quantification is required to investigate its prognostic implications.

Disclosures

None.

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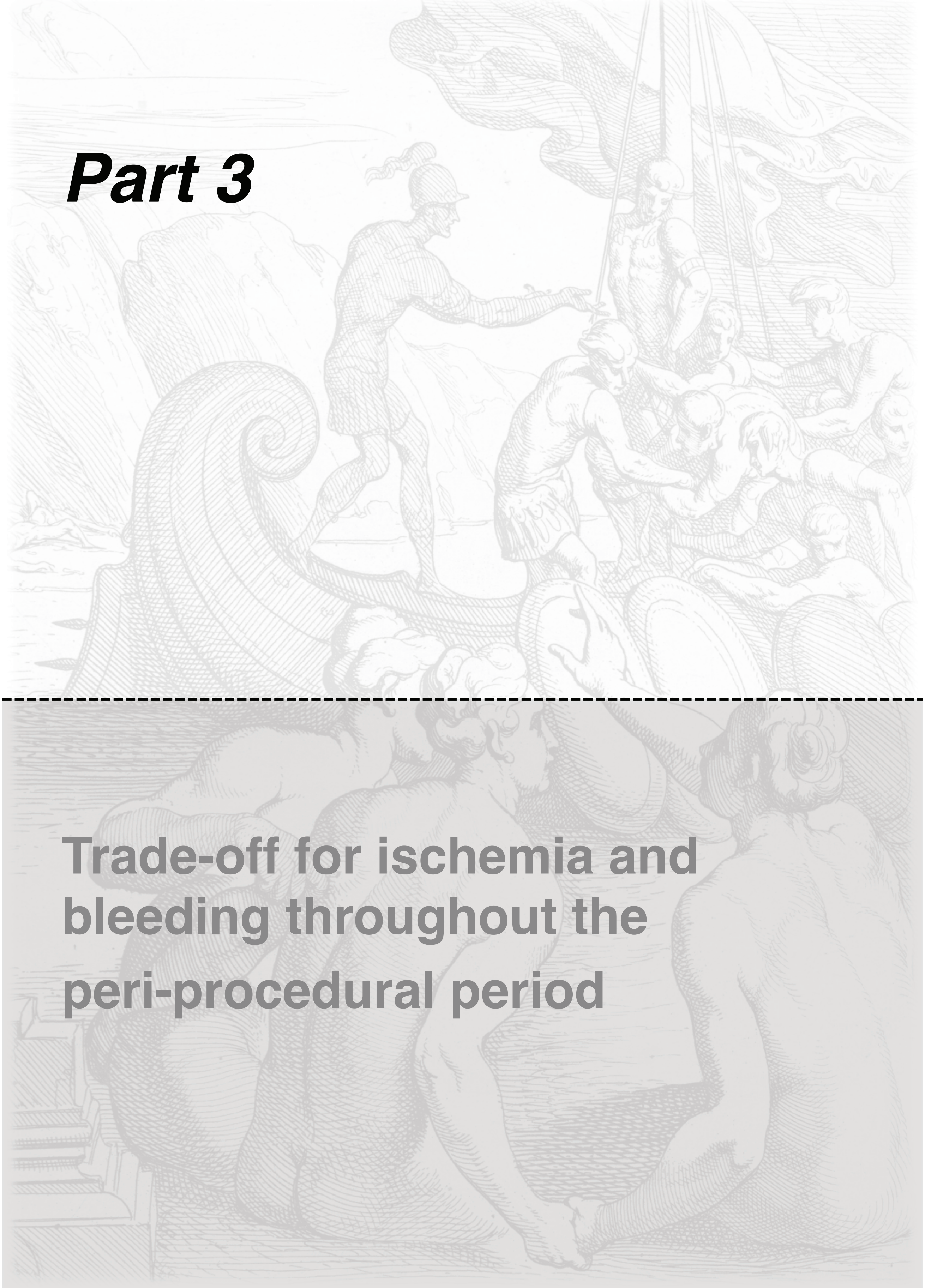

Part 3

Trade-off for ischemia and bleeding throughout the peri-procedural period

Chapter 3.1

Radial and femoral access in percutaneous intervention

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Chapter 24
Radial and Femoral Access in Percutaneous Intervention

Francesco Costa and Marco Valgimigli

Abstract Femoral and radial accesses are the most commonly used approaches in interventional cardiology. Femoral access-site has been implemented for many years in percutaneous coronary intervention and still today is the most used approach in several countries. Radial access, more recently introduced, guarantees a less invasive procedure and a reduced incidence of vascular access site complications.

The purpose of this chapter is to review critically the most recent evidence comparing radial and femoral approaches for percutaneous coronary intervention. Advantages and limitations of each technique will be evaluated with respect to the most recent interventional procedures.

Keywords Percutaneous coronary intervention • PCI • Radial access • Femoral access • Bleeding • Vascular access site complications • STEMI • Non-ST elevated myocardial infarction • Myocardial infarction • Coronary artery disease

Introduction

Femoral and radial access sites are the most commonly used approaches in current interventional cardiology. However, it is interesting to mention that at the inception of invasive cardiology, the brachial access, introduced by Sones in the early 50's, [1] was the default access for left cardiac catheterization. The brachial artery, first

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approached with a surgical cutdown and later percutaneously with the Seldinger's technique [2], was extensively used until the late 60's when Amplatz and Judkins demonstrated the feasibility of the percutaneous femoral access in a large case series [3]. Afterwards, interventional cardiology made huge progress in the techniques and devices used and femoral access became the default approach for almost all of them.

In the last 20 years, after Campeau's report of a transradial approach (TRA) for coronary angiography, the radial artery has been increasingly employed as an alternative access site for both diagnostic and therapeutic procedures [4].

The main advantage of the radial artery use is a reduced invasiveness, given by its superficial position, the smaller caliber and the high predictability of its compression. The lack of important adjacent structures decreases the hazard during the puncture. However, these benefits come at the cost of an increased complexity in the maneuverability of the catheters, with an increased procedure time and radiation exposure, especially in non-experienced operators [5]. Moreover, its anatomical limitations do not permit the use of bulky devices or bigger catheters, occasionally needed for more complex procedures.

Discussion

The Bleeding Issue: Access Site and Non-access Site Bleeding During Percutaneous Coronary Intervention (PCI) and Their Impact on Patients' Outcome

Bleeding is a frequent complication during PCI and 30–70 % of these events are related to the access site. This broad variability depends mostly on the patient's clinical presentation. In fact, acute patients are more prone to access site bleeding, whereas in stable patients two-thirds are not access site related [6].

The radial approach brings a 65 % reduction of major vascular access site complications, 49 % of non–CABG-related major bleeding, and 35 % reduction of the transfusion rate compared with the femoral approach [7]. Interestingly, radial access benefit persisted when vascular closure devices were used in the femoral cohort [8].

The reduction of bleeding events is of paramount importance considering the strong correlation between major bleeding and mortality [9, 10]. In a study of over 26,000 patients with non–ST-segment elevation ACS, there was a significant interaction between bleeding severity and the rate of death at 30-days, death at 6 months or the composite of death and MI [11].

A sub-analysis of the TRITON-TIMI 38 trial [12] showed that serious spontaneous bleeding tended to have a sustained impact on mortality for approximately 1 month, as it was shown by an elevated hazard ratio within the first 30 days after PCI followed by a non-significant trend thereafter. Similarly, a recent analysis from the PLATO trial also demonstrated that procedure-related bleeding is strongly associated with short-term mortality [13].

To further corroborate these findings, the application of bleeding prevention strategies demonstrated a better survival during an acute coronary syndrome. The OASIS-5 trial compared fondaparinux with enoxaparin in a court of 20,078 patients with non-ST-segment elevation ACS. This study showed that fondaparinux was not inferior to enoxaparin with respect to 9 day composite ischemic endpoints, and superior with respect to major bleeding at 9 days (fondaparinux 2.2 % vs. enoxaparin 4.1 %, $p<0.001$) [14] eventually resulting in a significant reduction of death from all causes at 1 month (deaths in fondaparinux arm 574 vs. deaths in enoxaparin arm 638, $p=0.05$).

Similarly, in HORIZONS AMI, the implementation of the direct thrombin inhibitor bivalirudin, compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing primary PCI, resulted in both a reduction of major bleeding (4.9 % vs. 8.3 %, $p<0.001$) and mortality at 30 days (2.1 % vs. 3.1 %, $p=0.047$) [15].

However, it is worth mentioning that patients with a higher bleeding risk usually carry also a higher ischemic risk. In fact, bleeding more frequently occurs in sicker patients, and a possible lack of cause-effect between the two events could be argued, being this correlation driven by host or putative mechanisms [16]. On the other hand, discontinuation of antithrombotic therapy, transfusions and severe anemia after bleeding are likely to be important prognostic modifiers and all need to be prevented [17].

Finally, it has been demonstrated that non-access site related bleeding carries a relatively higher risk of death compared with access site bleeding (HR 2.2) [18, 19]. Access site selection hardly affects non-access-site bleeding, on the other hand, the application of a modern antithrombotic regimen and optimal anti platelet therapy could mitigate the excess bleeding risk and improve the outcome [15, 20].

Is Radial Access Effective as Femoral?

The limits of the radial technique have been pushed far forward since its first introduction. The advances in experience and technology allow today the treatment of complex PCI cases like bifurcations, unprotected left main coronary artery [21] and chronic total occlusions [22] from the radial access. Importantly, the rates of procedural success are similar to the femoral approach [23] but only for experienced radial operators.

Many studies tried to delineate the learning curve of the radial technique. Ball et al. prospectively collected from 1999 to 2008 a total of 1672 patients with non-urgent, single vessel disease, underwent TR-PCI by 28 operators. The outcomes were stratified into chronological groups of cases for operators starting transracial technique in their institution: the first group from case 1 to case 50 and so on 51–100, 101–150, 151–300. The control group consisted of experienced radial operators with more than 300 TR-PCI. The study found that the PCI failure rate was inversely related with the case volume, with a 32 % decrease in PCI failure every additional 50 PCIs performed. The author's eventually concluded that a case volume of at least 50 PCI is needed to achieve an outcome comparable with an expert radial operator.

However, considering that this study included non-urgent, single vessel disease, the learning curve for more complex PCI is likely to be steeper [24]. Similarly, Looi et al. showed how after 6 months of practice in diagnostic radial angiography, fellows reached results comparable with senior operators [25].

Interestingly, another single study about the radial approach learning curve showed that the left radial approach had a shorter learning curve compared to right radial access [26]. These results could be explained by a lower impact of subclavian tortuosity in the left radial artery (OR 2,7) and by an easier maneuverability of the catheters that, originally designed for the femoral route, adapt better to the left radial anatomy [26].

Certainly, the more complex is the radial anatomy, the more difficult and longer is the procedure with consequences on procedural times and radiation exposure. This is particularly true for the diagnostic angiograms whereas the impact on PCI is milder. As could be expected, procedural times and radiation dose decrease with operator's expertise [5].

Radial vs. Femoral: The Evidence

In the past few years an important burden of evidence has been collected for the comparison of femoral and radial access approaches.

The MORTAL registry, published in 2008 by Chase et al. retrospectively analyzed 38,872 patients treated with PCI either via TRA (7,972 patients) or TFA (30,900 patients). The results showed that TRA reduced the need for blood transfusion (1.4 % vs. 2.8 %) and 1-year mortality (3.9 % vs. 2.8 %). Importantly, the patient population mainly consisted of ACS treated on an urgent basis [27]. Other observational studies demonstrated afterwards the same conclusions.

The lack of a randomized trial comparing the two strategies was finally overcome with the presentation of the pivotal radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL) trial. RIVAL recruited 7,021 patients in 32 countries, of which 3,507 patients were randomly assigned to radial access and 3,514 to femoral access. The primary outcome was the composite of death, myocardial infarction, stroke, or non- coronary artery bypass graft (non-CABG)-related major bleeding at 30 days. The trial ultimately failed to demonstrate a significant superiority of the radial access with respect to the primary endpoint (3.7 % vs. 4.0 %, [HR] 0.92, 95 %CI 0.72–1.17; $p=0.50$). Major vascular access site complications were significantly reduced in the radial arm (1.4 % vs. 3.7 % $P<0.0001$), whereas non-CABG-related TIMI major bleeding (0.5 % vs. 0.5 % $P=1.00$) and access site major bleeding (0.2 % vs. 0.3 % P = NS) were similar in the two groups [7].

Importantly, it has been shown that, in patients with STEMI, there was a benefit with radial access for the composite of death, MI and stroke ($P_{int}=0.011$), and death for all causes (interaction $P_{int}=0.001$). A significant interaction for the primary outcome was finally noted in the highest tertile volume radial centers (HR 0.49, 95 %CI

0.28–0.87; p=0.015). These findings strongly questioned the previous results suggested by the observational studies. However, at a deeper analysis some of the reasons of such a divergence could be identified.

First, a post-hoc analysis that evaluated the actual location of the access-site major bleeding showed that all the six reported events found in the radial group did not consist of real radial-related complications but of consequences of IABP or radial-to-femoral cross-over confounded by the intention-to-treat design of the study. Thus, after reallocating the bleeding events in the pertinent group, a significant relation between access-site major bleeding and femoral access (0 vs. 18 events) was present also in RIVAL [7].

Second, the bleeding definition used to adjudicate the events is of paramount importance. In fact, the use Acute Catheterization and Urgent Intervention strategy (ACUITY) trial bleeding criteria showed a significant reduction of major bleeding in the radial cohort ($p<0.0001$).

Third, the number of bleeding events was unusually low in the RIVAL population compared with previous ACS trials and only 32 % were access site related. Therefore, the trial may have been underpowered to detect a difference in non–CABG-related major bleeding and consequently to demonstrate a superiority of radial access on the primary endpoint [7].

The RIVAL result left many perplexities, and further evidence was needed. The Radial versus Femoral Randomized Investigation in ST- Elevation Acute Coronary Syndrome (RIFLE-STEACS) trial, presented in 2011, randomized 1,001 patients undergoing primary PCI to radial or femoral access. The aim of the study was to demonstrate a benefit on hard endpoints of the radial access in the STEMI population [28]. The trial used the new Bleeding Academic Research Consortium (BARC) definition and was powered to assess the superiority over the primary endpoint of death, MI, TLR, stroke or non–CABG-related major bleeding at 30 days. RIFLE-STEACS demonstrated a net reduction of the primary endpoint (13.6 % vs. 21 %; P=0.003), of the non–CABG-related major bleeding (7.8 % vs. 12.2 %; P=0.026) and of mortality (5.2 % vs. 9.2 % P=0.02) in the radial arm at 30 days.

This apparently striking results need to be critically analyzed.

Firstly, the operators in the RIFLE-STEACS were all expert radialists performing more than 300 PCI/year. Notwithstanding, the crossover rate from radial to femoral was 9.6 %, mainly due to shock, peripheral vascular disease and previous thrombolysis.

Secondly, the total mortality and the bleeding rates of the RIFLE-STEACS population were particularly high compared to previous STEMI trials, probably because the population included higher risk patients with cardiogenic shock and rescue PCIs, and the treatment frequently included GP inhibitors (70 %).

Finally, even if the access-site bleeding was reduced by the radial access in the main study, at a post-hoc analysis this benefit was no longer present when the TIMI bleeding definition was used [28].

Another recent randomized trial evaluated the effect of the access-site in patients undergoing PCI. The STEMI-RADIAL randomized 707 patients with STEMI to radial and femoral approach before the primary PCI [29]. The primary endpoint, consisting of a composite of major bleeding and vascular access site complications at 30 days, occurred significantly more in the femoral access group (1.4 % vs. 7.2 %; P<0.0001). The rate of net adverse clinical events (NACE) defined as a composite of death, MI, stroke, and major bleeding/vascular complications was also reduced by the radial access strategy (4.6 % vs. 11 %; P=0.0028). In contrast with the RIFLE-STEACS, mortality at 30 days in the STEMI-RADIAL was similar in the two groups (2.3 % vs. 3.1 %; P=0.64), result probably driven by the exclusion of very high-risk patients.

Mortality: Does the Access Site Matter?

The impact of access-site on mortality has been tested by numerous randomized trials, observational studies and metanalysis.

Before the RIVAL publication many observational studies including the already mentioned MORTAL registry showed a mortality reduction with the radial approach. The PREVAIL, a non randomized prospective study, also showed a benefit of radial on hard endpoints including death (1.1 % vs. 4.9 %) [30]. Similarly, a systematic review of the literature involving 2,808 STEMI patients, who were largely recruited in a non-randomized fashion, showed that trans-radial intervention was associated with almost 50 % decrease of overall mortality [31].

The RIVAL overturned these data, not showing a significant mortality difference between the two groups. However, the subgroup analysis of patients with STEMI showed an impressive 54 % mortality reduction after the trans-radial treatment. Conversely, patients with NSTEACS showed a worrisome trend towards a 66 % increase in mortality (P=0.082) [7].

Finally in the RIFLE-STEACS trial a 50 % mortality reduction was found in the radial group [28]. Consistent with these findings, an observational region-wide study compared the medium-term outcomes of trans-radial versus trans-femoral intervention in 12,407 patients who underwent PCI for STEMI. This study showed a 30 % mortality reduction at 2 years in favor of the trans-radial intervention reflecting an early significant mortality benefit within 30 days after treatment [32].

From all the data collected so far, radial access emerged as the most important single mortality reducer during primary PCI. However, the reason of such an impressive impact on survival is not completely clear. The reduction in access site major bleeding is a clear benefit of the radial access but can hardly explain these massive differences. Furthermore, non-access site bleeding affects mortality two times more than access site bleeding and reasonably cannot be influenced by the access selection [6].

Analyzing the detailed cause of death in the RIFLE-STEACS trial, most of the patients died early after PCI and frequently from acute heart failure. Accordingly, it is difficult to speculate why the radial approach provides such a significant benefit.

Potential beneficial mechanisms of the radial approach could be related to the earlier ambulation (lower risk of venous thromboembolism) and earlier hospital discharge (lower risk of nosocomial infection) but these hypotheses have yet to be tested [33].

Although the impact of the radial approach on mortality remains elusive, this should not underestimate the growing evidence showing a sensible benefit from the radial approach.

Cost and Hospitality stay:

Radial access sensibly reduces the hospital costs. Safley et al. examined costs among 61,509 procedures and observed a reduction of expenses in radial procedures, mostly driven by a reduced in hospital length of stay [34]. This benefit was consistent in the RIFLE-STEACS and in the STEMI-RADIAL trials.

Limitations of the Radial Artery

Trans-radial approach carries several limitations.

First of all radial artery anatomy is still a technical limitation, being 50–70 % smaller than the femoral artery, it does not allow the same flexibility in the device and procedure strategy selection as compared to the femoral approach. In fact, the rate of vascular access site failure in the RIVAL study was higher in the radial group (7 % vs. 0.9 %). Access site failure was mostly related to radial spasm (5 %) and vessel tortuosity in the radial (1.3 %) and in the subclavian segment (1.9 %).

Part of the technical complexity of the radial approach is obtaining an optimal support of the guiding catheter, especially during left coronary artery intervention [35]. This could be challenging for the imperfect compatibility of the standard catheters, designed for the femoral route, with the radial anatomy [36]. Even if some of these technical difficulties could be overcome with left radial access, [37] more than 90 % of operators use the right approach [36] and dedicated radial catheter are not commonly utilized.

Noteworthy, the radial approach reduces dramatically access-site complication but it cannot be considered a complication-free procedure. Compartmental syndrome or catheter entrapment with radial avulsion are rare, but must be carefully prevented. More frequent is the radial artery patency loss that occurs in up to 12 % of patients at 24 h after radial catheterization [38]. This should not be considered a minor complication because it might hinder the potential future use of the radial artery (arterial fistula for dialysis, arterial harvesting for CABG, further catheterizations), and could eventually be prevented with the systematic use of the patent hemostasis technique [38].

Lastly, the radiation dose appears to be higher with the radial approach [5]. This is true especially during the first part of the learning curve, and it is reduced with operator experience.

When Femoral Artery Is Necessary

Given the strong relationship between radial access and reduced vascular complications, the American College of Cardiology Foundation, American Heart Association, Society for Cardiovascular Angiography and Interventions PCI practice guidelines now give a strong recommendation to the radial approach [39], and the European Association of Percutaneous Cardiovascular Interventions group has recently stated in a position paper that it should be the default access site for PCI [40].

Nevertheless, in many situations the femoral approach is still essential. Not mentioning the imperative necessity of the femoral access for all structural heart disease procedures, the use of bulky devices such as intra-aortic balloon pump, Impella device or ECMO require a large diameter arterial access. Moreover, femoral access is still the first choice during complex PCI's when better control and flexibility are needed.

Conclusion

The benefit of the radial use in clinical practice has been shown in many different randomized trials. Although the mechanism of benefit for some end points remains unclear, a continuous effort should be made to improve proficiency in the radial approach without loosing expertise in the femoral technique.

Furthermore, the implementation of strategies to prevent non-access site related bleeding, such as the use of bivalirudin and the optimal adjustment of anti-platelet therapy, are likely to be important steps to improve the prognosis of ACS patients.

In the near future ongoing trials such as SAFARI-STEMI (NCT01398254) and MATRIX (NCT01433627) will give useful information about the role of vascular access in the context of a modern anticoagulant therapy.

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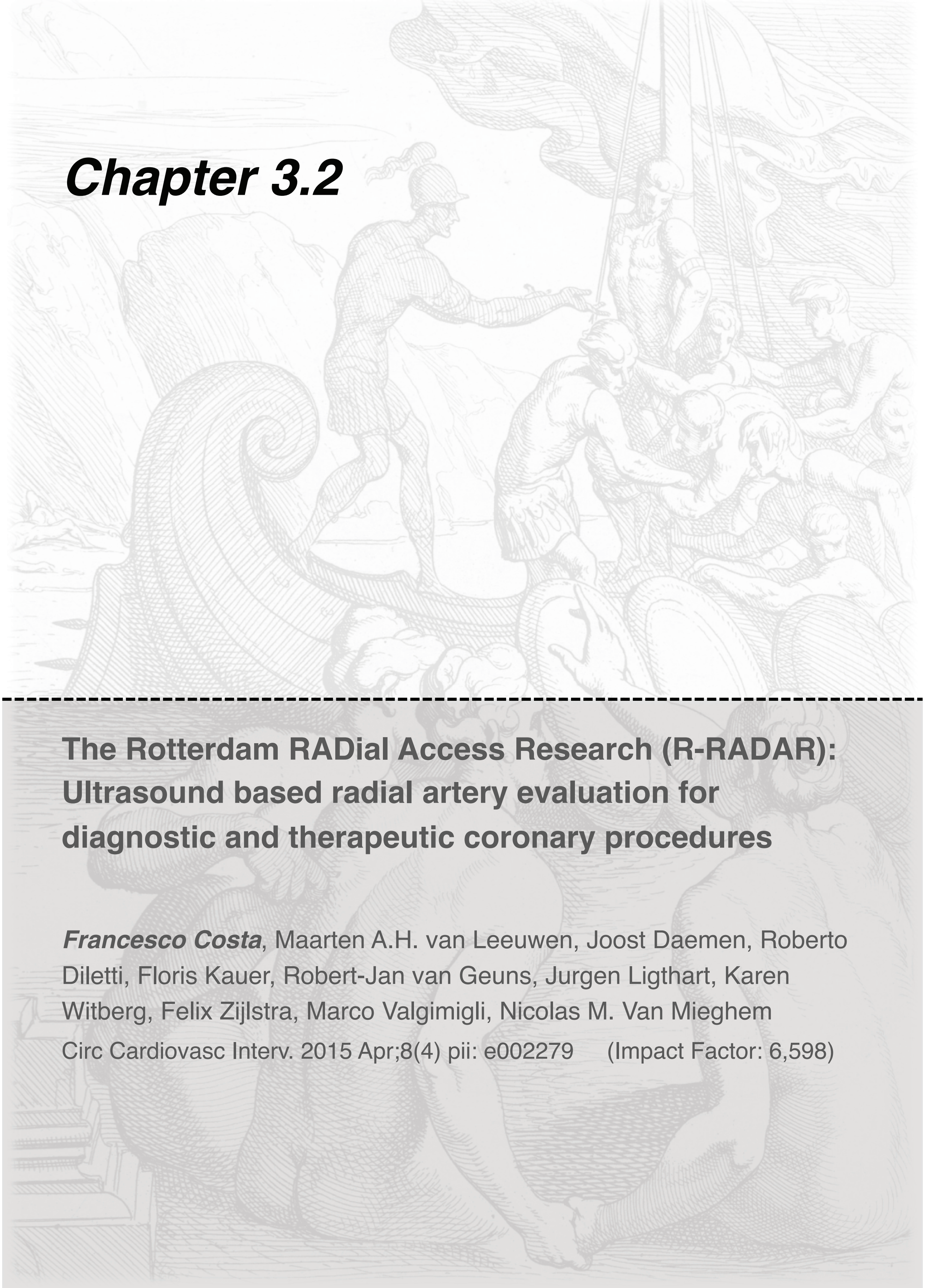

Chapter 3.2

The Rotterdam RADial Access Research (R-RADAR): Ultrasound based radial artery evaluation for diagnostic and therapeutic coronary procedures

Francesco Costa, Maarten A.H. van Leeuwen, Joost Daemen, Roberto Diletti, Floris Kauer, Robert-Jan van Geuns, Jurgen Ligthart, Karen Witberg, Felix Zijlstra, Marco Valgimigli, Nicolas M. Van Mieghem

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Cardiac Catheterization

3

The Rotterdam Radial Access Research

Ultrasound-Based Radial Artery Evaluation for Diagnostic and Therapeutic Coronary Procedures

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Background—Radial artery wall might be damaged after cannulation for cardiac catheterization. We investigated structural changes of the radial artery wall after catheterization to understand whether these might predict radial pulsation loss or occlusion and local pain or functional impairment of the upper extremity.

Methods and Results—Ninety patients underwent transradial coronary angiography or intervention and were scanned with a high-resolution 40-MHz ultrasound before cannulation and at 3 hours and 30 days after procedure. Acute injuries of the radial artery occurred in all patients: dissection and intramural hematoma were the most common. However, these phenomena did not predict loss of radial pulsation or occlusion, local pain, or functional impairment at 30 days. Overall, the radial artery lumen was significantly reduced distal to the puncture site. Radial artery intima and total wall thickness increased 3 hours after puncture and persisted at 30 days. Radial occlusion and pulsation loss were observed in 3.9% and 9.2% of patients, respectively, at 30 days. Smaller radial artery lumen at baseline increased the risk of radial pulsation loss at 30 days (odds ratio, 1.23; P=0.049). The number of radial puncture attempts predicted pulsation loss (odds ratio, 2.64; P=0.027), occlusion (odds ratio, 3.49; P=0.022), and symptoms (odds ratio, 2.24; P=0.05) at 30-day follow-up.

Conclusions—After catheterization, radial artery puncture site is associated with increased intima and total wall thickness and with modest decrease of inner lumen diameter. Acute injuries of the vessel wall were ubiquitous, but contrary to repeated puncture attempts, did not seem to affect postprocedural radial occlusion or loss of pulsation.

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Key Words: cardiac catheterization ■ coronary angiography ■ percutaneous coronary intervention ■ punctures ■ radial artery

The use of the radial artery as preferred access site for coronary diagnostics and interventions is rapidly increasing worldwide given the extensive evidence demonstrating its benefit on vascular complications and mortality,[1–3] its cost-effectiveness,[4] and the increased patient satisfaction in comparison with the femoral approach.[2] However, this approach could be complicated by radial artery occlusion (RAO), which only rarely causes hand ischemia but more commonly impede future utilization of the radial artery as an access site for catheterization or as a conduit for hemodialysis and coronary artery bypass graft. The occurrence of RAO after catheterization has been reported in ≤30% of patients,[5] and thrombosis or intimal hyperplasia caused by the vascular damage are suggested pathophysiological mechanisms. In addition, radial artery cannulation has also been related with several nonocclusive modifications as acute wall injuries, endothelial dysfunction, and impaired vasomotion.

The aim of the Rotterdam Radial Access Research (R-RADAR) study was to describe with high-resolution ultrasound structural changes in the radial artery wall at its puncture site after transradial catheterization and investigate whether these changes might predict RAO or loss of pulsation, local pain, or functional impairment of the upper extremity.

Methods

Study Population

A total of 100 consecutive patients undergoing transradial catheterization for diagnostic coronary angiography with or without intervention

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WHAT IS KNOWN

- Radial over femoral access provides less access site complications and potentially improved survival.
- Radial access complications include occlusion and spasm, which may increase the difficulty of repeat catheterizations from the same site.

WHAT THE STUDY ADDS

- Traumatic injuries to the radial artery, as assessed by high-resolution ultrasound imaging, were ubiquitous in patients undergoing transradial cannulation.
- Radial artery intima and total wall thickness increased after cannulation.
- Radial artery size, calcification at baseline and number of puncture attempts, might have an impact on radial occlusion and pulse loss at follow-up.

were enrolled in this prospective single-center registry. Radial artery catheterization within 2 months or clinical instability (including presentation with ST-segment–elevation myocardial infarction) were the main exclusion criteria. The Erasmus Medical Center Review Board approved the trial, and all patients gave written informed consent to participate. Eventually, 90 patients were treated through the preselected radial artery and constitute the final population.

Ultrasound Evaluation

Ultrasound studies were performed by 2 experienced sonographers (K.W. and J.L.) with a Visualsonics MS550D and a 22 to 55-MHz probe (VisualSonics Inc., Toronto, Canada), a high-resolution ultrasound system with a spatial resolution of 30 to 50 µm.[6–8] At baseline, an estimated puncture site with adequate radial pulsation was marked. The area was photographed and digitally stored as a reference for the evaluation at follow-up (Figure I in the Data Supplement). Ultrasound evaluation was then performed before radial cannulation, 3 hours after the procedure when the compressive device was removed, and again after 4 to 6 weeks. Longitudinal and cross-sectional views were acquired (Figure II in the Data Supplement). Interpretable ultrasound studies could be obtained in all patients. However, 10 patients were excluded from the analysis because the studied right radial artery was eventually not used for catheterization (Table I in the Data Supplement).

Transradial Coronary Catheterization

After local anesthesia of the puncture site with xylocaine 2%, a 6F sheath (Radifocus, Terumo, Japan; outer diameter, 2.45 mm) was inserted at or close to the previously marked site. The anterior wall technique was used to achieve artery cannulation in all patients of the study. Sheath insertion was followed by an intra-arterial bolus of 2500 IU of unfractionated heparin in diagnostic procedures, whereas for percutaneous coronary intervention, 100 IU/kg body weight of unfractionated heparin or bivalirudin at the product-labeling dose was used. A mixture of 0.2-mg nitroglycerin and 2.5-mg verapamil for prevention of radial artery spasm was injected in all patients. At the end of the procedure, the radial sheath was removed and a dedicated compression device (TR BAND, Terumo, Japan) was applied. It was recommended to achieve nonocclusive compression by performing the reverse Barbeau test.[9] In 30-minute intervals, air was released from the compression device until removal after 3 hours. All patients underwent physical and ultrasound examination of the radial artery at baseline before the catheterization, 3 hours after sheath removal, and 4 to 6 weeks after the procedure.

Echographic End Points

The echographic measurements were prespecified in the study protocol and included the radial artery inner lumen diameter, the total wall thickness, and the relative intima and media thickness at the puncture site. The region of interest around the puncture site was arbitrarily defined 4 mm proximally and distally to the entry site (Figure III in the Data Supplement). The inner lumen diameter was measured in a longitudinal view and defined as the distance between the leading edges of the intima–lumen interface of the near wall and the lumen–intima interface of the far wall. Inner diameter was acquired at the entry site and at the distal and proximal landmark sites (Figure III in the Data Supplement). The total wall thickness, including the intima, the media, and the adventitia, was measured in a cross-sectional view within the puncture site region of interest in a frame showing a 3-layer appearance of the vessel wall (Figure IV in the Data Supplement). Intima thickness was defined as the distance from the leading edge of the lumen–intima interface to the interface between intima and media and separately measured as in previous report using the same technology.[8] The media thickness was calculated by subtracting the intima thickness from the intima–media thickness.

The definitions of specific acute wall injuries of the radial artery are provided in the Methods in the Data Supplement.

Clinical End Points

Clinical end points evaluated at 3-hour and 30-day follow-up were (1) radial artery pulsation loss (RAPL), defined as any loss of radial artery pulsation at the puncture site, which was normally detected at baseline; (2) RAO, defined as imaging confirmed lack of anterograde flow in the radial artery, that was present at baseline; (3) symptoms

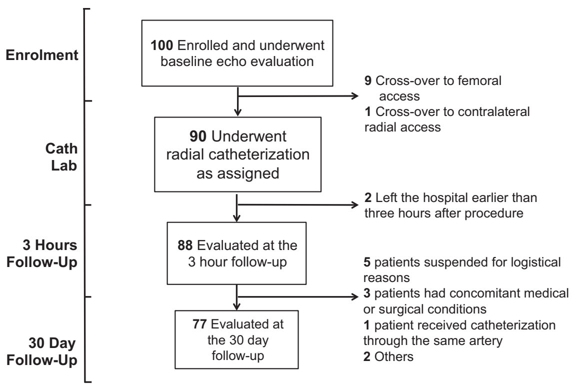

Figure 1. Study profile.

Table 1. Patient Characteristics

Age, y	64.6±10.5
Male sex, n (%)	72.2% (65/90)
Body mass index, kg/m^2	27.9±4.0
Diabetes mellitus, n (%)	15.6% (14/90)
Hypertension, n (%)	56.7% (51/90)
Hyperlipidemia, n (%)	60% (54/90)
Smoking, n (%)	20% (18/90)
Previous myocardial infarction, n (%)	20% (18/90)
Previous PCI or CABG, n (%)	41.1% (37/90)
Peripheral vascular disease, n (%)	20% (18/90)

CABG indicates coronary artery bypass graft; and PCI, percutaneous coronary intervention.

of pain or discomfort of the upper extremity reported by the patients at follow-up; (4) functional impairment, defined as any kind of functional compromise of the upper extremity reported by the patients at follow-up, that was likely related to the procedure.

Statistical Analysis

The sample size of this exploratory study was arbitrarily set at 100 patients. Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as mean±SD. Repeated measures ANOVA with a Greenhouse–Geisser correction was used to compare echographic measures at baseline with the respective values at the 3-hour and 30-day follow-up. Post hoc testing between the 3 timepoints was performed using the Bonferroni correction for multiple comparisons (2-sided α=0.05/3=0.0167). Mixed-design ANOVA was used to test the consistence of paired measurements results among subgroups (ie, sex, diabetes mellitus, current smoking, hypertension, dyslipidemia, previous myocardial infarction, and peripheral vascular disease).

Correlations between variables were assessed with the Pearson *r* correlation coefficient. Univariate regression analysis was used to investigate the predictive value for the occurrence of clinical end points. Statistical significance was set at a P<0.05.

Results

A total of 100 patients who were scheduled for coronary diagnostic angiography or intervention underwent ultrasound assessment of the radial artery in the R-RADAR study. Nine patients were eventually treated through the femoral artery and 1 through the contralateral radial artery. The preselected radial artery was successfully cannulated in 90 patients, who thus represent the final population of this analysis (Figure 1). Eighty-eight and 77 patients completed the echographic evaluation at 3 hours and 30 days, respectively.

Baseline characteristics are displayed in Table 1. Procedure duration was on average 50 minutes (Table 2). RAPL was observed in 10 patients, 5 (6.1%) at 3 hours and 7 (9.2%) at 30 days. Three patients (3.4%) developed RAO immediately after procedure, which persisted at 30-day follow-up. In total, 44 patients experienced pain or discomfort of the upper extremity, 32 (36.8%) at 3-hour follow-up and 24 (32.0%) at 30 days, whereas any kind of functional compromise occurred in 19 patients, 12 (14.1%) at 3-hour follow-up and 9 (12.0%) at 30-day follow-up. All patients having radial occlusion were symptomatic, but only 1 experienced functional compromise. Two patients with RAO at 30 days also had loss of radial pulsation.

Ultrasound Findings

The mean radial artery lumen at puncture site was 2.25 mm. The presence of wall calcification and artery spasm at baseline was reported in 7% and 10% of patients, respectively.

After the procedure, acute wall injuries at the puncture site were ubiquitous (Figures 2 and 3; Movies I–VII in the Data Supplement). Eighty-six (97.7%) patients showed acute injuries at 3 hours and 74 (96.1%) at 30 days. Radial dissection and wall hematoma were most frequent both at 3 hours (dissection, 89.8%; hematoma, 73.9%) and 30 days (dissection, 83.1%; hematoma, 64.9%). More than half of the patients had lumen narrowing at any timepoint. Pseudoaneurysms was observed in 14.8% of patients at 3 hours, increasing to 55.8% at 30-day follow-up. Thrombus formation at any timepoint was seen in 4% of patients (Figure 4).

Radial artery inner lumen diameter in the region of interest changed over time (Figure 5). At the entry site, it slightly decreased 3 hours after the procedure (baseline, 2.25±0.50 versus 3 hours, 2.02±0.66; P=0.01) and partially restored at 30-day follow-up (3 hours, 2.02±0.66 versus 30 days, 2.14±0.68; P=0.38; Table 3). The lumen diameter remained unchanged during follow-up proximally to the entry site, whereas it consistently decreased over time distally (Figure 5; Table 3). No interaction was observed between the change in lumen diameter overtime and the baseline characteristics explored (ie, sex, diabetes mellitus, current smoking, hypertension, dyslipidemia, previous myocardial infarction, and peripheral vascular disease).

The total wall thickness of the radial artery at the puncture site tripled 3 hours after cannulation, and further increased by 28% at 30 days (Figure 5; Table 3). The artery intima thickened at 3 hours and persisted at 30 days, whereas the media did not change significantly over time (Figure 5; Table 3).

Impact of Ultrasound Findings and Procedural Characteristics on Clinical End Points

Injuries to the radial wall detected at 3-hour or 30-day follow-up did not correlate with clinical end points (Table 4). RAO

Table 2. Procedural Characteristics

Allen test positive (%)	85.5% (65/76)
Spasm at baseline (%)	10% (9/90)
Punctures no. of attempts	1 (1–2)
Range	1–4
>1 attempt	16.1% (14/87)
Coronary angiography only (%)	56.7% (51/90)
PCI performed (%)	43.3% (39/90)
PCI no. of treated vessels	1 (1–2)
Procedure duration, min	50 (34–77)
Coronary angiography only	35 (27–46)
PCI performed	77 (62–104)
Heparin used, n (%)	93.3% (84/90)
Heparin total dose, IU	7500 (6250–10 000)
Bivalirudin used, n (%)	6.7% (6/90)
Bivalirudin total dose	265.5 (161.2–383.4)
Active coagulation time	284±104

PCI indicates percutaneous coronary intervention.

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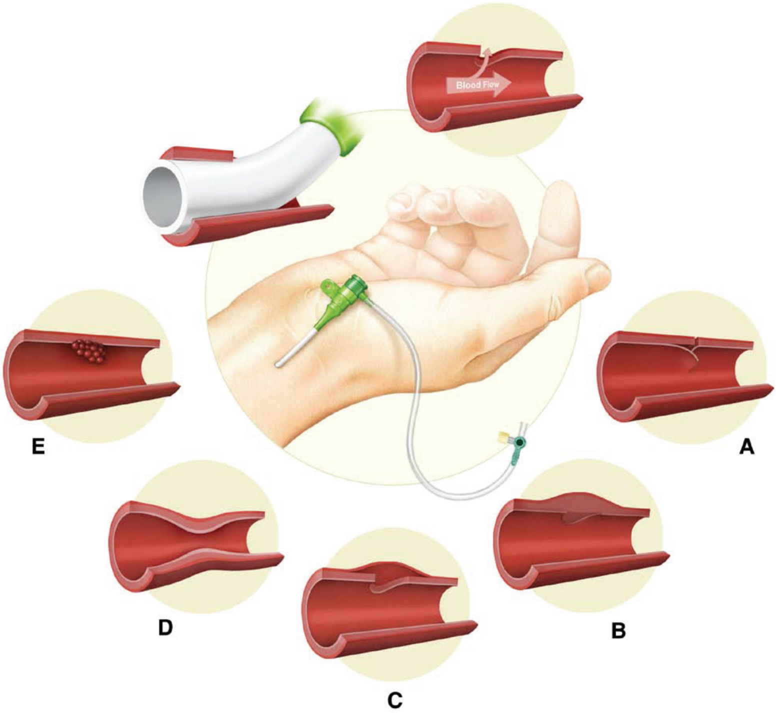

Figure 2. Radial cannulation and injuries. In the upper part, sheath removal and consequent trauma. In the lower part, acute wall injuries of the radial artery after cannulation observed with high-resolution ultrasound: dissection (**A**), intramural hematoma (**B**), pseudoaneurysm (**C**), spasm (**D**), and thrombus formation (**E**).

was caused by thrombus formation in one case, spiral dissection in another and to wall hematoma in the last. RAPL at 30 days occurred in 2 of 3 patients with RAO, in 4 patients with radial artery spasm, and in 1 patient with slow-flow and spontaneous contrast.

Smaller radial arteries at baseline had higher risk for RAPL both at 3-hour (odds ratio [OR], 1.42 per 0.1-mm reduction; 95% confidence interval [CI], 1.08–1.88; *P*=0.013) and 30-day follow-up (OR, 1.23 per 0.1-mm reduction; 95% CI, 1.00–1.52; *P*=0.049), but no higher risk of RAO, pain and discomfort, or functional impairment (Table 4). Intima, media, or overall wall thickness did not affect clinical end points at any timepoint (Table 4). The presence of radial artery calcification at baseline was associated with RAPL at 3 hours (OR, 12.33; 95% CI, 1.58–96.0; *P*=0.016) with a consistent trend at 30 days (OR, 6.60; 95% CI, 0.96–45.3; *P*=0.055; Table 4). The number of puncture attempts required to achieve radial cannulation predicted the occurrence of RAPL (OR, 2.64; 95% CI, 1.11–6.24; *P*=0.027), RAO (OR, 3.49; 95% CI, 1.20–10.1; *P*=0.022), and pain and discomfort (OR, 2.24; 95% CI, 1.00–5.04; *P*=0.05) at 30 days, with an increased risk after each further attempt (Figure 6). At 3 hours, the number of puncture attempts also correlated with RAO (OR, 3.49; 95% CI, 1.22–9.96; *P*=0.020), with a similar trend for RAPL (OR, 2.17; 95% CI, 0.75–6.29; *P*=0.15), pain and discomfort (OR, 1.71; 95% CI, 0.84–3.49; *P*=0.14), but not for functional impairment (OR, 1.05; 95% CI, 0.40–2.76; *P*=0.91) at this timepoint. When we searched for correlation between the number of puncture attempts and ultrasound measurements, we observed a strong, negative correlation between the number of attempts and the radial lumen diameter at puncture site both at 3-hour and 30-day follow-up. We did not observe any correlation between the number of puncture attempts and the total wall, intima, and media thickness at 3-hour and 30-day follow-up (Table 5).

Discussion

In this prospective mechanistic study, we evaluated the radial artery by noninvasive high-resolution ultrasound after transradial catheterization. We found that

1. The radial artery puncture site could be assessed, noninvasively and in detail with high-resolution ultrasound.
2. The incidence of RAO and pulsation loss at 30 days was 3.9% and 9.2%, respectively.
3. Traumatic injuries to the radial artery were ubiquitous, but did not result in any apparent clinical consequence.
4. The lumen of the radial artery at the puncture site modestly varied during follow-up and was slightly reduced only in the distal part of the region of interest. Intima and overall arterial thickness increased at 3 hours, which persisted at 30 days.

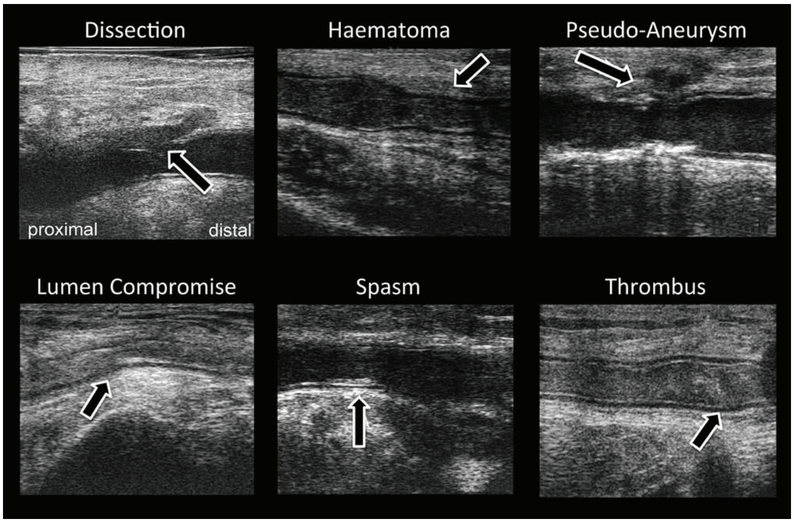

Figure 3. Ultrasound evidence of radial artery acute wall injuries at puncture site. Radial dissection: The arrowhead indicates the disruption of the vessel layers at the longitudinal view. Wall hematoma: the arrowhead indicates the hematoma with evidence of blood between the vessel layers. Pseudoaneurysm: arrowhead indicates the pseudoaneurysm at the longitudinal view, with evidence of blood outside the vessel wall. Lumen compromise: compromise of the arterial lumen caused by any injury. Spasm: the arrowhead indicates spasm, shown as vessel shrinkage and a thickened intima. Thrombus: arrowhead indicates the thrombus presenting as a still mass in the vessel lumen, characterized by the clear transition between its surface and the intima.

5. Smaller radial artery size and presence of wall calcification at baseline predicted radial pulse loss at 3 hours and 30 days.
6. A higher number of puncture attempts to cannulate the radial artery predicted radial occlusion, loss of pulsation, and symptoms at 30-day follow-up.

To the best of our knowledge, this is the first study evaluating in vivo the radial artery puncture site, before and after cannulation, with a noninvasive high-resolution imaging technique. Invasive imaging studies already demonstrated structural changes in the proximal segments of the radial artery after cannulation.[10,11] However, an intrinsic limitation of intravascular imaging is the inability to examine vessel segments distal to the sheath tip, precluding a comprehensive evaluation of the puncture site. Noninvasive ultrasound was used to evaluate radial artery after cannulation for coronary catheterization[5] and in the emergency

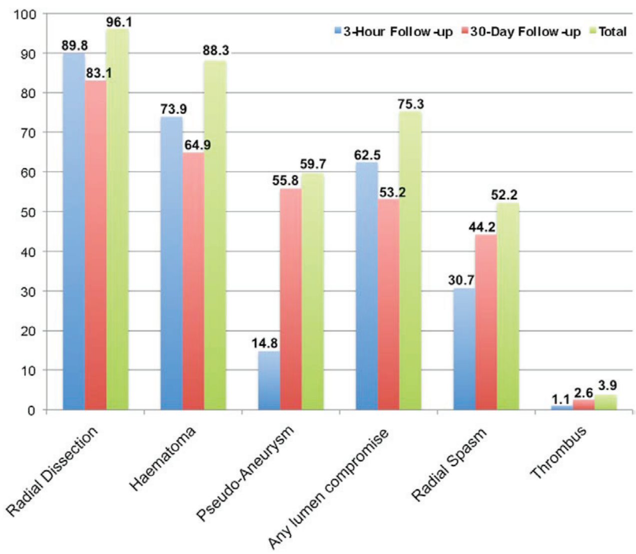

Figure 4. Incidence of radial artery acute wall injuries at puncture site. The histogram expresses the percentage of the population presenting each injury at 3-h and 30-d follow-up and overall. Injuries observed were not mutually exclusive.

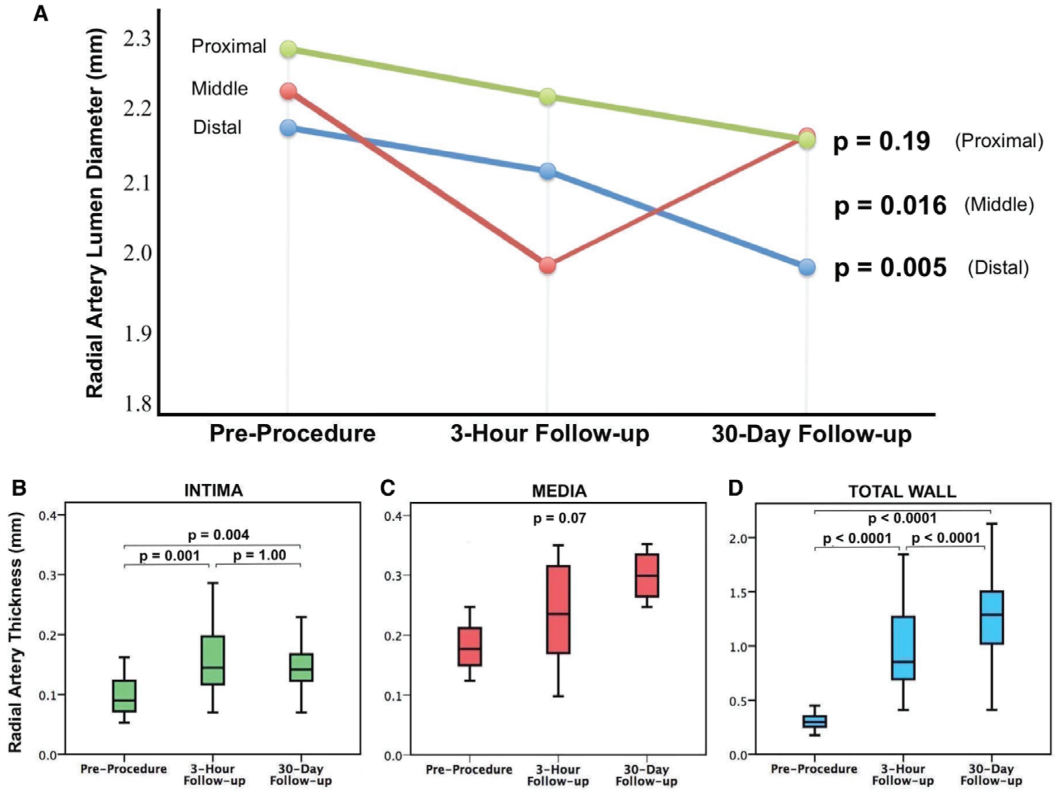

Figure 5. Evolution of radial artery measurements at the puncture site over time. **A**, Radial artery inner lumen diameter evolution at the puncture site region of interest at the 3 timepoints (ie, before cannulation, at 3-h and at 30-d follow-up). Box plots for the radial artery intima (**B**), media (**C**), and total wall (**D**) thickness at the 3 timepoints.

medicine setting.[12] Yet, conventional ultrasound systems use vascular probes with a frequency between 7 and 10 MHz, producing a spatial resolution of 300 µm, thus incapable to discriminate subtle changes of the radial wall such as the intima/media thickness and local wall injuries observed with histopathology.[13] In the current study, we used a high-resolution ultrasound system with a frequency of 40 MHz, and a spatial resolution of 30 µm similar to intravascular ultrasound.[6,7]

We found a variety of radial wall injuries after radial catheterization, occurring in all patients. These could be related to puncture trauma or to the mismatch between sheath size and artery diameter.[14] The average inner diameter of the radial artery in our study (ie, 2.25 mm) was significantly smaller than the outer diameter of the 6F sheath used (ie, 2.45 mm), hence producing an angioplasty-like effect during insertion. Yonetsu et al[10] reported similar injuries—intimal tears in 44.1% of patients and radial dissection in 24.7%—with optical coherence tomography in the proximal segment of the radial artery. In our data set, the acute wall injuries of the radial artery were not associated with RAO, RAPL, symptoms, or functional impairment. This may be related to a lack of statistical power caused by the relatively low occurrence of RAO and RAPL. In our study, the occurrence of RAO and RAPL was lower

Table 3. Radial Artery Ultrasound Measurements at the Puncture Site Region of Interest

	Preprocedure (1)	Three-Hour Follow-Up (2)	Thirty-Day Follow-Up (3)	*P* Value (1–2–3)	*P* Value (1–2)	*P* Value (2–3)	*P* Value (1–3)
Mid lumen diameter, mm	2.25±0.50	2.02±0.66	2.14±0.68	0.016	0.01	0.38	0.57
Distal lumen diameter, mm	2.21±0.50	2.10±0.45	1.99±0.53	0.005	0.32	0.38	0.001
Proximal lumen diameter, mm	2.29±0.53	2.22±0.48	2.17±0.53	0.19	…	…	…
Total wall thickness, mm	0.32±0.10	1.01±0.49	1.28±0.41	<0.0001	<0.0001	<0.0001	<0.0001
Intima thickness, mm	0.11±0.09	0.16±0.06	0.16±0.08	<0.0001	0.001	1.00	0.004
Media thickness, mm	0.18±0.04	0.26±0.14	0.32±0.13	0.07	…	…	…

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Table 4. Impact of Ultrasound Findings on Clinical End Points

	Three-Hour Follow-Up			Thirty-Day Follow-Up		
	End Point, n (%)	Odds Ratio (95% CI)	*P* Value	End Point, n (%)	Odds Ratio (95% CI)	*P* Value
Radial artery pulse loss	5/82 (6.1)	…	…	7/76 (9.2)	…	…
Acute wall injuries*						
No dissection	0/7 (0)	…	…	1/7 (14.3)	…	…
Dissection	5/75 (6.7)	n.a.	…	6/69 (8.7)	0.56 (0.06–5.48)	0.62
No hematoma	2/21 (9.5)	…	…	3/21 (14.3)	…	…
Hematoma	3/61 (4.9)	0.52 (0.08–3.23)	0.49	4/55 (7.3)	0.50 (0.10–2.43)	0.39
No pseudoaneurysm	5/70 (7.1)	…	…	6/64 (9.4)	…	…
Pseudoaneurysm	0/12 (0)	n.a.	…	1/12 (8.3)	0.89 (0.10–8.17)	0.92
No lumen compromise	0/30 (0)	…	…	2/28 (7.1)	…	…
Any lumen compromise	5/52 (9.6)	n.a.	…	5/48 (10.4)	1.48 (0.27–8.17)	0.65
No spasm	3/57 (5.3)	…	…	4/51 (7.8)	…	…
Spasm	2/25 (8.0)	1.50 (0.23–9.56)	0.67	3/25 (12.0)	1.53 (0.32–7.42)	0.60
No thrombus	5/81 (6.2)	…	…	7/75 (9.3)	…	…
Thrombus	0/1 (0)	n.a.	…	0/1 (0)	n.a.	…
Measurements and characteristics						
No calcifications at baseline	3/76 (3.9)	…	…	5/70 (7.1)	…	…
Calcifications at baseline	2/6 (33.3)	12.33 (1.58–96.0)	0.016	2/6 (33.3)	6.60 (0.96–45.3)	0.055
Diameter at puncture site at baseline (0.1-mm decrease)†	…	1.42 (1.08–1.88)	0.013	…	1.23 (1.00–1.52)	0.049
Total wall thickness at baseline (0.1-mm decrease)	…	1.40 (0.71–2.77)	0.33	…	1.45 (0.55–3.84)	0.44
Intima thickness at baseline (0.01-mm decrease)	…	1.04 (0.98–1.10)	0.22	…	1.03 (0.88–1.20)	0.71
Media thickness at baseline (0.01-mm decrease)	…	0.90 (0.75–1.07)	0.24	…	1.11 (0.95–1.30)	0.20
Radial artery occlusion	3/87 (3.4)	…	…	3/76 (3.9)	…	…
Acute wall injuries*						
No dissection	1/9 (11.1)	…	…	1/7 (14.3)	…	…
Dissection	2/78 (2.6)	0.21 (0.02–2.55)	0.22	2/69 (2.9)	0.18 (0.01–2.24)	0.18
No hematoma	1/22 (4.5)	…	…	1/21 (4.8)	…	…
Hematoma	2/65 (3.1)	0.70 (0.06–8.08)	0.77	2/55 (3.6)	0.79 (0.07–9.21)	0.85
No pseudoaneurysm	3/75 (4.0)	…	…	3/64 (4.7)	…	…
Pseudoaneurysm	0/12 (0)	n.a.	…	0/12 (0)	n.a.	…
No lumen compromise	1/33 (3.0)	…	…	1/28 (3.6)	…	…
Any lumen compromise	2/54 (3.7)	1.21 (0.10–13.8)	0.88	2/48 (4.2)	1.15 (0.10–13.3)	0.91
No spasm	1/60 (1.7)	…	…	1/51 (2.0)	…	…
Spasm	2/27 (7.4)	4.53 (0.39–52.3)	0.22	2/25 (8.0)	4.17 (0.36–48.2)	0.25
No thrombus	3/86 (3.5)	…	…	3/75 (4.0)	…	…
Thrombus	0/1 (0)	n.a.	…	0/1 (0)	n.a.	…
Measurements and characteristics						
No calcifications at baseline	3/81 (3.7)	…	…	3/70 (4.3)	…	…
Calcifications at baseline	0/6 (0)	n.a.	…	0/6 (0)	n.a.	…
Diameter at puncture site at baseline (0.1-mm decrease)†	…	1.20 (0.89–1.61)	0.24	…	1.19 (0.89–1.59)	0.24
Total wall thickness at baseline (0.1-mm decrease)	…	0.42 (0.07–2.38)	0.33	…	2.27 (0.41–12.5)	0.44
Intima thickness at baseline (0.01-mm decrease)	…	0.90 (0.61–1.31)	0.58	…	1.08 (0.76–1.56)	0.65
Media thickness at baseline (0.01-mm decrease)	…	0.90 (0.72–1.14)	0.39	…	1.11 (0.88–1.39)	0.39
Pain and discomfort	32/87 (36.8)	…	…	24/75 (32.0)	…	…
Acute wall injuries*						
No dissection	3/9 (33.3)	…	…	2/7 (28.6)	…	…
Dissection	29/78 (37.2)	1.16 (0.27–4.99)	0.84	22/68 (32.4)	1.17 (0.21–6.51)	0.86

(*Continued*)

Table 4. Continued

	Three-Hour Follow-Up			Thirty-Day Follow-Up		
	End Point, n (%)	Odds Ratio (95% CI)	*P* Value	End Point, n (%)	Odds Ratio (95% CI)	*P* Value
No hematoma	9/23 (39.1)	…	…	8/20 (40.0)	…	…
Hematoma	23/64 (35.9)	0.93 (0.35–2.47)	0.89	16/55 (29.1)	0.67 (0.23–1.92)	0.45
No pseudoaneurysm	29/74 (39.2)	…	…	22/63 (34.9)	…	…
Pseudoaneurysm	3/13 (23.1)	0.48 (0.12–1.87)	0.29	2/12 (16.7)	0.38 (0.08–1.90)	0.24
No lumen compromise	12/33 (36.4)	…	…	8/27 (29.6)	…	…
Any lumen compromise	20/54 (37.0)	1.00 (0.41–2.45)	0.99	16/48 (33.3)	1.15 (0.42–3.19)	0.79
No spasm	20/60 (33.3)	…	…	15/50 (30.0)	…	…
Spasm	12/27 (44.4)	1.50 (0.60–3.77)	0.39	9/25 (36.0)	1.23 (0.45–3.39)	0.68
No thrombus	32/86 (37.2)	…	…	24/74 (32.4)	…	…
Thrombus	0/1 (0)	n.a.	…	0/1 (0)	n.a.	…
Measurements and characteristics						
No calcifications at baseline	29/81 (35.8)	…	…	23/69 (33.3)	…	…
Calcifications at baseline	3/6 (50.0)	1.83 (0.35–9.64)	0.48	1/6 (16.7)	0.41 (0.04–3.70)	0.43
Diameter at puncture site at baseline (0.1-mm decrease)†	…	1.01 (0.92–1.11)	0.80	…	1.00 (0.90–1.10)	0.98
Total wall thickness at baseline (0.1-mm decrease)	…	1.21 (0.79–1.85)	0.39	…	1.16 (0.52–1.42)	0.55
Intima thickness at baseline (0.01-mm decrease)	…	1.02 (0.97–1.08)	0.39	…	1.02 (0.95–1.08)	0.65
Media thickness at baseline (0.01-mm decrease)	…	1.07 (0.99–1.15)	0.10	…	1.04 (0.95–1.14)	0.41
Functional impairment	12/85 (14.1)			9/75 (12.0)		
Acute wall injuries*						
No dissection	0/9 (0)	…	…	1/7 (14.3)	…	…
Dissection	12/76 (15.8)	n.a.	…	8/68 (11.8)	0.79 (0.08–7.40)	0.83
No hematoma	5/22 (22.7)	…	…	3/20 (15.0)	…	…
Hematoma	7/63 (11.1)	0.45 (0.13–1.59)	0.22	6/55 (10.9)	0.73 (0.17–3.25)	0.68
No pseudoaneurysm	10/72 (13.9)	…	…	8/63 (12.7)	…	…
Pseudoaneurysm	2/13 (15.4)	1.14 (0.22–5.95)	0.87	1/12 (8.3)	0.64 (0.07–5.61)	0.68
No lumen compromise	7/32 (21.9)	…	…	4/27 (14.8)	…	…
Any lumen compromise	5/53 (9.4)	0.36 (0.10–1.26)	0.11	5/48 (10.4)	0.65 (0.16–2.67)	0.55
No spasm	8/59 (13.6)	…	…	6/50 (12.0)	…	…
Spasm	4/26 (15.4)	1.11 (0.30–4.05)	0.88	3/25 (12.0)	0.96 (0.22–4.18)	0.95
No thrombus	12/84 (14.3)	…	…	9/74 (12.2)	…	…
Thrombus	0/1 (0)	n.a.	…	0/1 (0)	n.a.	…
Measurements and characteristics						
No calcifications at baseline	12/79 (15.2)	…	…	9/69 (13.0)	…	…
Calcifications at baseline	0/6 (0)	n.a.	…	0/6 (0)	n.a.	…
Diameter at puncture site at baseline (0.1-mm decrease)†	…	1.07 (0.93–1.25)	0.30	…	0.94 (0.83–1.07)	0.38
Total wall thickness at baseline (0.1-mm decrease)	…	0.93 (0.50–1.75)	0.82	…	1.19 (0.55–1.56)	0.66
Intima thickness at baseline (0.01-mm decrease)	…	0.93 (0.78–1.10)	0.40	…	1.10 (0.88–1.35)	0.41
Media thickness at baseline (0.01-mm decrease)	…	1.08 (0.96–1.19)	0.24	…	0.96 (0.84–1.09)	0.54

CI indicates confidence interval.
*Acute wall injuries detected at 3-hour follow-up.
†Diameter at puncture site was considered at the mid-entry site.

than previously reported and may result from a strict protocol including routine use of periprocedural anticoagulation, non-occlusive compression, and relatively short total compression times.[5,15,16]

Our study confirmed modest reductions of the radial artery lumen size after cannulation.[5,10,11,13] This could be mechanistically explained by impaired vasomotion and by the increase in wall thickness. Impaired vasomotion after radial cannulation could be the result of endothelial dysfunction[17] after endothelial stripping caused by sheath insertion or smooth-muscle cell damage.[18] We also confirmed histopathology and imaging data that indicated a consistent increase in the intimal and total wall thickness.[10,13] In our study, this was related to the development of acute wall

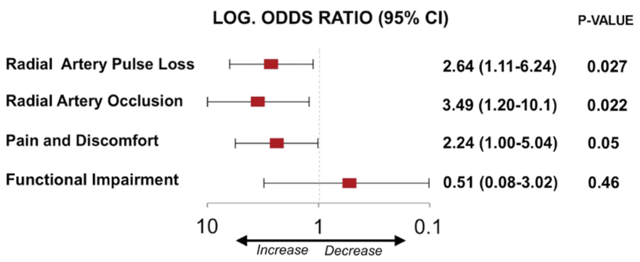

Figure 6. Impact of the number of puncture attempts on clinical end points. Forest plot with odds ratio, confidence interval (CI), and *P* value for the occurrence of each clinical end point at 30 d is presented. An odds ratio >1 represent to an increase of the risk of each end point to occur at 30 d.

injuries that increased the distance between the intimal and the adventitial layers. Over half of patients had pseudoaneurysms at 30-day follow-up. This high rate can be explained by the unprecedented high spatial resolution of the noninvasive 40-MHz ultrasound technology used. The majority of these pseudoaneurysms would not be visible by standard 10-MHz vascular probes. Notably, we detected an increase in the rate of pseudoaneurysms from 3 hours to 30 days after the procedure. It could be speculated that early removal of the compressive device before complete hemostasis may result in continued blood accumulation into the arterial wall resulting in pseudoaneurysm formation. However, a previous study demonstrated, on the contrary, a reduction of RAO with an early deflation of the radial compressive device,[15] suggesting an early deflation protocol may lead to pseudoaneurysm formation that, however, does not result in RAO. We observed a relatively high proportion of radial artery spasm occurrence at 30 days (44.2%), which has not been previously described. However, this finding should be interpreted with caution. Spasm implied a thickening of the vessel wall layers. Still, vessel wall thickening after cannulation could also be because of vessel remodeling. The exact pathophysiological mechanism cannot be discerned with current technology.

Multiple puncture attempts were associated with RAO, RAPL, and symptoms at 30 days. Previous reports already suggested that multiple puncture attempts might increase radial artery spasm,[19] while reducing radial artery trauma by several means might reduce vascular complications.[5,14,20] The application of subcutaneous nitrates and the implementation of ultrasound-guided puncture may facilitate radial artery cannulation and reduce the number of puncture attempts needed to achieve cannulation.[21,22] In addition, we also observed a negative correlation between radial lumen at 30 days and the number of puncture attempts. This might have important consequences for future catheterizations through the same radial access considering that smaller and less pulsatile arteries might be more difficult to cannulate.

Table 5. Correlation Between Number of Punctures and Ultrasound Measurements at 3 Hours and 30 Days

	Three-Hour Follow-Up		Thirty-Day Follow-Up	
	Correlation Coefficient	*P* Value	Correlation Coefficient	*P* Value
Mid lumen diameter, mm	−0.49	<0.0001	−0.45	<0.0001
Distal lumen diameter, mm	−0.21	0.069	−0.25	0.037
Proximal lumen diameter, mm	−0.37	0.001	−0.47	<0.0001
Total wall thickness, mm	0.10	0.356	0.02	0.871
Intima thickness, mm	−0.02	0.829	−0.21	0.076
Media thickness, mm	−0.18	0.431	−0.05	0.853

Limitations

This is a single-center mechanistic study with a relatively small sample size. To explore predictors of RAO or pulse loss, we developed a univariate predictive model, which was not adjusted for many potential confounders. As such, the clinical impact of the radial wall injuries observed with high-resolution ultrasound should be tested in larger studies. The occurrence of symptoms and functional impairment was self reported by the patients, and as such could have been biased. However, these end points were secondary in our study, and recent reports confirmed the lack of impact of radial catheterization on the upper limb function.[23]

Radial spasm definition was prespecified in the study protocol according to accepted intravascular ultrasound consensus.[24] Still, radial spasm was evaluated only in the acute phase and the evidence of an image resembling spasm long after cannulation might be related with vessel remodeling. However, current technology does not allow a clear distinction between spasm and permanent vessel remodeling.

Noninvasive ultrasound evaluation exposes radial artery to an external compression, which might eventually affect measurements. However, the extent of this change is likely to be small because of the higher blood pressure of the arterial system.

Conclusions

The radial artery puncture site can be assessed noninvasively and in detail by high-resolution ultrasound. Arterial wall healing after transradial catheterization is a dynamic process characterized by increased intimal and total wall thickness and a modest reduction in lumen size. Acute wall injuries of the radial artery were ubiquitous after cannulation, but contrary to repeated puncture attempts, did not seem to affect postprocedural radial occlusion or loss of pulsation.

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Disclosures

None.

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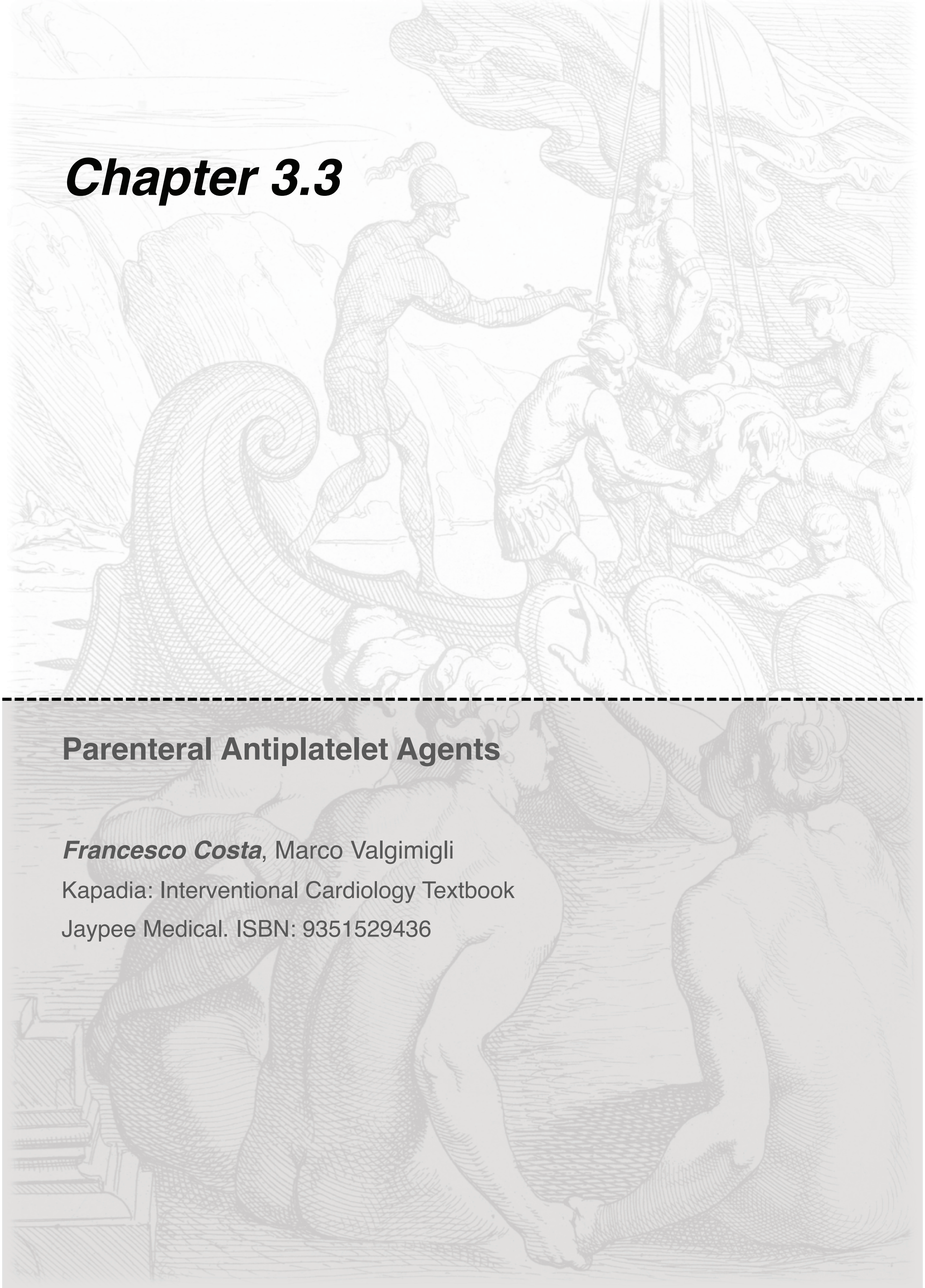

Chapter 3.3

Parenteral Antiplatelet Agents

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Parenteral Antiplatelet Agents:

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3

Background

Platelet reactivity plays a pivotal role in the pathogenesis of ischemic cardiovascular disorders (1). It has been shown that both platelet activation and aggregation are heightened in acute coronary syndromes (ACS) and from current evidence emerges a strong and independent correlation between the propensity to clot formation (2) and the clinical outcome. Platelet aggregation blockade has been demonstrated to provide unequivocal benefit in a broad population of patients (3-5). The current parenteral anti platelet drugs act on different activation and aggregation pathways, including the P2Y12 ADP receptor, mediating upstream activation and the glycoprotein IIb/IIIa, the so called final common aggregation pathway. While no approved oral anti-platelet agent acts by inhibiting the final common pathway of platelet aggregation, there are currently numerous oral compounds inhibiting the P2Y12 receptor. As more extensively discussed below, the availability of parenteral platelet blockers remains of paramount importance when a prompt and predictable inhibitory effect is needed, especially in the acute setting of patients with acute coronary syndrome undergoing immediate coronary intervention.

This chapter aims at reviewing the currently approved parenteral glycoprotein IIb/IIIa inhibitors, including eptifibatide, tirofiban and abciximab, as well as discussing current evidence for the $P2Y_{12}$ receptors cangrelor and elinogrel. The intravenous formulation of the acetylsalicylic acid has been widely described in literature and will not be part of this review.

Glycoprotein IIb/IIIa inhibitors:

Among the proposed pharmacologic targets for antiplatelet therapy, glycoprotein IIb/IIIa (GPIIb/IIIa) continues to be attractive as it represents the common final step in the pathway that leads to platelet aggregation (6). GPIIb/IIIa inhibitors (GPI), are currently considered the most powerful and specific platelet inhibitors in acute thrombosis. GPI inhibit also thrombin generation and fibrin clot formation (7). This explains why GPI display a moderate prolongation effect on activated clotting time (ACT) measurement and, moreover, why GPI interact with UFH, which dose should be lowered during PCI.

The three GPIIb/IIIa inhibitors currently on the market have profoundly different characteristics despite binding to the same receptor.

Abciximab is an anti-integrin Fab fragment of a human–mouse chimeric monoclonal antibody with high affinity and a slow dissociation rate from the GPIIb/IIIa platelet receptor (8, 9). Despite a short plasma half-life of 10–30 minutes, Abciximab has a long biologic half-life, mainly due to its strong and irreversible binding to the GPIIb/IIIa receptor. Platelet function returns to baseline days after therapy cessation, as platelet cellular turnover is required to overcome drug irreversible receptor blockade (8, 9). Complete receptor blockade is obtained at approximately 5µg/mL. The binding site of abciximab is located on the ß-chain of the GPIIb/IIIa receptor and is different from the binding site for the low molecular weight inhibitors eptifibatide and tirofiban (8, 9). Unlike other GPIs, abciximab has no renal clearance. Hence, no dose adjustment needs to be carried out in patients with renal dysfunction and it can be administered in patients with end stage renal disease. However abciximab has been shown to have a high antigenicity, with an increased risk of thrombocytopenia, especially after re-administration (10). This downside is possibly due to the size of the molecule or to the murine origin, and it has never been shown with the other GPIs (11).

Tirofiban (9) is a small synthetic nonpeptide competitive GPI with high specificity and affinity for GPIIb/IIIa receptors conferred by a tyrosine analogue structurally similar to the RGD (arginine–glycine–aspartic acid)-loop of the GPIIb/IIIa receptor. Tirofiban has a long plasma half-life and short biologic half-life resulting in a rapid recovery of platelet activity approximately 3-4 hours following therapy cessation. It is about 35% unbound in the circulation with predominant renal clearance (65%) and can be hemodialyzed. Dosing adjustment needs to be implemented in patients with creatinine clearance below 30 ml/min. Different dosing regimens may be required based on the patient's diagnosis and the timing of PCI. A regimen with a loading infusion of 0.4 µg/kg/min run over 30 minutes followed by a 0.10 µg/kg/min maintenance infusion has proven to be quite effective in the management of patients with non- ST-elevation acute coronary syndromes when administered at least four hours prior to PCI. Otherwise a regimen including a high dose bolus of 25 µg/kg followed by a maintenance infusion of 0.15 µg/kg/min, has shown a higher platelet inhibition (12) then is deemed more appropriate when administered immediately before PCI.

Eptifibatide is a small, cyclic heptapeptide, which has a modified lysine–glycine–aspartate amino acid sequence. It is highly specific for the GPIIb/IIIa receptor, with a relatively low binding affinity and a rapid dissociation from its receptor, leading to early restoration of platelet function after discontinuation of the infusion (13, 14). Inhibition of platelet aggregation by eptifibatide is dose dependent. Regarding drug elimination, eptifibatide clearance largely occurs via renal mechanisms, with a half-life of 2.7 hours. As such, unlike abciximab or tirofiban, dose adjustment is required in patients with creatinine clearance below 50 ml/min and the drug is contra-indicated in patients with creatinine clearance below 30 ml/min. A double 180 µg/kg bolus followed by a 2.0 µg/kg/min infusion has been validated to provide a proper platelet inhibition when administered immediately before PCI (15) in patients with normal renal function.

Clinical trials

All three drugs have been trialed in two different clinical scenarios: the *downstream use*, i.e., given immediately before PCI; and (b) *upstream use*, i.e., administered well before intervention and as early as possible after diagnosis in patients with ACS. While numerous studies have suggested that starting GPI upstream may further reduce ischemic events both before and during PCI as compared to downstream administration (16, 17), this treatment strategy has always been associated to a definite bleeding hazard. Hence, American and European guidelines currently discourage the upstream utilization of this therapy whereas a downstream use, especially in patients at high ischemic risk and or with high thrombus burden remains a viable treatment option.

Abciximab

Given shortly before PCI, abciximab administered as a bolus followed by a 12-hour infusion is superior to placebo on top of unfractionated heparin in reducing the acute risk of ischemic complications. This statement is mainly supported by three landmark studies: the EPIC trial (Evaluation of 7E3 for the Prevention of Ischemic Complications) (18), the EPILOG trial (Evaluation in Percutaneous Transcateter Coronary Angioplasty to Improve Long-term Outcome with Abciximab GP IIb/IIIa blockade), and the EPISTENT trial (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting). A major limitation of these early landmark studies is the absence of pretreatment with clopidogrel on top of aspirin.

The ISAR-REACT 2 study (Intracoronary Stenting and Antithrombotic Regimen:

Rapid Early Action for Coronary Treatment) (19), enrolling patients with NSTEACS, showed a 25% reduction in the risk of recurrent ischemic events among patients treated with Clopidogrel at a loading dose of 600 mg on top of aspirin and abciximab. Notably among patients with an elevated troponin level, the risk of recurrent ischemic events was considerably higher and was reduced by 29% by abciximab.

Several trials have been conducted to test the effectiveness of abciximab in the setting of STEMI. A meta-analysis including 1101 patients presenting for primary PCI from ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction regarding Acute and Long-term Follow-up) (20), ISAR 2 (21), and ACE (Abciximab and Carbostent Evaluation) (22) trials, demonstrated a significant reduction of the primary end point of death or reinfarction with abciximab versus placebo (12.9% vs 19.0%).

Tirofiban

The RESTORE and TARGET trials tested the efficacy and safety of tirofiban, given at a bolus dose of 10 ugr/kg as compared to placebo or abciximab, respectively. The results of this studies indicated that tirofiban, when given at this bolus regimen, may be inadequate to suppress ischemic events and subsequent PK/PD studies showed that this regimen falls short in fully inhibiting ADP-induced platelet activation. An higher bolus regimen of 25 ugr/kg, the so called high dose bolus (HDB) has been subsequently developed.

In the ADVANCE trial, high-risk PCI patients pretreated with thienopyridines, were consecutively randomized to HDB tirofiban and infusion for 24–48 hours or placebo. The cumulative incidence of the primary composite end point death, MI, TVR, and bailout use of GPIIb/IIIa inhibitors was 35% and 20% in the placebo and HDB tirofiban groups respectively (23). Similarly On-TIME 2 trial (24) provided recent and further evidence of the added benefit of utilizing HDB tirofiban on top of dual antiplatelet therapy in STEMI patients. Thus, taken together current evidence suggests that use of tirofiban in a single HDB is beneficial even on top of upstream use of aspirin and clopidogrel across the whole spectrum of ACS patients, spanning from NSTE- to STE-ACS.

Eptifibatide

The ESPRIT trial (25) compared eptifibatide to placebo in reducing ischemic complications in patients undergoing elective coronary stent implantation and concomitant thienopyridine therapy. The trial was stopped in February 2000 for efficacy when results showed a highly significant 37% reduction in the combined primary end point of death, MI, urgent TVR or "thrombotic bail-out.

Are all three glycoprotein IIb/IIIa inhibitors equally effective and safe?

The comparison between the three GPI have been described. The most studied comparison was between tirofiban and abciximab, whereas data on the comparison abciximab vs eptifibatide is limited. Finally no randomized comparison exists between eptifibatide and tirofiban.

Currently there are nine studies involving 7132 patients regarding the comparison between Abciximab and Tirofiban. The overall pooled effect estimate analysis showed that tirofiban at 30 days led to similar mortality rate (OR = 0.90; 95% CI, 0.53–1.54; $p = 0.70$), but tended to increase the composite of death or MI (6.0% vs 5.1%; OR = 1.18; 95% CI, 0.96–1.45; $p = 0.11$) when compared to abciximab. However these results mainly mirrored the findings of the TARGET study (26) which, trialed a tirofiban 10 µg/kg 3 minute bolus and 0.15 µg/kg/min infusion regimen. Indeed, when tirofiban given as a high dose bolus, mortality (OR = 0.73; 95% CI, 0.36–1.47; $p = 0.38$), the composite of death or MI (OR = 0.87; 95% CI 0.56–1.35; $p = 0.54$) or MACE rate (OR = 0.87; 95% CI, 0.57–1.32; $p = 0.51$) were similar compared to abciximab. The rate of major bleeding did not differ in the two groups (OR= 1.24; 95% CI, 0.78–1.98; $p = 0.35$), whereas minor bleedings (3.1% vs 4.8%; OR = 0.64; 95% CI 0.50–0.82; $p < 0.001$) and any thrombocytopenia (0.3% vs 2.4%; OR = 0.28; 95% CI, 0.08–0.94; $p = 0.04$) were both markedly reduced in the tirofiban group.

Glycoprotein IIb/IIIa inhibitors and P2Y12 oral receptor blockers

As GPI were largely trialed and developed in the pre-clopidogrel era, much of the evidence generated through their use was questioned after the advent of the oral

P2Y12 inhibitors. However emerging evidence suggests that inhibition of P2Y12 and GPIIb/IIIa receptors may potentially play a complementary role in further reducing the incidence of ischemic events in patients with ACS.

Currently, there are multi-single randomized controlled studies (19, 23, 24) as well as a meta- analysis (27) showing that the benefit of glycoprotein inhibitors seems to be at least maintained even in patients properly pretreated with both aspirin and clopidogrel. Conversely there is still limited evidence about the effect of GPI in patients treated with the more potent oral P2Y12 blockers prasugrel or ticagrelor (28) .

Cangrelor:

Cangrelor is an intravenous, non thienopyridine antagonist of the $P2Y_{12}$ receptor. It's unique pharmacological profile makes this molecule attractive, especially in the acute emergency setting such as ST segment elevated myocardial infarction (STEMI) and non-ST segment elevated myocardial infarction (NSTEMI) in which the time to cardiac catheterization is becoming shorter and a rapid onset of platelet inhibition is essential.

In this setting, neither ticagrelor, nor prasugrel provided pharmacodynamic evidence of a rapid effect, in fact at 2 hours from the administration of the loading dose, one third to half of patients with STEMI had high platelet reactivity as

assessed with the VerifyNow assay, irrespective of the drug used (28-30).
Moreover, the administration of oral $P2Y_{12}$ inhibitors imply a relatively long-term platelet inhibition for at least 3-5 days, hence making problematic the immediate or urgent referral to surgery. In this case, the availability of a drug with a fast offset of action is of paramount importance.
Furthermore is worth mentioning how the usefulness of oral $P2Y_{12}$ can be impaired in patients who cannot swallow or absorb medications. This eventuality is particularly frequent in patients with acute coronary syndromes that often presents with vomit, shock or need for intubation.
Cangrelor, when administered as a bolus of 30 µg/kg, achieves an almost complete and immediate inhibition of ADP-induced platelet aggregation, and his action is sustained on a high stable degree of inhibition during continuous infusion. The plasma half-life is approximately 3-5 minutes and the platelet function comes back to normal within one hour after the cessation of infusion. Cangrelor does not have a relevant hepatic and renal metabolism, unlike the current oral $P2Y_{12}$ inhibitors.
Cangrelor (N-2-methylthio-ethyl-2-(3,3,3-trilfluoropropylthiol)-5'-adenyl acid, is an analogue of adenosine triphosphate (ATP), the natural antagonist of the receptor $P2Y_{12}$.
ATP has a low affinity to the $P2Y_{12}$ because is rapidly metabolized by the ectonucleotidases (31).
The design of cangrelor, with the replacement of anhydride with methylene

groups and an halogen, conferred to the molecule a higher affinity to the $P2Y_{12}$ receptor and a longer half life. Furthermore the modification at the adenine C2 position with 3,3,3-trifluoropropylhio and N6 methylthioethyl groups increased potency six times with respect to ATP (32, 33). These structural changes brought important pharmacological advantages.

Cangrelor interaction with oral $P2Y_{12}$ inhibitors have been studied. A randomized study showed a competitive interaction between Clopidogrel and Cangrelor when clopidogrel was administered simultaneously or immediately after cangrelor discontinuation (bolus of 30 µg/kg and 1-h infusion of 4 µg/kg/min). The high affinity of Cangrelor to $P2Y_{12}$ prevents the active metabolite of clopidogrel to bind to the receptor during or immediately after its administration, hindering clopidogrel induced platelet inhibition (34). The same effect was demonstrated after prasugrel administration. Conversely the use of Cangrelor after preincubation with active metabolites of clopidogrel or prasugrel led to a sustained platelet inhibition (35).

Importantly these findings emphasize the need of a correct transition between cangrelor and oral $P2Y_{12}$ receptor inhibitors. So far the most studied transition was between cangrelor and clopidogrel during the Champion trial: this study demonstrated how clopidogrel should be administered after cangrelor infusion discontinuation for the competitive interaction between the two drugs to be avoided. There is little evidence regarding the transition between cangrelor and both prasugrel and ticagrelor. Recently a small study reported the effects of the

transition between cangrelor and ticagrelor and vice-versa: the authors demonstrated how ticagrelor given before or during infusion of cangrelor did not attenuate the pharmacodynamic effect of cangrelor. Furthermore the pharmacodynamic effects of ticagrelor were preserved when ticagrelor was administered during infusion of cangrelor. In fact the pharmacodynamic effect of ticagrelor are greater when the drug is given earlier, even if in this study the difference was not statistically significant (30 min vs 75 min after initiation of cangrelor infusion) (36).
However bigger studies over the transition between cangrelor and novel oral $P2Y_{12}$ inhibitors have yet to be reported. Two randomized trial, TRANSITION I and TRANSITION II, testing the transition to and from ticagrelor and prasugrel respectively, have been completed but not yet published.

The promising results raised from the phase II studies of Cangrelor led to the foundation of the phase III program that consisted of two large parallel randomized trials, the Platelet Inhibition with Cangrelor in Patients Undergoing PCI (CHAMPION-PCI) trial (37) and the Intravenous Platelet Blockade with Cangrelor during PCI (CHAMPION-PLATFORM) trial (38). Both trials tested the hypothesis that Cangrelor, administered as a bolus of 30 µg/kg within 30 min to the PCI start and followed by a 4 µg/kg/min infusion (for at least 2 h and no longer than 4 h), could reduce the thrombotic events compared to Clopidogrel at a loading dose of 600 mg. The primary end point for both studies was a composite of death from any cause, myocardial infarction (MI), and ischemia-driven revascularization (IDR) at 48 h post randomization.

In CHAMPION-PCI, patients were randomized to receive cangrelor plus loading dose of clopidogrel at the end of the infusion in the study arm, or loading dose of clopidogrel prior to the start of PCI in the comparator arm.

In CHAMPION-PLATFORM patients were randomized to receive cangrelor plus clopidogrel at the end of the infusion or placebo plus clopidogrel at the end of PCI.

In both trials, patients randomized to cangrelor, received their loading dose of clopidogrel after infusion discontinuation in order to avoid interaction between clopidogrel and cangrelor. Patients with STEMI and on prior clopidogrel therapy were eligible for CHAMPION-PCI but excluded from CHAMPION-PLATFORM. Enrollment was prematurely terminated for futility, given the low likelihood of achieving the primary end-point, and both trials failed to demonstrate the superiority of adjunctive cangrelor therapy. At that moment, 98% patients were enrolled in CHAMPION-PCI and 86% in CHAMPION-PLATFORM, the primary end point rate was similar between cangrelor and control in both studies (7.5% for cangrelor, 7.1% for clopidogrel, odds ratio (OR) 1.05, 95% confidence interval (CI), 0.88 to 1.24; P=0.59; and 7.0% vs 8.0%, OR 0.87; 95% CI, 0.71 to 1.07; P=0.17 respectively).

However a benefit of cangrelor was shown in secondary end points not depending on biomarkers such as death, stent thrombosis and Q-wave myocardial infarction.

In fact, the primary end point of the study was importantly driven by the occurrence of MI, which was difficult to assess in this population. Indeed post-procedure MI is problematic when biomarkers are elevated before the procedure and importantly, in the CHAMPION trials population, the time from hospital admission to PCI was short (6.3 h mean in CHAMPION PCI and 7.9 h mean in CHAMPION PLATFORM). Furthermore the definition of MI of the CHAMPION studies preceded the Universal definition of MI (39) and the presence of stable or falling biomarkers at the time of PCI was not required to define PCI-related MI endpoint. Considering all this issues a pooled analysis of data from the CHAMPION trials using the universal definition of MI was performed (40). According to this definition, if the biomarkers before the procedure are elevated and not falling or stable, the diagnosis of periprocedural MI based on biomarkers is not recommended. With this analysis the authors demonstrated that at 48 h cangrelor significantly reduced the primary end point (3.1% vs 3.8%; OR 0.82; 95% CI, 0.68-0.99 ; P = 0.037). These findings pushed the investigators to a new attempt, and the CHAMPION PHOENIX trial (41) was designed. The study design had many similarities with the previous PCI and PLATFORM, but some important differences. First the definition of MI endpoint followed the Universal definition of MI. Second, the dose of clopidogrel in the comparator arm changed from 600 mg to 300-600 mg at the investigator discretion and the enrollment was restricted to clopidogrel naive patients. Third the primary endpoint was a composite of death, MI, IDR, or stent thrombosis at 48 hours.

In the CHAMPION-PHOENIX trial, cangrelor significantly reduced the primary end point (4.7 vs 5.9; OR 0.78; 95 % CI, 0.66-0.93; P= 0.005). The result was mostly driven by a reduction in the rate of MI (3.8% vs 4.7%; OR 0.80; 95% CI 0.67-0.97; P = 0.02) and was persistent at 30 days. Stent thrombosis, the key secondary endpoint, was also significantly reduced in the cangrelor group by 38 % (OR 0.62, 95% CI, 0.43-0.90; P = 0.01). Finally, the rate of severe bleeding was not significantly increased in the cangrelor group with the GUSTO criteria (0.16% vs 0.11%; OR 1.50; 95% CI, 0.53-4.22; P= 0.44) nor with other bleeding definitions.

Recently all the three CHAMPION trials, using the Universal MI definition, were included in a patient level meta-analysis (□25,000 patients) that showed a significant reduction of the primary endpoint death, MI, ischemic driven revascularization (IDR), and stent thrombosis at 48 h with cangrelor by 19% (3.8% for cangrelor vs 4.7% for control; OR 0.81, 95% CI, 0.71-0.91, P = 0.0007) and a reduction of stent thrombosis by 41% (0.5% vs 0.8%, OR 0.59, 95% CI 0.43-0.80, P = 0.0008). These results persisted at 30 days and the safety outcome, evaluated with the GUSTO criteria, was not significantly different in the two groups. (42)

The potential benefit of cangrelor was tested also in a different scenario: the bridge to surgery. The BRIDGE trial, a small randomized phase II study, enrolled

210 patients already on thienopyridine therapy and scheduled for CABG surgery. The patients, after the thionopyridine therapy discontinuation, 2 to 7 days before surgery, were randomized in two arms that received cangrelor or placebo respectively. Cangrelor administered without bolus with an infusion of 0.75 ug/kg/min was discontinued 1 to 6 hours before surgery. The primary efficacy endpoint expressed as the proportion of patients with a platelet reactivity < 240 PRU during infusion prior to surgery, was significantly reduced in the cangrelor arm (98.8% vs 19%, RR 5.2, 95% CI, 3.3-8.1, P = 0.01), with no significant differences in CABG related bleeding and major bleeding prior to CABG surgery (43).

Elinogrel:

Elinogrel is a reversible, direct-acting agent, that competitively binds with platelet $P2Y_{12}$ receptor (44). Elinogrel has a more rapid onset and offset effect compared to clopidogrel and is available in both the oral and intravenous ways of administration.

The INNOVATE- PCI (A Randomised, Double-Blind, Active-Controlled Trial to Evaluate Intravenous and Oral PRT060128, a Selective and Reversible P2Y12 Inhibitor, vs. Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-Urgent PCI) phase II trial have shown that both intravenous and oral doses of elinogrel (80–120 mg intravenous loading dose plus 50–150 mg twice daily) achieved more potent and rapid platelet inhibition than clopidogrel in patients undergoing elective PCI. This benefit was not associated with a significant increase in major or minor bleeding (45) (46). However, elinogrel was more commonly associated with elevation in liver enzymes than clopidogrel (45). At present time, there is no plan for Elinogrel to get engaged into a phase III program and thus to possible market approval.

3

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Table 1 Pharmacology of the three available GPIIb/IIIa inhibitors

	Abciximab	Eptifibatide	Tirofiban
Molecular weight (Da)	47.615	831.96	495.08
Molecular structure	Monoclonal antibody	Synthetic cyclic heptapeptide	Synthetic nonpeptide
Reversibility	No	Yes	Yes
Kd (nmol/L)	5	120	15
Affinity to GPIIb/IIIa	High	Low	High
Antigenicity	Yes	No	No
Duration of antiplatelet effect	For life of platelet	5 hours after discontinuation	4 hours after discontinuation
Half-life	10–30 minutes	2.5 hours	1.8 hours
Adjustment needed in renal insufficiency			
Mild (Cr/Cl >60 mL/min)	No	No	No
Moderate (Cr/Cl <60 mL/min)	No	Yes	No
Severe (Cr/Cl <30 mL/min or dialysis)	No	Contraindicated	Yes
Cost	$$$$ / €€€€	$$$ / €€	$$ / €€

Kd, constant of dissociation.

Table 2 Trials assessing different uses of abciximab

<col head>Downstream use				Upstream use	
	EPISTENT	ISAR-REACT 2	BRAVE 3	CAPTURE	GUSTO IV-ACS
Inclusion criteria	Elective, urgent or emergency PCI	NSTEMI	STEMI	Refractory unstable angina	NSTEMI
Patients (n)	2399	2022	800	1265	7800
Primary end point	Death and MI at 1-year follow-up	Death, MI, urgent TVR (30 days)	Infarct size measured by SPECT	Death, MI, urgent TVR (30 days)	Death and MI (30 days)
Results (abciximab vs placebo)					
Primary end point	5.3% vs 11.0% (*p* <0·001)	8.9% vs 11.9% (*p* = 0.03)	15.7% vs 16.6% (NS)	11.3% vs 15.9% (NS)	Abciximab 24-hour infusion: 8.2% vs 8% (NS) Abciximab 48-hour infusion: 9.1% vs 8% (NS)
Severe bleeding (TIMI criteria)		1.4 vs 1.4 % (NS)	1.8 vs 1.8 % (NS)	3.8% vs 1.9% (NS)	Abciximab 24 h infusion: 0.6% vs. 0.3% (ns) Abciximab 48 h infusion: 1% vs. 0.3% (P<0·05)

PCI, percutaneous coronary intervention; NSTEMI, non–ST-elevation myocardial infarction; MI, myocardial infarction; TVR, target vessel revascularization; SPECT, single-photon emission computed tomography; NS, nonsignificant.

Table 3 Trials assessing different uses of tirofiban

Downstream use				Upstream use	
	ADVANCE	On-TIME 2	3T/2R	PRISM	PRISM-PLUS
Inclusion criteria	Elective, urgent PCI	STEMI	Elective PCI	Unstable angina	SCA
Patients (n)	202	984	1277	3232	1915
Primary end point	Death, MI, urgent TVR, thrombotic bailout open-label tirofiban therapy	Extent of residual ST-segment deviation 1 hour after PCI	Troponin I/T elevation ≥ 3 ULN	Death, MI, or refractory ischemia at 48 hours	Death, MI, or refractory ischemia within 7 days after randomization
Results	(tirofiban vs placebo)			(tirofiban vs heparin)	Tirofiban plus heparin vs. Heparin
Primary end point	35% vs 20% (p = 0.01)	3.6<t#>mm vs 4.8<t#>mm (p = 0.003)	20.4% vs 35.1% (p = 0.009)	3.8% vs 5.6% (p = 0.01)	12.9% vs 17.9% (p = 0.004)
Severe bleeding (TIMI criteria)	0% vs 0% (NS)	4% vs 3% (NS)	0% vs 0% (NS)	0.4 % vs 0.4 % (NS)	4 % vs 3% (NS)

PCI, percutaneous coronary intervention; NSTEMI, non–ST-elevation myocardial infarction; SCA, acute coronary syndrome; MI, myocardial infarction; TVR, target vessel revascularization; ULN, upper limit of normal; NS, nonsignificant.

Table 4 Trials assessing different uses of eptifibatide

Table 4 Trials assessing different uses of eptifibatide

Downstream use			Upstream use	
	IMPACT-II	ESPRIT	PURSUIT	EARLY-ACS
Inclusion criteria	Elective, urgent or emergency PCI	Elective, urgent PCI	NSTEMI	NSTEMI
Patients (n)	4010	2064	10<t#>948	9492
Primary end point	All-causes death, nonfatal MI, urgent or emergency revascularization (30 days)	Death, MI, urgent TVR, thrombotic bailout open-label eptifibatide therapy (48 hours)	All-cause death, nonfatal MI (30 days)	Death, MI, urgent TVR, thrombotic bailout open-label eptifibatide therapy (96 hours)
Results (eptifibatide vs placebo)				
Primary end point	Eptifibatide 130/0.5 dose: 9.2% vs 11.4% (NS) Eptifibatide 130/0.75 dose: 9.9% vs 11.4% (NS)	6.6% vs 10.5% (p = 0·0015)	14.2% vs 15.7% (p = 0.04)	9.3% vs 10.0% (p = 0.23) (early vs delayed eptifibatide)
Severe bleeding (TIMI criteria)	Eptifibatide 130/0.5 dose: 5.1% vs 4.8% (NS) Eptifibatide 130/0.75 dose: 5.2% vs 4.8% (NS)	1.3% vs 0.4% (p = 0.027)	10.6% vs 9.1% (p = 0.02)	2.6% vs 1.8% (p = 0.02) (early vs delayed eptifibatide)

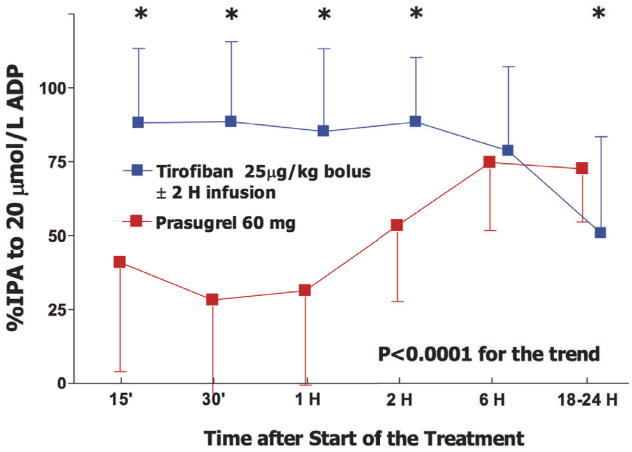

Fig. 1: Kinetics of Platelet Inhibition Over Time After 20 μmol/l ADP after treatment with tirofiban or prasugrel alone. To note the late action of prasugrel compared with tirofiban.
*p 0.05 versus %IPA measured in the prasugrel-alone group at post hoc analysis. Vertical bars represent SD of the mean value. Adapted with permission from Valgimigli M, Tebaldi M, Campo G, Gambetti S, Bristot L, Monti M, et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. JACC Cardiovascular interventions. 2012;5(3):268-77. (28)
IPA, inhibition of platelet aggregation

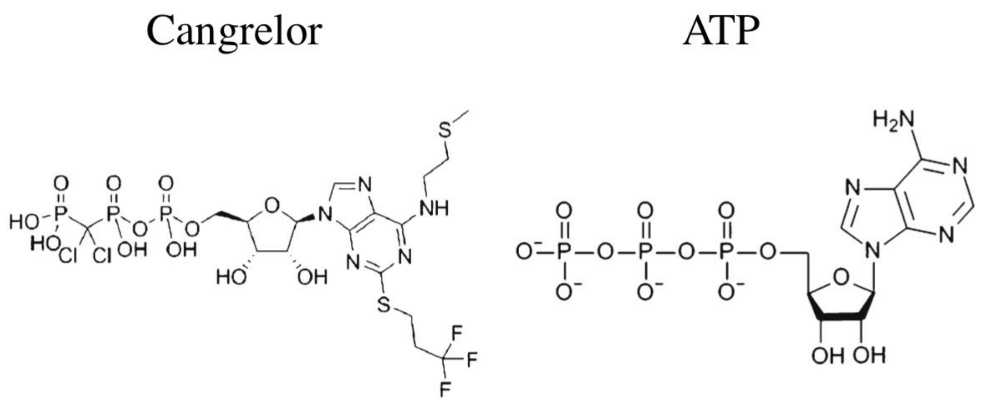

Fig. 2: Chemical structure of Cangrelor and ATP. Cangrelor is an analogue of ATP.

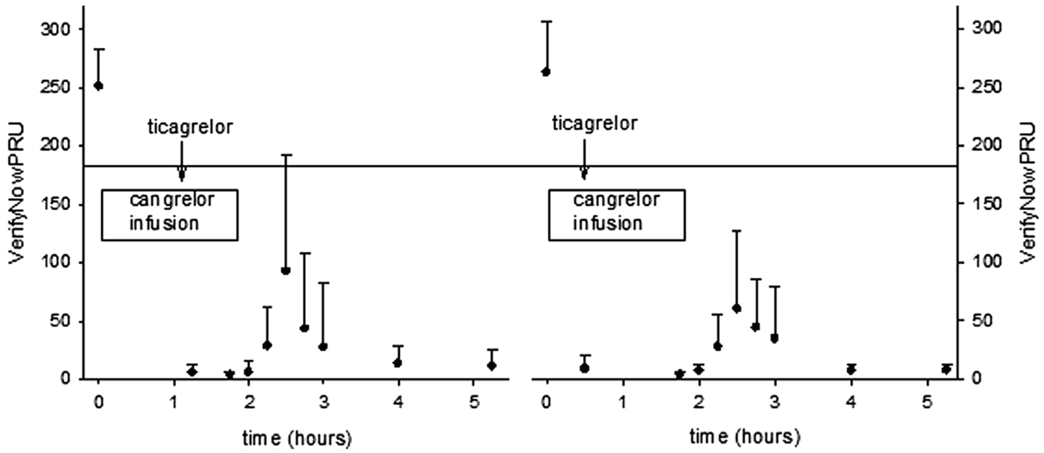

Fig. 3: Transition from Cangrelor to Ticagrelor
Evaluation of platelet reactivity through VerifyNow P2Y12 assay, before and during infusion of cangrelor and after the transition to ticagrelor. On the left are results from patients given ticagrelor at 1.25 h , and on the right are results from patients given ticagrelor at 0.5 h. Mean values plus the upper bound of the 95th percentile are shown. From Schneider DJ, Seecheran N, Raza SS, Keating FK, Gogo P. Pharmacodynamic effects during the transition between cangrelor and prasugrel. Coronary artery disease. 2014. (36)
<f/N> PRU, platelet reactivity unit.

	CHAMPION PCI	CHAMPION PLATFORM	CHAMPION PHOENIX
Patient population	70% troponin elevated at baselineP2Y12 inhibitor naivePlacebo or clopidogrel control (all patients received 600 mg) loaded at the end of PCI PCI required with: NSTEMI: troponin elevatedUA: ECG changes and pain and age/diabetes Stable angina: capped (15%)	70% troponin elevated at baselinePrevious chronic clopidogrel allowedPlacebo or clopidogrel control (all patients received 600 mg) loaded at the start of PCIPCI required with:STEMI: ECG changes including persistent (>20 min) ST-segment elevation in ≥2 contiguous leads NSTEMI: troponin elevatedUA: ECG changes and pain and age/diabetesStable angina: capped (15%)	35% troponin elevated at baselineP2Y12 inhibitor naivePlacebo or clopidogrel (300 mg or 600 mg) loaded at the start (96·5% and 50·5%) or at the end of PCI (3·5% and 49·5%)PCI required (stable angina, NSTE-ACS, STEMI)
Number of patients (mITT)	5301	8667	10 942
Comparator Endpoint	600 mg clopidogrel Loaded at the end of PCI Primary: death/MI/IDR at 48 h	600 mg clopidogrel Loaded at the end of PCI Primary: death/MI/IDR at 48 h	300 or 600 mg (per hospital standard of care) Loaded at the start or at the end of PCI per physician Primary: death/MI/IDR/ST at 48 h Key secondary: ST at 48 h
MI definition	Not UDMI: reliance on cardiac markers alone to define PCI MI1 baseline sampleBiomarker normal at baseline: MI defined as CK-MB ≥3×ULN post-PCI Biomarker elevated at baseline: elevation in CK-MB ≥3×ULN and 50% increase from baseline sample or ECG changes	Not UDMI: reliance on cardiac markers alone to define PCI MI1 baseline sampleBiomarker normal at baseline: MI defined as CK-MB ≥3×ULN post PCI Biomarker elevated at baseline: elevation in CK-MB ≥3×ULN and 50% increase from baseline sample or ECG changes	UDMI implemented: reliance on cardiac markers and other evidence of ischaemia to define PCI MI2 baseline samples ≥6 h apart required in NSTE-ACS patients to confirm resolving MI at baseline Baseline normal patients: MI defined as CK-MB ≥3×ULN post PCI Baseline abnormal patients were classified into MI increasing or decreasing at baseline:Increasing: re-elevation in CK-MB post PCI (≥3×ULN and 50% increase from baseline)+additional evidence of ischaemia (2 of 2): ECG changes AND angiographic evidence Decreasing: re-elevation in CK-MB post PCI (≥3×ULN and 50% increase from baseline)+additional evidence of ischaemia (at least 1 of 3): ischaemic symptoms, ECG changes, or angiographic evidence.
Stent thrombosis definition	Non-standard definitionAngiographic stent thrombosis associated with IDRConfirmed by clinical events committee using angiographic source data	Non-standard definitionAngiographic stent thrombosis associated with IDRConfirmed by clinical events committee using angiographic source data	Either definite stent thrombosis as per ARC definition, for post PCI eventsorintraprocedural stent thrombosis for events occurring within PCI=(any procedural new or worsened thrombus related to the stent, based on angiographic evidence)

Table 5: Comparison of design and characteristics of the Champion trials. Adapted from: Steg PG, et al; CHAMPION Investigators. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. Lancet. 2013 Dec 14;382(9909):1981–92. Steg PG 2013 (41) ACS, acuteelectrocardiogram. IDR, ischaemia-driven revascularization. MI, myocardial infarction. mITT, modified intention-to-treat. NSTE-ACS, non-ST- elevation acute coronary syndromes. NSTEMI, non-ST-segment elevation myocardial infarction. ST, stent thrombosis. STEMI, ST-segment elevation myocardial infarction. UA, unstable angina. UDMI, universal definition of myocardial infarction. ULN, upper limit of normal.

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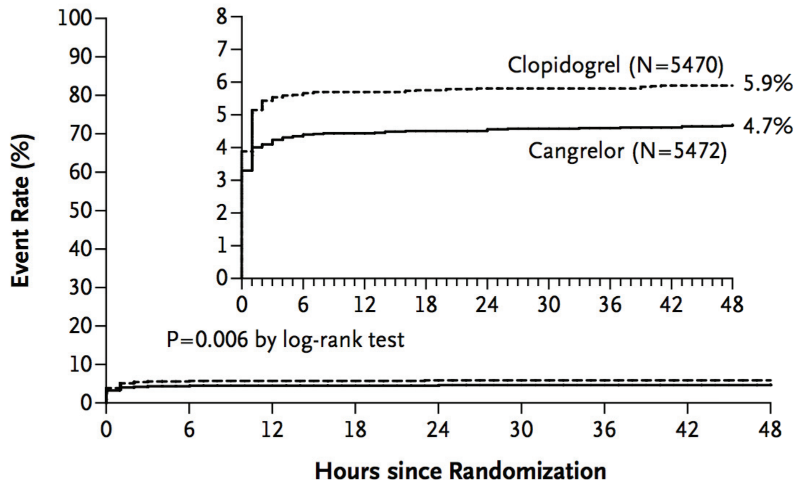
48 h (primary)	Cangrelor (n=12475)	Clopidogrel (n=12435)	Cangrelor vs clopidorel OR (95% CI)	p*
Death/MI/IDR/ST	473/12 459 (3.8%)	579/12 422 (4.7%)	0.81 (0.71–0.91)	0.0007
ST	62/12 459 (0.5%)	105/12 422 (0.8%)	0.59 (0.43–0.80)	0.0008
Death/MI/IDR	446/12 459 (3.6%)	543/12 422 (4.4%)	0.81 (0.71–0.92)	0.0014
Death/Q-wave MI/IDR	102/12 459 (0.8%)	150/12 422 (1.2%)	0.68 (0.52–0.87)	0.0022
Death	33/12 459 (0.3%)	45/12 422 (0.4%)	0.73 (0.47–1.15)	0.1694
MI	387/12 459 (3.1%)	453/12 422 (3.6%)	0.85 (0.74–0.97)	0.0182
IDR	66/12 459 (0.5%)	92/12 422 (0.7%)	0.71 (0.52–0.98)	0.0363
Q-wave MI	19/12 459 (0.2%)	36/12 422 (0.3%)	0.53 (0.30–0.92)	0.0211
Death/MI/ST	450/12 459 (3.6%)	550/12 422 (4.4%)	0.81 (0.71–0.92)	0.0011
Death/Q-wave MI/ST	103/12 459 (0.8%)	162/12 422 (1.3%)	0.63 (0.49–0.81)	0.0002
Death/MI	414/12 459 (3.3%)	495/12 422 (4.0%)	0.83 (0.73–0.95)	0.0054
Death/IDR	92/12 459 (0.7%)	130/12 422 (1.0%)	0.70 (0.54–0.92)	0.0098
Death/ST	89/12 459 (0.7%)	140/12 422 (1.1%)	0.63 (0.48–0.82)	0.0007
30 days				
Death/MI/IDR/ST	657/12 407 (5.3%)	748/12 357 (6.1%)	0.87 (0.78–0.97)	0.0099
ST	113/12 407 (0.9%)	162/12 357 (1.3%)	0.69 (0.54–0.88)	0.0027
Death/MI/IDR	631/12 407 (5.1%)	710/12 357 (5.7%)	0.88 (0.79–0.98)	0.0218
Death/Q-wave MI/IDR	287/12 407 (2.3%)	323/12 357 (2.6%)	0.88 (0.75–1.04)	0.1269

Death	137/12 407 (1.1%)	141/12 357(1.1%)	0.97 (0.76–1.23)	0.7832
MI	418/12 407 (3.4%)	487/12 357 (3.9%)	0.85 (0.74–0.97)	0.0165
IDR	153/12 407 (1.2%)	178/12 357 (1.4%)	0.85 (0.69–1.06)	0.1555
Q-wave MI	31/12 407 (0.2%)	51/12 357 (0.4%)	0.60 (0.39–0.95)	0.0257
Death/MI/ST	586/12 407 (4.7%)	681/12 357 (5.5%)	0.85 (0.76–0.95)	0.0049
Death/Q-wave MI/ST	238/12 407 (1.9%)	293/12 357 (2.4%)	0.81 (0.68–0.96)	0.0139
Death/MI	538/12 407 (4.3%)	609/12 357 (4.9%)	0.87 (0.78–0.98)	0.0266
Death/IDR	277/12 407 (2.2%)	301/12 357 (2.4%)	0.91 (0.78–1.08)	0.2895
Death/ST	224/12 407 (1.8%)	268/12 357 (2.2%)	0.83 (0.69–0.99)	0.0405

Table 6: Clinical efficacy outcomes at 48 h and at 30 days in the Champion trials. Adapted from: Steg PG, Bhatt DL, Hamm CW, Stone GW, Gibson CM, Mahaffey KW, Leonardi S, Liu T, Skerjanec S, Day JR, Iwaoka RS, Stuckey TD, Gogia HS, Gruberg L, French WJ, White HD, Harrington RA; CHAMPION Investigators. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. Lancet. 2013 Dec 14;382(9909):1981–92. Steg PG 2013 (41)



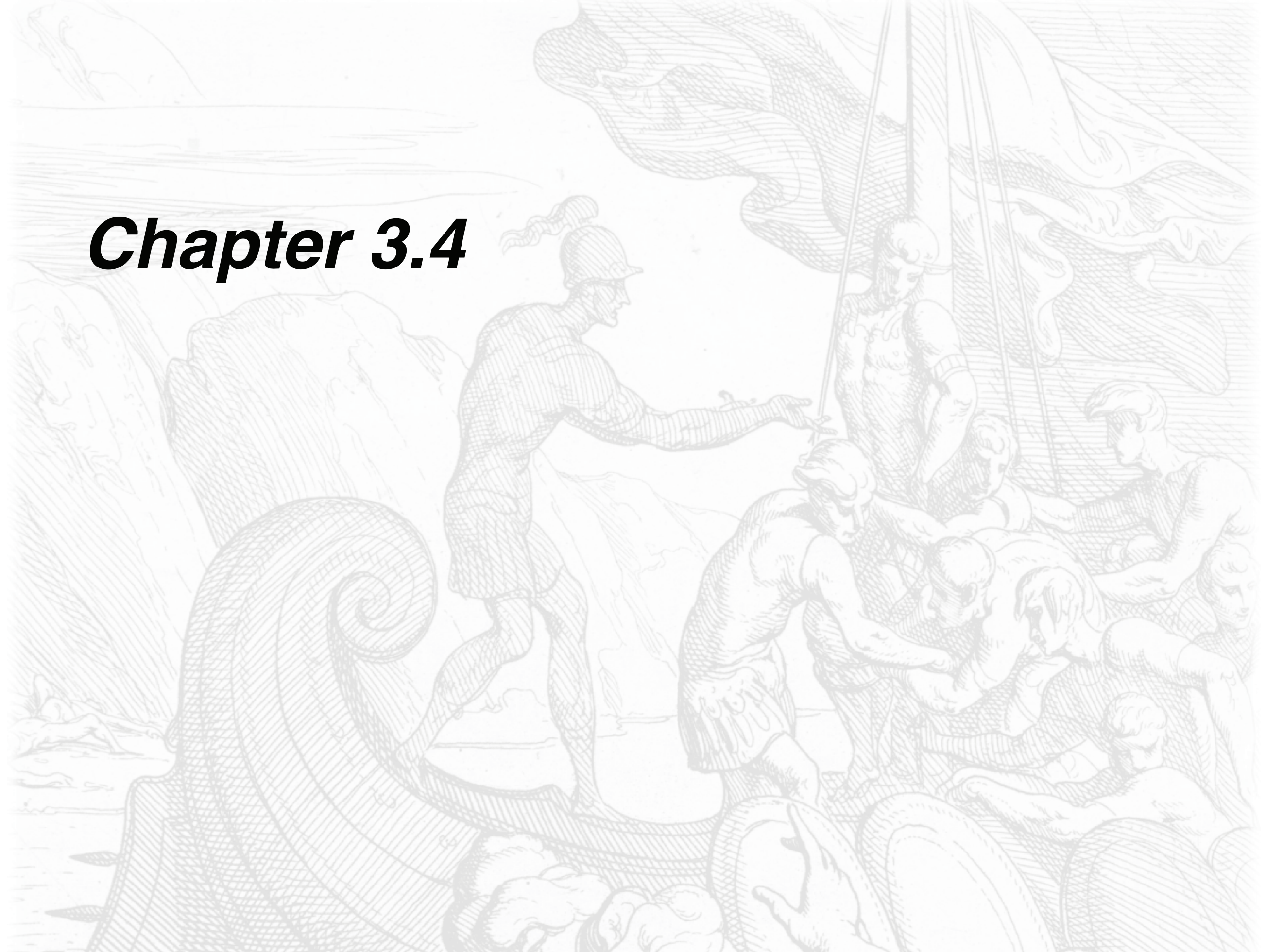
No. at Risk

Cangrelor	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel	5470	5162	5159	5155	5152	5151	5151	5147	5147

Fig. 4: Kaplan-Meier curves for the primary efficacy endpoint from the Champion Phoenix trial.

The primary efficacy endpoint was a composite of death for any cause, myocardial infarction, ischemia driven revascularization or stent thrombosis at 48 hours after randomization. From Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. The New England journal of medicine. 2013;368(14):1303-13. (41)

Chapter 3.4



Phosphate- or Citrate-buffered Tirofiban versus Unfractionated Heparin on the Rates of Thrombocytopenia and Outcomes in Patients With Non-ST Segment Elevation Acute Coronary Syndrome. A Post-hoc Analysis From The PRISM Trial

Marianna Adamo, Sara Ariotti, ***Francesco Costa***, Salvatore Curello, Aris Moschovitis, Ton de Vries, Harvey D. White, Stephan Windecker, Marco Valgimigli

JACC Cardiovasc Interv. 2016 Aug 22;9(16):1667-76 (Impact Factor: 8.841)

Phosphate- or Citrate-Buffered Tirofiban Versus Unfractionated Heparin and its Impact on Thrombocytopenia and Clinical Outcomes in Patients With Acute Coronary Syndrome

A Post Hoc Analysis From the PRISM Trial

3

Marianna Adamo, MD,[a,b] Sara Ariotti, MD,[a,c] Francesco Costa, MD,[a,d] Salvatore Curello, MD,[b] Aris Moschovitis, MD,[c] Ton de Vries, MA,[e] Harvey D. White, DSc,[f] Stephan Windecker, MD, PhD,[c] Marco Valgimigli, MD, PhD[a,c]

ABSTRACT

OBJECTIVES The aim of this study was to investigate whether the 2 tirofiban formulations tested in the early and late phases of the PRISM (Platelet Receptor Inhibitor in Ischemic Syndrome Management) trial might differ with respect to risk for thrombocytopenia and clinical outcomes compared with unfractionated heparin (UFH).

BACKGROUND Citrate-buffered tirofiban is currently marketed as brand-name drug. However, tirofiban has recently been promoted in some countries as a generic drug with different formulations, such as phosphate-buffered product.

METHODS In the PRISM trial 3,232 patients were randomly assigned to receive tirofiban or UFH. In the early phase, 879 patients were allocated to phosphate-buffered tirofiban and 874 patients to UFH group. After a protocol amendment due to a study drug instability report, citrate-buffered tirofiban replaced the phosphate-buffered formulation. Therefore, in the late phase, 737 and 742 patients were treated with citrate-buffered tirofiban and UFH, respectively.

RESULTS The relative risk for thrombocytopenia (nadir $<90,000/mm^3$ or $<100,000/mm^3$) was increased in patients treated with phosphate-buffered tirofiban in the early phase (odds ratio [OR]: 3.51; 95% confidence interval [CI]: 1.15 to 10.73; $p = 0.027$; and OR: 2.83; 95% CI: 1.11 to 7.22; $p = 0.029$, respectively) but not in patients treated with citrate-buffered tirofiban in the late phase (OR: 1.01; 95% CI: 0.20 to 5.05; $p = 0.987$; and OR: 0.99; 95% CI: 0.26 to 3.45; $p = 0.991$, respectively). Using a combined definition of thrombocytopenia (nadir $<150,000/mm^3$ or a decrease $\geq$50%), the randomization period significantly modified the effect of the treatment (tirofiban vs. UFH) on platelet decrease (p for interaction $= 0.024$). Thrombocytopenia was associated with a 5- to 10-fold increased risk for TIMI (Thrombolysis In Myocardial Infarction) bleeding and a 2-fold increased risk for net adverse cardiovascular events.

CONCLUSIONS Phosphate-buffered tirofiban, currently marketed as a generic drug, is associated with a higher rate of thrombocytopenia with a potentially increased risk for adverse clinical outcomes compared with citrate-buffered tirofiban. (J Am Coll Cardiol Intv 2016;9:1667–76) © 2016 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CI = confidence interval

GPI = glycoprotein IIb/IIIa inhibitor

HR = hazard ratio

MI = myocardial infarction

NACE = net adverse cardiovascular event

OR = odds ratio

RGD = arginine-glycine-aspartic acid

UFH = unfractionated heparin

Patients with acute coronary syndromes (ACS) are frequently treated with intravenous glycoprotein IIb/IIIa inhibitors (GPI) (1,2). Among these agents, tirofiban was first approved by the U.S. Food and Drug Administration in 1998. Since initial approval, the dose has been revised, and tirofiban given as a high-dose bolus is currently the most frequently used GPI (3,4).

PRISM (Platelet Receptor Inhibitor in Ischemic Syndrome Management) was the first randomized clinical study investigating the safety and efficacy of tirofiban, and it demonstrated a clinical benefit of this GPI compared with unfractionated heparin (UFH) with respect to acute ischemic events and 30-day mortality in the absence of an increased risk for bleeding. At variance with all other placebo-controlled studies, PRISM reported a significant increase in the rate of thrombocytopenia in the tirofiban compared with UFH group (5).

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Two different formulations of tirofiban were used in the PRISM trial in a sequential manner. After a protocol amendment due to a drug instability report, the phosphate-buffered product, which was used as the study drug during the early phase of the study, was replaced by the citrate-buffered formulation, which is currently marketed as a brand-name drug (Aggrastat; Correvio Ltd. in the United Kingdom and Medicure Pharma in the United States) (6). However, tirofiban has been recently promoted as a generic drug in several European countries with different formulations, such as phosphate-buffered tirofiban.

In this post hoc analysis of the PRISM trial, we sought to investigate whether the 2 tirofiban formulations used during the early and late phases of the study and currently marketed as generic and brand-name drugs might differ with respect to rates of thrombocytopenia and clinical outcomes compared with UFH.

METHODS

The design and the main findings of the PRISM trial were previously reported (5).

Briefly, PRISM was a randomized, controlled, multicenter, double-blind trial including patients with non-ST-segment elevation ACS. Patients were randomly assigned to receive tirofiban (bolus of 0.6 μg/kg/min over 30 min followed by 0.15 μg/kg/min infusion for 48 h) or UFH (bolus of 5,000 IU followed by infusion of 1,000 IU/h for 48 h, adjusted for activated partial thromboplastin time at 6 and 24 h).

During the early recruitment phase of the trial, tirofiban was administered as a phosphate-buffered product that ranged in concentration from 0.17 to 0.5 mg/ml; sodium chloride was used to render the product iso-osmotic. During the late recruitment phase, this composition was abandoned and substituted by a citrate-buffered product (10 mmol/l) containing sodium chloride. The change in composition was deemed necessary because of instability report of the phosphate-buffered composition and the finding of precipitates in vials stored for 24 months or more (6). Sodium porcine heparin was provided as 1,000 U/ml (10-ml fill) or as 10,000 U/ml (5-ml fill) without differences through the early and late recruitment phases.

STUDY ENDPOINTS. To maintain the randomization scheme, we primarily aimed to compare outcomes in patients treated with phosphate-buffered tirofiban versus UFH during the early phase and those treated with citrate-buffered tirofiban versus UFH during the late phase. As sensitivity analyses, we also compared patients receiving the 2 tirofiban formulations throughout the 2 different time periods.

Thrombocytopenia was defined as platelet nadir $<90{,}000/mm^3$ (used in the PRISM trial [5]), as platelet count $<100{,}000/mm^3$ (the most frequent cutoff used in previous studies [7–9]), and as a combination of nadir value $<150{,}000/mm^3$ and decrease of platelet count $\geq 50\%$ (used in a previous large registry [10]). Severe thrombocytopenia was defined as platelet count $<50{,}000/mm^3$.

We also investigated the 30-day ischemic endpoints reported in the PRISM trial (2): death, myocardial infarction (MI), refractory ischemia; readmission for unstable angina, a composite of major adverse cardiovascular events including all single endpoints previously mentioned and a composite of death and MI.

Bleeding events were defined according to the TIMI (Thrombolysis In Myocardial Infarction) classification (11).

Finally, a composite endpoint of net adverse cardiovascular events (NACEs) including major adverse cardiovascular events and major or minor TIMI bleeding was assessed.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD and were compared using the Student *t* test. Categorical variables were expressed as counts and percentages and were compared using the chi-square or Fisher exact test, as appropriate.

The proportionality assumptions were checked by visual estimation after plotting the log cumulative hazard versus (log) time at follow-up after the index procedure and by applying a test for nonproportional hazards using Schoenfeld residuals, which failed to reject the null hypothesis that bleeding and ischemic event rate was affected by time. Therefore, a multivariate Cox regression analysis stratified by center, including baseline variables differently distributed at an alpha level of 0.10, was performed to calculate the relative risk of these endpoints and to evaluate whether thrombocytopenia was an independent predictor of outcomes. Each result was expressed as hazard ratio (HR) and corresponding 95% confidence interval (CI).

A stepwise logistic regression model was used to calculate the relative risk for thrombocytopenia according to the 3 different definitions and adjusted for baseline imbalances. Each result was reported as odds ratio (OR) and corresponding 95% CI.

Interaction tests between randomization period (early vs. late) and treatment (tirofiban vs. UFH) were done with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero.

The Kaplan-Meier method was used to plot the cumulative incidence of bleeding events according to the presence of thrombocytopenia.

For all analyses, a 2-sided alpha value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, Illinois).

RESULTS

BASELINE CHARACTERISTICS AND DURATION OF STUDY DRUG INFUSION. In the PRISM trial, 3,232 patients were randomly assigned to receive tirofiban or UFH treatment. Before a formal study protocol amendment, during the early recruitment phase, 1,753 patients were enrolled, of whom 879 (50.1%) were allocated to the phosphate-buffered tirofiban group and 874 (49.9%) to the UFH arm. During the late recruitment phase, 737 of 1,479 patients (49.8%) were treated with citrate-buffered tirofiban and 742 (50.2%) with UFH.

The baseline features within the randomized arms during both the early and late recruitment periods are shown in Table 1. During the early phase, patients treated with UFH more frequently had prior coronary artery bypass graft surgery compared with those receiving phosphate-buffered tirofiban (20.4% vs. 16.5%, $p = 0.037$), whereas during the late phase, patients treated with UFH more commonly had non-ST-segment elevation MI compared with those receiving citrate-buffered tirofiban (27.4% vs. 21.4%, $p = 0.008$) (Table 1).

Among tirofiban-treated patients, those receiving citrate-buffered tirofiban more commonly had hypercholesterolemia (52% vs. 43.7%, $p < 0.001$) or previous heart failure (14.8 vs. 10.4%, $p = 0.007$),

TABLE 1 Baseline Features

	M1 (n = 879)	H1 (n = 874)	p Value, H1 vs. M1	M2 (n = 737)	H2 (n = 742)	p Value, H2 vs. M2	p Value, M1 vs. M2
Male	587 (66.8)	607 (69.5)	0.239	500 (67.8)	504 (68.4)	1.000	0.670
Age (yrs)	62 ± 11	62 ± 11	1.000	63 ± 11	62 ± 11	1.000	0.270
Race (white)	733 (83.4)	731 (83.6)	0.889	616 (83.6)	623 (84.5)	0.843	0.918
Smoking	234 (26.6)	243 (27.8)	0.359	185 (25.1)	180 (24.4)	0.880	0.646
Hypertension	477 (54.3)	470 (53.8)	0.848	399 (45.7)	412 (55.9)	0.602	0.960
Diabetes	182 (20.7)	199 (22.8)	0.298	147 (16.8)	159 (21.6)	0.521	0.710
Hypercholesterolemia	384 (43.7)	406 (46.5)	0.230	383 (52.0)	359 (48.7)	0.176	<0.001
Previous MI	416 (47.3)	405 (46.3)	0.679	340 (46.1)	356 (48.3)	0.498	0.652
Previous CABG	145 (16.5)	178 (20.4)	0.037	129 (17.5)	110 (14.9)	0.162	0.591
Previous PCI	125 (14.2)	144 (16.5)	0.190	104 (14.1)	107 (14.5)	0.941	0.950
History of heart failure	91 (10.4)	103 (11.8)	0.361	109 (14.8)	100 (13.5)	0.469	0.007
Clinical presentation			0.211			0.008	0.018
NSTEMI	223 (25.4)	209 (23.9)		158 (21.4)	203 (27.4)		
Unstable angina	656 (74.6)	665 (76.1)		579 (78.6)	539 (72.6)		
Multivessel disease*	373 (70.4)	364 (69.5)	0.747	277 (66.9)	311 (71.7)	0.134	0.253
Treatment							
CABG	162 (18.4)	146 (16.7)	0.570	134 (18.2)	123 (16.6)	0.413	0.421
PCI	177 (20.1)	167 (19.1)	0.588	171 (23.2)	185 (24.9)	0.436	0.728
Medical therapy	555 (63.1)	568 (65.0)	0.420	437 (59.3)	439 (59.2)	0.959	0.114

Values are n (%) or mean ± SD. *Calculated on patients who underwent coronary angiography (530 patients belonging to the phosphate-buffered group, 524 treated with unfractionated heparin in the early period, 414 receiving citrate-buffered tirofiban, and 434 treated with unfractionated heparin in the late period).

CABG = coronary artery bypass grafting; H1 = unfractionated heparin in the early phase; H2 = unfractionated heparin in the late phase; M1 = phosphate-buffered tirofiban in the early phase; M2 = citrate-buffered tirofiban in the late phase; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

whereas patients treated with phosphate-buffered tirofiban were more frequently admitted for non-ST-segment elevation MI (25.4% vs. 21.4%, $p = 0.018$) (**Table 1**).

Approximately 60% of patients underwent medical management, and 70% of patients undergoing coronary angiography had multivessel coronary artery disease, which did not differ across groups (**Table 1**).

The duration of study drug infusion was well matched across groups. Phosphate-buffered (early phase) and citrate-buffered (late phase) tirofiban formulations were infused for a mean of 45.1 ± 10.6 h and 44.8 ± 10.5 h, respectively, whereas UFH was administered for a mean of 45.5 ± 9.5 h and 45.1 ± 10.1 h during the early and late phases, respectively.

THROMBOCYTOPENIA. Baseline platelet counts did not differ across groups. The rate of thrombocytopenia was significantly higher during the early recruitment phase, when phosphate-buffered tirofiban was compared with UFH, using a cutoff of 90,000/mm^3 (1.7% vs. 0.5%, respectively, $p = 0.030$) or 100,000/mm^3 (2.0% vs. 0.7%, respectively, $p = 0.034$) but not during the late recruitment phase, when citrate-buffered tirofiban was compared with UFH (0.3% vs. 0.1% [$p = 0.621$] and 0.7% vs. 0.7% [$p = 0.971$]) (**Figure 1A**). The rate of thrombocytopenia did not differ across groups on the basis of platelet nadir value <150,000/mm^3 or decrease in platelet count ≥50% (**Figure 1A**).

Severe thrombocytopenia was observed in 4 patients treated with phosphate-buffered tirofiban versus none treated with UFH during the early recruitment phase (0.5% vs. 0%, $p = 0.046$) and in 1 patient treated with citrate-buffered tirofiban versus no patients allocated to the UFH group during the late recruitment phase (0.1% vs. 0%, $p = 0.49$).

Among tirofiban-treated patients, the rate of thrombocytopenia (nadir <90,000/mm^3 or <100,000/mm^3) was significantly higher in those treated with phosphate-buffered compared with those treated with citrate-buffered tirofiban, and a trend toward a more frequent platelet nadir <150,000/mm^3 or a decrease in platelet count ≥50% in patients receiving phosphate-buffer tirofiban was observed (**Figure 1A**).

On multivariate-adjusted analysis, the relative risk for thrombocytopenia (nadir <90,000/mm^3 or <100,000/mm^3) was approximately 3-fold higher in patients treated with tirofiban during the early (OR: 3.51; 95% CI: 1.15 to 10.73; $p = 0.027$; and OR: 2.83; 95% CI: 1.11 to 7.22; $p = 0.029$, respectively) but not during the late recruitment phase, although formal statistical testing for interaction did not reach conventional thresholds of significance (**Figure 1B**).

The randomization period, however, emerged as a possible treatment modifier with respect to the risk for thrombocytopenia under the combined definition of platelet nadir <150,000/mm^3 or decrease in platelet count ≥50% (p for interaction = 0.024) (**Figure 1B**).

Among patients receiving tirofiban, the phosphate-buffered formulation was associated with an increased risk for a platelet decrease <90,000/mm^3 (OR: 3.99; 95% CI: 1.13 to 14.05; $p = 0.031$) or 100,000/mm^3 (OR: 2.78; 95% CI: 1.02 to 7.63; $p = 0.047$) compared with citrate-buffered tirofiban.

CLINICAL ENDPOINTS AT 30 DAYS. After adjustment for baseline differences, citrate-buffered tirofiban was associated with a reduced risk for 30-day mortality compared with UFH (HR: 0.49; 95% CI: 0.27 to 0.89; $p = 0.019$), whereas no difference was observed between phosphate-buffered tirofiban and UFH (HR: 0.87; 95% CI: 0.49 to 1.54; $p = 0.629$). However, no significant interaction was observed between the randomization period and treatment with respect to the mortality endpoint (p for interaction = 0.151) (**Figure 2**). There were no differences between tirofiban and UFH with regard to other explored ischemic or bleeding endpoints (**Figure 2**).

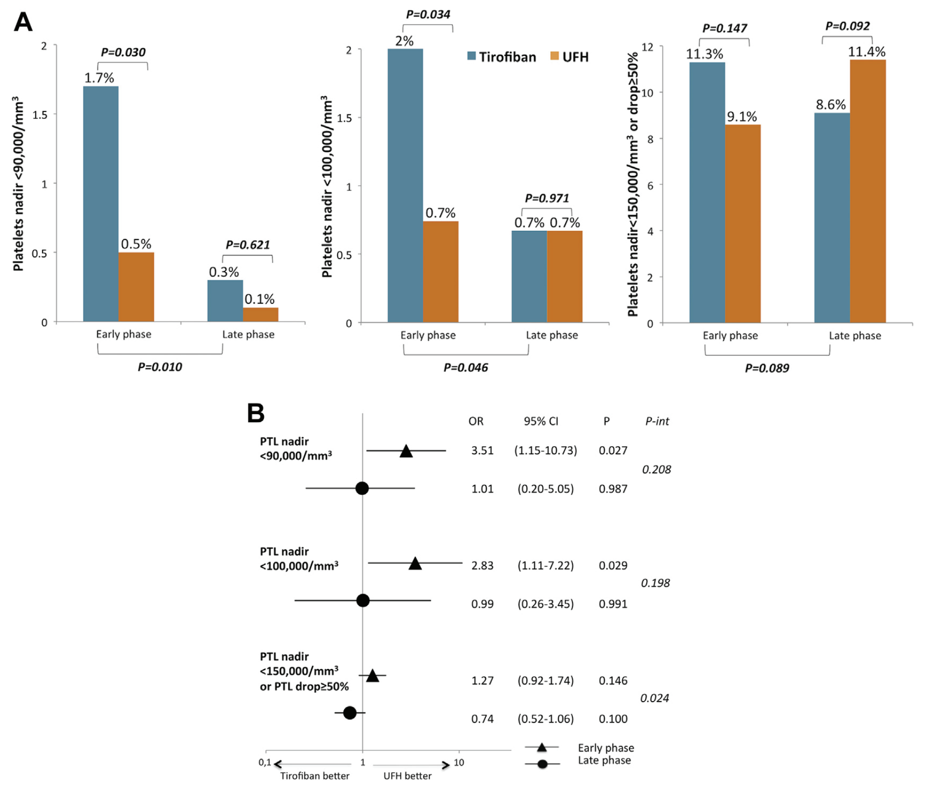
Among tirofiban treated patients, no significant differences were noted between the 2 tirofiban formulations with respect to 30-day mortality and other clinical endpoints. A trend toward a higher rate of refractory ischemia in the citrate-buffered group was observed (Online Table 1).

THROMBOCYTOPENIA EFFECT ON ISCHEMIC AND BLEEDING OUTCOMES. Baseline characteristics of patients who did compared with those who did not develop thrombocytopenia according to different definitions are reported in **Table 2** and Online Table 2.

Premature study drug discontinuation was deemed necessary in approximately 50% of patients among those who developed thrombocytopenia (platelet nadir <90,000/mm^3 or 100,000/mm^3), whereas this was infrequent in patients without thrombocytopenia (45.8% vs. 1.7% and 42.2% vs. 1.6%, respectively, $p < 0.001$ for all).

After adjustment for differences in baseline characteristics, thrombocytopenia was associated with a 5- to 10-fold increased risk for TIMI minor or major bleeding (**Figure 3**) and major bleeding (**Table 3**, Online Table 3). Patients who experienced a platelet nadir <100,000/mm^3 also had a 2-fold increased risk for NACEs (HR: 2.36; 95% CI: 1.31 to 4.23; $p = 0.004$) (**Table 3**). Under the combined definition, a trend toward a higher risk for refractory ischemia was observed in patients with thrombocytopenia (**Table 3**).

FIGURE 1 **Thrombocytopenia in Patients Treated With Tirofiban or Unfractionated Heparin in the Early and Late Phases According To Different Definitions**

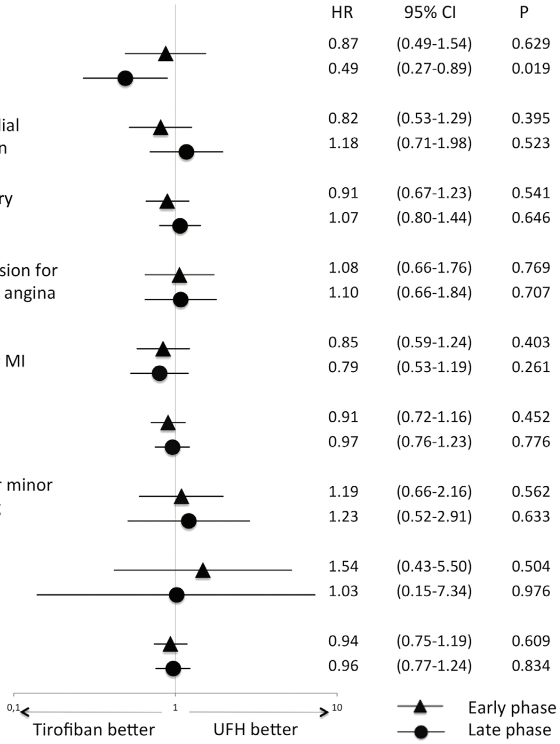


(A) The incidence of thrombocytopenia (platelet nadir <90,000/mm^3 or 100,000/mm^3) was significantly higher in patients receiving tirofiban versus unfractionated heparin (UFH) in the early phase but not in the late phase. Among tirofiban-treated patients, a higher incidence of thrombocytopenia was observed in the phosphate-buffered (early-phase) versus citrate-buffered (late-phase) group. **(B)** An increased relative risk for thrombocytopenia (platelet nadir <90,000/mm^3 or 100,000/mm^3) was reported in patients treated with phosphate-buffered tirofiban versus UFH in the early phase. The randomization period was a treatment modifier with respect to the risk for platelet decrease <150,000/mm^3 or ≥50%. CI = confidence interval; OR = odds ratio; PTL = platelet.

DISCUSSION

The main findings of the present study can be summarized as follows. 1) Patients treated with phosphate-buffered tirofiban during the early recruitment phase of the PRISM trial more frequently experienced thrombocytopenia, with a 3-fold increased risk for platelet decrease <90,000/mm^3 or 100,000/mm^3 compared with those receiving UFH during the same randomization period. No difference was observed between citrate-buffered tirofiban and UFH during the late recruitment phase. 2) The randomization period (early vs. late) significantly modified the effect of treatment (tirofiban vs. UFH) with respect to the risk for thrombocytopenia (platelet nadir <150,000/mm^3 or decrease in platelet count ≥50%). 3) Outside the randomization scheme, phosphate-buffered tirofiban was associated with a significantly higher risk for thrombocytopenia (platelet nadir <90,000/mm^3 or 100,000/mm^3) compared with the corresponding citrate-buffered product. 4) Thrombocytopenia was confirmed to be an independent predictor of adverse outcomes, with a 5- to 10-fold increased risk for TIMI minor or major bleeding and a 2-fold increased risk for NACEs. 5) After adjustment for baseline differences, citrate-

FIGURE 2 **Clinical Outcomes at 30 Days in Patients Treated With Tirofiban Versus Unfractionated Heparin According to Randomization Phase**



Outcome	HR	95% CI	P	*P-int*
Death	0.87	(0.49-1.54)	0.629	*0.151*
	0.49	(0.27-0.89)	0.019	
Myocardial infarction	0.82	(0.53-1.29)	0.395	*0.318*
	1.18	(0.71-1.98)	0.523	
Refractory angina	0.91	(0.67-1.23)	0.541	*0.518*
	1.07	(0.80-1.44)	0.646	
Readmission for unstable angina	1.08	(0.66-1.76)	0.769	*0.934*
	1.10	(0.66-1.84)	0.707	
Death or MI	0.85	(0.59-1.24)	0.403	*0.724*
	0.79	(0.53-1.19)	0.261	
MACE	0.91	(0.72-1.16)	0.452	*0.861*
	0.97	(0.76-1.23)	0.776	
Major or minor Bleeding	1.19	(0.66-2.16)	0.562	*0.954*
	1.23	(0.52-2.91)	0.633	
Major Bleeding	1.54	(0.43-5.50)	0.504	*0.737*
	1.03	(0.15-7.34)	0.976	
NACE	0.94	(0.75-1.19)	0.609	*0.956*
	0.96	(0.77-1.24)	0.834	

The relative risk for death was 50% reduced in patients treated with tirofiban versus unfractionated heparin (UFH) in the late but not in the early phase. CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; NACE = net adverse cardiovascular event.

buffered tirofiban was associated with a reduced risk for death compared with UFH, whereas no difference in mortality was observed between phosphate-buffered tirofiban and UFH.

TIROFIBAN USE AND FORMULATIONS. American College of Cardiology and American Heart Association guidelines suggest the administration of GPIs in high-risk patients with non-ST-segment elevation ACS undergoing percutaneous coronary intervention irrespective of pre-treatment status with $P2Y_{12}$ inhibitors (12,13). European Society of Cardiology guidelines recommend GPIs for patients with ACS in bailout situations or with thrombotic complications (14,15). As a result, these drugs are frequently used in clinical practice in patients with ACS undergoing invasive management, and tirofiban is currently the most frequently used GPI worldwide.

Citrate-buffered tirofiban is marketed as brand-name product (Aggrastat, Correvio [UK] Ltd. and Medicure Pharma [US]). In several European countries, tirofiban is marketed as a generic drug with formulations different from the citrate-buffered, including phosphate-buffered tirofiban (Hexal, Hikma, and MEDAC). No generic tirofiban products are currently marketed in the United States. Seven generic versions are available in India; at least 1 of these is a citrate-buffered product (Gland Pharma). No information regarding the excipients is in the public domain for the remaining 6 products.

THROMBOCYTOPENIA AND OUTCOMES. The association between thrombocytopenia and adverse clinical outcomes in the setting of ACS is well established, and patients receiving GPIs should be carefully scrutinized for changes in platelet count during and

TABLE 2 Baseline Characteristics of Patients With or Without Thrombocytopenia According to Different Definitions (Platelet Nadir <100,000/mm³ and Platelets Decrease <150,000/mm³ or ≥50%)

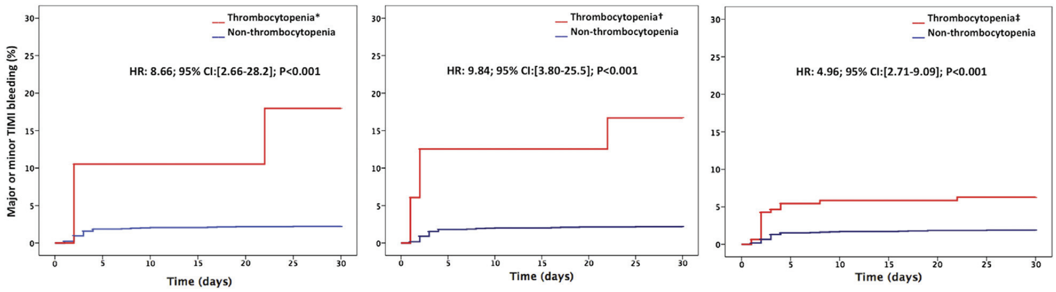
	TCP* (n = 33)	Non-TCP (n = 3,056)	p Value	TCP† (n = 312)	Non-TCP (n = 2,777)	p Value
Male	24 (72.7)	2,085 (68.2)	0.581	235 (75.3)	1,874 (67.5)	0.005
Age (yrs)	64.0 ± 11.0	62.4 ± 11.1	0.405	64.5 ± 10.9	62.2 ± 11.1	<0.001
Race (white)	28 (84.8)	2,561 (83.8)	0.871	264 (84.6)	2,325 (83.7)	0.746
Smoking	7 (21.2)	795 (26.0)	0.531	65 (20.8)	737 (26.5)	0.029
Hypertension	21 (63.6)	1,656 (54.2)	0.279	178 (57.1)	1,499 (54.0)	0.309
Diabetes mellitus	12 (36.4)	641 (21.0)	0.031	90 (28.8)	563 (20.3)	0.001
Hypercholesterolemia	12 (36.4)	1,458 (47.7)	0.194	131 (42.0)	1,339 (48.2)	0.042
Previous MI	18 (54.5)	1,441 (47.2)	0.398	156 (50.0)	1,303 (46.9)	0.310
Previous CABG	7 (21.2)	533 (17.4)	0.571	72 (23.1)	468 (16.9)	0.007
Previous PCI	5 (15.2)	454 (14.9)	0.962	51 (16.3)	408 (14.7)	0.450
History of heart failure	6 (18.2)	377 (12.3)	0.311	48 (15.4)	335 (12.1)	0.102
Baseline PTL (n/mm³)	194.5 ± 56.0	240.2 ± 60.4	<0.001	246.4 ± 58.4	180.5 ± 46	<0.001
Clinical presentation (MI)	12 (36.4)	758 (24.8)	0.127	96 (30.8)	674 (24.3)	0.013

Values are n (%) or mean ± SD. *TCP was defined as platelet nadir <100,000/mm³. †TCP was defined as platelet nadir <150,000/mm³ or platelet decrease ≥50%. PTL = platelets; TCP = thrombocytopenia; other abbreviations as in Table 1.

immediately after drug administration. Patients who experience significant platelet decreases after GPI administration are at increased risk for bleeding, recurrent MI, and death (7-10). In the Global Registry of Acute Coronary Events (GRACE) population, thrombocytopenia after GPI treatment was associated with a 4-fold increased risk for in-hospital mortality and a 2- to 3-fold increased risk for stroke and recurrent infarction (16). In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) registry, patients who developed thrombocytopenia had a 3- and 4-fold increased risk for mortality and bleeding, respectively (10). In the PRISM population, thrombocytopenia emerged as an independent predictor of both bleeding and ischemic clinical outcomes, with a 5- to 10-fold increased risk for TIMI bleeding, a 2-fold increased risk for NACEs, and a trend toward an increased risk for refractory ischemia at 30-day follow-up. The lack of an association between thrombocytopenia and mortality in our cohort of patients may reflect a type II error.

MECHANISM OF THROMBOCYTOPENIA. Drug-induced immune thrombocytopenia is a common hematologic problem. More than 200 drugs have been reported to

FIGURE 3 Effect of Thrombocytopenia on Bleeding



The cumulative incidence of minor or major TIMI (Thrombolysis in Myocardial Infarction) bleeding was significantly higher in patients who did compared with those who did not experience thrombocytopenia, regardless of definition. *Thrombocytopenia with platelet nadir <90,000/mm³. †Thrombocytopenia with platelet nadir <100,000/mm³. ‡Thrombocytopenia with platelet nadir <150,000/mm³ or decrease ≥50%. CI = confidence interval; HR = hazard ratio.

TABLE 3 Clinical Outcomes in Patients With or Without Thrombocytopenia According to Different Definitions (Platelet Nadir <100,000/mm^3 and Platelet Decrease <150,000/mm^3 or ≥50%)

	TCP* (n = 33)	Non-TCP (n = 3,056)	Adjusted HR† (95% CI)	p Value	TCP‡ (n = 312)	Non-TCP (n = 2,777)	Adjusted HR§ (95% CI)	p Value
Death	1 (3.0)	89 (2.9)	1.10 (0.15–8.08)	0.924	13 (4.2)	77 (2.8)	1.34 (0.70–2.53)	0.376
MI	3 (9.0)	128 (4.2)	2.48 (0.77–8.00)	0.128	16 (5.1)	115 (4.1)	1.18 (0.67–2.07)	0.570
Refractory ischemia	5 (15.2)	326 (10.7)	1.55 (0.63–3.78)	0.341	45 (14.4)	286 (10.3)	1.40 (1.00–1.97)	0.052
Readmission for UA	2 (0.6)	119 (3.9)	1.87 (0.45–7.76)	0.387	10 (3.2)	111 (4.0)	0.72 (0.36–1.45)	0.363
Death or MI	4 (12.1)	195 (6.4)	2.01 (0.73–5.51)	0.176	25 (8.0)	174 (6.3)	1.13 (0.72–1.77)	0.605
MACEs	9 (27.3)	504 (16.5)	1.71 (0.87–3.34)	0.118	60 (19.2)	453 (16.3)	1.11 (0.83–1.48)	0.493
Minor or major bleeding	5 (15.2)	61 (2)	9.84 (3.80–25.5)	<0.001	19 (6.1)	47 (1.7)	4.96 (2.71–9.09)	<0.001
Major bleeding	1 (3.0)	12 (0.4)	11.2 (1.42–87.5)	0.022	4 (1.3)	9 (0.3)	6.40 (1.81–22.6)	0.004
NACEs	12 (36.4)	542 (17.7)	2.36 (1.31–4.23)	0.004	71 (22.8)	483 (17.4)	1.27 (0.97–1.67)	0.087

*TCP was defined as platelet nadir <100,000/mm^3. †Variables used for the adjustment were diabetes mellitus and baseline platelet value. ‡TCP was defined as platelet nadir <150,000/mm^3 or platelet decrease ≥50%. §Variables used for the adjustment were age, male sex, smoking, diabetes mellitus, hypercholesterolemia, prior coronary artery bypass graft surgery, non-ST-segment elevation MI, and baseline platelet value.

CI = confidence interval; HR = hazard ratio; MACE = major cardiovascular adverse event; NACE = net cardiovascular adverse events; UA = unstable angina; other abbreviations as in Tables 1 and 2.

cause immune thrombocytopenia (17); these include commonly used drugs such as antibiotics, anticonvulsants, and arginine-glycine-aspartic acid (RGD) mimetic agents such as tirofiban and eptifibatide. Immune thrombocytopenia can occur on first exposure to an RGD mimetic agent, and the platelet count usually drops abruptly within hours of commencement of drug administration (18), suggesting the presence of a naturally occurring antiplatelet antibody. Binding of fibrinogen, RGD peptides, or RGD mimetic drugs to the RGD recognition site of αIIbβ3 induces conformational changes and the emergence of cryptic epitopes previously "unseen" by the immune system (18). In the majority of patients with eptifibatide- and tirofiban-induced thrombocytopenia, antibody binding was found to be drug specific (19,20).

Extrapolating these findings to our analysis, it may be speculated that conformational changes in αIIbβ3 induced by phosphate-buffered tirofiban are more frequently recognized by naturally occurring antiplatelet antibodies compared with citrate-buffered tirofiban, thereby being more frequently associated with thrombocytopenia.

Our findings confirm previous observations that thrombocytopenia appears to be more a drug- than a class-specific side effect (21-23). The current observation that 2 distinct tirofiban formulations, which exert comparable antiplatelet effects, are associated with a remarkable difference in terms of drug safety, notably thrombocytopenia, reinforces the notion that the chemical structure of a given drug more than its anticipated target effect is associated with the risk for thrombocytopenia.

GENERIC DRUGS AND SIDE EFFECTS. Our current observation should also raise a word of caution with respect to current regulations for generic drug approval. The main principle underpinning the safe and effective use of generic drugs is the concept of bioequivalence (24).

The purpose of establishing bioequivalence is to demonstrate equivalence between a generic medicine and the original medicine in order to allow extrapolation of the pre-clinical and clinical testing performed with the original drug.

Although the active pharmaceutical ingredient does not differ between original and generic medicines, other (supposedly inactive) ingredients, known as excipients, may differ, and a number of pharmaceutical excipients are known to cause adverse effects or result in contraindications (25). As excipients may differ between originator medicines and generic preparations, which have been shown to be bioequivalent and therefore substitutable, there needs to be an awareness in the medical and health care community of differences in excipients and thus, the potential for generic formulations to induce safety issues. This may be particularly relevant when treating life-threatening disease such as ACS. Evidence has been published that differences in excipients between originator medications and their generic counterparts can cause problems (26,27); our present findings expand on previous observations (28).

STUDY LIMITATIONS. First, the analysis was not prespecified, and the small number of events, in particular with regard to thrombocytopenia, may have affected the results. However, sensitivity analyses performed using different definitions of thrombocytopenia and comparing patients treated with tirofiban versus UFH during the early versus late recruitment phases and patients receiving the 2 tirofiban formulations throughout the 2 different periods provided consistent results.

Second, in the PRISM trial, tirofiban was used as upstream treatment, which is discouraged in current guidelines, and was administered at a bolus dose of 0.6 μg/kg/min for 30 min followed by 0.15 μg/kg/min infusion for 48 h. This treatment modality differs from the approved high-dose bolus regimen of 25 μg/kg over 3 min, followed by 0.15 μg/kg/min infusion up to 48 h, which is currently used in clinical practice. However, the difference in the total dose of tirofiban administered according to the PRISM regimen versus the one currently in use is negligible. In a patient weighing 70 kg with normal renal function undergoing 48-h post-bolus infusion, the total drug exposure is 31.5 mg in 48.5 h for the PRISM scheme and 32 mg in 48.05 h for current use.

Third, the bleeding events were classified using the TIMI criteria because at the time of study recruitment, the Bleeding Academic Research Consortium classification was not available.

CONCLUSIONS

Phosphate-buffered tirofiban, currently marketed as a generic drug in several countries, is associated with a higher risk for thrombocytopenia and potentially increased risk for adverse clinical outcomes compared with a citrate-buffered tirofiban formulation. Careful post-marketing surveillance of both the brand-name and generic formulations of tirofiban is warranted.

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PERSPECTIVES

WHAT IS KNOWN? Citrate-buffered tirofiban is currently marketed as a brand-name drug, whereas a phosphate-buffered product has recently been promoted as a generic drug in several European countries. In the PRISM trial, the 2 tirofiban formulations were used in the late and early phases of the study, respectively.

WHAT IS NEW? Phosphate-buffered tirofiban is associated with a higher rate of thrombocytopenia with potentially increased risk for adverse outcomes compared with citrate-buffered formulation.

WHAT IS NEXT? Post-marketing surveillance of the different tirofiban formulations is needed to ascertain whether brand-name tirofiban has a better safety profile compared with the generic products.

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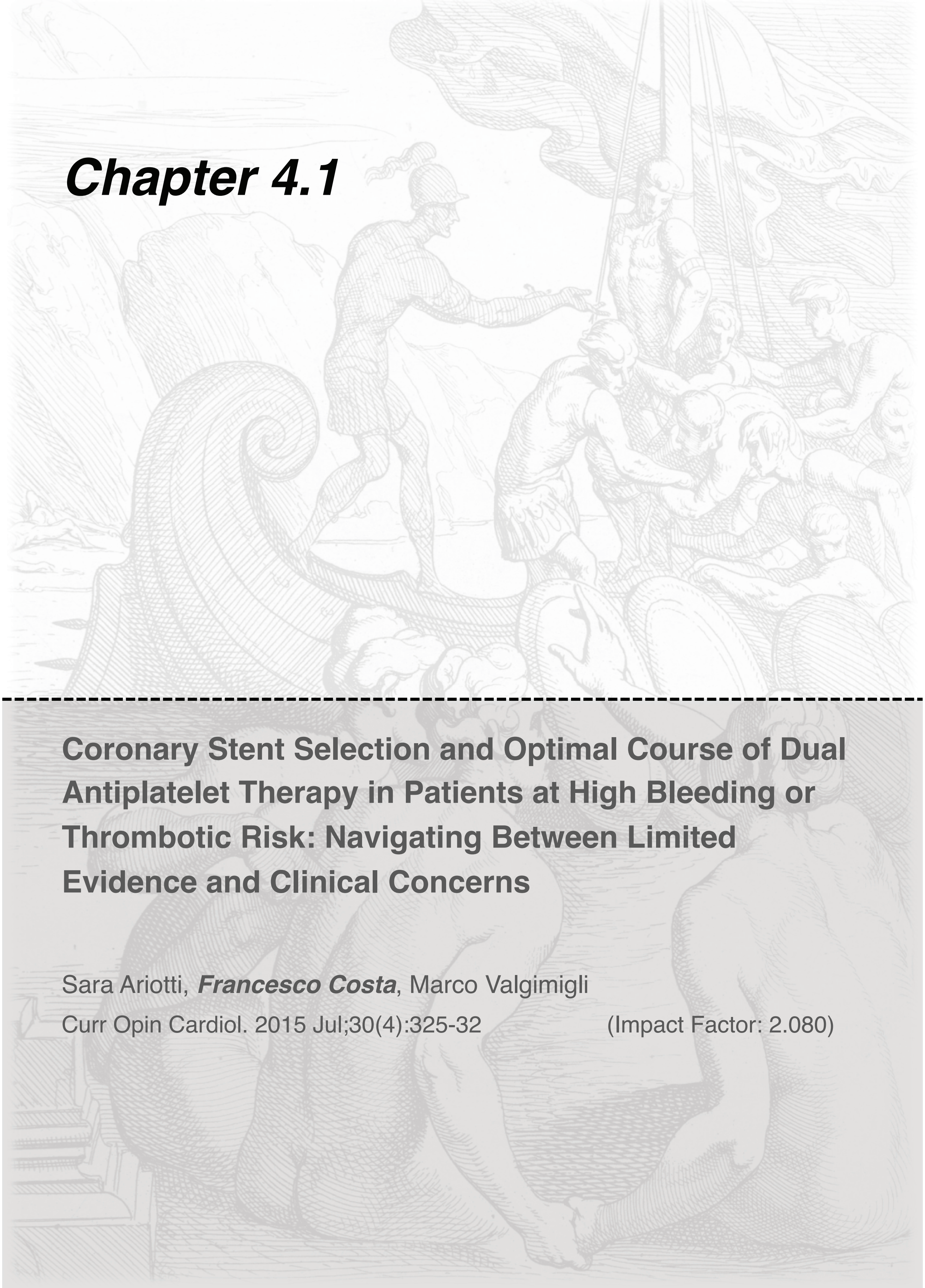
KEY WORDS buffers, non-ST-segment elevation acute coronary syndrome, thrombocytopenia, tirofiban

APPENDIX For supplemental tables, please see the online version of this article.

Part 4

Trade-off for Ischemia and bleeding in the early period after percutaneous coronary intervention



Chapter 4.1

Coronary Stent Selection and Optimal Course of Dual Antiplatelet Therapy in Patients at High Bleeding or Thrombotic Risk: Navigating Between Limited Evidence and Clinical Concerns

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CURRENT OPINION

Coronary stent selection and optimal course of dual antiplatelet therapy in patients at high bleeding or thrombotic risk: navigating between limited evidence and clinical concerns

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Purpose of review

Optimal duration of dual antiplatelet therapy (DAPT) after coronary revascularization, in particular after drug-eluting stent (DES) implantation, is a matter of ongoing debate.

Recent findings

First generation of DES, as compared with bare metal stents (BMS), reduce restenosis rates but increase very late stent thrombosis rates, thus requiring a prolonged course of DAPT. As a consequence, patients with high thrombotic and/or bleeding risk: have been systematically excluded from randomized trials comparing DES versus BMS; remain 'uncertain' DES candidates; should preferentially undergo BMS implantation at the time of percutaneous coronary intervention instead of DES. The Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) trial is the first randomized study that demonstrated the superiority of the Zotarolimus-eluting Endeavor Sprint versus BMS in uncertain DES candidates who followed a personalized DAPT duration, which was tailored to patients's, not stent's, characteristics.

Summary

The results of the ZEUS trial may support a paradigm shift in our current understanding of the most proper use of DES in practice and should trigger further research in patients at high bleeding or thrombotic risk, who have been so far largely deprived of the potential benefit provided by DES.

Keywords

drug-eluting stents, dual antiplatelet therapy, high bleeding risk, high thrombotic risk, Zotarolimus-eluting stent

INTRODUCTION

Cardiovascular disease is the main cause of death in industrialized countries and coronary artery disease (CAD) is the most common cause of cardiovascular events, and is associated with high morbidity and mortality due to myocardial infarction (MI), heart failure, and ventricular arrhythmias [1]. The majority of patients admitted to the hospital with diagnosis of CAD, whether silent ischemia, stable angina (SCAD), unstable angina, non ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI), undergo percutaneous revascularization with stent implantation.

STENT THROMBOSIS AND DUAL ANTIPLATELET THERAPY: FROM INCEPTION TO MAINSTREAM

The threat of acute or subacute (i.e., within the first 30 days) stent thrombosis has accompanied percutaneous coronary intervention since the early days of stent intervention [2]. The initial attempts to mitigate that risk with aspirin, a single antiplatelet therapy, in conjunction with parenteral and oral anticoagulant medications, paved the way for the dual antiplatelet therapy (DAPT) regimen consisting of a P2Y12 inhibitor, at that time, ticlopidine, and aspirin, an irreversible cyclooxygenase-1 (COX-1) inhibitor [3,4]. This dual-pathway antiplatelet therapy was shown to be more effective and well tolerated than aspirin in combination with other previously explored antithrombotic medications,

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KEY POINTS

- Drug-eluting stents (DES) *per se* are regarded as more thrombogenic devices and as such they should not be implanted in patients who cannot tolerate or undergo a prolonged course of dual antiplatelet therapy (DAPT).
- Patients at high bleeding or thrombotic risk, including advanced age, requiring anticoagulation therapy, recent or previous bleeding requiring medical attention, presenting allergy/intolerance to aspirin or any available P2Y12-inhibitor, planned surgery within 12 months of percutaneous coronary intervention, or cancer have been so far excluded from trials, and international guidelines still today recommend bare metal stents (BMS) preferentially over DES.
- The recent Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) trial provided new evidence that patients at high bleeding or thrombotic risk may have improved outcomes after Zotarolimus-eluting Endeavor Sprint implantation followed by a personalized short DAPT duration as compared with BMS.
- Further research in the field is awaited to confirm and extend current findings to other new generation, potentially more efficacious DES platforms.

including vitamin K antagonists [3,4]. As the majority of stent thrombosis cases were noted to occur within the first weeks after stent implantation, an arbitrary 30-day [3,4] to 6 weeks [5] duration of DAPT has been investigated in studies, and as a consequence a 30-day duration of therapy has become the standard of care approach after bare metal stent (BMS) implantation.

Yet, proper stent expansion was also acknowledged in these early days as a key factor to minimize the risk of stent reocclusion [6], and optimal stent expansion in some DAPT studies even as a prerequisite for patients' eligibility [3,4]. Since then, the multifactorial nature of stent thrombosis has been well characterized across literature [7].

The advent of first-generation drug-eluting stents (DES) has triggered renewed interest in reassessing optimal DAPT duration after stent placement. In the absence of complete supportive evidence, DES *per se* have been initially regarded as more thrombogenic devices. This was due to their intrinsic capability to minimize late loss and as such potentially compromise stent coverage. Inflammation was also noted in experimental animal models. In the pivotal studies designed for stent approval, DAPT was recommended for 2 [8] or 3 [9] months after sirolimus-eluting stent implantation or 6 months [10] after paclitaxel-eluting stent studies. No safety issues were noted early on, up to at least 1 year, as compared with the uncoated stents [8–10].

Following the observation that first-generation DES were associated with higher mortality as compared with traditional BMS [11], the community reacted by endorsing a long-term, or even an indefinite, DAPT regimen after DES implantation, and also continued the development of novel materials, designs, and delivery systems, with biocompatible polymers, and new antiproliferative agents compared with their predecessors.

The mechanistic interpretation behind the postulated higher mortality hazard after first-generation DES was centered on the perceived higher risk of stent thrombosis associated with these devices [11]. An extraordinary amount of scientific scrutiny has been devoted to the safety profile of first-generation DES, which has populated general medicine and more specialized journals since their introduction into the market. Although results from registries have been inconsistent (perhaps not surprisingly, given the relatively low incidence of stent thrombosis and the presence of residual unmeasured confounders), there has not been a single randomized controlled study or meta-analysis of randomized studies showing that the risk of early, including either acute or subacute, as well as late (from 30 days to 1 year) stent thrombosis is higher after first-generation DES as compared with BMS [12]. Meta-analysis has actually provided evidence that the risk of stent thrombosis within the first year may be lower after first-generation DES as compared with BMS [13].

On the contrary, first-generation DES were consistently shown later on to be associated with four-fold to five-fold higher risk of very late (i.e., after the first year) stent thrombosis as compared with BMS [12,13]. This observation corroborated the perception of increased thrombogenicity of DES as compared with BMS and fueled 'the longer the better notion' for DAPT duration in DES-treated patients [14]. Although underpowered for stent thrombosis, at least two controlled studies, randomizing patients to different DES platforms and DAPT duration regimens, conveyed signals in support of the need for prolonged DAPT after first-generation devices [15,16]. These findings have now been established by the results of the DAPT trial [17▪▪], which clearly showed ischemic benefit in terms of stent thrombosis and MI reduction in patients receiving first-generation DES.

The high bleeding risk and high thrombotic risk population represents a sizable proportion of CAD patients undergoing coronary stent implantation. Managing these patients in terms of stent type selection (i.e., BMS or DES) and decision on the most appropriate course of DAPT after stent implantation remains a clinical challenge. The uncertainty largely reflects the fact that these patients have been systematically excluded from major randomized controlled trials testing and contrasting various stent types. Accordingly, it is still today generally recommended that these patients should be treated with traditional BMS implantation. The aim of this review is to discuss current evidence on the relationship among stent type, individual clinical features, and optimal DAPT duration, with particular regard to patients who have been traditionally regarded as uncertain DES candidates, that is, those at high bleeding and/or thrombotic risk.

OPTIMAL DAPT DURATION AFTER DRUG-ELUTING STENT IMPLANTATION: ARE ALL PATIENTS ALIKE?

In spite of the current recommendations, the optimal duration of DAPT after coronary stenting in general and DES in particular remains unclear [18]. The recent DAPT trial [17▪▪], which compared 30-month versus 12-month duration of DAPT after first-generation or second-generation DES in patients with stable or unstable CAD, confirmed a significant decrease of definite very late stent thrombosis and major adverse cardiovascular and cerebrovascular events at 30 months after stent implantation in the long-term DAPT arm (12 and 18 months) but with a borderline and significant increase in overall mortality at 30 and 33 months, respectively. The reasons why a significant and clear reduction in stent thrombosis and MI failed to correspondingly lower cardiovascular mortality remain unclear. A distinct increase of bleeding events, which have been systematically associated with prolonged DAPT regimen in this as well as almost all previous studies, may potentially at least partially explain this unexpected finding. Among the patients enrolled, a total of 954 patients had a history of cancer prior to enrollment, 45 patients developed a cancer prior to randomization and 182 patients developed a cancer after randomization. The number of cancer-related deaths was significantly higher in the prolonged DAPT arm (31 patients) as compared with the placebo arm (14 patients; $P = 0.02$) and bleeding-mediated deaths occurred in three patients of the first group. Among the main exclusion criteria were hypersensitivity or allergy to aspirin or P2Y12-inhibitors, planned surgery with discontinuation of DAPT more than 14 days, switch among thienopyridines in the first 12 months, indication for long-term anticoagulant therapy, and absence of bleeding or thrombotic events in the first 12 months of DAPT administration. Hence, patients at high bleeding or thrombotic risk were excluded from the DAPT trial.

HIGH THROMBOTIC RISK POPULATION

Allergy/intolerance to aspirin or any available P2Y12-inhibitor, planned surgery within 12 months of percutaneous coronary intervention (PCI), cancer and thrombotic diathesis (coagulopathy or immunological disorders) confer high thrombotic risk to patients undergoing coronary stent insertion. In patients with acetyl salicylic acid (ASA) hypersensitivity, the current guidelines [19] recommend the execution of a rapid desensitization attempt, ideally to take place before PCI, or long-term therapy with clopidogrel as an alternative. The new P2Y12 inhibitors, prasugrel and ticagrelor, may be preferred as single antiplatelet therapy for a limited duration (1–6 months) after PCI, as they provide more reliable and predictable platelet inhibition. In patients with planned cardiac or noncardiac surgery under DAPT, current recommendations [19] are to proceed to surgery in case of emergency, to consider the discontinuation of one or none of the two antiplatelet agents on the basis of bleeding and thrombotic risk, in semielective and urgent surgery, and to wait until completion of the mandatory dual antiplatelet regime when the surgery is elective, without discontinuation of aspirin if possible. In patients with cancer there are no definite recommendations for optimal DAPT duration. In the DAPT trial, an increase of fatalities in patients with cancer in the 30-month DAPT arm was observed, and this contributed to a significant increase in noncardiovascular death, partially due to bleeding events. Obviously, this subgroup of patients presents a group with a worse prognosis *per se* but a prolonged DAPT might increase the bleeding risk as a consequence of immunological and coagulation disorders related to the underlying disease. The choice of optimal type and duration of antiplatelet therapy remains a challenge in these subsets of patients.

HIGH BLEEDING RISK POPULATION

The criteria that confer higher bleeding risk are: advanced age; clinical indication for anticoagulation therapy; recent or previous bleeding requiring hospitalization or medical attention; systemic conditions associated with increased bleeding risk (i.e., coagulopathy or thrombocytopenia $<100\,000/\text{mm}^3$); known anemia (hemoglobin repetitively <10 g/dl); and need for chronic treatment with steroids or nonsteroidal anti-inflammatory drugs. Among these conditions, patients with clinical

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indication for oral anticoagulants (OAC) have been investigated in multiple retrospective and few prospective studies. Long-term OAC is currently recommended (class I) in patients with atrial fibrillation and at least one risk factor for stroke [20], in those with mechanical heart valves [21] and in those with deep venous thrombosis and/or pulmonary embolism [22]. A significant proportion of these patients have concomitant CAD and need antiplatelet therapy. It is well known that the risk of bleeding increases when aspirin, clopidogrel or both are added to OAC [23▪]. The recent use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention (WOEST) trial [24▪▪] was the first randomized clinical trial to study the possibility of reducing the risk of bleeding in patients receiving OAC and undergoing PCI. A total of 573 patients receiving OAC (~70% due to atrial fibrillation) were randomly assigned to clopidogrel alone (experimental treatment) or clopidogrel and aspirin (control treatment) for a period of 1 month after BMS and 12 months after DES implantation. The primary endpoint, Thrombolysis In Myocardial Infarction (TIMI) bleeding, was significantly lower in the dual therapy group (even if there was no difference in terms of major bleeding), without an increase in MI, target vessel revascularization (TVR), stroke, or stent thrombosis. Even all-cause mortality was significantly reduced in the dual therapy arm, but this observation requires caution due to the modest sample size. Patients with history of intracranial bleeding, peptic ulcer in the previous 6 months, TIMI major bleeding in the previous year, thrombocytopenia ($<50\,000/mm^3$), and age greater than 80 years were excluded. At present, current guidelines [20] and the 2014 consensus document [25▪▪] recommend 4 weeks of triple therapy in patients with atrial fibrillation, stable or unstable CAD, and high bleeding risk (HAS-BLED bleeding risk score ≥ 3; Class IIa, level of evidence C), except patients with low thrombotic risk (SCAD and CHA_2DS_2-VASC = 1 in men), in whom dual therapy with OAC and clopidogrel may be considered on the basis of the WOEST trial results. As of the publication of the 2014 consensus document new studies are available. The Intracoronary Stenting and Antithrombotic Regimen-Testing of a six-week versus a six-month clopidogrel treatment Regimen In Patients with concomitant aspirin and oraL anticoagulant therapy following drug-Eluting stenting (ISAR-TRIPLE) trial [26▪] is the largest randomized trial investigating triple therapy after stenting and the first trial that compared different durations of triple therapy after DES positioning in patients with clinical indication for OAC (~85% due to atrial fibrillation). A total of 614 patients were randomly assigned to 6-week clopidogrel therapy ($n=307$) or 6-month clopidogrel therapy ($n=307$). The null hypothesis was that 6-week was superior to 6-month triple therapy in this patient population. The primary end-point, a composite of death, MI, stent thrombosis, stroke, or TIMI major bleeding, did not significantly differ between groups. Among different components, there was a significant increase of MI in the 6-week group ($n=6$) as compared with the 6-month group ($n=0$) but five events occurred in the first 6 weeks, when both groups were in triple therapy, and one event occurred at 7 months, when clopidogrel was stopped in both groups. This trial demonstrated that shortening the duration of triple therapy neither reduced the incidence of major bleeding nor increased the incidence of ischemic events (Sarafoff *et al.* presented at: Transcatheter Cardiovascular therapeutics; 15 September 2014; Washington, DC, USA). Major exclusion criteria were previous stent thrombosis and DES in the left main coronary artery.

THE ZOTAROLIMUS-ELUTING ENDEAVOR SPRINT STENT IN UNCERTAIN DES CANDIDATES TRIAL

Randomized controlled trials, which have so far compared DES versus BMS, have recommended either a longer DAPT regimen in the DES arm or a similarly prolonged course of DAPT in BMS patients so to match the extended course of therapy after DES. Hence, no study has so far disentangled the effects of DES versus BMS from those offered by long-term DAPT.

The Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) was a multinational, randomized, single-blinded trial [27,28▪▪], conducted at 20 sites in four European countries designed to evaluate whether Zotarolimus-eluting Endeavor Sprint (E-ZES) implantation followed by a shorter than currently recommended course of DAPT, that is, based on the clinical profile of the patient (tailored DAPT), would decrease the incidence of 12-month major adverse cardiovascular events as compared with BMS in uncertain DES candidates. Eligible patients were those at high bleeding risk and/or high thrombotic risk and/or low restenosis risk (Table 1) admitted to the hospital because of SCAD or acute coronary syndrome (ACS). It was the first trial that prospectively studied these subpopulations of patients. A total of 1606 patients undergoing elective, urgent, or emergent PCI were randomly assigned to E-ZES or a thin-strut BMS. E-ZES is a hydrophilic polymer-based second-generation device with a unique drug fast-release profile.

Table 1. Inclusion criteria for eligible patients

Elective, urgent, or emergent PCI with intended stent implantation in patients with at least one of the following:		
High bleeding risk	**High thrombotic risk**	**Low restenosis risk**
Need for OAC	Intolerance to aspirin	Planned stent at least 3.0 mm, apart from LMCA and SVG intervention or for ISR lesions
Previous or recent bleeding requiring hospitalization or medical attention	Intolerance to any available P2Y12-inhibitor	
Age more than 80 years	Planned surgery (other than skin) within 12 months after PCI	
Bleeding diathesis (including coagulopathy and thrombocytopenia less than 100 000/mm^3)	Malignancy with life expectancy more than 1 year	
Known anemia (Hb repeatedly less than 10 g/dl)	Thrombotic diathesis (coagulopathy and immunological disorders)	
Need for chronic treatment with steroids or NSAID		

Hb, hemoglobin; ISR, in-stent restenosis; LMCA, left main coronary artery; NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SVG, saphenous vein graft.

Unlike other DES on the market, including the Resolute stent, Zotarolimus is eluted 100% from the stent within 14 days of implantation and no drug is detectable in the arterial tissue 28 days after stent implantation; although the rapid release profile results in less powerful inhibition of intimal hyperplasia, it also leads to more rapid and complete stent coverage compared with other DES, raising the possibility of shorter DAPT duration. Moreover, the phosphorylcholine coating has been shown to reduce thrombus formation as compared with BMS. Patients with high bleeding risk criteria were 51.6%, predominantly elderly (26.5%) and/or needing OAC (19.4%); patients with high thrombotic risk criteria were 17.7%, predominantly waiting for planned cardiac or noncardiac surgery (7.3%), neoplastic (5.2%) or intolerant to aspirin or any P2Y12-inhibitor (4.6%); patients with low restenosis

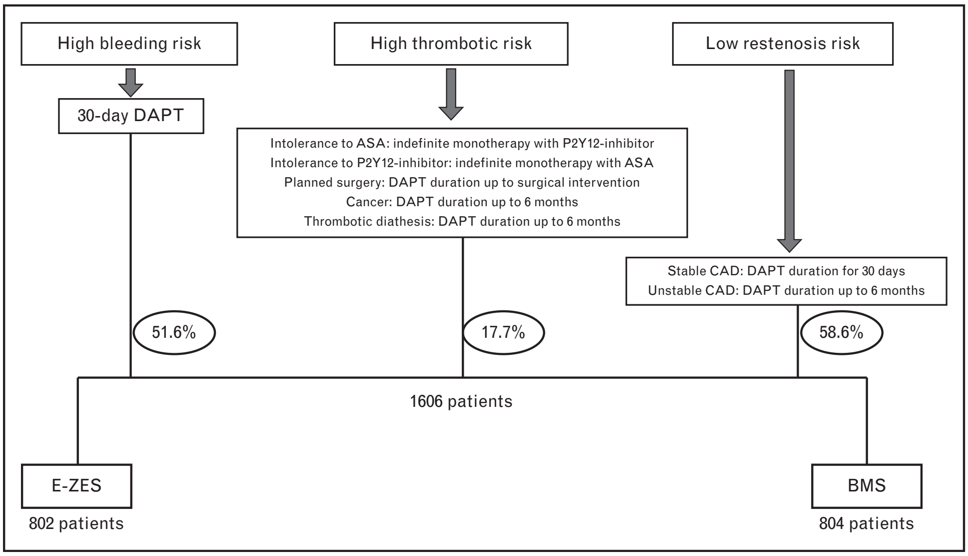

FIGURE 1. Tailored dual antiplatelet therapy in the Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) trial. figure shows the prespecified duration of dual antiplatelet therapy in relation to different inclusion criteria and the percentage of patients included in each main category. Each patient could have one or more inclusion criteria in one or more of the main categories. DES, drug-eluting stents.

risk criteria were 21% with stable CAD and 37.6% with unstable CAD. Finally, 318 patients (19.8%) had inclusion criteria included in two or three different categories; in particular, 94 patients (5.9%) were at the same time at high bleeding and thrombotic risk, and each patient could have two or more inclusion criteria in each category. DAPT duration was prespecified considering the patient's inclusion criteria instead of the stent type (Fig. 1) and was administered in 1532 patients, whereas 74 patients (4.6%) received a monotherapy due to intolerance to aspirin or P2Y12-inhibitor. The primary endpoint was a composite of all-cause death, nonfatal MI, or any TVR. Secondary endpoints included each component of the primary endpoint, cardiac death, Academic Research Consortium defined stent thrombosis, all-cause or ischemic stroke, target lesion revascularization, and bleeding. With a median DAPT duration of about 32 days in both groups, the primary endpoint at 12 months was significantly lower in the E-ZES arm as compared with the BMS arm due to a significant reduction in MI and TVR (Fig. 2). Although all-cause and cardiovascular mortality did not differ between groups, the composite of any death or nonfatal MI as well as of cardiovascular death or nonfatal MI was significantly reduced in the E-ZES population. With a declining trend in definite stent thrombosis, the composite of definite or probable stent thrombosis was significantly lower after E-ZES implantation (Fig. 3), whereas TIMI or Bleeding Academic Research Consortium (BARC) [29] classification bleeding did not differ between groups. No signal for by-treatment interaction was shown for the primary endpoint based on age, sex, presence of diabetes mellitus, indication for the procedure, predefined duration of DAPT, and location or complexity of treated lesion(s). In conclusion, the ZEUS study demonstrated that in patients with high bleeding and/or high thrombotic and/or low restenosis risk E-ZES implantation followed by a tailored DAPT, including no (monotherapy in patients intolerant to aspirin or any available P2Y12) or a 30-day (high bleeding risk population) DAPT course of therapy, reduced the rate of major adverse cardiovascular events as compared with BMS. Given the unique properties of E-ZES, these results should not be extrapolated to other newer-generation DES

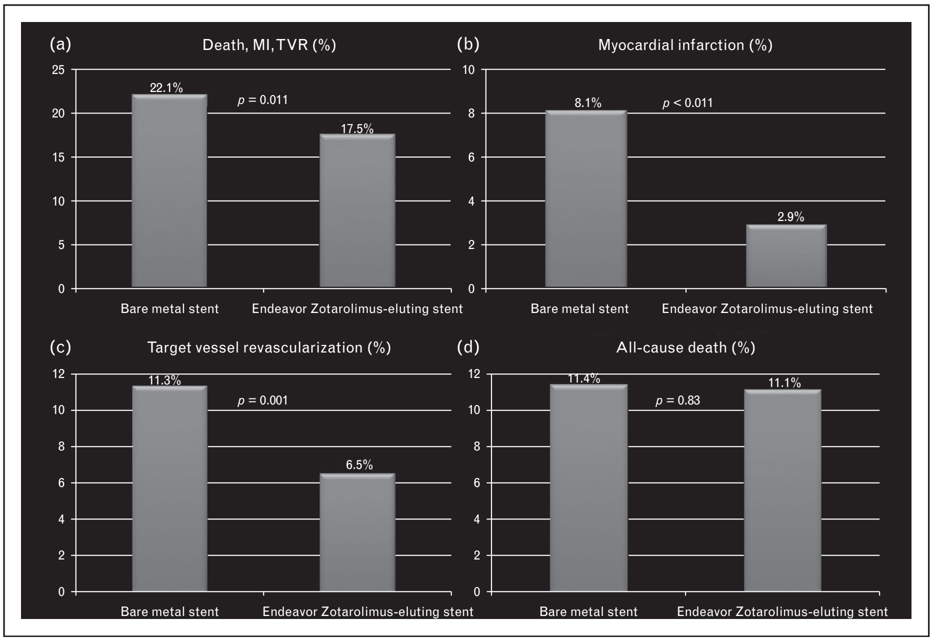

FIGURE 2. Primary endpoint in the Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) trial. (a) The significant difference in the composite primary endpoint between the BMS and E-ZES groups. Panels (b) to (d) show the incidence of each component of the primary endpoint between the two different arms and the corresponding *P* value: (b) myocardial infarction; (c) target vessel revascularization; (d) all-cause death the BMS, bare metal stent; DES, drug-eluting stent; E-ZES, Zotarolimus-eluting Endeavor Sprint.

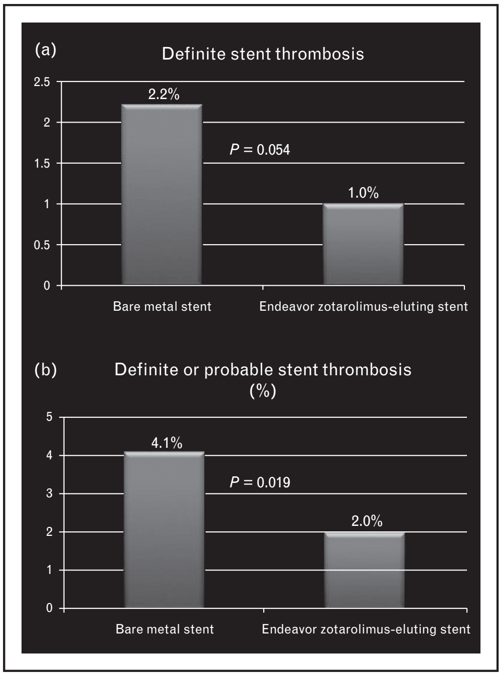

FIGURE 3. Stent thrombosis in the Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) trial. (a) The declining trend in terms of definite stent thrombosis in the E-ZES group as compared with the BMS group; (b) The significant difference in the composite endpoint of definite or probable stent thrombosis in the two different arms. BMS, bare metal stent; DES, drug-eluting stent; E-ZES, Zotarolimus-eluting Endeavor Sprint.

coated with the same or other antiproliferative agents and diverse polymers. As the E-ZES has been associated with a lower efficacy in preventing TVR as compared with other more potent first-generation or second-generation DES [30], it remains unclear whether other DES may offer similar advantages, especially in patients at high-bleeding or thrombotic risk.

Further research is needed to ascertain whether the tailored DAPT regimen tested in our study can be safely implemented in patients receiving other DES. The ongoing BioFreedom drug-coated stent vs the Gazelle bare metal stent in patients at high bleeding risk using a short (1 month) course of dual antiplatelet therapy (LEADERS-FREE) trial [31], which compares the BioFreedom drug-coated stent with the Gazelle BMS (i.e., the corresponding BMS platform) in high bleeding risk patients under 1-month DAPT, is awaited to further extend available treatment options for this challenging patient subset.

CONCLUSION

Although several studies provided some reassurance that a short course of DAPT might be well tolerated in certain patients treated with a particular type of DES, the optimal duration of DAPT remains uncertain, particularly in patients with high risk of bleeding or thrombotic events. Importantly, in the DAPT trial, the majority of screened patients (15 761 out of 25 682) at the time of intervention were not subsequently randomized to stop or continue DAPT beyond 1 year, including 616 patients who were subsequently excluded due to the occurrence of moderate-to-severe Global Utilization Of Streptokinase And Tpa For Occluded Arteries (GUSTO) bleeding within the first 12 months. The ZEUS trial provides for the very first time data showing that a BMS-like DAPT regimen (30 days or even shorter) in the E-ZES group did not pose safety concerns while achieving superior clinical efficacy in patients with high bleeding risk, extending and confirming the results of the ISAR-TRIPLE trial, and suggesting that long-term DAPT should be reserved for patients without significant risk of bleeding events, as observed in the DAPT trial. Moreover, in patients with planned surgery and in neoplastic patients, a course of DAPT up to surgery or up to 6 months, respectively, was shown to be well tolerated and apparently more effective than BMS in patients assigned to E-ZES implantation. Although the current guidelines recommend the use of BMS, wherein a long course of DAPT is contraindicated [19,32], this study suggests that E-ZES may become the device of choice also in patients who cannot tolerate a prolonged DAPT regimen or in those with indication for indefinite monotherapy. This study had paradigm-shift potential, as it suggested that, contrary to original belief, the optimal duration of DAPT after stent implantation should be guided by a careful assessment of the balance between the ischemic and bleeding risks independently of the type of stent used (BMS or DES). Further randomized trials are needed to confirm or refute these findings for other types of DES.

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None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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This is a recent and important trial that confirms the advantages of prolonged DAPT after DES implantation in terms of ischemic events but with an increased risk of bleeding. This evidence is regarding only a selected population because patients with high bleeding or thrombotic risk were excluded.

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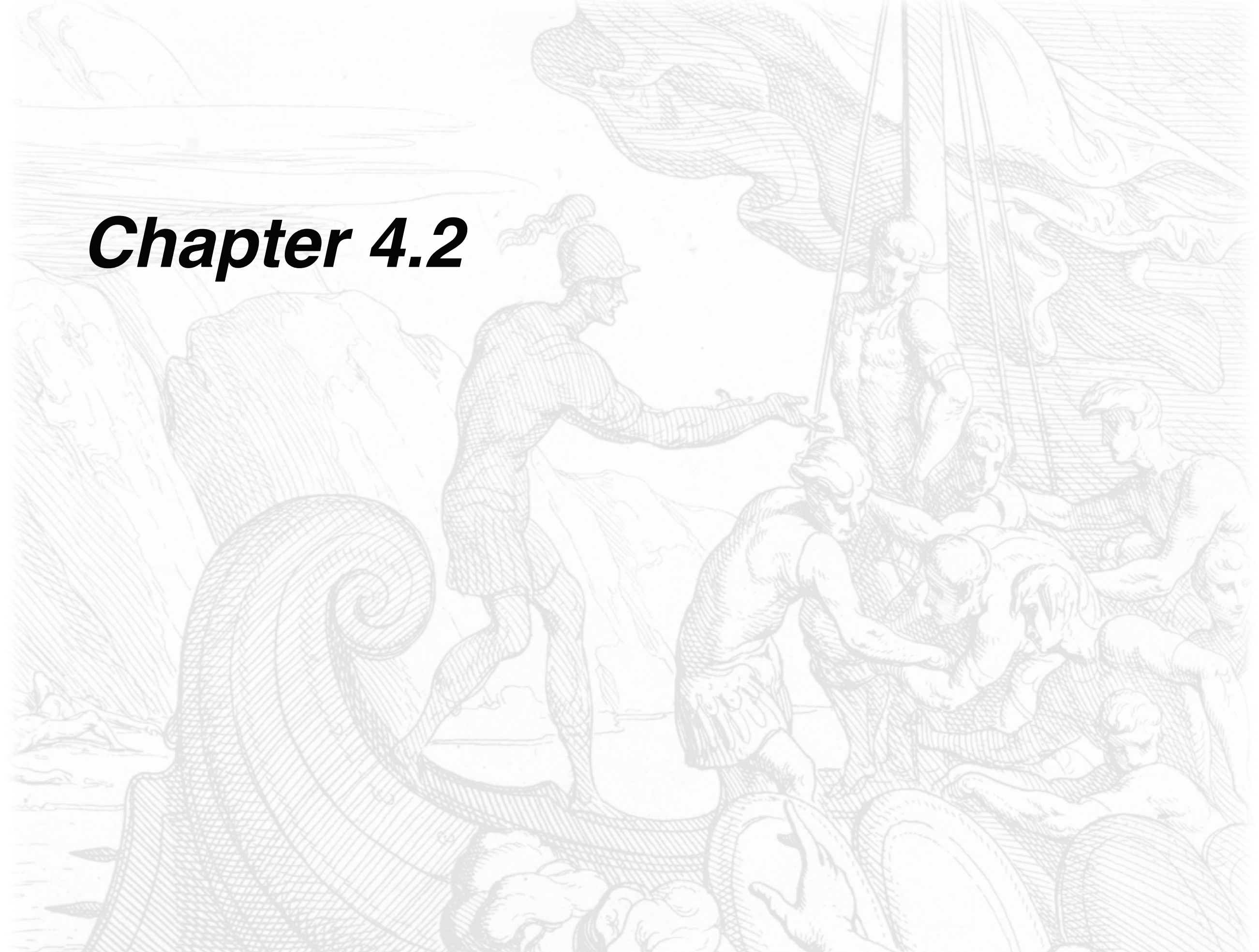
Chapter 4.2



Is Bare-metal Stent implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention? A pre-specified analysis from the ZEUS (Zotarolimus-Eluting Endeavor sprint stent in Uncertain DES candidates) trial

Sara Ariotti, Marianna Adamo, ***Francesco Costa***, Athanasios Patialiakas, Carlo Briguori, Attila Thury, Salvatore Colangelo, Gianluca Campo, Matteo Tebaldi, Imre Ungi, Stefano Tondi, Marco Roffi, Alberto Menozzi, Nicoletta De Cesare, Roberto Garbo, Emanuele Meliga, Luca Testa, Henrique Mesquita Gabriel, Marco Ferlini, Pascal Vranckx, Marco Valgimigli

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CLINICAL RESEARCH

CORONARY

Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?

A Pre-Specified Analysis From the ZEUS Trial

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ABSTRACT

OBJECTIVES This study sought to investigate the ischemic and bleeding outcomes of patients fulfilling high bleeding risk (HBR) criteria who were randomized to zotarolimus-eluting Endeavor Sprint stent (E-ZES) or bare-metal stent (BMS) implantation followed by an abbreviated dual antiplatelet therapy (DAPT) duration for stable or unstable coronary artery disease.

BACKGROUND DES instead of BMS use remains controversial in HBR patients, in whom long-term DAPT poses safety concerns.

METHODS The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) is a multinational, randomized single-blinded trial that randomized among others, in a stratified manner, 828 patients fulfilling pre-defined clinical or biochemical HBR criteria—including advanced age, indication to oral anticoagulants or other pro-hemorrhagic medications, history of bleeding and known anemia—to receive E-ZES or BMS followed by a protocol-mandated 30-day DAPT regimen. The primary endpoint of the study was the 12-month major adverse cardiovascular event rate, consisting of death, myocardial infarction, or target vessel revascularization.

RESULTS Compared with patients without, those with 1 or more HBR criteria had worse outcomes, owing to higher ischemic and bleeding risks. Among HBR patients, major adverse cardiovascular events occurred in 22.6% of the E-ZES and 29% of the BMS patients (hazard ratio: 0.75; 95% confidence interval: 0.57 to 0.98; $p = 0.033$), driven by lower myocardial infarction (3.5% vs. 10.4%; $p < 0.001$) and target vessel revascularization (5.9% vs. 11.4%; $p = 0.005$) rates in the E-ZES arm. The composite of definite or probable stent thrombosis was significantly reduced in E-ZES recipients, whereas bleeding events did not differ between stent groups.

CONCLUSIONS Among HBR patients with stable or unstable coronary artery disease, E-ZES implantation provides superior efficacy and safety as compared with conventional BMS. (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates [ZEUS]; NCT01385319) (J Am Coll Cardiol Intv 2016;9:426–36) © 2016 by the American College of Cardiology Foundation.

Drug-eluting stents (DES) reduce the restenosis rates as compared to bare-metal stents (BMS) (1-3). However, an excessive inhibition of neointimal formation with incomplete endothelialization, observed in the first-generation devices, has been associated with an increased risk of very-late stent thrombosis (ST) after dual antiplatelet therapy (DAPT) discontinuation (4,5). Second-generation DES have been developed to overcome safety concerns and maintain the efficacy similar to first-generation DES. Yet, a minimum course of 3- or 12-month DAPT duration is currently mandated after implantation of newer-generation DES according to current European or American guidelines, respectively (6,7). As a consequence, the use of DES instead of BMS remains controversial in high bleeding risk (HBR) patients, in whom long-term DAPT poses safety concerns.

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The zotarolimus-eluting Endeavor Sprint stent (E-ZES) is a hydrophilic polymer-based second-generation device with a unique drug fast-release profile (8), resulting in less powerful inhibition of intimal hyperplasia, but also in a rapid and/or complete stent strut coverage. This characteristic raises the possibility that it might be feasible to shorten DAPT duration while maintaining superior efficacy compared with BMS (9). The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) study, which mandated a tailored DAPT duration based on patients' characteristics, showed a lower incidence of major adverse cardiovascular events (MACE) after E-ZES as compared with BMS in uncertain DES recipients. More than 50% of the patients fulfilled at least 1 HBR criterion in this study, and they were to be treated with a 30-day course of DAPT only.

We sought to investigate: 1) the ischemic and bleeding outcomes in relation to the presence or absence of at least 1 HBR criterion within the study population; and 2) assess the efficacy and safety of E-ZES or BMS implantation in HBR patients.

METHODS

STUDY POPULATION. The design and main study findings, including consistency of study results across inclusion criteria, of the ZEUS trial were previously reported (10,11).

Briefly, it was a multinational, randomized single-blinded trial including patients with at least 1 qualifying criterion among the pre-specified uncertain DES recipients undergoing elective, urgent, or emergent percutaneous coronary intervention with intended stent implantation. They were randomly allocated 1:1 to receive E-ZES or a thin-strut (thickness <100 μm) BMS followed by a DAPT regimen independent of stent type, but clinical-profile-driven. Randomization was stratified based upon the presence or absence of HBR status. Patients were deemed at HBR provided they fulfil at least 1 of the pre-specified criteria, including: age older than 80 years; clinical indication for treatment with oral anticoagulant agents; recent bleeding episode(s) that required medical attention or hospitalization if the bleeding diathesis has not been completely resolved; systemic conditions associated with increased bleeding risk (e.g., hematological disorders or any known coagulopathy determining bleeding-diathesis, including prior or current thrombocytopenia, which was defined as platelet count <100,000/mm^3); known anemia, defined as repeatedly documented hemoglobin <10 g/dl; and need for long-term treatment with steroids or nonsteroidal anti-inflammatory drugs.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

BMS = bare-metal stent(s)

CI = confidence interval

DES = drug-eluting stent(s)

DAPT = dual antiplatelet therapy

E-ZES = zotarolimus-eluting Endeavor Sprint stent(s)

HBR = high bleeding risk

HR = hazard ratio

IQR = interquartile range

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

ST = stent thrombosis

TIMI = Thrombolysis In Myocardial Infarction

TVR = target vessel revascularization

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committees of all participating centers independently approved the protocol, and all participants gave written informed consent.

DEVICES AND THERAPY. The Endeavor stent (Medtronic Vascular, Minneapolis, Minnesota) is constituted by a cobalt-based alloy platform (91-µm strut thickness) and a phosphorylcholine-polymer (4.8-µm) loaded with zotarolimus at the dose concentration of 10-µg/mm stent length. The drug is eluted within 15 days of implantation, and concentration within surrounding vascular tissue is not detected already at 30 days after stent deployment (8,9).

All commercially available thin-strut BMS were allowed by the protocol. All patients received aspirin and clopidogrel (300 to 600 mg orally as loading dose followed by 75 mg/day), or prasugrel (60 mg as loading dose followed by 10 or 5 mg/day) or ticagrelor (180 mg as loading dose followed by 90 mg twice a day). All HBR patients were treated with DAPT for a pre-specified 30-day period after stent implantation. In case of a staged procedure, DAPT had to be prolonged or restarted for 30 additional days. Patients who were not eligible for DAPT were treated with aspirin or $P2Y_{12}$ inhibitor monotherapy. Unfractionated heparin or bivalirudin was used during percutaneous coronary procedure according to guideline-recommended regimens.

STUDY ENDPOINTS AND FOLLOW-UP. The primary endpoint of the ZEUS trial was MACE at 12 months, defined as a composite of all-cause death, nonfatal MI, and any target vessel revascularization (TVR).

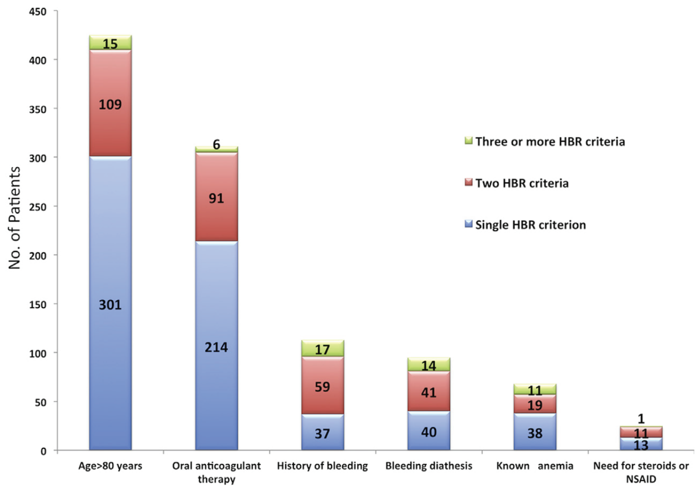
Secondary efficacy endpoints were the composite of death and MI; the composite of cardiovascular death and MI; each component of the primary endpoint; target lesion revascularization, ischemic stroke; definite, probable, possible ST and the composite of definite and probable ST. Secondary safety endpoints comprised bleeding events according to both Bleeding Academic Research Consortium (BARC) and Thrombolysis In Myocardial Infarction (TIMI) classifications. All study endpoint definitions were previously reported (11).

Thirty-day and 6- and 12-month follow-up visits were performed according to study protocol in order to assess potential adverse events and compliance with medications and to record a 12-lead electrocardiogram.

All endpoints were confirmed on the basis of the documentation collected at each site and were centrally adjudicated by the clinical events committee, whose members were unaware of treatment assignment.

STATISTICAL ANALYSIS. In this pre-specified analysis of the ZEUS trial, categorical variables were

FIGURE 1 HBR Criteria in the Study Population



The number of patients fulfilling each high bleeding risk (HBR) criterion is shown in decreasing order. There was a considerable overlap among HBR criteria, with 643 patients (78%) fulfilling 1, 330 (40%) 2, and 65 (8%) ≥3 HBR qualifying features. NSAID = nonsteroidal anti-inflammatory drugs.

expressed as frequency and percentage, and compared using the Fisher exact test, whereas continuous variables were expressed as median and interquartile range, and compared with the Wilcoxon rank sum test.

Estimation of the cumulative incidence of events was performed by the Kaplan-Meier method, and hazard ratios (HRs) with 95% confidence intervals (CIs) and p values were calculated using the stratified Cox regression model. The proportionality assumptions were checked by visual estimation after plotting the log cumulative hazard versus (log) time at follow-up after index procedure and by applying a test for nonproportional hazards using the Schoenfeld residuals, which failed to reject the null hypothesis that event rate was affected by time ($p = 0.48$). Sensitivity analyses were performed testing the consistency of study results in patients with only 1 or at least 2 HBR criteria, as well as investigating the effect of allocated stent type on outcomes according to each HBR criterion when separately appraised.

A 2-sided p value <0.05 was considered significant. All analyses were performed on the basis of the intention-to-treat principle using SPSS version 21.0 (SPSS, Chicago, Illinois).

RESULTS

STUDY POPULATION. From June 2011 to September 2012, a total of 5,288 patients were screened and 1,606 were finally randomized. A total of 828 patients fulfilled 1 or more HBR criteria, of whom 425 (51.3%) age >80 years, 311 (37.6%) had clinical indication to oral anticoagulant (Online Table 1), 113 (13.6%) reported previous or recent bleeding requiring hospitalization or medical attention, 95 (11.5%) presented bleeding diathesis, 68 (8.2%) had known anemia, and 25 (3.0%) were in need of long-term treatment with steroids or nonsteroidal anti-inflammatory drugs. There was a considerable overlap among HBR criteria, with 643 patients (78%) fulfilling 1, 330 (40%) 2. and 65 (8%) ≥3 HBR qualifying features (Figure 1).

Baseline patient characteristics stratified according to the presence or absence of HBR status are shown in Online Tables 2 and 3.

Among HBR patients, of whom 424 (51.2%) were randomized to receive E-ZES, and 404 (48.8%) to BMS, baseline clinical and angiographic features were well-matched between stent groups (Tables 1 and 2). The median age was 80 years; diabetes was observed in roughly one-third of the population, hypertension in more than 80%, impaired kidney function in approximately 60% of the patients, and 65% of patients had acute coronary syndrome at presentation (Table 1). One third of the patients underwent multivessel intervention, and at least 1 complex lesion was treated in approximately three-fourths of the patients (Table 2).

TABLE 1 Baseline Characteristics of Patients at HBR

	Bare-Metal Stent (n = 404)	Endeavor Stent (n = 424)	p Value
Age, yrs			
Median	80.5	80.4	0.83
Interquartile range	72.3-84.4	72.8-84.9	
Female	145 (35.9)	150 (35.4)	0.89
Body mass index, kg/m^2			
Median	26	26	0.96
Interquartile range	24-29	24-29	
Diabetes	117 (29.0)	137 (32.3)	0.33
Hypertension	336 (83.2)	344 (81.1)	0.47
Hyperlipidemia	193 (47.8)	191 (45.0)	0.44
Current cigarettes use	45 (11.1)	44 (10.4)	0.36
Creatinine clearance, ml/min*			
Median	54.3	54.8	0.90
Interquartile range	39.1-69.9	38.7-69.9	
Patients with GFR <60 ml/min*	242 (61.3)	241 (59.5)	0.61
Patients with GFR <30 ml/min*	51 (12.9)	52 (12.8)	>0.99
Patients on dialysis	6 (1.5)	14 (3.3)	0.11
Prior MI	114 (28.2)	117 (27.6)	0.88
Prior PCI	83 (20.5)	90 (21.2)	0.86
Prior CABG	38 (9.4)	39 (9.2)	>0.99
Prior stroke or TIA	34 (8.4)	32 (7.5)	0.70
COPD	43 (10.6)	32 (7.5)	0.15
PAD	94 (23.3)	76 (17.9)	0.06
Left ventricular ejection fraction†			
Median	49	48	0.59
Interquartile range	40-55	40-55	
Clinical presentation			
Stable angina pectoris	140 (34.7)	147 (34.7)	>0.99
Acute coronary syndrome			
Unstable angina	69 (17.1)	72 (17.0)	>0.99
Non-ST-segment elevation MI	133 (32.9)	140 (33.0)	>0.99
ST-segment elevation MI	62 (15.3)	65 (15.3)	>0.99
Angiographic features			
Single-vessel disease	125 (30.9)	138 (32.5)	0.716
Double-vessel disease	144 (35.6)	146 (34.4)	
Triple-vessel disease	132 (32.7)	139 (32.8)	

Values are n (%), unless indicated otherwise. *Calculated in 395 patients in the BMS arm and in 405 patients in the E-ZES arm. †Calculated in 380 patients in the BMS arm and in 397 patients in the E-ZES arm.

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtrate rate; HBR = high bleeding risk; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

DUAL ANTIPLATELET THERAPY. The duration of DAPT—which largely consisted of aspirin and clopidogrel—was almost 5-fold shorter in patients with HBR criteria (median [interquartile range]: 30 [20 to 30] days) as compared with those without HBR criteria (median [interquartile range]: 174 [30 to 190] days; $p < 0.0001$).

TABLE 2 Procedural Results and Use of Medications During the Trial in Patients at HBR

	Bare-Metal Stent (n = 404)	Endeavor Stent (n = 424)	p Value
Treated lesions, n			
Median	1	1	0.82
Interquartile range	1-2	1-2	
≥2 Treated lesions*	154 (38.1)	151 (35.7)	0.47
Multivessel intervention	130 (32.2)	141 (33.3)	0.77
LAD treated	196 (48.5)	234 (55.2)	0.06
CFX treated	155 (38.4)	141 (33.3)	0.13
RCA treated	161 (39.9)	162 (38.2)	0.67
LMCA treated	27 (6.7)	26 (6.1)	0.78
SVG treated	6 (1.5)	8 (1.9)	0.79
At least 1 complex (type B2 or C) lesion	310 (76.7)	321 (75.7)	0.75
Total ACC/AHA score†			
Median	7	7	0.94
Interquartile range	4–11	4–11	
Stents implanted, n			
Median	1	1	>0.99
Interquartile range	1-2	1-2	
Length of stent, mm			
Median	28	30	0.96
Interquartile range	18-46	18-44	
Mean stent diameter, mm‡			
Median	3	3	0.14
Interquartile range	2.75-3.50	2.75-3.25	
Patients receiving ≥2 stents	182 (45.0)	191 (45.0)	>0.99
Patients receiving ≥3 stents	73 (18.1)	77 (18.2)	>0.99
Patients with overlapping stents	103 (25.5)	106 (25.0)	0.87
Quantitative coronary analysis			
Lesion length, mm§	16.88 ± 10.44	16.44 ± 10.64	0.28
Reference vessel diameter, before, mm§	2.65 ± 0.59	2.67 ± 0.61	0.90
Minimal lumen diameter, before, mm§	0.89 ± 0.48	0.88 ± 0.51	0.28
Stenosis, before, %§	66 ± 15	68 ± 16	0.23
Reference vessel diameter, after, mm‡	2.86 ± 0.50	2.86 ± 0.51	0.89
Minimal lumen diameter, after, mm§	2.65 ± 0.52	2.64 ± 0.55	0.81
Stenosis, after, %§	7.4 ± 8.6	7.5 ± 11.4	0.47
Drug therapy at discharge			
Aspirin	377 (93.3)	386 (91.0)	0.25
$P2Y_{12}$ inhibitor	387 (95.8)	410 (96.7)	0.58
ACE inhibitor	234 (57.9)	240 (56.6)	0.73
Beta-blocker	307 (76.0)	299 (70.5)	0.08
Statin	321 (79.5)	347 (81.8)	0.43
Oral anticoagulation	96 (23.8)	100 (23.6)	>0.99
Proton pump inhibitor‖	290 (71.8)	293 (69.4)	0.49
Drug therapy at 30 days			
Aspirin	373 (92.3)	383 (90.3)	0.33
$P2Y_{12}$ inhibitor	364 (90.1)	389 (91.7)	0.47
ACE inhibitor¶	213 (52.7)	242 (57.1)	0.40
Beta-blocker¶	297 (73.5)	297 (70.0)	0.54
Statin¶	303 (75.0)	336 (79.2)	0.25
Oral anticoagulation	100 (24.8)	97 (22.9)	0.81
Proton pump inhibitor#	267 (69.0)	270 (66.5)	0.49

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Among HBR patients, 14 (3%) patients in each stent group received treatment with a single antiplatelet agent after stent implantation; among those who received DAPT, treatment was stopped within the first 15, 30, and 60 days in 5 (1.2%), 151 (37.4%), and 291 (72.0%) patients in the BMS and 10 (2.4%), 245 (57.8%), and 323 (76.2%) in the E-ZES group, respectively ($p < 0.001$). Reasons for prolonging DAPT beyond 30 days included planned or unplanned procedures in de novo lesions, which were evenly distributed between stent groups, or need for reintervention in previously instrumented coronary segments, which explained the longer DAPT duration in the BMS group.

BLEEDING RISK CRITERIA AND OUTCOMES. Any actionable BARC bleeding was almost 2-fold higher in patients with (7.7%) as compared with those without (3.9%; HR: 2.32; 95% CI: 1.49 to 3.62; $p < 0.001$) at least 1 HBR criterion whereas major BARC (4.2% vs. 1.5%; HR: 2.93; 95% CI: 1.51 to 5.70; $p = 0.001$) and major or minor TIMI bleeding (2.8% vs. 1.0%; HR: 2.87; 95% CI: 1.28 to 6.41; $p = 0.011$) were almost three-fold greater in the former group. There was evidence of an additive effect on bleeding outcomes with respect to the presence of only 1 or more than 1 HBR features (**Figure 2**).

The cumulative risk of death, MI or TVR was doubled in HBR (25.7% vs. 13.5%; $p < 0.001$) as compared with other patients, driven by higher rates of death (16.5% vs. 5.7%; $p < 0.001$) or MI (6.9% vs. 4.0%; $p = 0.012$). Definite or probable ST was also increased in HBR patients (4.3% vs. 1.7%; $p = 0.002$).

When adjustment was implemented for baseline imbalances, residual bleeding (BARC type 2, 3, or 5 HR: 1.33, 95% CI: 0.75 to 2.36, $p = 0.332$; BARC type 3 or 5 HR: 2.05, 95% CI: 0.84 to 4.98, $p = 0.114$; TIMI major or minor HR: 2.15, 95% CI: 0.73 to 6.29, $p = 0.163$) and mortality (adjusted HR: 1.46; 95% CI: 0.95 to 2.25; $p = 0.083$) risks no longer differed.

STENT TYPES AND OUTCOMES IN HBR PATIENTS. At 12 months, the primary endpoint occurred in 96 (22.6%) patients in the E-ZES and in 117 (29%) patients in the BMS group (HR: 0.75; 95% CI: 0.57 to 0.98; $p = 0.033$), owing to lower MI (3.5% vs. 10.4%; HR: 0.33; 95% CI: 0.18 to 0.60; $p < 0.001$) and TVR (5.9% vs. 11.4%; HR: 0.50; 95% CI: 0.30 to 0.80; $p = 0.005$) rates in the E-ZES compared with BMS cohort (**Figure 3**, **Table 3**). The composite of death and MI (18.4% vs. 24.8%; HR: 0.72; 95% CI: 0.53 to 0.96; $p = 0.027$) as well as cardiovascular death or MI (14.6% vs. 20.3%; HR: 0.70; 95% CI: 0.50 to 0.97; $p = 0.032$) were lower in the E-ZES group, whereas mortality did not differ (**Table 3**). Definite or probable ST (2.6% vs. 6.2%; HR: 0.42; 95% CI: 0.21 to 0.85; $p = 0.016$) and definite, probable or possible ST (6.6% vs. 10.6%; HR: 0.61; 95% CI: 0.38 to 0.98; $p = 0.042$) were respectively more than halved or reduced by almost 40% in E-ZES-treated patients (**Table 3**).

Interestingly, the occurrence of ST appeared evenly distributed in the BMS group when considering the on versus off-DAPT follow-up duration, whereas only 1 of 11 ST cases in patients allocated to E-ZES occurred while patients were off DAPT.

A trend towards a lower bleeding risk was noted in the E-ZES cohort with respect to BARC 2, 3, or 5 events (6.1% vs. 9.4%; HR: 0.65; 95% CI: 0.39 to 1.07; p = 0.089), whereas major BARC or TIMI major or minor events did not differ between stent groups (**Table 3**).

ADDITIONAL ANALYSES. The consistency of outcomes with respect to the presence of a single or multiple HBR features is shown in **Figure 4**. The primary endpoint outcomes in relation to each HBR criterion are shown in Online Figure 1. A further sensitivity analysis focusing on patients with atrial fibrillation showed consistent findings (Online Figure 2).

DISCUSSION

Patients at HBR represent a well sizable portion of coronary artery disease population undergoing percutaneous coronary stenting. However, these patients have been largely excluded from major randomized controlled trials evaluating different stent types. Although multiple bleeding risk scores or single individual risk factors for bleeding exist (12-14), HBR status is rarely defined according to objective risk criteria (15-17). The lack of standardized algorithms for the identification of HBR patients hampers comparability across studies and limit their external validity in clinical practice.

TABLE 2 Continued

	Bare-Metal Stent (n = 404)	Endeavor Stent (n = 424)	p Value
Dual antiplatelet therapy duration			
Median	31	30	0.009
Interquartile range	30-177	30-53	
Range	0-365	0-365	

Values are n (%) or mean ± SD, unless indicated otherwise. *Calculated in 404 patients in the BMS arm and in 423 in the E-ZES arm. †Calculated in 402 patients in the BMS arm and in the 422 in the E-ZES arm. ‡Calculated in 395 patients in the BMS arm and in the 416 patients in the E-ZES arm. §Calculated in 396 patients in the BMS arm and in 422 patients in the E-ZES arm. ||Calculated in 404 patients in the BMS arm and in 422 in the E-ZES arm. ¶Calculated in 389 patients in the BMS arm and in 407 patients in the E-ZES arm. #Calculated in 387 patients in the BMS arm and in the 406 patients in the E-ZES arm.

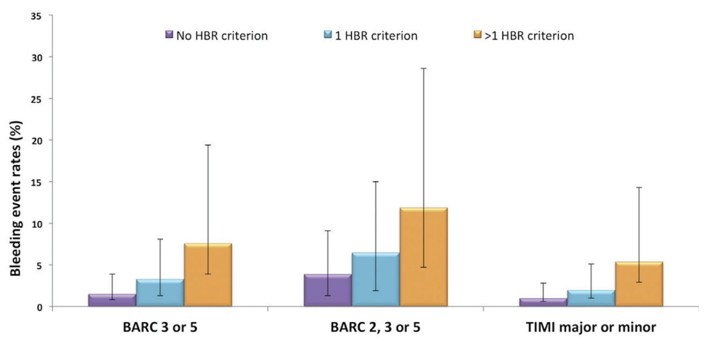
ACC/AHA = American College of Cardiology/American Heart Association; ACE = angiotensin-converting enzyme; HBR = high bleeding risk; LAD = left anterior descending coronary artery, CFX = circumflex coronary artery, RCA = right coronary artery, LMCA = left main coronary artery, SVG = saphenous vein graft.

As a reflection of limited evidence for the use of DES in this population, 6 of 10 (576 of 946) participants preferred BMS whereas only 1 out of 20 (44 of 946) responders vouched for the value of newer-generation DES for HBR patients in a recent European survey (18).

MAIN STUDY FINDINGS. In the ZEUS trial, 828 patients fulfilling at least 1 pre-specified HBR criterion were randomized to receive BMS or E-ZES, which is a hydrophilic polymer-based second-generation device with a unique drug, fast-release profile. In this selected high-risk patient population, the study protocol mandated 30-day DAPT irrespective of the stent type. The results of our study can be summarized as follows:

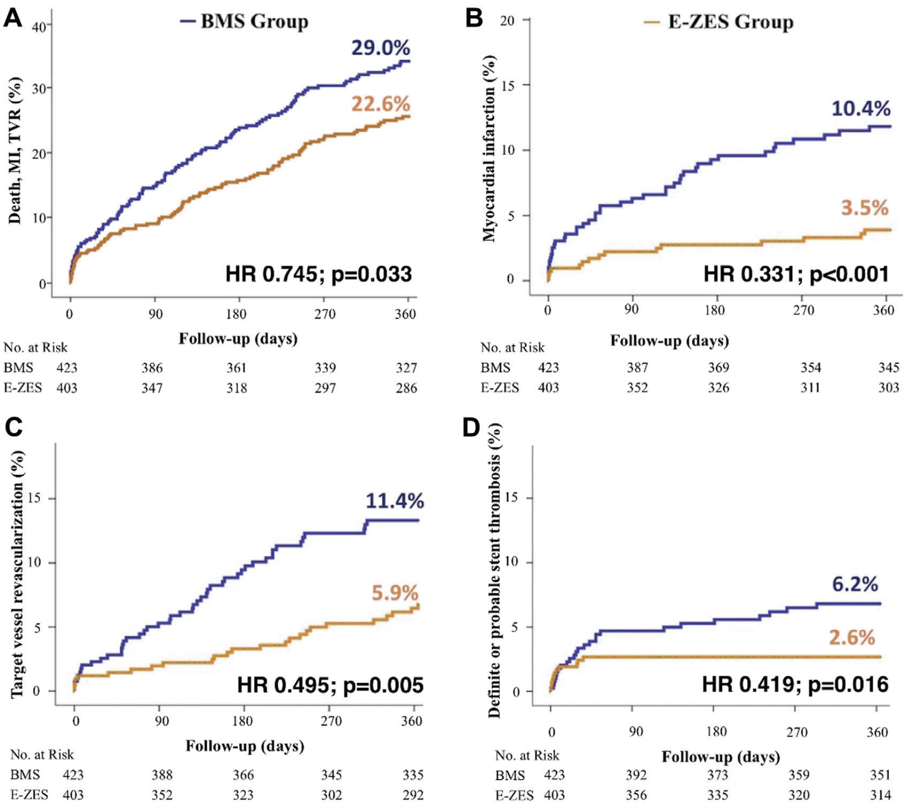
- Patients at HBR, who have been selected according to pre-specified objective criteria, displayed higher

FIGURE 2 Bleeding Event Rates According to The Presence and Number of HBR Criteria



There was evidence of an additive effect on bleeding outcomes with respect to the presence of only 1 or more than 1 high bleeding risk (HBR) features; p value for trend <0.001. **Vertical bars** represent 95% confidence intervals. BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis In Myocardial infarction.

FIGURE 3 **Clinical Outcomes in the HBR Population Treated With Zotarolimus-Eluting Stents Versus BMS**



Rate of events for primary composite endpoint of death, myocardial infarction (MI), and target vessel revascularization (TVR) **(A)**, MI **(B)**, TVR **(C)**, or definite or probable stent thrombosis **(D)** at 12 months. BMS = bare-metal stent(s); E-ZES = zotarolimus-eluting Endeavor Sprint stent(s); HBR = high bleeding risk; HR = hazard ratio.

risk of bleeding, consistently across all assessed bleeding scales, which was proportionally greater depending on the number of HBR criteria simultaneously fulfilled as compared with patients without HBR features.

- Patients at HBR were also at higher MACE risk as compared with patients who were not at HBR status, driven by higher death and MI rates. ST was almost 3-fold greater in patients with as compared with those without HBR criteria. This observation reinforces the notion that bleeding predictors largely overlap with risk factors for ischemic complications and highlights the challenge of identifying a safe and effective anti-thrombotic treatment in this patient population in clinical practice.
- HBR patients derived benefits in terms of reductions of MACE, MI, TVR, and ST when treated with E-ZES as compared with BMS, which is consistent with study results observed in the overall population (11). At sensitivity analyses, results remained entirely consistent focusing on patients who displayed 2 or more HBR features, or evaluating each HBR criterion separately. A further analysis restricted to patients with atrial fibrillation, which was the most frequent indication to oral anticoagulation, confirmed overall study findings.
- Despite comparable protocol-mandated DAPT durations in both stent groups, cumulative treatment duration with aspirin and $P2Y_{12}$ inhibitor was significantly longer in BMS as compared with E-ZES

TABLE 3 Outcome Rates at 12 Months According to Treatment Group in Patients at HBR

	Bare-Metal Stent (n = 404)	Endeavor Stent (n = 424)	Hazard Ratio (95% Confidence Interval)	p Value
Primary efficacy endpoint				
Death for any cause, myocardial infarction, or target vessel revascularization	117 (29.0)	96 (22.6)	0.745 (0.568-0.977)	0.033
Secondary efficacy endpoints				
Death for any cause or myocardial infarction	100 (24.8)	78 (18.4)	0.715 (0.531-0.963)	0.027
Death for cardiovascular cause or myocardial infarction	82 (20.3)	62 (14.6)	0.695 (0.499-0.968)	0.032
Death for any cause	70 (17.3)	67 (15.8)	0.913 (0.652-1.278)	0.595
Death for cardiovascular cause	51 (12.6)	50 (11.8)	0.931 (0.629-1.378)	0.720
Myocardial infarction	42 (10.4)	15 (3.5)	0.331 (0.184-0.598)	<0.001
Target vessel revascularization	46 (11.4)	25 (5.9)	0.495 (0.304-0.806)	0.005
Target lesion revascularization	45 (11.1)	22 (5.2)	0.443 (0.266-0.739)	0.002
Ischemic stroke	11 (2.7)	5 (1.2)	0.432 (0.150-1.245)	0.120
Definite stent thrombosis*	10 (2.5)	4 (0.9)	0.381 (0.119-1.217)	0.103
Probable stent thrombosis*	15 (3.7)	7 (1.7)	0.448 (0.182-1.099)	0.079
Possible stent thrombosis*	18 (4.5)	17 (4.0)	0.870 (0.448-1.689)	0.681
Definite or probable stent thrombosis*	25 (6.2)	11 (2.6)	0.419 (0.206-0.853)	0.016
Definite, probable, or possible stent thrombosis*	43 (10.6)	28 (6.6)	0.610 (0.379-0.983)	0.042
Safety endpoints				
TIMI classification				
Major or minor	13 (3.2)	10 (2.4)	0.734 (0.322-1.674)	0.462
Major	10 (2.5)	6 (1.4)		0.318
Minor	3 (0.7)	4 (0.9)		>0.99
Requiring medical attention	25 (6.2)	16 (3.8)		0.148
BARC classification†				
Type 5 or 3	20 (5.0)	15 (3.5)	0.718 (0.368-1.404)	0.333
Type 5, 3, or 2	38 (9.4)	26 (6.1)	0.648 (0.393-1.068)	0.089
Type 5	4 (1.0)	2 (0.5)		0.441
Type 5A	3 (0.7)	1 (0.2)		0.362
Type 5B	1 (0.2)	1 (0.2)		>0.99
Type 4	0	0		–
Type 3	16 (4.0)	13 (3.1)		0.572
Type 3A	5 (1.2)	2 (0.5)		0.276
Type 3B	9 (2.2)	10 (2.4)		>0.99
Type 3C	2 (0.5)	1 (0.2)		0.616
Type 2	18 (4.5)	11 (2.6)		0.185

Values are n (%), unless indicated otherwise. *Stent thrombosis was defined according to the criteria of the Academic Research Consortium. †Type 5 refers to fatal bleeding; Type 4 are coronary artery bypass–related bleedings; Type 3 bleedings are divided into 3A: overt bleeding plus hemoglobin drop of 3 to <5 g/dl or any transfusion with overt bleeding, 3B: overt bleeding plus hemoglobin drop ≥5 g/dl or cardiac tamponed or bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) or bleeding requiring intravenous inotropes, 3C: intracranial hemorrhage or intraocular bleed compromising vision; Type 2 are any overt, actionable sign of hemorrhage that does not fit the criteria for Types 3, 4, or 5, but does meet at least 1 of the following criteria: 1) requiring nonsurgical, medical intervention by a health care professional; 2) leading to hospitalization or increased level of care; and 3) prompting evaluation.

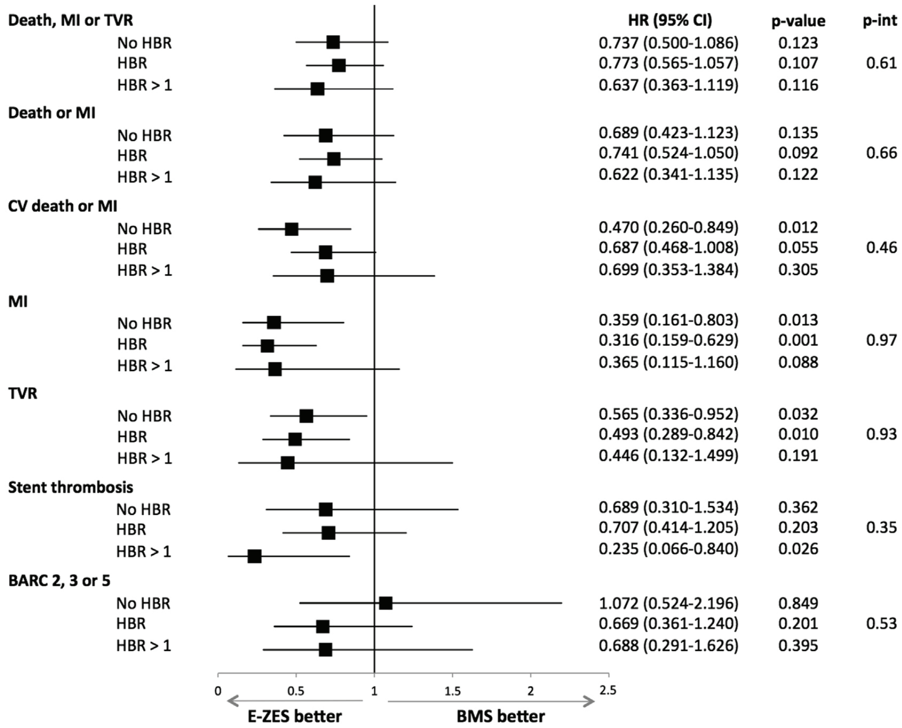
BARC = Bleeding Academic Research Consortium; HBR = high bleeding risk; TIMI = Thrombolysis In Myocardial Infarction.

patients (Table 2), reflecting a higher TVR rate in the former group of patients. Bleeding events trended higher in the BMS compared with the E-ZES groups, reflecting the longer DAPT after BMS implantation.

COMPARISON WITH OTHER STUDIES. Randomized controlled trials, which have so far compared DES versus BMS, have recommended either a longer DAPT regimen in the DES arm or a similarly prolonged course of DAPT in BMS patients so to match the extended course of therapy after DES (19,20). Hence, no study has so far disentangled the effects of DES versus BMS from those offered by long-term DAPT.

The recent DAPT trial (21) that compared 30- versus 12-month duration of DAPT after stent implantation in patients with stable or unstable coronary artery disease, showed a significant decrease of very late stent thrombosis and major adverse cardiovascular and cerebrovascular events at 30 months after stent implantation in the long-term DAPT arm. Yet, patients exposed to long-term DAPT also experienced a borderline and significant increase in overall mortality at 30 and 33 months, respectively (21). Patients

FIGURE 4 **Clinical Outcomes in Zotarolimus-Eluting Stents Versus BMS According to the Absence or Presence of a Single or Multiple HBR Features**



Patients without HBR criteria (No HBR), fulfilling 1 (HBR 1) or more than 1 (HBR>1) HBR criteria are shown, with HR and 95% confidence intervals (CI), for the primary endpoint of all-cause death, MI, and TVR; death or MI; cardiovascular (CV) death or MI; MI; TVR; definite, probable, or possible stent thrombosis and BARC type 2, 3, or 5 bleeding events among patients randomly assigned to either E-ZES or BMS group. P-int = p value for interaction. Abbreviations as in **Figures 2 and 3**.

who received BMS implantation, at discretion of the treating physician were excluded from primary analysis, whereas only patients who were free from ischemic and bleeding events after 12-month DAPT were included in the study. Hence, patients at HBR were excluded from the DAPT trial, and this study was not designed to answer the question as to which type of stent should be better used at the time of intervention in patients fulfilling 1 or more HBR criteria.

The WOEST (What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) trial (22) included a total of total of 573 patients receiving oral anticoagulant (~70% due to atrial fibrillation) who were randomly assigned to clopidogrel alone (experimental treatment) or clopidogrel plus aspirin (control treatment) for a period of 1 month after BMS and 12 months after DES implantation. The primary endpoint, consisting of any TIMI bleeding, was significantly lower in the dual therapy group, largely driven by minimal or minor bleeding, without an increase in MI, TVR, stroke or stent thrombosis.

The ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen–Testing of a Six-Week Versus a six-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting) trial (23) is the largest randomized trial investigating triple therapy after DES implantation in patients with clinical indication to oral anticoagulant (~85% due to atrial fibrillation). A total of 614 patients were randomly assigned to therapy with clopidogrel for 6 weeks (n = 307) or 6 months (n = 307). The primary endpoint, a composite of death, MI, ST, stroke, or TIMI major bleeding, failed to show the anticipated superiority of short- versus long-term triple therapy duration.

The ZEUS study is therefore the first randomized controlled trial comparing 2 different stent types in HBR patients after mandating a similarly short course of DAPT. An interesting observation was that BMS patients received a longer cumulative DAPT duration as compared with those assigned to E-ZES, reflecting the more frequent need to re-start DAPT after reintervention for in-stent restenosis or ST. Given the observation that long-term DAPT duration may be paramount in patients receiving DES implantation for the treatment of an in-stent restenosis (24), our current findings may further justify the selection of a safe DES over a BMS in this patient population to minimize the risk of in-stent restenosis, which would then require reintervention followed by a prolonged course of DAPT.

The lower risk of MI or ST observed in patients treated with E-ZES as compared to BMS, despite a similarly short DAPT duration in both stent groups, is consistent with the mounting evidence that lower in-stent intimal hyperplasia may carry not only greater efficacy (e.g., lower TVR), but also improved safety (e.g., lower ST or stent-related MIs) (4, 25,26).

STUDY LIMITATIONS. By design, our study does not address the topic of optimal DAPT duration after stenting. On the other hand, the results of our investigation challenge the current wisdom that BMS is per se a safer coronary device as compared with DES under a similarly short DAPT duration. Because of the unique properties of the E-ZES, our results should not be extrapolated to newer-generation DES coated with the same or other antiproliferative agents and diverse or no polymers. As for all substudies, type I and type II errors are not corrected for. Hence, our results should be hypothesis-generating. Further research is needed to ascertain whether the tailored DAPT regimen tested in our study can be safely implemented in patients receiving other DES. The recently reported LEADERS-FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent) trial (27) largely reproduced our study findings in terms of both better efficacy and safety in an HBR population after the use of a drug-coated stent as compared with the corresponding BMS. Therefore, it remains to be seen whether other permanent or bioresorbable polymer-based DES could be safely employed after a 30-day DAPT regimen.

CONCLUSIONS

Our study provides proof of concept that in HBR patients who undergo stent implantation, E-ZES as compared with conventional BMS followed by 30-day DAPT regimen provides superior efficacy and safety. Future studies are needed to assess the tolerability and safety of more contemporary DES when followed by an abbreviated DAPT duration in this challenging patient population.

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PERSPECTIVES

WHAT IS KNOWN? The use of DES instead of BMS is matter of debate in patients at high bleeding risk, in whom the benefits of DES in terms of ischemic endpoints could be reduced by an increase of bleeding events due to a long-term DAPT.

WHAT IS NEW? Our study demonstrated that the use of a specific drug-eluting stent (zotarolimus-eluting Endeavor Sprint stent), followed by a very short DAPT regimen, in a HBR population with stable or unstable coronary artery disease, provides superior efficacy and safety as compared with available BMS.

WHAT IS NEXT? Further research is needed to ascertain whether an abbreviated DAPT regimen, as tested in our study, can be safely implemented in patients receiving other types of DES.

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KEY WORDS dual antiplatelet therapy, high bleeding risk, zotarolimus-eluting stent(s)

APPENDIX For supplemental figures and tables, please see the online version of this article.

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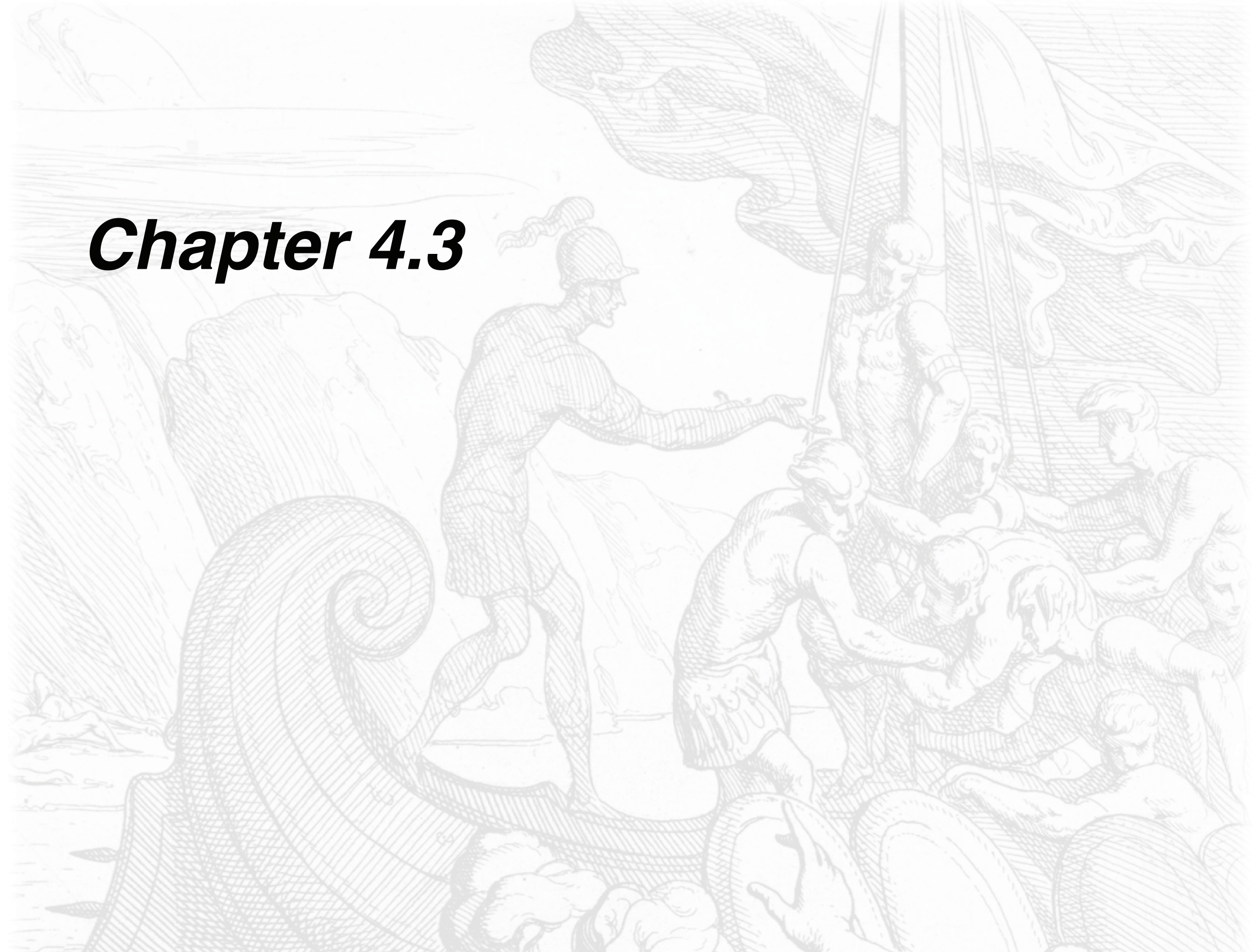

Chapter 4.3

Role of stent type and of duration of dual antiplatelet therapy in patients with chronic kidney disease undergoing percutaneous coronary interventions. Is bare metal stent implantation still a justifiable choice? A post-hoc analysis of the all comer PRODIGY trial.

Gabriele Crimi, Sergio Leonardi, ***Francesco Costa***, Marianna Adamo, Sara Ariotti, Marco Valgimigli

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Role of stent type and of duration of dual antiplatelet therapy in patients with chronic kidney disease undergoing percutaneous coronary interventions. Is bare metal stent implantation still a justifiable choice? A post-hoc analysis of the all comer PRODIGY trial☆

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ABSTRACT

Aim: Chronic kidney disease (CKD) is a powerful predictor of major cardiovascular events and stent thrombosis (ST) in patients undergoing percutaneous coronary interventions (PCI). No randomized data are available to compare, and guide the selection of type of stent between bare metal (BMS) or drug eluting stent (DES) in this population.

Methods and results: We performed a post-hoc analysis of the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY) trial, in which stable or unstable patients with coronary artery disease undergoing PCI were randomized 1:1:1:1 to receive BMS, paclitaxel- (PES), zotarolimus- (ZES-S), or everolimus- (EES) eluting stent. A total of 2003 patients were randomized, and 22 patients were excluded for missing serum creatinine leading to a final population of 1981 patients. Primary outcome was definite or probable ST. We also assessed MACE (myocardial infarction, stroke, or death), and all-cause death, as secondary outcome.

CKD, defined with estimated glomerular filtration rate <60 ml/min/1.73 m^2, was found in 373 patients (18.8%). The incidence of ST at 2 years was 5.1% in CKD and 2.1% in non-CKD patients (HR 2.57, 95% confidence interval (CI) 1.46 to 4.52, $p < 0.001$). At multivariable regression we found that patients randomized to EES or ZES-S, but not PES, had lower risk of ST at two years as compared with BMS: adjusted HR = 0.288, 95% CI [0.107–0.778, p = 0.014] and HR = 0.394, 95% CI [0.164–0.947, p = 0.037] respectively. The number of patients needed to be treated to prevent 1 ST with an EES vs BMS was 20 in CKD and 50 in patients without CKD. EES patients had the lowest incident MACE events 26.4% as compared to BMS 35.1%, ZES-S 33.0%, or PES 35.7% patients, p = 0.551. All-cause death was lowest in ZES-S group 10.6% as compared to BMS 18.1%, PES 25.5% and EES 14.9%, p = 0.040. We found no significant interaction between DAPT duration (6 vs 24 months) and stent type on primary outcome, $P_{INT} = 0.47$ for BMS, $P_{INT} = 0.57$ for PES, $P_{INT} = 0.41$ for ZES-S and $P_{INT} = 0.28$ for EES.

Conclusions: In an all-comer population of patients with stable and unstable CAD, CKD at baseline was associated with a double risk of ST and MACE. CKD patients receiving EES had less than half risk of ST 2 years after PCI as compared with BMS and PES. Our analysis suggests that 2nd generation limus-based stent should be favored over paclitaxel-based DES or BMS to reduce ST and MACE in CKD patients.

1. Introduction

Chronic kidney disease (CKD) is common in patients undergoing percutaneous coronary interventions (PCI), especially in those presenting with acute coronary syndromes [1–3], and has been consistently associated with an increased risk of ischemic events, including stent thrombosis (ST) [4]. CKD is a powerful predictor of subsequent ST with more than 6-fold increased risk [5] thus raising possible concerns of using of drug eluting stents (DES) in these patients [6]. The European Guidelines for myocardial revascularization (2010) have recommended that DES should not be preferred and used indiscriminately over bare metal stents (BMS) in patients with CKD [7] although this recommendation was reformulated in the subsequent edition.

While randomized data are lacking in this setting, observations on safety and efficacy of DES in CKD patients have not supported these

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concerns and showed similar safety [8–10] or potential reduction of major adverse cardiovascular events (MACE) of DES compared with BMS [3,11]. These data however have several limitations: i) Stent type (DES or BMS) was left at operator's preference [3,8–11], ii) first-generation DES, which are known to be more susceptible to ST, were used [3,8–11] and iii) ST was not systematically collected using the Academic Research Consortium (ARC) criteria [3,10,11].

To overcome in part these limitations we performed a post-hoc analysis of the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY trial) [12,13] with the primary purpose to assess, in an all-comer population of patients with stable or unstable coronary artery disease undergoing PCI, long term outcome of patients with CKD at presentation who were randomized to receive BMS, paclitaxel-eluting stent (PES), zotarolimus-eluting stent (ZES-S) or everolimus-eluting stent (EES) at the time of PCI.

2. Methods

2.1. Study design and population

The design of the PRODIGY trial has been published [14]. PRODIGY was an open label, 2 by 4 randomized, multicenter, controlled trial, testing the hypothesis that 24 months of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel could reduce the composite of all-cause death, stroke, or MI as compared with 6 months DAPT in an all-comer population undergoing PCI [12]. At day 0 patients with an indication to coronary stenting randomly underwent implantation BMS (no active late loss inhibition), Endeavor Sprint ZES-S (mild late loss inhibition), PES (moderate late loss inhibition), or Xience V EES (high late loss inhibition). At 30 days, patients within each stent group were randomly assigned to receive 6 months or up to 24 months of DAPT (80 to 160 mg aspirin orally and 75 mg clopidogrel orally). The key inclusion criterion was the presence of coronary atherosclerosis requiring PCI, thus including patients with stable coronary artery disease (CAD), non-ST-segment elevation acute coronary syndrome (NSTE-ACS), or ST-segment elevation acute coronary syndrome (STE-ACS). Key exclusion criteria were: known acetylsalicylic acid or clopidogrel allergy; major surgery within 15 days; planned surgery in the following 24 months, active bleeding or bleeding diathesis; and concomitant or foreseeable oral anticoagulant treatment. All patients received an office visit at 30 days, 6 months, and 24 months after randomization.

2.2. Definitions

CKD was defined by glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. The modification of diet in renal disease formula was used to compute eGFR:

eGFR [ml/min/1.73 m^2] = 186 ∗ baseline SCr [mg/dl] − 1.154 ∗ Age [years] − 0.203 ∗ (0.742 if Female) ∗ (1.21 if African descent).

Our primary endpoint was the incidence of definite or probable ST based on the ARC criteria [15]. Secondary endpoints considered were: the composite of all-cause death, stroke or myocardial infarction; all-cause death; myocardial infarction; stroke; and target lesion revascularization. All endpoints were assessed at 24 months. All potential endpoints were individually adjudicated by a clinical event committee blinded to randomized treatment allocation.

2.3. Statistical analysis

Baseline categorical variables were expressed as count (percentage) and compared with the χ^2 test. Baseline continuous variables were expressed as median (interquartile range) and compared with the Wilcoxon rank sum between the groups defined by CKD (binary) and ANOVA rank sum test between the groups defined by stent type (four levels).

The hazard ratios (HR) and 95% confidence interval (CI) of the four randomized groups of patients defined by stent type on outcome were estimated by fitting a Cox proportional hazard regression model with the bare metal stent group set as reference category. The association between stent type and clinical outcome was adjusted for potential confounders and established risk factors of stent thrombosis [5]. In addition to CKD (as defined above), the following covariates were included a priori into the model for risk adjustment: age, left ventricular ejection fraction (LVEF), diabetes mellitus, ACS at presentation (vs stable angina), and total stent length. Additionally, the experimental treatments 6 vs 24 month duration of dual antiplatelet therapy and stent type were included in the model.

There were no missing observations for all the covariates except for LVEF (N = 139, 6.9%) and stent length (N = 6, 0.3%). Sensitivity analysis using case-deletion and the exclusion of the aforementioned covariates were used to address the role of missingness. Sensitivity analysis by including eGFR as a continuous variable was also performed. The proportionality assumption was checked either by visual estimation of the log-cumulative hazard versus log-time (sFigure 1) or by using Schoenfeld residuals which failed to reject the null hypothesis that event rate was affected by time (p = 0.46). A 2-sided probability value p ≤ 0.05 was considered significant. Data were analyzed in the R version 3.1.3 software environment [16] and "Survival" package.

3. Results

3.1. Patients

From December 2006 to December 2008, 2789 patients were screened for eligibility, 2013 were randomized to one of four different stent types [12,13]. Ten patients, who withdrawn informed consent within 30 days of visit, and 22 patients who had incomplete baseline SCr data, were excluded (Fig. 1). This led to a final population of 1981 patients. Baseline variables are outlined in Table 1; 1833 were censored at 2 years of follow-up.

Overall, 373 (18.8%) patients had CKD at baseline. Within this group of patients, baseline (Table 1) and procedural (Table 2) characteristics were fairly balanced across the four stent arms. Patients allocated to the BMS group were older 78 [71–82] years compared with the ZES-S group 72 [66–79] years, PES group 76 [70–81] years and EES 75

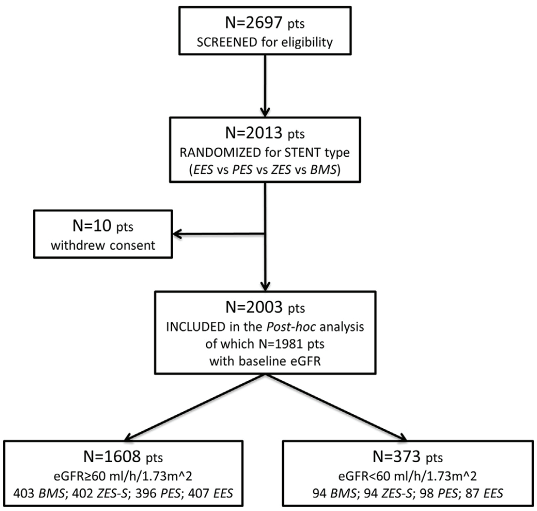

Fig. 1. Patient flow.

Table 1
Baseline characteristics. Data are count (percentage) or median [interquartile range]. eGFR was calculated with the modification of diet in renal disease formula. Abbreviations: BMS = bare metal stent, ZES-S = zotarolimus eluting stent Endeavor Sprint, PES = paclitaxel eluting stent, EES = everolimus eluting stent. BMI = body mass index, CAD = coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary interventions, CABG = coronary artery bypass grafting, NSTE = non ST-elevation, ACS = acute coronary syndrome, STE = ST-elevation, PAD = peripheral artery disease, LVEF = left ventricular ejection fraction, eGFR = estimated glomerular filtration rate.

	eGFR ≥ 60 ml/min/1.73 m^2						eGFR < 60 ml/min/1.73 m^2						
	BMS	ZES-S	PES	EES	p-Value within eGFR ≥ 60	Overall	BMS	ZES-S	PES	EES	p-Value within eGFR < 60	Overall	p-Value between eGFR groups
	N = 403	N = 402	N = 396	N = 407		N = 1608	N = 94	N = 94	N = 98	N = 87		N = 373	
Male gender	283 (70.2)	308 (76.6)	301 (76)	319 (78.4)	0.043	1211 (75.3)	76 (80.9)	81 (86.2)	77 (78.6)	70 (80.5)	0.571	304 (81.5)	0.013
Age (years)	68 [60–75]	67 [59–74.8]	67 [58–75]	67 [59–75]	0.381	67 [59–75]	78 [71.2–81.8]	72.5 [66.2–79]	76 [70.2–81]	75 [71–80]	0.017	75 [70–81]	<0.001
BMI (kg/m^2)	26.8 [24.6–29.4]	26.8 [24.6–29.1]	26.4 [24.2–29.1]	26.8 [24.4–29]	0.579	26.7 [24.5–29.3]	26.1 [24.3–28.1]	25.7 [24.2–29.3]	27.4 [25.2–30.4]	26.9 [24.2–30]	0.067	26.4 [24.4–29.4]	0.699
Diabetes	77 (19.1)	92 (22.9)	93 (23.5)	90 (22.1)	0.447	352 (21.9)	33 (35.1)	25 (26.6)	52 (53.1)	22 (25.3)	<0.001	132 (35.4)	<0.001
Current smoking	112 (27.9)	108 (27)	100 (25.3)	105 (25.8)	0.827	425 (26.5)	13 (13.8)	20 (21.3)	9 (9.2)	12 (14)	0.124	54 (14.5)	<0.001
Hyperlipidemia	209 (51.9)	216 (53.9)	227 (57.3)	229 (56.3)	0.405	881 (54.8)	44 (46.8)	45 (47.9)	51 (52)	59 (67.8)	0.017	199 (53.4)	0.648
Hypertension	295 (73.2)	262 (65.5)	286 (72.2)	274 (67.3)	0.048	1117 (69.6)	78 (83)	77 (81.9)	76 (77.6)	75 (86.2)	0.489	306 (82)	<0.001
Previous MI	89 (22.1)	88 (22)	114 (28.8)	99 (24.3)	0.087	390 (24.3)	24 (25.5)	32 (34.4)	42 (42.9)	41 (47.7)	0.011	139 (37.5)	<0.001
Previous PCI	48 (11.9)	65 (16.2)	88 (22.2)	74 (18.2)	0.001	275 (17.1)	10 (10.6)	19 (20.2)	33 (34.4)	27 (31)	<0.001	89 (24)	0.003
Previous CABG	16 (4)	42 (10.5)	42 (10.6)	55 (13.5)	<0.001	155 (9.7)	11 (11.7)	15 (16)	12 (12.2)	17 (19.8)	0.39	55 (14.8)	0.005
Emergency setting	101 (25.1)	114 (28.4)	96 (24.2)	117 (28.7)	0.36	428 (26.6)	24 (25.5)	14 (14.9)	16 (16.3)	19 (21.8)	0.224	73 (19.6)	0.006
Diagnosis at admission					0.152						0.02		<0.001
Stable CAD	97 (24.1)	110 (27.4)	112 (28.3)	100 (24.6)		419 (26.1)	13 (13.8)	20 (21.3)	30 (30.6)	16 (18.4)		79 (21.2)	
NSTE-ACS	164 (40.7)	136 (33.8)	162 (40.9)	166 (40.8)		628 (39.1)	44 (46.8)	52 (55.3)	47 (48)	49 (56.3)		192 (51.5)	
STE-ACS	142 (35.2)	156 (38.8)	122 (30.8)	141 (34.6)		561 (34.9)	37 (39.4)	22 (23.4)	21 (21.4)	22 (25.3)		102 (27.3)	
Dialysis	NA	NA	NA	NA	NA	NA	6 (9.8)	5 (8.9)	2 (2.9)	2 (3.4)	0.241	15 (6.1)	NA
PAD	40 (9.9)	43 (10.7)	39 (9.8)	38 (9.3)	0.935	160 (10)	17 (18.1)	31 (33)	19 (19.4)	24 (27.6)	0.055	91 (24.4)	<0.001
Cardiogenic shock	4 (1)	5 (1.2)	7 (1.8)	2 (0.5)	0.381	18 (1.1)	3 (3.2)	2 (2.1)	3 (3.1)	1 (1.1)	0.882	9 (2.4)	0.09
LVEF (%)	55 [45–50]	55 [45–60]	55 [55–60]	55 [45–60]	0.985	55 [45–60]	43 [40–55]	51 [45–60]	45 [35–55]	50 [40–55]	0.01	50 [40–55]	<0.001
Hemoglobin (g/dl)	13.5 [12.7–14.7]	13.9 [12.7–14.9]	13.9 [12.7–14.9]	14.0 [13.0–14.8]	0.046	13.9 [12.8–14.9]	12.8 [11.3–15.0]	13.3 [12.4–14.5]	12.5 [11.1–14.4]	12.9 [11.6–14.2]	0.128	13.0 [11.5–14.4]	<0.001
eGFR (ml/min/1.73 m^2)	87 [76–102]	84.5 [74–101]	86 [76–102]	85 [72.5–100]	0.331	85 [75–101]	48 [41–56]	52 [42.5–57]	51 [44–55.8]	52 [41–57]	0.527	51 [42–56]	<0.001

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Table 2
Procedural variables. Data are count (percentage) or median [interquartile range]. Abbreviations: VD = vessel disease, LM = left main, LAD = left anterior descending artery, CFX = circumflex artery, RCA = right coronary artery, SVG = saphenous vein graft, PCI = percutaneous coronary interventions. Other abbreviations as in Table 1.

	eGFR ≥ 60 ml/min/1.73 m²						eGFR < 60 ml/min/1.73 m²						
	BMS	ZES-S	PES	EES	p-Value within eGFR ≥ 60	Overall	BMS	ZES-S	PES	EES	p-Value within eGFR < 60	Overall	p value between eGFR groups
	N = 403	N = 402	N = 396	N = 407		N = 1608	N = 94	N = 94	N = 98	N = 87		N = 373	
Vessel disease													
1VD	151 (37.5)	117 (29.1)	125 (31.6)	123 (30.2)	0.014	516 (32.1)	23 (24.5)	22 (23.4)	22 (22.4)	13 (14.9)	0.567	80 (21.4)	<0.001
2VD	142 (35.2)	162 (40.3)	150 (37.9)	132 (32.4)		586 (36.4)	27 (28.7)	29 (30.9)	36 (36.7)	28 (32.2)		120 (32.2)	
3VD	110 (27.3)	123 (30.6)	121 (30.6)	152 (37.3)		506 (31.5)	44 (46.8)	43 (45.7)	40 (40.8)	46 (52.9)		173 (46.4)	
Number treated lesions	1 [1–2]	1 [1–2]	1 [1–2]	1 [1–2]	0.288	1 [1–2]	1 [1–2]	1 [1–2]	1 [1–2]	1 [1–2]	0.218	1 [1–2]	0.584
Number treated vessels	1 [1–1.5]	1 [1–2]	1 [1–2]	1 [1–2]	0.723	1 [1–2]	1 [1–1.8]	1 [1–2]	1 [1–2]	1 [1–2]	0.663	1 [1–2]	0.187
Artery treated													
LM	6 (1.5)	24 (6)	25 (6.3)	24 (5.9)	0.004	79 (4.9)	7 (7.4)	6 (6.4)	7 (7.1)	13 (14.9)	0.151	33 (8.8)	0.005
LAD	226 (56.1)	227 (56.5)	223 (56.3)	193 (47.4)	0.022	869 (54)	48 (51.1)	42 (44.7)	47 (48)	38 (43.7)	0.742	175 (46.9)	0.015
CFX	120 (29.8)	113 (28.1)	131 (33.1)	149 (36.6)	0.048	513 (31.9)	25 (26.6)	33 (35.1)	31 (31.6)	34 (39.1)	0.325	123 (33)	0.735
RCA	153 (38)	139 (34.6)	133 (33.6)	142 (34.9)	0.597	567 (35.3)	37 (39.4)	39 (41.5)	40 (40.8)	34 (39.1)	0.985	150 (40.2)	0.083
SVG	3 (0.7)	9 (2.2)	10 (2.5)	9 (2.2)	0.25	31 (1.9)	1 (1.1)	4 (4.3)	2 (2)	4 (4.6)	0.399	11 (2.9)	0.301
At least 1 complex (B2–C lesion)	247 (61.3)	271 (67.4)	271 (68.4)	249 (61.2)	0.047	1038 (64.6)	67 (71.3)	75 (79.8)	73 (74.5)	60 (69)	0.373	275 (73.7)	
Number of stent	1 [1–2]	2 [1–2]	2 [1–2]	1 [1–2]	0.581	1 [1–2]	1 [1–2]	2 [1–2]	1 [1–2]	2 [1–3]	0.011	1 [1–2]	0.996
Stent diameter	3 [2.6–3.2]	3 [2.8–3.3]	3 [2.8–3.2]	3 [2.6–3.2]	0.563	3 [2.7–3.2]	3 [2.8–3.5]	2.9 [2.6–3.5]	3 [2.8–3]	3 [2.8–3.3]	0.354	3 [2.8–3.3]	0.241
Total stent length	28 [18–46]	30 [24–48]	32 [20–51]	28 [18–46]	0.008	30 [20–48]	24 [18–42.5]	36 [24–50]	28 [20–48]	38 [23–62]	0.066	30 [20–51]	0.709
Quantitative coronary analysis													
Lesion length (mm)	11.6 [8–16.1]	11.4 [7.7–16.9]	10.6 [7.8–17.9]	11.3 [7.8–15.9]	0.789	11.3 [7.8–17.1]	11.8 [7.8–15.8]	10.3 [8–18.3]	13.5 [8–23.5]	11.4 [7.6–16.6]	0.075	11.8 [7.8–18.4]	0.199
Stenosis before PCI (%)	79 [70–90]	76.8 [68–88]	80 [69.5–91]	80 [70–90]	0.072	79.2 [69–90]	75.5 [69–88]	82 [69–90]	80.5 [70–83]	76.5 [67–85]	0.301	77 [68.6–87.8]	0.199
Stenosis after PCI (%)	9 [4–14]	9 [3–14]	10 [4–14.5]	10 [6.2–14.8]	0.265	9 [4–14.5]	12 [8–17]	8 [3–12]	8 [5.5–13]	9 [4–12.8]	<0.001	9 [4–13]	0.56
In stent restenosis PCI	0 (0)	26 (6.5)	30 (7.6)	20 (4.9)	<0.001	76 (4.7)	0 (0)	4 (4.3)	10 (10.2)	6 (6.9)	0.015	20 (5.4)	0.703

Table 3
Procedural variables. Data are count (percentage). Abbreviations: MACE = major adverse cardiovascular events. MI = myocardial infarction. ST = stent thrombosis (Academic Research Consortium definition). TLR = target lesion revascularization. TVR = target vessel revascularization. TIMI = Thrombolysis In Myocardial Infarction. GUSTO = Global Utilization Of Streptokinase And TPA For Occluded Arteries. BARC = Bleeding Academic Research Consortium. Other abbreviations as in Table 1.

	eGFR ≥ 60 ml/min/1.73 m^2						eGFR < 60 ml/min/1.73 m^2						
	BMS	ZES-S	PES	EES	p-Value within eGFR ≥ 60	Overall	BMS	ZES-S	PES	EES	p-Value within eGFR < 60	Overall	p value overall
	N = 403	N = 402	N = 396	N = 407		N = 1608	N = 94	N = 94	N = 98	N = 87		N = 373	
MACE													
Death	28 (6.9)	24 (6)	24 (6.1)	18 (4.4)	0.481	94 (5.8)	17 (18.1)	10 (10.6)	25 (25.5)	13 (14.9)	0.040	65 (17.4)	<0.001
MI	50 (12.4)	37 (9.2)	58 (14.6)	40 (9.8)	0.061	185 (11.5)	20 (21.3)	22 (23.4)	15 (15.3)	14 (16.1)	0.416	71 (19.0)	<0.001
Stroke	14 (3.5)	8 (2)	7 (1.8)	5 (1.2)	0.145	34 (2.1)	4 (4.3)	3 (3.2)	6 (6.1)	1 (1.1)	0.357	14 (3.8)	0.048
Death MI, or stroke	76 (18.9)	65 (16.2)	75 (18.9)	58 (14.3)	0.231	274 (17)	33 (35.1)	31 (33)	35 (35.7)	23 (26.4)	0.551	122 (32.7)	<0.001
Stent related events													
Definite or probable ST	11 (2.7)	6 (1.5)	13 (3.3)	3 (0.7)	0.045	33 (2.1)	7 (7.4)	1 (1.1)	9 (9.2)	2 (2.3)	0.026	19 (5.1)	0.002
Definite, probable, or possible ST	19 (4.7)	17 (4.2)	19 (4.8)	7 (1.7)	0.076	62 (3.9)	13 (13.8)	7 (7.4)	19 (19.4)	6 (6.9)	0.019	45 (12.1)	<0.001
TLR	74 (18.4)	43 (10.7)	24 (6.1)	15 (3.7)	<0.001	156 (9.7)	12 (12.8)	14 (14.9)	10 (10.2)	11 (12.6)	0.780	47 (12.6)	0.117
TVR	77 (19.1)	46 (11.4)	29 (7.3)	20 (4.9)	<0.001	172 (10.7)	15 (16)	14 (14.9)	10 (10.2)	11 (12.6)	0.628	50 (13.4)	0.126
Bleeding events													
TIMI minor or major	4 (1.0)	12 (3.0)	12 (3.0)	3 (0.7)	0.244	31 (1.9)	7 (7.4)	2 (2.1)	6 (6.1)	4 (4.6)	0.348	19 (5.1)	<0.001
GUSTO moderate or severe	4 (1.0)	11 (2.7)	13 (3.3)	4 (1)	0.033	32 (2.0)	8 (8.5)	6 (6.4)	5 (5.1)	9 (10.3)	0.545	28 (7.5)	<0.001
BARC 3 or 5	5 (1.2)	14 (3.5)	15 (3.8)	4 (1)	0.011	38 (2.4)	8 (8.5)	4 (4.3)	7 (7.1)	9 (10.3)	0.458	28 (7.5)	<0.001

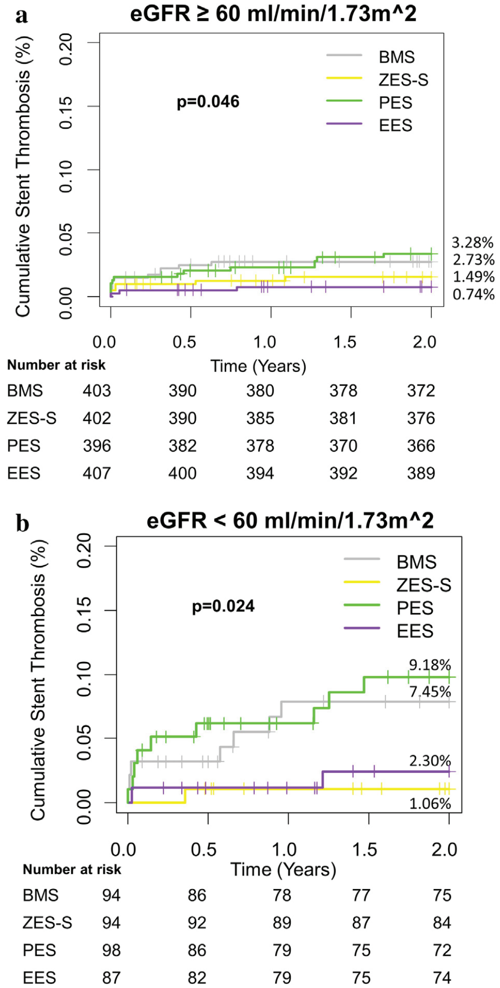

Fig. 2. Cumulative incidence of definite or probable stent thrombosis (Academic Research Consortium definition) in non-CKD patients (panel A) and CKD patients (panel B), vertical lines represent single event. Abbreviations as in Table 1.

[71–80] years, ($p < 0.017$). Diabetes was less prevalent in EES 22 (25.3%) as compared with the ZES-S group 25 (26.6%), BMS 33 (35.1%) or PES 52 (53.1%), $p < 0.001$. ACS at admission was more prevalent in the BMS group 81 (86.2%) compared to ZES-S 74 (78.7%), PES 68 (69.4%) and EES 71 (81.6%), $p = 0.02$. LVEF was lower in the BMS group 43 [40–55] % compared to ZES-S 51 [45–60] %, PES 45 [35–55] % and EES 50 [40–55] %, $p = 0.01$.

3.2. Stent thrombosis

Definite and probable ST incidence in CKD patients after a 2 year follow-up was 5.1%. As compared with patients with normal renal function, CKD patients had an increased risk of ST at two years with a hazard ratio of 2.57, 95% confidence interval (CI) [1.46–4.52] Table 3; Fig. 2a,b.

After adjusting for established risk factors and potential confounders, we observed that CKD patients randomized to EES or ZES-S, but not PES, had lower risk of ST at two years of follow-up as compared with BMS, adjusted HR = 0.288, 95% CI [0.107–0.778, $p = 0.014$] and

HR = 0.394, 95% CI [0.164–0.947, p = 0.037] respectively, Table 4. Similar patterns of reduced incidence of definite or probable ST were observed in patients without CKD Table 3. Other independent predictors of ST were: eGFR < 60 ml/min/1.73 m^2, HR = 2.218 95% CI [1.189–4.138, p = 0.012], LVEF (%), HR = 0.969 95% CI [0.945–0.994, p = 0.015] and ACS at presentation vs stable CAD, HR = 3.981 95% CI [1.219–13.9 p = 0.022].

The number of patients needed to be treated with an EES vs BMS to prevent 1 definite or probable ST at 2 years was 20 in patients with CKD and 50 in patients without CKD.

We found no significant interaction between either DAPT duration (6 vs 24 months) $P_{INT} = 0.47$ for BMS, $P_{INT} = 0.57$ for PES, $P_{INT} = 0.41$ for ZES-S and $P_{INT} = 0.28$ for EES, or eGFR level (<60 vs ≥60 ml/min/1.73 m^2) $p_{int} = 0.78$ for BMS, $p_{int} = 0.63$ for PES, $p_{int} = 0.20$ for ZES-S and $p_{int} = 0.79$ for EES on ST outcome.

Both EES and ZES-S were associated with lower adjusted ST risk also when compared with PES, Table 5.

3.3. Major adverse cardiovascular events

Patients with CKD at baseline had an increased risk of MACE at two years of follow-up with a hazard ratio of 2.04, 95% CI [1.65–2.52] as compared with patients with eGFR > 60 ml/min/1.73 m^2, Table 3; Fig. 3a,b.

CKD patients randomized to EES had lower incident MACE events 26.4% as compared to patients randomized to BMS 35.1%, ZES-S 33.0%, or PES 35.7%, p = 0.551 (Fig. 3b). The individual components of the composite endpoint were significantly different among the stent allocation arms (Table 3): all-cause death was lowest in the ZES-S group 10.6% as compared with BMS 18.1%, PES 25.5% and EES 14.9%, p = 0.040, Fig. 4b. At multivariable analysis age, eGFR < 60 ml/min/1.73, LVEF, diabetes and total stent length, but not stent type were independent predictors of MACE after two years of follow-up, sTable 1, the result was maintained by including eGFR as a continuous variable. Consistently age, eGFR < 60 ml/min/1.73 and LVEF, but not stent type were independent predictors of all-cause death, sTable 2.

3.4. Target lesion revascularization

Patients with CKD had non-significantly more TLR at two years of follow-up as compared with patients without CKD, with a hazard ratio of 1.330, 95% CI [0.957–1.840, p = 0.089]. TLR was not significantly different among the four stent arms in CKD patients Table 3, sFigure 2b. However, the use of drug eluting stents including either ZES-S, or PES or EES significantly reduced TLR as compared with BMS at multivariable analysis, sTable 3, sFigure 2a,b.

Table 4
Cox proportional hazard regression. Patients included N = 1845, patients excluded for missing data N = 158. Definite and probable stent thrombosis events = 51. Abbreviation as in Tables 1 and 2.

y = ST (definite or probable)	Hazard ratio	Lower 95% CI	Upper 95% CI	p-Value
Age (years)	1.000	0.976	1.026	0.973
eGFR < 60 ml/min/1.73 m^2	2.218	1.189	4.138	0.012
LVEF (%)	0.969	0.945	0.994	0.015
Diabetes	1.121	0.604	2.081	0.718
ACS vs stable CAD	3.981	1.219	13.00	0.022
6 vs 24 months DAPT	1.398	0.798	2.448	0.241
Total stent length (mm)	1.000	0.990	1.009	0.973
Stent type				
BMS (reference)				
ZES-S	0.394	0.164	0.947	0.037
PES	1.180	0.626	2.226	0.608
EES	0.288	0.107	0.778	0.014

4. Discussion

In an all-comer population of patients with stable and unstable CAD, CKD was observed in ≈ one out of five patients and was associated with doubled risk of MACE and ST.

Similar to prior observations in PRODIGY patients without CKD [12,13], we observed that CKD patients randomized to receive EES or ZES-S had lower adjusted risk of definite or probable ST as compared with patients receiving BMS or PES, with an adjusted hazard ratio of 0.409 [0.209–0.797] for EES, which was directionally consistent for ZES-S 0.789 [0.459–1.357] as compared with BMS. Patients who received EES had also lower adjusted risk of ST as compared with patients who received PES 0.360 [0.187–0.969], but not ZES-S 0.518 [0.257–1.041], Table 5. This association was not modified by DAPT duration (6 vs 24 months) as the interaction test was non-significant for each stent type.

CKD patients who were randomized to receive EES had the lowest numerical MACE and all-cause death incidence after two years of follow-up as compared with BMS, ZES-S or PES patients. However, unlike ST, the association between reduced MACE and specifically all-cause death with EES was not maintained after adjusting for confounders and covariates with multivariable analysis. This suggests that it may be either a spurious association or β type error. In fact ST incidence in CKD patients may only explain part of the worse outcome of these patients which were older and associated with several baseline variables of increased risk (Table 1).

CKD patients had a trend toward higher TLR after two years of follow-up, however, there was no difference between BMS, and either 1st or 2nd generation DES. This finding may be explained by a numerically higher TLR incidence in the DES group (both 1st and 2nd generation), while TLR with BMS was numerically similar in both CKD and non-CKD patients (Table 3, sTable 3, sFigure 2a,b).

There may be several possible reasons to explain increased ST incidence in CKD patients as compared to patients without CKD patients.

First, CKD is associated with systemic persistent inflammation endothelial dysfunction [17,18], which may interact differently in patients receiving BMS as compared with 1st and 2nd generation DES. This may eventually amplify the coronary inflammation process after stent deployment and delay strut re-endothelialization. In this regard EES with its thinner strut design, more biocompatible polymers, less polymer mass and limus-based antiproliferative drugs may induce lower local inflammatory response and explain lower ST incidence as compared to both BMS and first generation DES. Our findings in CKD patients are aligned with recent trials [19,20] and meta-analysis [21] which showed that second generation DES is associated with lower ST rate than BMS and first generation DES. Importantly in CKD population the number needed to treat with EES vs BMS to prevent one ST (NNT = 20) was much lower than the non-CKD population (NNT = 50), indicating a much higher absolute benefit.

Second, the presence of CKD is associated with higher atherosclerotic burden, diffuse coronary disease and coronary calcification which may in turn favor stent malapposition, under-expansion, eventually leading to ST. Of note, reduced ST with EES was maintained even after adjusting for total stent length, which may partly account for this issue. Coronary calcification and diffuse disease are also well-known risk factors for in-stent restenosis and TLR. Both 1st and 2nd generation DES, which have lower late loss than BMS, did not significantly reduce TLR in our population (sFigure 2ab) as previously reported [3,4]. This finding reinforces the inflammation hypothesis as a predominant explanation of the lower ST with EES, on the other side raises the doubt on the efficacy of DES in preventing TLR in calcified vessels like those found in CKD patients and needs further investigations (sFigure 2b).

Finally, CKD patients may be poor responders to DAPT. It was demonstrated that diabetic patients with eGFR < 60 ml/min/1.73 m^2 receiving aspirin and clopidogrel had much higher platelet reactivity after ADP stimuli and a 2-fold increase in high platelet reactivity after ADP

Table 5
Multivariable adjusted hazard ratios and 95% confidence intervals for definite and probable stent thrombosis. Covariate included in the model as in Table 4, abbreviations as in Table 1.

Covariate	BMS (ref.)	ZES-S (ref.)	PES (ref.)	EES (ref.)
BMS	1	2.535 [1.056–6.088]	0.847 [0.449–1.598]	3.467 [1.285–9.352]
ZES-S	0.394 [0.164–0.947]	1	0.334 [0.141–0.789]	1.367 [0.434–4.312]
PES	1.180 [0.626–2.226]	2.993 [1.268–7.062]	1	4.092 [1.539–10.88]
EES	0.288 [0.107–0.778]	0.731 [0.232–2.306]	0.244 [0.092–0.650]	1

stimuli [22] as compared to patients without these conditions. These findings may indicate a dysfunctional purinergic signaling mediated ADP receptor, but also of the presence of a hyper-reactive platelet phenotype. In our analysis, the lack of significant interaction between DAPT duration (6 vs 24 months) and either eGFR or each stent on ST primary outcome, suggests that DAPT prolongation with clopidogrel may not be sufficient to reduce the occurrence of ST in CKD patients (like in non-CKD patients) consistently with the previously reported post-hoc analysis of CREDO [23] and CHARISMA [24]. These considerations may not apply for novel $P2Y_{12}$ inhibitors like prasugrel and ticagrelor (which were not used in the PRODIGY trial) and have showed to reduce cardiovascular events in ACS patients [25,26].

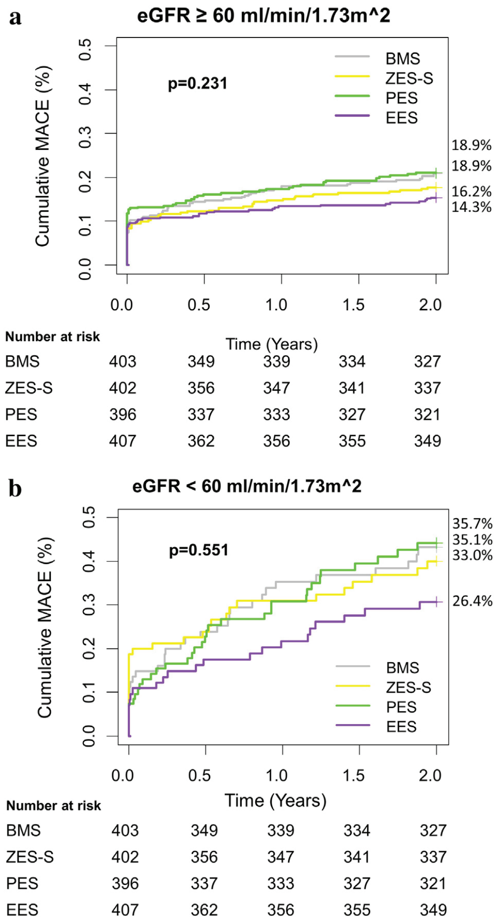

Fig. 3. Cumulative incidence of death, recurrent myocardial infarction, or stroke in non-CKD patients (panel A) and CKD patients (panel B). Abbreviation as in Table 1.

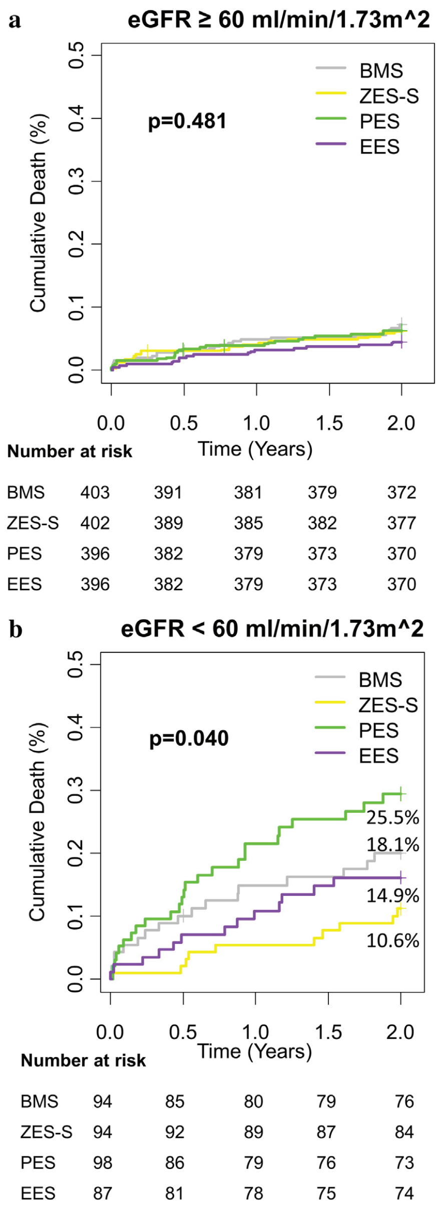

Fig. 4. Cumulative incidence of all-cause death in non-CKD patients (panel A) and CKD patients (panel B). Abbreviations as in Table 1.

5. Study limitations

There are limitations to acknowledge in this study. Serum creatinine was used for the calculation of GFR, however GFR estimation with the modification of diet in renal disease formula is mostly used in clinical practice especially in patients undergoing urgent PCI.

Although stent type was randomized in the overall PRODIGY population, the selection of CKD population may have introduced some bias. To overcome this potential limitation we adjusted the association between stent type and outcome with multivariable regression including a priori established risk factors and confounders.

The population with eGFR < 30 ml/min/1.73 m^2 and dialysis was relatively underrepresented in the PRODIGY trial and the final population may be slightly underpowered to test clinical outcome. However, given the high incidence of stent thrombosis in those population, the long term follow-up (up two years) and the lack of randomized ad-hoc studies we believe that this analysis may add to the current evidence in favor of 2nd generation DES use in higher risk population to reduce stent thrombosis.

6. Conclusions

In an all-comer population of patients with stable and unstable CAD, the presence of CKD at baseline was associated with a double risk of ST and MACE. CKD patients randomized to receive EES had less than half the risk of developing incident definite or probable ST at 2 years as compared with patients who received BMS and 1st generation DES. These data suggest that 2nd generation limus-based stent should be favored over paclitaxel-based DES and BMS to reduce MACE and ST in CKD patients.

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Contributorship

GC is responsible for the rationale, design, statistical analysis and reporting of the present manuscript.

SL and MV are responsible for the study design, and reporting.

FC, MA, and SA are responsible for reporting.

GC and MV are guarantors for the manuscript content.

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Conflict of interests

None.

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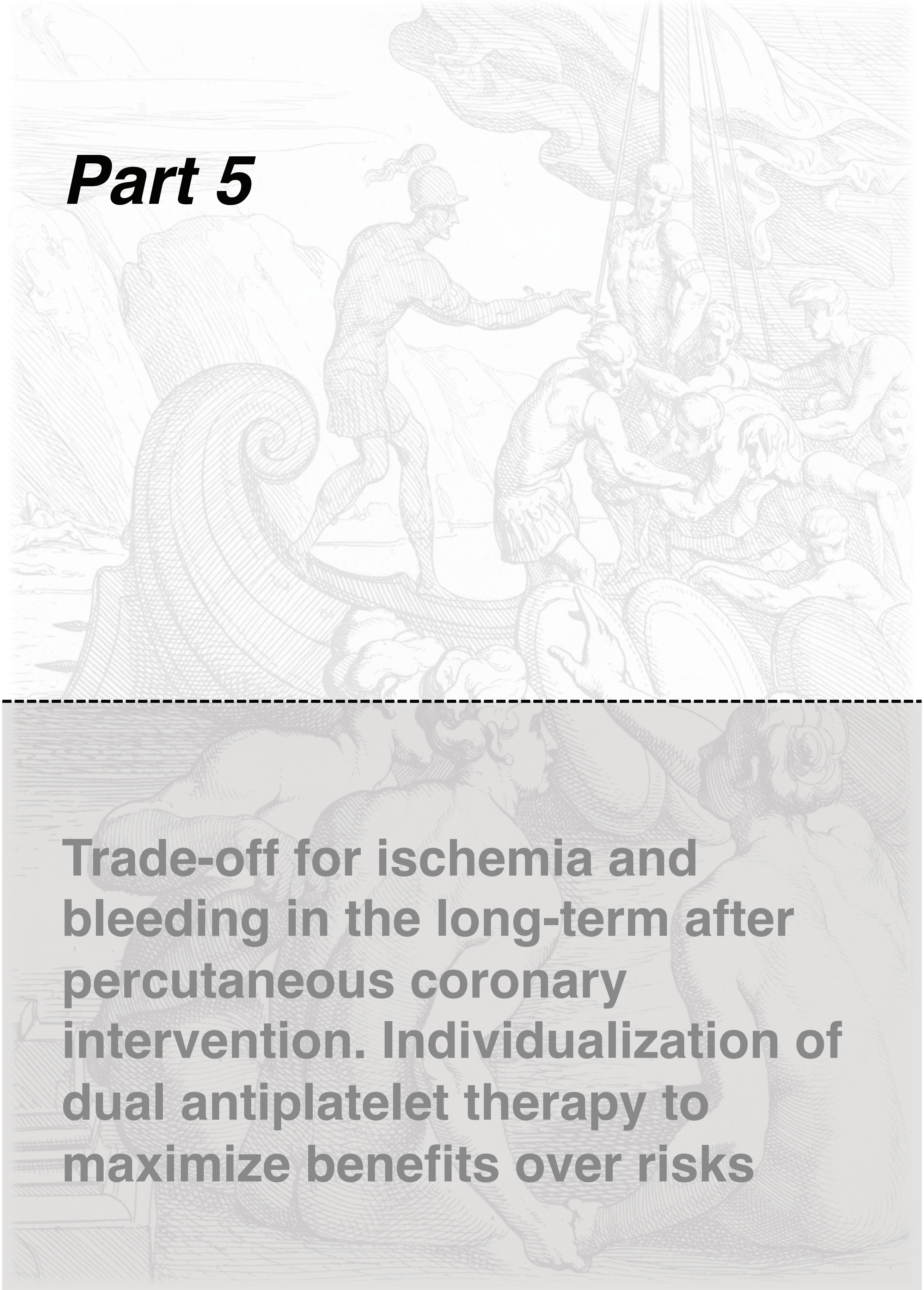
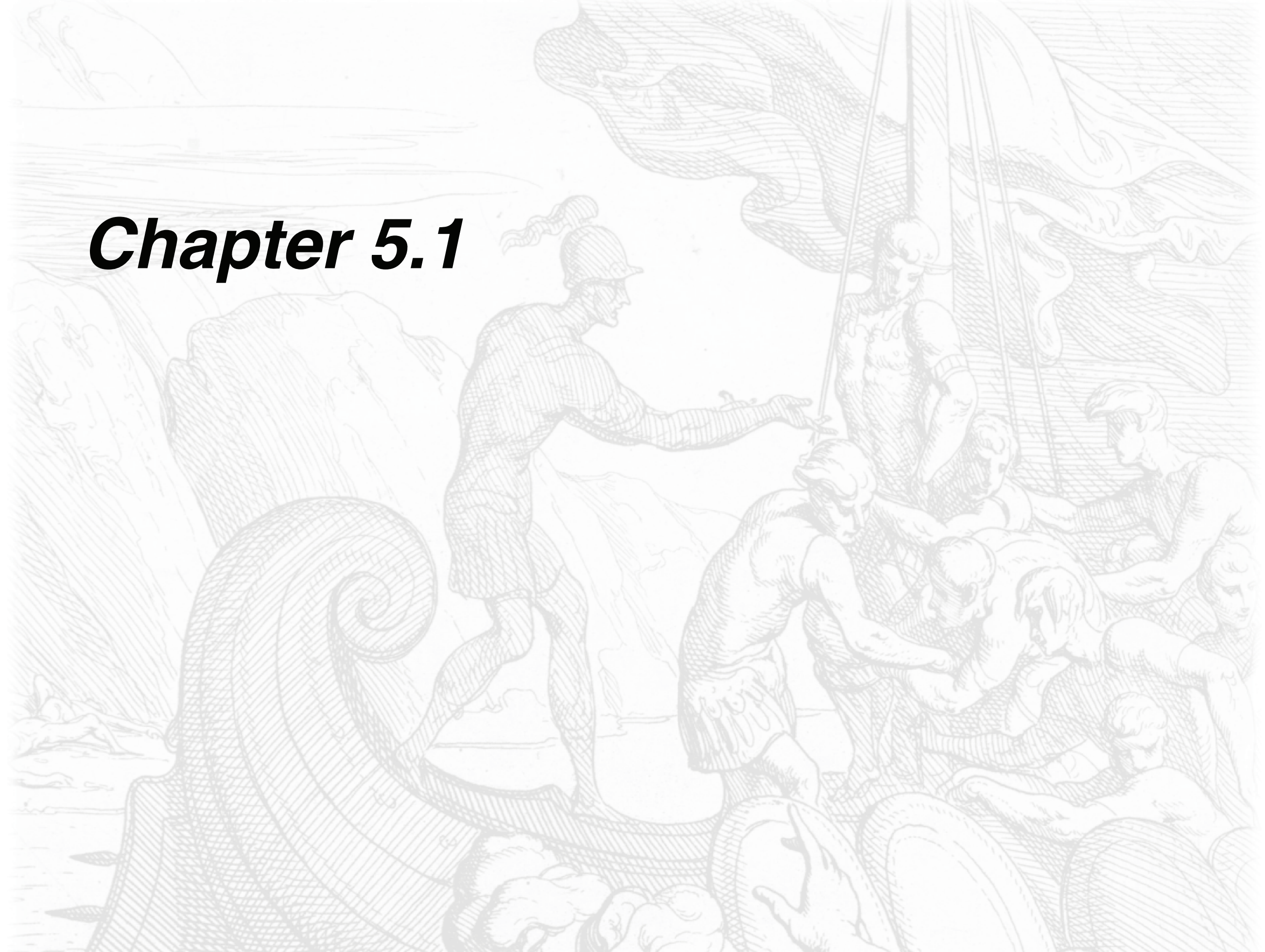


Part 5

Trade-off for ischemia and bleeding in the long-term after percutaneous coronary intervention. Individualization of dual antiplatelet therapy to maximize benefits over risks

Chapter 5.1



Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials.

Eliano Pio Navarese, Felicita Andreotti, Volker Schulze, Michalina Kołodziejczak, Antonino Buffon, Marc Brouwer, ***Francesco Costa***, Mariusz Kowalewski, Gianfranco Parati, Gregory Y H Lip, Malte Kelm, Marco Valgimigli

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Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials

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ABSTRACT

OBJECTIVE
To assess the benefits and risks of short term (<12 months) or extended (>12 months) dual antiplatelet therapy (DAPT) versus standard 12 month therapy, following percutaneous coronary intervention with drug eluting stents.

DESIGN
Meta-analysis of randomised controlled trials.

DATA SOURCES
PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Scopus, Web of Science, Cochrane Library, and major congress proceedings, searched from 1 January 2002 to 16 February 2015.

REVIEW METHODS
Trials comparing short term (<12 months) or extended (>12 months) DAPT regimens with standard 12 month duration of therapy. Primary outcomes were cardiovascular mortality, myocardial infarction, stent thrombosis, major bleeding, and all cause mortality.

RESULTS
10 randomised controlled trials (n=32 287) were included. Compared to 12 month DAPT, a short term course of therapy was associated with a significant reduction in major bleeding (odds ratio 0.58 (95% confidence interval 0.36 to 0.92); P=0.02) with no significant differences in ischaemic or thrombotic outcomes. Extended versus 12 month DAPT yielded a significant reduction in the odds of myocardial infarction (0.53 (0.42 to 0.66); P<0.001) and stent thrombosis (0.33 (0.21 to 0.51); P<0.001), but more major bleeding (1.62 (1.26 to 2.09); P<0.001). All cause but not cardiovascular death was also significantly increased (1.30 (1.02 to 1.66); P=0.03).

CONCLUSIONS
Compared with a standard 12 month duration, short term DAPT (<12 months) after drug eluting stent implementation yields reduced bleeding with no apparent increase in ischaemic complications, and could be considered for most patients. In selected patients with low bleeding risk and very high ischaemic risk, extended DAPT (>12 months) could be considered. The increase in all cause but not cardiovascular death with extended DAPT requires further investigation.

WHAT IS ALREADY KNOWN ON THIS TOPIC
Dual antiplatelet therapy is currently recommended after the implantation of drug eluting stents, but the optimal duration is a matter of debate

The currently recommended 12 month duration is of uncertain value

WHAT THIS STUDY ADDS
Compared with a 12 month duration, short term (<12 months) dual antiplatelet therapy yields reduced bleeding without increasing ischaemic complications

Dual antiplatelet therapy extended beyond 12 months reduces ischaemic and thrombotic events compared with a 12 month regimen, but at the price of greater risk of major bleeding and all cause death

The increase in all cause but not cardiovascular death seen with extended therapy requires further investigation

Introduction
Drug eluting stents have consistently improved the safety and efficacy of percutaneous coronary intervention as compared with bare metal stents.[1-4] While drug eluting stents have reduced in-stent restenosis, uncertainty has arisen regarding the risk of associated late and very late stent thrombosis. Dual antiplatelet therapy consisting of aspirin plus a P2Y12 receptor antagonist is recommended after drug eluting stent implantation for at least 12 months by the American College of Cardiology/American Heart Association and for six to 12 months by European guidelines,[5 6] followed by aspirin monotherapy. Current recommendations, however, are based largely on observational data with few randomised controlled trials.

The most recent trials and meta-analyses have suggested comparable efficacy of short term dual antiplatelet therapy versus therapy of at least 12 months, especially with newer generation drug eluting stents,[7-9] but these studies are underpowered to draw definitive conclusions. On the other hand, very late stent thrombosis still occurs with drug eluting stents, especially after first generation devices, raising the question of whether prolongation of dual antiplatelet therapy offers clinical benefit. One randomised controlled trial recently showed a significant reduction of stent thrombosis with dual antiplatelet therapy extended beyond 12 months at the price of increased bleeding.[10] Thus, the optimal duration of dual antiplatelet therapy is debated, with short term and extended protocols not yet compared to standard 12 month treatment within the same trial. We aimed to perform a meta-analysis of randomised controlled trials to compare the efficacy and safety of short term and extended dual antiplatelet therapy with standard 12 month therapy.

Methods
Data sources and search strategy
Established methods were used in compliance with the Preferred Reporting Items for Systematic reviews and

5

Meta-Analyses (PRISMA) statement in healthcare interventions.[11] We screened Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature, Scopus, Web of Science, the Cochrane Register of Controlled Clinical Trials, as well as congress proceedings from major cardiac societies, for randomised data comparing different durations of dual antiplatelet therapy. Dual antiplatelet therapy was defined as aspirin plus a P2Y12 receptor inhibitor, after percutaneous coronary intervention with implantation of a drug eluting stent. The search period took place from 1 January 2002 to 16 February 2015.

Search terms according to medical subjects headings were: "DAPT", "dual antiplatelet therapy", "clopidogrel", "Plavix", "prasugrel", "Efient", "ticagrelor", "Brilinta", "thienopyridine", "P2Y12", "shortened DAPT", "prolonged DAPT", "extended DAPT", "premature cessation", "early discontinuation", "randomised trial", and "trial". No language or publication status restriction was imposed. The most updated or inclusive data for each study were used for abstraction. In addition, landmark analysis data at 12 months were available from the original PROlonging Dual antIplatelet treatment after Grading stent-induced intimal hyperplasia studY (PRODIGY)[7] and were therefore incorporated into the present article.

Study design and selection criteria

The design of the current meta-analysis compared two strategies of dual antiplatelet therapy involving three durations after percutaneous coronary intervention with drug eluting stent implantation. The first comparison was between a short term (<12 months) and 12 month therapy, and the second between an extended duration (>12 months) and 12 month therapy. The original PRODIGY randomised controlled trial[7] assigned patients to either six or 24 month durations. Because the randomisation process in PRODIGY began one month after the index percutaneous coronary intervention, the availability of landmark data at 12 months allowed inclusion of the study in the short term versus 12 month comparison, after censoring events that occurred after 12 months and keeping the original randomisation design. We did additional sensitivity analyses by including PRODIGY trial data in the extended duration versus 12 month comparison. The analyses included only events that occurred beyond 12 months in both study arms (postrandomisation subgroups).

The main exclusion criteria for this meta-analysis were: observational design, patients without documented coronary artery disease or patients with peripheral or cerebrovascular disease, percutaneous coronary intervention without stents or with bare metal stents only, and duration timeframes of dual antiplatelet therapy selected by the meta-analysis not reported. Two independent reviewers (VS and MK) selected the studies for inclusion and extracted the study characteristics and relevant outcomes; divergences were solved by consensus after discussion with a third reviewer (EPN). Three authors (EPN, MK, and VS) independently reassessed the trials' eligibility and ranked their risk of bias. Risk of bias was graded using the components recommended by the Cochrane Collaboration—that is, random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.[12]

Outcome measures

Primary clinical endpoints were cardiovascular mortality, myocardial infarction, stent thrombosis, major bleeding, and overall mortality; secondary endpoints were repeat revascularisation, and cerebrovascular accident, and the combination of cardiac and cerebrovascular accidents. We classified stent thrombosis as definite/probable, definite, late (between 30 days and one year after percutaneous coronary intervention), and very late (>one year after percutaneous coronary intervention) according to criteria from the Academic Research Consortium.[13] For major bleeding, trial definitions were applied. Major bleeding according to TIMI criteria,[14] and a composite endpoint of major adverse cardiac and cerebrovascular accidents were also assessed.

Statistical analyses

Data were analysed according to the intention to treat principle. Odds ratios and 95% confidence intervals were used as summary statistics. Heterogeneity was assessed by Cochran's Q test.[15] We also used the statistical inconsistency test ($I^2=(Q-df)/Q\times100\%$, where $Q=\chi^2$ statistic and df=its degrees of freedom) to overcome the low statistical power of Cochran's Q test. Pooled odds ratios were calculated using a fixed effect model with the Mantel-Haenszel method, because of the absence of moderate or significant inconsistency (>50%) across studies. We also did prespecified sensitivity analyses using a random effects model. Potential publication bias was examined by constructing funnel plots for the clinical outcomes in which the standard error of the log of the odds ratio was plotted against the odds ratio. The asymmetry of the plot was estimated both visually and by Harbord's regression test.[16] Prespecified analyses assessed the effect of different durations of dual antiplatelet therapy in the following subgroups: age older than 65 years or younger than 65 years, patients with or without acute coronary syndrome, and those treated with either clopidogrel or new P2Y12 inhibitors (prasugrel and ticagrelor). $P<0.05$ was considered significant and reported as two sided.

Results

Studies and patients

The PRISMA statement flowchart (web fig 1) describes the literature screening, study selection, and reasons for exclusion. From 338 initial studies, 295 were discarded at title or abstract level. Another 33 studies did not meet the prespecified inclusion criteria and were therefore excluded. A total of 10 randomised controlled trials (n=32287)[7 8 10 17-28] were finally included in the meta-analysis. Tables 1 and 2 list the characteristics and references of the included studies. Web fig 2 summarises the quality of included studies, along with potential sources of bias. Web table 1 outlines the full electronic Medline

Table 1 | Characteristics of included studies comparing short term (<12 month) versus 12 month dual antiplatelet therapy

Inclusion criteria	Exclusion criteria	Primary endpoints	Secondary endpoints	Time to randomisation
EXCELLENT[22] (2012), n=1443, 6 months v 12 months of DAPT duration				
≥1 de novo lesion; native coronary vessel; RVD ≥2.25-4.25 mm; >50% DS; stable angina, unstable angina, recent MI, silent ischaemia, positive functional study, or reversible changes on ECG consistent with ischaemia	<72 h MI; <25% LVEF or cardiogenic shock; any stent implantation in target vessel before enrolment; major bleeding <3 months; major surgery <2 months; elective surgery planned <12 months; >50% DS on LM; CTO; true bifurcation lesions requiring a planned two stent strategy	Target vessel failure (composite of cardiac death, MI, or ID-TVR)	Cardiac death; MI; ID-TVR; all cause death; death or MI; ST; TIMI[14] major bleeding; MACCE (composite of death, MI, stroke, or any revascularisation); safety endpoint (composite of death, MI, stroke, ST, or TIMI major bleeding)	At index PCI
ISAR-SAFE[23] (2014), n=4005, 6 months v 12 months of DAPT duration				
Patients on clopidogrel at 6 (−1/+2) months after PCI with DES; written informed consent	Clinical symptoms or signs of ischaemia or angiographic lesions requiring revascularisation; active bleeding; bleeding diathesis; history of intracranial bleeding; STEMI and NSTEMI during last 6 months after DES; previous ST; DES in LM at index intervention; oral anticoagulation; planned major surgery within next 6 months with need to discontinue APT	Composite of death, MI, ST, stroke, or TIMI major bleeding	Composite of death, MI, ST, stroke; TIMI major and minor bleeding; death; MI; ST; stroke; TIMI major bleeding; BARC bleeding ≥class 2	6 months after index PCI
ITALIC[28] (2014), n=1850, 6 months v 12 months of DAPT duration				
Patients ≥18 years old, eligible for PCI, with ≥1 Xience V DES (Abbott Vascular Devices, Santa Clara, CA, USA) implanted, in all clinical situations excluding primary PCI for acute MI and treatment of LM	Patients non-responders to aspirin; previous DES implantation within 1 year; known platelet level <100 000/μL or known haemorrhagic diathesis; oral anticoagulation therapy or abciximab treatment during hospital stay; contraindications to aspirin or clopidogrel (prasugrel or ticagrelor); major surgery within preceding 6 weeks; evidence of active gastrointestinal or urogenital bleeding; severe liver failure; any surgery scheduled within 1 year after enrolment; or severe concomitant disease with <2 years' life expectancy	Composite of death, MI, repeat emergency revascularisation, stroke, or major bleeding	Composite at 24 and 36 months, death, MI, or repeat emergency revascularisation, and stroke requiring readmission	At index PCI
OPTIMIZE[24 25] (2013), n=3211, 3 months v 12 months of DAPT duration				
Stable angina or silent ischaemia or low risk ACS as defined by unstable angina or recent (but not acute) myocardial infarction (<30 days)	Elevated biomarker levels at time of index procedure and ≥1 lesion with stenosis >50% (MVD allowed) located in a native vessel >2.5 mm diameter with indication for PCI with stent implantation; STEMI presenting for primary or rescue PCI; PCI with BMS in non-target lesions <6 months before index procedure; previous treatment with any DES; scheduled elective surgery within 12 months after index procedure; contraindication, intolerance, or known hypersensitivity to aspirin, clopidogrel, or both; lesion in a saphenous vein graft; or in-stent restenosis of DES	Net adverse clinical and cerebral events (composite of all cause death, MI, stroke, or major bleeding)	ST according to ARC; target lesion and target vessel revascularisation; MACE (including all cause death, MI, emergent CABG surgery, or target lesion revascularisation); and any bleeding, including major bleeding and bleeding events that did not meet criteria for major or severe or life threatening bleeding (according to modified major REPLACE-2 and severe or life threatening GUSTO criteria)	At index PCI
PRODIGY[7 26] (2012), n=1970, 6 months v 24 months of DAPT duration*				
≥18 years old; ≥1 coronary artery lesion; >50% DS; PCI suitability; RVD ≥2.25 mm; chronic stable coronary artery disease or ACS (NSTEMI or STEMI)	Elective surgery planned 24 months after index PCI (unless DAPT could be maintained during perisurgical period); bleeding diathesis; major surgery <15 days; active bleeding or previous stroke <6 months; concomitant or foreseeable need for anticoagulants	Composite of all cause death, MI, or CVA	All cause death; MI; CVA; cardiac death; ST; bleeding	1 month after index PCI
RESET[27] (2012), n=2117, 3 months v 12 months of DAPT duration				
20-85 years old; ≥50% DS; RVD ≥2.5-4.0 mm; elective PCI; stable or unstable angina, or acute MI	Cerebral or peripheral atherosclerotic arterial disease, thromboembolic disease or ST history; <40% LVEF; restenotic lesion; CTO; LM disease requiring intervention; cardiogenic shock; <48 h STEMI	Composite of cardiac death, MI, ST, ID-TVR, and TIMI major or minor bleeding	Composite of all cause death, MI and ST, cardiac death, MI, ST, ID-TVR and TIMI[14] major or minor bleeding	At index PCI
SECURITY[8] (2014), n=1399, duration 6 months v 12 months of DAPT duration				
>18 years old; stable angina, as defined by CCS or unstable angina, as defined by Braunwald classification, or patients with documented silent ischaemia, treated with ≥1 second generation DES implanted in the target lesion in past 24 h; presence of ≥1 de novo stenosis ≥70% in a native coronary artery; no other DES implanted before target procedure and no BMS implanted in 3 months before target procedure	STEMI in 48 h before the procedure, NSTEMI in previous 6 months; LVEF <30%; known hypersensitivity to aspirin, thienopyridines, heparin, limus analogues, cobalt, chromium, nickel, molybdenum, or contrast media; target lesion in saphenous vein graft, in-stent restenosis, unprotected LM; history of significant thrombocytopenia with aspirin or thienopyridines; patients with chronic kidney disease (creatinine >2 mg/dL†); women during pregnancy or lactation; active bleeding or significant risk of bleeding; uncontrolled hypertension; life expectancy <24 months and any medical condition that could preclude follow-up as defined in protocol	Composite of cardiac death, MI, stroke, definite or probable ST or BARC type 3 or 5 bleeding	Composite of cardiac death, spontaneous MI, stroke, definite or probable stent thrombosis, or BARC type 2, 3, or 5 bleeding at 12 and 24 months (cumulative incidence of individual components of the primary endpoint); MI, urgent target vessel revascularisation (CABG or PCI because of acute cardiac ischaemia), all bleeding events and all cause mortality	At index PCI

Data classified by study name (year), no of patients, and comparison of DAPT durations after index percutaneous coronary intervention. DAPT=dual antiplatelet therapy; PCI=percutaneous coronary intervention; DES=drug eluting stent; STEMI=ST segment elevation myocardial infarction; MI=myocardial infarction; ST=stent thrombosis; BMS=bare-metal stent; MACCE=major adverse cardiac and cerebrovascular events; GUSTO=global utilization of streptokinase and TPA for occluded arteries; CABG=coronary artery bypass grafting; BARC=Bleeding Academic Research Consortium; MACE=major adverse cardiovascular events; ACS=acute coronary syndrome; RVD=reference vessel diameter; ECG=electrocardiogram; LVEF=left ventricle ejection fraction; DS=diameter stenosis; LM=left main artery; CTO=chronic total occlusion; ID-TVR=ischaemia driven target vessel revascularisation; NSTEMI=non-ST segment elevation myocardial infarction; APT=antiplatelet therapy; MVD=multivessel disease; ARC=Academic Research Consortium; REPLACE-2=randomized evaluation in PCI linking angiomax to reduced clinical events; CVA=cerebrovascular accidents; CCS=Canadian Cardiovascular Society.

*Available landmark data at 12 and 12-24 months.

†1 mg/dL=88.4 μmol/L.

Table 2 | Characteristics of included studies comparing extended (>12 month) versus 12 month dual antiplatelet therapy

Inclusion criteria	Exclusion criteria	Primary endpoints	Secondary endpoints	Time to randomisation
ARCTIC Interruption[17 18] (2014), n=1286, 12 months *v* 18 months of DAPT duration*				
≥18 years and eligible for PCI with planned use of ≥1 DES; without use of a GPIIb/IIIa inhibitor at randomisation; able to understand study requirements and comply with study procedures and protocol	Anticoagulation with vitamin K antagonists; contraindication to aspirin or clopidogrel, GPIIb/IIIa inhibitors, or increased dose regimen of aspirin/clopidogrel; ongoing or recent bleeding or major surgery <3 weeks; severe liver insufficiency; thrombocytopenia <80 000/µL; GPIIb/IIIa inhibitor before randomisation; primary PCI for STEMI; history of major bleeding with contraindication to APT; scheduled surgery <12 months; high risk feature of poor compliance to DAPT	Composite of all cause death, MI, stroke or TIA, urgent coronary revascularisation, and ST	Composite of ST (whether revascularised or not) and urgent revascularisation, all cause death, MI, stroke or TIA, urgent coronary revascularisation, and ST; main safety endpoint was STEEPLE major bleeding	12 months after index PCI
DAPT[10 19] (2014), n=9961, 12 months *v* 30 months of DAPT duration				
>18 years old, undergoing percutaneous intervention with stent deployment	Index procedure stent placement with stent diameter <2.25 mm or >4.0 mm; pregnancy; planned surgery necessitating discontinuation of APT within 30 months after enrollment; life expectancy of <3 years; enrollment in another device or drug study whose protocol specifically rules out concurrent enrollment or involves blinded placement of a DES or BMS other than those included as DAPT study devices; warfarin or similar anticoagulant therapy; hypersensitivity or allergies to one of the drugs or DES components; patient treated with both DES and BMS during index procedure	Definite/probable ST and MACCE defined as composite of death, MI or stroke	Moderate or severe bleeding according to GUSTO[14] classification; clinically actionable non-CABG related bleeding according to BARC (type 2, 3, and 5); MI, stroke, cardiac and vascular mortality	12 months after index PCI
DES LATE[20 21] (2010), n=5045, 12 months *v* 24 months of DAPT duration				
<12 months DES implantation; no MACE (MI, stroke, repeat PCI) or major bleeding since PCI; DAPT on board	DAPT contraindications due to bleeding diathesis or major bleeding history; long term DAPT indication due to concomitant vascular disease or recent ACS	MI or cardiac death	All cause death; MI, stroke; ST; repeat revascularisation; composite of MI or all cause death; composite of MI, stroke, or all cause death; composite of MI, stroke, or cardiac death; TIMI[14] major bleeding	12 months after index PCI

Data classified by study name (year), no of patients, and comparison of DAPT durations after index percutaneous coronary intervention. DAPT=dual antiplatelet therapy; PCI=percutaneous coronary intervention; DES=drug eluting stent; GP=glycoprotein; STEMI=ST segment elevation myocardial infarction; APT=antiplatelet therapy; MI=myocardial infarction; ST=stent thrombosis; TIA=transient ischaemic attack; STEEPLE=the safety and efficacy of enoxaparin in PCI patients, an international randomized evaluation; BMS=bare-metal stent; MACCE=major adverse cardiac and cerebrovascular events; GUSTO=global utilization of streptokinase and TPA for occluded arteries; CABG=coronary artery bypass grafting; BARC=Bleeding Academic Research Consortium; MACE=major adverse cardiovascular events; ACS=acute coronary syndrome.
*Available landmark data at 12 and 12-24 months.

search process. No publication bias was suggested by the funnel plots (web figs 3-8) and by Harbord's regression test (web table 7). Seven studies tested short term regimens (<12 months) of dual antiplatelet therapy against 12 months' duration (table 1),[7 8 22–28] and three studies tested extended regimens (>12 months; table 2).[10 17-21]

Clopidogrel and aspirin was the most frequent drug combination in dual antiplatelet therapy; prasugrel or ticagrelor were available in three[8 10 17-19] and two[8-28] studies, respectively. Of 32 287 patients, 7975 were randomly allocated to short term regimens and 8196 to extended regimens of dual antiplatelet therapy; 16 116 patients constituted the 12 month control group. Web table 2 lists the patients' baseline characteristics. Patients presented evenly, with either stable angina/silent ischaemia or non-ST segment elevation acute coronary syndrome (48% and 45%, respectively); fewer than 10% presented with ST segment elevation myocardial infarction. Web table 3 lists procedural characteristics of each study. Web table 4 lists definitions of major adverse cardiac and cerebrovascular events.

Cardiovascular mortality and myocardial infarction

Eight studies including 26 996 patients provided data for cardiovascular mortality. Cardiovascular mortality after short term and 12 month dual antiplatelet therapy did not differ significantly (event rate 1.13% (68/5997 patients) *v* 1.20% (72/6013); odds ratio 0.95 (95% confidence interval 0.68 to 1.33); P=0.76; I^2=0%; fig 1). Similarly, cardiovascular mortality did not differ significantly between extended dual antiplatelet therapy and 12 month therapy (1.03% (78/7551) *v* 0.95% (71/7455); 1.09 (0.79 to 1.50); P=0.62; I^2=34%; fig 1).

All 10 randomised controlled trials (n=32 287) were included in the myocardial infarction analysis. Myocardial infarction rates were similar in patients randomised to either short term or 12 month dual antiplatelet therapy (1.65% (132/7975 patients) *v* 1.50% (120/8020); odds ratio 1.11 (95% confidence interval 0.87 to 1.43); P=0.40; I^2=0%; fig 1). We saw a reduction of roughly 50% in the odds of myocardial infarction with extended dual antiplatelet therapy, compared with 12 month therapy (1.55% (127/8196) *v* 2.89% (234/8096); 0.53 (0.42 to 0.66); P<0.001; I^2=37%; fig 1).

Stent thrombosis

All 10 studies (n=32 287) contributed to the analysis of definite/probable stent thrombosis (fig 2). We saw no significant difference in the rates of stent thrombosis when comparing short term dual antiplatelet therapy with 12 month therapy (0.53% (42/7975 patients) *v* 0.40% (32/8020); odds ratio 1.32 (95% confidence interval 0.83 to 2.08); P=0.24; I^2=0%). Similarly, the analysis of definite stent thrombosis demonstrated identical rates (0.3%) for both short term and 12 month dual antiplatelet therapy (1.00 (0.40 to 2.53); P=0.99; I^2=0%; fig 2).

By contrast, a 67% reduction in the odds of definite/probable stent thrombosis was observed with extended versus 12 month dual antiplatelet therapy (odds ratio 0.33 (95% confidence interval 0.21 to 0.51); P<0.001; I^2=18%; fig 2). The corresponding rates were 0.32% (26/8196 patients) versus 0.98% (79/8096), with a number needed

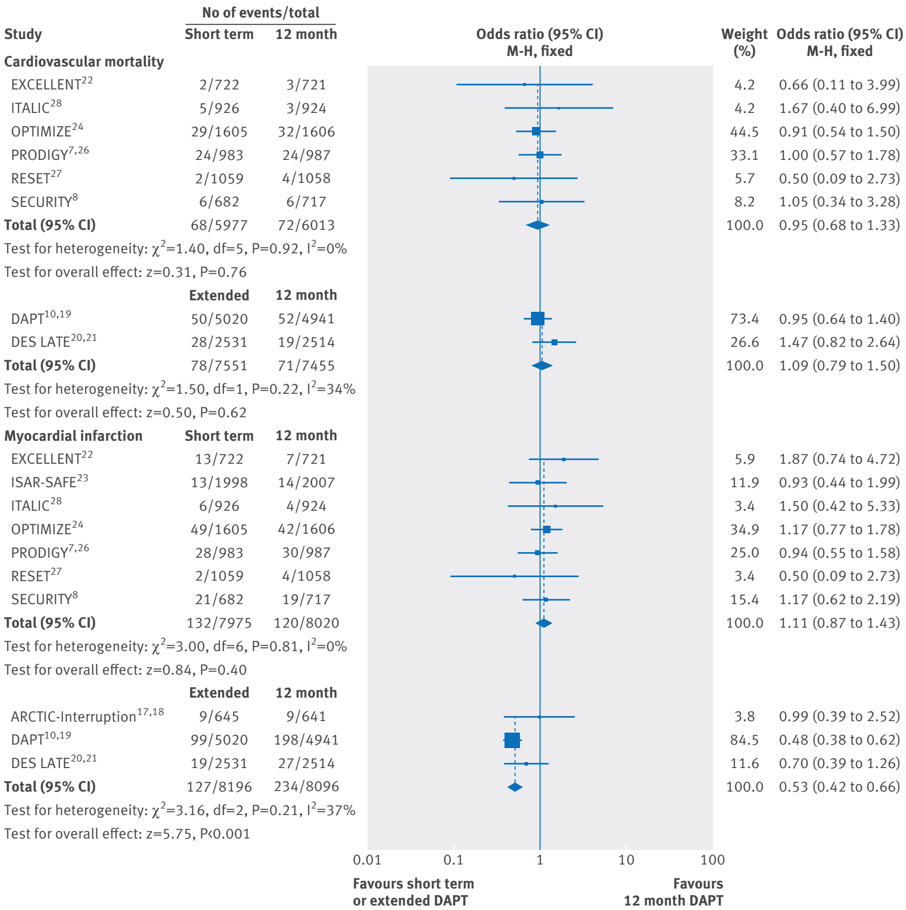


Fig 1 | **Individual and summary odds ratios for the endpoints of cardiovascular mortality and myocardial infarction. M-H=Mantel-Haenszel. Data stratified by duration of dual antiplatelet therapy: short term (<12 months) versus 12 months, and extended (>12 months) versus 12 months**

to treat of 152. Similarly, the analysis of definite stent thrombosis showed a 70% reduction in the odds of stent thombosis with extended versus 12 month dual antiplatelet therapy (0.30 (0.19 to 0.49); P<0.001; I^2=32%; corresponding rates 0.27% (22/8196) *v* 0.89% (72/8096; fig 2).

Timing of stent thrombosis

We saw similar rates of late stent thrombosis when comparing short term with 12 month dual antiplatelet therapy (0.36% (20/5501 patients) *v* 0.31% (16/5089); odds ratio 1.24 (95% confidence interval 0.65 to 2.36); P=0.50; I^2=40%). By contrast, the odds of very late stent thrombosis were significantly reduced by 67% when comparing extended with 12 month therapy (0.32% (26/8196) *v* 0.98% (79/8096); 0.33 (0.21 to 0.51); P<0.001; I^2=18%; fig 2).

Major bleeding

Major bleeding rates were available in all studies (n=32 287). Short term versus 12 month dual antiplatelet therapy was associated with a roughly 40% reduction in the odds of major bleeding (event rate 0.35% (28/7975 patients) *v* 0.61% (49/8020); odds ratio 0.58 (95% confidence interval 0.36 to 0.92); P=0.02; I^2=0%); the corresponding number needed to treat to prevent a major bleed was 385. Conversely, continuation of dual antiplatelet therapy beyond 12 months significantly increased the odds of major bleeding by 62% (1.95% (160/8196) *v* 1.21% (98/8096); 1.62 (1.26 to 2.09); P<0.001; I^2=7%; fig 3); the corresponding number needed to harm by causing a major bleed was 135.

All cause mortality

All 10 randomised controlled trials (n=32 287) provided data for all cause death. We found no significant differences in all cause mortality between short term and 12 month dual antiplatelet therapy (event rate 1.43% (114/7975 patients) *v* 1.56% (125/8020); odds ratio 0.91

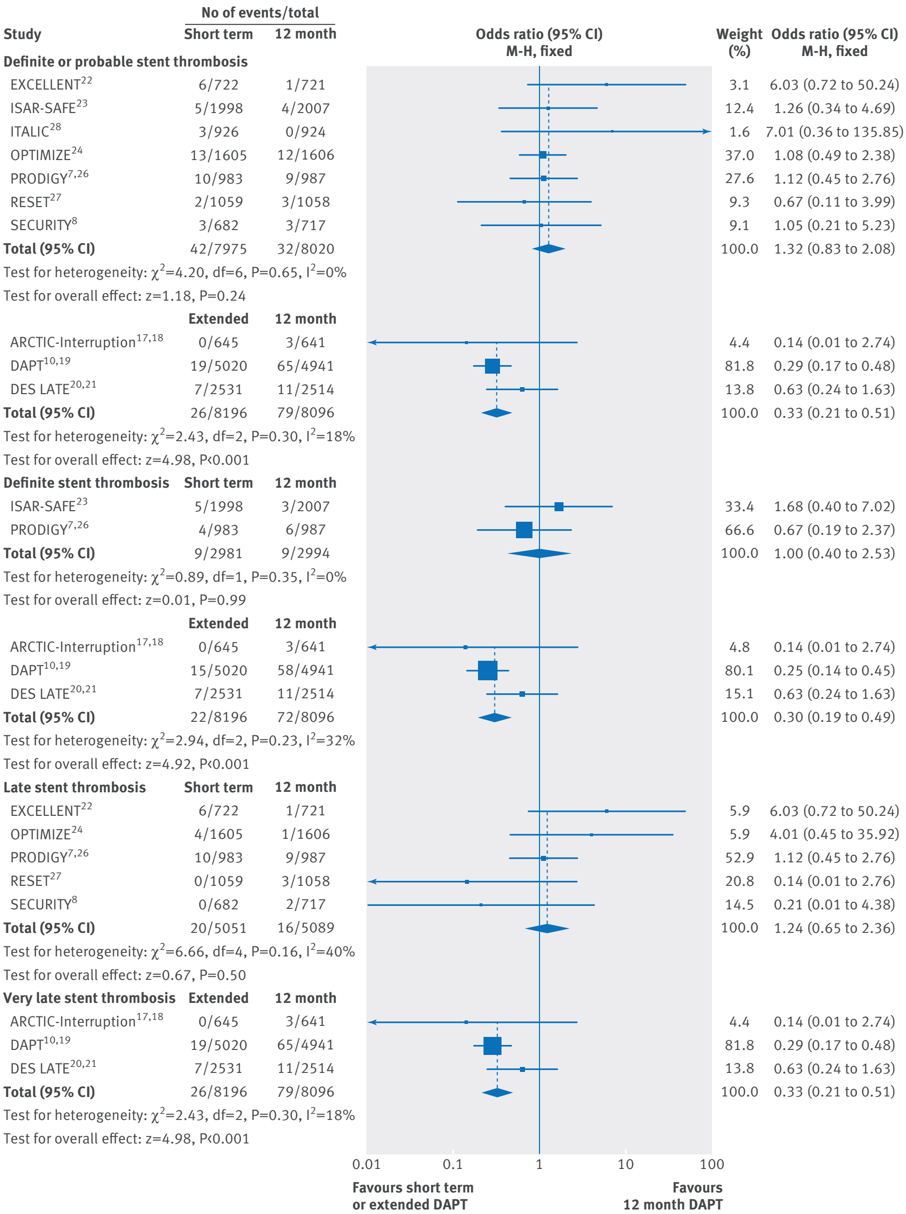
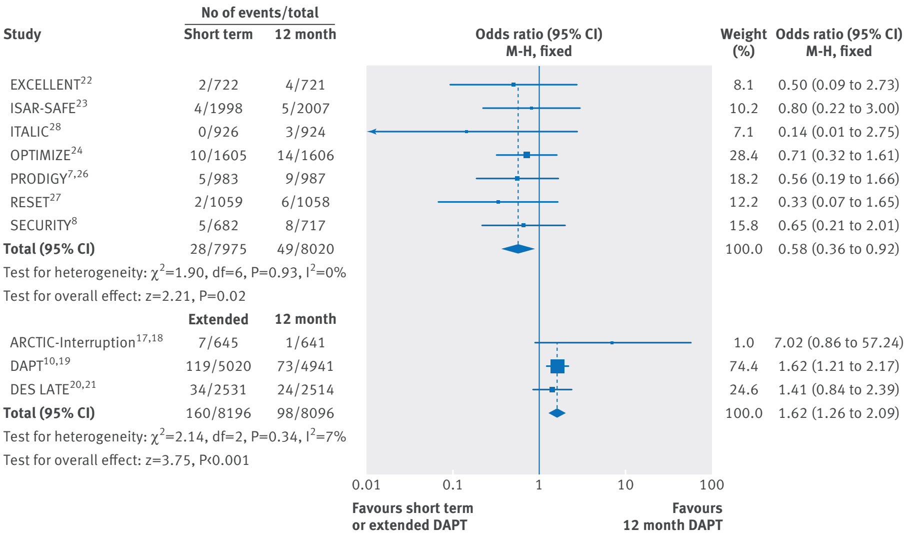


Fig 2 | **Individual and summary odds ratios for the endpoints of definite/probable stent thrombosis and definite stent thrombosis, and analysis of late and very late stent thrombosis. Data stratified by duration of dual antiplatelet therapy: short term (<12 months) versus 12 months, and extended (>12 months) versus 12 months**

(95% confidence interval 0.71 to 1.18); P=0.49; I^2=0%; fig 4). By contrast, extended versus 12 month dual antiplatelet therapy was associated with a higher risk of all cause death (1.84% (151/8196) *v* 1.42% (115/8096); 1.30 (1.02 to 1.66); P=0.03; I^2=0%; fig 4). The number needed to harm was 238.

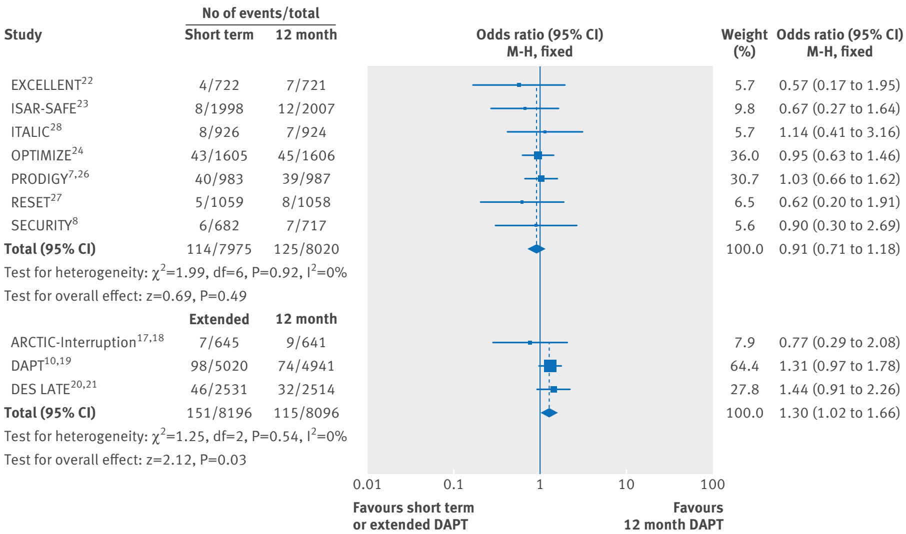
Repeat revascularisation and cerebrovascular accidents

Repeat revascularisation data were available from seven studies (n=16 351). Short term duration of dual antiplatelet therapy yielded similar results compared with 12 month duration (event rate 3.06% (153/4994



Study	No of events/total: Short term	12 month	Weight (%)	Odds ratio (95% CI) M-H, fixed
EXCELLENT[22]	2/722	4/721	8.1	0.50 (0.09 to 2.73)
ISAR-SAFE[23]	4/1998	5/2007	10.2	0.80 (0.22 to 3.00)
ITALIC[28]	0/926	3/924	7.1	0.14 (0.01 to 2.75)
OPTIMIZE[24]	10/1605	14/1606	28.4	0.71 (0.32 to 1.61)
PRODIGY[7,26]	5/983	9/987	18.2	0.56 (0.19 to 1.66)
RESET[27]	2/1059	6/1058	12.2	0.33 (0.07 to 1.65)
SECURITY[8]	5/682	8/717	15.8	0.65 (0.21 to 2.01)
Total (95% CI)	28/7975	49/8020	100.0	0.58 (0.36 to 0.92)
Test for heterogeneity: χ^2=1.90, df=6, P=0.93, I^2=0%				
Test for overall effect: z=2.21, P=0.02				
	Extended	**12 month**		
ARCTIC-Interruption[17,18]	7/645	1/641	1.0	7.02 (0.86 to 57.24)
DAPT[10,19]	119/5020	73/4941	74.4	1.62 (1.21 to 2.17)
DES LATE[20,21]	34/2531	24/2514	24.6	1.41 (0.84 to 2.39)
Total (95% CI)	160/8196	98/8096	100.0	1.62 (1.26 to 2.09)
Test for heterogeneity: χ^2=2.14, df=2, P=0.34, I^2=7%				
Test for overall effect: z=3.75, P<0.001				

Fig 3 | **Individual and summary odds ratios for the endpoint of major bleeding. Data stratified by duration of dual antiplatelet therapy: short term (<12 months) versus 12 months, and extended (>12 months) versus 12 months**



Study	No of events/total: Short term	12 month	Weight (%)	Odds ratio (95% CI) M-H, fixed
EXCELLENT[22]	4/722	7/721	5.7	0.57 (0.17 to 1.95)
ISAR-SAFE[23]	8/1998	12/2007	9.8	0.67 (0.27 to 1.64)
ITALIC[28]	8/926	7/924	5.7	1.14 (0.41 to 3.16)
OPTIMIZE[24]	43/1605	45/1606	36.0	0.95 (0.63 to 1.46)
PRODIGY[7,26]	40/983	39/987	30.7	1.03 (0.66 to 1.62)
RESET[27]	5/1059	8/1058	6.5	0.62 (0.20 to 1.91)
SECURITY[8]	6/682	7/717	5.6	0.90 (0.30 to 2.69)
Total (95% CI)	114/7975	125/8020	100.0	0.91 (0.71 to 1.18)
Test for heterogeneity: χ^2=1.99, df=6, P=0.92, I^2=0%				
Test for overall effect: z=0.69, P=0.49				
	Extended	**12 month**		
ARCTIC-Interruption[17,18]	7/645	9/641	7.9	0.77 (0.29 to 2.08)
DAPT[10,19]	98/5020	74/4941	64.4	1.31 (0.97 to 1.78)
DES LATE[20,21]	46/2531	32/2514	27.8	1.44 (0.91 to 2.26)
Total (95% CI)	151/8196	115/8096	100.0	1.30 (1.02 to 1.66)
Test for heterogeneity: χ^2=1.25, df=2, P=0.54, I^2=0%				
Test for overall effect: z=2.12, P=0.03				

Fig 4 | **Individual and summary odds ratios for the endpoint of all cause mortality. Data stratified by duration of dual antiplatelet therapy: short term (<12 months) versus 12 months, and extended (>12 months) versus 12 months**

patients) *v* 2.63% (132/5026); odds ratio 1.17 (95% confidence interval 0.92 to 1.48); P=0.20; I^2=0%). Results with extended dual antiplatelet therapy were comparable to those with 12 month therapy (2.80% (89/3176) *v* 2.35% (74/3155); 1.20 (0.88 to 1.64); P=0.25; I^2=0%; fig 5).

All studies (n=32 287) provided data for cerebrovascular accidents. These events occurred in 0.45% of patients (36/7975) with short term dual antiplatelet therapy versus 0.49% (39/8020) with 12 month therapy (odds ratio 0.93 (95% confidence interval 0.59 to 1.46); P=0.75; I^2=0%). Similarly, we did not see any significant differences in cerebrovascular accidents when comparing extended duration with 12 month duration (0.78% *v* 0.84%; 0.93 (0.66 to 1.31); P=0.67; I^2=0%; web fig 9).

Sensitivity analyses

The results obtained by repeating the analyses using random effects models were highly consistent with the

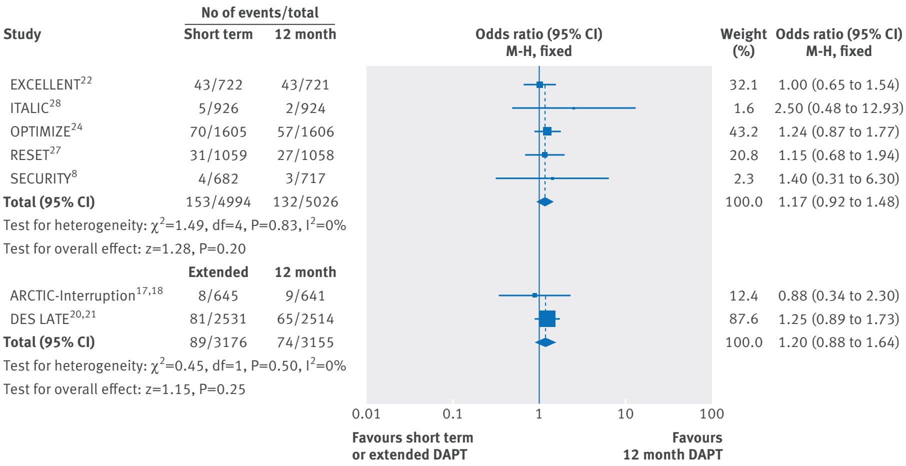


Fig 5 | **Individual and summary odds ratios for the endpoint of repeat revascularisation. Data stratified by duration of dual antiplatelet therapy: short term (<12 months) versus 12 months, and extended (>12 months) versus 12 months**

main findings (web table 5). Seven studies (n=17 716) reported major bleeding events by TIMI criteria.[14] Short term dual antiplatelet therapy compared with 12 month therapy was associated with a significantly reduced rate of TIMI major bleeding (odds ratio 0.49 (95% confidence interval 0.26 to 0.94); P=0.03; I^2=0%). Converse results were found with therapy continuation beyond 12 months compared with 12 month therapy (1.60 (0.97 to 2.64); P=0.07; I^2=42%; web fig 10).

Nine studies reported the incidence of major adverse cardiac and cerebrovascular accidents. No significant differences were seen with short term versus 12 month dual antiplatelet therapy (odds ratio 1.02 (0.86 to 1.22); P=0.81; I^2=0%). The odds of major adverse cardiac and cerebrovascular accidents were significantly reduced by 22%, when extended therapy was compared with 12 month therapy (0.78 (0.67 to 0.92); P=0.002; I^2=47%; web fig 11). Analyses in patients with and without acute coronary syndrome, younger or older than 65 years, and treated with different P2Y12 inhibitors (web table 6) showed no significant outcome differences among those subgroups. Sensitivity analyses for the extended versus 12 month regimen comparison after inclusion of the PRODIGY landmark analysis are in web figs 12-18. These analyses showed highly consistent findings with the main results, except for all cause mortality, which became of borderline significance (P=0.05) in the extended versus 12 month regimen comparison.

Discussion

The current meta-analysis compares the efficacy and safety of three different durations of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention with drug eluting stents. To our knowledge, by its unique design, it is the first report focusing on outcomes with either short term or extended (beyond 12 months) duration of dual antiplatelet therapy versus 12 month therapy. By incorporating the most recent evidence from randomised controlled trials, this report forms the largest database on duration of dual antiplatelet therapy ever analysed (n=32 287).

There were two main findings. First, short term dual antiplatelet therapy, when compared to 12 month therapy, was associated with a similar rate of stent thrombosis or myocardial infarction, with a reduced risk of major bleeding. Second, extended therapy, compared with a 12 month regimen, reduced the odds of definite/probable stent thrombosis, very late stent thrombosis, and myocardial infarction, but increased the odds of major bleeding. While all cause mortality also increased in the extended versus 12 month regimen comparison, driven by non-cardiovascular events, this study finding becomes mitigated by the inclusion of the landmark analysis at 12 months of patients enrolled in the PRODIGY trial. Nevertheless, given the potential profound implications of this observation if confirmed to be true, further studies are needed to validate or confute this preliminary finding.

Coronary drug eluting stents—by inhibiting in-stent neointimal proliferation—have effectively reduced the need for repeat revascularisation compared with bare metal stents and have achieved widespread use worldwide.[4] Concerns about drug eluting stents have arisen, however, regarding the propensity for thrombotic events occurring more than one year after implantation.[1 2]

Based on these considerations, current guidelines from the American College of Cardiology/American Heart Association advocate at least 12 months of dual antiplatelet therapy after implantation of drug eluting stents.[5] The European Society of Cardiology endorses six to 12 months of dual therapy after implantation, and 12 months for all patients with acute coronary syndrome irrespective of revascularisation strategy.[6] Prolonged dual antiplatelet therapy (beyond 12 months), while protecting against thrombosis, will invariably increase the risk of major bleeding with an uncertain net impact on patient outcomes after percutaneous coronary intervention.[29-31] This benefit-risk dualism has raised controversies around the optimal duration of dual antiplatelet therapy that would maximise the effect against stent thrombosis while minimising the associated bleeding risk. As a result, recent randomised controlled trials have adopted a triad of duration models: short term, 12 months, and beyond 12 months.

Short term (<12 month) versus 12 month dual antiplatelet therapy

We did not observe any significant differences in myocardial infarction and stent thrombosis outcomes with short term dual antiplatelet therapy as compared with 12 month therapy, in the face of reduced bleeding complications. This neutral effect on ischaemic endpoints testifies for a similar efficacy and a greater safety profile with shortened therapy as compared with 12 month therapy. Our findings are consistent with those of recent trials (which were, however, limited in sample size) and two previous meta-analyses of four trials comparing short term with longer durations.[9 32] The two analyses, however, included fewer studies that were, in addition, heterogeneous as to duration of prolonged dual antiplatelet therapy, spanning 12-24 months.

Extended (>12 month) versus 12 month dual antiplatelet therapy

Although previous studies had suggested that short term dual antiplatelet therapy is effective and safe, especially with the availability of modern interventional techniques and new generation drug eluting stents, the benefit to harm ratio of therapy beyond one year had remained largely unknown. Registry data had suggested improvements in ischaemic outcomes with prolonged dual antiplatelet therapy; however, registries are prone to bias owing to their observational design.[33 34] An important finding was the 67% reduction in cumulative odds of definite/probable stent thrombosis and, specifically, of very late (>1 year) stent thrombosis with extended dual antiplatelet therapy when compared with 12 month therapy, at the price of higher major bleeding and all cause mortality. In practical terms, the numbers needed to treat and to harm were similar for thrombotic (number needed to treat 152) and bleeding (number needed to harm 135) events, highlighting the importance of balancing the patients' thrombotic profile against their bleeding risk in case of prolonged dual antiplatelet therapy.

The pathophysiology of very late stent thrombosis has been attributed to incomplete re-endothelialisation caused by drug or scaffold induced inhibition of endothelial cell proliferation, belated stent malapposition, neoatherosclerosis, and inflammation induced by the durable polymers, which occur over time after drug eluting stent implantation.[35 36] The results of the present meta-analysis suggest that in a subgroup of patients, both patient and stent related factors can interact adversely over time through retarded endothelialisation and persistent inflammation, culminating in very late stent thrombosis[37] once dual antiplatelet therapy is withdrawn. On the other hand, major bleeding and apparently also all cause deaths (number needed to harm 238) were more common with prolonged dual antiplatelet therapy. It remains unclear whether this observation on total mortality is real and whether it might be explained by the effect of bleeding on fatal outcomes.

The DAPT trial,[10 19] which is the largest to explore the effect of extended versus 12 month dual antiplatelet therapy, found ischaemic protection with extended therapy at the price of increased bleeding risk. In the present meta-analysis, a large number of myocardial infarctions were derived from the DAPT trial, which was only partly justified by the trial's bigger sample size than the other trials. Indeed, the annual incidence of myocardial infarction in the DAPT trial was more than twice that reported by other studies. On the other hand, the annual incidence of other thrombotic complications (such as stent thrombosis) or of bleeding events in the DAPT trial seemed more consistent with those observed in the other included trials. Reasons for the marked difference in myocardial infarction rates—in the range of three extra events per 100 aspirin treated patients per year in the control group of the DAPT trial as compared to the other studies—remain unclear. Moreover, the consistency of direction of estimates testified by the very low heterogeneity across trials in our pooled analysis suggests that the overall effect of this meta-analysis is robust and can be interpreted with confidence. In view of the residual uncertainty on overall mortality and the clear bleeding liability associated with prolonged dual antiplatelet therapy, a long term regimen should probably be reserved to patients at high ischaemic risk and low bleeding risk, in whom such treatment would have been well tolerated for the first 12 months.

Implications for clinical practice

There are distinct effects associated with short term and extended dual antiplatelet therapy. Shorter duration yields fewer bleeding events than a longer duration, with comparable efficacy against ischaemic complications. Furthermore, extended therapy leads to a marked reduction of thrombotic complications at the price of increased bleeding rates with a signal towards increased all cause mortality. The currently recommended 12 month duration of dual antiplatelet therapy after drug eluting stent implementation is a compromise between ischaemic and bleeding risks. However, based on this meta-analysis, the 12 month recommendation seems to be a less appealing strategy to minimise bleeding risk or maximise ischaemic benefit than a short term or an extended therapy regimen, respectively.

The lack of clear-cut benefits observed with the 12 month strategy raises the question of whether this average duration of dual antiplatelet therapy might be replaced by a shorter or longer duration in patients at high or low bleeding risk, respectively.

The apparently discordant finding of similar ischaemic risks in trials comparing a short term versus

12 month duration of dual antiplatelet therapy—as opposed to an ischaemic protection conferred by an extended versus 12 month duration—may reflect differences in the selection of patient populations included in the studies. In trials randomising patients to a 12 month versus short term regimen, those at high bleeding risk were not excluded, and randomisation occurred relatively early after stent implantation (that is, immediately, or after one, three, or six months). Studies comparing 12 month with extended regimens randomised patients only after several months of dual antiplatelet therapy provided that no major bleeding episodes had occurred in the preceding months. These studies most likely selected, by design, a patient population at relatively lower risk of bleeding while receiving therapy.

In view of the possible association between bleeding and subsequent ischaemic and fatal events, it may be hypothesised that in less carefully selected populations (such as those patients included in short term *v* 12 month studies), the detrimental effect of bleeding on ischaemic endpoints and death would have counterbalanced the ischaemic protection potentially offered by dual antiplatelet therapy. On the other hand, prolonging therapy in the long term in patients at relatively lower bleeding risk (that is, those who tolerate this therapy for at least 12 months) could result in a more favourable reduction of ischaemic events, at the cost of some major haemorrhagic complications.

From an individual patient's perspective, the results of this article suggest that the 12 month cut-off for dual antiplatelet therapy should not necessarily be considered as the optimal standard of care choice. Rather, durations shorter or longer than 12 months should be calibrated, taking into consideration the patient's bleeding and ischaemic risk profile, in addition to procedural variables and acuity of presentation. Further, well powered trials are warranted to test the clinical effect of tailored dual antiplatelet therapy. A practical approach for clinicians, given the results of our pooled analysis, would be to offer to many patients, especially those at high bleeding risk, a duration of less than one year after coronary implantation of a drug eluting stent. Prolonged dual antiplatelet therapy beyond one year could represent an option for selected patients who present very high ischaemic and low bleeding risks.

Effect of dual antiplatelet therapy on all cause mortality

In the present article, all cause but not cardiovascular mortality was found to be increased with extended dual antiplatelet therapy as compared with 12 month regimens. These findings were at variance with a recent Bayesian non-standard meta-analysis, in which no difference in all cause, cardiovascular, and non-cardiovascular mortality was found between treatment durations.[38] The Bayesian meta-analysis focused only on the mortality outcome and had broad inclusion criteria. It comprised patients with coronary artery disease undergoing medical management (that is, without coronary stent implantation) and patients without coronary artery disease, who qualified for inclusion based on multiple atherothrombotic risk factors, peripheral artery disease, or presence of atrial fibrillation. This recent pooled analysis also included a highly heterogeneous duration of regimens. Dual antiplatelet therapy spanned from six to 40 months in the so-called "extended DAPT" arm, which was compared to a similarly heterogeneous shorter "DAPT duration" group; this second group included not only a shortened regimen but also no dual antiplatelet therapy at all. Hence, while the finding of the mortality increase in our meta-analysis might be due to chance, it could also indicate an excess of deaths attributed to non-cardiovascular causes (for example, cancer related deaths, as observed in the large DAPT trial[10 19]) or to major bleeding.

Limitations

The results were analysed on trial level data and not on patient level data; individual patient information would have added further insights to the analysis. Furthermore, the criteria for inclusion of patients in this meta-analysis were broad, comprising both stable low risk and unstable high risk patients, according to the original trial designs, and reflecting more closely the case mix encountered in clinical practice. Different types of P2Y12 antagonists (clopidogrel, prasugrel, and ticagrelor) and drug eluting stents were used across and within trials. These data should be viewed as reflecting real world routine practice in all patients treated with different antiplatelet drugs and drug eluting stents, based on clinical settings, operator choices, and drug availability.

On the other hand, all the main and sensitivity analyses performed were consistent, suggesting that the effects of the different durations of dual antiplatelet therapy were robust and justified. Since most randomised trials were performed under clopidogrel, and first generation drug eluting stents were implanted in a sizable fraction of patients, further randomised controlled trials are needed to explore the effect of novel P2Y12 inhibitors and new stents on the duration of dual antiplatelet therapy. Finally, no data were available to specifically test the interaction of different stents and different DAPT durations.

Conclusions

Discontinuation of dual antiplatelet therapy before the recommended 12 month period following percutaneous coronary intervention with drug eluting stents yields significantly reduced bleeding without increasing ischaemic outcomes. By contrast, dual antiplatelet therapy maintained well beyond 12 months (that is, up to 24 or 30 months) reduces the incidence of thrombotic complications, in particular stent thrombosis and myocardial infarction, at the price of increased major bleeding and possibly all cause death. The effect of extended dual antiplatelet therapy on mortality rates observed in the DAPT trial[10 19] and confirmed in this meta-analysis remains preliminary, as a play of chance cannot be excluded. However, this observation warrants further investigation as, if true, could have profound consequences on public health.

Contributors: EPN and MV conceived and designed the study. EPN, MK, and VS collected and abstracted the data. EPN undertook the statistical analysis; EPN and MV drafted the manuscript. All authors analysed and interpreted the data and critically revised the manuscript for important intellectual content. EPN is the guarantor.

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Ethical approval: None was required.

Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Web appendix: Supplementary material

Chapter 5.2

Impact of greater than 12-month Dual Antiplatelet Therapy Duration on Mortality: Drug-specific or a Class-effect? A Meta-analysis

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Letter to the Editor

Impact of greater than 12-month dual antiplatelet therapy duration on mortality: Drug-specific or a class-effect? A meta-analysis

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To the editor:

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is currently recommended for one year after coronary stent implantation or an episode of acute coronary syndrome. Recently two large clinical trials demonstrated benefits in reducing stent- and non-stent related myocardial infarction extending DAPT with the use of thienopyridines (i.e. clopidogrel or prasugrel) or ticagrelor beyond the recommended 12-month period [1,2]. However, a greater than 12-month course of DAPT with thienopyridines was also associated with higher mortality in the DAPT trial [1], which was confirmed by subsequent meta-analyses [3]. It remains unclear if this effect on mortality is class- or thienopyridine-specific. We therefore performed a systematic revision of the literature and meta-analysis of the available clinical trials that randomized patients to 12-month vs. greater than 12-month DAPT duration based on thienopyridines or ticagrelor, to explore the differential impact of $P2Y_{12}$ inhibitor type on all-cause mortality, cardiovascular and non-cardiovascular mortality.

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The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplemental material) [4]. We selected for our analysis randomized clinical trials that assigned patients to a standard 12-month DAPT vs. extended DAPT beyond 12 months. The final search was performed on May 2, 2015. Statistical pooling of odds ratios (OR) was performed with random effects. A 2-tailed alpha of 5% was used for hypothesis testing. Statistical interaction was assessed with Cochran Q via a chi-square test and quantified with the I^2 test.

We identified 4 relevant studies, of which 3 tested the effect of thienopyridines (i.e. clopidogrel/prasugrel) and one of ticagrelor [1,2,5,6]. Data extraction was limited to all-cause, cardiovascular and non-cardiovascular mortality. On-treatment events and those occurring at the longest available follow-up were appraised in the main and sensitivity analyses, respectively. All analyses were intention-to-treat and performed with RevMan v5.3.5 (the Cochrane Collaboration).

Among 37,427 patients, all-cause mortality after an extended DAPT course was increased by 30% in patients receiving thienopyridines (OR 1.30; 95% CI 1.02–1.66), but not in those treated with ticagrelor (OR 0.94; 95% CI 0.82–1.08) with significant interaction between duration and type of treatment (P_{int}: 0.02) (Fig. 1A). The differential impact of thienopyridines vs. ticagrelor on all-cause mortality was driven by both cardiovascular and non-cardiovascular death. Cardiovascular mortality trended lower with an extended use of ticagrelor beyond 12 months (OR: 0.85; 95% CI 0.72–1.01), whereas no such effect was observed with thienopyridines (OR: 1.08; 95% CI 0.79–1.49) (P_{int}: 0.19) (Fig. 1B). At sensitivity analysis, interaction became more pronounced (P_{int}: 0.10) when events at longest available follow-up were considered. Non-cardiovascular mortality was increased from an extended treatment with thienopyridines (OR: 1.85; 95% CI 1.23–2.79) but not after prolonged treatment with ticagrelor (OR: 1.14; 95% CI 0.92–1.42) (P_{int}: 0.04) (Fig. 1C). To further corroborate our findings we evaluated the differential impact on cardiovascular and non-cardiovascular mortality on each treatment group. An extended course of DAPT with thienopyridines had a different impact on cardiovascular mortality as compared to non-cardiovascular mortality (P_{int}: 0.04), characterized by a null-effect on the former and a significant 87% increase on the latter

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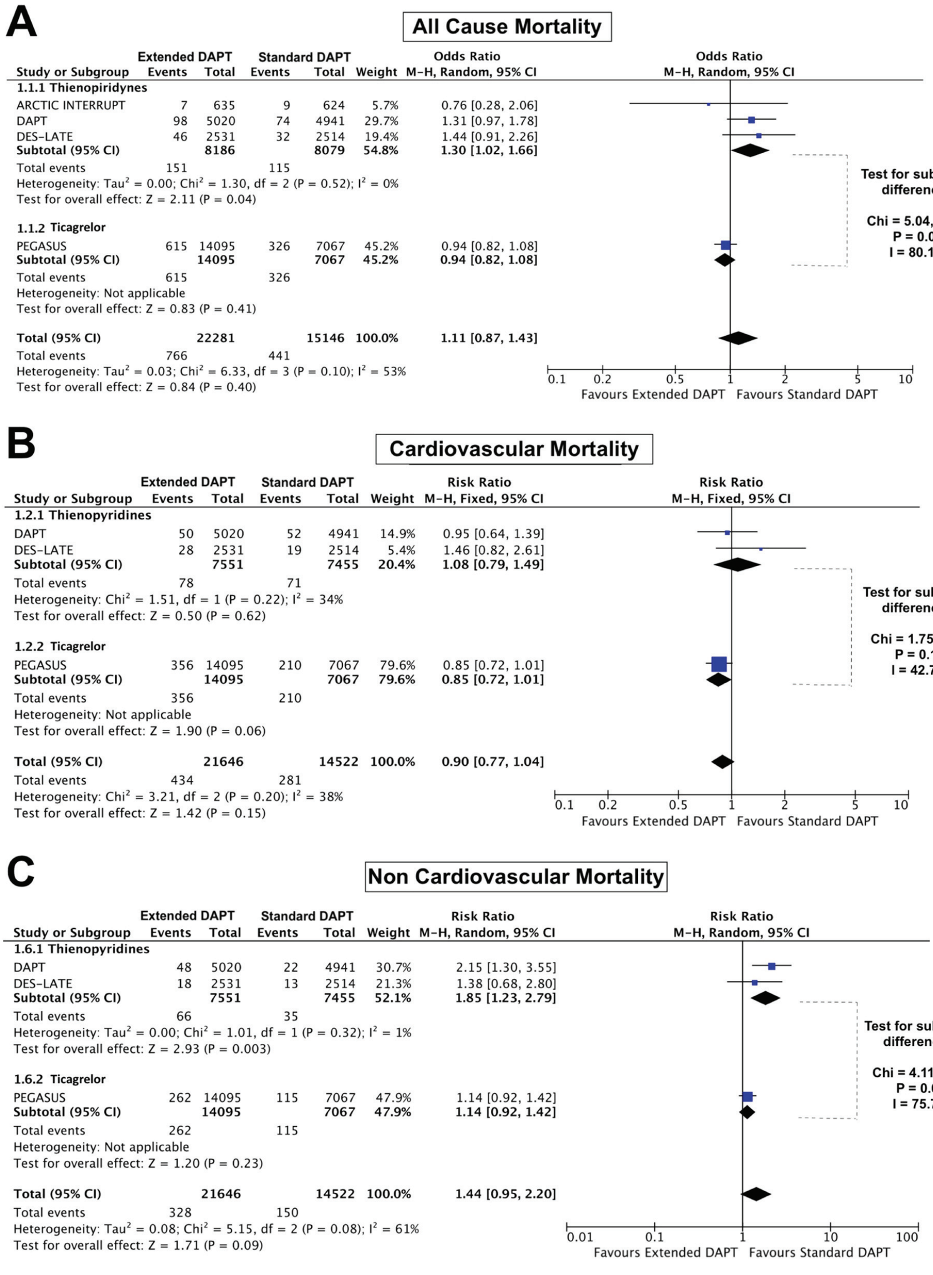

Fig. 1. The odds ratio for standard vs. extended DAPT duration regarding all-cause (A), cardiovascular (B) and non-cardiovascular (C) mortality is presented among the studies implementing thienopyridines and ticagrelor.

outcome (Fig. 2A). On the other hand, an extended DAPT with ticagrelor was associated to a trend towards cardiovascular mortality reduction and a null-effect on non-cardiovascular fatality (Fig. 2B).

Our pooled analysis suggests that the type of $P2Y_{12}$ inhibitor used in combination with aspirin may exert a differential effect on mortality and type thereof after an extended DAPT duration beyond 12 months.

While a prolonged treatment with thienopyridines increased fatality risk, in keeping with previous reports [3], ticagrelor provided a more favorable impact on mortality. This was driven by a trend towards cardiovascular mortality reduction and a null-effect on non-cardiovascular death. While it may be argued that ticagrelor did not reduce significantly cardiovascular mortality in PEGASUS, this finding is highly consistent

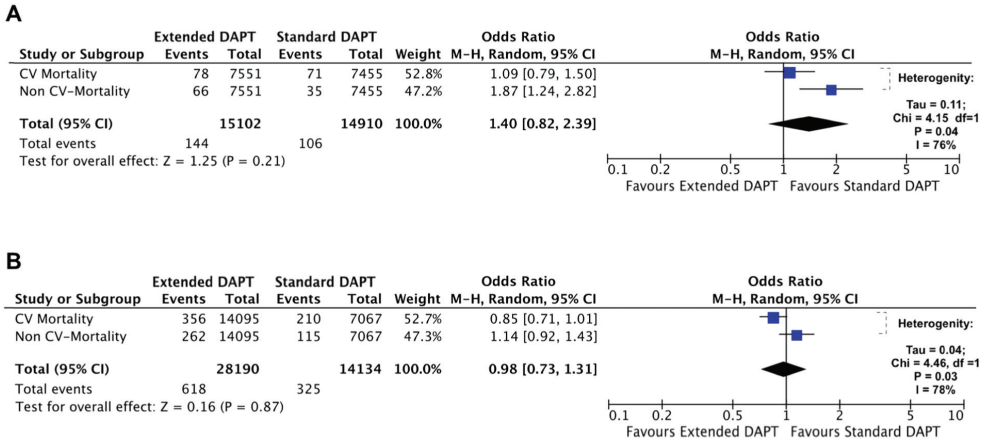

Fig. 2. The odds ratio for extended DAPT vs. standard DAPT duration is shown for cardiovascular and non-cardiovascular mortality among studies implementing thienopyridines (A) and ticagrelor (B).

with the PLATO trial [7], where all-cause and cardiovascular mortality were both significantly lower after ticagrelor as compared to clopidogrel. On this other hand, no contemporary study has reported mortality reduction after treatment with clopidogrel as compared to placebo or after prasugrel as compared to placebo or clopidogrel.

The putative reasons behind the differential effect of ticagrelor vs. clopidogrel/prasugrel on non-cardiovascular mortality remain speculative. It is tempting to speculate that while ticagrelor exerts a more powerful inhibition of platelet activity compared to clopidogrel and as such be more protective towards ischemic recurrences, its reversible inhibition of the $P2Y_{12}$ receptor may mitigate the detrimental consequences of bleeding on mortality and type thereof. In keeping with this, in both the PEGASUS and PLATO, no excess of fatal bleeding was observed with ticagrelor despite overall higher bleeding risks [2, 7]. Off-target effects exerted by ticagrelor, mainly related to the inhibition of the ENT-1 receptor, may also concur explaining our findings.

Our study suffers of several limitations. The effect of an extended course of ticagrelor beyond 12 months was studied only in a single, yet large-scale trial, which recruited patients with history of myocardial infarction [2]. Differently, the three studies that appraised a similar treatment extension with thienopyridines included patients with stable coronary artery disease at presentation. However, it seems unlikely that clinical presentation alone may explain the observed effect on mortality considering that none of the studies so far performed demonstrated interaction between clinical presentation and duration of DAPT on mortality [8,9]. In addition, among thienopyridines studies, the DAPT trial was the only in which a portion of patients received a treatment with prasugrel, thus it may be questioned if our findings are clopidogrel-specific or they may also apply to prasugrel [1,5,6]. However, Garratt et al. reported no mortality benefit with 30-month treatment with prasugrel as compared to standard 12-month treatment [10].

In conclusion, an extended treatment with ticagrelor, as compared to a similar strategy with thienopyridines, exerted a more favorable effect on all-cause mortality due to a trend towards reduction of cardiovascular death and a null-effect on non-cardiovascular death. Our analysis suggests that type of $P2Y_{12}$ inhibitor used in combination with aspirin may be a treatment modifier on mortality and type thereof in patients undergoing >12-month therapy.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.08.058.

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Chapter 5.3

Long-term use of ticagrelor in patients with prior myocardial infarction

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N Engl J Med. 2015 Sep 24;373(13):1271-2 (Impact Factor: 72.406)

CORRESPONDENCE

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Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

TO THE EDITOR: In their report on the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack using Ticagrelor Compared to Placebo on the Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial, Bonaca et al. (May 7 issue)[1] suggest that the benefit of dual antiplatelet therapy comes at a cost of an increased risk of bleeding events. A dual antiplatelet regimen administered at an even lower dose than the one used in this study could confer a reduced risk of bleeding events and improved secondary prophylaxis against recurrent ischemic events as compared with aspirin.

We successfully tested a strategy of alternate-day administration of clopidogrel 1 year after percutaneous coronary intervention with placement of a drug-eluting stent.[2] We hypothesized that the degree of antiplatelet effect that was required to prevent very late stent thrombosis decreases with time as the stent undergoes endothelialization — in other words, the therapeutic threshold that is required to prevent very late stent thrombosis decreases with time. The antiplatelet effect of clopidogrel lasts 5 to 7 days. Typically, after the interruption of clopidogrel therapy, stent thrombosis occurs after 3 to 4 days, which signifies the recovery of enough platelet function to produce stent thrombosis (i.e., above the therapeutic threshold). The use of clopidogrel every other day or a lower dose of ticagrelor among patients receiving a drug-eluting stent may be sufficient to cross the much reduced therapeutic threshold that is required to prevent very late stent thrombosis after 1 year and to avert recurrent coronary events from spontaneous plaque rupture without much bleeding risk (a so-called Goldilocks dose).

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Dr. Sharma reports receiving lecture fees from Eli Lilly and Daiichi Sankyo and being an investigator for the PEGASUS-TIMI 54 trial. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Bonaca et al. report higher rates of cancer-related death among patients receiving either 90 mg or 60 mg of ticagrelor than among those receiving placebo (1.10% and 0.92% vs. 0.76%) (Table S2 in the Supplementary Appendix,

Study	Extended Therapy	Standard Therapy	Hazard Ratio (95% CI)	P Value
	no. of events/total no.			
Mauri et al.	25/5012	14/4940	1.76 (0.92–3.39)	
Bonaca et al.	141/14,095	53/7067	1.33 (0.97–1.83)	
All patients	166/19,107	67/12,007	1.41 (1.06–1.87)	0.02
Heterogeneity, I^2=0%				

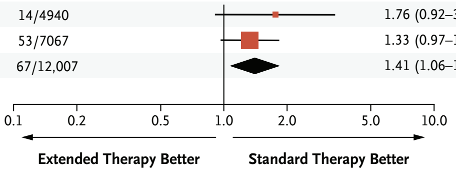

Figure 1. Pooled Analysis of Cancer-Related Deaths among Patients Receiving Extended Dual Antiplatelet Therapy, as Compared with Standard Therapy, in Two Studies.

In the trial by Mauri et al. (Dual Antiplatelet Therapy [DAPT] study), patients who had received 1 year of treatment with a thienopyridine (clopidogrel or prasugrel) were randomly assigned to continue receiving a thienopyridine or to receive a placebo for another 18 months. In the trial by Bonaca et al. (PEGASUS-TIMI 54), all patients were followed for a median of 33 months, including those receiving ticagrelor (who are included in the extended-therapy group in the pooled analysis) and those receiving placebo (who are included in the standard-therapy group). The size of the squares is proportional to the size of the study. The diamond incorporates the overall hazard ratio and 95% confidence interval.

available with the full text of the article at NEJM.org). Similar findings have been reported by Mauri et al.[1] with an extended use of thienopyridines beyond 1 year.

A pooled analysis of these two studies suggests a significant relative increase of 41% in the number of cancer-related deaths among patients who were treated with extended dual antiplatelet therapy (Fig. 1). In this analysis, the number of patients who would need to be treated to cause one cancer death was 322. Could the author indicate whether there was an imbalance in the diagnosis of cancer before and after randomization in the two study groups? If this is not the case, the reason for an increase in cancer-related deaths with an extended duration of dual antiplatelet therapy should be investigated.

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TO THE EDITOR: Bonaca et al. are missing the most important finding of the PEGASUS-TIMI 54 study — namely, that drugs that cause excess bleeding also increase the risk of solid cancers. This study showed an increasing dose–response relationship for deaths from cancer: 77 in the group receiving 90 mg of ticagrelor and 64 in those receiving 60 mg of ticagrelor, as compared with 53 receiving placebo. In the Study of Platelet Inhibition and Patient Outcomes (PLATO), the administration of ticagrelor was too short and the follow-up was too incomplete to provide reliable data about cancer.[1]

A review of prasugrel by the Food and Drug Administration (FDA)[2] first reported the association between bleeding and solid cancers. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38),[3] the hazard ratios in the prasugrel group, as compared with the clopidogrel group, for the incidence of solid cancers and death were both approximately 1.6 (P=0.001). An FDA review[4] of the DAPT study documented that the relative risk of the incidence of a solid cancer was about 1.2 with clopidogrel and 1.3 with prasugrel, as compared with placebo. The rates of cancer-related death (relative risk, 2.2; P=0.02) were higher with continued use of thienopyridines.[5] The latter FDA review[4] also provides an overview of bleeding and cancer results for all major antiplatelet and anticoagulant trials submitted to the FDA. The most serious hazard of long-term antiplatelet use is cancer, not bleeding.

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No potential conflict of interest relevant to this letter was reported.

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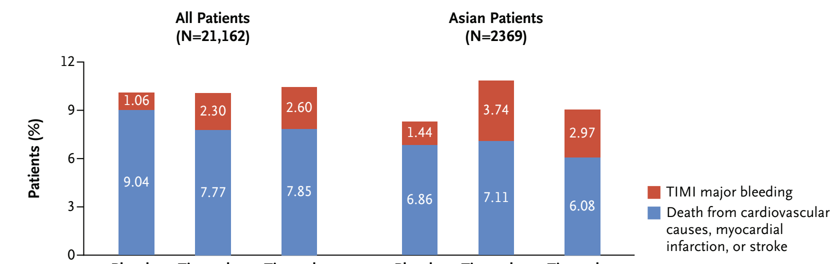
DOI: 10.1056/NEJMc1508692

TO THE EDITOR: The PEGASUS-TIMI 54 and DAPT[1] trials have both shown that intensified platelet inhibition with dual antiplatelet therapy ($P2Y_{12}$ antagonist plus aspirin) after 1 year effectively reduces the risk of ischemic events in patients with high-risk coronary artery disease at the expense of clinically serious bleeding. Therefore, a personalized antiplatelet strategy that is based on a risk-profile analysis including a therapeutic-window concept for platelet reactivity may improve the balance between efficacy and safety during long-term dual antiplatelet therapy.[2]

East Asians have less thrombophilia and a greater bleeding tendency than do Western populations during antiplatelet therapy.[3,4] Furthermore, active metabolite concentrations of prasugrel and ticagrelor are up to 50% greater among East Asians than among white patients, findings that translate into more potent platelet inhibition among East Asians.[4] In PEGASUS-TIMI 54, the net clinical benefit of the addition of long-term ticagrelor among Asian patients appears to be less favorable than among white patients (Fig. 1). (East Asians made up approximately three quarters of the Asian cohort.) A more judicious approach in adapting the strategy outlined in the PEGASUS-TIMI 54 trial for Asians without further dedicated studies in the Asian population



	All Patients: Ticagrelor, 60 mg	All Patients: Ticagrelor, 90 mg	Asian Patients: Ticagrelor, 60 mg	Asian Patients: Ticagrelor, 90 mg
No. Needed to Treat	78.7	84.0	NA	128.2
No. Needed to Harm	80.6	64.9	400.0; 43.5	65.4

Figure 1. Net Clinical Benefit for Asian Patients, as Compared with All Patients, in the PEGASUS-TIMI 54 Trial.
Shown are the percentages of Asian patients, as compared with all patients, who had a composite cardiovascular event (death from cardiovascular causes, myocardial infarction, or stroke at 3 years) or who had a major bleeding episode (as defined by the Thrombolysis in Myocardial Infarction [TIMI] criteria at 3 years), according to the dose of ticagrelor or placebo. The values below the graph show the number of patients who would need to be treated to prevent one cardiovascular event and the number of patients who would need to be harmed to cause one cardiovascular or bleeding event. Among Asian patients, the numbers needed to harm for ticagrelor (60 mg) are 400.0 for a cardiovascular event and 43.5 for a major bleeding event. NA denotes not applicable.

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will be an essential challenge, given these observations.

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TO THE EDITOR: There is uncertainty about the balance between bleeding and efficacy in the PEGASUS-TIMI 54 trial, since the absolute reduction of approximately 1 percentage point in the composite of death from cardiovascular causes, myocardial infarction, or stroke seems to be offset by a similar elevation in the risk of major bleeding. To help apply these results to practice, first, we need more details about major bleeding events, especially whether these events were spontaneous or related to surgical or interventional procedures. Second, a formal analysis of efficacy and safety on the basis of baseline clinical and bleeding risk would be helpful to guide treatment — for example, using adapted scores from the Global Registry of Acute Coronary Events (GRACE)[1] study and the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly)[2] study. Third, no information is presented on platelet-function studies that might provide important insights into risks of bleeding.[3] Finally, the results provide no information on cost-effectiveness. Investigators are to be congratulated on a landmark trial, but global economic and health-policy constraints mean that providing all relevant information on new treatments as early as possible will help increase adoption into practice.

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Dr. Flather reports receiving fees for lectures and serving on advisory boards from AstraZeneca and serving on events-adjudication committees for and receiving grant support from Eli Lilly, Daiichi Sankyo, and Novartis; and Dr. Bakhai, receiving fees for serving on advisory boards from AstraZeneca and consulting fees from Eli Lilly. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In response to the comments of Sharma and colleagues: we agree that the intensity of long-term antiplatelet therapy that best balances benefit and risk may be lower for patients who are further removed from their myocardial infarction, as we discussed in our article on the design of the PEGASUS-TIMI 54 trial.[1] For that reason, we tested two doses of ticagrelor and indeed found similar efficacy and a tendency toward a better safety and side-effect profile with the lower dose. Whether even lesser degrees of platelet inhibition would be as effective for secondary prevention in this population is a hypothesis that remains to be proved but should be tested.

Costa and Valgimigli as well as Marciniak raise the issue of an association between long-term antiplatelet therapy and an increase in the risk of cancer and cite data from the DAPT trial. However, with the exclusion of DAPT, in a meta-analysis involving more than 50,000 patients in trials of prolonged $P2Y_{12}$ inhibition, as compared with placebo, in which more than 1000 patients died from noncardiovascular causes, the hazard ratio for noncardiovascular death was 0.98 for patients receiving $P2Y_{12}$ inhibitors.[2] Marciniak cites his previous analysis noting an excess of cancers with prasugrel, as compared with clopidogrel, in TRITON-TIMI 38. However, in reviewing the totality of evidence, the FDA concluded that causality of cancer was unlikely and that the chance of a false positive finding was high.[3] That conclusion was later supported by the prospective assessment of cancer in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, which showed no excess with prasugrel versus clopiogrel.[4] Similarly, with ticagrelor, although there was a numeric imbalance in PEGASUS-TIMI 54, there was no excess of cancers with the 90-mg dose of ticagrelor, as compared with clopidogrel, in PLATO.[5] Imbalances that were seen in some studies may be due to ascertainment bias, with bleeding leading to imaging studies that reveal cancers, so deaths of patients are classified as being from these cancers. Ongoing analyses should help shed light on this matter.

Jeong et al. raise the issue of a different response to antiplatelet therapy among Asian patients. However, as we noted in our article, there was no heterogeneity with ticagrelor for ischemic or bleeding events among Asians as compared with other populations. We agree that larger, dedicated studies in Asia would be valuable, rather than attempting to perform risk–benefit assessments by extrapolating event rates from small subgroups of patients in whom the number of events in some groups was only eight.

We appreciate the enthusiasm of Flather and colleagues to see more secondary analyses. Indeed, we agree that the analyses they mention are of value.

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Since publication of their article, the authors report no further potential conflict of interest.

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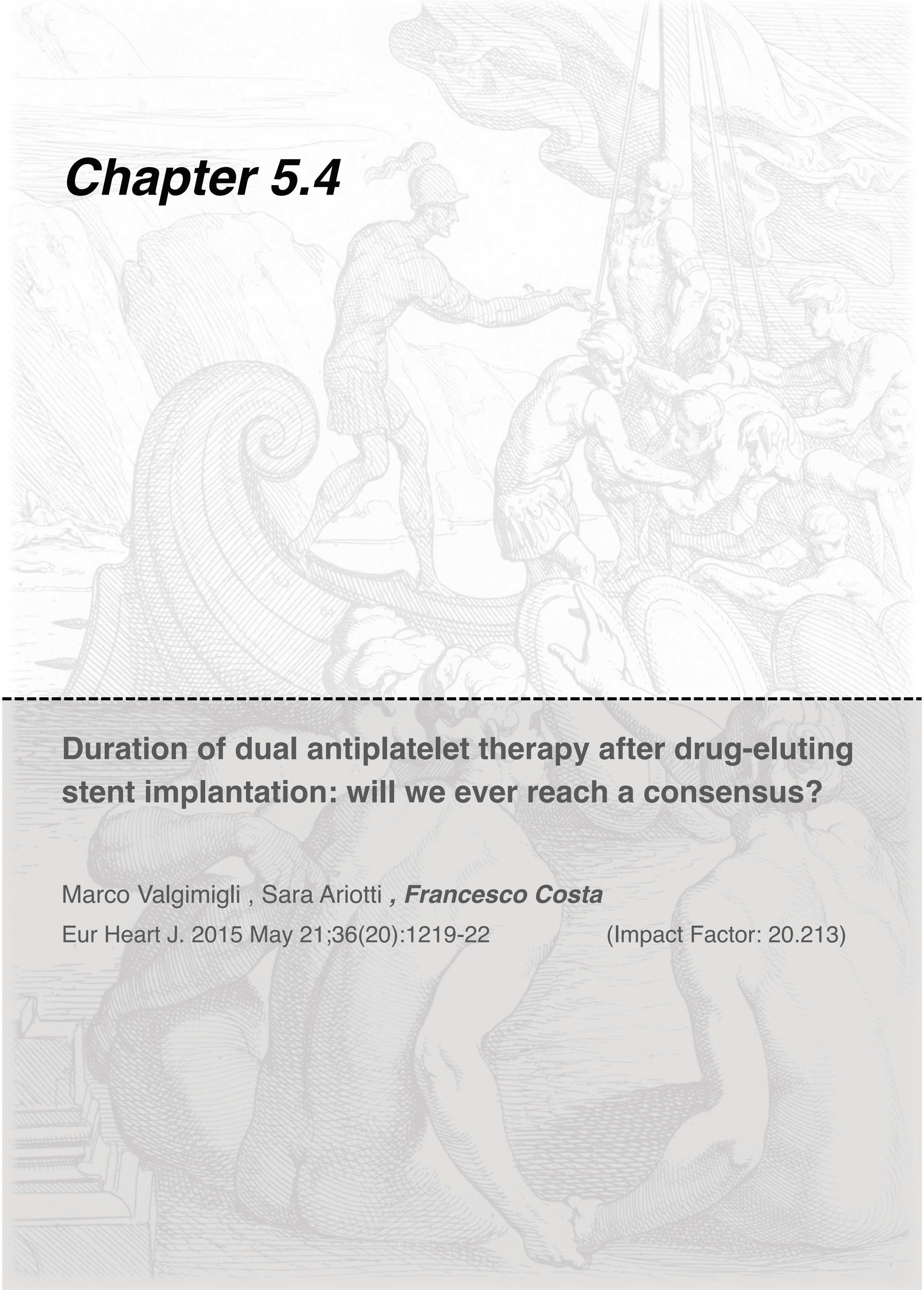

Chapter 5.4

Duration of dual antiplatelet therapy after drug-eluting stent implantation: will we ever reach a consensus?

Marco Valgimigli , Sara Ariotti ***, Francesco Costa***

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EDITORIAL

Duration of dual antiplatelet therapy after drug-eluting stent implantation: will we ever reach a consensus?

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This editorial refers to 'ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting', by S. Schulz-Schüpke *et al.*, on page doi:10.1093/eurheartj/ehu523.

'Well? Shall we go?'—'Yes, let's go'. 'They do not move.'
Waiting for Godot, by Samuel Beckett,

Combined treatment with aspirin and a P2Y12 inhibitor, the so-called dual antiplatelet therapy (DAPT) regimen, exerts protection against ischaemic myocardial recurrences via a double mechanism of action.

First, it prevents sudden thrombotic occlusion of previously implanted stent(s) in the coronary arteries, thereby reducing the risk of stent thrombosis that occurs as a result of inflammation during healing.[1,2] Since the vast majority of stent thrombosis cases are known to occur within the first weeks after stent implantation, an arbitrary 30 day to 6 weeks duration of DAPT has been investigated and a 30 day duration of therapy has become the standard of care approach after uncoated stent implantation.

Secondly, DAPT has also been shown to mitigate the risk of subsequent myocardial infarction in patients not previously treated with coronary stents or arising from non-previously stented coronary segments.[3,4] While the capability of DAPT to limit the progression of atherosclerosis *per se* has never been demonstrated, it remains likely—even if not proven—that DAPT protects the patient from the consequences of spontaneous coronary plaque rupture.

The reasons why long-term prolongation of DAPT is debated, despite its unquestionable value, are two-fold. Long-term DAPT carries a time-dependent risk of major and clinically relevant bleeding complications, which affects morbidity and mortality at least as much as ischaemic recurrences.[4–7]

Moreover, the advent of drug-eluting stents (DES) has prompted attention to be paid to delayed healing and persistent polymer-induced inflammation at the sites of stent placement, thereby potentially requiring long-standing DAPT continuation.

First-generation DES were associated with a four- to five-fold higher risk of very late (i.e. after the first year) stent thrombosis as compared with bare metal stents (BMS).[8,9] This observation corroborated the perception of increased thrombogenicity of DES as compared with BMS and fuelled 'the longer the better' notion for DAPT duration in DES-treated patients.[10]

Yet, stent thrombogenicity is a multifactorial process and the drug-elution capability *per se* does not appear nowadays (i.e. at variance with the original belief) clearly related to it.[11]

Emerging evidence of superior safety with respect to stent thrombosis and target vessel myocardial infarction has been generated for some of the newly introduced devices when compared with first-generation DES.[12–14] Moreover, there is a growing literature suggesting that at least some second-generation devices may be safer when compared not only with first-generation devices but also with the corresponding BMS counterparts.[14–16] Therefore, the original belief according to which a DES *per se* should trigger a prolonged course of DAPT does not seem to be supported by currently available comparative safety and efficacy data amongst different stent platforms.

The complexity and importance of the topic can only be addressed by properly performed randomized clinical trials. Yet, after multiple dedicated randomized controlled studies, the issue of the optimal duration of DAPT after DES implantation remains apparently unsettled.

In this issue of the journal, Schulz-Schüpke and colleagues report on the long awaited primary findings of the Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) trial, which randomized 4000 patients, out of the previously planned 6000, to undergo 6- vs. 12-month therapy with aspirin and clopidogrel, largely after second-generation DES implantation.[17]

Beyond the specific clinical and scientific value of the study, this trial does represent a major academic achievement, in light of its global representativeness, and investigator-initiated and placebo-controlled design. The hurdles of conducting such a study, which led investigators to stop inclusion prematurely, reinforce the notion that it is becoming increasingly more challenging for physicians (and also expert trialists!) to provide answers to clinically relevant

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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questions without the direct involvement of industries. This observation should prompt a profound reflection within the medical community on the sustainability of spontaneous research in the future and highlights the value of this specific study despite its inherent limitations, largely related to limited study power, which are well acknowledged by the authors.

Waiting for Godot?

In the tragicomedy entitled *Waiting for Godot*, by Samuel Becket, Vladimir and the struggling Estragon wait for the mysterious Mr Godot, who never shows up. The ISAR-SAFE along with the DAPT trials have been eagerly awaited by the community as the studies are supposed to bring a final word on the optimal DAPT duration after DES. Unlike Mr Godot, ISAR-SAFE and DAPT trials finally arrived. However, similarly to Mr Godot, both studies, for very different reasons, did not entirely fulfil the expectations set by the community. The incidence of the primary endpoint of the ISAR-SAFE study, consisting of death, myocardial infarction, stent thrombosis (definite or probable), stroke, or Thrombolysis in Myocardial Infarction (TIMI) major bleeding, was virtually identical in both groups at 9 months after randomization, fulfilling the pre-specified non-inferiority criteria. Absolute non-inferiority delta between the two treatment groups was set at 2%, corresponding to 20% of the anticipated background event rate (i.e. 10%). While the originally planned relative 20% non-inferiority boundary was appropriately stringent, the five-fold lower than expected observed event rate resulted in non-inferiority criteria being even greater than the actual event rate observed in the study. As a result, the ISAR-SAFE trial cannot be regarded as a conclusive investigation *per se*. The selection of mainly stable patients at the time of percutaeous coronary intervention (<20% myocardial infarction patients), the relatively short treatment duration difference (6 months) and follow-up (9 months), the application of a noise avoidance strategy, i.e. setting randomization at the time the treatment started to diverge in the two study groups, and perhaps the need to stick to clopidogrel instead of newer P2Y12 inhibitors may account for such an unexpected low event rate. It may be argued that in the era of more potent and consistent P2Y12 inhibitors, the restriction to their use in the ISAR-SAFE trial, which mandated the use of clopidogrel only, may have led to the exclusion of patients at highest risk of adverse events after stenting. A parallel registry, describing reasons for patients' exclusion in the study and their outcomes, would have proven extremely helpful to understand conclusively the external validity of this trial.

No difference in TIMI major bleeding was also noted in the two study groups. Yet, TIMI minor bleeding trended in favour of the 6-month DAPT regimen [0.1% vs. 0.4%; hazard ratio (HR) 0.25, 95% confidence interval (CI) 0.05–1.17; $P = 0.08$] and when the BARC (Bleeding Academic Research Consortium) classification was applied, which captures any type of actionable or non-actionable bleeding complications, the 6-month DAPT regimen was associated with 50% lower risk of events (1.4% vs. 2.8%; HR 0.49, 95% CI 0.31–0.77; $P = 0.002$). An interesting observation arising from the ISAR-SAFE trial is the complete lack of rebound phenomenon after DAPT discontinuation, both at 6 (experimental arm) and at 12 (control group) months. This is in agreement with the results of the patterns of non-adherence to anti-platelet regimens in stented patients (PARIS) registry,[18] where only patients who discontinued DAPT due to a bleeding episode or non-compliance experienced an increased risk of adverse events thereafter. Yet, this observation appears in contrast to the results of the DAPT trial where a three-fold increased risk of myocardial infarction in the 90 days following DAPT discontinuation has been reported at both 12 (control group) and 30 months (experimental arm). The inspection of the 95% CIs of the HRs capturing events in the 90 days after DAPT discontinuation in ISAR-SAFE and DAPT trials suggests that this discrepant finding with respect to rebound effect after stopping DAPT cannot easily be attributed to a type II error. Moreover, no single randomized controlled trial (RCT) testing different DAPT durations has so far reported this observation, apart from the DAPT trial. Hence, a proper explanation for the observed rebound effect, or lack thereof, of protocol-mandated DAPT discontinuation in the DAPT trial vs. ISAR-SAFE and other RCTs remain elusive and warrants further investigation.

Pooled analysis

Including ISAR-SAFE, seven studies, recruiting 15 378 patients have so far compared <12-month DAPT duration (ranging from 3 to 6 months), with 12-month (5 studies)[19–22] or 24-month (two studies)[5,23] DAPT duration. Three additional studies, including the DAPT trial, evaluated the value of prolonging vs.stopping DAPT beyond 12 months. While multiple meta-analyses exist pooling together all available evidence, irrespective of actual DAPT duration in the control and experimental arm, this generates a methodological issue as it would lead to inclusion of the 12-month DAPT duration in both study arms. As the aim of ISAR-SAFE is to assess whether DAPT can be safely stopped at 6 as compared with 12 months, only including studies comparing a shorter than 12-month vs. a ≥12-month regimen may add clarity to the results provided now by ISAR-SAFE itself. The mean age was comparable across these seven studies, ranging from 62 to 68 years, and the prevalence of diabetes mellitus ranged from 25% up to 39%. The prevalence of ST-segment elevation myocardial infarction at presentation varied widely amongst the included studies. Importantly, in all trials, DAPT consisted of aspirin and clopidogrel. Loss at follow-up was variable across studies: SECURITY[19] and the ISAR-SAFE trials had the highest loss at follow-up, while in the EXCELLENT[22], RESET[21], PRODIGY,[5] and ITALIC[23] trials, loss at follow-up was minimal. ISAR-SAFE is the only study among those included based on a double-blind design. No detectable heterogeneity for the explored endpoints, as assessed by the Q χ^2 test was found, and I^2 was consistently equal to 0. We specifically looked into the four endpoints, which were combined, in the primary endpoint of the ISAR-SAFE Trial.

Compared with at least 12-month DAPT duration, patients receiving <12 months DAPT therapy had a similar risk of death from all cause [odds ratio (OR) 0.89; 95% CI 0.68–1.15; $P = 0.37$, fixed-effects] (*Figure 1*), myocardial infarction (OR 1.14; 95% CI 0.89–1.47; $P = 0.30$, fixed-effects) (*Figure 1*), definite or probable stent thrombosis (OR 1.36; 95% CI 0.85–2.16; $P = 0.19$, fixed-effects) (*Figure 1*), and stroke (OR 0.84; 95% CI 0.53–1.31; $P = 0.30$, fixed-effects) (*Figure 1*), and lower risk of major bleeding (OR 0.53; 95% CI 0.34–0.84; $P = 0.007$, fixed-effects) (*Figure 1*).

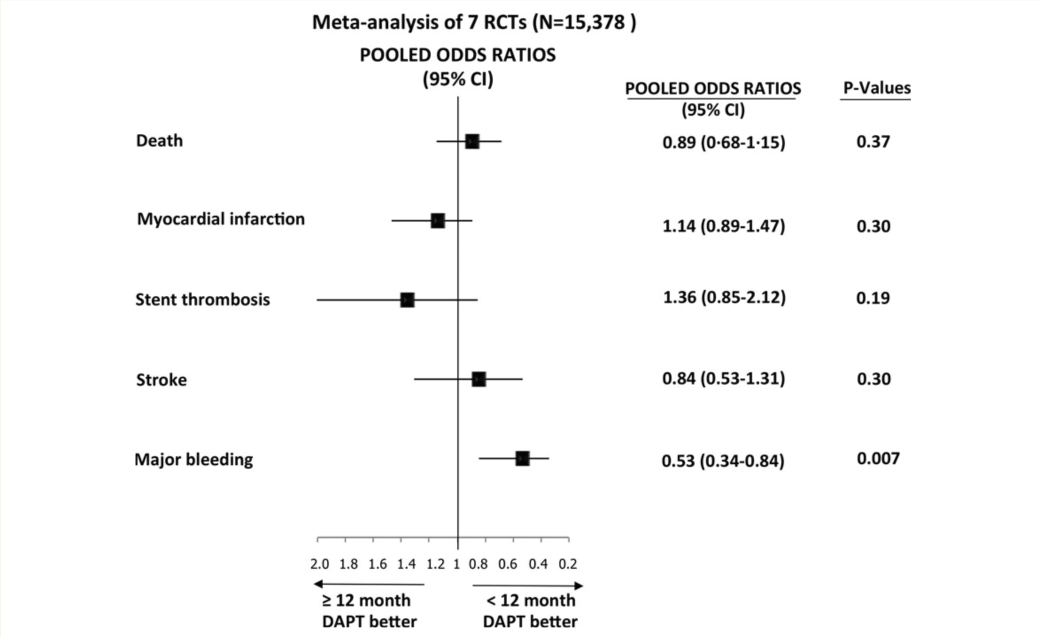

Figure 1 Pooled analysis of studies comparing shorter than 12-month dual antiplatelet therapy (DAPT) vs. at least 12 months DAPT. Forest plot reporting summary odds ratios with 95% confidence intervals (CIs) for the comparison of shorter than 12-month DAPT vs. at least 12 months DAPT at the intention to treat analysis with respect to death from any cause; myocardial infarction; definite or probable stent thrombosis; major bleeding. RCT, randomized controlled trial.

In summary, despite the fact that ISAR-SAFE has limited power to answer the original study question (i.e. is it safe to stop DAPT at 6 months after DES as compared with 12 month therapy?) the results of this pooled analysis of all studies so far conducted comparing shorter than 12 months vs. at least 12 months or longer DAPT duration after DES implantation are consistent with the overall study results. It suggests that a shorter DAPT regimen halves the risk of major bleeding and does not seem to be associated, in return, with extra ischaemic risk. This observation is in keeping with the PARIS registry, where patients who discontinued DAPT under medical guidance were not exposed to a higher risk of major adverse cardiovascular events or stent thrombosis as compared with patients who remained on DAPT for 2 years.[18]

What does the future hold?

The lack of clear ischaemic benefit associated with an at least 12-month DAPT regimen arising from the pooled analysis of all studies comparing shorter than vs. at least 12-month DAPT duration contrasts with the results of the DAPT trial.[4] In that study, an unquestionable benefit in terms of both stent- and patient-oriented ischaemic endpoints has been reported, even if the excess of bleeding risk and the increase of non-cardiovascular mortality remain a matter of concern.[4] Reconciliation of these apparently contrasting findings in clinical practice remains challenging. Difference in patient selection, timing of randomization, proportion of patients receiving newer as compared with first-generation DES,[24,25] and use of newer P2Y12 inhibitors are elements which may at least partially account for these different results.

Hence, after 10 randomized controlled studies including >30 000 patients, the only possible conclusion to be drawn by the clinician is that one standard DAPT regimen does not seem to benefit all patients equally. A personalized DAPT duration based on the individual bleeding hazard or the balance of bleeding and ischaemic risk seems the most logical way for the future, which will require dedicated studies.[26]

The selection of which single antiplatelet agent to carry forward after DAPT discontinuation, i.e. aspirin as conventionally recommended[27] or the P2Y12 inhibitor and type thereof, remains an area of research for the future, but they hold promise to shorten overall DAPT duration without compromising efficacy.

Conflict of interest: M.V. has received honoraria for lectures/advisory board and research grants from Astra Zeneca, Medtronic, Terumo, and The Medicines Company; and honoraria for advisory board and lectures from St Jude and Abbott Vascular and Alvimedica. The other authors have no conflicts to declare.

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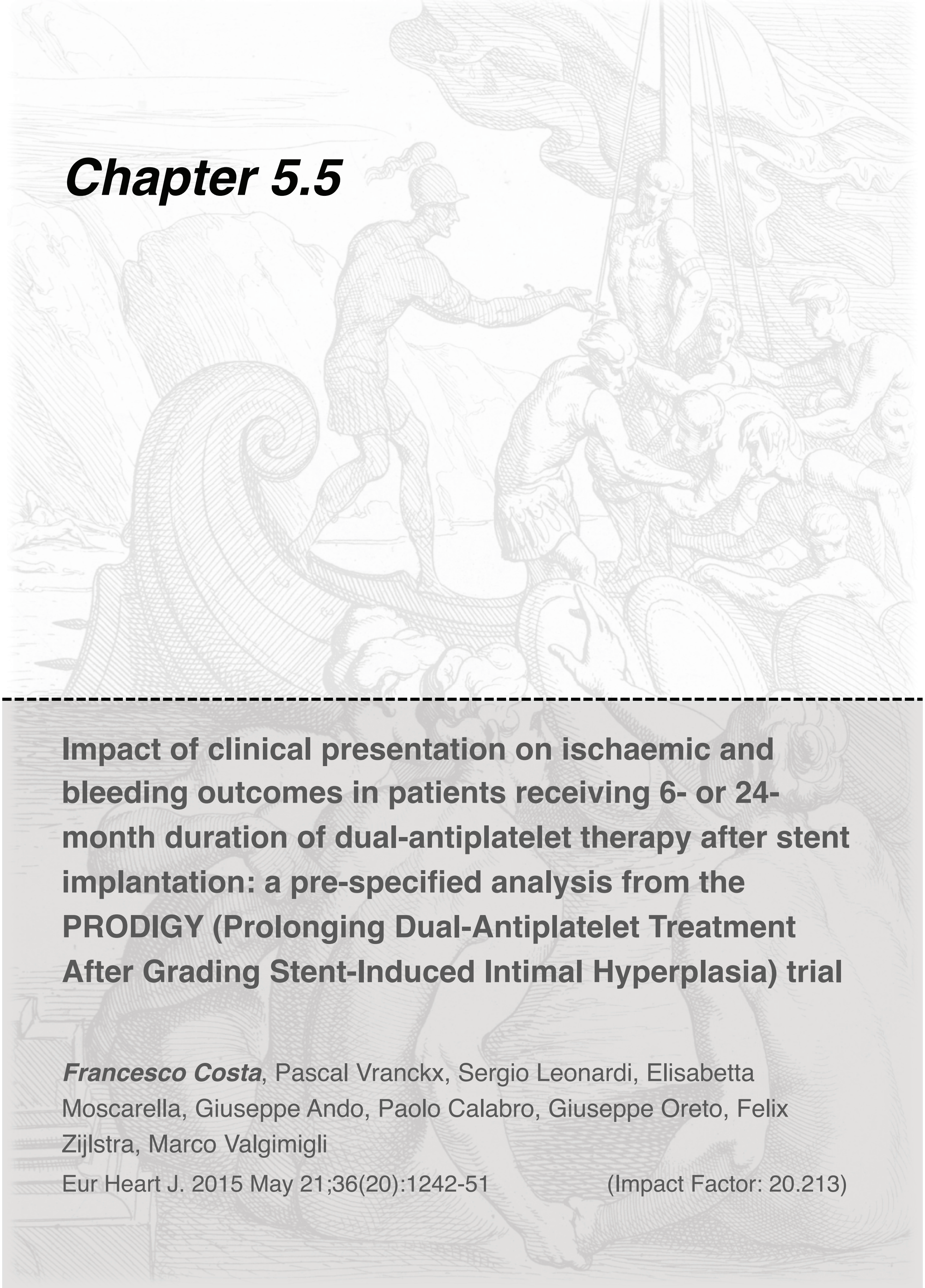
Chapter 5.5



Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial

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5

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Aims We investigated if acute coronary syndrome (ACS) rather than stable coronary artery disease (SCAD) presentation is an outcome modifier with respect to the duration of dual-antiplatelet therapy (DAPT) in patients undergoing coronary stenting.

Methods and results In the Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) trial, a total of 1465 (74.3%) patients presented ACS whereas 505 (25.7%) had SCAD and were randomized to 6- or 24-month DAPT. At 24 months, the composite of death, myocardial infarction (MI), or cerebrovascular accident (CVA) did not differ between the long- and short-term DAPT arms in both ACS (11.1 vs. 11.7%; $P = 0.67$) and SCAD (7.5 vs. 4.8%; $P = 0.21$) patients, respectively. Long-term DAPT was associated with a 75% increase of Bleeding Academic Research Consortium (BARC)-class 2, 3, or 5 bleeding in ACS [7.1 vs. 4.1%; hazard ratio (HR) 1.75, 95% confidence interval (CI) 1.11–2.74, $P = 0.015$; number needed to treat for harm (NNTH): 33.3] and a five-fold increase in SCAD (8.2 vs. 1.6%; HR 5.37, 95% CI 1.84–15.74, $P = 0.002$; NNTH: 15.1) patients, with a borderline quantitative interaction ($P_{INT} = 0.056$). As a result, net adverse cardiovascular events (death, MI, CVA, BARC class 2, 3, or 5 bleeding) were more than doubled in SCAD patients receiving 24-month DAPT, whereas they did not differ in ACS patients ($P_{INT} = 0.024$).

Conclusions This analysis suggests that clinical presentation may be a treatment modifier with respect to DAPT duration after stenting consistent with the hypothesis that SCAD—but not ACS—patients are exposed to a significant increase in bleeding and net adverse clinical events when treated with 24-month compared with 6-month therapy.

Trial registration clinicaltrials.gov Identifier: NCT00611286. http://clinicaltrials.gov/ct2/show/NCT00611286?term=prodigy&rank=2.

Keywords Clopidogrel • Dual-antiplatelet therapy • Drug-eluting stents • Bleeding

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Introduction

A 30-day course of therapy with a $P2Y_{12}$ inhibitor in addition to aspirin (i.e. dual-antiplatelet therapy, DAPT) is the current standard for the prevention of stent thrombosis (ST) after bare metal stent implantation.[1] Similarly, 12-month of DAPT is recommended for acute coronary syndrome (ACS) patients, irrespective of the revascularization strategy.[1–3] The advent of first generation drug-eluting stent (DES) has prompted renewed interest in re-assessing optimal DAPT duration after stent placement. Drug-eluting stent *per se* has been initially regarded as more thrombogenic devices.[4,5] Hence, without compelling evidence, an at least 6- or 12-month DAPT duration regimen has been recommended in patients receiving DES irrespective of clinical presentation.[2,3]

Interestingly, the most recent ESC guidelines on myocardial revascularization provide a differential set of recommendations after DES,[1] based upon the stability of clinical presentation, whereas the ACC/AHA guidelines uniformly support at least 12-month DAPT duration after DES, irrespective of the indication to percutaneous coronary intervention (PCI).[2,3]

Multiple randomized trials have investigated the optimal DAPT duration after stent placement but given the relatively low number of ACS patients included in many of those studies, it remains unclear whether ACS is a treatment modifier of DAPT duration after coronary stenting.[6,7]

Hence, we aimed at investigating whether clinical presentation (SCAD vs. ACS) in the setting of an all-comer PCI population may modify the effect of DAPT duration with regard to ischaemic and bleeding events in patients undergoing a short or a prolonged course of DAPT after coronary stenting.

Methods

The design and main study findings for the Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) were previously reported.[6,8] In brief, all-comer patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation DES at three Italian sites were randomly allocated at 30 days to either 6 or 24 months of dual-antiplatelet treatment. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was performed at 30 days and it was stratified by centre, ongoing ST-segment-elevation myocardial infarction (MI), the presence of diabetes mellitus, and need for intervening on at least one in-stent restenotic lesion. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committees of the three participating centres independently approved the protocol, and all participants gave written informed consent.

Treatment protocol

All patients received aspirin (80–160 mg orally indefinitely) and clopidogrel (75 mg/day) according to the randomization scheme as follows: for either 6 months in the short dual-antiplatelet group or 24 months in the prolonged dual-antiplatelet arm irrespective of the previously implanted stent type or indication for the coronary procedure.

Table 1 Baseline characteristics of the patients

Characteristic	Acute coronary syndrome			Stable coronary artery disease		
	24-Month clopidogrel (*n* = 732)	6-Month clopidogrel (*n* = 733)	*P*-value	24-Month clopidogrel (*n* = 255)	6-Month clopidogrel (*n* = 250)	*P*-value
Age (year)	67.7 ± 11.8	68.2 ± 11.8	0.38	68.2 ± 8.8	67.04 ± 9.8	0.15
Male sex, no. (%)	555 (75.8)	550 (75.0)	0.73	209 (82.0)	197 (78.8)	0.37
Body mass index (kg/m^2)	26.1	26.4	0.36	27.3	27.1	0.53
Diabetes, no. (%)	165 (22.5)	162 (22.1)	0.51	78 (30.5)	70 (28.0)	0.68
Hypertension, no. (%)	510 (69.7)	499 (68.1)	0.51	211 (82.7)	194 (77.6)	0.16
Hyperlipidaemia, no. (%)	370 (50.5)	354 (48.3)	0.39	183 (71.8)	171 (68.4)	0.45
Current cigarette use, no. (%)	185 (25.3)	207 (28.2)	0.45	36 (14.1)	40 (16.0)	0.51
Creatinine clearance (mL/min)	75.0	73.5	0.50	73.9	77.8	0.38
Prior myocardial infarction, no. (%)	179 (24.4)	187 (25.5)	0.38	91 (35.6)	69 (27.6)	0.13
Left ventricular ejection fraction	50.0	50.0	0.13	60	60	0.57
Clinical presentation, no. (%)						
Non-ST-elevation acute coronary syndrome	411 (56.1)	406 (55.4)	0.77	–	–	–
Unstable angina	185 (25.3)	182 (24.8)	0.84	–	–	–
Non-ST-elevation MI	226 (30.9)	224 (30.6)	0.90	–	–	–
ST-segment-elevation MI	321 (43.9)	327 (44.6)	0.77	–	–	–
Bleedscore						
CRUSADE score	26	25	0.97	22.5	24	0.46
ACUITY score	17	16	0.38	11	11	0.75

Table 2 **Outcome rates at 24 months according to treatment group**

	Acute coronary syndrome				Stable coronary artery disease			
	24-Month clopidogrel (n = 732)	**6-Month clopidogrel (n = 733)**	**Hazard ratio (95% CI)**	***P*-value**	**24-Month clopidogrel (n = 255)**	**6-Month clopidogrel (n = 250)**	**Hazard ratio (95% CI)**	***P*-value**
Primary efficacy endpoint								
Death for any cause, myocardial infarction, or cerebrovascular accident	81 (11.1)	86 (11.7)	0.936 (0.691–1.268)	0.67	19 (7.5)	12 (4.8)	1.591 (0.773–3.278)	0.21
Safety endpoints								
Key safety endpoint (BARC type 2, 3, or 5)	52 (7.1)	30 (4.1)	1.746 (1.114–2.736)	0.01	21 (8.2)	4 (1.6)	5.371 (1.844–15.647)	0.002
BARC type 3 or 5	23 (3.1)	17 (2.3)	1.354 (0.723–2.534)	0.34	11 (4.3)	2 (0.8)	5.529 (1.226–24.945)	0.03
Type 5	5 (0.7)	5 (0.7)	0.999 (0.289–3.451)	0.99	4 (1.6)	0 (0.0)	n.a.	0.31
Type 5A	3 (0.4)	0 (0.0)			0 (0.0)	0 (0.0)		
Type 5B	2 (0.3)	5 (0.7)			4 (1.6)	0 (0.0)		
Type 3	18 (2.5)	12 (1.6)	1.501 (0.723–3.116)	0.28	7 (2.7)	2 (0.8)	3.506 (0.728–16.875)	0.12
Type 3A	13 (1.8)	10 (1.4)			3 (1.2)	1 (0.4)		
Type 3B	2 (0.3)	2 (0.3)			3 (1.2)	1 (0.4)		
Type 3C	3 (0.4)	0 (0.0)			1 (0.4)	0 (0.0)		
Type 2	29 (4.0)	13 (1.8)	2.237 (1.163–4.303)	0.02	10 (3.9)	2 (0.8)	5.015 (1.099–22.890)	0.04
Net clinical adverse events								
Death for any cause, myocardial infarction, cerebrovascular accident, or BARC 2, 3, or 5 bleeding	118 (16.1)	103 (14.1)	1.150 (0.883–1.498)	0.30	34 (13.3)	14 (5.6)	2.515 (1.349–4.686)	0.004
Death for any cause, myocardial infarction, cerebrovascular accident, or BARC 3–5 bleeding	92 (12.6)	93 (12.7)	0.985 (0.738–1.314)	0.92	24 (9.4)	13 (5.2)	1.872 (0.953–3.676)	0.07

Follow-up

All randomized patients returned for study visits at 30 days, and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events, asked for the antiplatelet therapy compliance and 12-lead electrocardiogram recordings were obtained.

Study endpoints

The primary efficacy endpoint of the PRODIGY trial was the composite of death, MI, or cerebrovascular accident (CVA), whereas the key safety endpoint included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. To appraise the net effect of DAPT duration in the stratified ACS and SCAD populations on the combined ischaemic and bleeding complications, two net adverse clinical event (NACE) endpoints were generated by combining the primary efficacy endpoint of death, MI, or CVA with either the primary safety endpoint of BARC type 2, 3, or 5 bleeding or with BARC type 3 or 5 events. Other endpoints included each component of the primary efficacy endpoint, cardiovascular death, ST defined on the basis of the Academic Research Consortium criteria,[9] and BARC type 3 or 5 bleeding. Other safety endpoints included bleeding events adjudicated according to the TIMI and GUSTO scales. All study endpoint definitions were previously reported.[8]

All endpoints were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment-group assignments. The time frame of interest for the primary endpoint was from 30 days (i.e. after the primary endpoint randomization) to 24 months.

Statistical analysis

In this pre-specified analysis of the PRODIGY trial,[8] categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (interquartile range). Continuous variables were compared between randomized groups using the Wilcoxon's rank sums test, whereas for binary variables the χ^2 test was used.

Estimation of the cumulative incidence of events was performed by the Kaplan–Meier method and events were compared by the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for long-term clopidogrel vs. short-term clopidogrel (i.e. values >1 indicated increased hazard in the long-term group) with a proportional hazards model. The number needed to treat for harm (NNTH) was appraised as 1/absolute risk reduction. The proportionality hazard assumptions were visually checked and verified by plotting the log cumulative hazard vs. (log) time at follow-up after the index procedure and by applying a test for non-proportional hazards using the Schoenfeld residuals. We performed a Cox regression analysis with interaction testing to determine whether the effect of duration of dual-antiplatelet therapy on the primary efficacy endpoint, on the key safety endpoint of BARC 2, 3, or 5 and on BARC 3 or 5 bleeding was consistent across important pre-specified subgroups. Interaction tests were performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A two-sided probability value of <0.05 was considered significant. All analyses, performed on the basis of the intention-to-treat principle, were performed with SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

From December 2006 to December 2008, a total of 2789 patients underwent screening and 2013 were finally recruited into the study.

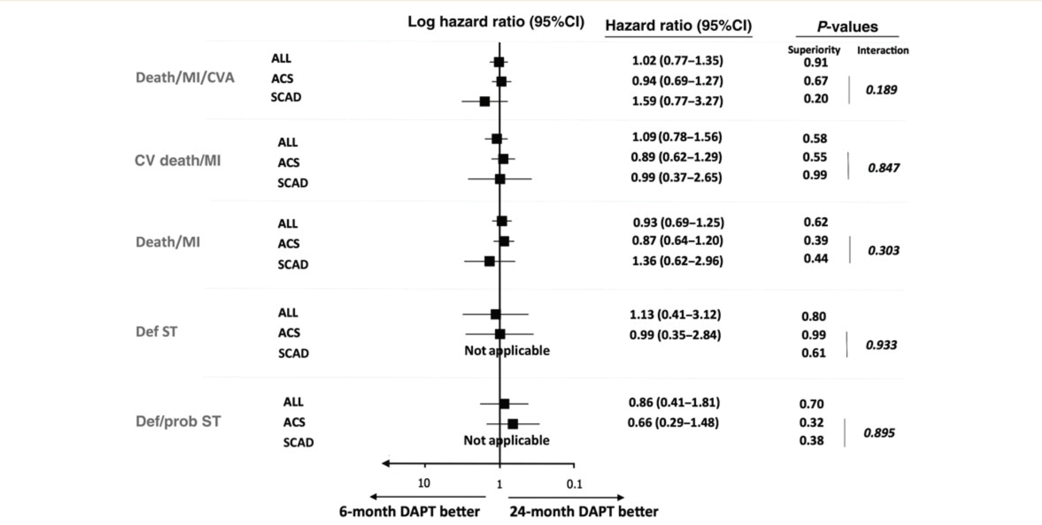

Figure 1 Ischaemic endpoints. The overall population, the stable (stable coronary artery disease), and the unstable (acute coronary syndrome) subgroups are shown, with hazard ratios and 95% confidence intervals, for the primary endpoint of death for any cause, myocardial infarction (MI), or cerebrovascular accident (CVA), cardiovascular (CV) death or myocardial infarction, death for any cause and myocardial infarction (Death/MI), definite stent thrombosis (def ST) and definite/probable stent thrombosis (Def/prob ST) among patients randomly assigned to either the 6-month or the 24-month dual-antiplatelet therapy.

Thirty-three (1.6%) patients died within 30 days and 10 patients withdrew consent, therefore, 1970 patients— of which approximately three-quarters ($n = 1465$) presented with ACS and 505 with SCAD—were randomly allocated at 30 days to receive 6-month (733 ACS and 250 SCAD) or 24-month (732 ACS and 255 SCAD) duration of clopidogrel therapy (see Supplementary material online, *Figure S1*).

Clinical and angiographic characteristics were balanced in the long- vs. short-term DAPT duration arms within both the SCAD and ACS strata (*Table 1* and Supplementary material online, *Table S2*). Adherence to protocol-mandated antiplatelet regimens was high and did not differ in SCAD or ACS patient populations (see Supplementary material online, *Figure S2*).

Clinical follow-up at 2 years was complete for 99.6% of patients in both ACS and SCAD arms.

Ischaemic outcomes

At 24 months, the primary efficacy endpoint (death, MI, or CVA) occurred in 167 (11.4%) patients in the ACS group and in 32 (5.8%) patients in the SCAD group (*Table 2*).

The primary endpoint event rate did not differ with respect to DAPT duration in both ACS (11.1% in the 24-month vs. 11.7% in the 6-month DAPT arms; HR 0.936, 95% CI 0.691–1.268; $P = 0.67$) and SCAD groups (7.5% in the 24-month vs. 4.8% in the 6-month DAPT arms; HR 1.591, 95% CI 0.773–3.278; $P = 0.21$), with no evidence of interaction between clinical presentation and randomized duration of therapy ($P_{INT} = 0.189$) (*Figures 1* and *2A*). Consistent findings were noted when each component of the primary endpoint was examined separately (see Supplementary material online, *Table S2* and *Figure 1*). Other patient-oriented ischaemic events including cardiovascular death alone or in combination with other non-fatal

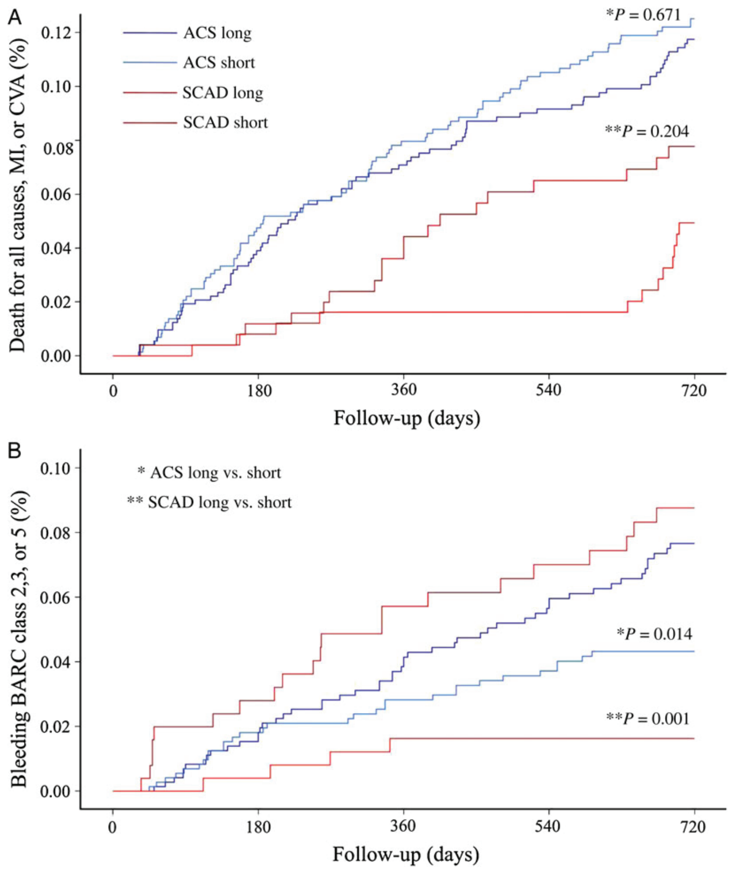

Figure 2 Cumulative incidence of ischaemic and bleeding events. Cumulative incidence curves are shown. (*A*) Death for any cause, myocardial infarction, or cerebrovascular accident in the stable and unstable group of the two treatment arms. (*B*) Bleeding according to the Bleeding Academic Research Consortium 2, 3, 5 criteria, in the stable and unstable group of the two treatment arms.

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ischaemic endpoints were homogenously distributed across treatment arms (see Supplementary material online, *Table S2*). Similarly, no signal of heterogeneity was noted for stent-oriented endpoints, including definite ($P_{INT} = 0.93$) and definite or probable ST ($P_{INT} = 0.89$), with respect to DAPT duration (*Figure 1*).

At further sensitivity analysis, the primary endpoint proved to be consistent across all pre-specified clinical or angiographic covariates within the ACS population (see Supplementary material online, *Figure S3*).

Bleeding outcomes

The key safety endpoint, consisting of BARC classification 2, 3, or 5 bleeding, occurred in 82 (5.6%) and 25 (4.5%) patients of the ACS and SCAD groups, respectively. Patients treated with longer DAPT experienced higher rate of bleeding events in both ACS (7.1 vs. 4.1%; HR 1.75, 95% CI 1.11–2.74, $P = 0.015$; NNTH: 33.3) and especially SCAD (8.2 vs. 1.6%; HR 5.371, 95% CI 1.84–15.74, $P = 0.002$; NNTH: 15.1) groups (*Table 2* and *Figure 2B*). When bleeding was restricted to BARC 3 or 5 criteria, there was an increase of bleeding complications in patients treated with 24-month when compared with 6-month DAPT in the SCAD (4.3 vs. 0.8%; HR 5.53, 95% CI 1.2–24.9, $P = 0.026$; NNTH: 28.6) but not in the ACS group (3.1 vs. 2.3%; HR 1.35, 95% CI 0.72–2.53; $P = 0.34$). Consistent findings were observed with TIMI and GUSTO bleeding scales (see Supplementary material online, *Table S2*).

There was a borderline quantitative interaction between clinical presentations and bleeding outcomes (*P*-values for interaction = 0.056 for BARC 2, 3, or 5; $P = 0.091$ for BARC 3 or 5), suggesting a higher hazard of bleeding in the 24-month DAPT when compared with the 6-month arm in the SCAD, which was not observed in the ACS patients (*Figures 2B* and *3*).

To further explore the consistency of increased bleedings in ACS patients, sensitivity analyses were performed for BARC 2, 3, or 5 as well as 3 or 5 events across various subgroups, with no clear signal for interaction between any of the tested covariates and bleeding outcomes (see Supplementary material online, *Figures S4 and S5*).

Net adverse cardiac events

The risk of NACE, consisting of the death, MI, CVA, or BARC 2, 3, or 5 bleeding, was significantly increased in the 24-month vs. 6-month DAPT arm in SCAD patients (13.3 vs. 5.6%; HR 2.5, 95% CI 1.35–4.69, $P = 0.004$; NNTH: 13) but not in the ACS population (16.1 vs. 14.1%; HR 1.15, 95% CI 0.88–1.50, $P = 0.29$), with positive quantitative interaction testing (*P* value for interaction = 0.024) (*Figures 4* and *5*). When BARC 3 or 5 was used in the combined ischaemic and bleeding endpoint, results remained consistent; despite interaction testing did not reach formal statistical significance ($P = 0.089$) (*Figure 4* and Supplementary material online, *Figure S6*).

Discussion

The main findings of our analysis of the PRODIGY trial can be summarized as follows:

(1) The lack of ischaemic benefit in favour of a 24-month course of DAPT, which was previously reported in the overall patient population, was confirmed in both SCAD and ACS patients, with no signal of heterogeneity across strata.
(2) Both SCAD and ACS patients displayed a significant increase in bleeding in the 24-month DAPT arm according to the key safety endpoint of BARC 2, 3, or 5 bleeding. Yet, the magnitude of such increase appeared relatively greater in the SCAD when

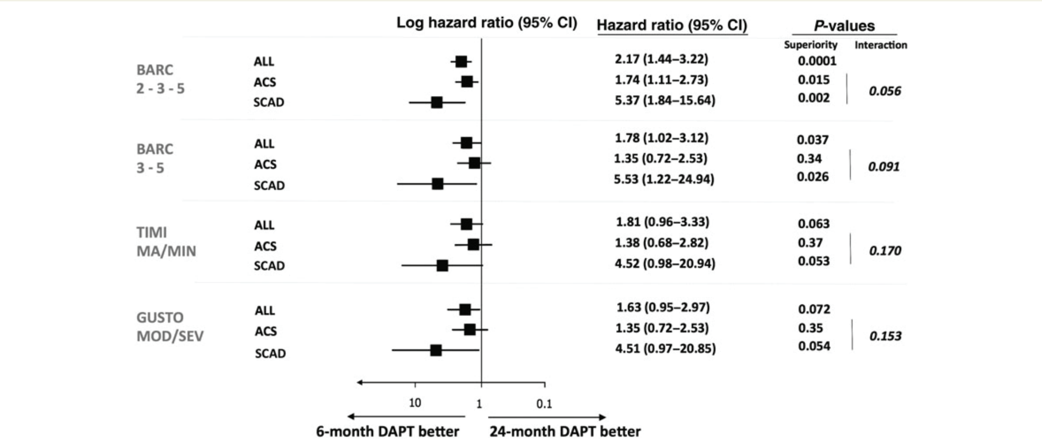

Figure 3 Bleeding endpoints. The overall population, the stable (stable coronary artery disease), and the unstable (acute coronary syndrome) subgroups are shown, with hazard ratios and 95% confidence intervals, for the key safety endpoint of Bleeding Academic Research Consortium 2, 3, 5 bleeding, and further safety outcomes of Bleeding Academic Research Consortium 3 or 5, TIMI major and minor (TIMI MA/MIN), and GUSTO moderate and severe (GUSTO MOD/SEV) bleeding among patients randomly assigned to either the 6-month or the 24-month clopidogrel therapy.

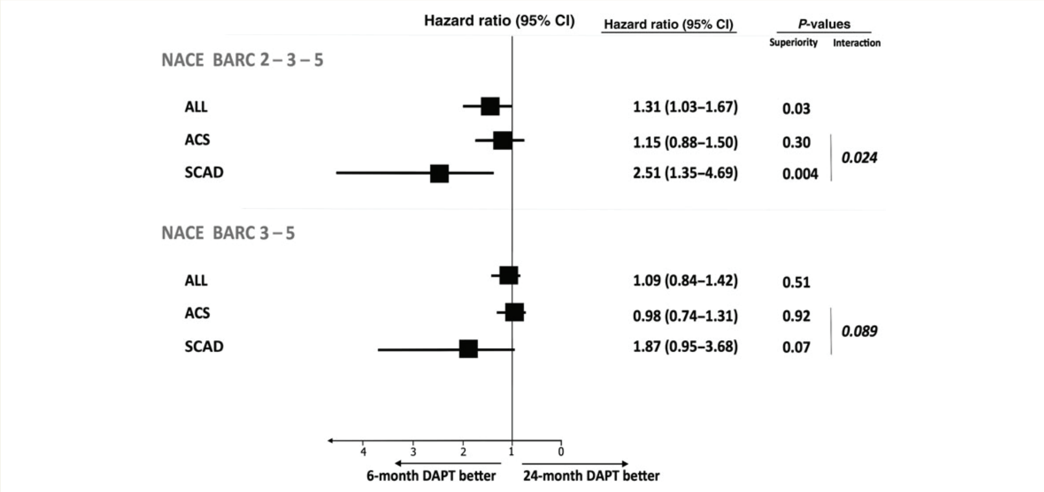

Figure 4 Net adverse clinical event. The overall population, the stable (stable coronary artery disease), and the unstable (acute coronary syndrome) subgroups are shown, with hazard ratios and 95% confidence intervals, for the net adverse clinical events of death for any cause, myocardial infarction, cardiovascular accident, or Bleeding Academic Research Consortium class 2, 3, 5 bleeding (NACE BARC 2−5), and for death for any cause, myocardial infarction, cardiovascular accident, or Bleeding Academic Research Consortium class 3, 5 bleeding (NACE BARC 3−5) among patients randomly assigned to either the 6-month or the 24-month clopidogrel therapy.

compared wih the ACS groups, with a borderline interaction ($P = 0.056$). The NNTH with a 24-month DAPT was halved in SCAD patients when compared with ACS patients. When more stringent criteria for bleeding were applied, excluding BARC 2 events, there was a significant increase in bleeding endpoints in the SCAD but not in the ACS populations receiving 24-month vs. 6-month DAPT.

(3) The NACE rates, including the primary efficacy and the key secondary endpoint, were significantly increased only in SCAD patients allocated to the 24-month group, whereas no such an increase was noted in the ACS population ($P_{INT} = 0.024$). After excluding BARC 2 bleeding, which was recently shown to lack prognostic implications in terms of overall mortality,[10] there appeared a numerical increase of NACE in SCAD patients only, with interaction testing providing consistent borderline results ($P = 0.089$).

The PRODIGY trial was designed to detect a 40% reduction of the composite endpoint of death, MI, or CVA in the prolonged DAPT arm. Our goal was to explore this conservative estimate of benefit in favour of prolonged DAPT that was previously shown by registry data, which informed guidelines and daily practice across the world since 2006.[11,12] Our study ultimately failed to provide evidence of a benefit of a prolonged course of DAPT in largely unselected patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation DES.[6] The lack of a clear benefit in favour of a prolonged course of DAPT after DES implantation has been confirmed by 9 of 10 randomized studies so far performed, which were all designed assuming prolonged DAPT to be associated with a considerable expected benefit.[7] In the recent DAPT trial, a 30-month DAPT duration resulted in a significant reduction of both ST and major adverse cardiovascular events (MACE). While no formal interaction testing was noted with respect to the benefit observed for ST across stent types, patients receiving zotarolimus- or everolimus-eluting stents did not show a clear and significant MACE reduction, with positive interaction test ($P = 0.048$). Yet, the 95% upper boundary for MACE reduction after second-generation DES did not exclude a possible overall benefit in the 30-month when compared with 12-month DAPT.[13]

Similarly, the boundary of the 95% confidence interval of primary endpoint in the PRODIGY trial entailed the possibility that a prolonged duration of clopidogrel therapy is associated with up to 26% reduction of patient-oriented ischaemic endpoints. Ultimately, the possible benefit of a very prolonged DAPT regimen has to be weighed against an increased bleeding risk. Multiple individual studies as well as all pooled analyses so far performed have confirmed a distinct increase bleeding risk in patients undergoing long-term DAPT,[6,7] including the DAPT trial. Despite including only patients who were free from bleeding events at 12 months, this latter study reported a possible increase of non-cardiovascular mortality in the 30-month DAPT arm, which remains a matter of concern.

Among the deaths from non-cardiovascular causes, bleeding related deaths accounted for 11 deaths in the group that continued to receive thienopyridine vs. 3 deaths in the placebo group, $P = 0.057$).[13]

We remain convinced that the balance between risks and benefits of prolonged DAPT may largely reflect intrinsic bleeding vs. ischaemic risk in the single individual patient.

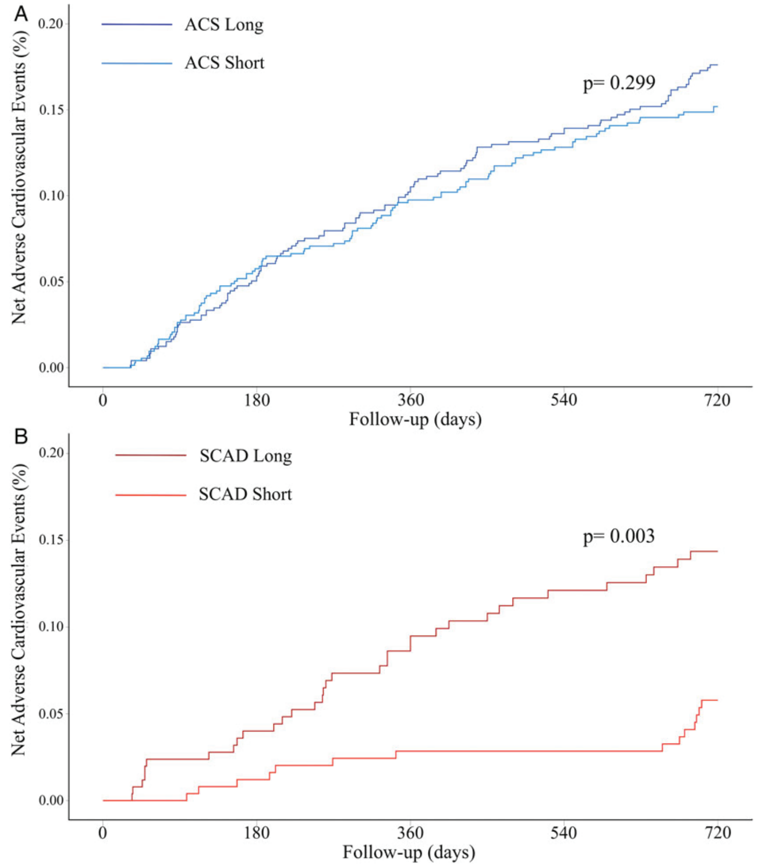

Figure 5 Cumulative incidence of net adverse clinical event. Cumulative incidence curves are shown for the net adverse clinical events consisting of death for any cause, myocardial infarction, cerebrovascular accident, and Bleeding Academic Research Consortium class 2, 3, 5 bleeding. (*A*) Acute coronary syndrome subgroup and (*B*) stable coronary artery disease subgroup.

In this sub-analysis, we stratified all-comer PCI patients recruited in the PRODIGY study-based clinical presentation as an accepted proxy towards both ischaemic and bleeding risk. Indeed, ACS patients have been previously shown to suffer from a heightened risk of both ischaemic and bleeding events.[14,15] This was confirmed in our study, as event rates for both endpoints were higher in ACS compared with SCAD patients. Yet, our analysis suggested that clinical presentation might be a treatment modifier with respect to the value of prolonged vs. shortened DAPT duration. Stable coronary artery disease—but not ACS patients—showed notable trends towards higher bleeding and combined ischaemic and bleeding risks based on the BARC 3–5 scale. Ischaemic events *per se* were also numerically higher in SCAD patients undergoing 24-month therapy. Equally, there was an increase of bleeding complications disfavouring the 24-month DAPT regimen, which was consistent across BARC, TIMI, and GUSTO bleeding scales. Acute coronary syndrome patients display higher platelet reactivity when compared with SCAD patients.[14] Hence, a more potent or prolonged course of platelet inhibition may have a greater efficacy with a lower bleeding trade-off in the former than the latter. Accordingly, our stratified analysis showed a numerical advantage on ischaemic endpoints and a relatively lower bleeding hazard in ACS patients undergoing 24-month DAPT duration. This hypothesis finds additional support in the results of TRITON TIMI 38 trial, where particularly high ischaemic risk subgroups, such as STEMI or diabetic ACS patients showed no apparent bleeding liability when treated with prasugrel when compared with clopidogrel.[16] In the CHARISMA trial, patients at lower ischaemic risk—the so-called 'asymptomatic' patient cohort—showed a relatively greater propensity to and a highly significant increase in severe GUSTO bleeding complications, whereas bleeding liability was apparently lower and not significant in patients at higher-risk ischaemic risk profile.[17]

Bleeding itself may predispose to ischaemic complication.[10,18] This provides a potential explanation for the trend towards higher ischaemic events in SCAD patients treated with 24-month DAPT. In CHARISMA, patients recruited with a lower cardiovascular risk, showed a 68% increase in GUSTO severe bleeding in the DAPT group and a concomitant 30 and 44% relative risk increase of mortality and cardiovascular mortality, respectively.[17] Whether this reflects a direct effect of bleeding events on ischaemic risk or it is explained by temporarily or permanently discontinuation of secondary prevention medications after bleeding is not entirely clear.

Moreover, it has been hypothesized that a more potent or prolonged antiplatelet therapy could induce haemorrhage of the atherosclerotic plaque, driving to an accelerated progression of the coronary artery disease.[19,20] This may become clinically relevant in patients at low propensity for spontaneous plaque rupture, such as SCAD patients.

To confirm or refute the *less is more* hypothesis, the GLOBAL LEADERS trial (NCT01813435) is prospectively comparing if a 30-day course of DAPT, followed by ticagrelor monotherapy leads to superior ischaemic outcomes when compared with 1-year DAPT followed by aspirin monotherapy in an all-comer PCI population including both ACS and SCAD patients.

Study limitations

Despite the current analysis was pre-specified, no assessment a priori of the power for subgroups was computed. Hence, our results should be interpreted bearing in mind the possibility of a type II error. In addition, the relatively small number of SCAD patients included, precluded meaningful analysis of the role of stent type within each presentation stratum. No formal correction was in place for the number of statistical tests performed, thereby potentially inflating type 1 error.

Randomization in PRODIGY was stratified based on the presence or absence of STEMI, but not for any ACS vs. SCAD presentation at entry. Hence, despite all baseline clinical and angiographic covariates were well matched within the SCAD and ACS strata in the long vs. short DAPT arms, our present analysis is based on post-randomization subgroups. In the PRODIGY trial, the antiplatelet agent evaluated was clopidogrel, accordingly the results of this analysis cannot be extrapolated to more potent antiplatelet agents. In addition, the original design of the PRODIGY trial did not include a randomization to 12-month DAPT, which is currently the recommended therapy duration in ACS patients.[1] The PRODIGY trial was underpowered to assess the effect of different DAPT duration on ST endpoints. Confidence intervals for definite or definite and probable ST are therefore wide and inconclusive.

In conclusion, our study suggests that clinical presentation is a potential treatment modifier with respect to the duration of DAPT after stenting, consistent with the hypothesis that SCAD—but not ACS—patients are exposed to a significant increase in bleeding and NACE when treated with 24-month when compared with 6-month therapy. Our findings lend support to the recently released ESC guidelines on myocardial revascularization, which recommends 6-month DAPT duration after DES implantation in SCAD but not ACS patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: M.V. reports personal fees from Correvio, personal fees from Medtronic, personal fees from Eli lilly/DS, grants, personal fees, and non-financial support from Medicines company, non-financial support from Alvimedica, grants and personal fees from Terumo, personal fees from Abbott Vascular, personal fees from St Jude, and outside the submitted work.

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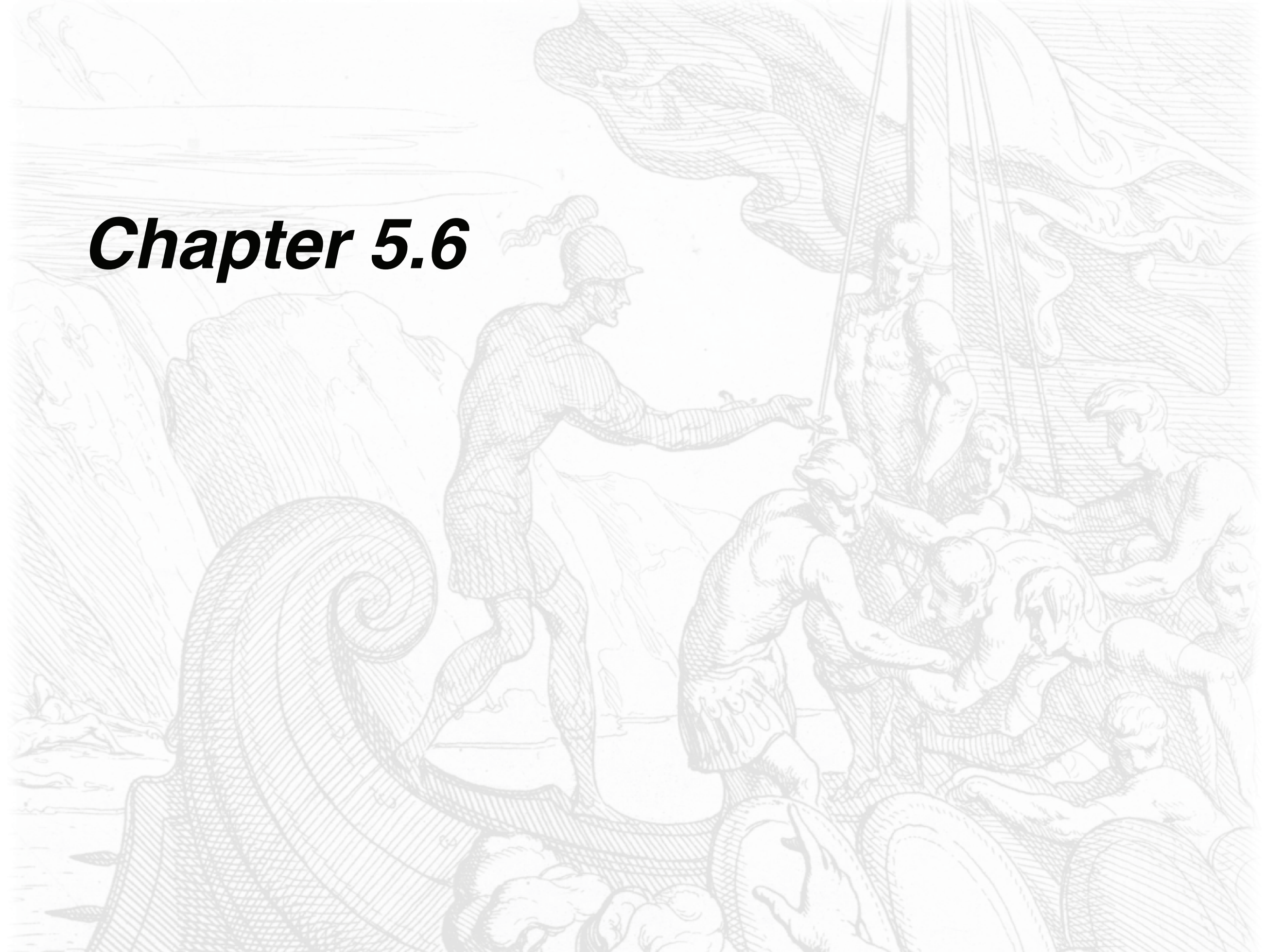
Chapter 5.6



Long-term Dual Antiplatelet Therapy for Secondary Prevention of Cardiovascular Events in Patients with Previous Myocardial Infarction: A Collaborative Meta-Analysis of Randomized Trials

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Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials

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Aims Recent trials have examined the effect of prolonged dual antiplatelet therapy (DAPT) in a variety of patient populations, with heterogeneous results regarding benefit and safety, specifically with regard to cardiovascular and non-cardiovascular mortality. We performed a meta-analysis of randomized trials comparing more than a year of DAPT with aspirin alone in high-risk patients with a history of prior myocardial infarction (MI).

Methods and results A total of 33 435 patients were followed over a mean 31 months among one trial of patients with prior MI (63.3% of total) and five trials with a subgroup of patients that presented with, or had a history of, a prior MI (36.7% of total). Extended DAPT decreased the risk of major adverse cardiovascular events compared with aspirin alone (6.4 vs. 7.5%; risk ratio, RR 0.78, 95% confidence intervals, CI, 0.67–0.90; $P = 0.001$) and reduced cardiovascular death (2.3 vs. 2.6%; RR 0.85, 95% CI 0.74–0.98; $P = 0.03$), with no increase in non-cardiovascular death (RR 1.03, 95% CI 0.86–1.23; $P = 0.76$). The resultant effect on all-cause mortality was an RR of 0.92 (95% CI 0.83–1.03; $P = 0.13$). Extended DAPT also reduced MI (RR 0.70, 95% CI 0.55–0.88; $P = 0.003$), stroke (RR 0.81, 95% CI 0.68–0.97; $P = 0.02$), and stent thrombosis (RR 0.50, 95% CI 0.28–0.89; $P = 0.02$). There was an increased risk of major bleeding (1.85 vs. 1.09%; RR 1.73, 95% CI 1.19–2.50; $P = 0.004$) but not fatal bleeding (0.14 vs. 0.17%; RR 0.91, 95% CI 0.53–1.58; $P = 0.75$).

Conclusion Compared with aspirin alone, DAPT beyond 1 year among stabilized high-risk patients with prior MI decreases ischaemic events, including significant reductions in the individual endpoints of cardiovascular death, recurrent MI, and stroke. Dual antiplatelet therapy beyond 1 year increases major bleeding, but not fatal bleeding or non-cardiovascular death.

Keywords Dual antiplatelet therapy • Myocardial infarction • Stable coronary heart disease • Clopidogrel • Prasugrel • Ticagrelor

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Introduction

Patients with myocardial infarction (MI) have heightened platelet activation and aggregation resulting in atherothrombosis following the rupture or fissuring of an unstable atherosclerotic plaque compared with patients with stable ischaemic heart disease (SIHD).[1–3] A higher predisposition to atherothrombosis may persist for years following an MI,[3–6] and SIHD patients with a history of an MI are at high risk for major adverse cardiovascular events (MACE).[7–9] As such, following MI, patients may have a persistent pathobiology that predisposes them to benefit more from therapies that intensely inhibit platelet activation and aggregation than patients following percutaneous coronary intervention (PCI) for stable ischaemia.[10]

However, dual antiplatelet therapy (DAPT) with a platelet adenosine diphosphate (ADP) antagonist in addition to aspirin is strongly recommended for only up to 1 year for reduction of cardiovascular events in patients with a prior MI, with a weak recommendation to continue thereafter in patients who underwent PCI based on expert consensus.[11–15] In the absence of definitive longer-term data, DAPT is often stopped after completion of 1 year of treatment in half of all patients.[16] Recently, two large randomized controlled trials (RCTs) demonstrated that extended duration of DAPT significantly reduced atherothrombotic events in patients 1 year or more following an MI[17] or a PCI[18] at the expense of higher bleeding and, in the case of the PCI trial,[18] potentially a higher risk of death from non-cardiovascular causes. Given these findings, and the heterogeneity in results of other trials testing extended duration DAPT, we sought to better understand the cardiovascular benefits and risks of DAPT beyond 1 year for secondary prevention in high-risk patients with a prior MI.

Methods

Study design

This systematic review and meta-analysis was conducted in accordance with the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[19] The previously published study protocol is available at the PROSPERO registry (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019657) and Supplementary material online, Appendix.

Eligibility criteria and trial selection

We considered prospective RCTs of secondary prevention eligible for inclusion if they followed patients beyond 1 year that either presented with or had a history of a prior MI and were randomized to a strategy of extended duration (beyond 12 months) DAPT compared with aspirin alone (with or without the use of a placebo for blinding). Eligible RCTs were considered irrespective of language, blinding, and publication status. We excluded observational studies. We excluded trials of DAPT among patients presenting with MI who were followed no longer than 12 months; if such trials followed patients longer, we considered 1-year landmark results of MI patients randomized to DAPT beyond 12 months as a sensitivity analysis. We also excluded trials of patients with SIHD alone undergoing PCI and trials of oral anticoagulant therapies.

Search strategy and data extraction

We conducted a literature search of OVID Medline (1950 to 2 April 2015) and the Cochrane central register of controlled trials databases, utilizing keyword search terms including: 'antiplatelet', 'DAPT', 'thienopyridine', 'secondary prevention', 'MI', 'acute coronary syndrome', 'major adverse cardiovascular events', 'death', 'mortality', and 'survival' (see Supplementary material online, Search Strategy). We reviewed Supplementary material online, Appendices and reference lists of eligible papers, cardiovascular conference abstracts between 2014 and 2015, and clinicaltrials.gov, to ensure identification of relevant published and unpublished studies. If published data were not available, we contacted the study principal investigator (PI) for input to maximize contribution to, and harmonize outcomes.

Baseline characteristics data and outcomes were abstracted for each study from the published manuscripts, appendices, or unpublished data by two investigators (J.A.U. and D.L.B.) independently. Baseline characteristics included patient data and study design characteristics [year, clinical setting (major inclusion and exclusion criteria) sample size, randomized intervention and control, duration of difference in intervention, duration of follow-up, blinding, and primary endpoint]. Results were compared and any disagreements were resolved by consensus.

Quality assessment

Quality was graded based on documentation of trial conduct criteria such as method of randomization, allocation concealment and blinding, blinded outcome adjudication, extent of outcome reporting and ascertainment, participant attrition and adherence metrics.[20] Studies were categorized as high quality if criteria were clearly described and accounted for, low quality if any aspect of the first three criteria was unaccounted for, or otherwise of uncertain risk of bias.

Outcomes

The primary endpoint for this analysis was the incidence of MACE, which was defined as a composite of cardiovascular death, non-fatal MI, and non-fatal stroke. Secondary endpoints included individual components of the composite primary endpoint, all-cause death, non-cardiovascular death, major bleeding events, and when relevant stent thrombosis. All cardiovascular endpoints were adjudicated and defined within the individual trials according to standard criteria. Major bleeding events were considered according to standardized bleeding endpoint definitions reported in each trial (see Supplementary material online, *Table S1* describes individual trial endpoint definitions).[21]

Statistical analysis

Data for patients that either presented with or had a history of a qualifying MI at baseline were extracted and descriptive characteristics were summarized using means (standard deviation), medians (interquartile range), or rates from each study weighted according to individual sample sizes. We extracted the originally reported hazard ratios (HRs) and 95% confidence intervals (CI) from each study when available and otherwise calculated risk ratios (RRs) and 95% CI from the reported number of events and patients at risk per treatment arm. Data from each trial were considered as per the intention-to-treat principle with pooled summary RR and 95% CI derived using a random effects meta-analysis model with weighting based on inverse variance. If a particular endpoint was not reported in a trial, and it could not be deduced from other outcomes or provided by the study PI, it was excluded only from that specific endpoint's pooled analysis. A correction factor of 0.5 was added to values of a treatment arm when no events were observed for calculation of the RR for an endpoint and its variance. We used the Cochran Q statistic and the I^2 measure to assess heterogeneity for treatment effects across trials, with an $I^2 > 75\%$ considered representative of high heterogeneity. We performed sensitivity analyses including sequentially removing studies from the pooled effect estimates and adding studies with applicable 1-year landmark analyses. Heterogeneity among selected subgroups was also explored according to age, sex, DAPT regimen, type of index myocardial event, time from the index MI, and in patients with and without a history of PCI, diabetes, additional MI, stroke or transient ischaemic attack (TIA), or chronic kidney disease. An interaction term representing each category was introduced into the model for MACE and major bleeding to test for differences in treatment effect between subgroups. Publication bias was evaluated by visual inspection of funnel plots, without further statistical testing given these tests have limited specificity and power when <10 studies are analysed.[22] Two-sided *P*-values were calculated with <0.05 considered significant for all analyses. Statistical analyses were performed with Review Manager version 5.3.5 (Nordic Cochrane Centre, Denmark) and Comprehensive Meta-Analysis version 3.0 (Biostat Inc., Englewood, NJ, USA).

Role of the funding source

There was no funding source for this study. J.A.U. and D.L.B. had full access to all the data in the study and had final responsibility for the decision to submit for publication. All included studies complied with the Declaration of Helsinki and individual ethics committees approved the research protocols and informed consent was obtained from subjects in each respective trial.

Results

Among 1342 records screened, we identified 36 RCTs to review in detail (see Supplementary material online, Results and *Figure S1*). After exclusions, the remaining six trials met criteria for eligibility in the primary meta-analysis.[17,18,23–29] These trials, which comprised 33 435 participants randomized to a strategy of extended DAPT ($n = 20\,203$) vs. aspirin alone ($n = 13\,232$), are summarized in *Table 1*. One trial exclusively randomized patients with a history of MI ($n = 21\,162$; 63.3% of the pooled population),[17] one randomized a subgroup of patients with prior MI ($n = 3846$; 11.5%),[23,24] while the remaining four trials randomized patients that recently underwent PCI and included a subgroup whose indication was an acute coronary syndrome ($n = 8427$; 25.2%).[18,25–29] Various ADP antagonists were studied across the six trials as outlined in *Table 1*, including clopidogrel, prasugrel, and ticagrelor.

At baseline, overall, the mean age of participants was 64.0 years, mean weight was 81.4 kg, 7900 (23.6%) were women, 28 064 (83.9%) underwent or had a history of PCI, 9888 (29.6%) had diabetes, 5439 (18.6%) had chronic kidney disease, and 16 340 (48.9%) presented with or had a history of ST-elevation or Q-wave MI (see Supplementary material online, *Table S2*). Enrolled patients infrequently presented with unstable angina ($n = 2384$; 7.1%), with a history of stroke/TIA ($n = 866$; 2.6%), or with a history of revascularization by coronary artery bypass grafting ($n = 2477$; 7.4%). The mean duration of follow-up of 31 months and the mean difference in the achieved duration of DAPT was 30 months (range 17–36 months).

Quality metrics of trial conduct, participant attrition, and therapeutic adherence across trials are summarized (see Supplementary material online, *Table S3*) and were reasonably comparable for trials that varied in length of follow-up, timing of randomization, and type of intervention. Three trials were double blind and placebo-controlled,[17,18,23,24,29] while three were unmasked open-label trials with blinded endpoint adjudication and standard care as the control.[25–28] Forgiving unblinded study designs, all trials were considered high quality. All trials reported or provided results for MACE, CV death, MI, stroke, major bleeding, non-CV death, and all-cause mortality (see Supplementary material online, *Table S1*). Cardiovascular endpoints, cause of death, and major bleeding events were defined in each trial according to standard diagnostic criteria and were adjudicated by a blinded endpoints committee in each trial allowing for comparisons across trials. Four of six trials provided data for stent thrombosis.[18,25–29] Causes of major bleeding events were also provided by all trials (see Supplementary material online, *Table S4*).

Major adverse cardiovascular events

Among the six trials, the individual and pooled HR/RRs for the composite primary endpoint of the 2273 MACE are provided in *Figure 1*. Among the 20 203 participants with a prior MI treated with DAPT beyond 1 year, 1286 (6.37%) patients developed a MACE compared with 987 of 13 232 (7.46%) patients treated with aspirin alone [RR 0.78 (95% CI 0.67–0.90); $P = 0.001$; *Figure 1*]. This risk reduction represented an absolute risk difference (ARD) of 1.09% (95% CI 0.53–1.65) or a number needed to treat (NNT) of 91 (95% CI 61–189) to prevent one MACE over a mean 31 months of follow-up.

Cardiovascular mortality

Extended DAPT for more than a year following an MI significantly reduced cardiovascular death (which comprised 60% of all observed deaths) (*Figure 2*), as 472 of 20 203 patients (2.3%) died from cardiovascular causes while treated with extended DAPT compared with 344 of 13 232 patients (2.6%) treated with aspirin alone [RR 0.85 (95% CI 0.74–0.98); $P = 0.03$; ARD = 0.26%; NNT = 380; see Supplementary material online, *Figure S2*].

Other individual cardiovascular endpoints

Extended DAPT also significantly reduced the risk of MI [RR 0.70 (95% CI 0.55–0.88); $P = 0.003$; ARD = 0.84%; NNT = 120; see Supplementary material online, *Figure S3*] and stroke [RR 0.81 (95% CI 0.68–0.97); $P = 0.02$ ARD = 0.31%; NNT = 324; see Supplementary material online, *Figure S4*]. Among trials that enrolled only PCI-treated patients, definite or probable stent thrombosis events were infrequent. Yet the risk of late stent thrombosis more than a year following an MI was significantly reduced with extended DAPT [RR 0.50 (95% CI 0.28–0.89); $P = 0.02$; ARD = 0.73%; NNT = 137; see Supplementary material online, *Figure S5*].

Major bleeding events and safety

These results occurred in the context of an increased risk of major bleeding events with extended DAPT [1.85 vs. 1.09%; RR 1.73 (95% CI 1.19–2.50); $P = 0.004$; ARD = 0.76%; NNH = 132; *Figure 2* and see Supplementary material online, *Figure S6*]. However, intracranial haemorrhage (ICH) [0.41 vs. 0.31%; RR 1.34 (95% CI 0.89–2.02); $P = 0.17$] and fatal bleeding events [0.14 vs. 0.17%; RR 0.91 (95% CI 0.53–1.58); $P = 0.75$] were infrequent and were not significantly

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Table 1 Characteristics of included trials

Trial	Population included in the present study	*N* (% of total trial enrolment)	Time from MI/ACS to randomization (months)[a]	Study design and time from randomisation to DAPT initiation or continuation (months)[a]	Difference in duration of DAPT (months)[a]	Follow-up (months)[a]	Intervention, *N*	Control, *N*
							Background of aspirin	
CHARISMA MI (2006)[23,24]	Patients ≥45 years of age with documented CAD, CVD, or PAD, or with multiple atherothrombotic risk factors. The subgroup of interest was patients with prior MI. Excluded patients with an existing indication for clopidogrel, including a recent ACS, or at high risk of bleeding, including long-term oral anticoagulation or NSAID use	3846 (24.6)	23.6 (NR)	DAPT initiation, 0	27.6 (NR)	27.6 (NR)	Clopidogrel, 1903	Placebo, 1943
PRODIGY (2012)[25,26]	The subgroup of stabilized patients ≥18 years of age with prior ACS treated with PCI. Excluded patients with a bleeding diathesis, oral anticoagulation, planned surgery, active bleeding, or prior stroke in the past 6 months	1465 (74.4)	1 (NR)	DAPT continuation, 5 (NR)	18 (NR)	24 (NR)	Clopidogrel, 732	No therapy 733
ARCTIC-Interruption (2014)[27]	The subgroup of stabilized patients ≥18 years of age with prior ACS treated with PCI who were free of MACE and major bleeding at 12 months. Excluded patients at physician's discretion, those >15 months from prior randomization, with aspirin resistance, chronic anticoagulation treatment, bleeding diathesis, bleeding GI ulcer, or presentation with STEMI	323 (25.7)	12 (NR)	DAPT continuation, 0	17 (15–18)	17 (15–18)	Clopidogrel or prasugrel, 156	No therapy, 167
DAPT (2014)[18,29]	The subgroup of stabilized patients >18 years of age with prior MI treated with PCI who were free of MACE and major bleeding at 12 months. Excluded patients with a bleeding diathesis, oral anticoagulation, planned surgery, and index PCI with concomitant DES and BMS	3576 (30.7)	12 (NR)	DAPT continuation, 0	18 (NR)	18 (NR)	Clopidogrel or prasugrel, 1805	Placebo, 1771

DES-LATE (2014)[28]	The subgroup of stabilized patients ≥18 years of age with prior ACS treated with PCI who were free of MACE and major bleeding at 12 months. Excluded patients with contraindication to antiplatelet drugs or an indication for long-term clopidogrel	3063 (60.7)	13.3 (12.1–16.1)	DAPT continuation, 0	36 (NR)	42.0 (24.7–50.7)	Clopidogrel, 1512	No therapy, 1551
PEGASUS-TIMI 54 (2015)[17]	Patients ≥50 years of age with prior MI 1–3 years before enrolment with one additional risk factor. Excluded patients with planned DAPT or anticoagulation, patients with a bleeding diathesis or recent (<6 months) GI bleed, recent major surgery (<1 month), and any prior ischaemic or haemorrhagic stroke	21 162 (100)	20.4 (14.4–27.6)	DAPT initiation, 0	33 (28–37)	33 (28–37)	Ticagrelor 90 mg b.i.d., 7050 60 mg b.i.d., 7045	Placebo, 7067
Total		33 435	18		30	31	20 203	13 232

Trial	No. of MACE events	Control group MACE rate	Control group major bleeding rate	Control group annualized MACE rate	Control group annualized major bleeding rate
CHARISMA MI (2006)[23,24]	287	8.3	2.0	3.6	0.87
PRODIGY (2012)[25,26]	132	9.4	0.8	4.7	0.4
ARCTIC-Interruption (2014)[27]	7	2.4	0	1.7	0
DAPT (2014)[18,29]	167	6.3	0.8	4.2	0.53
DES-LATE (2014)[28]	122	4.3	2.0	1.2	0.57
PEGASUS-TIMI 54 (2015)[17]	1558	9.0	1.1	3.3	0.39
Total	2273	7.5	1.1		

ACS, acute coronary syndrome; BMS, bare metal stent; CAD, coronary artery disease; CVD, cerebrovascular disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; GI, gastrointestinal; MACE, major adverse cardiovascular events; MI, myocardial infarction; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; PAD, peripheral arterial disease; STEMI, ST-segment elevation MI; TIA, transient ischaemic attack.

[a]Mean (standard deviation) or median (interquartile range).

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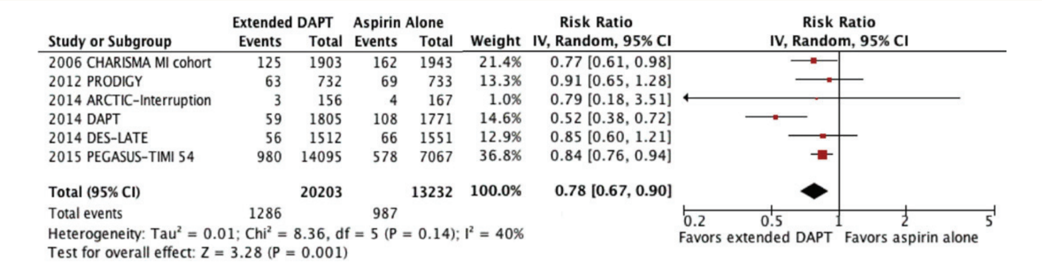

Figure 1 Risk of major adverse cardiovascular events comparing extended dual antiplatelet therapy vs. aspirin alone. Square data markers represent risk ratios and horizontal lines the 95% confidence intervals with marker size reflecting the statistical weight of the study using inverse variance random effects meta-analysis. A diamond data marker represents the overall risk ratios and 95% confidence intervals for major adverse cardiovascular events. There was no significant between-trial heterogeneity (Q statistic = 8.36, d.f. = 5; $P = 0.14$; $I^2 = 40\%$).

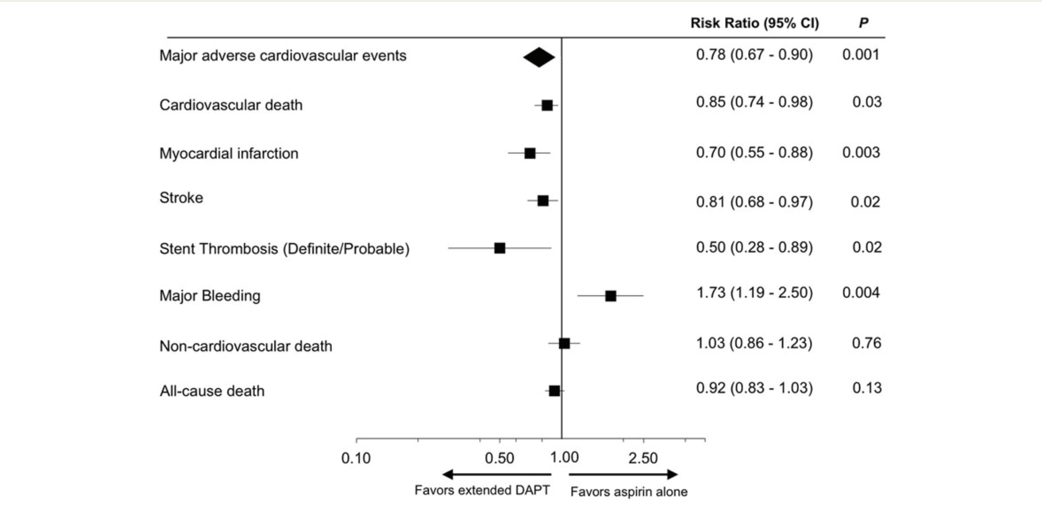

Figure 2 Risk of individual cardiovascular and bleeding endpoints comparing extended dual antiplatelet therapy vs. aspirin alone. Square data markers represent risk ratios and horizontal lines the 95% confidence intervals using inverse variance random effects meta-analysis.

different between extended DAPT-treated patients and aspirin alone. Treatment with extended DAPT had no significant effect on non-CV death [RR 1.03 (95% CI 0.86–1.23); $P = 0.76$; see Supplementary material online, *Figure S7*]. The net effect was a non-significant RR of 0.92 (95% CI 0.83–1.03; $P = 0.13$; see Supplementary material online, *Figure S8*) for all-cause mortality.

Sensitivity analyses

There was no meaningful heterogeneity in results across trials for either the primary or the secondary endpoints. No evidence of publication bias was suggested by visual inspection of the funnel plots for MACE (see Supplementary material online, *Figure S9*) or secondary endpoints. Results for the primary endpoint analysis remained significant after removal of any one trial from the pooled result (see Supplementary material online, *Table S5*). More so, after simultaneous removal of both the PEGASUS-TIMI 54 and DAPT results, the primary endpoint remained significant among the remaining four trials [RR 0.82 (95% CI 0.70–0.97); $P = 0.02$; ARD = 1.11% (95% CI 0.09–2.13)]. The addition of 1-year landmark results from two trials testing other strategies of more intensive antiplatelet therapy for secondary prevention among stabilized patients >1 year from an MI,[30,31] also did not materially change the results [RR 0.79 (95% CI 0.72–0.87); $P < 0.00001$; see Supplementary material online, Appendix *Figure S10*]. Finally, results did not significantly differ among any subgroup for MACE or major bleeding (all *P*-interactions ≥0.09; see Supplementary material online, *Tables S6 and S7*).

Discussion

Our meta-analysis of >33 000 high-risk patients stabilized following an MI found that, overall compared with aspirin alone, extended DAPT beyond 1 year resulted in a 22% relative and 1.1% absolute risk reduction for major adverse cardiovascular events over a mean 31 months of follow-up. The magnitude of this relative risk reduction was consistent, with no significant heterogeneity, or sensitivity to removing any one trial from the pooled results. The pooled data in our meta-analysis show for the first time that there is a significant 15% reduction in cardiovascular death in post-MI patients receiving long-term DAPT. There was a 0.8% absolute increase in the risk of major bleeding, but without significant excess of ICH or fatal bleeding and no impact on non-cardiovascular causes of death.

This meta-analysis differs in important ways from prior reports.[32–36] We elected to focus on stabilized patients with a history of prior MI since these patients are known to be at higher atherothrombotic risk compared with patients with SIHD treated with elective PCI.[9,24,37,38] As such, we reasoned that these patients would be expected to demonstrate a more favourable benefit-to-risk profile when treated with long-term DAPT compared with patients without a prior MI. We also focused on trials that randomized at least one arm of this population to a strategy of DAPT >1 year following a qualifying MI vs. aspirin alone. We did this in order to address the unresolved question of whether treatment of patients with a history of MI with DAPT beyond the currently recommended 1-year duration results in significant and clinically meaningful reductions in atherothrombotic events. As well, we leveraged the power of a larger population to better quantify the magnitude of bleeding risk with this strategy and refine risk estimates for cardiovascular and non-cardiovascular causes of death. Finally, we analysed eligible trials irrespective of whether, when, and how patients were treated with PCI, since data support up to a year of DAPT post-MI regardless of whether patients underwent PCI. Patients with MI treated with PCI have stent-related factors that may modify the benefit–risk trade-off of extended DAPT, including the timing and propensity for late stent thrombosis[39,40]; however, the benefit of extended DAPT was consistent regardless of whether trials exclusively enrolled patients undergoing PCI or not.

Our findings of reduced atherothrombotic risk with extended DAPT irrespective of whether trials enrolled only PCI-treated patients support prior research that suggests the mechanism of long-term cardiovascular benefit with extended DAPT in patients with a history of prior MI is likely an extension of the benefits seen following early treatment of an MI, and distinct from simply preventing stent thrombosis in patients with prior PCI. For instance, long term, the majority of ruptured coronary plaques that result in recurrent MI appear to occur in lesions other than earlier culprits treated with PCI in patients with coronary heart disease.[18,29,41] After an infarction, patients have a more susceptible coronary milieu and are more prone to recurrent plaque rupture with prolonged platelet activation and aggregation[1–3,42] and higher circulating markers of myonecrosis and inflammation[43] compared with stable patients which may mediate a preferential benefit from extended DAPT. Furthermore, prolonged DAPT in patients with a history of prior MI appeared to reduce ischaemic events in other arterial territories, in accordance with our observed results for stroke.

Coronary heart disease treatment guidelines recommend 1 year of DAPT in patients following MI, based simply on the original duration of pivotal secondary prevention RCTs,[11–15] although landmark analyses from these trials suggested continued divergence of event curves with time.[44–46] This recommendation was extended to patients treated with coronary revascularization by PCI,[15,47] based on expert consensus and observational studies suggesting a delayed propensity for complete endothelialization and subsequent risk of late stent thrombosis following discontinuation of DAPT in patients treated with early generation drug-eluting stents.[48,49] Subsequently, a number of small RCTs have randomized patients treated with PCI to shorter durations of DAPT and concluded that 1-year duration of DAPT may offer no benefit compared with shorter courses of therapy.[50–55] However, none of these prior trials were powered to study this question, each enrolled limited numbers of subjects with MI, and prior meta-analyses have not distinguished treatment effects between acute and stable coronary patients.[32–36] To the best of our knowledge, there are at least eight ongoing outcomes trials comparing experimental with traditional DAPT strategies enrolling patients following PCI (see Supplementary material online, *Table S8*). These trials will greatly inform the care of patients receiving stents. However, each of these trials is primarily focused on PCI, whereas our meta-analysis results pertain to the patient's underlying history of MI irrespective of PCI status.

Considering the inclusion and exclusion criteria of the trials we studied certain characteristics that may define stabilized high-risk patients with previous MI at low risk of bleeding that benefit from extended DAPT. The majority of patients studied were considered high risk for recurrent atherothrombotic events with 93% having a history of biomarker positive acute coronary syndrome often in the presence of additional risk factors such as older age, diabetes, or established atherosclerosis. Studies typically excluded patients with a bleeding diathesis such as a coagulation disorder or long-term anticoagulation therapy, recent (within 6–12 months) or active major bleeding such as gastrointestinal bleeding, recent (within 1 month) major surgery, or any history of ICH. In addition, very few patients enrolled had a history of a prior stroke or TIA (<3%). As such, our findings may not be generalizable to all acute coronary syndrome patients,[56] such as patients with unstable angina or a history of stroke, but may be most accurately applied to patients with a prior history of MI who have tolerated 1 year of DAPT without development of, or ongoing risk for, significant bleeding.

There are certain limitations to this study. First, we pooled trials with heterogeneous populations that varied in treatment strategy, study design, intended primary outcome, and major bleeding definitions. For logistical reasons, we did not evaluate individual patient-level data, but unpublished data for several endpoints were provided by individual PIs to compare standard endpoints among similar patients across trials. Second, some of the RCTs were unblinded, which may bias reporting of non-fatal adverse cardiovascular and bleeding events. However, these unblinded trials provided <15% of the total population studied and all trials utilized blinded central committee endpoint adjudication. Third, five of the six included trials focused on subgroups, as they were not prospectively designed to determine whether extended DAPT was beneficial in

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post-MI patients. However, meta-analysis of randomized comparisons within each subgroup of patients with a history of MI remain valid. Finally, although three-quarters of the primary outcome events analysed were contributed from the PEGASUS-TIMI 54 and DAPT trials, our primary endpoint results were robust and remained significant after removal of both trials from the pooled result. Additionally, for the first time, pooling of these trials allowed detection of a significant reduction in cardiovascular death.

In summary, compared with aspirin alone, extended DAPT beyond 1 year among stabilized high-risk patients with previous MI decreased the risk of MACE, including cardiovascular death alone, as well as recurrent MI and stroke. There was an increase in the risk of major bleeding, but not fatal bleeding, with no excess of non-cardiovascular causes of death. These findings now clarify that in patients with prior MI who are at low risk of bleeding, continuation of DAPT beyond a year offers a substantial reduction in important cardiovascular outcomes and should be considered.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

J.A.U., E.B., and D.L.B. conceived and designed the study; J.A.U. performed the literature search, statistical analysis, and wrote the first draft of the manuscript; all authors analysed the data, interpreted the findings; and provided critical revision of the manuscript for important intellectual content; J.A.U., E.B., and D.L.B. provided administrative, technical, and material support and supervised the study.

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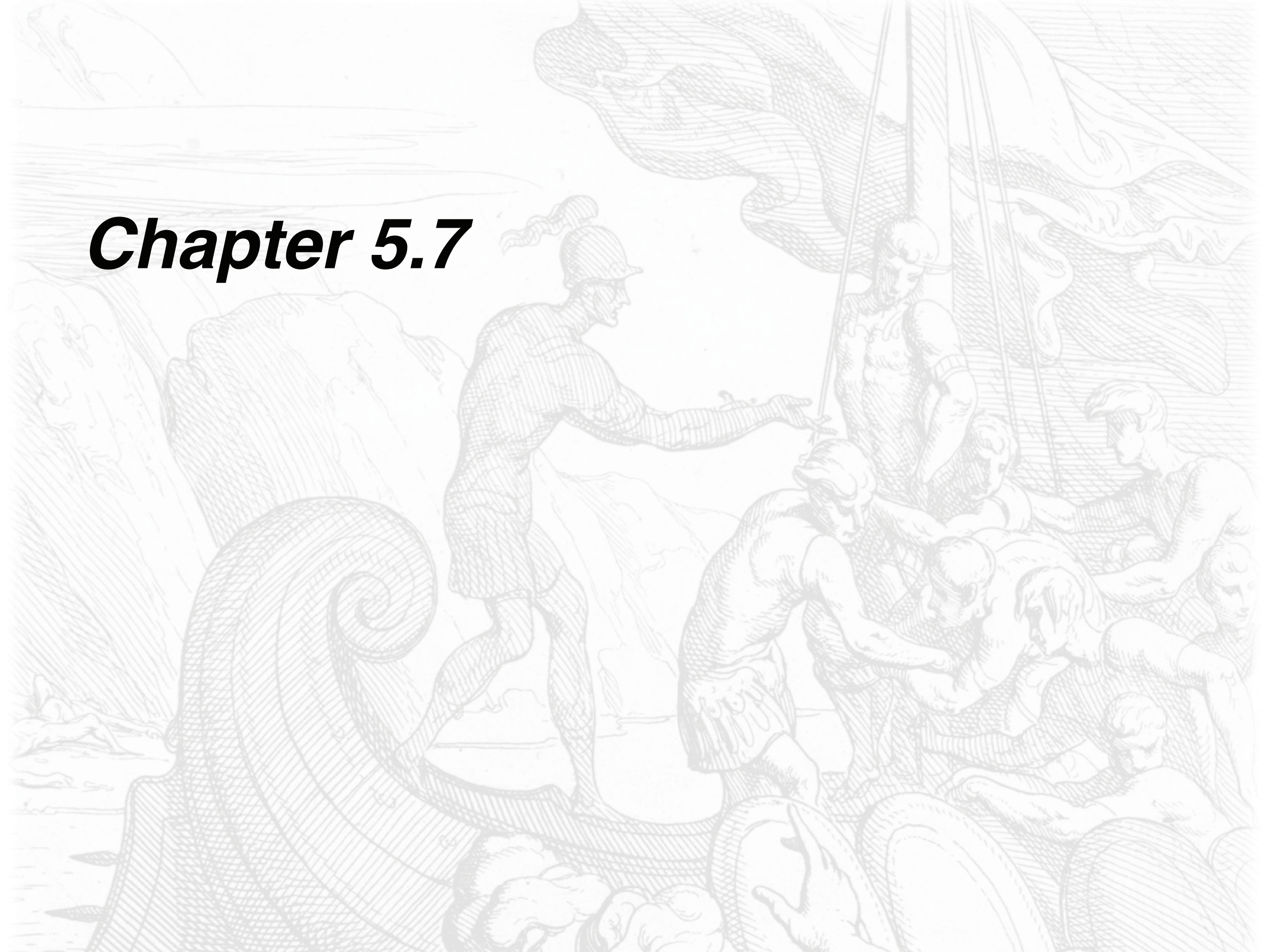

Chapter 5.7

Left Main or Proximal Left Anterior Descending Coronary Artery Disease Location identifies high-risk patients deriving potential greater benefit from prolonged DAPT duration (Prolonging Dual Antiplatelet Treatment After Grading Stent Induced Intimal Hyperplasia) PRODIGY Trial

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Left main or proximal left anterior descending coronary artery disease location identifies high-risk patients deriving potentially greater benefit from prolonged dual antiplatelet therapy duration

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KEYWORDS

- acute coronary syndrome
- clopidogrel
- dual antiplatelet therapy (DAPT)
- left main coronary artery
- proximal left anterior descending coronary artery
- stent thrombosis

Abstract

Aims: It is currently unclear if the location of coronary artery disease affects decision making with regard to dual antiplatelet therapy (DAPT). We investigated if the presence of at least 30% luminal narrowing in the left main (LM) and/or proximal left anterior descending (pLAD) coronary arteries on angiography is an outcome modifier with respect to DAPT duration.

Methods and results: In the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) study, 953 (54.3%) patients with and 801 (45.7%) without LM/pLAD lumen narrowing at the qualifying coronary intervention were randomised to six or 24 months of DAPT. Twenty-four month as compared to six-month DAPT reduced the occurrence of definite, probable or possible stent thrombosis by 50% in patients with (2.8% vs. 5.6%; HR 0.45, 95% CI: 0.23-0.89; p=0.02) but not in those without LM/pLAD lumen narrowing, with a highly significant interaction testing (P_{INT}= 0.002). This result remained consistent irrespective of whether stenting was (P_{INT}: 0.01) or was not (P_{INT}: 0.02) performed in the LM/pLAD.

Conclusions: Left main and/or proximal LAD lumen narrowing may be a treatment modifier with respect to the duration of DAPT. Patients fulfilling these angiographic characteristics seem to benefit from a prolonged dual antiplatelet treatment. Trial registration: ClinicalTrials.gov Identifier: NCT00611286

Abbreviations

ACS	acute coronary syndrome
BARC	Bleeding Academic Research Consortium
CVA	cerebrovascular accident
DES	drug-eluting stents
LM	left main coronary artery
MACE	major adverse cardiovascular events
MI	myocardial infarction
NSTEMI	non-ST-segment elevation myocardial infarction
pLAD	proximal left anterior descending coronary artery
PRODIGY	Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia
QCA	quantitative coronary angiography
ST	stent thrombosis
TCFA	thin-cap fibroatheroma

Introduction

Significant lumen narrowing of the left main coronary artery (LM) and/or of the proximal left anterior descending coronary artery (pLAD) carries worse prognostic implications as compared to coronary stenosis located elsewhere in the coronary tree. Previous studies have shown that successful revascularisation of lesions located in these critical coronary segments improves survival as compared to medical therapy only[1].

Editorial, see page 1218

The duration of dual antiplatelet therapy after coronary stenting, which maximises benefits over risks, remains debated. While clinical trials have shown an ischaemic benefit after a prolonged course of therapy beyond 12 months[2], recent meta-analyses have raised concerns about a possible increase in mortality after such treatment[3]. Consequently, the need for novel data informing clinical practice has been clearly voiced by the community[4]. Many have advocated the need to modulate DAPT length based on the balance between ischaemic versus bleeding hazard. However, it remains unclear how this balance should be quantified and standardised in clinical practice[5].

In particular, whether the presence of lumen narrowing of the LM and/or pLAD in patients undergoing stenting should affect the decision making with respect to the duration of DAPT remains unknown, as no previous studies investigating DAPT duration have specifically focused on this patient population or reported the outcomes for this high-risk patient subgroup.

We hypothesised that the presence of lumen narrowing in the LM and/or pLAD may help in identifying patients at higher ischaemic risk who may particularly benefit from a prolonged DAPT course. Thus, we retrospectively explored the differential outcomes of 24 or six-month DAPT in this high-risk population in the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) trial.

Methods

The design and main findings for the PRODIGY trial were previously reported[6,7]. All-comer patients received a balanced mixture of first and second-generation drug-eluting stents (DES) and bare metal stents during index intervention at three Italian sites. Thirty days later, they were randomly allocated to receive either six or 24 months of dual antiplatelet treatment. The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committees of the three participating centres independently approved the protocol, and all participants gave written informed consent.

TREATMENT PROTOCOL

All patients received aspirin (80 to 160 mg orally indefinitely) and clopidogrel (75 mg/d) according to the randomisation scheme as follows: for either six months in the short DAPT group or 24 months in the prolonged DAPT arm irrespective of the previously implanted stent type or indication for the coronary procedure. All randomised patients returned for study visits at 30 days, and then every six months up to two years.

DEFINITION OF THE STUDY GROUPS

A lumen stenosis of at least 30% on angiography, appraised by visual estimation, was used to define the LM/pLAD lumen-narrowing group as this information was prospectively collected in the case report form for each coronary segment, irrespective of the final revascularisation strategy. The decision to treat or not to treat these and other coronary segments was left to the operators' discretion.

STUDY ENDPOINTS

The primary efficacy endpoint of the PRODIGY trial was the incidence of major adverse cardiovascular events (MACE), a composite of death, myocardial infarction (MI), or cerebrovascular accident (CVA), whereas the key safety endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. Other endpoints included each component of the primary efficacy endpoint, cardiovascular death and stent thrombosis (ST), defined on the basis of the Academic Research Consortium criteria[8]. All study endpoint definitions were previously reported[6].

Additionally, in order to increase the specificity of the possible stent thrombosis definition (i.e., any cardiovascular death occurring at least 30 days after stent implantation), we also applied a "modified" possible stent thrombosis definition[9], restricting the adjudication of these events only to those who died suddenly or who experienced symptoms of myocardial ischaemia before death, occurring at least 30 days after stent implantation.

A blinded clinical events committee adjudicated all endpoints centrally. The time frame of interest was from 30 days (i.e., after pharmacological randomisation) to 24 months.

STATISTICAL ANALYSIS

In this retrospective analysis of the PRODIGY trial[7], categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (interquartile range). Continuous variables were compared between randomised groups using the Wilcoxon rank-sum test, whereas for binary variables the chi-square test was used.

To test the cumulative incidence of events in the two subgroups presenting with or without LM/pLAD lumen narrowing, we performed a Cox regression analysis with interaction testing. Hazard ratios with 95% confidence intervals (CIs) were calculated for short-term clopidogrel versus long-term clopidogrel (i.e., values >1 indicated increased hazard in the long-term group).

Adjustment for NSTEMI presentation was performed due to the imbalance of this characteristic between the two treatment arms. Interaction tests were performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A two-sided probability value <0.05 was considered significant. All analyses, performed on the basis of the intention-to-treat principle, were performed with SPSS, Version 21.0 (IBM Corp., Armonk, NY, USA).

Results

In total, the PRODIGY trial recruited 2,013 all-comer patients, 1,970 of whom were randomly allocated to receive DAPT for a duration of six or 24 months. For the current analysis, patients previously treated were eventually considered **(Figure 1)**.

The total number of patients with LM/pLAD lumen narrowing was 953 (54.3%), of whom 471 were randomised to 24-month DAPT and 482 to six-month DAPT, including 336 (35.2%) patients who received coronary stenting in the LM (7.3%) and/or in the pLAD (29.4%).

Patients with angiographic evidence of LM/pLAD lumen narrowing were older, more frequently had kidney function impairment, were less frequently smokers but more frequently had a history of PCI **(Table 1)**. Their angiographic features were consistent with a more extensive CAD, requiring a more complex interventional procedure as compared to patients without LM/pLAD lumen narrowing **(Appendix Table 1)**.

Amongst patients with or without LM/pLAD lumen narrowing, clinical and angiographic characteristics were well matched between the two DAPT duration groups, with the sole exception of a higher prevalence of non-ST-segment elevation myocardial infarction (NSTEMI) in patients with LM/pLAD lumen narrowing allocated to the 24 as compared to the six-month DAPT group **(Table 1)**. Clinical follow-up at two years was complete for 99.1% of patients.

PATIENT-ORIENTED OUTCOMES

The composite of death, myocardial infarction or CVA at 24 months occurred in 105 (11%) patients with, as compared to 65 (8.1%) without LM/pLAD lumen narrowing (HR 1.37, 95% CI: 1.00-1.87; p=0.04). This difference was driven by a trend towards an increase in myocardial infarction (4.5% vs. 2.7%; p=0.053). When patients who received a coronary stent in the LM and/or pLAD were excluded from the analysis, the composite of death, myocardial infarction or CVA at 24 months remained consistently higher in individuals with (11.3%) as compared to those without (8.1%) LM/pLAD lumen narrowing (HR 1.42, 95% CI: 1.01-1.98; p=0.04), due to a significant increase in myocardial infarction (4.9% vs. 2.7%; p=0.036). Conversely, patients stented in the LM/pLAD did not suffer a significant increase of the primary endpoint rate. After adjustment for clinical and angiographic imbalances between the two groups, the composite endpoint of death, MI or CVA was not increased in patients with as compared to those without LM/pLAD lumen narrowing (adjusted HR 1.22, 95% CI: 0.89-1.68; p=0.21) or in patients who underwent stenting in these coronary segments (adjusted HR 1.37, 95% CI: 0.97-1.94; p=0.07).

The composite of death, MI or CVA did not differ with respect to DAPT duration in patients with (11.0% in the 24-month vs.

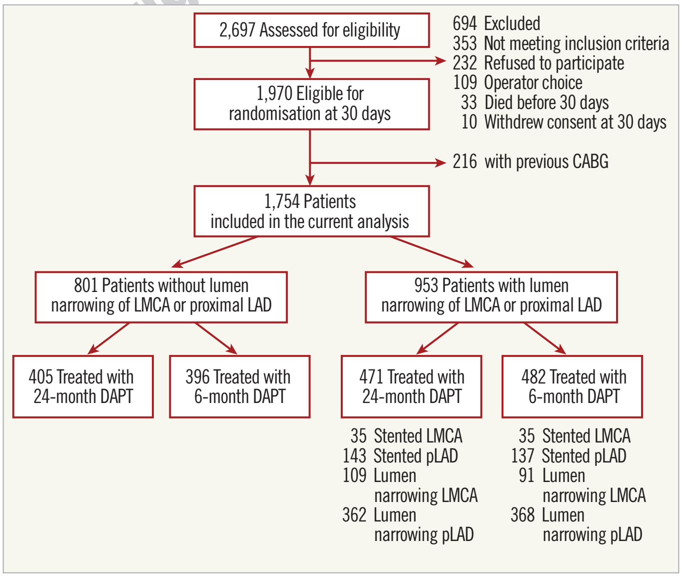

Figure 1. *Study profile. Description of the study population.*

Table 1. Baseline characteristics.

Characteristic	Patients with LM/pLAD lumen narrowing			Patients without LM/pLAD lumen narrowing			*p*-value*
	24-month clopidogrel (n=471)	6-month clopidogrel (n=482)	*p*-value	24-month clopidogrel (n=405)	6-month clopidogrel (n=396)	*p*-value	
Age, yrs	69.6 (70-77)	69.9 (60-77)	0.59	67.4 (59-74)	66.7 (59-75)	0.91	0.03
Male sex, % (n)	74.5 (351)	74.7 (360)	0.95	77.3 (313)	75.8 (300)	0.61	0.35
Body mass index, kg/m^2	26.2 (24-29)	26.6 (24-29)	0.82	27.3 (25-30)	26.4 (24-29)	0.39	0.27
Diabetes, % (n)	24.2 (114)	21.8 (105)	0.38	23.5 (95)	24.2 (96)	0.79	0.68
Insulin-dependent, % (n)	5.9 (28)	4.6 (22)		4.0 (16)	6.1 (24)		
Hypertension, % (n)	70.7 (333)	70.7 (341)	0.99	72.6 (294)	67.9 (269)	0.15	0.84
Hyperlipidaemia, % (n)	54.1 (255)	51.9 (250)	0.48	53.6 (217)	51.5 (204)	0.56	0.86
Current cigarette use, % (n)	23.1 (109)	23.2 (112)	0.59	26.2 (105)	30.3 (120)	0.14	0.02
Creatinine clearance, ml/min	74.4 (54-100)	73.3 (56-95)	0.71	79.0 (59-102)	77.7 (60-97)	0.28	0.005
Prior myocardial infarction, % (n)	21.4 (101)	20.7 (100)	0.41	24.4 (99)	22.5 (89)	0.49	0.21
Prior percutaneous coronary intervention, % (n)	13.6 (64)	14.9 (72)	0.17	20.2 (82)	16.2 (64)	0.10	0.02
Left ventricular ejection fraction	55 (40-60)	53 (45-60)	0.82	55 (45-60)	51 (45-60)	0.44	0.53
Clinical presentation, % (n)							
Stable angina pectoris	23.8 (112)	25.1 (121)	0.63	26.2 (106)	26.0 (103)	0.95	0.43
Acute coronary syndrome	76.2 (359)	74.9 (361)		73.8 (299)	74.0 (293)		
Unstable angina	17.2 (81)	19.5 (94)	0.35	16.5 (67)	14.6 (58)	0.46	0.14
Non-ST-elevation MI	26.8 (126)	20.5 (99)	0.02	18.8 (76)	23.5 (93)	0.10	0.21
ST-segment elevation MI	32.3 (152)	34.9 (168)	0.40	38.5 (156)	35.9 (142)	0.43	0.12

* *p*-value for the comparison between patients with and without LM/pLAD lumen narrowing.

11.0% in the six-month DAPT arm; HR 0.96, 95% CI: 0.65-1.41; p=0.84) or those without LM/pLAD lumen narrowing (9.4% in the 24-month vs. 6.8% in the six-month DAPT arm; HR 1.45, 95% CI: 0.88-2.38; p=0.14) **(Table 2, Figure 2)**. Similar findings were observed when each component of the primary endpoint was appraised separately. There was, however, a trend towards interaction (P_{INT}=0.056) with respect to DAPT duration and the presence of LM/pLAD lumen narrowing, suggesting greater ischaemic protection towards the composite endpoint of cardiovascular death or myocardial infarction (MI) in patients treated with 24 as compared to six-month DAPT **(Table 2, Figure 2)**.

Results remained consistent regardless of whether stenting was **(Appendix Table 2)** or was not **(Appendix Table 3)** accomplished in the LM and/or pLAD. No signal of heterogeneity in the subgroups of patients undergoing stenting versus those who did not receive stent implantation in the LM/pLAD was observed for patient-oriented outcomes with respect to DAPT duration **(Appendix Figure 1)**.

When the group of patients presenting with acute coronary syndrome (ACS) was appraised separately, the results were in line with those observed in the overall patient population **(Appendix Table 4)**.

STENT-ORIENTED OUTCOMES

The risk of definite, definite or probable and definite, probable or possible ST was not increased in patients with as compared to those without LM/pLAD lumen narrowing. Similarly, the cumulative risk of definite stent thrombosis did not differ with respect to DAPT duration in patients with (0.2% in the 24-month vs. 0.8% in the six-month DAPT arm; HR 0.24, 95% CI: 0.03-2.13; p=0.20) or those without LM/pLAD lumen narrowing (1.2% in the 24-month vs. 0.3% in the six-month DAPT arm; HR 4.93, 95% CI: 0.57-42.3; p=0.15), with a trend towards interaction between the presence of LM/pLAD lumen narrowing and the duration of treatment (P_{INT}=0.054) **(Figure 3)**. Consistent findings were noted for the composite of definite or probable ST **(Figure 3, Figure 4)**.

Definite, probable or possible ST was significantly reduced by 24-month, as compared to six-month treatment among patients with LM/pLAD lumen narrowing (2.8% in the 24-month vs. 5.6% in the six-month DAPT arm; HR 0.45, 95% CI: 0.23-0.89; p=0.02) whereas it was increased in patients without LM/pLAD lumen narrowing (5.2% in the 24-month vs. 2.5% in the six-month DAPT arm; HR 2.15, 95% CI: 1.01-4.58; p=0.046), with highly significant interaction testing (P_{INT}=0.002) **(Figure 3, Figure 4)**. Results remained consistent when the "modified" stent thrombosis endpoint was appraised in conjunction with definite or probable events **(Figure 3, Figure 5)**. At landmark analysis, after censoring all events occurring before six months, the time at which the two pharmacological arms started diverging, we still observed a reduction of definite, probable or possible stent thrombosis with 24 vs. six-month DAPT in patients with LM/pLAD lumen narrowing (HR 0.45, 95% CI: 0.20-0.99; p=0.05), whereas its increase in patients without LM/pLAD lumen narrowing was no longer present (HR 1.96, 95% CI: 0.59-6.53; p=0.27). A consistent, significant interaction effect

Table 2. Outcome rates at 24 months according to the treatment group.

		Patients with LM/pLAD lumen narrowing				Patients without LM/pLAD lumen narrowing				
		24-month clopidogrel (n=471)	6-month clopidogrel (n=482)	Hazard ratio (95% CI)	*p*-value	24-month clopidogrel (n=405)	6-month clopidogrel (n=396)	Hazard ratio (95% CI)	*p*-value	*p*-int.
Patient-oriented outcomes										
Death from any cause, myocardial infarction or cerebrovascular accident		52 (11.0)	53 (11.0)	0.96 (0.65-1.41)	0.84	38 (9.4)	27 (6.8)	1.45 (0.88-2.38)	0.14	0.20
Death from any cause or myocardial infarction		44 (9.3)	51 (10.6)	0.83 (0.56-1.25)	0.38	34 (8.4)	26 (6.6)	1.33 (0.80 -2.22)	0.27	0.16
Death from cardiovascular cause or myocardial infarction		31 (6.6)	40 (8.3)	0.74 (0.46-1.18)	0.21	25 (6.2)	16 (4.0)	1.59 (0.85-2.97)	0.15	0.056
Death from any cause		33 (7.0)	36 (7.5)	0.88 (0.55-1.43)	0.62	27 (6.7)	20 (5.1)	1.39 (0.78-2.48)	0.26	0.24
Death from cardiovascular cause		18 (3.8)	23 (4.8)	0.74 (0.40-1.37)	0.34	16 (4.0)	10 (2.5)	1.66 (0.75-3.66)	0.21	0.12
Myocardial infarction		21 (4.5)	22 (4.6)	0.91 (0.50-1.66)	0.76	12 (3.0)	10 (2.5)	1.18 (0.51-2.74)	0.69	0.61
Stent-oriented outcomes										
Definite stent thrombosis	Late	1 (0.2)	3 (0.6)	0.35 (0.03-3.25)	0.35	4 (1.0)	1 (0.3)	3.98 (0.44-35.6)	0.22	0.12
	Very late	0 (0.0)	1 (0.2)	n.a.	0.59	1 (0.3)	0 (0.0)	n.a.	0.61	–
	Cumulative	1 (0.2)	4 (0.8)	0.24 (0.03-2.13)	0.20	5 (1.2)	1 (0.3)	4.93 (0.57-42.3)	0.15	0.054
Definite or probable stent thrombosis	Late	2 (0.4)	5 (1.0)	0.38 (0.07-1.96)	0.25	6 (1.5)	3 (0.8)	1.99 (0.50-7.99).	0.33	0.13
	Very late	1 (0.2)	2 (0.4)	0.43 (0.04-4.75)	0.49	1 (0.3)	1 (0.3)	1.06 (0.07-17.1)	0.96	0.63
	Cumulative	3 (0.6)	7 (1.5)	0.39 (0.10-1.52)	0.17	7 (1.7)	4 (1.0)	1.75 (0.51-5.99)	0.37	0.11
Definite, probable or possible stent thrombosis	Late	7 (1.5)	15 (3.1)	0.44 (0.18-1.09)	0.08	17 (4.2)	8 (2.0)	2.17 (0.94-5.04)	0.07	0.01
	Very late	6 (1.3)	12 (2.6)	0.46 (0.17-1.24)	0.12	4 (1.0)	2 (0.5)	2.05 (0.37-11.24)	0.41	0.13
	Cumulative	13 (2.8)	27 (5.6)	0.45 (0.23-0.89)	0.02	21 (5.2)	10 (2.5)	2.15 (1.01-4.58)	0.046	0.002
Modified definite, probable or possible stent thrombosis		5 (1.1)	12 (2.5)	0.40 (0.14-1.15)	0.09	7 (1.7)	2 (0.5)	3.61 (0.75-17.4)	0.11	0.02
Bleeding outcomes										
BARC type 2, 3 or 5		41 (8.7)	17 (3.5)	2.51 (1.43-4.42)	0.003	27 (6.7)	14 (3.5)	1.94 (1.01-3.69)	0.04	0.65
BARC type 3 or 5		23 (4.9)	10 (2.1)	2.26 (1.08-4.78)	0.03	9 (2.2)	8 (2.0)	1.17 (0.45-3.04)	0.74	0.28

Adjusted for non-ST-segment elevation myocardial infarction. BARC: Bleeding Academic Research Consortium

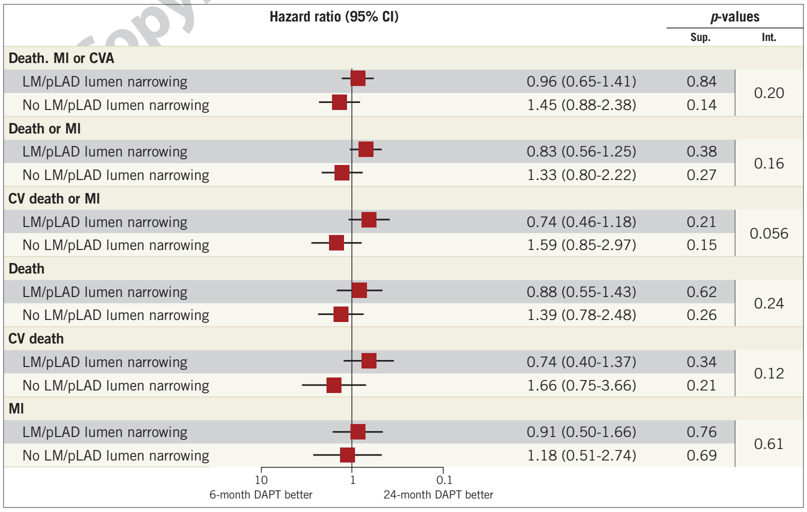

Figure 2. *Patient-oriented outcomes. The subgroups with and without LM/pLAD lumen narrowing are shown for the patient-oriented ischaemic endpoints among patients randomised to six-month or 24-month DAPT.*

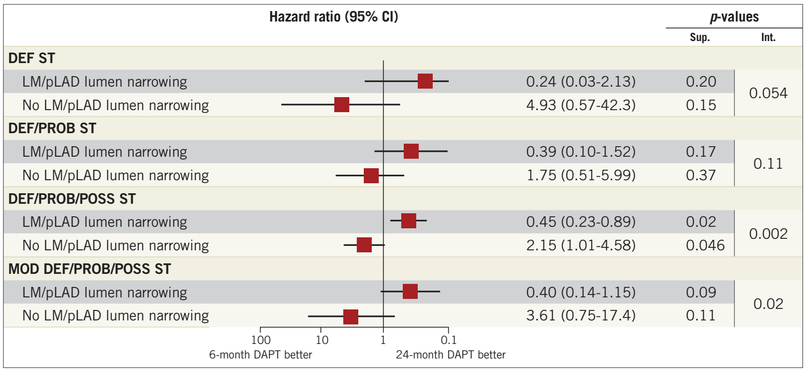

Figure 3. *Stent-oriented outcomes. The subgroups with and without LM/pLAD lumen narrowing are shown for the stent-oriented endpoints of definite (DEF ST), definite or probable (DEF/PROB ST) and definite, probable or possible stent thrombosis (DEF/PROB/POSS ST) as well as the "modified" definite, probable or possible stent thrombosis (MOD DEF/PROB/POSS ST) definition among patients randomised to six-month or 24-month DAPT.*

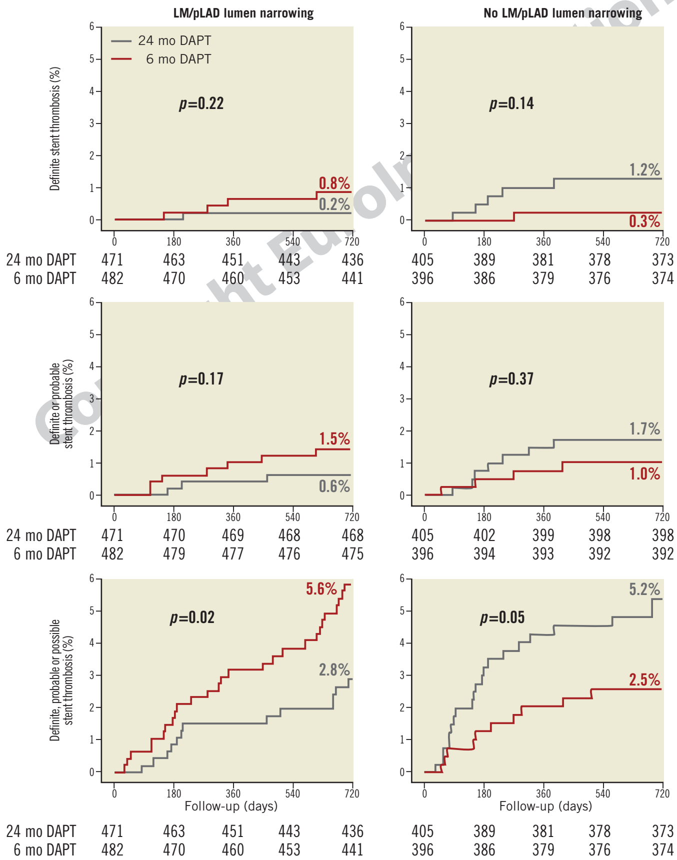

Figure 4. *Cumulative incidence of stent-oriented outcomes. Cumulative incidence curves for the subgroups with (left) or without (right) LM/pLAD lumen narrowing and for the endpoints of definite (upper panel), definite or probable (middle panel) or definite, probable or possible stent thrombosis (lower panel).*

between CAD location and duration of dual antiplatelet therapy was also observed at landmark analysis (P_{INT}=0.044) **(Appendix Figure 2)**. Consistently, when patients treated with first-generation DES were excluded, again similar findings were observed.

Results were also consistent regardless of whether stenting was performed or not performed in the LM and/or pLAD **(Appendix Table 2, Appendix Table 3)**. Again, no signal of heterogeneity was observed for stent-oriented endpoints between the subgroups treated or not treated with a coronary stent in the LM and/or pLAD with respect to DAPT duration **(Appendix Figure 3)**.

In the subgroup of patients presenting with ACS, stent-oriented outcomes remained consistent with the results of the overall patient population **(Appendix Table 4)**.

BLEEDING OUTCOMES

BARC 3 or 5 and 2, 3 or 5 bleeding occurred more frequently in the 24-month DAPT arm irrespective of CAD location within the coronary tree **(Table 2)**. No statistical interaction was noted between the presence of LM/pLAD lumen narrowing and the duration of antiplatelet treatment.

Discussion

Our findings could be summarised as follows:

1) In an all-comer population undergoing coronary stenting, patients presenting with angiographic evidence of lumen narrowing on the LM and/or pLAD had higher clinical and angiographic risk characteristics at baseline, and underwent a more complex percutaneous treatment.
2) After 24 months, the rate of death for all causes, myocardial infarction or CVA was significantly higher in patients with LM/pLAD lumen narrowing, regardless of whether stenting was finally accomplished in these coronary segments. When adjusted for baseline imbalances, MACE rates did not differ between patients with or without LM/pLAD lumen narrowing, suggesting that, at least in our data set, luminal CAD in these segments may qualify more as a marker than a driver of adverse outcomes.
3) Twenty-four as compared to six-month DAPT significantly reduced the rate of definite, probable or possible stent thrombosis in patients with, but not in those without, LM/pLAD lumen narrowing, suggesting that this angiographic finding could be a treatment modifier with respect to DAPT duration. A consistent trend towards interaction between CAD location and DAPT duration was also noted for the composite of cardiovascular death and MI.
4) The 24-month DAPT regimen remained associated with possible benefits in patients with LM/pLAD lumen narrowing irrespective of whether a stent was or was not implanted in these segments or whether patients presented with acute coronary syndrome.
5) Minor and major bleeding occurred more often in patients receiving prolonged dual antiplatelet therapy, independently from the presence or absence of LM/pLAD lumen narrowing.

The proximal LAD and left main coronary artery supply 45 to 55% and 84 to 100% of blood flow to the left ventricle, respectively[10]. Accordingly, ischaemic events occurring in these segments are more often fatal. Coronary revascularisation of significant LM/pLAD stenosis demonstrated a long-term survival benefit compared with medical therapy alone, whereas the clinical implication of non-significant lesions in these segments, especially in stable coronary artery disease (SCAD) patients, is unclear[1].

In the current analysis, we noted a higher incidence of ischaemic recurrences as well as a greater benefit from prolonged DAPT duration in patients with lumen narrowing of the LM/pLAD. A putative explanation for this finding could be the higher clinical and angiographic risk characteristics noted in these patients at baseline. This is consistent with previous studies which observed an additional benefit of a more potent antiplatelet therapy in patients at higher ischaemic risk[11].

As an alternative, not mutually exclusive, hypothesis, LM/pLAD location of the atherosclerotic plaques *per se* may be a driver for the greater ischaemic risk. In support of this possibility, invasive imaging studies showed that atherosclerotic plaques located on the LM or the pLAD present a significantly higher

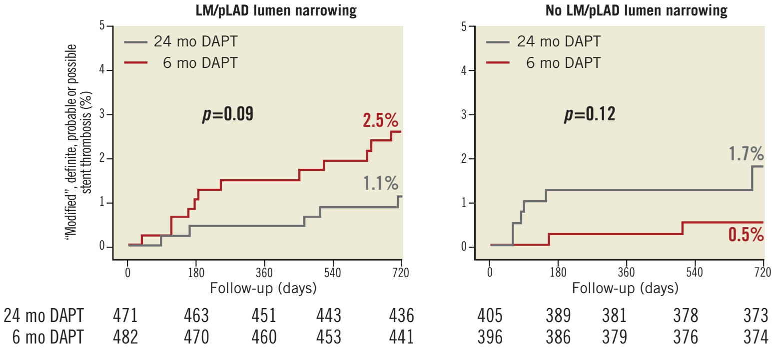

Figure 5. *Cumulative incidence of "modified" definite, probable or possible stent thrombosis. Cumulative incidence curves for the subgroups with (left) and without (right) LM/pLAD lumen narrowing with respect to "modified" definite, probable or possible stent thrombosis.*

percentage of lipidic and necrotic cores, entailing a higher vulnerability and increased risk of plaque rupture in this location[12,13]. In addition, thin-cap fibroatheroma (TCFA), a specific predictor of plaque vulnerability, was observed more frequently in the proximal segments of the coronary tree and in mild or moderate stenosis (i.e., stenosis <70% estimated visually during angiography)[14-16].

It is tempting to speculate that the excess of ischaemic events, as well as the increased protection by a prolonged antiplatelet treatment, observed in patients with LM/pLAD lumen narrowing could be partly related to the progression and destabilisation of atherosclerotic plaques deemed not significant at baseline angiography and left untreated. Lending support to this suggestion, the PROSPECT trial[17], which prospectively followed patients with acute coronary syndrome at presentation, showed that almost 50% of the recurrent ischaemic events observed during the three-year follow-up were not related to the coronary stent implanted, but rather to atherosclerotic lesions non-significant at baseline. In this context, an extended duration of DAPT could be beneficial to prevent, or at least mitigate, the effects of plaque rupture, as demonstrated by the recent DAPT trial[2], showing a reduction of MACE and stent thrombosis after a 30-month rather than 12-month dual antiplatelet therapy with thienopyridines. Interestingly, in this trial 55% of the benefit observed in the prolonged therapy group was due to events not related to the stent implanted at baseline.

Our analysis included 336 patients who underwent coronary stenting on LM and/or pLAD, in whom prolonged DAPT provided a consistent benefit as compared to six-month therapy. Stent thrombosis occurring in these segments is often lethal, though the reduction of stent-related events with a prolonged or more potent antiplatelet therapy is particularly appealing[2]. However, this population has frequently been excluded from clinical trials evaluating the optimal DAPT duration, and there is currently poor and inconsistent evidence guiding this decision[2].

To corroborate further the robustness of our findings, we evaluated the subgroup of patients with and without LM/pLAD lumen narrowing presenting with acute coronary syndrome. The current analysis showed a consistent benefit of a prolonged DAPT in patients with LM/pLAD lumen narrowing presenting with ACS, which is in keeping with previous findings from our study[18].

An increased bleeding risk was observed in patients undergoing a prolonged DAPT regimen irrespective of the presence of LM/pLAD lumen narrowing, which may be perceived as clinically acceptable in the light of the clear signals of benefit observed in this high-risk population.

Limitations

Our study suffers from the following limitations:

1) The main finding of our analysis refers to stent-related events that did not constitute the primary endpoint of the PRODIGY trial. As such, the findings reported in the current retrospective analysis should not be interpreted as conclusive but as hypothesis-generating. Adequately powered, prospective studies are needed to confirm or refute our findings.
2) The definition of the lumen narrowing status was based on the visual estimation by the interventional cardiologist. This method suffers from inter- and intra-individual variability that could have been prevented by implementing quantitative coronary angiography (QCA) analysis. However, this would have limited the applicability of our results in practice, where routine QCA analysis is rarely performed.
3) The effect of DAPT on ischaemic events is related to the characteristics of the implanted stent. Evaluating the role of CAD location and duration of DAPT for each stent used could have given further insights, but was not performed given the high dispersion of events into subgroups. However, after excluding first-generation DES, the results were consistent with those observed in the overall patient population.
4) Stratification of the lumen-narrowing group according to different stenosis severity categories could have provided further insights into the link between lumen narrowing and ischaemic risk. Unfortunately, this information was not prospectively collected during the study.

Conclusions

A prolonged treatment with dual antiplatelet therapy reduced stent thrombosis in patients with lumen narrowing of the left main and/or proximal left anterior descending coronary artery, but not in those without these angiographic characteristics. The presence of coronary artery disease in these segments may be a treatment modifier impacting on the duration of dual antiplatelet therapy.

Impact on daily practice

Left main and/or proximal LAD lumen narrowing may be a treatment modifier with respect to the duration of DAPT. The presence of coronary artery disease in these segments carries a higher risk of ischaemic events, and patients fulfilling these angiographic characteristics seem to benefit from a prolonged duration of dual antiplatelet treatment.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Appendix Table 1. Angiographic characteristics.

Appendix Table 2. Outcome rates at 24 months according to the treatment group, in the subgroup of patients treated with coronary stent on the LM and/or pLAD and in those without lumen narrowing in these segments.

Appendix Table 3. Outcome rates at 24 months according to the treatment group, in the subgroup of patients with lumen narrowing but not treated with coronary stent on the LM and/or pLAD and in those without lumen narrowing in these segments.

Appendix Table 4. Outcome rates at 24 months according to the treatment group in the subgroup of patients presenting with acute coronary syndrome.

Appendix Figure 1. Patient-oriented outcomes.

Appendix Figure 2. Landmark analysis at six months for the cumulative incidence of definite, probable or possible stent thrombosis.

Appendix Figure 3. Subgroup analysis among patients with lumen narrowing of the LM and/or pLAD.

5

Chapter 5.8

Does smoking habit affect the randomized comparison of 6 versus 24-month dual antiplatelet therapy duration? Insights from the PRODIGY Trial.

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Letter to the Editor

Does smoking habit affect the randomized comparison of 6 versus 24-month dual antiplatelet therapy duration? Insights from the PRODIGY trial

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Pharmacodynamics studies reported a greater inhibition of platelet aggregation among clopidogrel treated patients in smokers compared with non-smokers [1]. Cigarette smoking increases the catalytic activity of CYP1A2, which mediates the first oxidative step in the conversion of pro-drug clopidogrel to its active metabolite [2]. Therefore, in clopidogrel treated patients smoking habit may increase the effect of treatment, potentially leading to a higher protection against ischaemic events, but also to a higher bleeding risk. Based on available evidence, the impact of smoking habit on outcomes remains unclear [3–8].

We investigated whether smoking status may influence the effect of dual antiplatelet therapy (DAPT) duration with respect to ischaemic and bleeding events in an all-comer PCI population who were randomized either 6-month (short-term) or 24-month (long-term) treatment with clopidogrel on top of aspirin after coronary stenting.

The design of the Prolonging Dual Antiplatelet Treatment After Grading Stent Induced Intimal Hyperplasia Study (PRODIGY) was previously reported [9,10].

The study was conducted according to the ethical guidelines of the Declaration of Helsinki. The Ethics Committee approved the protocol; the informed consent was achieved from each patient.

Out of 2013 patients enrolled into the study, 33 died within 30 days and 10 withdrew consent. Smoking status was recorded in all but 8 patients who were excluded from this analysis.

The final population included 1962 patients: 984 were allocated to receive 24-month DAPT (222 smokers and 762 non-smokers) and 978 were assigned to 6-month DAPT (247 smokers and 731 non-smokers).

Compared with non-smokers, smokers were younger, less frequently had history of hypertension, myocardial infarction (MI) or coronary revascularization and more frequently presented with STEMI or had higher creatinine clearance. Demographic, clinical and procedural features were well balanced in the patients treated with long-term versus short-term DAPT within both smoker and non-smoker groups (Table 1).

The primary efficacy end-point (all-cause death, MI or cerebrovascular accident – CVA – at 2 years) occurred in 165 (11.1%) non-smokers and in 32 (6.8%) smokers without significant differences between the two groups after adjustment for variables which were differently distributed at an alpha of 5% (HR 1.03 with CI 95% of 0.67–1.50; $p = 0.989$).

Among patients allocated to the long-term DAPT arm compared with those assigned to receive the short-term DAPT, no significant differences of primary end-point rate were noted in both smokers (5.9% in the long-term vs 7.7% in the short-term DAPT arms; HR 0.70, 95% CI 0.34–1.45; $p = 0.339$) and non-smokers (11.3% in the long-term vs 10.8% in the short-term DAPT arms; HR 1.04, 95% CI 0.77–1.41; $p = 0.793$) with no evidence of interaction between smoking habit and DAPT duration ($P_{INT} = 0.426$) (Fig. 1). Similarly, no differences between short and long-term DAPT groups in terms of both

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Table 1
Baseline and procedural features.

	All population		Non-smokers		Smokers	
	Non-smokers (1493)	Smokers (469)	6-Month DAPT (731)	24-Month DAPT (762)	6-Month DAPT (247)	24-Month DAPT (222)
Sex (male), n (%)	1122 (75.2)	385 (82.1)[§]	548 (75)	547 (75)	197 (79.8)	188 (84.7)
Age (years) median (IQR)	71.4 (63.8–77.5)	60.3 (53.0–68.6)[*]	71.3 (64.1–77.8)	71.5 (62.9–77.2)	60.0 (53.8–68.4)	61.3 (52.1–68.6)
BMI (kg/m^2) median (IQR)	26.7 (24.5–29.4)	26.2 (24.2–29.0)	26.8 (24.4–29.4)	26.6 (24.6–29.4)	26.1 (24.0–28.7)	26.6 (24.5–29.4)
Hypercholesterolemia, n (%)	850 (56.9)	222 (47.3)[*]	402 (55.0)	448 (58.8)	119 (48.2)	103 (46.4)
Hypertension, n (%)	1144 (76.6)	266 (56.7)[*]	545 (74.6)	599 (78.6)	146 (59.1)	120 (54.1)
Diabetes, n (%)	394 (26.4)	80 (17.1)[*]	183 (25.1)	211 (27.7)	48 (19.4)	32 (14.4)
Previous stroke, n (%)	13 (1.1)	1 (0.3)	8 (1.4)	5 (0.9)	0 (0.0)	1 (0.6)
Previous MI, n (%)	444 (29.7)	81 (17.3)[*]	210 (28.7)	234 (30.7)	46 (18.6)	35 (15.8)
Previous PCI, n (%)	313 (21.0)	45 (9.6)[*]	145 (19.8)	168 (22.0)	25 (0.1)	20 (9.0)
Previous CABG, n (%)	191 (12.8)	22 (4.7)[*]	88 (12.0)	103 (13.5)	15 (6.1)	7 (3.2)
Creatinine clearance (ml/min), median (IQR)	69.4 (54.2–90.2)	93.4 (69.5–112.6)[*]	69.6 (53.8–89.3)	69.3 (54.2–92.0)	91.6 (69.3–112.6)	96.4 (70.7–112.7)
STEMI, n (%)	419 (28.1)	226 (48.2)[*]	205 (28.0)	214 (28.1)	19 (48.2)	107 (48.2)
NSTACS, n (%)	649 (43.5)	167 (35.6)[§]	318 (43.5)	331 (43.4)	88 (35.6)	79 (35.6)
SCAD, n (%)	425 (28.5)	76 (16.2)[*]	208 (28.5)	217 (28.5)	40 (16.2)	36 (16.2)
LVEF (%), median (IQR)	52.0 (45.0–60.0)	51.0 (44.0–60.0)	50.0 (43.3–60.0)	55.0 (45.0–60.0)	50.0 (43.5–60.0)	52.0 (44.0–60.0)
Multivessel disease, n (%)	1064 (71.3)	307 (65.5)[§]	518 (70.9)	546 (71.7)	161 (65.2)	146 (65.8)
At least 1 b2/c lesion, n (%)	978 (65.5)	323 (68.9)	486 (66.5)	492 (64.6)	176 (71.3)	147 (66.2)
Stent type BMS, n (%)	356 (24.4)	124 (26.4)	182 (24.9)	184 (24.1)	63 (25.5)	61 (27.5)
Stent type ENDEAVOR, n (%)	366 (24.5)	378 (25.3)	176 (24.1)	190 (24.9)	67 (27.1)	58 (26.1)
Stent type TAXUS, n (%)	378 (25.3)	109 (23.2)	183 (25.0)	195 (25.6)	60 (24.3)	49 (22.1)
Stent type XIENCE, n (%)	384 (25.7)	111 (23.7)	190 (26.0)	193 (25.3)	57 (23.1)	54 (24.3)

BMI = body mass index; BMS = bare metal stent, CABG = coronary artery bypass graft; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEACS = non ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease; STEMI = ST-elevation myocardial infarction.
[§] $P < 0.05$.
[*] $P < 0.001$.

relative risk and interaction with smoking were observed for all-cause-death and cardiovascular (CV) death or MI (Fig. 1).

The key safety end-point (Bleeding Academic Research Consortium — BARC— type 2, 3 or 5) occurred in 22 (4.7%) smokers and 85 (5.7%) non-smokers without significant differences between two groups (Adjusted HR 1.18; 95% CI 0.71–1.95; $p = 0.532$).

Patients who received long-term DAPT had a greater rate of BARC type 2, 3 or 5 events compared with those treated with short-term DAPT among non-smokers (8.0% vs 3.3%; HR 2.48, 95% CI 1.55–3.97; $p < 0.001$), whereas no formal significant difference was observed within smokers (5.4% vs 4.0%; HR 1.36, 95% CI 0.59–3.14; $p = 0.474$); however, the p-value for interaction between smoking status and DAPT duration was not significant ($P_{INT} = 0.220$) (Fig. 1), suggesting that smoking habit isn't a treatment modifier with respect to the bleeding risk in patients receiving different DAPT durations.

Sensitivity analysis on the per-protocol population was consistent in direction and magnitude with those derived from the intention-to-treat analysis (Fig. 1). Additional analysis performed dividing population in smokers, never-smokers and former-smokers confirmed absence of interaction between smoking status and DAPT duration for both death ($P_{INT} = 0.821$), death, MI or CVA ($P_{INT} = 0.367$), CV death or MI ($P_{INT} = 0.877$) and BARC type 2,3 or 5 ($P_{INT} = 0.889$).

There is conflicting evidence on the interaction between clopidogrel therapy and smoking status. In a selected STEMI population treated with fibrinolysis, smoking habit improved the effect of clopidogrel on TIMI-flow grade [3] and in a cohort of patients with acute coronary syndrome (ACS), it increased the effect of clopidogrel when double was compared to standard dose [4].

A large ACS registry reported similar efficacy and safety of early clopidogrel use in smokers and non-smoker patients [5]. Moreover, randomized trials comparing clopidogrel with other P2Y12 inhibitors observed a higher efficacy of prasugrel and ticagrelor compared with clopidogrel regardless of the smoking status [6,7]. Recently, a large trial failed to demonstrate a clinical advantage in smokers versus never-smokers in a clopidogrel versus aspirin treated population with stable coronary artery disease [8].

We analyzed an all-comer population including both stable and unstable patients undergoing PCI who were randomly allocated to different DAPT durations after coronary stenting. No significant interaction was observed for both efficacy and safety end-points between cigarette smoking and DAPT duration. A lower incidence of death, MI or CVA was observed in smokers compared with non-smokers in both long and short-term arms. Moreover, a trend toward a lower bleeding rate was noted in smokers compared with non-smokers in the long-term DAPT group. The better outcome of smokers with respect to both ischaemic and bleeding events was probably due to younger age and lower co-morbidity compared with non-smokers. This difference was less evident in short-term group, which may reflect a better matching in baseline risk factors between smokers and non-smokers observed in this arm. These results support the hypothesis that smoking status doesn't impact on clinical outcome of clopidogrel treated population. Smoking habit may just be a marker of lower global risk rather than a risk modifier in these patients.

This analysis was not pre-specified and the small number of patients included in the smoker group could affect the results; on the other hand, the several overall and sensitivity analyses performed converge in showing that the estimates can be interpreted with confidence.

In conclusion, smoking habit doesn't modify the impact of clopidogrel therapy duration on ischaemic and bleeding outcomes of patients undergoing coronary stenting.

Conflict of interest

Marco Valgimigli reports personal fees from Correvio, personal fees from Medtronic, personal fees from Eli lilly/DS, grants, personal fees, and non-financial support from Medicines company, non-financial support from Alvimedica, grants and personal fees from Terumo, personal

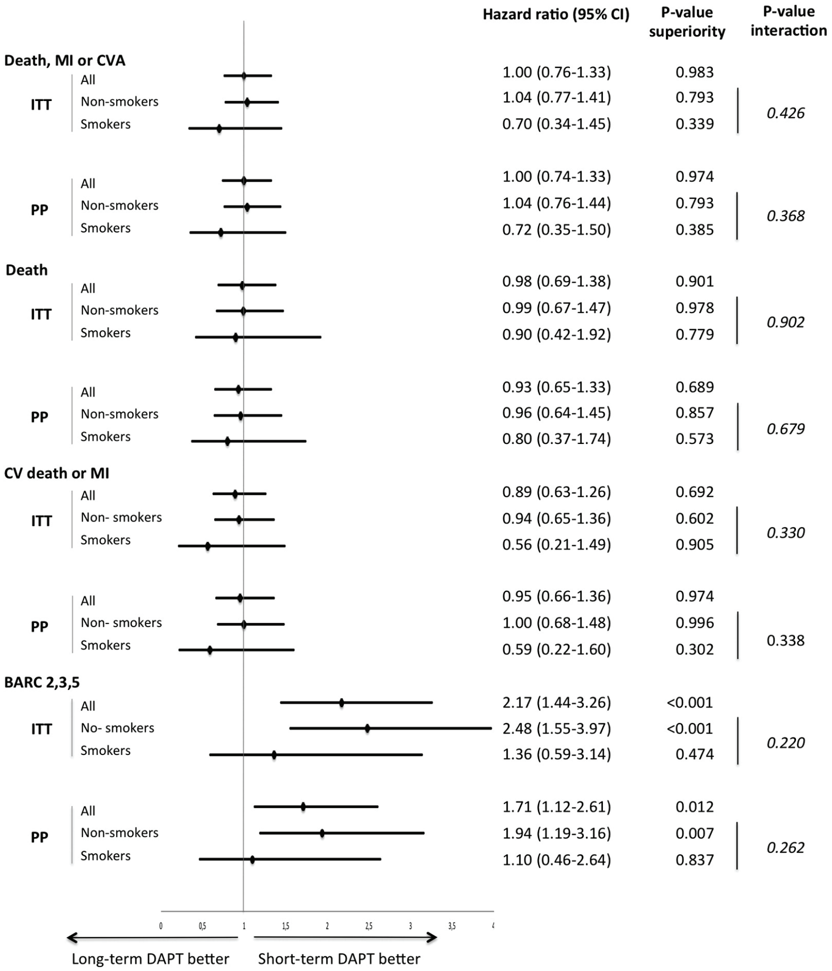

Fig. 1. Clinical outcomes. The overall population, non-smoker and smoker groups are shown for efficacy and safety end-points among patients randomly allocated to either 24 or 6-month dual antiplatelet therapy. BARC = Bleeding Academic Research Consortium; CV = cardiovascular; CVA = cerebrovascular accident; ITT = intention to treat; MI = myocardial infarction; PP = per protocol.

fees from Abbott Vascular, personal fees from St Jude, and outside the submitted work. The other authors have no conflict of interest to report.

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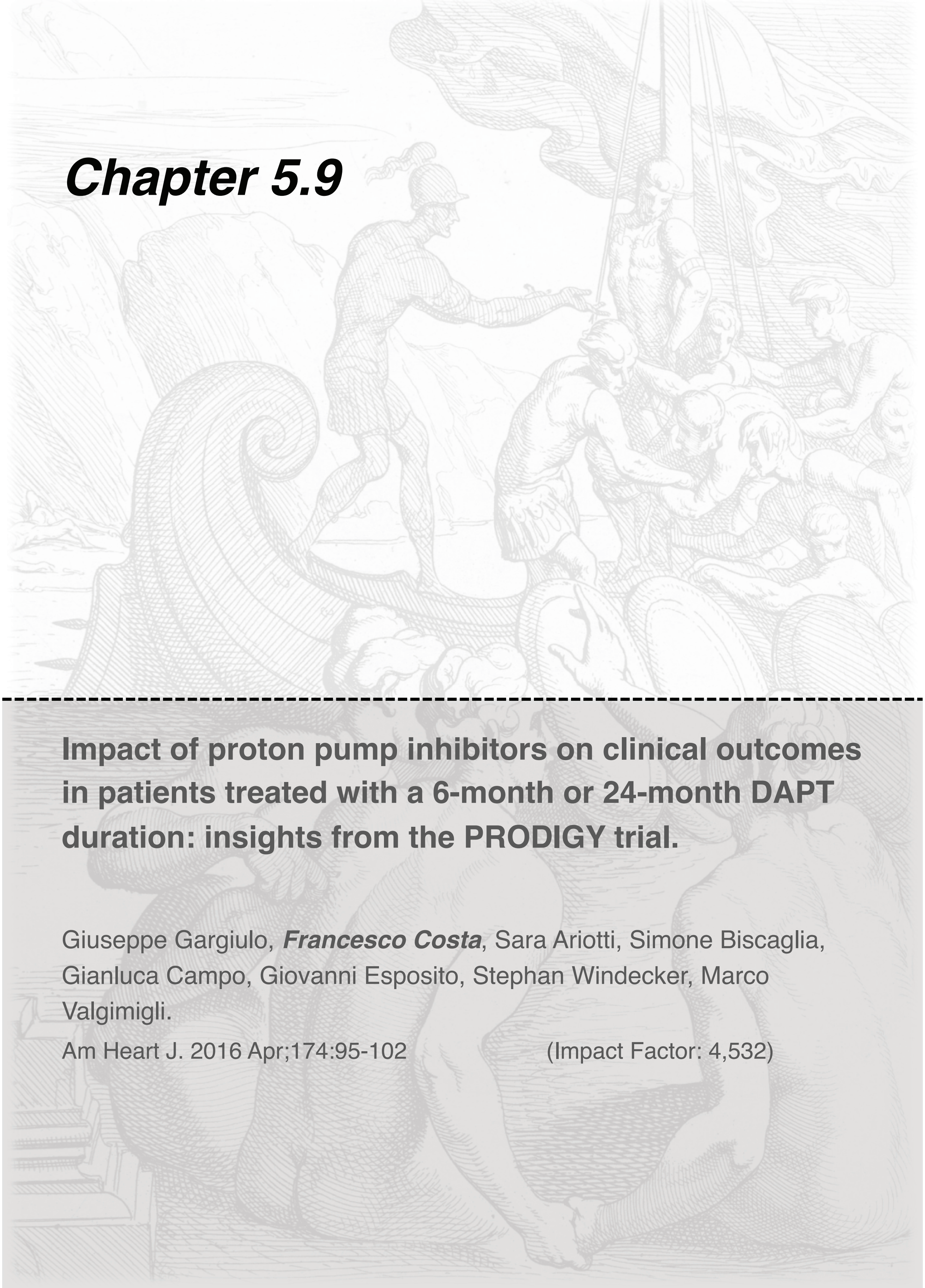

Chapter 5.9

Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6-month or 24-month DAPT duration: insights from the PRODIGY trial.

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Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6- or 24-month dual-antiplatelet therapy duration: Insights from the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY trial

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Background Proton pump inhibitors (PPIs) are frequently prescribed in combination with clopidogrel, but conflicting data exist as to whether PPIs diminish the efficacy of clopidogrel. We assessed the association between PPI use and clinical outcomes for patients treated with percutaneous coronary intervention (PCI) and dual-antiplatelet therapy (DAPT) with clopidogrel plus aspirin.

Methods and results In the PRODIGY trial, 1,970 patients were randomized to 6- or 24-month DAPT at 30 days from index procedure. Among them, 738 patients (37.5%) received PPI (mainly lansoprazole; 90.1%) at the time of randomization. Proton pump inhibitor users were older, were most likely to be woman, had a lower creatinine clearance, presented more frequently with acute coronary syndrome, and had a higher CRUSADE bleeding score. After adjustment, the primary efficacy end point (composite of all-cause death, myocardial infarction, and cerebrovascular accident) was similar between no PPI and PPI users (9.2% vs 11.5%, adjusted hazard ratio [HR] 1.051, 95% CI 0.788-1.400, *P* = .736). Bleeding rates did not differ between the 2 groups (Bleeding Academic Research Consortium type 2, 3, or 5: adjusted HR 0.996, 95% CI 0.672-1.474, *P* = .980). Net clinical adverse events were also similar in no PPI and PPI patients (12.9% vs 14.9%, adjusted HR 0.99, 95% CI 0.772-1.268, *P* = .93). Results remained consistent at sensitivity analysis when focusing on the 548 patients who remained on PPI for the whole study duration.

Conclusions The current findings suggest that the concomitant use of PPIs, when clinically indicated, in patients receiving clopidogrel is not associated with adverse clinical outcome. (Am Heart J 2016;174:95-102.)

Dual-antiplatelet therapy (DAPT) is the cornerstone of antithrombotic treatment in patients undergoing percutaneous coronary intervention (PCI), although its optimal duration still remains debated.[1-3] Notably, these patients are frequently treated with a proton pump inhibitor (PPI) to prevent gastrointestinal (GI) complications such as ulceration and bleeding or due to preexisting gastric disease.[4-7] However, clopidogrel is a prodrug that requires metabolic transformation in the liver by cytochrome P-450 isoenzyme (mainly CYP2C19) to elicit its antiplatelet effect. Proton pump inhibitors are also metabolized by CYP enzymes, leading to a potential inhibition of CYP2C19 (mainly omeprazole and esomeprazole) translating into reduced metabolic activation of clopidogrel when taken together. Indeed, some pharmacodynamic studies demonstrated a reduction of clopidogrel-induced antiplatelet effect when a PPI, mainly omeprazole, was concomitantly administered.[8-11] The Food and Drug Administration and the European Medicine Agency discourage the

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concomitant use of omeprazole and clopidogrel.[12,13] The clinical impact of the combined administration has been studied, but results have been discordant, with some studies reporting an increased risk of cardiovascular adverse events, whereas others did not confirm this concern.[5-7,11,14-23] Pooled analyses also provided inconclusive results, owing to the risk of misinterpretation related to poor-quality observational studies, thus supporting the need for high-quality studies.[14,15]

Therefore, the purpose of the present subanalysis of the PRODIGY randomized trial is to assess whether medical therapy with PPI compared to that without PPI may impact clinical outcomes in the setting of an all-comer population undergoing PCI and with a randomly allocated short (6 months) or prolonged (24 months) DAPT regimen, consisting of clopidogrel and aspirin.

Methods

The design and main findings of the PRODIGY have been previously reported.[1,24] Briefly, all-comer PCI patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation drug-eluting stent (DES) at 3 Italian sites were randomly allocated at 30 days to either 6 or 24 months of DAPT. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was stratified by center, ongoing ST-segment elevation myocardial infarction (MI), the presence of diabetes mellitus, and need for intervening of at least 1 in-stent restenotic lesion. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

Treatment protocol

All patients received aspirin (75-100 mg orally indefinitely) and clopidogrel (75 mg/d) according to the randomization scheme as follows: for either 6 months in the short DAPT arm or 24 months in the prolonged DAPT arm irrespective of the previously implanted stent type or indication for PCI.

Follow-up

The randomized patients returned for study visits at 30 days and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events and asked for the antiplatelet therapy compliance, and 12-lead electrocardiogram recordings were obtained.

Proton pump inhibitor use

The decision to start the treatment with a PPI as well as the type of PPI to be used was left at the physician's discretion and was not randomly assigned or mandated by protocol. Proton pump inhibitor use was identified both at study baseline and at each study follow-up visit, along with other concomitant medication use. For the present analysis, patients were defined as PPI users if on treatment at 30-day follow-up visit, at the time point when the randomization to short- versus long-term DAPT was performed. We performed sensitivity analyses to investigate the effect of PPI versus no PPI on clinical outcomes after excluding patients who had changed their initial status (no PPI or PPI) during the follow-up.

Table I. Baseline characteristics in PPI-treated versus non–PPI-treated patients

	No PPI (n = 1232)	PPI (n = 738)	*P*
Age (y)	68.1 (59.0-75.4)	71.2 (63.2-77.3)	<.0001
Male sex	79.2% (976)	72.5% (535)	.001
Body mass index (kg/m^2)	26.9 (24.7-29.4)	26.2 (24.2-29.3)	.923
Diabetes	24.8% (305)	23.3% (172)	.461
Insulin dependent	5.7% (70)	6.0% (44)	
Hypertension	71.3% (879)	72.5% (535)	.486
Hyperlipidemia	55.3% (681)	53.8% (397)	.596
Current cigarette use	24.4% (301)	22.6% (167)	.380
Creatinine clearance (mL/min)	77.7 (58.3-99.2)	69.5 (53.3-91.0)	<.0001
Prior MI	26.1% (321)	27.0% (199)	.520
Prior PCI	18.6% (229)	16.1% (119)	.180
LVEF	55.0 (45-60)	50.0 (43-60)	.080
Clinical presentation			
Stable angina pectoris	30.5% (376)	17.5% (129)	<.0001
ACS	69.5% (856)	82.5% (609)	
STEMI	30.2% (372)	37.4% (276)	.001
NSTEMI	21.3% (262)	25.5% (188)	.031
Unstable angina	18.0% (222)	19.6% (145)	.369
Multivessel disease	70.5% (868)	69.2% (511)	.569
No. of treated lesions	1 (1-2)	1 (1-2)	.370
≥2 treated lesions	37.3% (459)	37.5% (277)	.900
≥3 treated lesions	11.8% (145)	10.6% (78)	
Multivessel intervention	26.5% (327)	27.0% (199)	.837
At least 1 complex lesion (type B2 or C)*	67.0% (825)	65.2% (481)	.416
Total ACC/AHA score†	3 (2-5)	3 (2-4)	.600
CRUSADE score	24 (16-34)	27 (18-38)	<.0001
Aspirin	100% (1232)	100% (738)	>.999
Clopidogrel	98.8% (1230)	99.9% (737)	.882
Statin	90.3% (1093)	90.9% (671)	.627

Abbreviations: *LVEF*, Left ventricular ejection fraction; *STEMI*, ST-segment elevation myocardial infarction; *NSTEMI*, non–ST-segment elevation myocardial infarction; *ACC*, American College of Cardiology; *AHA*, American Heart Association.
*According to the American College of Cardiology/American Heart Association coronary lesion classification.
†Type A stenoses were coded 1 point; type B1 stenoses, 2 points; type B2 stenoses, 3 points; and type C stenoses, 4 points.

Study end points

The primary efficacy end point of the PRODIGY trial was the composite of death, MI, or cerebrovascular accident (CVA), whereas the key safety end point included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. The net effect on the combined ischemic and bleeding complications was obtained by 2 net adverse clinical event (NACE) end points that were generated by

Table II. Baseline characteristics in PPI versus no PPI treated patients stratified for the randomly allocated DAPT duration

	24-m clopidogrel			6-m clopidogrel		
	No PPI (n = 612)	PPI (n = 375)	*P*	No PPI (n = 620)	PPI (n = 363)	*P*
Age (y)	67.9 (58.9-74.5)	71.8 (63.8-77.7)	<.0001	68.1 (59.2-76.6)	70.1 (61.7-76.9)	.04
Male sex	80.6% (493)	72.3% (271)	.003	77.9% (483)	72.7% (264)	.070
Body mass index (kg/m^2)	27.0 (24.9-29.4)	26.0 (23.9-29.3)	.450	26.8 (24.2-29.2)	26.4 (24.2-29.3)	.200
Diabetes	24.7% (151)	24.8% (93)	.900	24.9% (154)	21.8% (79)	.290
Insulin dependent	6.2% (38)	5.6% (21)		5.2% (32)	6.3% (23)	
Hypertension	71.4% (437)	75.7% (284)	.140	71.3% (442)	69.1% (251)	.410
Hyperlipidemia	56.5% (346)	55.2% (207)	.680	54.0% (335)	52.3% (190)	.640
Current cigarette use	23.9% (146)	20.3% (176)	.200	25.3% (156)	25.1% (91)	.450
Creatinine clearance (mL/min)	77.7 (58.1-102.7)	68.9 (53.0-91.9)	.001	77.8 (58.4-96.5)	70.7 (53.8-90.6)	.002
Prior MI	28.3% (173)	25.9% (97)	.410	24.8% (154)	28.1% (102)	.300
Prior PCI	20.9% (128)	16.3% (61)	.070	17.7% (110)	16.5% (60)	.490
LVEF	54.0 (43-60)	55.0 (45-60)	.520	55.0 (45-60)	50.0 (40-60)	.002
Clinical presentation						
Stable angina pectoris	31.2% (191)	17.1% (64)	<.0001	29.8% (185)	17.9% (65)	<.0001
ACS	68.8% (421)	82.9% (311)		70.2% (435)	82.1% (298)	
STEMI	31.0% (190)	34.9% (131)	.210	29.4% (182)	39.9% (145)	.001
NSTEMI	21.1% (129)	25.9% (97)	.080	21.5% (133)	25.1% (91)	.190
Unstable Angina	16.7% (102)	22.1% (83)	.03	19.4% (120)	17.1% (62)	.370
Multivessel disease	70.4% (431)	70.4% (264)	.990	70.5% (437)	68.0% (247)	.420
No. of treated lesions	1 (1-2)	1 (1-2)	.320	1 (1-2)	1 (1-2)	.780
≥2 treated lesions	37.4% (229)	36.3% (136)	.720	37.1% (230)	38.8% (141)	.590
≥3 treated lesions	11.4% (70)	10.1% (38)	.520	12.1% (75)	11.0% (40)	.610
Multivessel intervention	25.8% (158)	25.3% (95)	.870	27.3% (169)	28.7% (104)	.640
At least 1 complex lesion (type B2 or C)*	67.3% (412)	61.3% (230)	.060	66.6% (413)	69.1% (251)	.410
Total ACC/AHA score†	3 (2-4)	3 (2-4)	.600	3 (2-5)	3 (2-5)	.840
CRUSADE score	24 (15-35)	28 (19-38)	<.0001	24 (18-33)	27 (18-38)	.004
Aspirin	100% (612)	100% (375)	>.999	100% (620)	100% (365)	>.999
Clopidogrel	99.8% (611)	99.7% (374)	.726	99.8% (619)	100% (363)	.444
Statin	89.2% (539)	90.4% (339)	.560	91.3% (554)	91.5% (332)	.920

* According to the ACC/AHA coronary lesion classification.
† Type A stenoses were coded 1 point; type B1 stenoses, 2 points; type B2 stenoses, 3 points; and type C stenoses, 4 points.

combining the primary efficacy end point of death, MI, or CVA with either the primary safety end point of BARC type 2, 3, or 5 bleeding or with BARC type 3 or 5 events. Other end points included each component of the primary efficacy end point, cardiovascular death, stent thrombosis (ST) defined based on the Academic Research Consortium criteria, and BARC type 3 or 5 bleeding. Other safety end points included bleeding events adjudicated according to the Thrombolysis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries scales. All study end point definitions were previously reported.

All end points were confirmed based on documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment-group assignments. The time frame of interest for the primary end point was from 30 days (ie, after the primary endpoint randomization) to 24 months.

Statistical analysis

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (interquartile range). Continuous variables were compared between randomized groups using the Wilcoxon rank sum test, whereas for binary variables the χ^2 test was used.

Hazard ratios (HRs) with 95% CIs were calculated for no PPI versus PPI treated patients (ie, values >1 indicated increased hazard in the PPI group) with a proportional hazards model. Cox regression was used for multivariate analysis. Clinical and angiographic characteristics that were imbalanced at a nominal 5% significance level between the 2 groups treated or not treated with PPI were identified and included the final adjusted model; these included sex, age, creatinine clearance, clinical presentation, and CRUSADE score. As sensitivity analyses, adjusted outcomes were also evaluated after excluding patients who had modified their PPI status (assumption of PPI in those with no PPI therapy at 30 days or interruption of PPI in those with PPI therapy at 30 days) during follow-up. Further sensitivity analyses included the assessment of adjusted outcomes with landmark analysis at 6 to 24 months and the analysis restricted to those patients treated with lansoprazole as PPI type (exclusion of other PPI types).

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Interaction testing was performed to determine whether the effect of DAPT duration was consistent irrespective of PPI treatment on the primary and secondary end points of the study. This was performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A 2-sided *P* value of <.05 was considered significant. All analyses were based on the intention-to-treat principle and were performed with SPSS, version 21.0 (SPSS, Inc, Chicago, IL).

For the present analysis, no extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

Results

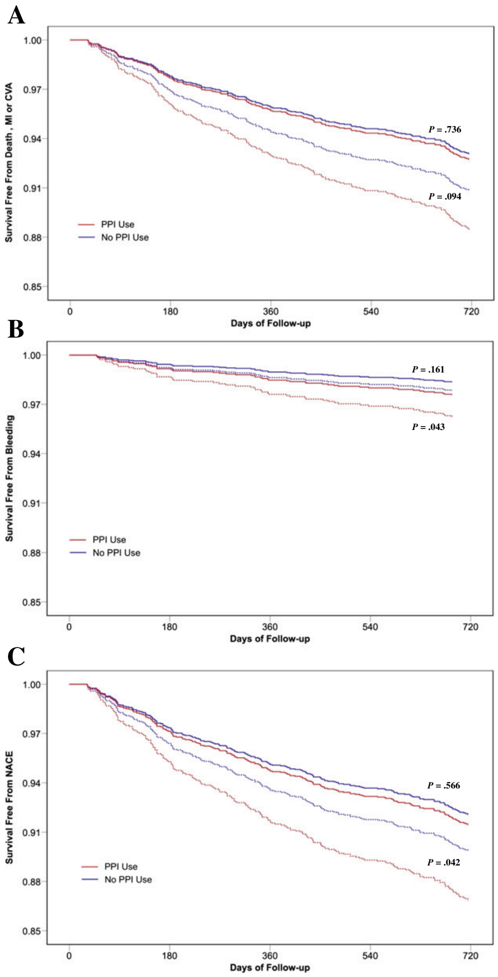
Among 1,970 patients randomized to 6- versus 24-month DAPT at 30 days from the PCI, 738 patients (37.5%) were receiving a PPI. Most of them were treated with lansoprazole (671 patients, 90.9%), whereas the others received pantoprazole (56 patients, 7.6%) and few patients received other PPI types (omeprazole, esomeprazole, and rabeprazole, 1.5%).

Baseline characteristics of population with PPI and without PPI are summarized in Table I, whereas Table II describes their characteristics in the setting of the 2 randomized arms of DAPT regimens (24 vs 6 months). Compared with patients who did not receive PPI, those receiving PPI were older, were more likely female, had a lower creatinine clearance, presented more frequently with acute coronary syndrome (ACS), and had a higher CRUSADE bleeding score (Tables I and II). The primary efficacy end point (composite of all-cause death, MI, and CVA) was similar between patients with PPI and without PPI use (9.2% vs 11.5%, adjusted HR 1.051, 95% CI 0.788-1.400, *P* = .736) (Figure 1). Results were consistent across other secondary end points as reported in Table III. Safety end points of bleeding did not differ between the 2 groups (BARC type 2, 3, or 5: adjusted HR 0.996, 95% CI 0.672-1.474, *P* = .980; BARC type 3 or 5: adjusted HR 1.478, 95% CI 0.856-2.553, *P* = .160) (Figure 1 and Table III). Overall, major bleeding evaluated with different definitions was more frequent in PPI users compared with those without PPI (BARC 3 or 5: 3.7% vs 2.1%, TIMI major 1.5% vs 0.9%, GUSTO moderate or severe 3.7% vs 1.9%); however, after adjustment for confounding factors, none of them remained significant (Table III). The composite of efficacy and safety end points in the NACE was also similar in no PPI and PPI patients (12.9% vs 14.9%, adjusted HR 0.99, 95% CI 0.772-1.268, *P* = .93) (Figure 1 and Table III).

Finally, there was no signal for heterogeneity between PPI use and explored clinical end points with respect to randomized DAPT duration (Figure 2, Supplementary Figure 1, Table IV, and Supplementary Tables I-III).

At sensitivity analyses, PPI therapy during follow-up was taken into account (1 month: 738 PPI patients 37%, 6 months: 685 PPI patients 35%, 12 months: 690 PPI patients 35%, 18 months: 709 PPI patients 36%, 24 months: 734 PPI patients 37%). A specific analysis of clinical outcomes was also performed in patients who remained consistently on a PPI throughout the follow-up period and excluding those who had started or interrupted PPI

Figure 1



Survival free from ischemic and bleeding events according to PPI treatment. Cox proportional model plot for the primary end point of death for all causes, MI, and CVA (**A**), bleeding defined as BARC class 3 or 5 (**B**), and NACEs (**C**) in patients treated or not treated with PPI. Dashed lines represent the unadjusted risk model. Solid lines represent the adjusted risk model.

Table III. Clinical outcomes in PPI-treated versus non–PPI-treated patients

	No PPI (n = 1232)	PPI (n = 738)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Primary efficacy end point						
Death for any cause, MI, or CVA	113 (9.2)	85 (11.5)	1.272 (0.960-1.685)	.094	1.051 (0.788-1.400)	.736
Secondary efficacy end points						
Death for any cause or MI	107 (8.7)	75 (10.2)	1.178 (0.877-1.582)	.278	0.957 (0.708-1.293)	.773
Death for any cause	77 (6.2)	53 (7.2)	1.150 (0.811-1.632)	.433	0.918 (0.642-1.311)	.636
Death for cardiovascular cause	44 (3.6)	29 (3.9)	1.101 (0.689-1.759)	.688	0.865 (0.534-1.400)	.554
MI	48 (3.9)	32 (4.3)	1.115 (0.713-1.744)	.633	0.941 (0.597-1.485)	.790
Definite or probable ST	19 (1.5)	9 (1.2)	0.780 (0.353-1.723)	.539	0.682 (0.306-1.523)	.350
Definite, probable, or possible ST	47 (3.8)	37 (5.0)	1.320 (0.858-2.030)	.207	1.028 (0.662-1.597)	.900
Safety end points						
BARC classification						
Key safety end point (type 2, 3, or 5)	64 (5.2)	43 (5.8)	1.127 (0.766-1.659)	.545	0.996 (0.672-1.474)	.980
Type 3 or 5	26 (2.1)	27 (3.7)	1.746 (1.019-2.992)	.043	1.478 (0.856-2.553)	.161
TIMI classification						
Minor	10 (0.8)	10 (1.4)	1.680 (0.699-4.036)	.246	1.434 (0.589-3.492)	.428
Major	11 (0.9)	11 (1.5)	1.679 (0.728-3.873)	.224	1.465 (0.627-3.421)	.378
Minor or major	21 (1.7)	21 (2.8)	1.684 (0.920-3.084)	.091	1.453 (0.786-2.687)	.234
GUSTO classification						
Moderate	13 (1.1)	14 (1.9)	1.803 (0.848-3.836)	.126	1.449 (0.676-3.110)	.341
Severe	12 (1.0)	13 (1.8)	1.820 (0.830-3.988)	.135	1.626 (0.732-3.613)	.232
Moderate or severe	24 (1.9)	27 (3.7)	1.893 (1.092-3.281)	.023	1.582 (0.905-2.763)	.107
NACE						
Death for any cause; MI; CVA; or BARC 2, 3, or 5 bleeding	159 (12.9)	110 (14.9)	1.172 (0.919-1.494)	.202	0.989 (0.772-1.268)	.933
Death for any cause, MI, CVA, or BARC 3 or 5 bleeding	125 (10.1)	97 (13.1)	1.317 (1.010-1.717)	.042	1.083 (0.826-1.419)	.566

Abbreviations: *GUSTO*, Global Use of Strategies to Open Occluded Coronary Arteries.

therapy. Results remained robust showing the absence of significant differences for ischemic and bleeding events (Supplementary Table IV). This was further confirmed by landmark analyses (Supplementary Table V) and by restriction of analysis to lansoprazole as PPI (Supplementary Table VI).

Discussion

The present post hoc analysis from the PRODIGY randomized trial investigated the impact of concomitant PPI use on clinical outcomes in all-comer patients undergoing PCI and receiving DAPT with clopidogrel as thienopyridine component.

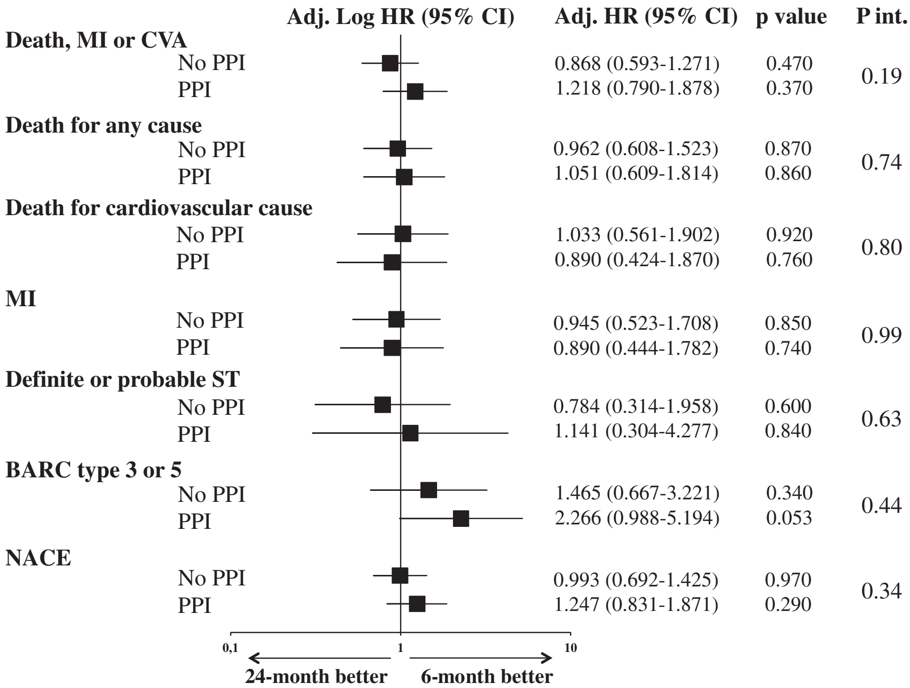
Although, at univariate analysis, PPI use was associated with an increased risk of ischemic and bleeding events, after multivariate adjustment, PPI therapy was no longer related to different rates of ischemic events, bleeding, or NACE at 2 years irrespective of the short or prolonged regimen of DAPT. The findings of our study are consistent with the results of the COGENT trial, showing thus no association of PPI use with increased risk of ischemic events.

Several studies assessing the inhibition of platelet aggregation suggested that PPIs may significantly reduce the antiplatelet effect of clopidogrel when the 2 drugs are coadministered.[8-11] In particular, some PPIs (omeprazole and esomeprazole) highly inhibit CYP2C19 isoenzyme, whereas other PPIs are weak inhibitors (lansoprazole) or do not inhibit this isoenzyme (pantoprazole). However, the findings from pharmacodynamic studies may not necessarily translate into differences in clinical outcomes, and the design and quality of studies might be the major determinant of such contrasting evidence.[14,15] Indeed, most studies supporting an increased risk of cardiovascular ischemic events when using any type of PPI in patients on clopidogrel are observational studies. Conversely, randomized trials and propensity score–matched studies did not support such concerns. Nonetheless, new evidence from a recent US analysis of >60,000 patients with gastroesophageal reflux disease exposed to PPIs raised new questions by reporting a 1.2-fold increased risk of MI and a 2-fold increased risk of cardiovascular mortality, irrespective of clopidogrel use.[20]

Proton pump inhibitor use was associated with an increased risk of Major Adverse Cardiovascular Events and MI but not death and target vessel revascularization in the subgroup analysis of the BASKET trial.[22] Similarly, the CAPRIE trial showed a higher rate of ischemic events among patients treated with PPIs and clopidogrel, whereas the most recent subanalysis from the ADAPT-DES trial showed increased rate of Major Adverse Cardiovascular Events due to death and target vessel revascularization rather than MI or ST.[17,23]

In contrast, the dedicated COGENT trial did not support these findings.[16] This trial randomly assigned patients with an indication for DAPT to receive clopidogrel in combination with either omeprazole or placebo, in addition to

Figure 2



Forest plots for clinical outcomes in short versus prolonged DAPT duration according to PPI treatment. Proton pump inhibitor and no-PPI subgroups are shown, with HRs and 95% CIs, for the primary end point of death for any cause, MI, or CVA; death for any cause; cardiovascular death; MI; definite or probable stent thrombosis; BARC type 3 or 5 bleeding; and NACEs among patients randomly assigned to either the 6- or 24-month DAPT.

aspirin. The composite of cardiovascular death, MI, revascularization, or stroke did not differ, but GI events were less frequent in the omeprazole group.[16]

In the subgroup analyses of the PRINCIPLE and TRITON-TIMI 38 trials, a significant impact of PPI therapy on reducing the effect of clopidogrel on platelet aggregation was further substantiated. However, the pharmacodynamic changes did not translate into adverse clinical outcomes.[11]

Our study is in line with and importantly adds to previous evidence indicating that the use of PPIs, largely consisting of lansoprazole, in conjunction with clopidogrel is safe. In addition, this observation held true in the 2 randomized groups of short- versus long-term DAPT, indicating that PPI therapy does not increase ischemic events irrespective of whether clopidogrel is administered for short periods (ie, 6 months) or prolonged times (ie, 24 months). The incidence of ST was low and did not differ in patients with or without concomitant PPI use.

In the subgroup analysis of the PLATO trial on PPI use, the association between PPI use and clinical adverse events in patients treated with clopidogrel was likely due to confounding (observed also in those receiving ticagrelor and in those receiving non-PPI GI drugs), with PPI use emerging as a marker for, rather than a cause of higher rates of cardiovascular adverse events.[18] Interestingly, the role of confounding factors appeared to also be relevant in the present study as the PPI population showed an increased risk of both ischemic and bleeding events. However, after multivariate adjustment, differences in outcomes were no longer present.

Proton pump inhibitors are often prescribed in patients with DAPT to reduce bleeding complications or due to specific clinical indication (ie, gastric disease). Generally, the PPI use is left to the discretion of clinicians, and often, a selection of patients is performed with those receiving PPI being at increased risk for ischemic and bleeding events. This explains at least in part the results of observational

Table IV. Adjusted clinical outcomes in PPI-treated versus non–PPI-treated patients stratified for the randomly allocated DAPT duration

	24-m clopidogrel				6-m clopidogrel				
	No PPI (n = 612)	PPI (n = 375)	Adjusted HR (95% CI)	*P*	No PPI (n = 620)	PPI (n = 363)	Adjusted HR (95% CI)	*P*	P_{int}
Primary efficacy end point									
Death for any cause, MI, or CVA	52 (8.5)	48 (12.8)	1.375 (0.916-2.064)	.125	61 (9.8)	38 (10.2)	0.852 (0.562-1.291)	.449	.19
Secondary efficacy end points									
Death for any cause or MI	48 (7.8)	40 (10.7)	1.218 (0.789-1.881)	.372	59 (9.5)	35 (9.6)	0.824 (0.538 -1.261)	.372	.33
Death for any cause	37 (6.0)	28 (7.5)	1.070 (0.645-1.777)	.792	40 (6.5)	25 (6.9)	0.865 (0.519-1.441)	.578	.74
Death for cardiovascular cause	22 (3.6)	14 (3.7)	0.877 (0.437-1.757)	.711	22 (3.5)	15 (4.1)	0.974 (0.494-1.923)	.941	.80
MI	23 (3.8)	16 (4.3)	0.980 (0.505-1.904)	.953	25 (4.0)	16 (4.4)	0.923 (0.490-1.739)	.803	.99
Definite or probable ST	8 (1.3)	5 (1.3)	0.718 (0.231-2.225)	.566	11 (1.8)	4 (1.1)	0.652 (0.204-2.085)	.471	.63
Definite, probable, or possible ST	19 (3.1)	19 (5.1)	1.431 (0.743-2.755)	.283	28 (4.5)	18 (5.0)	0.868 (0.473-1.593)	.647	.34
Safety end points									
BARC classification									
Key safety end point (type 2, 3, or 5)	41 (6.7)	32 (8.5)	1.227 (0.762-1.977)	.400	23 (3.7)	11 (3.0)	0.661 (0.321-1.362)	.261	.34
Type 3 or 5	15 (2.5)	19 (5.1)	1.881 (0.937-3.777)	.076	11 (1.8)	8 (2.2)	1.048 (0.418-2.627)	.920	.44
TIMI classification									
Minor	7 (1.1)	4 (1.1)	0.741 (0.212-2.592)	.639	3 (0.5)	6 (1.7)	3.572 (0.861-14.827)	.080	.15
Major	6 (1.0)	10 (2.7)	2.569 (0.905-7.290)	.076	5 (0.8)	1 (0.3)	0.264 (0.031-2.265)	.225	.11
Minor or major	13 (2.1)	14 (3.7)	1.559 (0.717-3.391)	.262	8 (1.3)	7 (1.9)	1.388 (0.479-3.739)	.579	.91
GUSTO classification									
Moderate	8 (1.3)	9 (2.4)	1.487 (0.562-3.934)	.424	5 (0.8)	5 (1.4)	1.488 (0.424-5.222)	.535	.96
Severe	6 (1.0)	10 (2.7)	2.569 (0.905-7.288)	.076	6 (1.0)	3 (0.8)	0.705 (0.175-2.843)	.623	.26
Moderate or severe	13 (2.1)	19 (5.1)	2.079 (1.007-4.292)	.048	11 (1.8)	8 (2.2)	1.050 (0.419-2.633)	.917	.31
NACE									
Death for any cause; MI; CVA; or BARC 2, 3, or 5 bleeding	87 (14.2)	65 (17.3)	1.140 (0.818-1.589)	.440	72 (11.6)	45 (12.4)	0.875 (0.599-1.277)	.489	.60
Death for any cause, MI, CVA, or BARC 3 or 5 bleeding	61 (10.0)	55 (14.7)	1.329 (0.911-1.939)	.141	64 (10.3)	42 (11.6)	0.928 (0.625-1.379)	.712	.34

studies on PPI use and increased ischemic risk. In the present study, PPIs were prescribed to patients with a greater bleeding risk, as indicated by a more advanced age, more female patients, and ACS, a worse renal function and a higher CRUSADE score. However, after adjustment for these confounding factors, the differences between PPI and no-PPI populations were not clinically relevant for most clinical outcomes. Although the COGENT trial excluded patients with prior indication for PPI use or H2-receptor antagonists and patients at higher risk for GI bleeding, the results of the present study can be extended to an all-comer population of patients undergoing PCI and DAPT therapy.

Limitations

This is a post hoc not randomized and not prespecified analysis of the PRODIGY trial, and the prescription of a PPI was left to the physician's discretion.

Rates of overall but not specifically GI bleeding were evaluated and available for this analysis, so potential benefits of PPI on reducing GI bleeding events could not be analyzed.

Although multivariate adjustment was performed, it cannot be excluded that unknown/unmeasured factors may have impacted findings.

Data on PPI dosage were not prospectively collected, so it was not possible to make specific analysis on dose-dependent effects.

"In the PRODIGY, lansoprazole was by far the most frequently used PPI. Hence, it remains unclear whether our findings may be extrapolated to other PPIs such as omeprazole or esmoprazole."

Genetic analysis to test the predisposition for reduced clopidogrel responsiveness was not available. Therefore, it cannot be excluded that PPIs may have a different impact on outcomes in this subgroup of patients.

Conclusion

Overall, PPI use was not associated with an increased risk of cardiovascular events in all-comer patients undergoing PCI and receiving DAPT. Our findings do not support the need to avoid concomitant use of PPIs and DAPT with aspirin plus clopidogrel, when clinically indicated.

Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.01.015.

5

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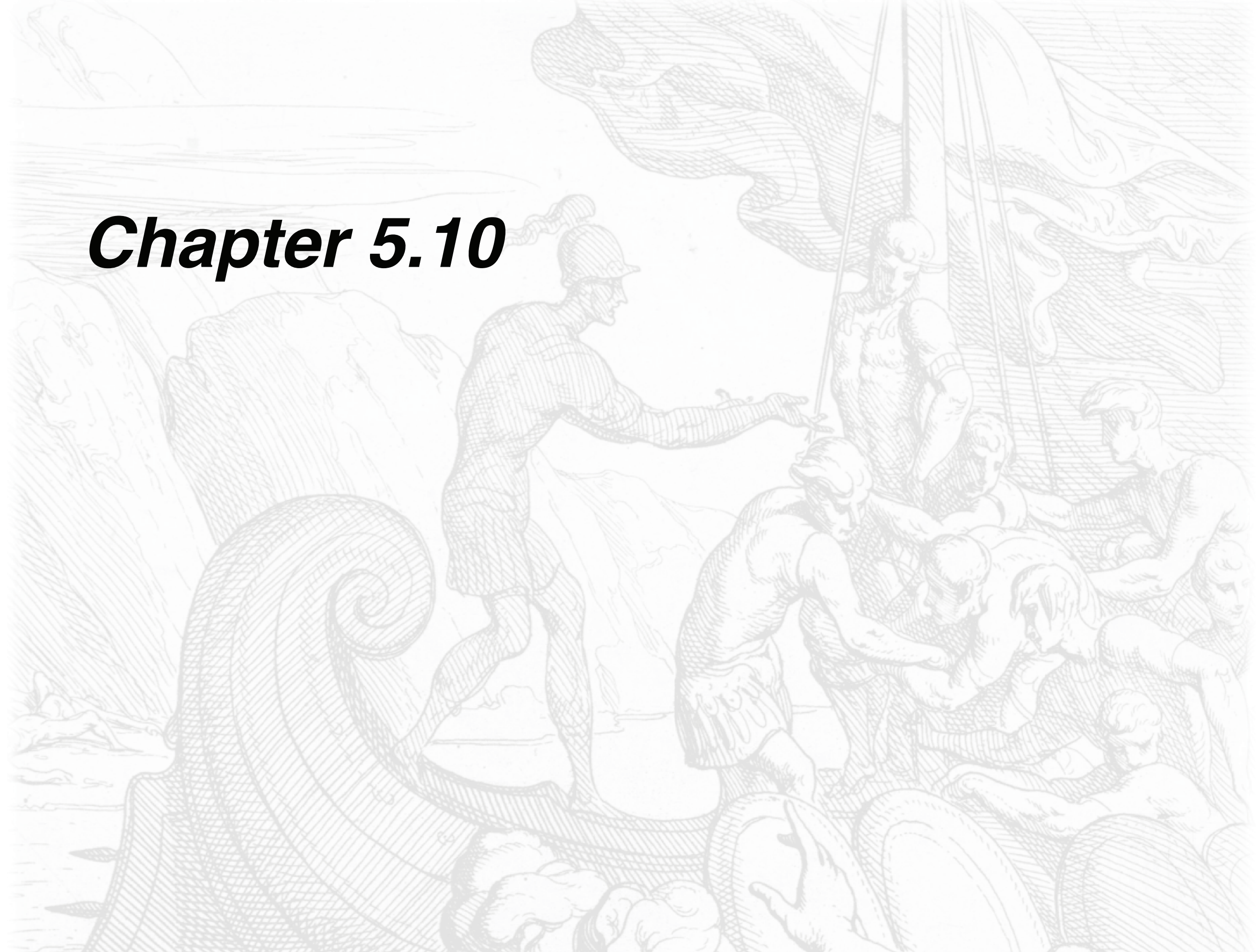
Chapter 5.10



The Incremental Value of the CRUSADE, ACUITY and HAS-BLED Risk Scores for the Prediction of Hemorrhagic (and Ischemic Adverse) Events after Coronary Stent Implantation in Patients Undergoing Long or Short Duration of Dual Antiplatelet Therapy.

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Incremental Value of the CRUSADE, ACUITY, and HAS-BLED Risk Scores for the Prediction of Hemorrhagic Events After Coronary Stent Implantation in Patients Undergoing Long or Short Duration of Dual Antiplatelet Therapy

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Background—Multiple scores have been proposed to stratify bleeding risk, but their value to guide dual antiplatelet therapy duration has never been appraised. We compared the performance of the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines), ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), and HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) scores in 1946 patients recruited in the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) and assessed hemorrhagic and ischemic events in the 24- and 6-month dual antiplatelet therapy groups.

Methods and Results—Bleeding score performance was assessed with a Cox regression model and C statistics. Discriminative and reclassification power was assessed with net reclassification improvement and integrated discrimination improvement. The C statistic was similar between the CRUSADE score (area under the curve 0.71) and ACUITY (area under the curve 0.68), and higher than HAS—BLED (area under the curve 0.63). CRUSADE, but not ACUITY, improved reclassification (net reclassification index 0.39, P=0.005) and discrimination (integrated discrimination improvement index 0.0083, P=0.021) of major bleeding compared with HAS-BLED. Major bleeding and transfusions were higher in the 24- versus 6-month dual antiplatelet therapy groups in patients with a CRUSADE score >40 (hazard ratio for bleeding 2.69, P=0.035; hazard ratio for transfusions 4.65, P=0.009) but not in those with CRUSADE score ≤40 (hazard ratio for bleeding 1.50, P=0.25; hazard ratio for transfusions 1.37, P=0.44), with positive interaction (P_{int}=0.05 and P_{int}=0.01, respectively). The number of patients with high CRUSADE scores needed to treat for harm for major bleeding and transfusion were 17 and 15, respectively, with 24-month rather than 6-month dual antiplatelet therapy; corresponding figures in the overall population were 67 and 71, respectively.

Conclusions—Our analysis suggests that the CRUSADE score predicts major bleeding similarly to ACUITY and better than HAS BLED in an all-comer population with percutaneous coronary intervention and potentially identifies patients at higher risk of hemorrhagic complications when treated with a long-term dual antiplatelet therapy regimen.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00611286. **(*J Am Heart Assoc*. 2015;4: e002524 doi: 10.1161/JAHA.115.002524)**

Key Words: ACUITY • bleeding risk score • clopidogrel • CRUSADE • duration of dual antiplatelet therapy • HAS-BLED

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/4/12/e002524/suppl/DC1

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Bleeding is a common adverse event after percutaneous coronary intervention and is associated with increased morbidity and mortality.[1–4] Bleeding predictors have been described extensively; they are related mostly to the patient's clinical characteristics, the invasiveness of the procedure, and the potency of the antithrombotic regimen. Antithrombotic therapies after coronary intervention reduce ischemic events but invariably increase bleeding risk, which in turn may adversely affect short- and long-term outcomes.[5,6] International guidelines recommend careful evaluation of both ischemic and bleeding risk based on the patient's clinical characteristics[7,8]; however, evidence supporting the individualization of antithrombotic therapy is still limited. In particular, the potency and duration of dual antiplatelet therapy (DAPT) after coronary stenting are currently based mainly on the patient's clinical presentation (ie, acute coronary syndrome or stable coronary artery disease) and the type of stent used (ie, drug-eluting or bare metal stent), with evanescent indications based on the patient's bleeding risk.[7–9] Many bleeding risk scores have been validated for the prediction of early and late bleeding events, and some have been tested on large cohorts with acute coronary syndrome, demonstrating reasonably good performance.[10–12] Among them, the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA [American College of Cardiology/American Heart Association] Guidelines) score has been validated in 17 857 patients with non–ST-segment elevation myocardial infarction (MI), and its predictive capability was consistent in terms of hemorrhagic risks in patients taking ≥2 antithrombotic medications.[10] Our study sought to compare the predictive performance of the CRUSADE, ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), and HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR [international normalized ratio], Elderly, Drugs/Alcohol Concomitantly) risk scores with respect to major bleeding events in an all-comer population treated with coronary stent. We also intended to determine the incidence of major bleeding after 24-month rather than 6-month DAPT in the subgroups of patients with high and low to intermediate bleeding risk.

Methods

The design and main study findings for the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) were reported previously.[5] In brief, all patients receiving a balanced mixture of stents with varying anti–intimal hyperplasia potency and including both first- and second-generation drug-eluting stents at 3 Italian sites were randomly allocated at 30 days to either 6 or 24 months of DAPT. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was performed at 30 days and stratified by center, ongoing ST-segment elevation MI, presence of diabetes mellitus, and need for intervention on at least 1 in-stent restenotic lesion. The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

Treatment Protocol

All patients received aspirin (80–160 mg orally, indefinitely) and clopidogrel (75 mg/day) according to the following randomization scheme: either 6 months in the short DAPT group or 24 months in the prolonged DAPT arm, regardless of the previously implanted stent type or indication for the coronary procedure.

Follow-up

All randomized patients returned for study visits at 30 days and then every 6 months for up to 2 years. During follow-up visits, patients were examined and assessed for adverse events and asked about antiplatelet therapy compliance; in addition, 12-lead ECG recordings were obtained.

Study End Points

The primary objective of this analysis was to compare the predictive performance of the CRUSADE, ACUITY, and HAS-BLED bleeding risk scores with respect to major bleeding events, adjudicated according to Bleeding Academic Research Consortium (BARC) class 3 or 5, among patients recruited to the PRODIGY trial. Further sensitivity analysis evaluated the consistency of the results obtained with the BARC classification with other widely accepted bleeding definitions, including the Thrombolysis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Arteries (GUSTO) scales. The CRUSADE, ACUITY, and HAS-BLED bleeding risk scores were calculated, as reported previously,[10–12] taking into account the following exceptions: For the ACUITY score, given the exclusive use of unfractionated heparin as an anticoagulant in the PRODIGY trial, the "antithrombotic medication" variable was set to zero; for the HAS-BLED score, given that patients with an indication for long-term anticoagulation were not included in the PRODIGY trial, the "labile INR" variable was set to zero.

To assess the effect of high bleeding risk status in the 24- and 6-month DAPT treatment arms, we selected the high-risk

Table 1. Baseline Characteristics

Characteristic	Major Bleeding (n=53)	No Major Bleeding (n=1893)	*P* Value
Age, y	76.3 (71.3–81.3)	68.9 (59.8–76.1)	<0.0001
Female sex	28.3% (15/53)	23.1% (438/1893)	0.38
Body mass index, kg/m^2	25.4 (24.0–28.7)	26.6 (24.3–29.4)	0.30
Diabetes	34.0% (18/53)	24.0% (455/1893)	0.09
Insulin dependent	7.5% (4/53)	5.8% (110/1893)	
Hypertension	77.4% (41/53)	71.7% (1358/1893)	0.37
Hyperlipidemia	52.8% (28/53)	54.9% (1039/1893)	0.76
Current cigarette use	13.2% (7/53)	24.3% (459/1893)	0.06
Creatinine clearance, mL/min	49.5 (36.3–65.5)	75.7 (57.0–96.5)	<0.0001
Prior myocardial infarction	41.5% (22/53)	25.9% (491/1893)	0.01
Prior PCI	24.2% (13/53)	18.3% (343/1893)	0.23
Prior CABG	5.7% (3/53)	11.0% (208/1893)	0.21
LVEF	45.0 (35.75–55.0)	52.0 (45–60.0)	0.001
Clinical presentation			
Stable angina pectoris	24.5% (13/53)	25.6% (485/1893)	0.85
Acute coronary syndrome	80.6% (40/53)	74.4% (1408/1893)	
Multivessel disease	79.2% (42/53)	69.7% (1319/1893)	0.17
No. of treated lesions	1 (1–2)	1 (1–2)	0.30
≥2 treated lesions	35.8% (19/53)	37.6% (712/1893)	0.76
≥3 treated lesions	7.5% (4/53)	11.5% (218/1893)	
Multivessel intervention	24.5% (13/53)	26.9% (509/1893)	0.70
At least 1 complex lesion (type B2 or C)*	66.0% (35/53)	66.0% (1250/1893)	0.99
Total ACC/AHA score†	3 (2–5)	3 (2–5)	0.48
Bleeding risk score			
CRUSADE score	38 (24–43)	25 (18–35)	<0.0001
ACUITY score	20 (14–28)	15 (9–20)	<0.0001
HAS-BLED score	2 (1–2)	1 (1–2)	<0.0001

ACC indicates American College of Cardiology; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; AHA, American Heart Association; CABG, coronary artery bypass grafting; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

*According to the ACC/AHA coronary lesion classification.

†Type A stenoses were coded as 1 point, type B1 stenoses were coded as 2 points, type B2 stenoses were coded as 3 points, and type C stenoses were coded as 4 points.

cutoff value of 40 for the CRUSADE score, as reported previously.[10] The incidence of major bleeding, red blood cell transfusion, and major adverse cardiac events—a composite of all-cause death, MI, and cerebrovascular accident—was appraised in the subgroup of patients with high CRUSADE scores (HCSs; >40) versus those with low to intermediate scores (≤40) in the 2 DAPT duration arms. All study end point definitions were reported previously,[13] confirmed on the basis of documentation collected at each hospital, and centrally adjudicated by the clinical events committee, the members of which were unaware of the patients' treatment-group assignments. The time frame of interest for the primary end point was from randomization (ie, 30 days after index procedure) to 24 months.

Statistical Analysis

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (interquartile range). Continuous variables were compared between randomized groups using the Wilcoxon rank sum test, whereas for binary variables, the χ^2 test was used.

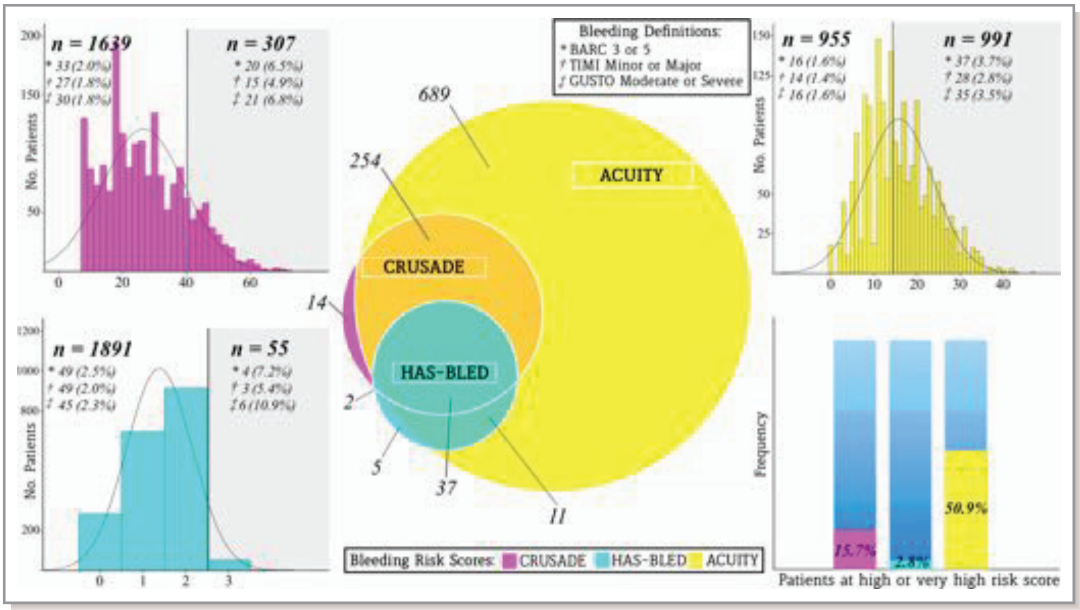

Figure 1. Distribution of bleeding risk scores and major bleeding events in the PRODIGY population. The Venn diagram (center) shows the patients included in the high bleeding risk category by each score. The ACUITY score had broader inclusion in the high-risk category, whereas CRUSADE and HAS-BLED were more restrictive (bottom right corner). Bleeding risk score distribution is presented for CRUSADE (top left corner), ACUITY (top right corner), and HAS-BLED (bottom left corner), with the number of patients with major bleeding in the high-risk category (gray section) and in the low- to intermediate-risk category according to 3 bleeding definitions. ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; BARC, Bleeding Academic Research Consortium; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; GUSTO, Global Use of Strategies to Open Occluded Arteries; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; TIMI, Thrombolysis in Myocardial Infarction.

In its original derivation, the CRUSADE score assigned patients to 5 risk strata (very low risk ≤20, low risk 21–30, moderate risk 31–40, high risk 41–50, very high risk >50). The ACUITY score defined 4 risk strata (low risk <10, moderate risk 10–14, high risk 15–19, very high risk ≥20), whereas HAS-BLED stratified patients into 3 risk strata (low risk <2, intermediate risk 2, high risk >2). For the purpose of this analysis, patients were categorized into 3 bleeding risk strata across all scores by jointly considering the *very high risk* and *high risk* (high risk) and *low risk* and *very low risk* categories (low risk) as 1 each. A detailed report of the components of each score is presented in Table S1.

The predictive value of CRUSADE, ACUITY, and HAS-BLED scores was assessed in Cox regression models and with receiver operating characteristics area under the curve (AUC) and category-free net reclassification improvement and integrated discrimination improvement.[14] The calibration of the models was evaluated using the Hosmer–Lemeshow goodness-of-fit statistical analysis. Net reclassification improvement and integrated discrimination improvement were calculated by analyzing the differences in patients' individual estimated probability of experiencing major bleeding events after the addition of the CRUSADE score result to the models containing the aforementioned bleeding risk scores. Net reclassification improvement represents the average weighted improvement in discrimination. Integrated discrimination improvement considers the change in the estimated prediction probabilities as a continuous variable and represents the average improvement in predicted probability.

Estimation of the cumulative incidence of events was performed using the Kaplan–Meier method, and events were compared with the log-rank test. Absolute risk difference with 95% CI was calculated for long-term versus short-term clopidogrel with the Newcombe–Wilson method without continuity correction. The Mantel–Haenszel χ^2 test was used

Table 2. Incidence of Major Bleeding Among Bleeding Risk Categories

	Major Bleeding	Hazard Ratio (95% CI)	*P* Value
All patients	2.7% (53/1946)	—	—
CRUSADE score			
Low (≤30)	1.4% (18/1282)	Reference	—
Intermediate (31–40)	4.2% (15/357)	3.10 (1.56–6.15)	0.001
High (>40)	6.5% (20/307)	5.62 (2.99–10.55)	<0.0001
ACUITY score			
Low (<10)	0.8% (4/480)	Reference	—
Intermediate (10–14)	2.5% (12/475)	3.08 (0.99–9.54)	0.052
High (>14)	3.7% (37/991)	4.93 (1.76–13.82)	0.002
HAS-BLED score			
Low (<2)	1.5% (15/977)	Reference	—
Intermediate (2)	3.7% (34/914)	2.56 (1.40–4.69)	0.002
High (>2)	7.3% (4/55)	5.45 (1.81–16.43)	0.003

Each hazard ratio is considered as compared with the reference low bleeding risk category. ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly.

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to assess the evidence of statistical interaction on an additive scale between randomized DAPT duration and bleeding risk status, according to CRUSADE. The number needed to treat for harm (NNTH) was calculated as 1 divided by the absolute risk difference (ARD). All analyses were performed on the basis of the intention-to-treat principle with Review Manager version 5.3 (RevMan; Cochrane Collaboration) and SPSS version 21.0 (IBM Corp).

Results

In the PRODIGY trial, a total of 1970 patients were randomly allocated at 30 days postprocedure to receive clopidogrel therapy for 6 or 24 months. Complete data regarding the 3 bleeding risk scores were available in 1946 patients (98.8%).

The 2-year cumulative risk of major bleeding and need for red blood cell transfusion was 2.7% and 2.0%, respectively

Table 3. Incidence of TIMI Minor and Major Bleeding Among Bleeding Risk Categories

	Events (n/N)	Hazard Ratio (95% CI)	*P* Value
All patients	2.1% (42/1946)	—	—
CRUSADE score			
Low (≤30)	1.2% (16/1282)	Reference	—
Intermediate (31–40)	3.0% (11/357)	2.50 (1.16–5.39)	0.019
High (>40)	4.9% (15/307)	4.20 (2.08–8.51)	<0.0001
ACUITY score			
Low (<10)	0.8% (4/480)	Reference	—
Intermediate (10–14)	2.1% (10/475)	2.56 (0.80–8.17)	0.112
High (>14)	2.8% (28/991)	3.47 (1.22–9.89)	0.02
HAS-BLED score			
Low (<2)	1.3% (13/977)	Reference	—
Intermediate (2)	2.8% (26/914)	2.17 (1.11–4.22)	0.023
High (>2)	5.4% (3/55)	4.79 (1.36–16.83)	0.015

Each hazard ratio is considered as compared to the reference low bleeding risk category. ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; TIMI, Thrombolysis in Myocardial Infarction.

Table 4. Incidence of GUSTO Moderate and Severe Bleeding Among Bleeding Risk Categories

	Events (n/N)	Hazard Ratio (95% CI)	*P* Value
All patients	2.6% (52/1946)	—	—
CRUSADE score			
Low (≤30)	1.3% (18/1282)	Reference	—
Intermediate (31–40)	3.6% (13/357)	2.80 (1.36–5.76)	0.005
High (>40)	6.8% (21/307)	5.58 (2.94–10.58)	<0.0001
ACUITY score			
Low (<10)	0.8% (4/480)	Reference	—
Intermediate (10–14)	2.5% (12/475)	3.08 (0.99–9.56)	0.052
High (>14)	3.5% (35/991)	4.35 (1.55–12.24)	0.005
HAS-BLED score			
Low (<2)	1.4% (14/977)	Reference	—
Intermediate (2)	3.4% (31/914)	2.40 (1.28–4.52)	0.006
High (>2)	10.9% (6/55)	9.05 (3.47–23.60)	<0.0001

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; GUSTO, Global Use of Strategies to Open Occluded Arteries; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly.

(2.2% and 2.6% for TIMI minor or major and GUSTO moderate to severe bleeding, respectively). Patients randomized to 24-month DAPT duration, compared with those allocated to 6-month DAPT, experienced a significant increase in major bleeding (3.5% versus 2.0%, P=0.042; NNTH 66.7) and received blood transfusions more frequently (2.7% versus 1.3%, P=0.041; NNTH 71.4). No bleeding event occurred in the 24 patients for whom bleeding scores were missing.

The median CRUSADE score was 25 (interquartile range 18–35; mean±SD: 26.5±12.8), whereas the median ACUITY and HAS-BLED scores were 15 (interquartile range 10–21; mean±SD: 15.8±7.9) and 1 (interquartile range 1–2; mean±SD: 1.3±0.7), respectively (Table 1 and Figure 1). By applying previously validated cutoffs, 307 patients (15.8%) based on CRUSADE, 991 patients (50.9%) based on ACUITY, and 55 patients (2.8%) based on HAS-BLED met the threshold for the high or very high bleeding risk category. Most patients with HCS also satisfied high bleeding risk criteria according to both HAS-BLED and ACUITY, whereas the vast majority of patients at high bleeding risk according to ACUITY did not reach the same risk category for the other 2 scores (Figure 1).

Table 5. Risk Classification of Major Bleeding According to the 3 Bleeding Risk Scores

				CRUSADE vs ACUITY		ACUITY vs HAS-BLED		CRUSADE vs HAS-BLED	
	CRUSADE	ACUITY	HAS-BLED	Difference	*P* Value	Difference	*P* Value	Difference	*P* Value
True-positive rate*	37.7% (20/53)	69.8% (37/53)	7.5% (4/53)	−32.1	<0.0001	62.3	<0.0001	30.2	<0.0001
False-positive rate†	15.2% (287/1893)	50.3% (954/1893)	2.7% (51/1893)	−35.1	<0.0001	47.6	<0.0001	12.5	<0.0001
False-negative rate‡	34.0% (18/53)	7.5% (4/53)	28.3% (15/53)	26.5	<0.0001	−20.8	<0.0001	5.7	<0.0001
True-negative rate§	66.7% (1264/1893)	25.1% (476/1893)	50.8% (962/1893)	41.6	<0.0001	−25.7	<0.0001	15.9	<0.0001

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly.

*Proportion of events categorized as CRUSADE >40, ACUITY >14, and HAS-BLED>2.

†Proportion of events categorized as CRUSADE >40, ACUITY >14, and HAS-BLED>2.

‡Proportion of events categorized as CRUSADE ≤30, ACUITY <10, and HAS-BLED<2.

§Proportion of events categorized as CRUSADE ≤30, ACUITY <10, and HAS-BLED<2.

Table 6. ROC: Predictive Performance of Major Bleeding With the 3 Risk Scores Used as Continuous Variables and as 3 Risk Score Categories (Low, Intermediate, and High Risk)

	Major Bleeding	
	AUC (95% CI)	*P* Value
CRUSADE score		
Continuous parameter	0.71 (0.64–0.77)	<0.0001
3 Categories	0.68 (0.60–0.75)	<0.0001
ACUITY score		
Continuous parameter	0.68 (0.61–0.75)	<0.0001
3 Categories	0.61 (0.55–0.68)	0.004
HAS-BLED score		
Continuous parameter	0.63 (0.56–0.70)	0.001
3 Categories	0.62 (0.55–0.70)	0.002

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; AUC, area under the curve; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; ROC, receiver operating characteristics.

The patients who bled were older, had reduced renal function and left ventricular ejection fraction, had more frequent history of MI and diabetes mellitus, and underwent left main coronary artery intervention more frequently. All 3 bleeding risk scores were significantly higher for patients with hemorrhagic events at follow-up compared with those without, consistently across bleeding definitions (Table 1).

Predictive Performance of the Bleeding Risk Scores

The transition from a lower to a higher risk category carried a significant increase in bleeding rates across bleeding risk scores (Table 2). This result was consistent among all explored bleeding definitions (Tables 3 and 4) and in the 6- and 24-month DAPT groups when assessed separately. The ACUITY score best classified patients with major bleeding in the high-risk group (higher sensitivity), but it was also the least specific, classifying only 25% of patients without events to the low-risk group. In contrast, the HAS-BLED score showed the lowest sensitivity, classifying 7.5% of those who

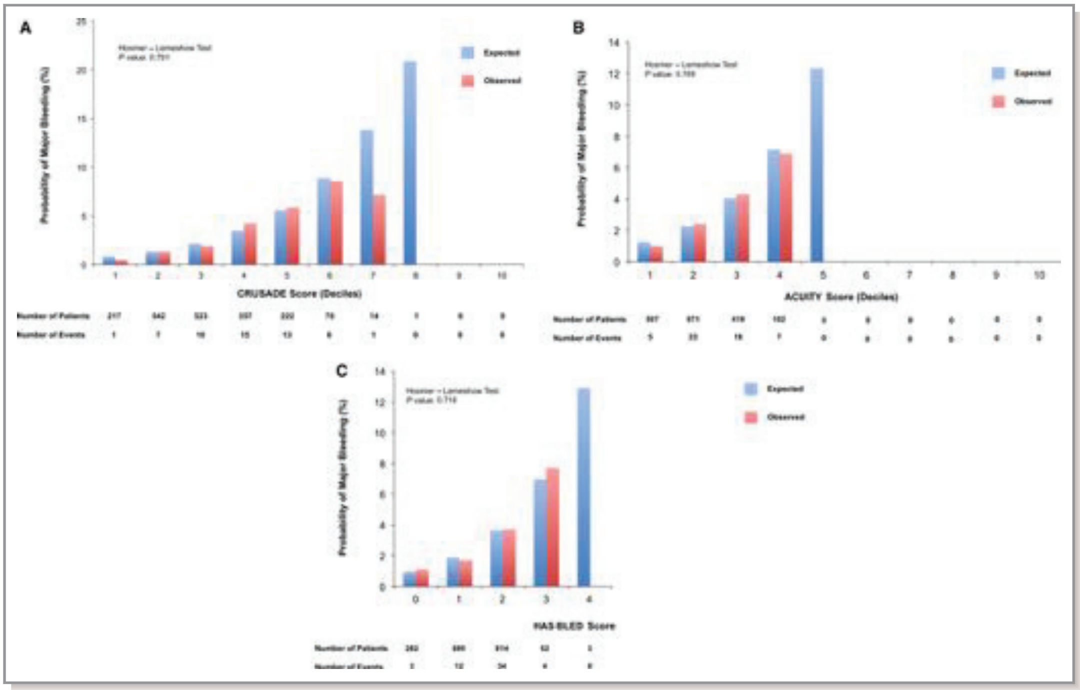

Figure 2. Calibration plots comparing the expected and observed probabilities of major bleeding. A, CRUSADE score. B, ACUITY score. C, HAS-BLED score. ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly.

Table 7. ROC: Predictive Performance of TIMI Minor or Major and GUSTO Moderate or Severe Bleeding for the 3 Risk Scores Used as Continuous Variables and as 3 Risk Score Categories (Low, Intermediate, and High Risk)

	TIMI Minor or Major		GUSTO Moderate or Severe	
	AUC (95% CI)	*P* Value	AUC (95% CI)	*P* Value
CRUSADE score				
Continuous parameter	0.68 (0.60–0.76)	<0.0001	0.71 (0.63–0.82)	<0.0001
3 Categories	0.65 (0.56–0.74)	0.001	0.68 (0.58–0.79)	<0.0001
ACUITY score				
Continuous parameter	0.65 (0.57–0.73)	0.001	0.67 (0.58–0.77)	<0.0001
3 Categories	0.59 (0.52–0.67)	0.036	0.61 (0.51–0.69)	0.009
HAS-BLED score				
Continuous parameter	0.62 (0.53–0.69)	0.010	0.65 (0.55–0.73)	<0.0001
3 Categories	0.61 (0.52–0.69)	0.019	0.64 (0.53–0.73)	0.001

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; AUC, area under the curve; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; GUSTO, Global Use of Strategies to Open Occluded Arteries; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; ROC, receiver operating characteristics; TIMI, Thrombolysis in Myocardial Infarction.

eventually bled as high risk. The CRUSADE score provided reasonable sensitivity and specificity, correctly classifying 67% of patients without events in the low-risk category (Table 5).

At the C statistic analysis, the point estimate of the AUC for the prediction of major bleeding was similar between the CRUSADE risk score (AUC 0.71, 95% CI 0.64–0.77) and ACUITY (AUC 0.68, 95% CI 0.61–0.75) and numerically higher than HAS-BLED (AUC 0.63, 95% CI 0.56–0.70), as both continuous and 3-risk categories, although 95% CIs remained partially overlapping among the 3 bleeding scores (Table 6). All 3 risk models were well calibrated according to the Hosmer–Lemershow test for goodness of fit (CRUSADE P=0.27; ACUITY P=0.33; HAS-BLED P=0.69) (Figure 2). These observations remained consistent when TIMI and GUSTO bleeding definitions were applied (Table 7). CRUSADE, but not ACUITY, successfully reclassified the risk of major bleeding compared with HAS-BLED, with better discriminatory power. When compared with ACUITY, CRUSADE was not significantly superior on net reclassification improvement and integrated discrimination improvement (Table 8 and Figure 3). These results were largely consistent across different bleeding scales (Table 9). In addition, the bleeding risk scores, especially CRUSADE, showed reasonably good discriminatory capability for ischemic events, including the composite of death, MI, or cerebrovascular accident; for MI alone; and for stent thrombosis alone (Table 10).

CRUSADE Score and DAPT Duration

Bleeding events

Patients meeting the threshold for HCS showed an almost 3-fold greater rate of major bleeding when treated with 24- versus 6-month DAPT (9.7% versus 3.7%; ARD 6%; 95% CI 0.4% to 12.3%; P=0.04); patients with low to intermediate

Table 8. Risk Reclassification and Integrated Discriminatory Improvement for Major Bleeding

	Bleeding Correctly Reclassified, *P* (n_1)	No Bleeding Correctly Reclassified, *P* (n_2)	Net Reclassification Improvement†	*P* Value	Integrated Discriminatory Improvement‡	*P* Value
CRUSADE vs ACUITY*	0.57 (30)	0.49 (921)	0.12	0.49	0.0015	0.488
ACUITY vs HAS-BLED*	0.49 (26)	0.57 (1076)	0.12	0.40	0.0067	0.069
CRUSADE vs HAS-BLED*	0.62 (33)	0.57 (1087)	0.39	0.005	0.0083	0.021

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly.

*The model considered each bleeding risk score as a reference value for the others.

†The net reclassification improvement was defined as (A+B)−([1−A]+[1−B]), in which A is the probability of bleeding correctly reclassified and B is the probability of no bleeding correctly reclassified.

‡The integrated discrimination improvement was defined as $\frac{(\sum_i \text{in bleeders } [p_{new(1)} - p_{old(1)}])}{n_1} - \frac{(\sum_i \text{in non-bleeders } [p_{new(2)} - p_{old(2)}])}{n_2}$.

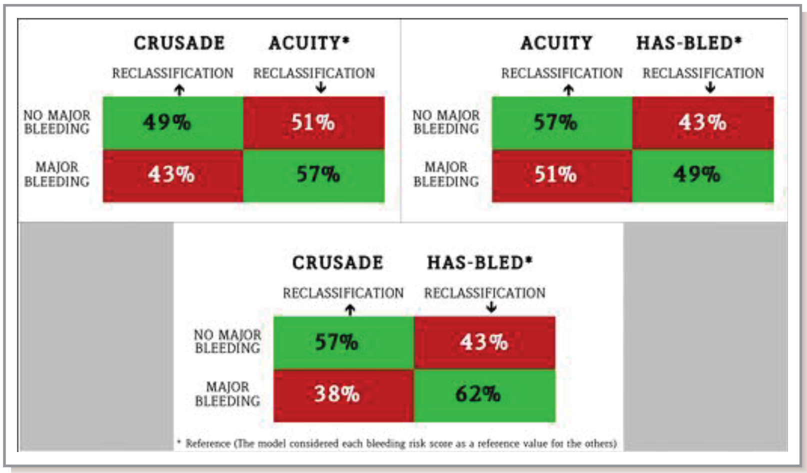

Figure 3. Reclassification tables. The 3 bleeding risk scores are compared using each score as reference for the others: The first score mentioned is the score to be tested, the second is considered the reference. The percentage of patients correctly reclassified by each score is displayed in green, whereas the percentage of patients not correctly reclassified is in red. ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly.

CRUSADE scores did not experience a significant increase in major bleeding when treated with long versus short DAPT duration (2.4% versus 1.6%; ARD 0.8%; 95% CI −0.6% to 2.2%; P=0.25) (Figure 4A and Table 11). A quantitative interaction was noted between bleeding risk and duration of antiplatelet therapy with respect to major bleeding (P_{int}=0.05) (Figure 5). The NNTH to experience major bleeding with prolonged DAPT in the HCS group was 17 (Figure 6). These findings remained

Table 9. Risk Reclassification and Integrated Discriminatory Improvement for TIMI Minor or Major and GUSTO Moderate or Severe Bleeding

	Bleeding Correctly Reclassified P (n_1)	No Bleeding Correctly Reclassified, P (n_2)	Net Reclassification Improvement†	P Value	Integrated Discriminatory Improvement ‡	P Value
TIMI Minor or Major						
CRUSADE vs ACUITY*	0.55 (23)	0.51 (974)	0.12	0.53	0.0022	0.198
ACUITY vs HAS-BLED*	0.45 (19)	0.55 (1055)	0.012	1.00	0.0031	0.256
CRUSADE vs HAS-BLED*	0.62 (26)	0.56 (1065)	0.37	0.03	0.0053	0.069
GUSTO Moderate or Severe						
CRUSADE vs ACUITY*	0.53 (27)	0.55 (1044)	0.16	0.26	0.004	0.11
ACUITY vs HAS-BLED*	0.47 (24)	0.53 (998)	−0.004	1.00	0.002	0.62
CRUSADE vs HAS-BLED*	0.59 (30)	0.54 (1029)	0.26	0.066	0.006	0.11

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; GUSTO, Global Use of Strategies to Open Occluded Arteries; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; TIMI, Thrombolysis in Myocardial Infarction.

*The model considered each bleeding risk score as a reference value for the others.

†The net reclassification improvement was defined as (A+B)−([1−A]+[1−B]), in which A is the probability of bleeding correctly reclassified and B is the probability of no bleeding correctly reclassified.

‡The integrated discrimination improvement was defined as $\frac{(\sum_i \text{in bleeders } |p_{new(1)} - p_{old(1)}|)}{n_1} - \frac{(\sum_i \text{in non-bleeders } |p_{new(2)} - p_{old(2)}|)}{n_2}$.

Table 10. Incidence of Ischemic Events Among Bleeding Risk Categories

	MACE*			Myocardial Infarction			Definite/probable ST†		
	Events (n/N)	HR (95% CI)	*P* Value	Events (n/N)	HR (95% CI)	*P* Value	Events (n/N)	HR (95% CI)	*P* Value
All patients	9.9% (193/1946)	—	—	3.9% (77/1946)	—	—	1.4% (27/1946)	—	—
CRUSADE score									
Low (≤30)	5.7% (73/1282)	Reference	—	2.3% (29/1282)	Reference	—	0.9% (12/1282)	Reference	—
Intermediate (31–40)	10.4% (37/357)	1.87 (1.26–2.77)	0.002	4.2% (15/357)	1.86 (1.00–3.48)	0.05	0.5% (2/357)	0.60 (0.13–2.71)	0.509
High (>40)	27.0% (83/307)	5.45 (3.98–7.46)	<0.0001	10.7% (33/307)	4.92 (2.99–8.11)	<0.0001	4.2% (13/307)	4.82 (2.20–10.6)	<0.0001
ACUITY score									
Low (<10)	4.2% (20/480)	Reference	—	1.7% (8/480)	Reference	—	0.8% (4/480)	Reference	—
Intermediate (10–14)	5.3% (25/475)	1.28 (0.71–2.30)	0.413	1.7% (8/475)	1.02 (0.38–2.71)	0.97	0.4% (2/475)	0.51 (0.09–2.79)	0.438
High (>14)	14.9% (148/991)	3.83 (2.40–6.11)	<0.0001	6.1% (61/991)	3.71 (1.78–7.76)	<0.0001	2.1% (21/991)	2.58 (0.89–7.52)	0.082
HAS-BLED score									
Low (<2)	5.5% (54/977)	Reference	—	2.2% (22/977)	Reference	—	1.0% (10/977)	Reference	—
Intermediate (2)	13.0% (119/914)	2.44 (1.77–3.36)	<0.0001	5.4 (50/914)	2.47 (1.5–4.09)	<0.0001	1.5% (14/914)	1.51 (0.67–3.40)	0.318
High (>2)	36.4% (20/55)	7.82 (4.68–13.07)	<0.0001	9.0 (5/55)	4.50 (1.70–11.8)	0.002	5.4% (3/55)	6.13 (1.69–22.3)	0.006

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; MACE, major adverse cardiovascular events; ST, stent thrombosis.

*MACE is intended as a composite of death from all causes, myocardial infarction, and cerebrovascular accident.

†Definite or probable ST was defined according to the academic research consortium.

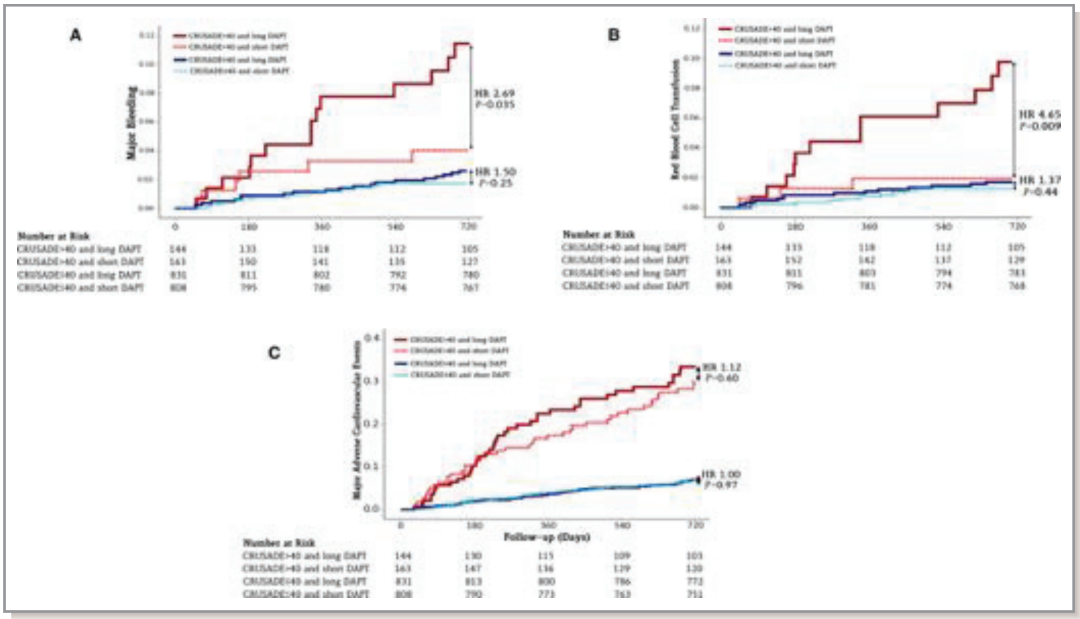

Figure 4. Kaplan–Meier curves during follow-up for hemorrhagic and ischemic events in the high and low to intermediate CRUSADE score categories after 24- or 6-month DAPT. A, Major bleeding. B, Red blood cell transfusion. C, Major adverse cardiovascular events including death for all causes, myocardial infarction, and cerebrovascular accident. CRUSADE indicates Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; DAPT, dual antiplatelet therapy; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; HR, hazard ratio.

consistent across bleeding scales (Table 11). Patients with HCS experienced an almost 5-fold increase in red blood cell transfusion in the 24- versus 6-month DAPT duration arms (8.3% versus 1.8%; ARD 6.5%; 95% CI 1.6% to 12.3%; P=0.02; NNTH: 15.4), whereas this did not differ in patients with low to intermediate CRUSADE score (1.7% versus 1.2%; ARD 0.5%; 95% CI −0.6% to 1.7%; P=0.45) (Figure 4B and Table 11), with positive interaction testing (P_{int}=0.01) (Figure 5).

Table 11. Hemorrhagic and Ischemic Outcomes in the High and Low to Intermediate CRUSADE Score Groups After 24- or 6-Month Dual Antiplatelet Therapy

	HCS (>40)				LICS (≤40)				
	24-Month DAPT (n=144)	6-Month DAPT (n=163)	ARD (95% CI)	*P* Value	24-Month DAPT (n=831)	6-Month DAPT (n=808)	ARD (95% CI)	*P* Value	P_{int}
Major Bleeding*	9.7% (14)	3.7% (6)	6% (0.4%, 12.3%)	0.04	2.4% (20)	1.6% (13)	0.8% (−0.6%, 2.2%)	0.25	0.05
Red blood cell transfusion	8.3% (12)	1.8% (3)	6.5% (1.6%, 12.3%)	0.02	1.7% (14)	1.2% (10)	0.5% (−0.6%, 1.7%)	0.45	0.01
MACE	28.5% (41)	25.8% (42)	2.7% (−7.2%, 12.6%)	0.59	6.7% (56)	6.7% (54)	0.0% (−2.5, 2.4%)	0.96	0.58

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; ARD, absolute risk difference; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; DAPT, dual antiplatelet therapy; GUSTO, Global Use of Strategies to Open Occluded Arteries; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; HCS, high CRUSADE score; int, interaction; LICS, low to intermediate CRUSADE score; MACE, major adverse cardiovascular events consistent with death from all causes, myocardial infarction, and cerebrovascular accident; TIMI, Thrombolysis in Myocardial Infarction.

*Results consistent among other bleeding definitions: TIMI minor or major and HCS (7.6% vs 2.4%; ARD 5.2%; 95% CI 0.2% to 10.9%; P: 0.05) and LICS (1.9% vs 1.4%; ARD 0.5%; 95% CI −0.6% to 1.9%; P=0.37) (P_{int}=0.02). GUSTO moderate or severe and HCS (9.7% vs 4.3%; ARD 5.4%; 95% CI 0.3% to 11.8%; P=0.08) and LICS (2.2% vs 1.5%; ARD 0.7%; 95% CI −0.6% to 2.1%; P=0.30) (P_{int}=0.08).

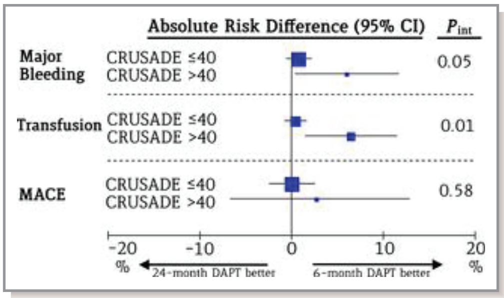

Figure 5. Hemorrhagic and ischemic outcomes in patients with high and low to intermediate CRUSADE scores. The forest plot shows the absolute risk difference and the *P* value of the interaction effect for major bleeding, red blood cell transfusion, and MACE after 24- versus 6-month DAPT in the groups of patients with high and low to intermediate CRUSADE scores. CRUSADE indicates Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; DAPT, dual antiplatelet therapy; int, interaction; MACE, major adverse cardiovascular events.

Ischemic events

The risk of death, MI, or cerebrovascular accident did not differ in the 24- versus 6-month DAPT groups, both in patients with HCS (28.5% versus 25.8%; ARD 2.7%; 95% CI −7.2% to 12.6%; P=0.59) and with low to intermediate CRUSADE score (6.7% versus 6.7%; ARD 0%; 95% CI −2.5% to 2.4%; P=0.96) (P_{int}=0.58). (Figure 4C and Table 11) Similarly, when separately assessed, the risk of all-cause death, MI, or definite or probable stent thrombosis remained homogeneously distributed between DAPT groups in patients with and without HCS (Table 12).

Discussion

The main findings of this study can be summarized as follows. First, the CRUSADE, HAS-BLED, and ACUITY risk scores demonstrated reasonably good predictive value with respect to major bleeding in the PRODIGY all-comer population, regardless of the bleeding definition used. Second, bleeding risk scores also displayed a significant capability to predict ischemic events in terms of major adverse cardiac events, MI, or stent thrombosis. Third, the CRUSADE risk score, predicted bleeding significantly better than HAS-BLED, with improved reclassification and discrimination performance. Fourth, patients with HCS treated with 24-month DAPT experienced a 3-fold higher risk of major bleeding and a 5-fold risk of red blood cell transfusion compared with 6-month DAPT, without clear evidence of benefit. The NNTH with an HCS was as low as 17 for major bleeding and 15 for red blood cell transfusion; these values were lower than corresponding values in the unselected patient cohort, suggesting that long-term DAPT has a narrow therapeutic window and high potential for harm in this selected patient population with high bleeding risk. Fifth, conversely, patients not meeting the threshold for the HCS category—corresponding to as many as 84.2% of the patients originally included in our study—did not have higher

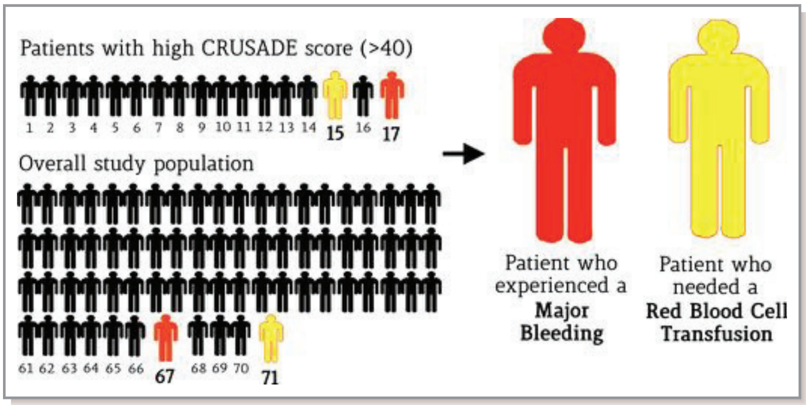

Figure 6. Effects of long- and short-term DAPT on patients with a high CRUSADE score and in the overall population. The number of patients needed to treat to experience major bleeding or red blood cell transfusion after 24-month DAPT compared with 6-month treatment is significantly lower in the group of patients with a high CRUSADE score (>40) than in the overall study population. CRUSADE indicates Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; DAPT, dual antiplatelet therapy.

Table 12. Other Ischemic Outcomes in the High and Low to Intermediate CRUSADE Score Groups After 24- or 6-Month Dual Antiplatelet Therapy

	HCS (>40)				LICS (≤40)				
	24-Month Clopidogrel (n=144)	6-Month Clopidogrel (n=163)	ARD (95% CI)	*P* Value	24-Month Clopidogrel (n=831)	6-Month Clopidogrel (n=808)	ARD (95% CI)	*P* Value	P_{int}
Death from all causes	20.1% (29)	20.9% (34)	−0.8% (−9.6% to 8.4%)	0.87	4.1% (34)	3.7% (30)	0.4% (−1.5% to 2.3%)	0.69	0.56
MI	11.1% (16)	10.4%(17)	0.7% (−6.3% to 7.9%)	0.86	2.5% (21)	2.8% (23)	−0.3% (−1.9% to 1.2%)	0.69	0.71
Definite/ probable ST*	1.4% (2)	1.2% (2)	0.2% (−3.1 to 3.8%)	0.90	1.3% (11)	1.6% (13)	−0.3% (−1.5 to 0.9%)	0.63	0.83

CRUSADE indicates Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; MI, myocardial infarction; ST, stent thrombosis.
*Definite or probable ST defined according to the academic research consortium.

bleeding risk, consistently across bleeding risk scales, if treated with 24- versus 6-month DAPT duration.

There is consensus currently about the need to choose intensity and/or duration of potent antithrombotic therapy after percutaneous coronary intervention through the assessment of actual individual bleeding risk. Nevertheless, it remains undefined how bleeding risk should be properly assessed and whether it should truly influence therapeutic decisions in clinical practice. The ultimate goal of this analysis was to select 1 bleeding risk score that could guide duration of DAPT in clinical practice to maximize benefits over risks. Among the risk scores explored, we found CRUSADE to have a better predictive profile for major bleeding compared with HAS-BLED and a similar profile compared to ACUITY. This observation is consistent with some previous studies and with the European Society of Cardiology guidelines that recommended the CRUSADE score for bleeding risk stratification in non–ST-segment elevation MI.[9,15,16] It might be speculated that the set of covariates used to predict bleeding risk for the CRUSADE score better reflects the bleeding risk in patients undergoing stent implantation and subsequent DAPT. Accordingly, we stratified the PRODIGY patient population into high versus nonhigh bleeding risk status based on CRUSADE and assessed whether a priori bleeding risk could be a treatment modifier with respect to DAPT duration. We failed to identify a specific patient population (eg, those at low or intermediate bleeding risk) for which long-term DAPT was associated with lower rates of ischemic end points compared with a shortened DAPT regimen. This may reflect the null finding of the PRODIGY trial with respect to the benefit of long-term DAPT on death, MI, or stroke. In contrast, our study, which recruited an all-comer patient population, observed a distinct increase in bleeding end points in patients treated with 24-month DAPT. The current stratified analysis largely expands on previous findings by showing that in patients with low to intermediate risk, prolonging DAPT was not associated with a significant bleeding risk consistently across bleeding scales. Conversely, we observed bleeding and blood transfusion hazards associated with long-term DAPT in the selected cohort of patients with high bleeding risk. Given the magnitude of this association on both relative and absolute scales, it may be reasonable to stop DAPT after 6 months in this selected patient population, given that the risks seem to largely outweigh the potential benefits. At the same time, in patients not meeting high bleeding risk criteria according to the CRUSADE score, bleeding risk appears acceptable and not different from those undergoing 6-month therapy duration. This may be the ideal patient population in which to prolong DAPT for long-term secondary prevention.

The recent DAPT trial[6] demonstrated that 30-month DAPT with clopidogrel or prasugrel resulted in a significant reduction of both stent thrombosis and major adverse cardiac event rates compared with patients treated with 12-month DAPT. Importantly, patients were eligible for randomization only if they were free of both ischemic and bleeding events at 12 months. The implementation of the DAPT study results into practice would imply that clinicians should adopt a 2-step strategy for deciding whether DAPT should or should not be prolonged beyond 12 months and that only patients free from bleeding events may be selected to continue DAPT. This approach may expose patients already identifiable as potential bleeders to treatment-related side effects that could be prevented by stopping DAPT earlier. Current European Society of Cardiology revascularization guidelines call for a shorter DAPT duration in patients at high bleeding risk.[8] ACC/AHA guidelines state that if the bleeding risk is greater than the anticipated benefit, a shortened duration of DAPT should be considered.[7] The results of our study may help standardize risk assessment for bleeding in clinical practice and may have implications for tailored DAPT duration.

Our study has several limitations. First, as a retrospective analysis, the results provided are hypothesis generating, and a specifically designed randomized trial is needed to confirm or refute our findings. Second, the scores evaluated in this study were not validated in an all-comer population and were designed mostly to predict events in the first 30 days after the index procedure. When assessed individually, all variables included in each score were independent bleeding predictors. Third, the outcome of interest for the current analysis was clinically significant major bleeding defined according to the BARC class 3 or 5 definition. These events are relatively rare in modern clinical trials and occurred in only 2.7% of the PRODIGY population. As such, bigger sample sizes are needed to further corroborate our findings. Fourth, CRUSADE, ACUITY, and HAS-BLED scores were validated using a bleeding definition that was different from BARC class 3 or 5, as used in the PRODIGY trial; however, at sensitivity analysis, the result observed for BARC were confirmed using TIMI minor or major and GUSTO moderate and severe definitions. Fifth, we did not evaluate the performance of other bleeding risk scores apart from those presented in this analysis; consequently, their incremental value in an all-comer population should be investigated. Sixth, the bleeding risk scores were collected only on admission. Considering the sudden variability of clinical status in this population, the result of the scores at the moment of randomization or during follow-up may change over time. Continuous and progressive evaluation of bleeding risk would be ideal but, unfortunately, hardly feasible.

Conclusions

The CRUSADE, ACUITY, and HAS-BLED bleeding risk scores displayed reasonable predictive performance in an all-comer population treated with coronary stenting; among them, CRUSADE showed the best predictive profile in our dataset. DAPT for 24 months was associated with a higher risk of major bleeding in patients at high risk based on the CRUSADE score but not in those with low or intermediate risk profiles. The CRUSADE score has potential to guide DAPT duration based on standardization of bleeding risk assessed for each individual patient.

Disclosures

None.

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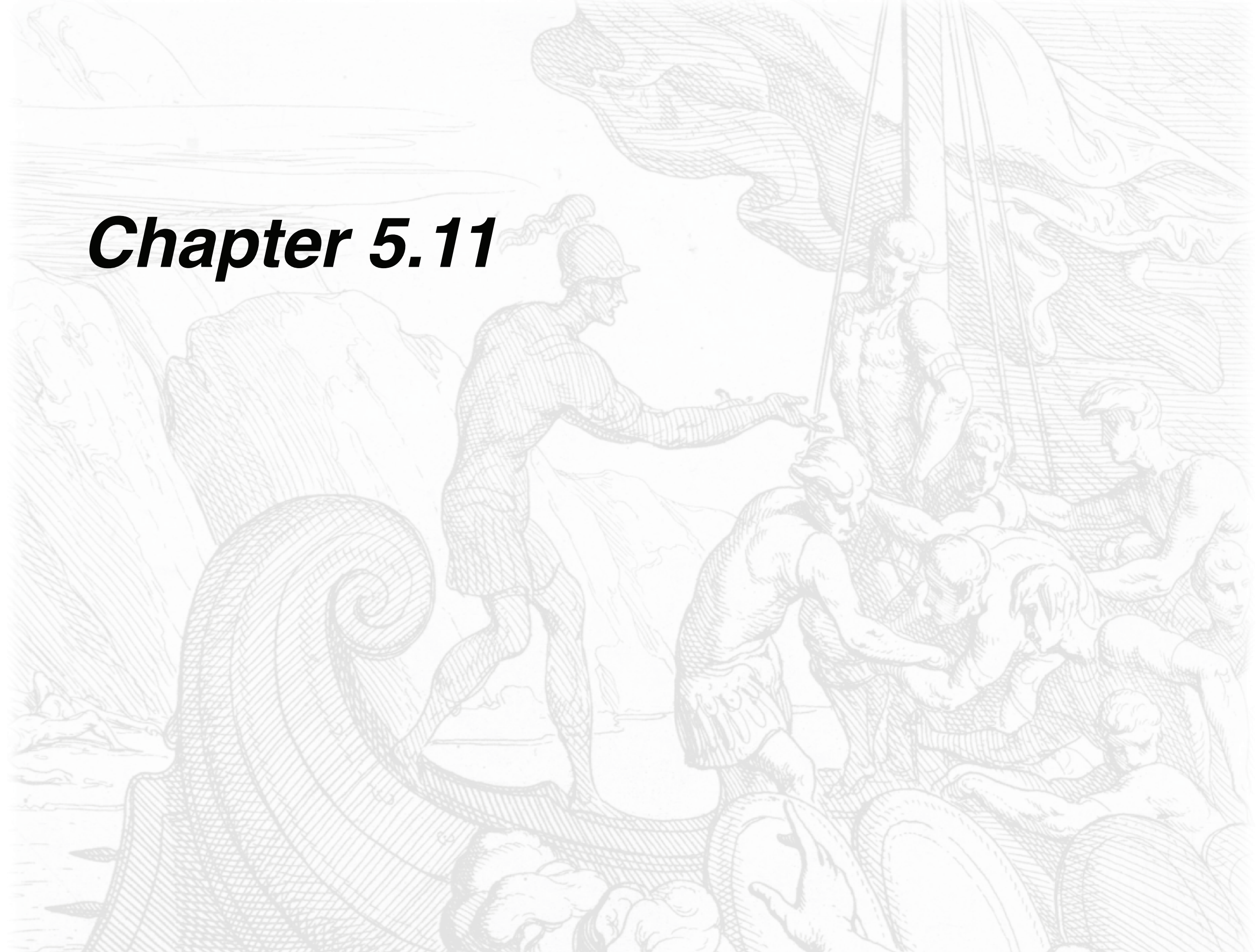
Chapter 5.11



Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials

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Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials

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Summary

Background Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor prevents ischaemic events after coronary stenting, but increases bleeding. Guidelines support weighting bleeding risk before the selection of treatment duration, but no standardised tool exists for this purpose.

Methods A total of 14 963 patients treated with DAPT after coronary stenting—largely consisting of aspirin and clopidogrel and without indication to oral anticoagulation—were pooled at a single-patient level from eight multicentre randomised clinical trials with independent adjudication of events. Using Cox proportional hazards regression, we identified predictors of out-of-hospital Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding stratified by trial, and developed a numerical bleeding risk score. The predictive performance of the novel score was assessed in the derivation cohort and validated in patients treated with percutaneous coronary intervention from the PLATelet inhibition and patient Outcomes (PLATO) trial (n=8595) and BernPCI registry (n=6172). The novel score was assessed within patients randomised to different DAPT durations (n=10 081) to identify the effect on bleeding and ischaemia of a long (12–24 months) or short (3–6 months) treatment in relation to baseline bleeding risk.

Findings The PRECISE-DAPT score (age, creatinine clearance, haemoglobin, white-blood-cell count, and previous spontaneous bleeding) showed a c-index for out-of-hospital TIMI major or minor bleeding of 0·73 (95% CI 0·61–0·85) in the derivation cohort, and 0·70 (0·65–0·74) in the PLATO trial validation cohort and 0·66 (0·61–0·71) in the BernPCI registry validation cohort. A longer DAPT duration significantly increased bleeding in patients at high risk (score ≥25), but not in those with lower risk profiles ($p_{interaction}$=0·007), and exerted a significant ischaemic benefit only in this latter group.

Interpretation The PRECISE-DAPT score is a simple five-item risk score, which provides a standardised tool for the prediction of out-of-hospital bleeding during DAPT. In the context of a comprehensive clinical evaluation process, this tool can support clinical decision making for treatment duration.

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Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor reduces ischaemic recurrences in patients with coronary artery disease treated with coronary stents.[1–3] However, this benefit is counterbalanced by higher bleeding risk, which is linearly related to the treatment duration. Both ischaemic and bleeding risks have potential to negatively impact prognosis.[4] As a result, although 12 months of DAPT after stenting has been commonly suggested, the optimal duration of treatment is still debated.[5,6]

Shortening DAPT duration from 12 months to 6 or 3 months significantly reduced bleeding liability.[4] However, a prolonged treatment beyond 12 months reduced both stent-related and non-stent-related ischaemic events in selected patients who tolerated the first year of treatment without bleeding.[4,7]

International guidelines encourage weighting bleeding risk before selection of treatment duration and suggest a shorter than 12 month treatment regimen in patients at high bleeding risk.[5,6] No standardised tool exists to weigh bleeding risk at the time of DAPT initiation. A prediction rule was recently proposed for patients who tolerated 12 month DAPT to select those eligible for treatment prolongation.[8] This strategy cannot be applied earlier, at the time of treatment initiation, to select a shorter than 12 month treatment duration in patients at high bleeding risk. Thus, no standardised algorithm is available for defining optimal DAPT duration at the time of coronary stent implantation.

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Research in context

Evidence before this study

Spontaneous bleeding during treatment with dual antiplatelet therapy (DAPT) is the most common complication after coronary stenting, and its incidence increased with the introduction of novel and more potent antithrombotic agents. Despite recommendations from international guidelines, methods to gauge out-of-hospital bleeding risk in patients treated with DAPT are limited. A dedicated risk score specifically designed to predict spontaneous on-DAPT bleeding events might improve risk assessment and support clinicians' decisions with respect to dual antiplatelet therapy.

We searched PubMed without language or date restrictions for publications until Sept 30, 2016, about bleeding risk scores in patients treated with DAPT. We used the search terms "percutaneous coronary intervention", "coronary stent", "acute coronary syndrome", "stable coronary artery disease", "bleeding risk score", "bleeding", "antiplatelet therapy", "dual antiplatelet therapy", "clopidogrel", "prasugrel", and "ticagrelor". We excluded articles regarding antithrombotic treatment in atrial fibrillation, concomitant use of oral anticoagulants, and risk prediction models for in-hospital bleeding. We identified two reports focused on out-of-hospital events in patients treated with DAPT, and one was only applicable after a 12 month course with DAPT was completed without complications.

Added value of this study

We propose a novel risk score for the prediction of out-of-hospital bleeding in patients treated with DAPT using age, creatinine clearance, white-blood-cell count, haemoglobin, and history of bleeding. The PRECISE-DAPT score is a simple bedside risk assessment tool, which can be easily implemented in everyday clinical practice, and that might be particularly useful for its applicability at the time of treatment initiation. The PRECISE-DAPT score showed potential to identify patients at high bleeding risk (score ≥25) who might benefit from a shortened (ie, <12 months) DAPT duration. Patients not at high bleeding risk (score <25) might receive a standard (ie, 12 months) or prolonged (ie, >12 months) treatment without being exposed to significant bleeding liability.

Implication of all the available evidence

Our study provides awareness to clinicians regarding out-of-hospital bleeding risk factors in patients treated with DAPT after coronary stent implantation and offers an objective and standardised tool to quantify such risk in clinical practice. Systematic evaluation of these predictors with the novel PRECISE-DAPT bleeding risk score has potential to support clinical decision making with respect to the optimal duration of DAPT, selecting patients at high bleeding risk (score ≥25) to a shorter treatment and patients at non-high risk to a standard or long treatment.

We created a bleeding risk score for patients treated with DAPT after coronary stent implantation, in a large pooled dataset of contemporary randomised clinical trials implementing different DAPT duration strategies. We externally validated this novel risk score in two independent cohorts of patients treated with percutaneous coronary intervention (PCI) from a large randomised clinical trial and a contemporary real-world registry. The score was retrospectively applied among patients randomly assigned to a shortened or prolonged DAPT duration to assess ischaemic and bleeding outcomes according to each bleeding risk category with each DAPT regimen.

Methods

Study design and population

The PRECISE-DAPT collaborative study included a total of 14 963 patients with coronary artery disease who underwent elective, urgent, or emergent PCI with coronary stent implantation and subsequent DAPT (appendix p 24). DAPT consisted of an association of aspirin plus a $P2Y_{12}$ inhibitor, most commonly clopidogrel (88%), whereas patients with an indication for long-term oral anticoagulation were excluded. Patients were pooled at an individual level from eight contemporary multicentre randomised clinical trials.[9–16] The patients were enrolled in 139 different clinical sites from 12 countries worldwide (appendix p 25). Extensive details regarding the pooled datasets are provided in the appendix (p 4). Inclusion and exclusion criteria are presented in the appendix (p 6). Details regarding population type, randomisation, DAPT duration, and drug adherence are presented in the appendix (p 8). All clinical trials were approved by the ethics committees at each study centre, and all patients provided written informed consent.

See Online for appendix

Outcomes

All clinical and laboratory variables included in this analysis were prospectively collected. The primary endpoint of this analysis was out-of-hospital bleeding defined according to the Thrombosis in Myocardial Infarction (TIMI) definition, and occurring 7 days or later after the initial invasive procedure, while bleeding occurring earlier was censored. We selected the 7 day timeframe as a conservative estimate based on the upper limit of current hospitalisation trends in patients with acute coronary syndrome, and to exclude events occurring during hospital stay, which are largely related to invasive procedures.[17] Further definitions for bleeding and clinical variables are provided in the appendix (p 4).

Validation cohorts

An external validation of the risk score was done in the context of two independent PCI-treated populations from the PLATelet inhibition and patient Outcomes (PLATO) trial and the BernPCI Registry (appendix p 24).[2] In brief, the PLATO trial (NCT00391872) included patients with ST elevation or non-ST elevation acute coronary syndrome randomly assigned to receive DAPT with either clopidogrel or ticagrelor in addition to aspirin for up to 12 months. In the current study, we restricted our analysis to patients undergoing PCI during index hospitalisation. The BernPCI registry (NCT02241291) included all patients undergoing PCI at Bern University Hospital, Switzerland, between Feb 23, 2009, and Dec 31, 2014.

The novel score was calculated and assigned to each participant in a similar manner as in the derivation cohort. The information on previous bleeding in PLATO was related to previous gastrointestinal bleeding, as no other previous bleeding types were prospectively collected in the study case report form. We calculated the PARIS bleeding risk score (age, body-mass index, current smoking, anaemia, creatinine clearance, triple therapy on discharge) in the external validation cohorts to provide comparative assessment of two prediction models.[18] Further details for score calculation in the validation cohorts are provided in the appendix (p 4). The primary endpoint for score validation was the occurrence of TIMI major or minor bleeding at 7 days or later after study inclusion and at up to 12 months. Data in both validation cohorts were prospectively collected and a blinded clinical events committee independently adjudicated adverse events. All patients enrolled provided written informed consent.

Statistical analysis

A detailed description of the statistical analysis is provided in the appendix (p 4). We estimated the 1 year cumulative incidence of bleeding by one minus the Kaplan-Meier estimate of bleeding-free survival at 1 year, to take loss to follow-up into account. We studied the associations between possible predictors and TIMI bleeding from day 7 onwards with a Cox regression analysis, stratified by trial. Potential predictors of bleeding were selected at univariable analysis ($p<0·10$).[19] Independent bleeding predictors were selected with multivariable backward selection ($p<0·10$). Linear predictor values were scaled and rounded to a score with integer values between 0 and 100. Discrimination of the bleeding risk score was assessed by trial-specific Harrell's c-indices, which were pooled with a random effects meta-analysis.[20,21] We evaluated the score performance by censoring patients' follow-up time and events occurring after the intended DAPT treatment duration and excluded patients who were not treated with DAPT at discharge (1·7%). The ability to identify patients at high bleeding risk was visualised by Kaplan-Meier cumulative bleeding incidence curves in bleeding risk score quartiles. Calibration was assessed by comparing predicted probabilities with 1 year Kaplan-Meier bleeding incidence estimates. Furthermore, discrimination and calibration of the bleeding risk score were assessed in the two external validation cohorts. c-Indices, integrated discrimination improvement (IDI), and net reclassification improvement (NRI) were computed to compare the performance of the PRECISE-DAPT score with the PARIS bleeding score in both validation cohorts.[22,23] Finally, we evaluated the effect of short (ie, 3–6 months) and long (ie, 12–24 months) DAPT duration on bleeding and ischaemic events across bleeding risk score quartiles in patients (n=10 081) randomly allocated to DAPT duration. Interaction between high (highest quartile) versus non-high (lowest three quartiles) bleeding risk score and DAPT duration was assessed by the heterogeneity in absolute risk differences for bleeding and ischaemic events. The analyses were done in accordance with the TRIPOD statement.[24] Data were analysed with R version 3.6 (R Foundation, Vienna, Austria).

Role of the funding source

All trials included in the PRECISE-DAPT collaborative study were investigator initiated and each sponsor had no role in the data analysis, interpretation, or writing of the report. The corresponding and first, second, and fourth authors (MV, FC, DvK, and DH) had full access to the data and had final responsibility for the decision to submit for publication.

Results

The study population included 14 963 patients with established coronary artery disease, and treated with coronary stent implantation (appendix p 9). DAPT at discharge was implemented in most patients (14 590 of 14 848 patients; 98·3%) with a median treatment duration of 360 days (IQR 95–365).

In a total of 21 963 person-years of follow-up (median follow-up 552 days, IQR 365–725), out-of-hospital TIMI major or minor bleeding occurred in 218 patients (incidence at 1 year 12·5 per 1000 patients), 124 of whom were major (incidence at 1 year 6·9 per 1000 patients). The median time to first occurrence of TIMI major or minor bleeding was 158 days (IQR 57–333) and 150 days (62–326) for TIMI major bleeding. The rate of bleeding stratified by clinical trial

	Hazard ratio (95% CI)	p value
Age (for each increase of 10 years)	1·34 (1·11–1·48)	0·005
Previous bleeding	4·14 (1·22–14·02)	0·023
White-blood-cell count (for each increase of 10^3 cells per µL)	1·06 (0·99–1·13)	0·078
Haemoglobin at baseline (for each increase of 1 g/dL)	0·67 (0·53–0·84)	0·001
Creatinine clearance (for each increase of 10 mL/min)	0·90 (0·82–0·99)	0·004

Age was truncated above 90 years and below 50 years. Haemoglobin at baseline was truncated above 12 g/dL and below 10 g/dL. Creatinine clearance was truncated above 100 mL/min. White-blood-cell count was truncated above 20×10^3 cells per µL and below 5×10^3 cells per µL.

Table 1: Multivariable analysis for out-of-hospital Thrombosis in Myocardial Infarction major or minor bleeding, study stratified with backward selection at an α level of 0·1

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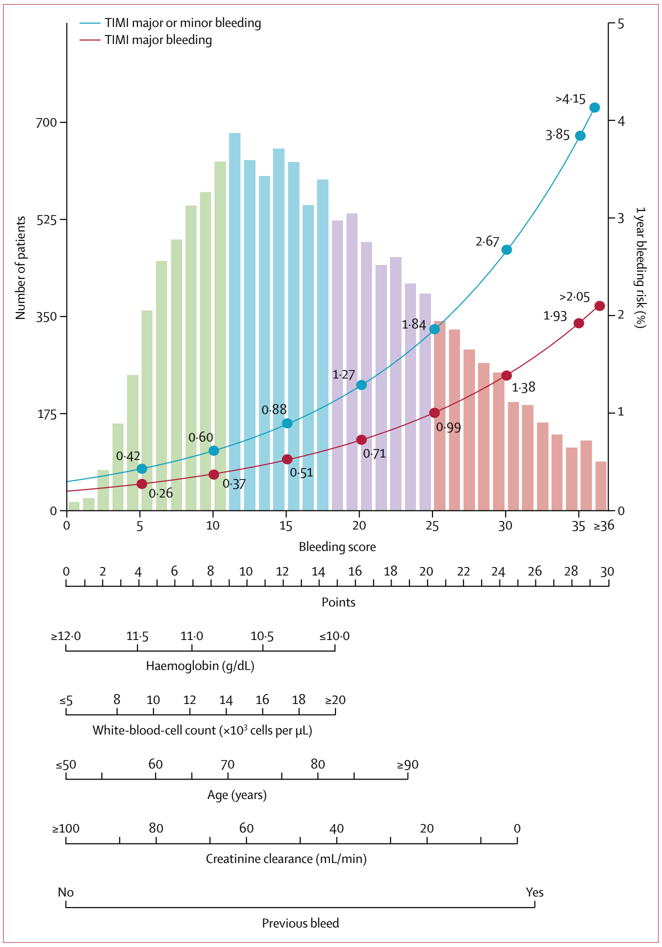

***Figure 1:* The PRECISE-DAPT score nomogram for bedside application**

Risk curves refer to out-of-hospital Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding and TIMI major bleeding at 12 months while on-treatment with dual antiplatelet therapy (DAPT). Histogram refers to the PRECISE-DAPT score distribution in the derivation cohort: green bars, the first score quartile (very low risk); blue bars, the second score quartile (low risk); purple bars, the third score quartile (moderate risk); and red bars, the fourth score quartile (high risk).

For the **web calculator and mobile app** see www.precisedaptscore.com

and type of $P2Y_{12}$ inhibitor are presented in the appendix (pp 12, 26).

Predictors with a p value less than 0·10 at univariable analysis (appendix p 9) were included in the multivariable model. Use of proton-pump inhibitors at discharge was excluded because of lack of prediction within studies where DAPT duration was randomised. Five predictors remained in the final model at a p value less than 0·10 (table 1), and showed consistent association with bleeding during the first trimester after treatment initiation as well as beyond (appendix p 13). An alternative model, which has been generated after excluding white-blood-cell count, is shown in the appendix (p 14).

From the final multivariable model, we developed a five-item bleeding risk score (age, creatinine clearance, haemoglobin, white-blood-cell count at baseline, and previous spontaneous bleeding—the PRECISE-DAPT score) assigning points to each factor based on the magnitude of association of each predictor with bleeding. A nomogram to calculate the score and the risk of bleeding at 12 months is presented in figure 1.

Similar information derived from the model lacking white-blood-cell count is presented in the appendix (p 27). A web calculator and mobile app are available online.

The PRECISE-DAPT score showed a c-index of 0·73 (95% CI 0·61–0·85) for out-of-hospital TIMI major or minor bleeding and 0·71 (0·57–0·85) for TIMI major bleeding within 12 months (table 2). c-Indices for each of the included studies are presented in the appendix (p 15). The score discrimination was consistent regardless of the clinical presentation at the time of PCI or treatment with clopidogrel or ticagrelor, but was apparently lower for patients treated with prasugrel and higher for those treated with proton-pump inhibitors (appendix pp 16–18). The performance of the score lacking white-blood-cell count is presented in table 2 and the appendix (p 29). Kaplan-Meier bleeding rates were consistently separated by score quartiles (very low risk: score ≤10; low risk: score 11–17; moderate risk: score 18–24; and high risk risk: score ≥25; figure 2).

The PRECISE-DAPT score was validated in 8595 PCI patients from the PLATO trial and 6172 participants from the BernPCI registry (appendix p 19). TIMI major or minor bleeding occurred in 145 patients (1·69%) in the PLATO trial and 94 patients (1·52%) in the BernPCI registry. TIMI major bleeding was noted in 94 patients (1·09%) in the PLATO trial and 62 patients (1·00%) in the BernPCI registry. The c-indices for out-of-hospital TIMI major or minor bleeding were 0·70 (95% CI 0·65–0·74) in the PLATO trial and 0·66 (0·61–0·71) in the BernPCI registry (table 2). Calibration appeared good between the derivation and BernPCI validation cohorts. In the PLATO validation cohort, the score maintained a consistent association between predicted probabilities and observed frequencies, whereas bleeding risk was slightly underestimated (appendix p 28). Score discrimination appeared consistent for Bleeding Academic Research Consortium (BARC) bleeding in the BernPCI cohort (BARC 3 or 5: c-index 0·68 [95% CI 0·63–0·73]; BARC 2, 3, or 5: c-index 0·68 [0·63–0·72]; appendix p 22). Score performance was also consistent, including bleeding occurring earlier than 7 days after PCI (appendix p 23). Discrimination for the score lacking white-blood-cell count was similar to the score including white-blood-cell count in the PLATO trial, whereas it was lower in the BernPCI registry (table 2, appendix p 29).

The PRECISE-DAPT score showed improved integrated discrimination and reclassification performance as

	TIMI major or minor bleeding						TIMI major bleeding					
	c-Index (95% CI)	p value*	NRI		IDI		c-Index (95% CI)	p value*	NRI		IDI	
			Index	p value	Index	p value			Index	p value	Index	p value
Derivation cohort												
PRECISE-DAPT	0·73 (0·61–0·85)	..	..	..	..	..	0·71 (0·57–0·85)	..	..	..	..	..
PRECISE-DAPT alternative	0·71 (0·57–0·84)	..	..	..	..	..	0·69 (0·53–0·85)	..	..	..	..	..
Validation cohort 1 (PLATO)												
PRECISE-DAPT	0·70 (0·65–0·74)	0·06	0·16	0·047	0·004	0·007	0·68 (0·63–0·74)	0·01	0·23	0·02	0·004	0·002
PRECISE-DAPT alternative	0·70 (0·66–0·74)	0·02	0·20	0·02	0·005	0·003	0·68 (0·63–0·74)	0·008	0·23	0·02	0·004	0·002
PARIS	0·66 (0·61–0·70)	Ref	Ref	..	Ref	..	0·62 (0·56–0·68)	Ref	Ref	..	Ref	..
Validation cohort 2 (BernPCI)												
PRECISE-DAPT	0·66 (0·61–0·71)	0·09	0·21	0·037	0·004	0·01	0·65 (0·58–0·71)	0·17	0·14	0·23	0·002	0·049
PRECISE-DAPT alternative	0·63 (0·58–0·68)	0·82	0·09	0·37	0·001	0·07	0·62 (0·55–0·68)	0·57	0·03	0·77	0·0001	0·15
PARIS	0·63 (0·58–0·67)	Ref	Ref	..	Ref	..	0·62 (0·56–0·69)	Ref	Ref	..	Ref	..

PRECISE-DAPT score is age, creatinine clearance, haemoglobin, white-blood-cell count at baseline, and previous spontaneous bleeding. PRECISE-DAPT alternative score is age, creatinine clearance, haemoglobin at baseline, and previous spontaneous bleeding. PARIS is age, body-mass index, current smoking status, presence of anaemia (haemoglobin <12 g/dL in men and <11 g/dL in women), creatinine clearance <60 mL/dL, and treatment with triple therapy (ie, aspirin plus $P2Y_{12}$ inhibitor plus oral anticoagulant) at discharge. TIMI=Thrombosis in Myocardial Infarction. NRI=net reclassification improvement. IDI=integrated discrimination improvement. *The PARIS score has been used as reference to test c-indices, IDI, and NRI as compared with the PRECISE-DAPT scores.

Table 2: **Discriminative ability of the PRECISE-DAPT score in the derivation cohort and discriminative–reclassification ability in comparison with the PARIS score in the validation cohorts for out-of-hospital bleeding occurring while on-treatment with dual antiplatelet therapy (DAPT)**

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compared with the PARIS score in both validation cohorts for TIMI major or minor bleeding (table 2). Discriminative ability according to the c-index was similar between the two scores (table 2). The alternative version of the score lacking white-blood-cell count showed improved discrimination and reclassification in the PLATO validation cohort, and similar performance as compared with the PARIS score in the BernPCI second validation cohort.

DAPT duration was randomly allocated in five of the eight studies included in the generation dataset, with 5050 patients assigned to either 12 months or 24 months of treatment and 5031 to 3 months or 6 months.[11–15] We observed a significant increase in bleeding with a long (12–24 months) rather than short (3–6 months) duration of treatment exclusively in patients at high bleeding risk (absolute risk difference [ARD] +2·59% [95% CI +0·82 to +4·34]; number needed to treat: 38) but not in those without a high bleeding risk profile (ie, very low risk, low risk, and moderate risk: mean of the first three quartiles ARD +0·14% [–0·22 to +0·49]; $p_{interaction}$=0·007; figure 3). This remained consistent after censoring events occurring beyond 1 year after PCI ($p_{interaction}$ =0·047; appendix p 30). Concurrently, longer DAPT duration reduced the composite ischaemic endpoint of myocardial infarction, definite stent thrombosis, stroke, or target vessel revascularisation in those at non-high bleeding risk (ARD –1·53% [95% CI –2·64 to –0·41]; number needed to treat: 65), but not in those at high bleeding risk (ARD +1·41% [–1·67 to +4·50]; $p_{interaction}$=0·07; figure 4). When the composite of myocardial infarction, definite ST, or stroke was assessed, longer DAPT duration was not associated with a clear benefit in patients at non-high bleeding risk (ARD –0·42% [95% CI –1·02 to +0·17]) and to the possibility of harm in those at high bleeding risk (ARD +1·96% [–0·39 to +4·30]; $p_{interaction}$=0·054; appendix p 31). The resulting net effect on bleeding and ischaemia suggested a favourable outcome with 12–24 month DAPT in patients at non-high bleeding risk, but not in those at high PRECISE-DAPT risk (figure 4).

At sensitivity analysis, we tested the effect of randomised DAPT duration among bleeding risk strata in the subgroup of patients presenting with acute coronary syndrome at the time of PCI, with results remaining largely consistent with those observed in the overall population (appendix pp 32, 33). Patients presenting with acute coronary syndrome and with a PRECISE-DAPT score of at least 25 showed a significant increase in TIMI bleeding after treatment with longer DAPT (ARD +2·61% [95% CI +0·19 to +4·99]; number needed to treat: 38), whereas those with a non-high PRECISE-DAPT risk score did not (ARD +0·14% [–0·22 to +0·49]; $p_{interaction}$=0·034). At the same time, longer DAPT duration reduced the composite ischaemic endpoint in patients with acute coronary syndrome at a non-high PRECISE-DAPT score (ARD –4·13% [95% CI –6·09 to –2·15]; number needed to treat: 24), but not in those with a PRECISE-DAPT score of at least 25 (ARD +1·54% [–3·27 to +6·32]; $p_{interaction}$=0·032; appendix p 32).

Discussion

Ischaemic recurrences after stenting have dropped considerably in the last years thanks to the introduction of novel stent technologies and progressive refinement of pharmaco-interventional techniques. However, due to more potent and prolonged platelet inhibition, the incidence of major bleeding has increased.[25] DAPT-

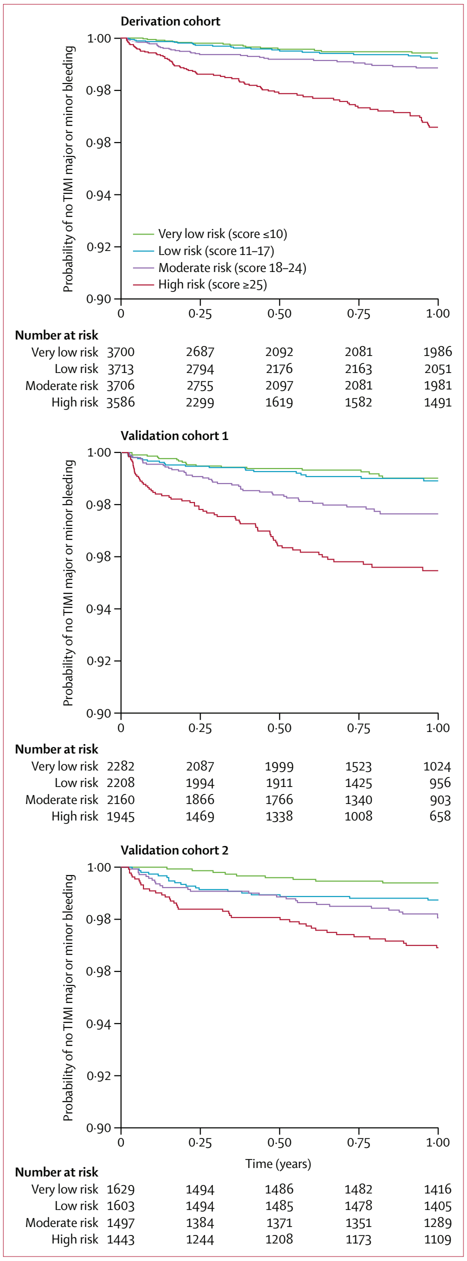

Figure 2: **Kaplan-Meier estimates of survival free from bleeding in both derivation and validation cohorts stratified by score quartiles**
Estimates for Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding occurring while on-treatment with dual antiplatelet therapy are presented. Validation cohort 1 from the PLATO trial. Validation cohort 2 from the BernPCI registry.

related bleeding is the most common complication after coronary stent implantation in current practice, and it is associated with lower survival, lower quality of life, and higher health costs.[26,27]

Numerous bleeding and ischaemic risk scores have been proposed for the prediction of events occurring alternatively in-hospital or out-of-hospital after PCI.[8,18,28,29] However, most failed to be implemented in everyday clinical practice largely because their use did not affect treatment decisions.[8,29]

This study developed and validated the PRECISE-DAPT score, a tool for the prediction of out-of-hospital bleeding in patients undergoing coronary stenting. The novel score showed reasonable discrimination and calibration in two independent validation cohorts of patients with contemporary use of all three oral $P2Y_{12}$ inhibitors and has potential to inform decision making on DAPT duration. We confirmed the role of well-known risk factors associated with out-of-hospital bleeding such as age and haemoglobin at baseline. Similarly, covariates, which have been previously associated with in-hospital bleeding, such as renal function, and white-blood-cell count, remained associated with bleeding occurring at later timepoints.[27,30] Additionally, we featured the relevance of previous bleeding, which is commonly appraised in practice,[31] and emerged as the strongest predictor of bleeding in our score.

International guidelines suggest individualisation of the antiplatelet treatment duration,[5,6] as all randomised studies invariably showed real or potential bleeding liability associated with prolonged versus shortened DAPT duration regimens.[4,7,13] We observed that among patients deemed at high bleeding risk based on the PRECISE-DAPT score, prolonged DAPT was associated with no ischaemic benefit but a remarkable bleeding burden leading to a number needed to treat for harm of 38. A longer treatment in patients without high bleeding risk was associated with a marginal or even no increase of bleeding and a significant reduction of the composite ischaemic endpoint. Selecting upfront a shorter than 12 month treatment duration in patients deemed at high bleeding risk (PRECISE-DAPT score ≥25) might prevent exposing them to an excessive bleeding hazard. In turn, patients at non-high bleeding risk (PRECISE-DAPT score <25) might receive a standard (ie, 12 months) or a prolonged (ie, >12 months) course of treatment if tolerated. A separate assessment of this treatment strategy in patients with acute coronary syndrome provided consistent findings. Current recommendations for DAPT duration suggest that patients with acute coronary syndrome should undergo at least 12 month treatment unless the bleeding outweighs ischaemic risks.[5] The PRECISE-DAPT score was able to select patients with acute coronary syndrome with an excessive bleeding risk, who failed to derive ischaemic benefit from 12 month or 24 month DAPT duration, whereas a more favourable net outcome was observed in these selected patients with a shorter DAPT duration.

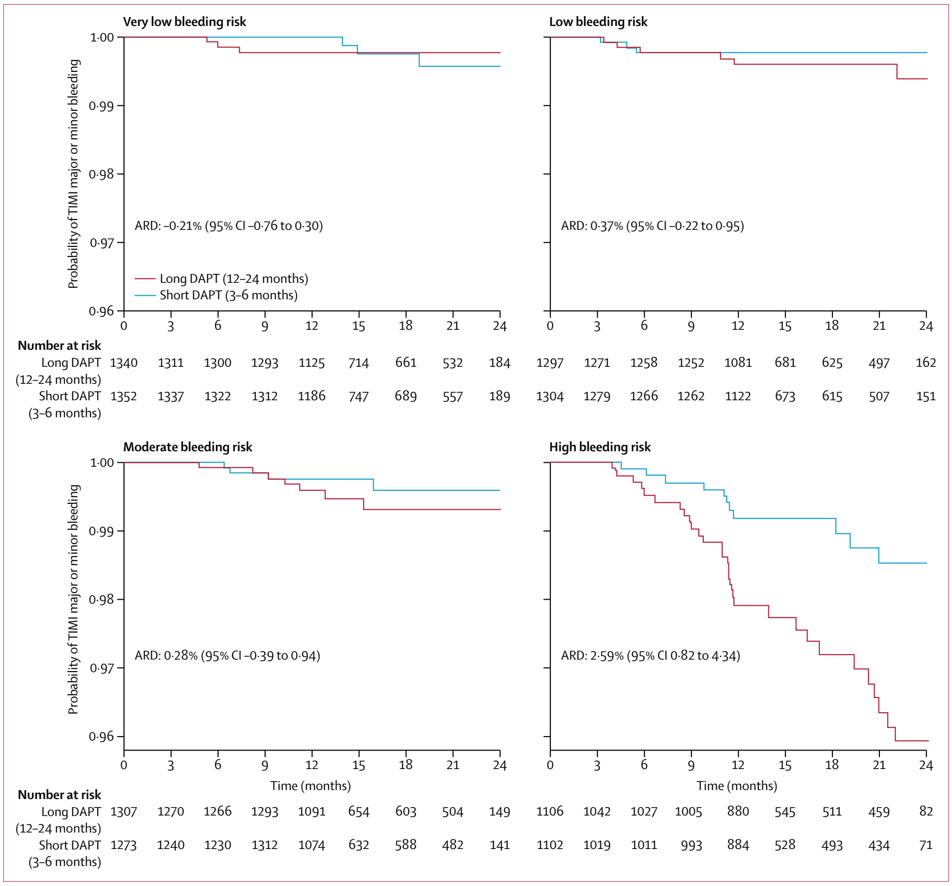

***Figure 3:* 24 month Kaplan-Meier estimates of survival free from Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding among PRECISE-DAPT bleeding risk quartiles (ie, very low, low, moderate, and high bleeding risk) for patients randomly assigned to long (12–24 months) or short (3–6 months) dual antiplatelet therapy (DAPT)**

Absolute risk differences (ARDs) are presented: a positive ARD represents the risk increase for a long, as compared with a short, course of DAPT.

A prediction algorithm was recently proposed for patients who tolerated 12 month DAPT to select those eligible for treatment prolongation.[8] However, this strategy cannot be applied earlier at the time of treatment initiation, to select a shorter than 12 month treatment duration in patients at high bleeding risk. Earlier decision making is especially desirable for bleeding prevention, considering that, as observed in our analysis, median time to bleeding was 5–6 months.

Two risk scores have been developed to evaluate the absolute ischaemic and bleeding risk after coronary stenting in the context of the PARIS registry.[18] At variance with our analysis, the PARIS study did not provide a decision-making algorithm for deciding upon DAPT duration. With respect to bleeding risk prediction, our score ultimately proved at least as good as PARIS, showing improved integrated discrimination and net reclassification, whereas c-indices were numerically but not always statistically superior.

Our study had a number of strengths. We derived a simple risk score that was developed and validated from three largely representative, prospectively investigated patient cohorts with rigorous event adjudication, and based on a well standardised and accepted bleeding definition.[2,5,6] At variance with previous scores designed to predict in-hospital bleeding,[28] our model was developed to predict out-of-hospital bleeding events, which are more relevant in the decision making on secondary prevention with antithrombotic medications. This novel score is the first being validated in patients

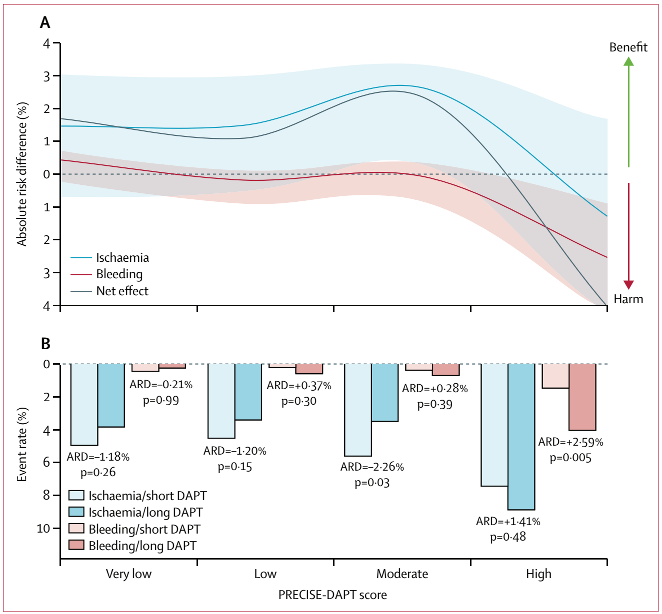

***Figure 4:* Absolute risk difference (ARD) for a long (12–24 months) as compared with a short (3–6 months) dual antiplatelet therapy (DAPT) duration with respect to ischaemia (myocardial infarction, definite stent thrombosis, stroke, or target vessel revascularisation) and bleeding (Thrombosis in Myocardial Infarction major or minor bleeding) within the four PRECISE-DAPT score quartiles**

ARD curves plotted on the upper side of the zero line represent benefit from a long DAPT treatment, whereas curves plotted on the lower side of the zero line represent harm from a long DAPT as compared with a short treatment (A). Event rate for ischaemia and bleeding after a long or short DAPT treatment within the four PRECISE-DAPT quartiles. A positive ARD represents the risk increase for a long as compared with a short course of DAPT (B).

treated with more potent $P2Y_{12}$ inhibitors, which represent the standard of care for patients with acute coronary syndrome. This score was retrospectively applied among patients randomly assigned to a shortened or prolonged DAPT duration to propose and validate simple DAPT duration treatment strategy according to bleeding risk. A simplified score modelled without white-blood-cell count was also derived and validated, which might prove useful in cases where white-blood-cell count is not available.

Among the limitations, we acknowledge that event discrimination in our score ranged from moderate to good. Emerging predictors for bleeding, including frailty, might be missing in our model,[32] and future studies should implement clinical, laboratory, or genetic factors to possibly improve its discriminative capability. Information regarding single patients' drug adherence was lacking in our dataset and each patient was considered on-DAPT treatment according to the prespecified or randomised treatment duration at the time of PCI. A granular collection of patient on-treatment or off-treatment status during follow-up would have been desirable. Information regarding previous bleeding in the PLATO validation cohort was limited to previous gastrointestinal bleeding. Our score slightly underestimated bleeding risk in the PLATO PCI population possibly because of the higher bleeding risk in the PLATO trial, which included only patients with acute coronary syndrome, or as a reflection of chance. However, given the calibration results observed in the all-comer BernPCI registry, our score appears well suited to predict bleeding risk status in real-world patients. Discrimination in patients treated with prasugrel was poorer. Since prasugrel administration was not randomised in both derivation and BernPCI validation cohorts, and its use in individuals older than 75 years or with increased bleeding liability is discouraged, patients at lower bleeding risk might have been selected for this treatment, potentially hampering the score's ability to correctly discriminate bleeding. Based on similar considerations, the score did slightly better in patients taking proton-pump inhibitors. The PARIS score discrimination might have been underestimated since patients on oral anticoagulants were not included in our study. However, these patients are per se considered at high bleeding risk. Dedicated bleeding risk score for patients on oral anticoagulants should probably be used to better estimate bleeding risk and corresponding treatment strategies. Whether the routine use of the PRECISE-DAPT risk score in an unselected population substantially mitigates bleeding risk by better informing decision making remains to be prospectively ascertained.

In conclusion, we developed and validated the PRECISE-DAPT score, a simple five-item prediction algorithm for the prediction of out-of-hospital bleeding in patients treated with DAPT. The PRECISE-DAPT score identified patients in whom the benefits of prolonged DAPT outweighed the risks and vice versa. In the context of a comprehensive clinical evaluation process, this tool can support clinical decision making for treatment duration. Prospective validation of this score in practice remains desirable.

Contributors

MV and FC conceived, designed and interpreted the study, drafted the manuscript, and revised and approved the final manuscript. DvK designed the study, analysed and interpreted data, and revised and approved the final manuscript. EWS, SJ, FF, LR, TP, DH, TZ, M-KH, H-SK, AC, PGS, TP, LW, DLB, GWS, and SW interpreted data, and revised and approved the final version of the manuscript.

Declaration of interests

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Summary and Conclusions:

In the last years there was a radical change in the perception of the ischemia/bleeding balance in patients undergoing percutaneous coronary intervention (PCI), which was reflected in both guidelines and the community (Chapter 1.1, 1.2, 1.3). Despite the reduction of ischemic recurrences has been traditionally the main focus of clinical research, recent data pointed the attention towards bleeding events, which are common after more potent and prolonged treatments. In patients managed with antithrombotics after an acute coronary syndrome, the impact of major bleeding as compared to recurrent myocardial infarction appeared similar or even greater in particular cases (Chapter 2.1). This data reinforces the concept that both ischemia and bleeding should be prevented, and a careful assessment of ischemia/bleeding risk should be made.

Many pharmacological and mechanical strategies have been proposed to reduce bleeding and ischemia early and late after PCI.

The use of the radial artery rather than femoral artery as access site for PCI reduces access site bleeding (Chapter 3.1). However, radial intervention is technically more challenging and might be complicated by radial artery occlusion, which hampers future catheterizations from this route. Radial catheterization, provoke ubiquitous acute injuries to the radial artery wall and increase arterial intima and total wall thickness (Chapter 3.2). Still, these changes did not seem to be associated with radial artery occlusion or symptoms onset up to one month after the procedure. Bigger studies with novel lesion definition and classification are required to unravel the association of these microscopic injuries and radial artery occlusion, as well as the eventual role of antithrombotic therapy to prevent this complication.

Similarly, the use of intravenous antiplatelet agents such as glycoprotein IIb/IIIa inhibitors (GPI) during the procedure reduce peri-procedural ischemic complications in selected patients at the cost of increased bleeding risk (Chapter 3.3). Tirofiban, a GPI with a short half-life, is now distributed in Europe as a generic drug in a phosphate buffered formulation and as a branded drug in a citrate buffered formulation. Phosphate buffered formulation of tirofiban as compared with unfractionated heparin (UFH) was associated with a higher rate of thrombocytopenia with a potentially increased risk for serious bleeding events. In contrast, this effect was not present with the citrate buffered formulation (Chapter 3.4). These findings warrant caution and further evaluation of the safety profile of the generic formulation of tirofiban, which is currently marketed in Europe.

Coronary stent selection has been traditionally considered a major determinant of post-procedural antithrombotic treatment duration, hence impacting bleeding/ischemia balance (Chapter 4.1). Since drug-eluting stents (DES) have traditionally been considered more thrombogenic, based on the preliminary data coming from first-generation devices, it was common practice to provide longer DAPT treatments to patients treated with DES as compared to bare-metal stents (BMS). Consequently, patients deemed at high bleeding risk, which would not tolerate prolonged DAPT courses, have been more commonly selected for BMS implantation (Chapter 1.2). Nonetheless, modern DES demonstrated better outcomes as compared to BMS in patients at high bleeding risk and a fixed short DAPT duration (Chapter 4.2). These results were also replicated in patients with chronic kidney disease that were randomized to short vs. long DAPT duration (Chapter 4.3). These evidence, together with that coming from recent randomized trials, set the basis for a paradigm shift for stent selection in patients at high bleeding risk, in which the routine use of BMS does not seem anymore justifiable.

Despite the fact that adverse event rate is relatively higher during the first month after the procedure, the vast majority of ischemic and bleeding complications occur late after revascularization, and might be modulated by adjusting DAPT duration. As such the selection of optimal DAPT duration after PCI has a central role in the balance of ischemic/bleeding risk (Chapter 1.1). Longer DAPT duration was associated with a consistent reduction of major adverse cardiovascular events (MACE) and stent thrombosis (Chapter 5.1). Still, longer treatment duration was also associated with an increase in major bleeding and a worrisome increase in mortality (Chapter 5.1), which raised concern in the community (Chapter 1.3). This was mostly driven by events occurred in the DAPT trial, in which longer DAPT was associated with a significant mortality increase among patients with stable coronary artery disease (CAD) but not among patients with acute coronary syndrome (ACS) at the time of PCI. In addition, at least part of the increased risk of mortality in DAPT and PEGASUS trials was related to cancer. The higher incidence of malignancy related mortality in patients treated with longer DAPT was observed when data from these two trials were pooled, prompting careful evaluation for longer treatment duration in patients with active or recent malignancy (Chapter 5.3). The definitive impact of DAPT duration on mortality remains unclear, and whether this effect is class-specific or drug-specific should be further investigated (Chapter 5.2).

"It is more important to know what sort of person has a disease than to know what sort of disease a person has." With this statement more than 2,400 years ago, Hippocrates, the father of western medicine, recognized the individuality of each patient and the importance of adapting treatment accordingly. Since than, clinicians struggled understanding patients' characteristics that predict a different response to treatment. Adjusting treatment based on baseline characteristics, biohumoral or genomic markers is the premise of *Precision Medicine*, which aims to the construction of an evidence-based medical model for customized decision-making based on single patient characteristics. This assumes particular importance when treatment benefits might be outweighed by its harm, like it is in the case of antithrombotic drug selection. Unravelling patients' characteristics, which might modify DAPT duration selection appears of paramount importance. Clinical presentation at the time of PCI (i.e. stable vs. unstable CAD) is an important factor to be considered for DAPT selection. Patients with prior myocardial infarction showed a significant benefit in terms of MACE and stent thrombosis reduction after extended DAPT duration (i.e. more than 12 months). Despite this was associated with a consistent increase of non-fatal bleeding, this strategy was associated with a significant reduction of cardiac mortality (Chapter 5.6). Similarly, serious bleeding complications were relatively more frequent after 24- as compared to 6-months DAPT in stable patients as compared to unstable patients at the time of PCI (Chapter 5.5). As a consequence, net adverse clinical events were significantly more common after a prolonged DAPT treatment in patients with stable CAD, but not in those with unstable CAD at the time of PCI (Chapter 5.5). This evidence strongly suggests that clinical presentation

should be a primary factor in DAPT duration selection (Chapter 5.5 and 5.6). Similarly, anatomical considerations for lesion complexity should also be accounted. The presence of a lumen narrowing (i.e. >30%) or stenting in the left main or proximal left anterior descending coronary artery was associated with a significant ischemic benefit after a 24- as compared to 6-months DAPT treatment (Chapter 5.7). This remained consistent irrespective coronary stenting was performed in these proximal segments, underscoring how the presence of CAD in proximal segments might be itself a marker of more extensive coronary disease, which benefit from a more aggressive antithrombotic approach.

International guidelines support weighting bleeding risk prior to selection of treatment duration and suggest a shorter than 12 month DAPT regimen in patients at high bleeding risk. Although this seems a reasonable strategy to at least reduce the risk for harm, no standardized tool exists to weigh bleeding risk at the time of DAPT initiation. Clinical risk scores, which integrate predictors to establish an individual's absolute risk of a condition, are often used in practice to estimate the bleeding risk in patients with atrial fibrillation who are treated with oral anticoagulants, but their application in the field of DAPT has never been evaluated. We tested three different bleeding risk scores which has been developed to predict bleeding events occurring in-hospital in patients with ACS (i.e. CRUSADE and ACUITY) or out-of-hospital in patients with atrial fibrillation (i.e. HAS BLED) to a population of patients randomized to 6 vs. 24 months DAPT (Chapter 5.10). We observed that CRUSADE score predicted bleeding significantly better than HAS BLED and similar to ACUITY. CRUSADE score showed ability to select patients at high bleeding risk, which were significantly harmed from a longer treatment with DAPT in terms of major bleeding and transfusion. However, CRUSADE score was developed to predict in hospital bleeding, and might not be the best tool to predict bleeding occurring months or years after the initial hospital admission. In order to develop a novel tool to predict bleeding during DAPT and potentially supporting decision-making for DAPT duration we developed the PRECISE-DAPT score (Chapter 5.11). This score was developed in a pooled dataset of almost 15,000 patients and externally validated in two independent large cohorts of patients with clinically adjudicated events. PRECISE-DAPT showed good discrimination and calibration for out-of-hospital major bleeding in both derivation and validation cohorts. Among patients randomized to different DAPT duration, a longer DAPT (i.e. 12-24 months) as compared to a short treatment (i.e. 3-6 months) significantly increased the rate of major bleeding without providing any ischemic benefit in patients deemed at high bleeding risk (PRECISE-DAPT score ≥25). Contrariwise, longer DAPT in patients deemed at low bleeding risk (PRECISE-DAPT score <25) provided a significant reduction of ischemic events with no significant trade-off in bleeding (Chapter 5.11). The PRECISE-DAPT score might be useful to objectively define long term bleeding risk in patients treated with PCI, hence supporting decision-making for DAPT duration.

Samenvatting en Conclusies:

In recente jaren heeft een radicale verandering plaatsgevonden in de perceptie over de balans tussen ischemie en bloedingen in patiënten die een percutane coronaire interventie (PCI) ondergaan, wat zichtbaar werd in de zowel de behandelrichtlijnen als in de wetenschappelijke gemeenschap (Hoofdstuk 1.1, 1.2). Ondanks de traditioneel sterke focus van klinisch onderzoek op de reductie van ischemische herhalingen, hebben recente data de aandacht verlegt naar bloedingen, die vaker voorkomen na krachtigere en langere behandelingen. In patiënten die na een acuut coronair syndroom met antitrombotica behandeld worden, is de impact van ernstige bloedingen vergelijkbaar of in specifieke gevallen sterker dan die van een herhaald hartinfarct (Hoofdstuk 2.1). Deze data benadrukken het concept dat zowel ischemie als bloedingen voorkomen moeten worden, en dat een voorzichtige afweging van ischemisch risico en bloedingsrisico moet worden gemaakt.

Een groot aantal farmacologische en mechanische strategieën is voorgesteld om bloedingen en ischemie na PCI, zowel vroeg als laat, te reduceren.

Het gebruik van de radiale slagader in plaats van de femorale slagader als toegang voor PCI reduceert toegangslocatie-gerelateerde bloedingen (Hoofdstuk 3.1). Echter, radiale interventie is technisch uitdagender en kan leiden tot radiale arteriële occlusie, wat toekomstige radiale katheterisatie bemoeilijkt. Radiale katheterisatie leidt onomstreden tot acute beschadiging van de radiale slagaderwand en vergroot de dikte van de arteriële intima en de totale vaatwand (Hoofdstuk 3.2). Toch lijken deze veranderingen niet geassocieerd te zijn met radiale arteriële occlusie of het ontstaan van symptomen tot een maand na de procedure. Grotere studies met een grondige definitie en classificatie van slagadervernauwingen zijn noodzakelijk om het verband te ontrafelen tussen deze microscopisch beschadigingen en radiale arteriële occlusie, en de eventuele rol van antitrombotische therapie om deze complicatie te voorkomen.

Evenzo vermindert het gebruik bij geselecteerde patiënten van intraveneuze antibloedplaatjesagentia, zoals glycoproteïne IIb/IIIa-remmers (GPI), peri-procedurele ischemische complicaties tijdens de procedure ten koste van een verhoogd bloedingsrisico (hoofdstuk 3.3). Tirofiban, een GPI met een korte halfwaardetijd, wordt nu in Europa gedistribueerd als een generiek geneesmiddel in een fosfaat-gebufferde formulering en als een merkgeneesmiddel in een citraat gebufferde formulering. De fosfaat-gebufferde formulering van tirofiban was geassocieerd met een hoger percentage trombocytopenie in vergelijking met ongefractioneerde heparine (UFH), met mogelijk een verhoogd risico op ernstige bloeding. Dit effect was echter niet aanwezig met de citraat-gebufferde formulering (hoofdstuk 3.4). Deze bevindingen vereisen voorzichtigheid en verdere evaluatie van het veiligheidsprofiel van de generieke formulering van tirofiban die momenteel in Europa op de markt wordt gebracht.

Coronaire stent-selectie wordt van oudsher beschouwd als een belangrijke bepalende factor voor de post-procedurele antithrombotische behandelingsduur, en heeft derhalve invloed op de bloeding / ischemiebalans (Hoofdstuk 4.1). Aangezien drug-eluting stents (DES) van oudsher als meer trombogeen werden beschouwd – gebaseerd op gegevens afkomstig van de eerste generatie stents – was het gebruikelijk om langere DAPT-behandelingen te bieden aan patiënten die met DES werden behandeld in in plaats van met bare-metal stents (BMS). Patiënten met een hoog bloedingsrisico, die geen langdurige DAPT-behandeling zouden tolereren, werden daarom vaker geselecteerd voor BMS-implantatie (hoofdstuk 1.2). Desalniettemin lieten moderne DES betere resultaten zien in vergelijking met BMS bij patiënten met een hoog bloedingsrisico en een vaste korte DAPT-duur (hoofdstuk 4.2). Deze resultaten werden gerepliceerd in patiënten met chronische nierziekte die werden gerandomiseerd naar een korte versus lange DAPT-duur (hoofdstuk 4.3). Dit bewijsmateriaal, samen met dat van recente gerandomiseerde studies, heeft de basis gelegd voor een paradigmaverschuiving in stentselectie bij patiënten met een hoog bloedingsrisico, waarbij het routinematige gebruik van BMS niet meer te rechtvaardigen lijkt.

Ondanks het feit dat de mate van complicaties in de eerste maand na de procedure relatief hoog is, treedt de overgrote meerderheid van de ischemische en bloedingscomplicaties pas lang na revascularisatie op en kan deze worden beïnvloed door de DAPT-duur aan te passen. Als zodanig heeft de selectie van de optimale DAPT-duur na PCI een centrale rol in de balans van ischemisch en bloedingsrisico (hoofdstuk 5.4). Langere DAPT-duur ging gepaard met een consistente vermindering van ernstige ongunstige cardiovasculaire voorvallen (MACE) en stenttrombose (Hoofdstuk 5.1). Toch was langere behandelingsduur ook geassocieerd met een toename van ernstige bloedingen en een zorgwekkende toename van de mortaliteit (Hoofdstuk 5.1), die bezorgdheid wekte in de gemeenschap (Hoofdstuk 1.2). Dit werd voornamelijk veroorzaakt door voorvallen in de DAPT-trial, waarbij langere DAPT geassocieerd was met een significante mortaliteitstoename bij patiënten met stabiele coronaire hartziekte (CAD) maar niet bij patiënten met een acuut coronair syndroom (ACS) op het moment van PCI.

Bovendien was minstens een deel van de verhoogde mortaliteit in de DAPT- en de PEGASUS-trials gerelateerd aan kanker. De hogere maligniteit-gerelateerde mortaliteit bij patiënten die met langere DAPT werden behandeld, werd waargenomen in de samengevoegde data van deze twee trials, wat een zorgvuldige evaluatie instigeert van de langere behandelingsduur bij patiënten met actieve of recente maligniteit (Hoofdstuk 5.3). De precieze impact van de DAPT-duur op mortaliteit blijft onduidelijk en of dit effect klasse-specifiek of specifiek voor het geneesmiddel is, moet verder worden onderzocht (hoofdstuk 5.2).

"Het is belangrijker om te weten wat voor soort persoon een ziekte heeft dan te weten wat voor soort ziekte een persoon heeft." Met deze verklaring meer dan 2400 jaar geleden, erkende Hippocrates, de vader van de westerse geneeskunde, de individualiteit van elke patiënt en het belang om de behandeling dienovereenkomstig aan te passen. Sindsdien worstelden clinici met het begrijpen van de kenmerken van patiënten die een andere reactie op de behandeling voorspellen. Aanpassing van de behandeling op basis van baselinekenmerken, bio-humorale of genomische markers is de premisse van de *Precisiegeneeskunde*, die gericht is op de constructie van een evidence-based medisch model voor gepersonaliseerde besluitvorming op basis van de individuele kenmerken van een patiënt.

Dit is in het bijzonder belangrijk wanneer de voordelen van de behandeling teniet kunnen worden gedaan door de nadelen, zoals het geval is bij de antitrombotische geneesmiddelenkeuze. Het ontrafelen van de patiëntkenmerken die de duur van DAPT-selectie zouden kunnen bepalen, lijkt van het allergrootste belang. Klinische presentatie op het moment van PCI (d.w.z. stabiele vs. instabiele CAD) is een belangrijke factor waarmee rekening moet worden gehouden voor DAPT-selectie. Patiënten met een voorafgaand myocardinfarct vertoonden een significant voordeel in reductie van MACE en stenttrombose na verlengde DAPT-duur (dat wil zeggen meer dan 12 maanden). Ondanks dat dit gepaard ging met een consistente toename van niet-fatale bloedingen, was deze strategie geassocieerd met een significante verlaging van de cardiale mortaliteit (Hoofdstuk 5.6). Evenzo kwamen ernstige bloedingscomplicaties relatief vaker voor na 24 in vergelijking met 6 maanden DAPT bij stabiele patiënten in vergelijking met instabiele patiënten ten tijde van PCI (hoofdstuk 5.5). Als gevolg hiervan kwamen klinische ongewenste voorvallen significant vaker voor bij een langdurige DAPT-behandeling bij patiënten met stabiele CAD, maar niet bij patiënten met instabiele CAD op het moment van PCI (Hoofdstuk 5.5). Dit bewijs suggereert krachtig dat klinische presentatie een primaire factor zou moeten zijn bij de selectie van de DAPT-duur (hoofdstuk 5.5 en 5.6). Evenzo moeten ook anatomische overwegingen van de complexiteit van de laesie in aanmerking worden genomen. De aanwezigheid van een vernauwing van het lumen (d.w.z.> 30%) of stent implantatie in de linker grote kransslagader of de proximale linker voorste dalende kransslagader was geassocieerd met een significant ischemisch voordeel na 24 vergeleken met 6 maanden durende DAPT-behandeling (Hoofdstuk 5.7). Dit effect bleef consistent ongeacht of coronaire stent implantatie plaatsvond in deze proximale segmenten, wat onderstreept hoe de aanwezigheid van CAD in proximale segmenten zelf een marker kan zijn van een uitgebreidere coronaire ziekte, die baat heeft bij een agressievere antitrombotische aanpak.

Internationale richtlijnen ondersteunen de weging van het bloedingsrisico voorafgaand aan de selectie van de behandelingsduur en suggereren een DAPT-regime van minder dan 12 maanden bij patiënten met een hoog bloedingsrisico. Hoewel dit een redelijke strategie lijkt om het risico op schade op zijn minst af te laten nemen, bestaat er geen gestandaardiseerd hulpmiddel om het risico op bloedingen te wegen op het moment van de DAPT-initiatie. Klinische risicoscores, die voorspellers integreren om het absolute risico van een aandoening vast te stellen, worden in de praktijk vaak gebruikt om het bloedingsrisico te schatten bij patiënten met atriale fibrillatie die worden behandeld met orale anticoagulantia, maar hun toepassing op het gebied van DAPT is nooit geëvalueerd. We hebben drie verschillende bloedingsrisico-scores getest die zijn ontwikkeld om bloedingen in het ziekenhuis bij patiënten met ACS (CRUSADE en ACUITY) of na ontslag uit het ziekenhuis bij patiënten met atriale fibrillatie (HAS BLED) te voorspellen voor een populatie van patiënten gerandomiseerd naar 6 versus 24 maanden DAPT (hoofdstuk 5.10). We hebben vastgesteld dat CRUSADE een bloeding significant beter voorspelde dan HAS BLED en vergelijkbaar met ACUITY. CRUSADE score toonde mogelijkheid om patiënten te selecteren met een hoog bloedingsrisico, die significant werden geschaad door een langere behandeling met DAPT in termen van ernstige bloedingen en transfusie. CRUSADE-score werd echter ontwikkeld om bloedingen in het ziekenhuis te voorspellen en is mogelijk niet het beste hulpmiddel om bloedingen te voorspellen die zich maanden of jaren na de eerste ziekenhuisopname voordoen. Om een nieuw hulpmiddel te ontwikkelen om bloeding tijdens DAPT te voorspellen en mogelijk de besluitvorming over DAPT-duur te ondersteunen, hebben we de PRECISE-DAPT-score ontwikkeld (hoofdstuk 5.11). Deze score is ontwikkeld op basis van een gepoolde dataset van bijna 15.000 patiënten en extern gevalideerd in twee onafhankelijke grote cohorten patiënten met klinisch beoordeelde voorvallen. PRECISE-DAPT toonde goede discriminatie en kalibratie voor ernstige bloedingen na ontslag uit het ziekenhuis, in zowel ontwikkel- als validatiecohorten.

Van de patiënten die werden gerandomiseerd naar verschillende DAPT-duren, verhoogde een langere DAPT (12-24 maanden) – in vergelijking met een korte behandeling (3-6 maanden) – significant het aantal ernstige bloedingen, zonder een ischemisch voordeel te bieden bij patiënten met een hoog voorspeld bloedingsrisico (PRECISE-DAPT score ≥25). Daarentegen gaf een langere DAPT bij patiënten met een laag voorspeld bloedingsrisico (PRECISE-DAPT score <25) een significante vermindering van het aantal ischemische voorvallen zonder significante toename in bloedingen (Hoofdstuk 5.11). De PRECISE-DAPT-score kan nuttig zijn om langdurig bloedingsrisico's objectief te definiëren bij patiënten die worden behandeld met PCI, en ondersteunt daarmee de besluitvorming over de DAPT-duur.

Acknowledgements:

"Life can only be understood backwards; but it must be lived forwards."

If I dig back into my memory to the first time I have heard of the Thoraxcenter, I think it was at the 1st year of my residency in Cardiology: when I asked which was the very best center for interventional cardiology in Europe the answer was firm: "The Thoraxcenter in Rotterdam". While my interest for interventional cardiology was increasing during my residency training, I remember perusing the Thoraxcenter internet page in search of a possible way to start a fellowship there, but all seemed out of my reach.
A couple of years later, in May 2014 I was covering my shift in echocardiography in Messina (my hometown), and I have been summoned down in the cath-lab by one of the senior interventionalists, Giuseppe Andò, which was quite uncommon at that time. Walking down the 6 floors separating the echo-lab and the cath-lab, I was trying to quickly review all the possible things that I could have done wrong during the previous week, preparing a persuasive explanation for the possible scenarios. Yet, the topic of the conversation was different than I expected: "There is a possible opening for a fellowship with Prof. Valgimigli, he is moving to Rotterdam, Are you interested?". I believe it took me 1.5 seconds to answer to that proposal (1.3 were used to kill the previous "excuse primer"). Dr. Andò, I will always be grateful for this opportunity, if it wasn't for your work including the hospital in the MATRIX trial, that dream would have never become real. At that time my hospital was one main recruiter in the MATRIX trial, and the study coordinator, Enrico Frigoli, was a former colleague resident in Messina. I called Enrico the very same day to see if that possibility was viable and trying to schedule an introductory call with Prof. Valgimigli. Enrico, you

have always been supportive, I am sure that your great patience and human skills will allow you to coordinate the MASTER-DAPT in the very successful way as it was for the MATRIX. I did a preliminary call with Prof. Valgimigli and he explained me some of the projects that he had in mind and some of the “rules” of the Thoraxcenter world: first and foremost the fellow-interview run by all the staff members. Two weeks after I was in Rotterdam for my very first time to undergo the interviews. Stepping into the Thoraxcenter entrance, at the bottom of a colossal white building, I remember I felt deeply out of place. I know now that this sensation would have accompanied me every time I happened making a good decision in my career. Walking in the dedalus of the Thoraxcenter, I went up to the 5th floor and met Elles Schaap, the secretary of Prof. Zijlstra that gave me an accurate (and minute pointing) schedule of my interviews for that day. Elles and Wil you have been nice and patient to me since that very first moment, thank you for all the support (also at a distance) you gave me during these years.

After completing the interview with all the cath-lab staff members I finally met for the first time, what would have became my mentor for the years to come, Prof. Valgimigli. During that very first meeting, he was organizing his new office in the room BA-593, located in the fifth floor, together with all the other faculty members. He anticipated me that the interview was successful and I could start the fellowship in July. A dream was coming true. In the same meeting, he also gave me a detailed outlook of the possible areas of research I could be involved: duration of dual antiplatelet therapy with a focus on special populations, risks scores, bleeding vs. ischemic risk, coronary stents, endothelial function etc. all these were beautifully drawn in a detailed flow-chart which I store like a treasure (*see picture section*). While discussing about my expectations from the period at the Thoraxcenter, I confessed that I would have liked to write a PhD thesis. By saying that I suddenly captured all his attention. He started searching his library and he finally handed me a book that was more or less 3 cm thick. It was the Vasim Farooq's PhD thesis, one of the former fellows of Prof. Serruys, which was defeinding his PhD that year. “This is what a thesis looks like here, do you still want to do this?” That thesis was incredible: a huge book including more than 20 articles, most as first author, and all in top journals, including the original SYNTAX II score paper, published in the Lancet, and a research letter in the New England Journal of Medicine. Vasim I don't know you in person and I hope I could meet you someday. Reading your thesis gave me the first impression of what was like to be a fellow in Rotterdam, and it totally inspired me.

During those days I was also struggling finding a place to stay in Rotterdam: Ramon Rodriguez, a clinical fellow that was completing his first year shared some precious information regarding how to find a place to live in Rotterdam. Ramon, thank you for the support in the early stage of my adventure. Finally I happened to find one small flat that was just 10 minutes away from the hospital. The landlord, a Turkish-Dutch man called Ugur, with a terrible English, showed me the house. The house was quite eccentric as it was full of souvenirs that Ugur collected from his travels around the world: there were three crystal lamps (for this reason renamed “la casa dei lampadari”), a 1.5mt tall jar accommodating a huge plant, at least 5 statues of Buddha, 2 stuffed birds and a wooden giraffe (..yes a giraffe). Ugur, even if our communication in English was very problematic, thank you for your kindness and positive attitude, believe me or not, I felt your house as a home.

My first month in Rotterdam was quite tough. Getting used to the new place, without any friend close, was a challenge that I am happy I endured. My office was in the fellows' room BD-412 in the old building. I was initially sharing the room with the three clinical fellows

Joost Daemen, Bert Everaert and Ramon Rodriguez. Joost was the only native dutch, and had completed both his residency and PhD at the Thoraxcenter. In the fellows room there was a big shelf hosting all PhD thesis from the interventional cardiology group. Joost's thesis was lying there and was intimidating. By contrast, he was a very sociable and friendly person, with an exquisite dutch attitude, sharp and direct. Thank you Joost for helping me surviving the Thoraxcenter, and for all the good tips for my future career. In one of our lunches in the canteen you once told me about the beautiful landscape from the rooftop restaurant at the Inselspital in Bern (where you have also been as a fellow), admiring the snowcapped Alps. I couldn't imagine that I would be see that view someday, which was indeed fantastic, but the restaurant in turn, was way too expensive.
Bert instead was coming from Belgium, he was extremely funny, sociable and with an excellent taste for good wines and whiskies (owe him a great introduction to the various Talisker, Laphroaig and Lagavulin). Bert, I really enjoyed our conversations. I could never forgive myself for not attending your champagne-tasting trip in Antwerp, hope we will have another occasion in the future.
In that period I was mostly occupied with patients' inclusion in the MATRIX trial, and I spent most of my time in the cath-lab. That gave me the opportunity of knowing better the cath-lab staff and all nurses and technicians. The level of competence of all the people working there was simply impressive. It is impossible to count the number of things related and not related to interventional cardiology that I learnt in the cath-lab of the Thoraxcenter, and it's very difficult to properly thank all the senior staff for their teachings. Roberto Diletti, being both Italians was a great advantage to get to know you better, thank you for your advices and for the great time when you invited us in your house, I wish you all the best with your career and with the little Riccardo. Prof. De Jaegere it was great attending your

TAVI sessions in the lab, that was top notch. Nicolas van Mieghem, seeing you defending your thesis was so impressive and high-level. Luckily I was reassured by the nurses that that was not by far the average level of a doctorate. I had the opportunity of witnessing both your talent and tenacity as an operator and as a researcher. Your idea for the R-RADAR central figure (I keep the first draft - *see pictures section*) was a game changer and it is really beautiful. Another memory that I keep in my mind is from one afternoon shift in the cath-lab (more or less at 19.30 – 20:00) when the last patient on schedule turns out having a severe lesion at the distal LM trifurcation and active chest pain. You treated with trifurcation stenting and used the crooked buddy technique… amazing. Nicolas, thank you for the time spent with me in the R-RADAR and for all our conversations about work/life balance, it definitely expanded my view of this difficult, but incredibly fascinating profession.

Alongside the great talent of the doctors, the competence and skills of the nurses and technicians was really incredible. Anne Marie you were my nurse guru, thank you being so kind especially when I didn't understand a single word in Dutch: "even wachten…ok, ga maar door!". Rob and Patrick, we had a great time in the lab, you are among the most skilled people I met, and your knowledge and curiosity was a great inspiration. Our paper on the rotational angiography of the dummy stent was no published in the end, but the video of the fractured cypher stent rotating in 3d was way too cool. Linda, Paul, Elco, Sander, Leonie, and all the other staff nurses and technicians, thank you for all the great time and all your teaching.

A big part of my job was carried in conjunction with the trial bureau. The trial bureau is a big office coordinating the myriad of studies that the Thoraxcenter was running. Two key people in that task were Arno Ruiter and Nico van der Berg. Arno, I always appreciated your good mood and your advices about running and running shoes, after 4 years of very bad results as a runner, sorry for wasting your time. Nico, thank you for helping me with all the visits of the MATRIX, we had a very great time together. Another initial task I had was adapting the protocol of the HI-TECH trial and preparing for its submission to the Rotterdam ethics committee and to EudraCT. For this project I worked with Mattie Lenzen. Thank you Mattie for all your help, and also for your advices while getting through the final stage of the BigRegister.

The 4th floor of the old building, was once the venue of the cathlab rooms, before they have been moved in a novel area. There it was also the office of the intravascular imaging group, and of one person in particular, Jurgen Lighthart. Jurgen is a real legend in the Thoraxcenter. He has been interpreting IVUS since the early days, and was considered the guru of intravascular imaging. Jurgen I will always remember your enthusiasm and curiosity for research, your sense of humor and your exquisite coffee preparation (I hope that the batch I brought from Messina was of an acceptable level!). I want also to thank Karen Witberg, thank you Karen for your great work.

Among the other people working in the 4th floor there were the “OCT guys” Antonios Karanasos, Jors van der Sijde and Fam which under the lead of Prof. Evelyn Regar, an absolute international expert in OCT, were working full time in intravascular imaging projects. Prof. Regar, I did not have the opportunity of working with you, but your kindness and enthusiasm towards all Italians was a great way to make me feel confortable. Antonios, Jors and Fam, thank you for all the coffees and the small-talk about Greece, Italy and the Netherlands. While I was desperate preparing my speech for the oral presentation at EuroPCR, I once asked Antonios how does he prepare his speeches, and

he answered with a “Olympic” greek calm: I never prepare a speech. That advice evidently got even me more nervous. At that time The Thoraxcenter was also hosting various italian fellows, engaged in different projects. Giulia Paoletti, Marcella De Paolis and Giorgia Galli, it was great sharing with you those (free) coffees in front of the fellows’ room. What would occur if they decide to put in an Italian hospital a free coffee machine was often a fun topic of conversation… I wish you the best for the future. Maybe Marcella’s talisman (do you remember that peculiar colorful owl), will work for all of us.

Unfortunately, due to my commitments I did not have the opportunity of meeting many of the Cardiology residents. Yet, I am very fortunate of getting to know one very well, Rohit Oemrawsingh. Rohit, you have been a great resource during my stay in Rotterdam, but most importantly you have been a great friend. Among our multiple snacks and dinners you taught me a lot of the surface and under-surface world of the Thoraxcenter. You are a wonderful person, and I am totally sure that your great scientific and clinical skills, together with your great social and human ability will give you a lot of satisfactions in the future. I really looking forward having you in Sicily for some serious “Gelato” tasting.

After the first few months my fellowship was often on a move. Roughly half of the time was spent in the Thoraxcenter, and the other half in Cardialysis, a world-renown clinical research organization, located just 1 km away from the hospital. The venue was impressive, located in a high building in the center of Rotterdam with a wonderful view of the skyline. Cardialysis runs some of the most important clinical trials in the cardiovascular field, and is the meeting place of prominent clinical trialists and researchers. On my second day strolling through Cardialysis rooms I run into Prof. Serruys, the living legend of interventional cardiology, that looking right at me said “Who is this young man here?” I thought so hard to a clever answer, but in the meantime he was already gone… I had the

opportunity of talking to him longer in a conference in Madrid, and I will never forget his advice about having a good accent during presentations “You are Italian, you don't have to talk like an English-man, having an accent is a trademark, a distinctive trait”.

Working so often in Cardialysis gave me the opportunity of knowing better its wonderful team: Garritte-Anne, Anna it was a great pleasure knowing you and participating to the meetings of the A-ARC. Yoshi, you are such a kind and pleasant person, I enjoyed your presence and your teachings regarding bioresorbable scaffolds. The latest acquisition of Cardialysis was Ernest Spitzer. Ernest is a cardiologist coming from Perù, who arrived at Cardalysis late during my stay in Rotterdam. He is a person that transmits a great calm but at the same time a resolute and ambitious attitude. As a native Spanish speaker was really easy getting to know each other and having also some time out of work. Thank you Ernest for your advices, for the discussion about our future, thank you for being so reassuring, it has been a lot of fun hanging out with you, I consider you a real friend. I hope we could have sometime the opportunity to hang out with Freddie, your friend from Dubai…you know what I mean. Cardialysis was a very exciting environment also because it was pullulating of fellows from around the world. Among them the one I could get to know better was Carlos Campos, a Brazilian cardiologist from Sau Paulo. Carlos, it was both great and extremely easy working with you. I am happy I had the opportunity of meeting you and your wonderful family. In Cardialysis I also met Eugene McFadden, an Irish interventional cardiologist who once used to be staff at the Thoraxcenter and now moved to Ireland, while remaining involved in many research projects. He has that kind of calm aura that put you immediately at ease, and is a formidable writer. Eugene I have learned a lot from your proofreading, I hope I will have the opportunity of meeting you again in the future.

Other two key people during my time in Rotterdam were frequent Cardialysis visitors. Pascal Vranckx. The first time I met him it was in the external advisors office, a beautiful angular office with glass walls projecting a beautiful view of the Rotterdam city center. I knew him by name, but his aura really impressed me: he has a very strong character, which challenges you at first, sometimes putting you at unease. After a while I understood that this is his way he weighs who has in front. Pascal was one of the key people for me in Rotterdam, not counting the never-ending sessions of events adjudication and brainstorming on clinical trials I assisted with him. I will never forget his support and advices, especially during congresses. American college of Cardiology, 2015, I was having my first oral presentation in front of a large audience, and public speaking was not a skill that I have invested much time upon. Pascal, thank you so much for those multiple sessions repeating over and over again the PRODIGY-ACS, that presentation was perfect in the end, and a bit of the style that you transmitted me on that occasion will always be part of my armamentarium, I really owe you a lot.

The second person I would like to mention is Prof. Jan Tijssen. Jan, I have been so fortunate working with you in several projects. Thank you for all the time you have been schooling me about all the possible statistical methods we could implement in the PRODIGY-SCORE paper, for all the pitfalls of different study design we have discussed in the NARC, and the basics for developing my own risk score. That all sounded scary and difficult at first, but you always had the capacity to explain in a disarmingly easy way even the more complex concepts.

The PRECISE-DAPT project was the last one I have started in Rotterdam and in the end came out to be, by far, the most demanding. All this started with a first seminal meeting with Prof. Steyerberg, the head of the Medical decision making department of the Erasmus

MC, and with David van Klaveren, a mathematician working with him in multiple research projects. Prof. Steyerberg, thank you for your key addresses and for steering the project at important stages. David, we have been working in close contact for years, even if always at a distance. Nevertheless, I always had the feeling of working side-by-side. You are clever and smart, a relentless worker, an elegant statistician and in general a great person. I am deeply honored that you will take part to my defense. I wish you could be able to come to Barcelona more often, we would definitely repeat the PRECISE-DAPT celebration, thank you. I would also like to deeply thank all the co-authors involved in the PRECISE-DAPT project, I have been privileged of working together with real legends of interventional cardiology, I am humbled having had the opportunity of being part of all this: Prof. James, thank you for your cooperation, with your help we have been able to achieve an important validation of the PRECISE-DAPT score. I will never forget the first time that I met you at the ACC, your attitude is an inspiration for all young researchers. Prof. Colombo I will always remember your advice in Madrid: "research is important, but is like the pepper in a dish, you have always to be a good doctor, or you will eat pepper only". Prof. Bhatt, I owe you the title of this thesis, which is coming from your great editorial on the TRITON trial in the NEJM. I borrowed it because it was perfect for my topic and for my Sicilian roots, I have been honored working with you in this project. Prof. Steg, thank you for your insightful comments, your capacity of synthetizing complex concepts in few lines is a great inspiration. Dr. Raber, the validation of the PRECISE-DAPT in the BernPCI registry was key to demonstrate the ability of this novel tool in a real-world setting, thank you for your invaluable cooperation. Dear Dik, the time of the validation and additional analysis asked during all revision rounds was tough, but your good attitude and character made that time more enjoyable. I have still to carry you a cake with the PRECISE-DAPT logo, I know.

Prof. Windecker, it has been an honor working with you in several projects, and being hosted in your institution during the time I have been working to the PRECISE-DAPT.
To conclude the list of the people I met in Cardialysis, and to which I am deeply connected until today, I want to mention Dr. Hector M. Garcia-Garcia. I met Hector for the first time during my initial visit in Rotterdam in June 2014. I was visiting Cardialysis and we were supposed to have dinner at Shabu Shabu, a Japanese restaurant in Blaack, right under the office, that would be the center of many memorable moments later on. Hector is the kind of person that with a simple glimpse can transmit such good vibrations. It's just impossible not to like him. He is able in any situation to understand the kind of person that he has in front, and adapt to make them feel at ease. Hector, you have been an example for me. When I was stubborn and conflictive with people, Victoria often suggested me: "Be Hector!" Following that advice t helped me a lot in these years, believe me. The first time you invited us to your home I was supposed to cook something from my region: I can admit now that it was the very first time I was cooking that pasta. The result was extremely surprising to me as well, and I was not able to replicate that dish anymore. A clear example of error due to limited observation.
I hope I will have sometimes the opportunity of showing you Sicily, staying in my place and cook real Italian/Mexican food while "platicar sobre las cosas de la vida". Dear Hector, I started seeing you as a famous researcher, than as a peer, and finally as a real friend. We always felt at home when we were with you and we could not ever thank you enough for being so supportive, friendly and honest with us. Thanks also to Lulu, Andres and to the small Matteo, you are a wonderful family and you will always be an example for us.

There is plenty of people in Italy and elsewhere that helped me during the period immediately before/after Rotterdam. I really hope not to forget anyone, and if I do please forgive me. First, nothing would have been possible without the unrestricted support from all the people at my home University in Messina. Prof. Oreto, thank you for your trust, your respect and your genuine politeness. I will always take with me your teaching both about cardiology and life. Your integrity and honesty is the greatest teaching that you could give to your students. Prof. Carerj, you have been mentoring me since my early days as a med student, thank you for being always an example of integrity and humanity. Your authentic devotion to work, enduring long hours in the hospital, has been a great teaching, as it was your ability of putting all the patients at ease in any situation. I would like to thank all the faculty of the cardiology department of the University of Messina, and all the doctors working in the cardiology department, thank you for all that you taught me.

To all the people of the cath-lab in Messina, Dr. Saporito, Andò and Di Giorgio, and all the technicians and nurse staff (Pierpaolo, Giacomo, Giovanni, Franco and Antonella) thank you for all your teaching and support, I have moved my first steps in that cath-lab, no matter where I go, it will always feel like home.

To Marco Cerrito, thank you for being there on my first day in cardiology and for mentoring me while I was an intern. You have been great igniting my interest and passion for cardiology and a major reason why I have chosen this career. You are born for being an educator; I hope you could transmit your enthusiasm, talent and passion to newer generations, as you did with me 10 years ago.

To all my colleagues sharing the residency training in Messina, but especially to the class of 2012, Anna, Angela, Peppe, Matteo, Maria, Marta e Alessandra. Thank you for letting me pursue this dream without ever pointing the finger, but instead defending me from the others. I have felt being part of a wonderful group, and I hope I will still feel it for a long time. Thank also to all the other colleagues that have shared that time with me: Pasquale, Giampiero, we should repeat some “time-out” in Barcelona, Ilaria, Salvina, Roberta, Antonio, Fausto, Giovanni, Vito, Gabriele, Irene and all the others (you are too much to quote you all!). To the interventional cardiology team of the Hospital Umberto I in Siracusa, the Director Marco Contarini, his wonderful staff, Giovanni De Velli, Paola Murè, Giorgio Sacchetta, Nadia Garro, Titta Barrano, and all the nurses and paramedicals (Giovanni, Danilo, Rita, Biagio, Lino, Luca, Maurizio, Massimo, Piero e Salvo). Thank you for hosting me and making me feel at home. I have learned a lot from you, about interventional cardiology, friendship and life. You work as a real team, without jealousy, deceits and hypocrisy; this translates in the superior quality and humanity that you put at service of your patients. I would also like to thank the fellows in Bern, that during my brief stay there have been extremely nice: thanks Giuseppe, Raffaele, Anna and Marco for the time spent together, I have appreciated your company and your advices during the Swiss survival bootcamp, I am sure you will have a wonderful career. To Prof. Davide Capodanno; Davide you believed in me when you were chair of the EAPCI young committee. Being Young national ambassador for Italy was a great honor, I hope I will serve well helping other young interventionalists pursuing their dream. Prof. Dominick Angiolillo, you have always been an example of an elegant researcher and a great mentor for young cardiologists. Thank you for the time and for all your precious advices.

I would finally like to thank all the team in Barcelona where I am currently working: Prof. Sabaté and Dr. Brugaletta that have been introducing me to this new experience and welcomed and supported me better than I could imagine. To the senior staff members Monica Masotti, Victoria Martin, Xavier Freixa and Ander Regueiro from which I am

learning new things everyday. To the great team of nurses and technicians (Marc, Dani, Rosa, las Montses, Jorge, Joan, Jordi, Tere, Eva and all the others). Your competence and knowledge is perfectly melted with your friendliness, creating an extremely familiar environment, an invaluable quality of this institution. And to my great colleagues Alberto, John, Elisabetta and Luis, that accepted me in the very best way I could imagine, thank you guys for all your support, we are a great team.

Going back to Rotterdam for a moment, I have to admit that my social life out of the hospital was definitely not super-active. Yet, I would never expect to find a person like Pietro Profeta. Pietro was the only friend I had outside the cardiology world and hanging out with him was a great way to wash-out some stress. Pietro, we had a lot of fun in many occasions, I really cannot count them. After discovering all your great qualities I am grateful that our path crossed. My time in Rotterdam would have never be the same without you. I wish you all the best my friend, 2018 will be an year to remember, and I am sure that you will be a great dad, thanks for everything.

Two additional people shared (in different moments) most of the time of my fellowship at the Thoraxcenter. I owe to these two people much more than I can write in these pages. I thank them for being formidable working partners, with whom I survived to the “Matrix crisis” and to the “A-A-Arc”. I also owe you my mental sanity, I think that I could never stand the pressure without having you at my side, simply talking about the events or laughing about the strange things that happens between that walls. Thank you girls, you made that experience one of the most constructive of my career, but also one of the most significant of my life. Marianna, I have always appreciated your determination, self-consciousness and indifference for political correctness. Your clarity of mind and your intellectual honesty are one of the best qualities a person could have. I wish you all the best for your career in interventional cardiology. I am sure that the patients in Brescia will have a great resource when they will need it. Sara, you have been the first fellow I have been sharing my work burden with, and we came across so much troubles, doubts and satisfactions I can hardly remember. Unfortunately, we have shared some of the worst experiences one person could face in life, the kind you ask yourself in the middle of the night, why me, why like this, what have I done to deserve it. For this reason you ultimately had to go back away early from Rotterdam. Thank you for your words in some of the worst moments of my life; you knew what you were talking about. On the other hand, I am happy to think that we also shared some good events: you have just started dating Mirko the month you hosted me in Bern (thank you for that one also!) and I had the occasion of meeting him in person. I am happy that after all the sufferings, faith gave you the occasion of meeting someone worth fighting for. I wish you guys all the best for your life together, and I hope that you will get all the happiness you really deserve.

Last and definitely not least, I would like to thank my promotors that accompanied me in this wonderful journey. Back in 2014, the very first interview for the selection in Rotterdam was with Prof. Felix Zijlstra, the head of the department. I couldn’t expect that he would become one of the most significant individuals during my stay there, and for the years following. Prof. Zijlstra is a real legend of interventional cardiology. His research and achievement shaped the history of medicine (primary angioplasty and thromboaspiration only to cite some). Despite his reputation and his position as head of department he always maintained a humble profile, surrounded by an aura of unimposed greatness. The close relationship he maintained with all the people in the cath-lab including physicians, nurses and fellows will always be an example for me. Prof. Zijlstra you have been a great example of what an excellent chief, a brilliant researcher, a good doctor and a great person should look like, thank you.

I have known Marco Valgimigli since four years now, he has been my mentor at the Thoraxcenter, and my promotor for this PhD thesis. I have been impressed, and I am continuously impressed, by different aspects of Prof. Valgimigli's personality: his creativity; his intelligence and the sharpness of his mind; his capacity of keeping focused; his curiosity that gives him the way to frame significant research questions; his clear vision on how to develop a project 1,2, 5 years away; and most importantly, his resiliency, accepting the drawbacks and working harder to get to the goal. Never satisfied, always on top of the next project, always hungry for novel achievements. What really impressed me though, was the way he managed to do all these things respecting the others, including colleagues, peers and a 27 year old fellow coming in a big center with only a minor research background; while being a father of two, wonderful, and intelligent kids. Life is not about all the steps you have taken, it's about the footprints you leave behind.

Marco, my key proposition for this thesis is a phrase that you told me during a GISE congress in 2015, probably you wouldn't even remember: "L'unica cosa che conta, è il contatto umano – All that really matters is the human connection". During these years working in close contact with you, I am even more convinced that, for every aspect in life, you were right. You have been more than a teacher, more than an advisor, more than a mentor. You teached me how to question, how to search, how to read, how to think, how to write and how to question again. I owe you all my scientific achievements and beyond.

I hope I could pay back your trust and dedication someday.

Finally, I would like to thank my family and my friends. My mother and sister that are with me everyday, wherever I am, I love you so much. Mamma, you dedicated your life to raise us with good principles, sacrificing your ambition. I hope you could be proud of us.
Roberta, you obtained your doctorate before your older brother, I am sure you will soon realize how strong and really talented you are, I am proud of you. To my friends (I don’t need to write names in here), that supports me no matter the distance. I have read that “We are the average of the five people we spend the most time with”. Well I am proud of myself for choosing such a group of talented and honest people.
You are the family that I have chosen.
To my wonderful girlfriend Victoria, that is the person that knows me the most, and that lived on her own skin the hard work needed to complete this thesis. Thank you for your support, for your patience and your sacrifice. For comforting me when I needed it, and for encouraging me when I needed it. For keeping my feet on the ground when I levitated, and for getting me back on my feet when I collapsed. You are my compass and my home.

And to my Father. I am sure that seeing this book would make you proud. Thank you for all you have been to me in the good and in the bad days. I owe you simply everything I am.
I miss you everyday. I love you.

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Francesco Costa was born on March 29th 1987 in Messina, Italy. He obtained his medical degree in 2011 with Summa cum Laude at the University of Messina, Italy. He completed his training in cardiology with Summa cum Laude at University of Messina in 2017. In 2014 he started a research fellowship in interventional cardiology at the Thoraxcenter, Erasmus Medical Center (Rotterdam, The Netherlands) under the supervision of Prof. Valgimigli and Prof. Zijlstra. In 2017 he started a clinical fellowship in interventional cardiology at the Clinic i provincial Hospital (Barcelona, Spain) under the supervision of Dr. Brugaletta and Prof. Sabaté.
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CLINICAL ACTIVITIES:
– Internal Medicine Clerkship at Krankenhaus der barmherzigen brüder (Prof A. Wechsler),Technische Universität München, Germany, 2009
– Student-Assistant, Clinical Cardiology (Prof J. Davia), Virginia Commonwealth University, Richmond, U.S.A. 2010
– Cardiac Surgery Clerkship (Prof M. Gaspar), Institutul Padurea Verde, Timišoara, Rumenia 2010
– Intensive Care Unit and Echo-lab Fellow (Prof L. Dei Cas), Spitali Civili, Brescia, Italy 2011
– Residency in Cardiology (Prof G. Oreto), University of Messina, Italy, 2012- 2017
– Research Fellowship in Interventional Cardiology (Prof. M. Valgimigli), Thoraxcenter, Erasmus Medical Center, The Netherlands, 2014-2015
– Fellowship in Interventional Cardiology (Dr. M. Contarini), Umberto I Hospital, Siracusa, Italy, 2015-2016
– Internship in Interventional Cardiology and Structural Heart Disease (Dr. J. Alonso-Briales), Hospital Virgen de la Victoria, Malaga, Spain, 2017
– Fellowship in Complex Coronary Intervention (Dr. Brugaletta/ Prof. Sabaté), Hospital Clinic, Barcelona, Spain, 2017-2018

ORAL CONTRIBUTIONS IN INTERNATIONAL CONGRESSES:
– Congress: American College of Cardiology (San Diego, United States of America 2015) **Title:** Impact of Clinical Presentation on Ischemic and Bleeding Outcomes in Patients Receiving 6 or 24 Month Duration of Dual Antiplatelet Therapy After Stent Implantation. A Pre-specified Analysis From the (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) PRODIGY Trial
– Congress: EuroPCR (Paris, France 2015) **Title:** Anatomical location and bleeding risk as potential drivers of DAPT duration: insights from PRODIGY trial.
– Congress: EuroPCR (Paris, France 2015) **Title:** Rotterdam radial access research: echo-based radial artery evaluation for diagnostic and therapeutic coronary procedures: the R-RADAR study.
– Congress: Italian Society of Cardiology (Rome, Italy 2015) **Title:** Impact of Clinical Presentation on Ischemic and Bleeding Outcomes in Patients Receiving 6 or 24 Month Duration of Dual Antiplatelet Therapy After Stent Implantation.
– Congress: American College of Cardiology (Chicago, United States of America 2016) **Title:** Tradeoff Between Myocardial Infarction Versus Bleeding Types on Mortality After Acute Coronary Syndrome: Lessons From the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) Randomized Trial
– Congress: EuroPCR (Paris, France 2016) **Title:** Impact of proton-pump inhibitors on clinical outcomes in patients treated with a six-month or 24-month DAPT duration: insights from the PRODIGY trial
– Congress: EuroPCR (Paris, France 2016) **Title:** Impellent impeller
– Congress: EuroPCR (Paris, France 2016) **Title:** Impact of greater than 12-month DAPT duration on mortality: drug specific or a class-effect?
– Congress: ANMCO (Rimini, Italy 2016) **Title:** Il valore incrementale del crusade risk score nella predizione di eventi emorragici in pazienti trattati con una doppia terapia antiaggregante di 6 o 24 mesi dopo stenting coronarico.
– Congress: GISE (Genova, Italy 2016) **Title:** Il ruolo dell'ambasciatore EAPCI Young
– Congress: Italian Society of Cardiology Regional Congress (Messina, Italy 2016) **Title:** Tradeoff Between Myocardial Infarction Versus Bleeding Types on Mortality After Acute Coronary Syndrome.
– Congress: Cardiology in practice (Madrid, Spain 2017) **Title:** One valve more, two vessels less
– Congress: EuroPCR (Paris, France 2017) **Title:** A novel risk score to predict out-of-hospital bleeding on DAPT
– Congress: TaoHeart 2.1 (Giardini Naxos, Italy 2017) **Title:** Il rischio cardiovascolare dopo sindrome coronarica acuta, luci ed ombre
– Congress: Italian Society of Cardiology Regional Congress (Catania, Italy 2017) **Title:** DAPT a lungo termine in pazienti con pregresso infarto del miocardio.

AWARDS AND APPOINTMENTS:
– **Society**: Italian Society of Cardiology (SIC) (Rome, Italy 2015) **Title**: Finalist for the Young Investigator Award at the Italian society of Cardiology (SIC) national congress.
– **Society**: European Association of Percutaneous Coronary Intervention - EAPCI (Paris, France 2016) **Title**: EAPCI Young National Ambassadors for Italy (2016-2018)
– **Society**: University of Messina – Unime Start Cup 2016 (Messina, Italy 2016) **Title**: Unime Start Cup 2016 – Grant Winner for the best innovative project "Cardio App Device" in the Start Up context.
– **Society**: Consortium of Sicilian Universities (Palermo, Italy 2016) **Title**: Winner for the best innovative project "Cardio App Device" in the Start Up context. Listed as best idea with a social impact.
– **Society**: PNI Cube and University of Modena (Modena, Italy 2016) **Title**: Selected for participation at the National Prize for Innovation 2016, category Lifescience
– **Society**: Italian Society of Cardiology (SIC) (Messina, Italy 2016) **Title**: Winner of the Young Investigator Award at the Italian society of Cardiology (SIC) regional congress.
– **Society**: European Association of Percutaneous Cardiovascular Intervention (EAPCI) (Paris, France 2017) **Title**: Winner of the EAPCI education and training grant 2017
– **Society**: European Society of Cardiology (ESC) (Barcelona, Spain 2017) **Title**: Winner of the ESC training grant 2017.

LIST OF PUBLICATIONS:

2013

1. Francesco Costa, Scipione Carerj, Simona Cammaroto, Maurizio Cusma Piccione, Giuseppe Oreto, Paolo Girlanda and Concetta Zito
Concurrent Pulmonary and Cerebral Embolism: Is Tricuspid Valve Endocarditis the Culprit?
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6. Marco Valgimigli, Sara Ariotti, Francesco Costa
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7. Carlos M Campos, Francesco Costa, Hector M Garcia-Garcia, Christos Bourantas, Pannipa Suwannasom, Marco Valgimigli, Marie-Angele Morel, Stephan Windecker, Patrick W Serruys
Anatomic Characteristics and Clinical Implications of Angiographic Coronary Thrombus: Insights From a Patient-Level Pooled Analysis of SYNTAX, RESOLUTE, and LEADERS Trials
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9. Francesco Costa, Sara Ariotti, Marco Valgimigli, Philippe Kolh, Stephan Windecker
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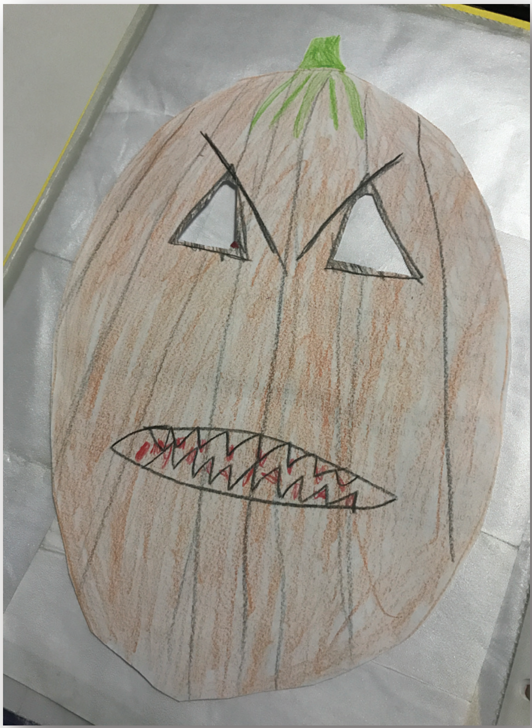
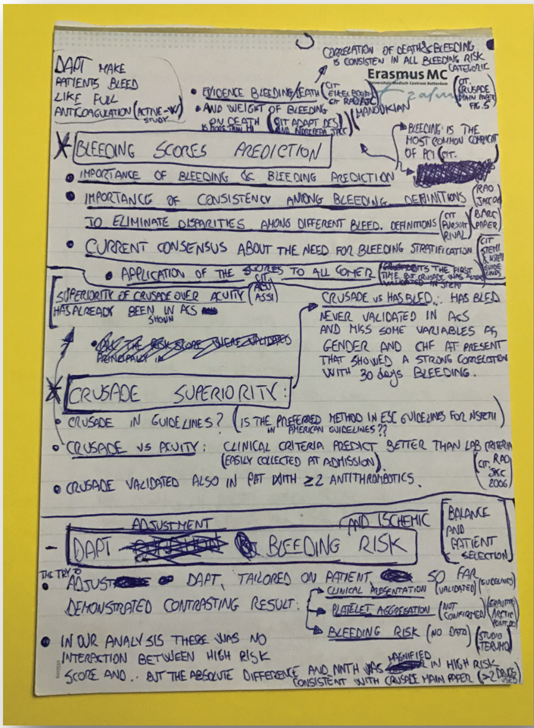
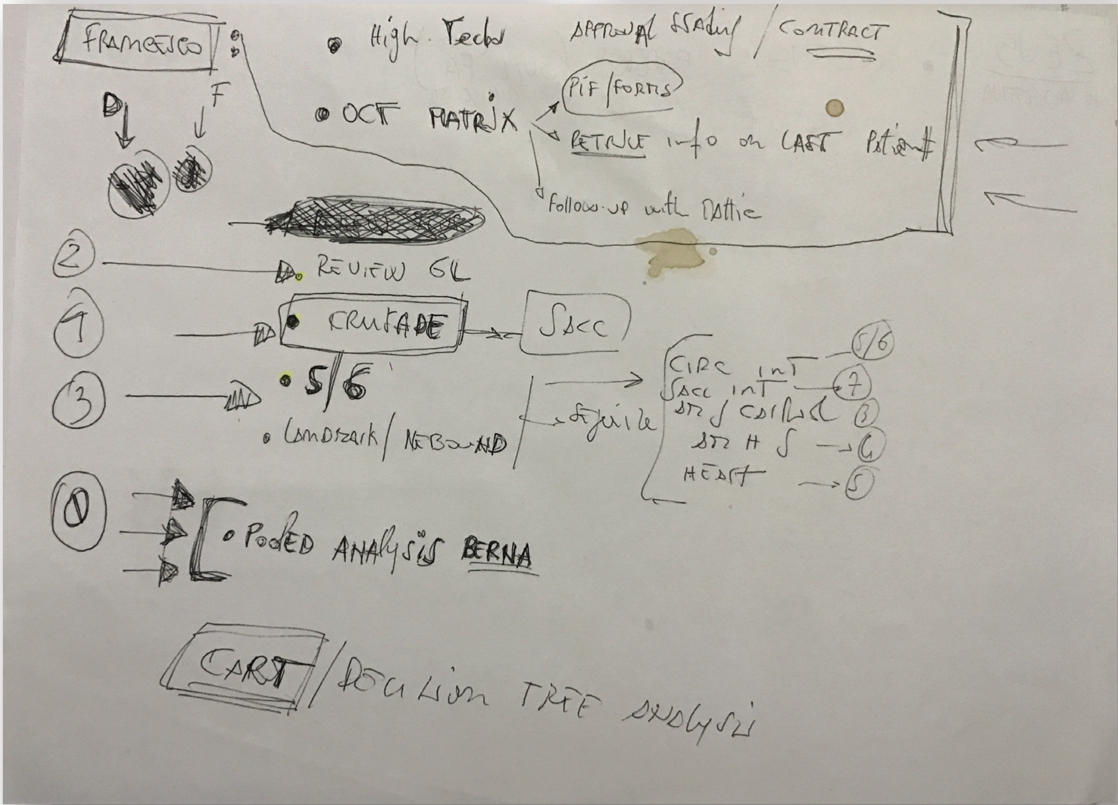
PICTURE SECTION:





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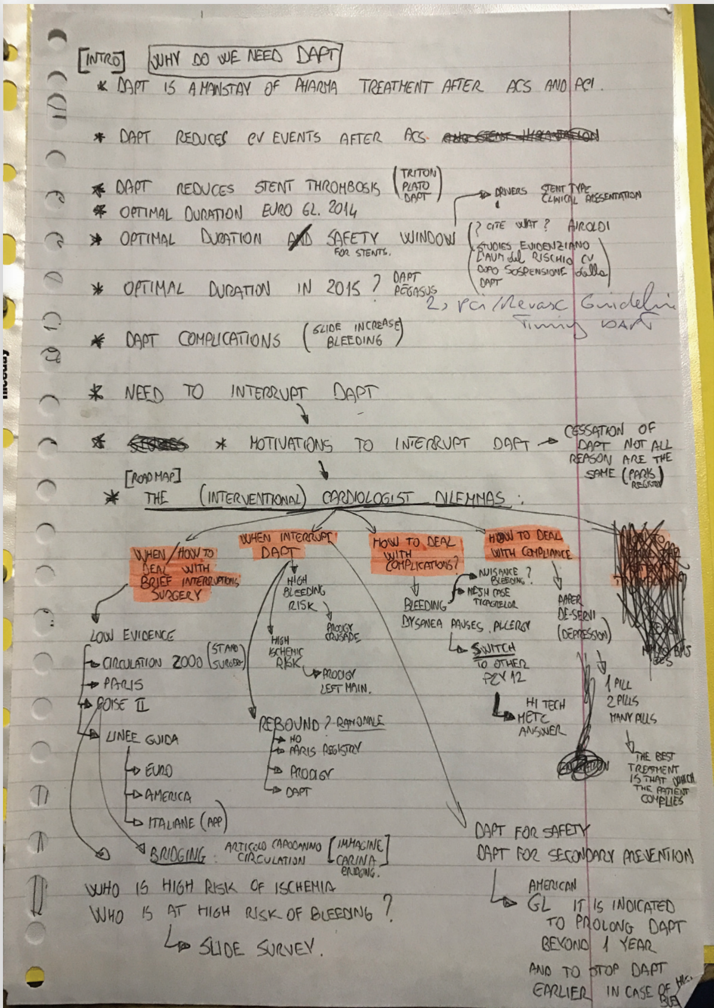
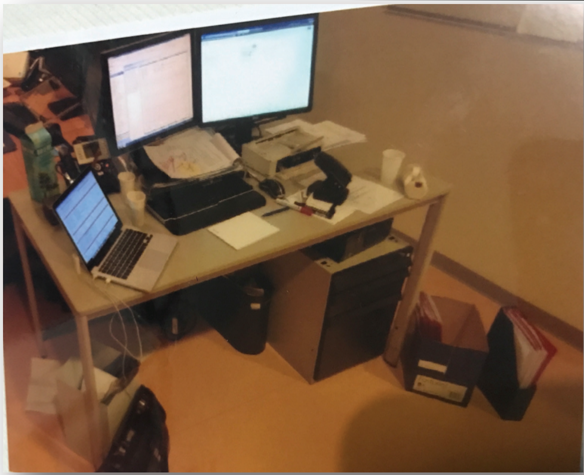
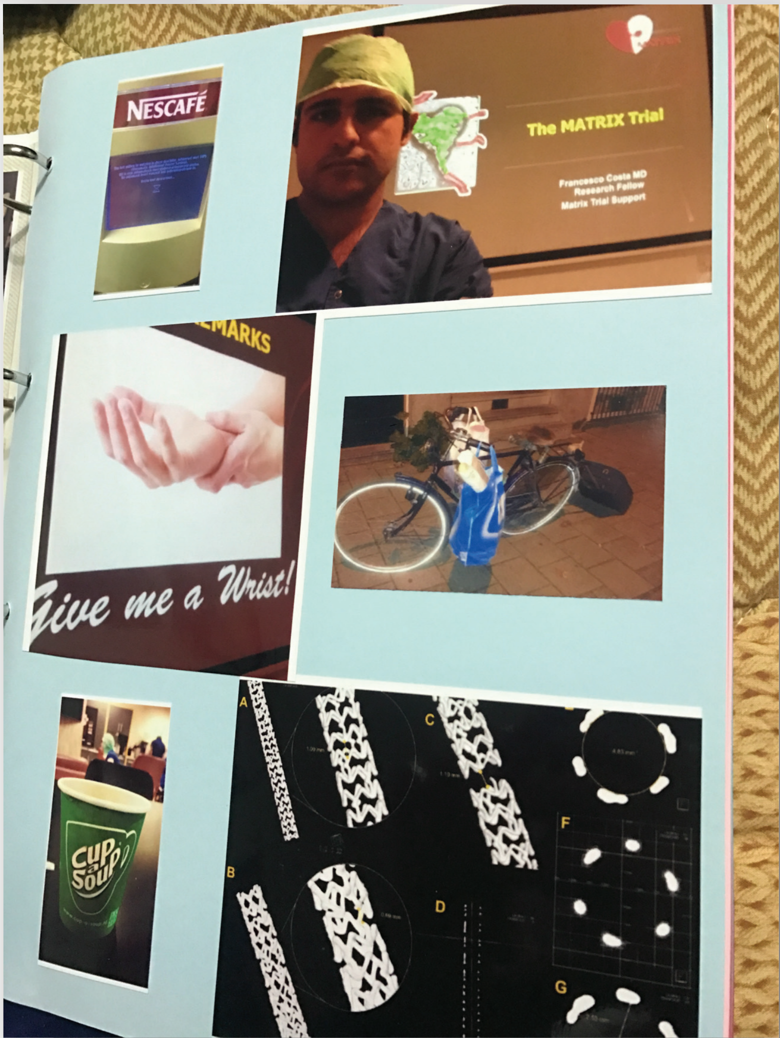
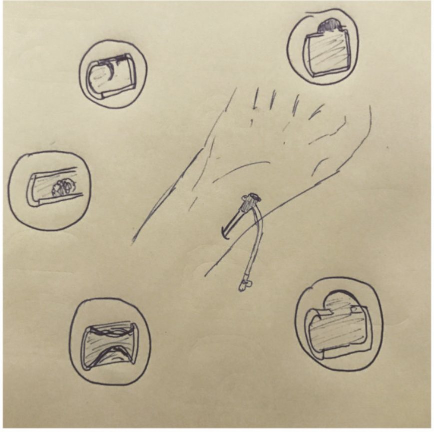
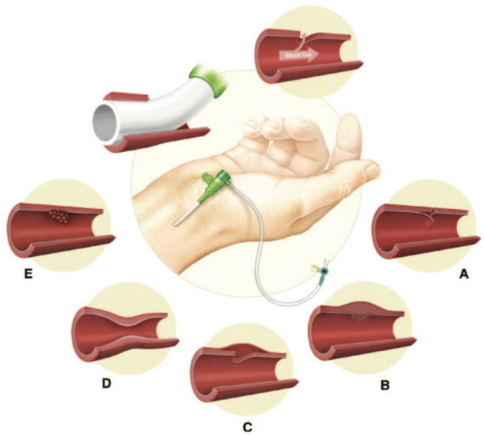

INTRO
WHY DO WE NEED DAPT
* DAPT IS A MAINSTAY OF PHARMA TREATMENT AFTER ACS AND PCI.
* DAPT REDUCES CV EVENTS AFTER ACS
* DAPT REDUCES STENT THROMBOSIS (TRITON PLATO DAPT)
DRIVERS STENT TYPE CLINICAL PRESENTATION
* OPTIMAL DURATION EURO 62. 2014
* OPTIMAL DURATION AND SAFETY WINDOW FOR STENTS.
* OPTIMAL DURATION IN 2015 ? DAPT PEGASUS
* DAPT COMPLICATIONS (SLIDE INCREASE BLEEDING)
* NEED TO INTERRUPT DAPT
* MOTIVATIONS TO INTERRUPT DAPT
CESSATION OF DAPT NOT ALL REASON ARE THE SAME (PARIS REGISTRY)
ROAD MAP
* THE (INTERVENTIONAL) CARDIOLOGIST DILEMMAS:
WHEN / HOW TO DEAL WITH BRIEF INTERRUPTIONS SURGERY
WHEN INTERRUPT DAPT
HOW TO DEAL WITH COMPLICATIONS?
HOW TO DEAL WITH COMPLIANCE
HIGH BLEEDING RISK
HIGH ISCHEMIC RISK
BLEEDING
DYSPNEA PAUSES ALLERGY
SWITCH TO OTHER P2Y 12
LOW EVIDENCE
CIRCULATION 2000
PARIS
ROISE II
LINEE GUIDA
EURO
AMERICA
ITALIANE
REBOUND ? RATIONALE
PRODIGY
DAPT
BRIDGING
1 PILL
2 PILLS
MANY PILLS
THE BEST TREATMENT IS THAT WHICH THE PATIENT COMPLIES
DAPT FOR SAFETY
DAPT FOR SECONDARY PREVENTION
AMERICAN GL IT IS INDICATED TO PROLONG DAPT BEYOND 1 YEAR AND TO STOP DAPT EARLIER IN CASE OF
WHO IS HIGH RISK OF ISCHEMIA
WHO IS AT HIGH RISK OF BLEEDING ?
SLIDE SURVEY.

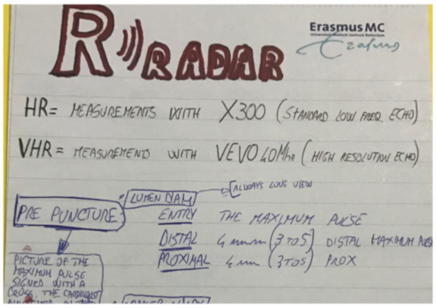

ACC.15
64th Annual Scientific Session & Expo




NESCAFÉ
The MATRIX Trial
Francesco Costa MD
Research Fellow
Matrix Trial Support
MARKS
Give me a Wrist!
Cup a Soup
A
B
C
D
F
G

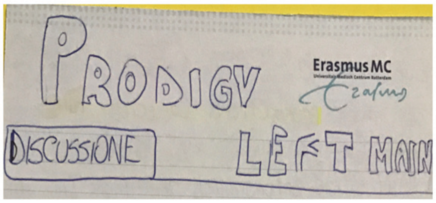


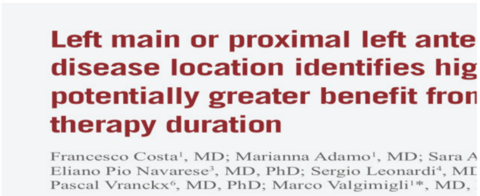




The Rotterdam Radial Access Research: Ultrasound-Based Radial Artery Evaluation for Diagnostic and Therapeutic Coronary Procedures (The R-RADAR study)

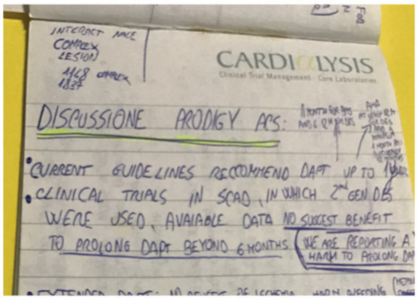
Francesco Costa, MD; Maarten A.H. van Leeuwen, MD; Joost Daemen, MD, PhD; Roberto Diletti, MD; Floris Kauer, MD; Robert-Jan van Geuns, MD, PhD; Jurgen Ligthart, RT; Karen Witberg, CCRN; Felix Zijlstra, MD, PhD; Marco Valgimigli, MD, PhD, Nicolas M. Van Mieghem, MD, PhD

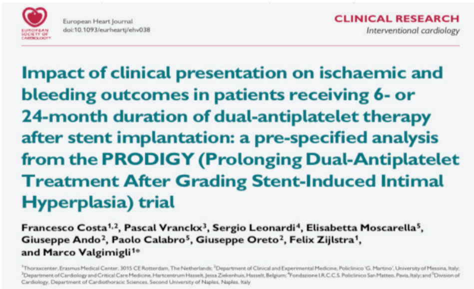




Left main or proximal left ante
disease location identifies hig
potentially greater benefit fron
therapy duration

Francesco Costa[1], MD; Marianna Adamo[1], MD; Sara A
Eliano Pio Navarese[3], MD, PhD; Sergio Leonardi[4], MD
Pascal Vranckx[6], MD, PhD; Marco Valgimigli[1]*, MD,



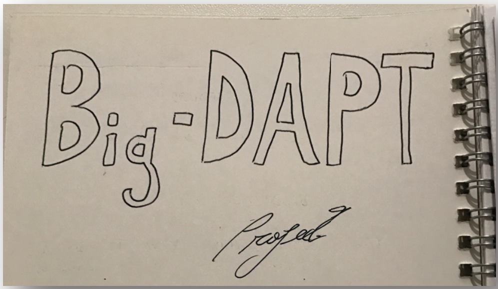


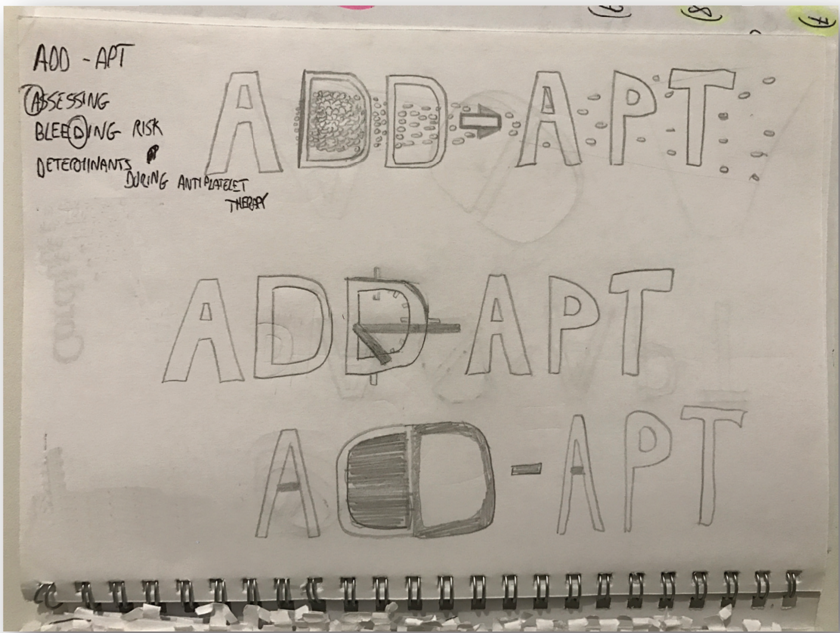
European Heart Journal
doi:10.1093/eurheartj/ehv038

CLINICAL RESEARCH
Interventional cardiology

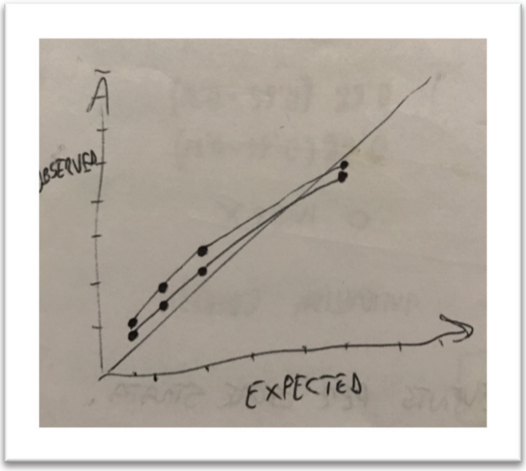
Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial

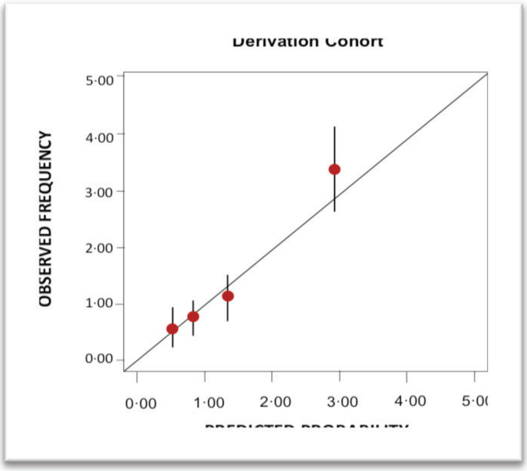
Francesco Costa[1,2], Pascal Vranckx[3], Sergio Leonardi[4], Elisabetta Moscarella[5], Giuseppe Ando[2], Paolo Calabro[5], Giuseppe Oreto[2], Felix Zijlstra[1], and Marco Valgimigli[1]*

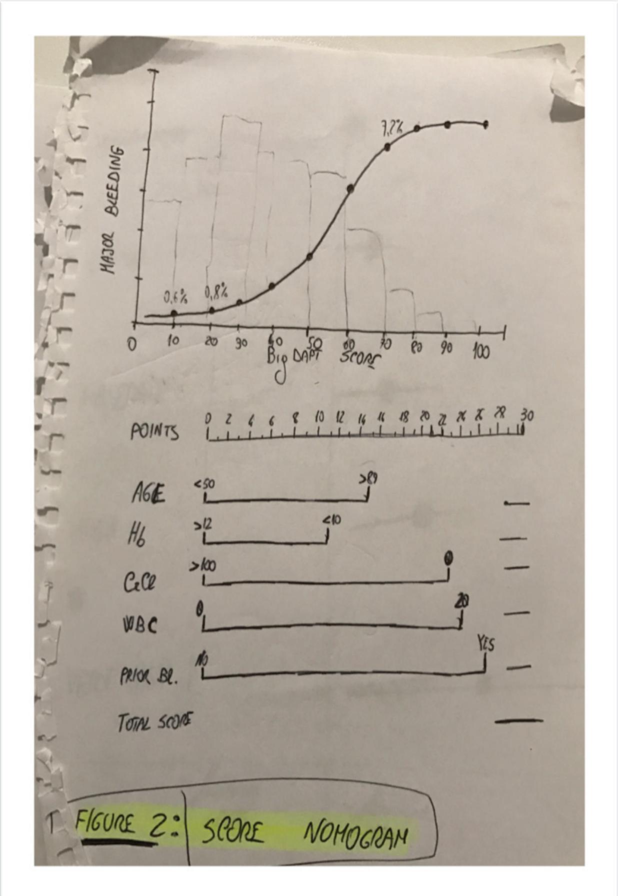


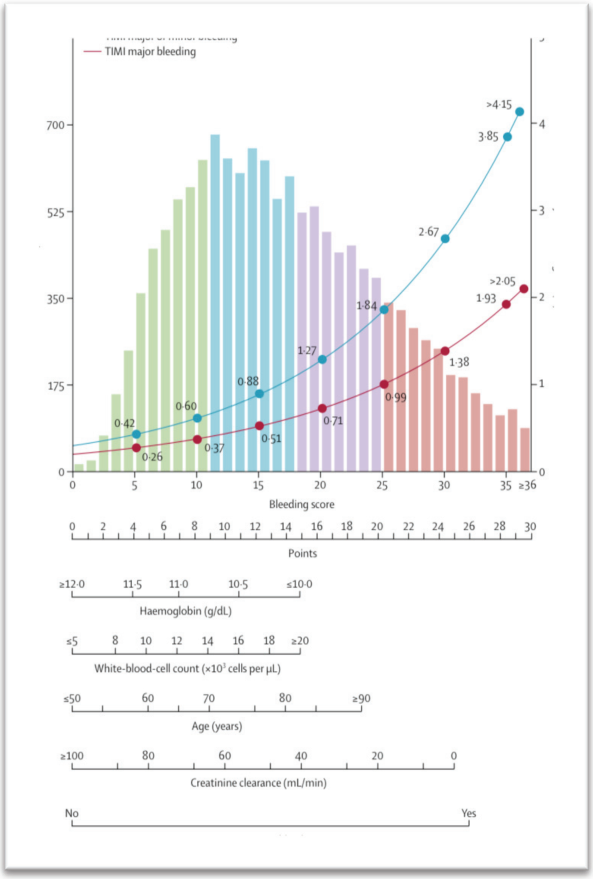


PRECISE
DAPT


OBSERVED
EXPECTED


Derivation Cohort
OBSERVED FREQUENCY
5·00
4·00
3·00
2·00
1·00
0·00
0·00 1·00 2·00 3·00 4·00


MAJOR BLEEDING
0,6%
0,8%
7,2%
0 10 20 30 40 50 60 70 80 90 100
BIG DAPT SCORE
POINTS
AGE
Hb
CrCl
WBC
PRIOR BL.
TOTAL SCORE
FIGURE 2: SCORE NOMOGRAM


TIMI major bleeding
700
525
350
175
0
>4·15
3·85
2·67
1·84
1·27
0·88
0·60
0·42
>2·05
1·93
1·38
0·99
0·71
0·51
0·37
0·26
0 5 10 15 20 25 30 35 ≥36
Bleeding score
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Points
≥12·0 11·5 11·0 10·5 ≤10·0
Haemoglobin (g/dL)
≤5 8 10 12 14 16 18 ≥20
White-blood-cell count (×10³ cells per μL)
≤50 60 70 80 ≥90
Age (years)
≥100 80 60 40 20 0
Creatinine clearance (mL/min)
No
Yes