Improving Clinical Outcomes After Contemporaneous Myocardial Revascularisation Strategies:

Percutaneous Coronary Intervention (PCI)

versus

Coronary Artery Bypass Grafting (CABG)

Daniël J.F.M. Thuijs

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Cover photo by Chris Burkard. Aerial view of glacial rivers forming sediment patterns due to glacial silt being deposited in the rivers systems and flowing out in braided patterns towards the beach in Iceland.

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Improving Clinical Outcomes After Contemporaneous Myocardial Revascularisation Strategies:

Percutaneous Coronary Intervention (PCI) versus Coronary Artery Bypass Grafting (CABG)

Verbeteren van klinische uitkomsten na hedendaagse revascularisatie strategieën:

Percutane Coronaire Interventie (PCI) versus Coronaire Arteriele Bypass Chirurgie (CABG)

Thesis

to obtain the degree of Doctor from
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Daniël Johannes Franciscus Maria Thuijs
born in 's-Hertogenbosch, the Netherlands.

Erasmus University Rotterdam

DOCTORAL COMMITTEE:

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For my parents
Alphons & Inge

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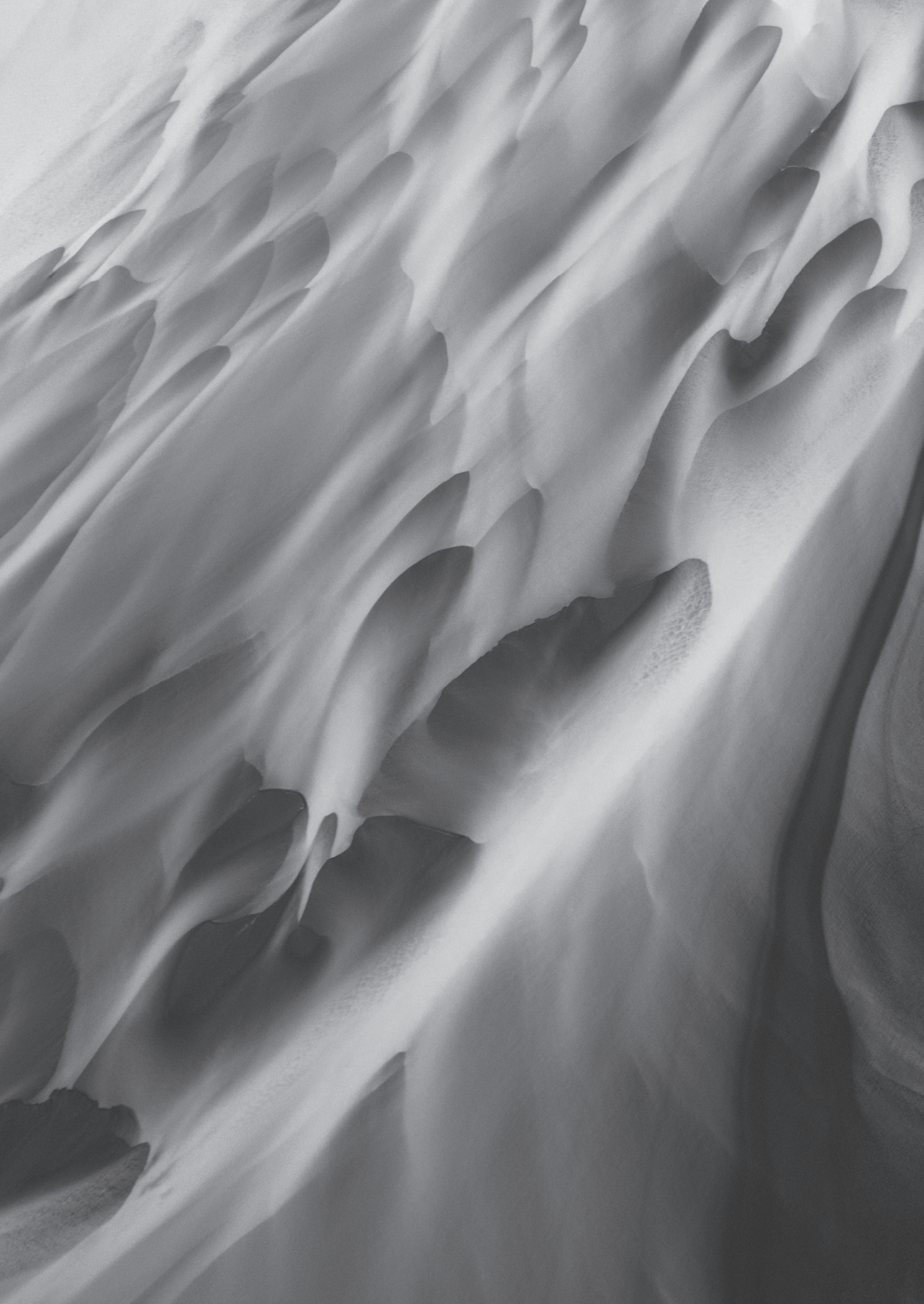


Chapter 1

General introduction, aims and outline

CORONARY ARTERY DISEASE

Although cardiovascular death rates has decreased over the past decades, ischemic heart disease remains the number-one cause of death worldwide (Figure 1).[1-3] Moreover, the increasing overall life-expectancy of men and women across the globe will lead to an increasing prevalence of coronary artery disease. This eventually could lead to a growing number of patients with complex coronary artery disease and advanced cardiovascular risk-profiles requiring revascularisation by either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). A more complex patient with coronary artery disease requires a well-defined and structured approach to determine the optimal revascularisation strategy. In order to provide evidence-based patient-tailored treatment suggestion, adequate preoperative risk assessment and multidisciplinary discussions in the form of a structured heart team meetings are warranted.[4,5]

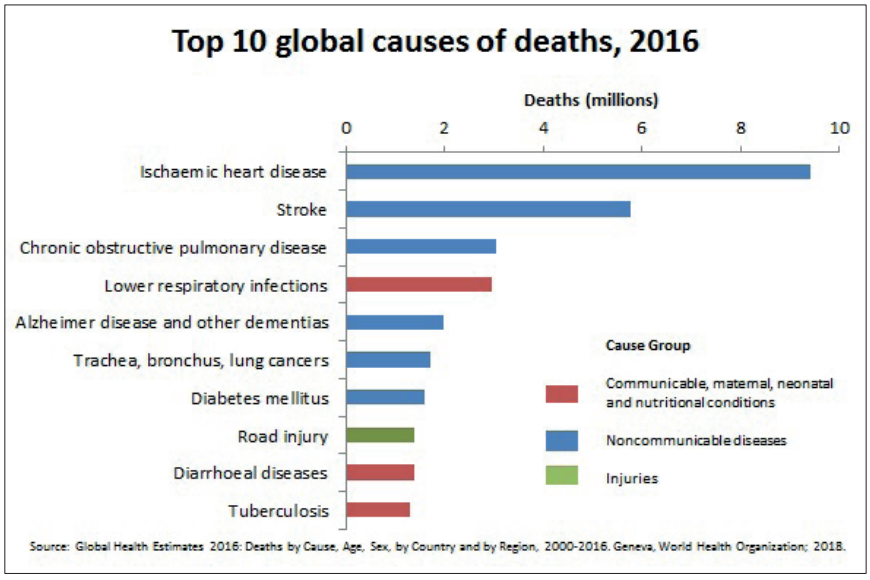


Figure 1. The World Health Organization Top-10 causes of death in 2016.[1]

The coronary heart team approach is designed to provide an evidence-based, multidisciplinary, patient-tailored treatment recommendation for a patient requiring myocardial revascularisation.[6] Treatment strategies consist of i) medical treatment, ii) percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The heart team consists of a cardiac surgeon, an interventional cardiologist, a clinical/non-interventional cardiologists and if necessary additional specialists.

Heart team meetings played a crucial role in well-respected randomized controlled trials (RCTs), such as the SYNTAX trial and the EXCEL trial.[7,8] Patients enrolled in these trials were discussed by a heart team that evaluated whether equivalent revascularisation could be achieved with either CABG or PCI. When clinical equipoise between the revascularisation strategies was determined, patients were randomized to either CABG or PCI. This method of randomization was crucial to adequately compare the treatment strategies head-to-head in PCI versus CABG trials. It furthermore encouraged open and structured discussions between cardiac surgeons and cardiologists to optimize coronary artery disease treatment strategy which ultimately leads to improved clinical outcomes.

The performance of such heart team meetings in 1000 consecutive patients with coronary artery disease discussed in the Thoraxcentre of the Erasmus University Medical Centre Rotterdam were assessed and clinical outcomes after treatment were determined.[9] Of 960 unique cases, almost one-third had complex left main or triple vessel coronary artery disease. Almost all patients (90%) were treated within 6 weeks after first referral, as advised by European Guidelines for myocardial revascularisation.[10] Furthermore, the majority of heart team decisions followed guideline-directed recommendations for treatment of patients with LM with 2- or 3VD (CABG: 71%)) and isolated LM or with 1VD (PCI: 81%). The recommendation for patients with 3VD was evenly divided between CABG and PCI (both 46%). Only 6% of patients with 1VD and 12% of patients with 2VD received medical therapy. This resulted in 5-year mortality rates of 26.9% for patients with LM and 2VD or 3VD, 17.1% for patients with 3VD without LMCAD and only 3.4% for patients with isolated LMCAD or 1VD. To conclude, the heart team approach at the Rotterdam Thoraxcentre was in agreement with contemporary myocardial revascularisation guidelines.

SURGICAL MYOCARDIAL REVASCULARISATION

On February the 25th, 1964, Vasilii I. Kolesov was the first surgeon that performed bypass surgery with the use of an internal thoracic artery (ITA) to the left anterior descending (LAD) coronary artery in a patient, performing a sutured anastomosis.[11] Michael DeBakey performed a venous aorta-coronary bypass later that year. Both techniques are still being used in contemporary CABG procedures.[12] It was René A. Favaloro that further developed CABG by consecutively operating patients with coronary artery disease that required revascularisation, and reporting on the surgical and clinical outcomes.[13] In this specific publication he described the clinical experience of 150 patients receiving CABG with the use of bilateral internal thoracic

arteries (BITA) at the Cleveland Clinic in Ohio, USA. As of today, the potential benefits of performing BITA revascularisation in selected patients is still being debated. In a high-definition core skills video tutorial, the surgical technique of performing CABG with a BITA Y-graft (e.g. LITA-Y-RITA ; LIMA-Y-RIMA) at the department of Cardiothoracic Surgery in the Erasmus Medical Centre, Rotterdam, is elucidated.[14]

Although surgical revascularisation was a relative experimental treatment when it was first introduced in the 1960s, for many patients it was their last resort to treat angina when medical therapy appeared insufficient. Perioperative mortality and morbidity rates were high during the early days of CABG. Therefore, meticulous selection of eligible patients to undergo surgical revascularisation appeared to be crucial (e.g. patients without recent myocardial infraction (MI), without severe left ventricular dysfunction or the need for other concomitant procedures).[15,16] To objectively compare CABG to other treatment modalities, structured and randomized studies were warranted. First CABG was only compared to medical treatment, however after the introduction of PCI, studies comparing revascularisation treatments head-to-head (PCI versus CABG) were designed. Over the past decades, CABG grew out to being one of the most often performed major surgical procedures, nonetheless the number of CABG procedures vary among countries.[17,18]

To further diminish adverse event rates, surgical and technical improvements deemed necessary. Cardiopulmonary bypass (CPB) systems improved and the systemic inflammatory response related to CPB was thereby reduced.[19] New surgical techniques such as off-pump coronary artery bypass (OPCAB) surgery, anaortic clampless CABG, minimally invasive direct coronary artery bypass (MIDCAB) surgery and eventually Hybrid coronary revascularisation (e.g. LITA to LAD with CABG followed by PCI of remaining coronary lesions) gained ground over the past years.[20] Currently, according to the 2018 European myocardial revascularisation guidelines, CABG is the gold standard for patients with complex and multivessel coronary artery disease requiring myocardial revascularisation.[10]

PERCUTANEOUS MYOCARDIAL REVASCULARISATION

Over the past decades percutaneous coronary intervention (PCI) has made a substantial impact on the way physicians treat patients with coronary artery disease requiring myocardial revascularisation. What once was the solitary playground of CABG, PCI is now a suitable alternative for selected patients with coronary artery disease requiring revascularisation.

A historical milestone took place when Andreas Grüntzig performed the first coronary balloon-angioplasty procedure in an awake patient with coronary artery disease on September the 16th, 1977 at the University of Zürich.[21] Although a major breakthrough, balloon angioplasty appeared not always to be an angina-relieving or life-saving procedure due to the risk of immediate restenosis of the coronary lumen. Julio Palmaz noted the shortcomings of balloon angioplasty and focused on developing a metal coronary stent. A decade later, the first successful in-human PCI procedure, by stenting a single-vessel lesion, was performed by Julio Palmaz and Richard Schatz in São Paola, Brazil in December 1987.[22]

The use of adequate secondary preventive treatment appeared to be of utmost importance to prevent restenosis and ensure stent patency.[23] To further optimize stent durability and decrease neo-intimal hyperplasia, drug eluting stents (DES) were developed.[24] As scientific and technological developments continued, first generation DES were followed up by second generation DES.[25,26] Currently, the field of stent developments keeps moving forward as third generation DES and bioresorbable stents are being used in contemporaneous PCI procedures.[23,27,28] According to the 2018 European myocardial revascularisation guidelines, PCI is a suitable treatment in selected patients with non-complex 1-or 2-vessel coronary artery disease.[10]

REVASCULARISATION STRATEGIES HEAD-TO-HEAD

Over the past decades, the boundaries of revascularisation strategies for patients with coronary artery disease have shifted, especially in patients with left main coronary artery disease and three-vessel disease. Where CABG once was the golden standard for myocardial revascularisation in left main disease, now PCI appears to become a suitable alternative in selected patients with non-complex coronary artery disease.[8,29] In patients with complex multivessel coronary artery disease (e.g. those patients with three-vessel disease and/or complex coronary anatomy) CABG remains the treatment of choice. The basis for these insights came from the international, multicenter randomized studies, such as the SYNTAX, FREEDOM, NOBLE and EXCEL trials, among others.[7,8,30,31] These trials empowered continuous advancements in the treatment of patients with coronary artery disease (Figure 2) and contributed to treatment-recommendations in the European and North-American myocardial revascularisation guidelines.[7,8,30,31] Besides distinguishing potential treatment benefits of either medical therapy, PCI or CABG in patients with coronary artery disease, these trials furthermore aimed to identify specific risk-predictors, such as diabetes and renal insufficiency, that may influence short-and long-term treatment

outcomes. The evidence presented by PCI versus CABG trials was accompanied with low rates of mortality and morbidity, indicating the constant developments of stent technology and improvements in surgical technique.

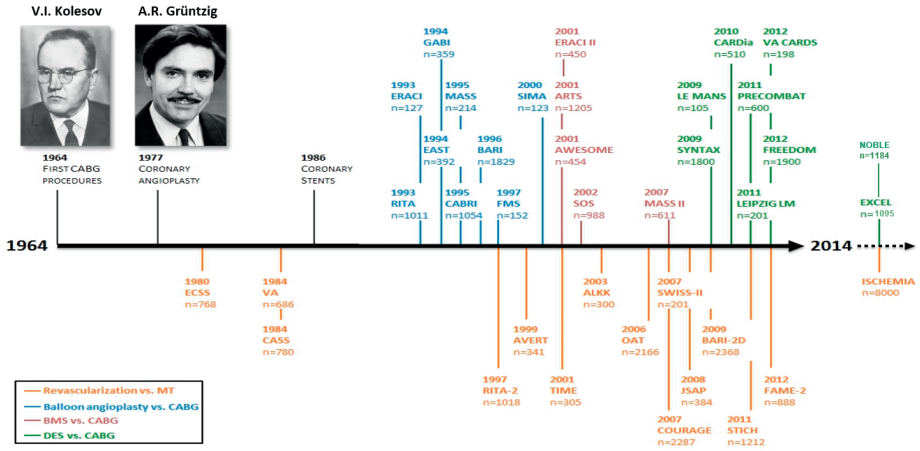


Figure 2. Scientific contributions in determining the optimal treatment strategy (medical therapy, percutaneous or surgical myocardial revascularisation) for patients with coronary artery disease.

To ensure continuous scientific and clinical advancements within the field of myocardial revascularisation, it is also beneficial to analyse revascularisation outcomes in patients that are treated within your own local institution, instead of only focussing on outcomes reported by large randomized and registry studies. Therefore, the life-long outcomes of patients that underwent PCI with balloon angioplasty or CABG in the Thoraxcentre at the Erasmus University Medical Centre in Rotterdam, were analyzed.[32] Included patients underwent primary revascularisation 40 years ago. At that time, these revascularisation treatments aimed to achieve complete revascularisation of significantly obstructed coronary segments of the major coronary arteries. During follow-up, the mean life-expectancy in 1041 patients treated with CABG was 18 years and 17 years in 856 patients treated with PCI. Important predictors of long-term survival were coronary artery disease complexity, hypertension, diabetes mellitus, nicotine abuse and left ventricular dysfunction. Overall, CABG and PCI demonstrated to be excellent treatment strategies for patients with coronary artery disease treated in the Thoraxcentre of the Erasmus University Medical Centre over 40 years ago.

The current thesis depicts analyses of clinical outcomes after myocardial revascularisation in subgroups of patients randomized to PCI versus CABG in the SYNTAX and EXCEL trials.

AIMS

This thesis provides an overview of the results of contemporaneous revascularisation strategies in patients with three-vessel (3VD) and/or left main coronary artery disease (LMCAD). We sought to distinguish treatment benefits and risk predictors for short-term (<1 year), mid-term (1 – 3 year) and long-term (≥10 year) follow-up in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Furthermore, we assessed the impact of using intraoperative quality assessment tools during CABG that could further improve surgical and patient-related outcomes.

OUTLINE

The short-term outcomes after CABG versus PCI in patients with LMCAD are described in **Chapter 2**, in which the predictive performance of the Society of Thoracic Surgeons (STS) mortality, stroke and length of hospital stay (LOS) risk score models in patients with left main coronary artery disease (LMCAD) undergoing PCI or CABG in in the multicentre randomized EXCEL trial, is reported. This study aimed to elucidate perioperative risk stratification in patients with LMCAD undergoing contemporary revascularisation.

The mid-term outcomes (1 – 3 year) after myocardial revascularisation in patients with LMCAD randomized to PCI versus CABG in the EXCEL trial are examined in **chapter 3** and **chapter 4**. The impact of patient and surgical characteristics, such as left ventricular ejection fraction (LVEF) and the use of bilateral internal thoracic arteries (BITA) during CABG, are assessed in relation to post-operative clinical outcomes. Moreover, **chapter 5** depicts a critical appraisal of the plethora of published meta-analyses on PCI versus CABG in patients with LMCAD and discusses major short-comings of this publication trend.

Long-term outcomes, treatment benefits and risk-predictors after percutaneous versus surgical myocardial revascularisation were assessed in **chapter 6** to **10**. These chapters focus on survival outcomes up to 10-years follow-up and beyond in the

investigator-driven SYNTAX Extended Survival (SYNTAXES) study. In **chapter 6**, 10-year all-cause death in patients the randomized to PCI versus CABG in the original SYNTAX cohort (n=1800; PCI=903 vs CABG=897) was analysed . Survival estimates at 10 years were determined in pre-specified subgroups of patients with *de novo* 3VD, LMCAD, diabetes, those without diabetes and according to coronary artery disease complexity defined by the SYNTAX score (low, intermediate and high SYNTAX scores). Additionally, long-term survival was assessed in those patients that were deemed unsuitable for randomization based on their clinical and angiographical characteristics and were therefore included in a PCI nested-registry (CABG-ineligible patients) and a CABG nested-registry (PCI-ineligible patients) (**chapter 7**). In **chapter 8** the impact of performing CABG with the use of multiple arterial grafts versus the use of a single arterial graft (MAG versus SAG) on 12.6-year all-cause death was assessed in patients that underwent CABG in the SYNTAX trial. **Chapter 9** evaluated the effect of PCI and CABG with incomplete versus complete revascularisation and the impact of any residual SYNTAX score on all-cause death outcomes at 10-year follow-up. Finally, the predictive performance of the SYNTAX score on long-term adverse events and vital status after PCI versus CABG is reported in **chapter 10**.

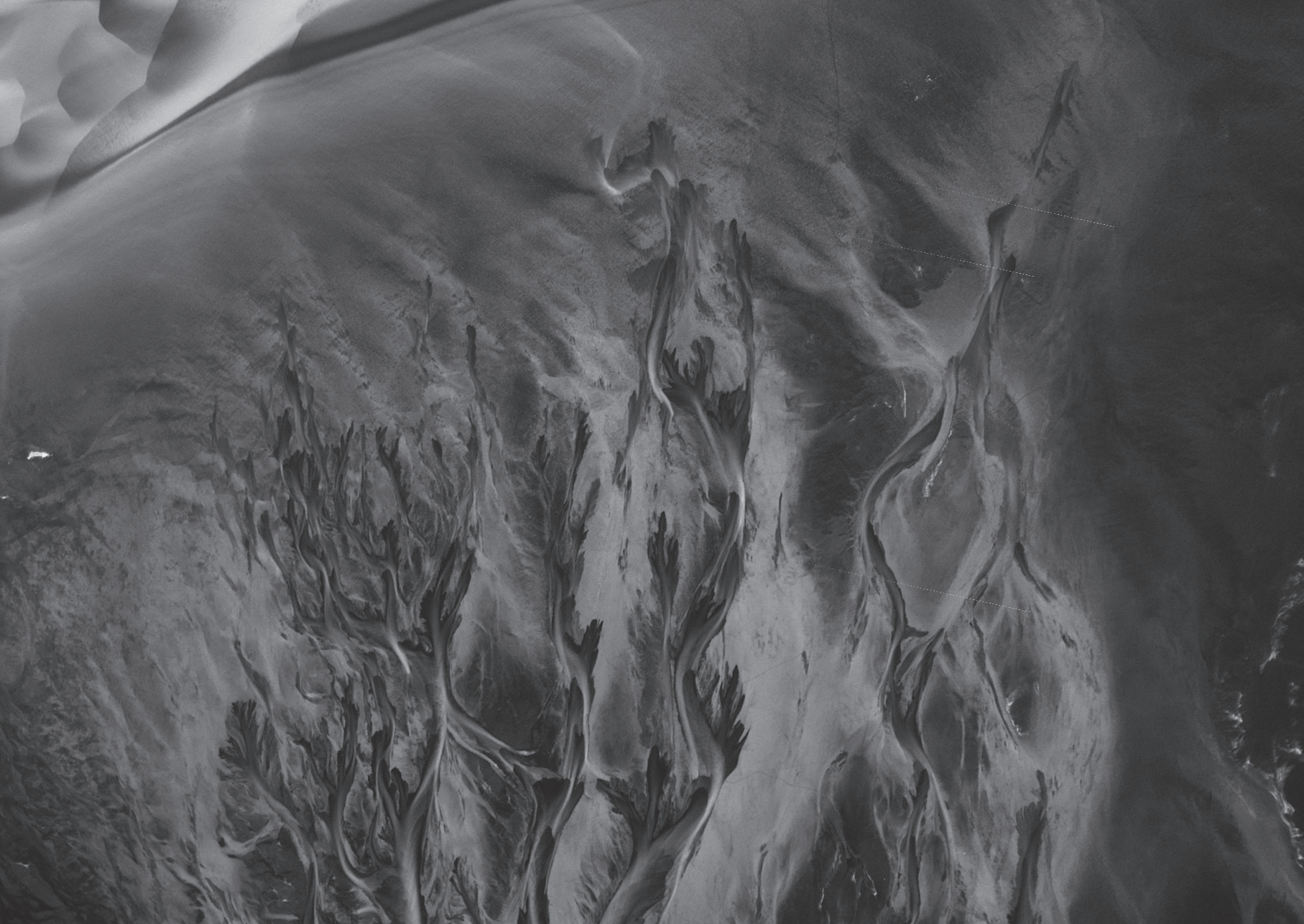
The final two chapters focus on appraising techniques that could further improve outcomes after surgical myocardial revascularisation. The impact of using intraoperative quality assessments by transit-time flow measurements (TTFM) was assessed with a systematic review and meta-analysis in **chapter 11**. Moreover, the multicenter, prospective REQUEST study set out to evaluate the impact of using TTFM in combination with high frequency ultrasound (HFUS) in 1016 patients undergoing CABG. This study (**chapter 12**) aimed to determine the number and type of surgical procedure changes that were made based on intraoperative guidance information using the combination of TTFM and HFUS.

A summary of the current thesis is reported in **chapter 13**, which is followed by the general discussion and conclusion in **chapter 14**. The post-script is described in **chapter 15** to **18**.

REFERENCES

1. World Health Organisation (WHO) - Top 10 causes of death. (Accessed March 2020, at https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.)
2. CardioPulse. European Heart Journal 2014;35:2929-33.
3. Organisation for Economic Cooperation and Development. Health at a Glance: Europe 2016: State of Health in the EU Cycle OECD Publishing, 2016. at https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-europe-2016_9789264265592-en.)
4. Farooq V, Brugaletta S, Serruys PW. The SYNTAX score and SYNTAX-based clinical risk scores. Semin Thorac Cardiovasc Surg 2011;23:99-105.
5. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1–coronary artery bypass grafting surgery. Ann Thorac Surg 2009;88:S2-22.
6. Head SJ, Kaul S, Mack MJ, et al. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. Eur Heart J 2013;34:2510-8.
7. Serruys P, Morice M, Kappetein A, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
8. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. N Engl J Med 2016;375:2223-35.
9. Domingues CT, Milojevic M, Thuijs D, et al. Heart Team decision making and long-term outcomes for 1000 consecutive cases of coronary artery disease. Interact Cardiovasc Thorac Surg 2018.
10. Sousa-Uva M, Neumann F-J, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Journal of Cardio-Thoracic Surgery 2018:ezy289-ezy.
11. Olearchyk AS. Vasilii I. Kolesov. A pioneer of coronary revascularization by internal mammary-coronary artery grafting. J Thorac Cardiovasc Surg 1988;96:13-8.
12. Garrett HE, Dennis EW, DeBakey ME. Aortocoronary bypass with saphenous vein graft. Seven-year follow-up. JAMA 1973;223:792-4.
13. Favaloro RG, Effler DB, Groves LK, Fergusson DJ, Lozada JS. Double internal mammary artery-myocardial implantation. Clinical evaluation of results in 150 patients. Circulation 1968;37:549-55.
14. Thuijs D, Durko A, Mahtab E, Bekkers J. Composite LITA-RITA-Y graft configuration for coronary artery bypass grafting. Multimed Man Cardiothorac Surg 2018;2018.
15. Cooley DA, Dawson JT, Hallman GL, et al. Aortocoronary saphenous vein bypass. Results in 1,492 patients, with particular reference to patients with complicating features. Ann Thorac Surg 1973;16:380-90.
16. Head SJ, Kieser TM, Falk V, Huysmans HA, Kappetein AP. Coronary artery bypass grafting: Part 1–the evolution over the first 50 years. Eur Heart J 2013;34:2862-72.
17. D'Agostino RS, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2019 Update on Outcomes and Quality. Ann Thorac Surg 2019;107:24-32.
18. Wilkins E WL, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N. European Cardiovascular Disease Statistics. European Heart Network, Brussels 2017.

19. Larm O, Larsson R, Olsson P. A new non-thrombogenic surface prepared by selective covalent binding of heparin via a modified reducing terminal residue. Biomater Med Devices Artif Organs 1983;11:161-73.
20. Head SJ, Borgermann J, Osnabrugge RL, et al. Coronary artery bypass grafting: Part 2--optimizing outcomes and future prospects. Eur Heart J 2013;34:2873-86.
21. Grüntzig A. TRANSLUMINAL DILATATION OF CORONARY-ARTERY STENOSIS. The Lancet 1978;311:263.
22. Tan C, Schatz RA. The History of Coronary Stenting. Interv Cardiol Clin 2016;5:271-80.
23. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. European Heart Journal 2015;36:3320-31.
24. Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. Circulation 1999;99:44-52.
25. Pendyala LK, Yin X, Li J, Chen JP, Chronos N, Hou D. The first-generation drug-eluting stents and coronary endothelial dysfunction. JACC Cardiovasc Interv 2009;2:1169-77.
26. Navarese EP, Kowalewski M, Kandzari D, et al. First-generation versus second-generation drug-eluting stents in current clinical practice: updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients. Open Heart 2014;1:e000064.
27. von Birgelen C, Sen H, Lam MK, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet 2014;383:413-23.
28. Iqbal J, Gunn J, Serruys PW. Coronary stents: historical development, current status and future directions. British Medical Bulletin 2013;106:193-211.
29. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391:939-48.
30. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.
31. Makikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. Lancet 2016;388:2743-52.
32. Milojevic M, Thuijs D, Head SJ, et al. Life-long clinical outcome after the first myocardial revascularization procedures: 40-year follow-up after coronary artery bypass grafting and percutaneous coronary intervention in Rotterdam. Interact Cardiovasc Thorac Surg 2019.



Chapter 2

Prognostic performance of the Society of Thoracic Surgeons risk score in patients with left main coronary artery disease undergoing revascularisation: a post hoc analysis of the EXCEL trial

Daniel J.F.M. Thuijs, Robert H. Habib, Stuart J. Head, John D. Puskas, David P. Taggart, Gregg W. Stone , Zixuan Zhang, Patrick W. Serruys, Joseph F. Sabik, A. Pieter Kappetein

EuroInterventions, May 2020

ABSTRACT

Aims

Accurate risk prediction in patients undergoing revascularisation is essential. We aimed to assess the predictive performance of Society of Thoracic Surgeons (STS) risk models in patients with left main coronary artery disease (LMCAD) undergoing coronary artery bypass grafting (CABG) or percutaneous coronary intervention with everolimus-eluting stents (PCI-EES).

Methods and results

The predictive performance of STS risk models for perioperative mortality, stroke and renal failure was evaluated for their discriminative ability (C statistic) and calibration (Hosmer-Lemeshow goodness-of-fit-test; χ^2 and p-values) among patients with LMCAD undergoing PCI-EES (n=935) and CABG (n=923) from the randomised EXCEL trial. STS risk scores, in CABG patients, showed good discrimination for 30-day mortality and average discrimination for stroke (C statistic 0.730 and 0.629, respectively) with average calibration. For PCI, STS risk scores had no discrimination for mortality (C statistic 0.507), yet good discrimination (C statistic 0.751) and calibration for stroke. The predictive performance for renal failure was good for CABG (C statistic 0.82), yet poor for PCI (C statistic 0.59).

Conclusions

In selected patients with LMCAD from the EXCEL trial, STS risk models showed good predictive performance for CABG yet lacked predictive performance for PCI for perioperative mortality and renal failure. The STS stroke risk model was surprisingly more discriminating in PCI compared to CABG. Improved and procedure-specific risk prediction instruments are needed to accurately estimate adverse events after LMCAD revascularisation by CABG and PCI. ClinicalTrials.gov Identifier: NCT01205776

Keywords

clinical trials, death, drug-eluting stent, revascularisation, risk stratification, stroke

INTRODUCTION

Accurate preoperative risk assessment is essential to decide between percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery in patients with advanced coronary artery disease (CAD). This is particularly true now as PCI is increasingly accepted as a suitable alternative to CABG in selected patients with multivessel and left main coronary artery disease (LMCAD)[1-8]. Moreover, it is unclear how risk score calculators perform in selected patients with isolated LMCAD undergoing revascularisation in the current era.

The randomised EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Grafting for Effectiveness of Left Main Revascularisation) trial showed that PCI with everoli-mus-eluting stents (EES) was non-inferior to CABG in patients with LMCAD and simple or moderate anatomic coronary complexity in terms of death, large myocardial infarction[9], or stroke at an intermediate follow-up time of three years. Patients who underwent PCI had fewer major adverse events in the periprocedural period compared with those who underwent CABG, yet had a higher three-year rate of ischaemia-driven repeat revascularisation[10]. Patients at low risk of surgical complications may thus have a more favourable risk-benefit profile after CABG.

Multiple risk stratification tools have been developed to predict perioperative outcomes after CABG[11-14]. These predictive models can guide cardiothoracic surgeons and cardiologists during Heart Team meetings to select the optimal treatment and predict their clinical outcomes, as recommended by the ESC/EACTS 2018 Guidelines on myocardial revascularisation[6,15].

It is unclear, however, whether the accuracy of isolated "CABG-only" STS risk models will remain as robust when applied in specific patient sub-cohorts (e.g., LMCAD EXCEL patients) treated with CABG or alternatively with PCI. We therefore sought to investigate the predictive performance of STS risk scores in patients who underwent CABG for LMCAD in the randomised EXCEL trial. We also examined the utility of STS risk models in PCI-treated subjects to determine whether these models enable the identification of those patients best managed by one or the other revascularisation modality.

METHODS

Study design

The design and results of the EXCEL study have been reported pre- viously[10,16]. In brief, the EXCEL trial was a multicentre randomised trial that compared CABG to PCI with EES (XIENCE; Abbott Vascular, Santa Clara, CA, USA) in patients with LMCAD. The trial was approved by the local ethics committees of all participating sites and is registered at ClinicalTrials.gov (NCT01205776). The EXCEL trial randomised 1,905 patients with LMCAD and a low or intermediate SYNTAX score (≤32, site-determined) to undergo CABG (n=957) or PCI with EES (n=948). Of the 957 patients randomised to CABG, 930 underwent revascularisation, with CABG being the primary procedure in 923 patients (as-treated). Of the 948 patients randomised to PCI, 942 underwent revascularisation and, of these, 935 patients underwent PCI as the primary procedure (as-treated). The current study included the as-treated randomised patients (CABG n=923 and PCI n=935) to assess whether 30-day clinical outcomes could be accurately predicted by the STS predicted risk of mortality (PROM), stroke, and renal failure risk models. STS risk scores were calculated by implementing the STS CABG risk models as per the specifications described by Shahian et al[12]; the accuracy of implementation was confirmed by robust cross-checking with the "online STS Adult Cardiac Surgery Risk Calculator" for "isolated coronary artery bypass"[17]. The definitions of death, stroke and renal failure used by the EXCEL trial are consistent with the definitions used by the STS adult cardiac surgery database.

Study endpoints

The primary endpoint was the predictive performance of the STS PROM and stroke risk scores in the as-treated LMCAD population that underwent CABG or PCI. The secondary endpoint was the predictive performance of the STS renal failure risk score in the CABG and PCI cohorts.

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD), and discrete variables were expressed as percentage with frequency, unless otherwise stated. An unpaired t-test was used to compare mean outcomes, and the Wilcoxon two-sample test was used to compare median outcomes. Overall observed to expected (O/E) ratios were visualised by bar plots. The χ^2 test was used to calculate p-values and 95% confidence intervals (CI) on the difference in observed to expected proportions (O/E ratios) between treatment groups. An O/E ratio of >1 indicated underprediction of the clinical outcome by the STS risk score.

Each treatment group was split into quintiles based on the mean predicted STS risk scores, ranking subgroups from lowest predicted risk scores to highest predicted risk scores. The PROM, stroke, and renal STS models were evaluated for their discriminating ability using the area under the receiver operating curve according to the "concordance" (C statistic) methodology. A C statistic outcome of 1.0 indicates perfect discriminative power, whereas 0.5 indicates no discriminative ability[18]. Risk model calibration competence was assessed using the Hosmer-Lemeshow goodness-of-fit test to examine the observed versus expected outcomes for all quintiles. Specifically for the Hosmer-Lemeshow goodness-of-fit test, a two-sided p-value of ≤0.05 indicates a statistically significant difference between observed and expected values; therefore, a p-value >0.05 indicates better predictive performance. For all other statistical tests, a $p<0.05$ was considered to be statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline and procedural characteristics

Baseline characteristics between the as-treated CABG and PCI groups were similar except for modest differences in New York Heart Association Class I, and distal left main stenosis anatomy **(**Table 1**)**. Off-pump CABG was performed in 29.4% of the procedures; bilateral internal thoracic arteries were used in 22.4%. Mean post-procedural in-hospital stay was 8.3±7.8 days for CABG and 2.2±2.9 days for PCI ($p<0.0001$) **(Supplementary** Table 1**)**.

Table 1. Baseline clinical and angiographic characteristics.

Characteristics		CABG (n=923)	PCI (n=935)
Age, years		65.9±9.5	66.0±9.6
Female sex		22.1% (204/923)	23.9% (223/933)
Coronary artery disease risk factors	Hypertension	73.7% (680/923)	74.2% (694/933)
	Hyperlipidaemia	68.9% (635/921)	70.8% (661/934)
	Diabetes mellitus	27.7% (256/923)	30.2% (282/933)
	Medically treated	25.7% (237/923)	27.0% (252/933)
	Recent smoker	20.4% (187/915)	23.7% (220/930)
	Family history of premature coronary artery disease	65.0% (506/779)	67.1% (521/777)

Table 1. Baseline clinical and angiographic characteristics. (*continued*)

Characteristics		CABG (n=923)	PCI (n=935)
Preoperative risk factors	Peripheral vascular disease	9.0% (83/919)	10.3% (96/932)
	Prior transient ischaemic attack or stroke	7.3% (67/923)	5.5% (51/934)
	Creatinine clearance (ml/min)	89.1±32.1 (908/923)	90.0±32.6 (922/935)
	Renal insufficiency[c]	15.1% (137/908)	17.4% (160/922)
	Dialysis	0.3% (3/923)	0.2% (2/933)
	Chronic obstructive pulmonary disease	8.4% (77/921)	6.9% (64/934)
	History of carotid artery disease	8.5% (78/919)	7.9% (74/931)
	History of anaemia[a]	8.8% (81/921)	10.6% (99/931)
	Body mass index, kg/m^2	28.5±5.0	28.8±4.9
Congestive heart failure	NYHA Class I[b]	0.7% (6/920)	1.7% (16/933)
	NYHA Class II	3.7% (34/920)	2.4% (22/933)
	NYHA Class III	1.7% (16/920)	2.8% (26/933)
	NYHA Class IV	0.2% (2/920)	0.1% (1/933)
Critical preoperative state[d]		2.0% (18/922)	1.1% (10/933)
Recent myocardial infarction'		14.8% (136/920)	15.0% (140/931)
STEMI		1.4% (14/917)	1.4% (13/928)
Non-STEMI		12.9% (118/917)	13.3% (123/928)
Coronary dominance, site assessed	Right	89.9% (816/908)	89.2% (814/913)
	Left	10.1% (92/908)	10.8% (99/913)
LM stenosis location, site assessed	Ostial	36.1% (333/923)	32.9% (308/933)
	Mid	18.6% (172/923)	20.3% (190/933)
	Distal [f]	51.9% (479/923)	59.1% (553/933)
	Bifurcation[f]	31.9% (294/923)	37.8% (353/933)
Left main diameter stenosis, site assessed	0 to <50%	0.4% (4/921)	0.3% (3/933)
	≥50 to <70%	16.8% (155/921)	16.7% (156/933)
	≥70%	82.7% (762/921)	83.0% (774/933)
SYNTAX score, site assessed		20.5±6.2	20.7±6.2
Low (≤22)		61.7% (569/922)	59.0% (551/934)
Intermediate (23-32)		38.3% (353/922)	41.0% (383/934)
High (≥33)		0% (0)	0% (0)
Left ventricular ejection fraction, site assessed		57.4±9.0	57.0±9.6

Values are % (n/N) or mean±standard deviation. [a]World Health Organization (WHO) criteria: haematocrit (Ht) at initial presentation: <13 g/dL (male) and <12 g/dL (female). [b]NYHA Class I: p=0.03. [c]Renal insufficiency was defined as a creatinine clearance of <60 ml/min according to the Cockcroft-Gault equation. [d]Critical preoperative state: ventricular tachycardia, ventricular fibrillation, or aborted sudden death; preoperative cardiac massage; preoperative ventilation before anaesthetic room; preoperative inotropes or IABP; preoperative acute renal failure (anuria or oliguria <10 mL/h). [e]Myocardial infarction within seven days of randomisation. [f]Left main stenosis lesion: distal (p=0.001) and bifurcation (p=0.008). All other p-values are non-significant. CABG: coronary artery bypass grafting; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

STS prom risk scores

The mean expected 30-day STS PROM scores were similar for patients who underwent CABG (0.85%±0.76%) versus PCI (0.90%±0.89%, p=0.21). Observed 30-day mortality rates were also similar between CABG (n=10, 1.1%) and PCI (n=9; 1.0%) (p=0.83). This resulted in comparable O/E ratios (1.27 vs 1.07, respectively, p=0.32) (Figure 1, **Supplementary** Table 1-**Supplementary** Table 3). The STS PROM C statistic for CABG was 0.73 (Figure 2A) and 0.51 for PCI (Figure 2B). The Hosmer-Lemeshow goodness-of-fit test was 10.21 (p=0.25) for CABG and 8.81 (p=0.36) for PCI (Figure 2C, Figure 2D).

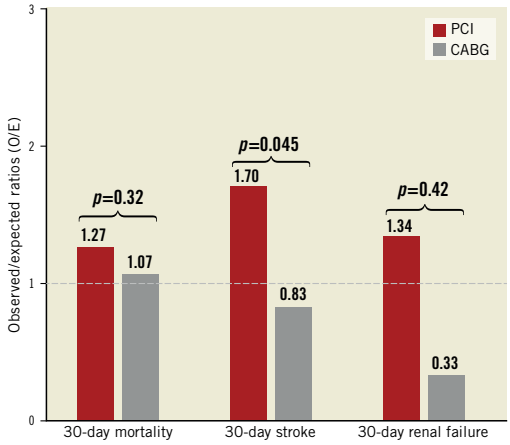


Figure 1. Observed to expected (O/E) ratios for 30-day all-cause mortality, 30-day stroke, and 30-day renal failure after coronary artery bypass grafting (CABG; n=923) and percutaneous coronary intervention (PCI; n=935).

STS stroke risk scores

The mean expected 30-day STS stroke scores were 0.76%±0.54% for CABG versus 0.77%±0.61% for PCI patients (p=0.86). Stroke occurred in 1.3% (n=12) after CABG versus 0.6% (n=6) after PCI (p=0.12). Consequently, stroke O/E ratios were 1.70 for CABG and 0.83 for PCI (p=0.045) (Figure 1, **Supplementary** Table 2-**Supplementary** Table 4). The C statistic for the STS stroke risk score was 0.63 for CABG compared with 0.75 for PCI (Figure 3A, Figure 3B). The Hosmer-Lemeshow goodness-of-fit test was 7.21 (p=0.51) for CABG and 6.13 (p=0.63) for PCI (Figure 3C, Figure 3D).

STS renal failure risk scores

No differences were found between the mean expected 30-day STS renal failure scores in the CABG cohort (1.95%±2.13%) and the PCI cohort (1.95%±2.35%, p=0.96). Observed renal failure rates, at 30 days, were 2.6% in patients who underwent CABG

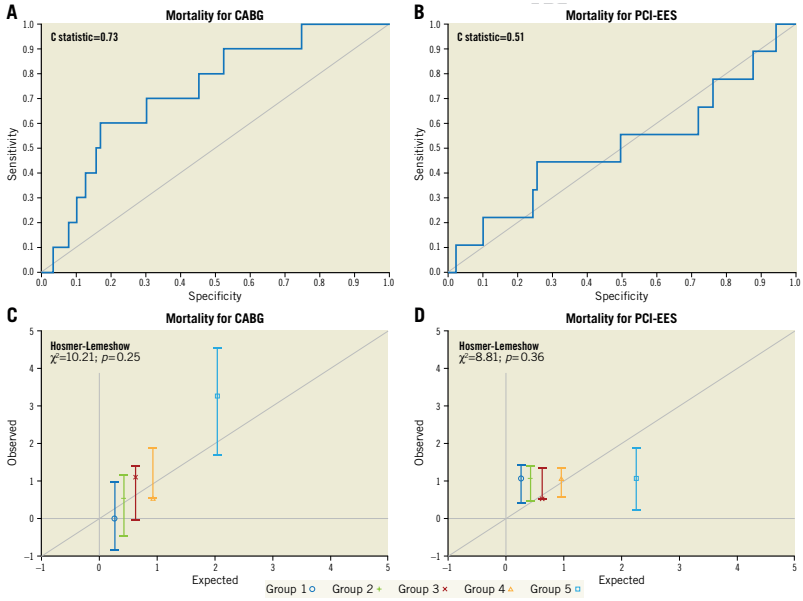


Figure 2. Representation of STS PROM score performance by C statistic (A & B) and Hosmer-Lemeshow goodness-of-fit tests (C & D) for coronary artery bypass grafting (CABG) and percutaneous coronary intervention with everolimus-eluting stents (PCI-EES). Panels C and D represent groups ordered by quintiles from the lowest predicted risk scores to the highest predicted risk scores.

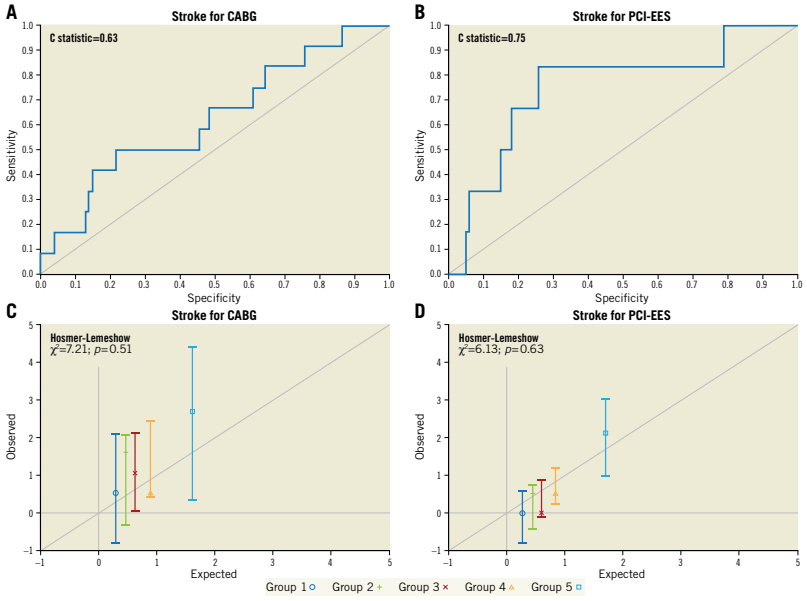


Figure 3. Representation of STS stroke risk score performance by C statistic (A & B) and Hosmer-Lemeshow goodness-of-fit tests (C & D) for coronary artery bypass grafting (CABG) and percutaneous coronary intervention with everolimus-eluting stents (PCI-EES). Panels C and D represent groups ordered by quintiles from the lowest predicted risk scores to the highest predicted risk scores.

(n=24) and 0.6% in patients who underwent PCI (n=6) (p<0.001). Subsequently, renal O/E ratios were 1.34 for CABG and 0.33 for PCI (p=0.42) (Figure 1, **Supplementary** Table 3-**Supplementary** Table 5). The C statistic was 0.82 for CABG and 0.59 for PCI (Figure 4A, Figure 4B), and the Hosmer-Lemeshow goodness-of-fit test was 14.73 (p=0.065) for CABG (Figure 4C) and 11.98 (p=0.15) for PCI (Figure 4D).

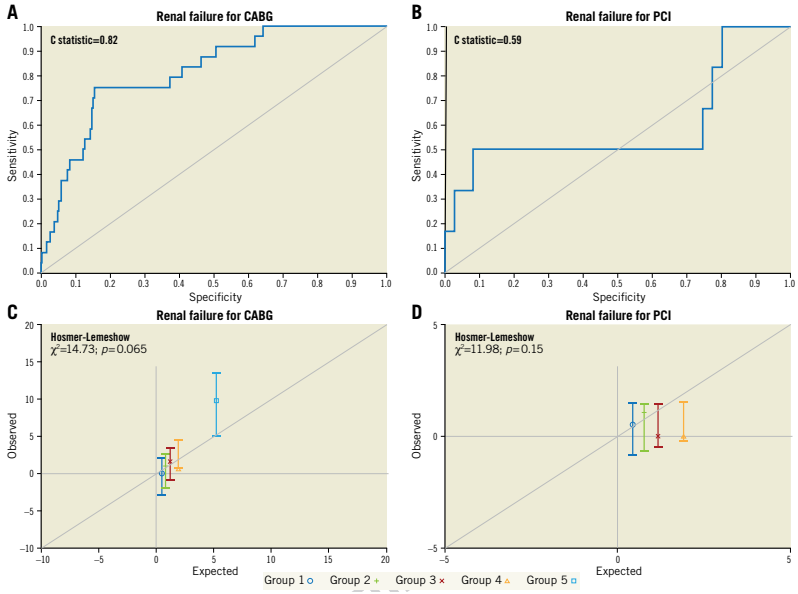


Figure 4. Representation of STS renal failure risk score performance by C statistic (A & B) and Hosmer-Lemeshow goodness-of-fit tests (C & D) for coronary artery bypass grafting (CABG) and percutaneous coronary intervention with everolimus-eluting stents (PCI-EES). Panels C and D represent groups ordered by quintiles from the lowest predicted risk scores to the highest predicted risk scores.

DISCUSSION

For patients with LMCAD undergoing revascularisation in the EXCEL trial, the perioperative STS PROM risk model for CABG patients showed good predictive performance based on the C statistic and was well calibrated according to the Hosmer-Lemeshow goodness-of-fit test, with modest underprediction of mortality among high-risk patients. Conversely, the STS PROM risk model was non-predictive after PCI with EES (C statistic 0.507; comparable to "flipping a coin"). In particular, perioperative mortality was overestimated by the STS PROM in the highest PCI risk quintile[10]; however, the number of very high risk patients was limited in EXCEL, potentially reducing the precision of the STS predictive ability in higher risk groups[19]. The predictive ability for stroke was reasonably good for both PCI and CABG. Finally,

the predictive performance of STS renal failure risk scores was good in the CABG cohort, but poor in the PCI group. As the number of more complex patients with CAD who are discussed during Heart Team meetings increases, it is important to be able to predict the risk of adverse events after CABG or PCI accurately. Therefore, evaluating the predictive performance of the STS risk score calculator provides valuable insights into perioperative risk assessment in the contemporary revascularisation era.

The STS isolated CABG risk models were developed and validated for short-term outcomes (in-hospital or 30-day mortality and other major morbidity) based on a large, national-scale and all-inclusive isolated CABG surgery patient population derived from the STS adult cardiac surgery database over a period of time (one to three years)[12]. It is therefore not surprising that STS risk models predicted outcomes less accurately in patients undergoing PCI with EES compared with those undergoing CABG. During structured Heart Team meetings, clinicians should combine the results from the STS and other risk scores with clinical judgement and current guidelines to determine the optimal patient-tailored and evidence-based revascularisation decision[6], [15]. Besides, it is important to account for the expected increased short-term risk of surgical intervention versus potential differential long-term outcomes of available treatment options.

In the current study, stroke within 30 days occurred less often after PCI compared to CABG. This finding is in line with a prior large-scale meta-analysis reporting a significantly lower 30-day rate of stroke after PCI compared with CABG in LMCAD (odds ratio [OR] 0.36, 95% CI: 0.16-0.82, p=0.007)[8], [20]. Nonetheless, it was surprising that the STS risk model underestimated the risk of stroke at 30 days in patients who underwent CABG (O/E 1.70). The STS stroke risk model was developed and validated in an all-inclusive (LMCAD and non-LMCAD) patient population without including LMCAD as a predictor variable of perioperative stroke. Risk models developed in specific sub-cohorts (e.g., LMCAD only) can differ appreciably from models based on overall patient populations. In the EXCEL trial, the PCI cohort had a lower 30-day stroke rate (n=6, 0.6%) compared with CABG (n=12, 1.3%; OR 0.5, 95% CI: 0.19-1.33, p=0.15)[9]. The risk of developing stroke is influenced by multiple underlying causes, in both CABG and PCI cohorts, such as (i) on-pump versus off- pump, (ii) usage of side-biting aorta clamp, (iii) single versus dual antiplatelet therapy, (iv) use of single versus bilateral internal thoracic arteries, (v) post-procedural atrial fibrillation, and (vi) femoral versus radial artery percutaneous access[20], [21]. STS risk models are solely based on demographic and preoperative CABG patient factors and comorbid-

ity. Therefore, a different way of modelling is warranted to take into account all periprocedural factors influencing the risk of stroke.

Renal failure is a well-known and serious complication after cardiopulmonary bypass, and the excess use of contrast agents during PCI[22] increases the risk of mortality and morbidity[23]. A subgroup analysis of patients with versus without chronic kidney disease from the EXCEL trial showed that PCI compared with CABG was associated with lower rates of acute renal failure in patients with (2.3% vs 7.6%; OR 0.28, 95% CI: 0.09-0.87) versus without chronic kidney disease (0.3% vs 1.3%; OR 0.20, 95% CI: 0.040.90)[24]. Nonetheless, no treatment interaction was identified (p for interaction=0.71). It is important to predict the risk of renal failure after revascularisation adequately in order to personalise treatment strategies in individual patients. The predictive performance of the STS renal failure risk model was excellent in the CABG cohort; however, it performed poorly in the PCI cohort.

To date, no risk model has focused exclusively on predicting perioperative outcomes in patients with LMCAD. The CABG-specific STS risk model did not include LMCAD as a predictor of the risk for mortality, stroke, renal failure, and reoperation. Rather, it only included LMCAD-specific coefficients for "prolonged ventilation" and "any composite adverse outcome"[12]. The SYNTAX score II did take LMCAD into account by grading the presence of a ≥50% left main with the highest possible weighting factor, but this risk score was developed and validated for predicting long-term (four-year) mortality in patients with complex CAD[14]. To determine perioperative clinical outcomes for LMCAD patients more accurately, risk models specifically and separately created for the LMCAD-CABG and LMCAD-PCI patient populations will probably prove to be more discriminating.

Limitations

In the current study, the predicted STS risk scores were computed based on the 2008 STS risk models. The STS Adult Cardiac Surgery Risk models were recently updated using a more recent patient population and considering a larger number of predictive variables[25]. Since not all variables that were used in the updated STS models were collected in the EXCEL trial, it was not possible to evaluate the predictive performance of the 2018 STS CABG risk models in the EXCEL trial population. Furthermore, the EXCEL trial excluded patients with high site-determined SYNTAX scores; therefore, the results of this study cannot be generalised to such patients (SYNTAX score ≥33).

CONCLUSIONS

In selected patients with LMCAD from the EXCEL trial, STS risk models showed good predictive performance for CABG yet were non-predictive for PCI regarding perioperative mortality and renal failure. The STS stroke risk model was surprisingly more discriminating in PCI compared to CABG. Derivation and validation of treatment- and cohort-specific risk models are warranted for optimal prediction of perioperative clinical outcomes in patients with LMCAD requiring revascularisation, bearing in mind the between- treatment differences emerging beyond 30 days.

IMPACT ON DAILY PRACTICE

In selected patients with LMCAD from the EXCEL trial, STS risk models showed good predictive performance for CABG yet lacked predictive ability for PCI regarding perioperative mortality and renal failure. The STS stroke risk model was surprisingly more discriminating in PCI compared to CABG. Derivation and validation of treatment- and cohort-specific risk models are warranted for optimal prediction of perioperative clinical outcomes of CABG and PCI in patients with LMCAD to guide clinical decision support better and to choose the best revascularisation treatment.

GUEST EDITOR

This paper was guest edited by Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France.

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CONFLICT OF INTEREST STATEMENT

G.W. Stone has served as a consultant to Matrizyme, Miracor, Neovasc, V-wave, Shockwave, Valfix, TherOx, Reva, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Abiomed and Ancora; has received speaker honoraria from Amaranth and Terumo; holds equity/options in Ancora, Cagent, Qool Therapeutics, Aria, Caliber, MedFocus family of funds, Biostar family of funds, Applied Therapeutics and SpectraWAVE; has served as a director for SpectraWAVE; and his employer, Columbia University, receives royalties for sale of the MitraClip from Abbott. P.W. Serruys reports receiving personal fees from Abbott, Biosensors, Medtronic, Micell Technologies, Qualimed, Sinomedical Technologies, St. Jude Medical, Stentys, Svelte, Philips/Volcano, Xeltis, and HeartFlow outside the submitted work. J. Sabik reports receiving personal fees from Medtronic, Edwards, and Sorin, and sits on the advisory board of Medtronic Cardiac Surgery. J. Puskas reports working as a consultant to Medtronic. A. Kappetein reports working as an employee of Medtronic, outside the submitted work. S. Head reports being an employee of Medtronic. The other authors have no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

Abbreviations

C statistic	concordance statistic
CABG	coronary artery bypass grafting
CAD	coronary artery disease
EACTS	European Association for Cardio-Thoracic Surgery
EES	everolimus-eluting stent
ESC	European Society of Cardiology
EXCEL	Evaluation of XIENCE versus Coronary Artery Bypass Grafting for Effectiveness of Left Main Revascularisation
LMCAD	left main coronary artery disease
O/E	observed/expected
OR	odds ratio
PCI	percutaneous coronary intervention
PROM	predicted risk of mortality
STEMI	ST-elevation myocardial infarction
STS	Society of Thoracic Surgeons
WHO	World Health Organization

REFERENCES

1. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kahler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet.* 2009;373:1190-7.
2. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Rodriguez-Granillo G, Hueb WA, Lemos PA, Serruys PW. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation.* 2008;118:1146-54.
3. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. *J Am Coll Cardiol.* 2011;58:1426-32.
4. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation.* 2014;129:2388-94.
5. Cavalcante R, Sotomi Y, Lee CW, Ahn JM, Farooq V, Tateishi H, Tenekecioglu E, Zeng Y, Suwannasom P, Collet C, Albuquerque FN, Onuma Y, Park SJ, Serruys PW. Outcomes After Percutaneous Coronary Intervention or Bypass Surgery in Patients With Unprotected Left Main Disease. *J Am Coll Cardiol.* 2016;68:999-1009.
6. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg.* 2019;55:4-90.
7. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2014;64:1929-49.
8. Palmerini T, Serruys P, Kappetein AP, Genereux P, Riva DD, Reggiani LB, Christiansen EH, Holm NR, Thuesen L, Makikallio T, Morice MC, Ahn JM, Park SJ, Thiele H, Boudriot E, Sabatino M, Romanello M, Biondi-Zoccai G, Cavalcante R, Sabik JF, Stone GW. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: A meta-analysis of 6 randomized trials and 4,686 patients. *Am Heart J.* 2017;190:54-63.

9. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol.* 2013;62:1563-1570.
10. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogats G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Pagé P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. *N Engl J Med.* 2016;375:2223-35.
11. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg.* 2012;41:734-44.
12. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery. *Ann Thorac Surg.* 2009;88:S2-22.
13. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation.* 2009;119:3053-61.
14. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet.* 2013;381:639-50.
15. Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes DR Jr, Leon MB, Marco J, Bogers AJ, Kappetein AP. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. *Eur Heart J.* 2013;34:2510-8.
16. Kappetein AP, Serruys PW, Sabik JF, Leon MB, Taggart DP, Morice MC, Gersh BJ, Pocock SJ, Cohen DJ, Wallentin L, Ben-Yehuda O, van Es GA, Simonton CA, Stone GW. Design and rationale for a randomised comparison of everolimus-eluting stents and coronary artery bypass graft surgery in selected patients with left main coronary artery disease: the EXCEL trial. *EuroIntervention.* 2016;12:861-72.
17. Isolated CAB - STS Adult Cardiac Surgery Database. Available at: http://riskcalc.sts.org/stswebriskcalc/calculate. Last accessed October 2017.
18. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology.* 2010;21:128-38.
19. Osnabrugge RL, Speir AM, Head SJ, Fonner CE, Fonner E, Kappetein AP, Rich JB. Performance of EuroSCORE II in a large US database: implications for transcatheter aortic valve implantation. *Eur J Cardiothorac Surg.* 2014;46:400-8.
20. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH,

Makikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF 3rd, Stables RH, Stone GW, Serruys PW, Kappetein AP. Stroke rates following surgical versus percutaneous coronary revascularization. *J Am Coll Cardiol.* 2018;72:386-98.

21. Shoji S, Kohsaka S, Kumamaru H, Sawano M, Shiraishi Y, Ueda I, Noma S, Suzuki M, Numasawa Y, Hayashida K, Yuasa S, Miyata H, Fukuda K. Stroke After Percutaneous Coronary Intervention in the Era of Transradial Intervention. *Circ Cardiovasc Interv.* 2018;11:e006761.
22. Faggioni M, Mehran R. Preventing Contrast-induced Renal Failure: A Guide. *Interv Cardiol.* 2016;11:98-104.
23. Pickering JW, James MT, Palmer SC. Acute kidney injury and prognosis after cardiopulmonary bypass: a meta-analysis of cohort studies. *Am J Kidney Dis.* 2015;65:283-93.
24. Giustino G, Mehran R, Serruys PW, Sabik JF 3rd, Milojevic M, Simonton CA, Puskas JD, Kandzari DE, Morice MC, Taggart DP, Gershlick AH, Genereux P, Zhang Z, McAndrew T, Redfors B, Ragosta M 3rd, Kron IL, Dressler O, Leon MB, Pocock SJ, Ben-Yehuda O, Kappetein AP, Stone GW. Left Main Revascularization With PCI or CABG in Patients With Chronic Kidney Disease: EXCEL Trial. *J Am Coll Cardiol.* 2018;72:754-65.
25. Shahian DM, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC Jr, Lobdell KW, Vassileva C, Wyler von Ballmoos MC, Thourani VH, Rankin JS, Edgerton JR, D'Agostino RS, Desai ND, Feng L, He X, O'Brien SM. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1-Background, Design Considerations, and Model Development. *Ann Thorac Surg.* 2018;105:1411-8.

SUPPLEMENTARY DATA

The supplementary data are also published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00417

Supplementary Table 1. Procedural characteristics.

Characteristics	CABG (n=923)	PCI (n=935)	*p*-value
Time from randomisation to first procedure, days	6.7±14.3	3.3±5.3	<0.0001
Arterial access site[a]			
Femoral	—	72.9% (744/1,021)	—
Radial	—	26.9% (275/1,021)	—
Brachial	—	0.2% (2/1,021)	—
Number of vessels treated			
Left main	—	100.0%	—
Left anterior descending	98.8% (907/918)	28.3% (265/925)	<0.0001
Circumflex artery	88.2% (810/918)	16.6% (155/925)	<0.0001
Right coronary artery	37.8 (347/918)	26.7% (250/925)	<0.0001
Number of stents implanted per patient	—	2.4±1.5	—
Total stent length per patient (mm)	—	49.1±35.6	—
On-pump bypass duration (min)	83.5±45.0	—	—
Cross-clamp duration	54.9±27.3	—	—
Number of conduits used per patient	2.6±0.8		
Arterial conduits	1.4±0.6	—	—
Venous conduits	1.2±0.9	—	—
Off-pump CABG	29.4% (271/923)	—	—
Bilateral internal thoracic artery	23.5% (217/923)	—	—
Any radial artery used	6.0% (55/923)	—	—
Length of hospital stay (days)	8.3±7.8	2.2±2.9	<0.0001

Values are % (n/N) or mean±standard deviation.
[a] All procedures, including index and planned staged (1,021 procedures in 935 PCI patients with one or more procedures).
CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

Supplementary Table 2. STS expected risk scores for mortality, stroke and renal failure based on demographic and baseline characteristics.

Variables	Entire population	*p*-value	Quintiles					*p*-value
			1	2	3	4	5	
Mortality								
CABG	0.85±0.76	0.21	0.26±0.04	0.42±0.05	0.62±0.07	0.93±0.12	2.03±0.95	<0.0001
PCI	0.90±0.89		0.27±0.05	0.41±0.05	0.62±0.08	0.95±0.14	2.25±1.17	<0.0001
Stroke								
CABG	0.76±0.54	0.86	0.27±0.07	0.45±0.05	0.62±0.05	0.88±0.10	1.60±0.60	<0.0001
PCI	0.77±0.61		0.26±0.07	0.44±0.04	0.60±0.05	0.83±0.09	1.71±0.74	<0.0001
Renal failure								
CABG	1.95±2.13	0.96	0.48±0.11	0.83±0.11	1.26±0.16	1.97±0.28	5.20±2.85	<0.0001
PCI	1.95±2.35		0.45±0.11	0.79±0.09	1.18±0.14	1.92±0.33	5.41±3.39	<0.0001

Values are mean±SD. For mortality and stroke primary endpoints, data were available for 923 CABG patients and 935 PCI patients. Scores represent predicted 30-day percentage rate unless otherwise noted.
CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

Supplementary Table 3. STS mean predicted risk of mortality, observed mortality percentages, and the observed/expected mortality ratios for the as-treated CABG versus PCI patients.

	Coronary artery bypass grafting				Percutaneous coronary intervention			
	n	Expected	Observed	O/E	n	Expected	Observed	O/E
Entire population	923	0.85	1.07	1.27	935	0.90	0.96	1.07
Quintile1	184	0.26	0	0	187	0.27	1.07	3.97
Quintile 2	185	0.42	0.54	1.28	187	0.41	1.07	2.60
Quintile 3	185	0.62	1.08	1.74	187	0.62	0.53	0.85
Quintile 4	185	0.93	0.54	0.58	187	0.95	1.07	1.12
Quintile 5	184	2.03	3.26	1.60	187	2.25	1.07	0.48

O/E: observed to expected ratio

Supplementary Table 4. STS mean predicted risk of stroke, observed stroke percentages, and the observed/expected stroke ratios for the as-treated CABG versus PCI patients

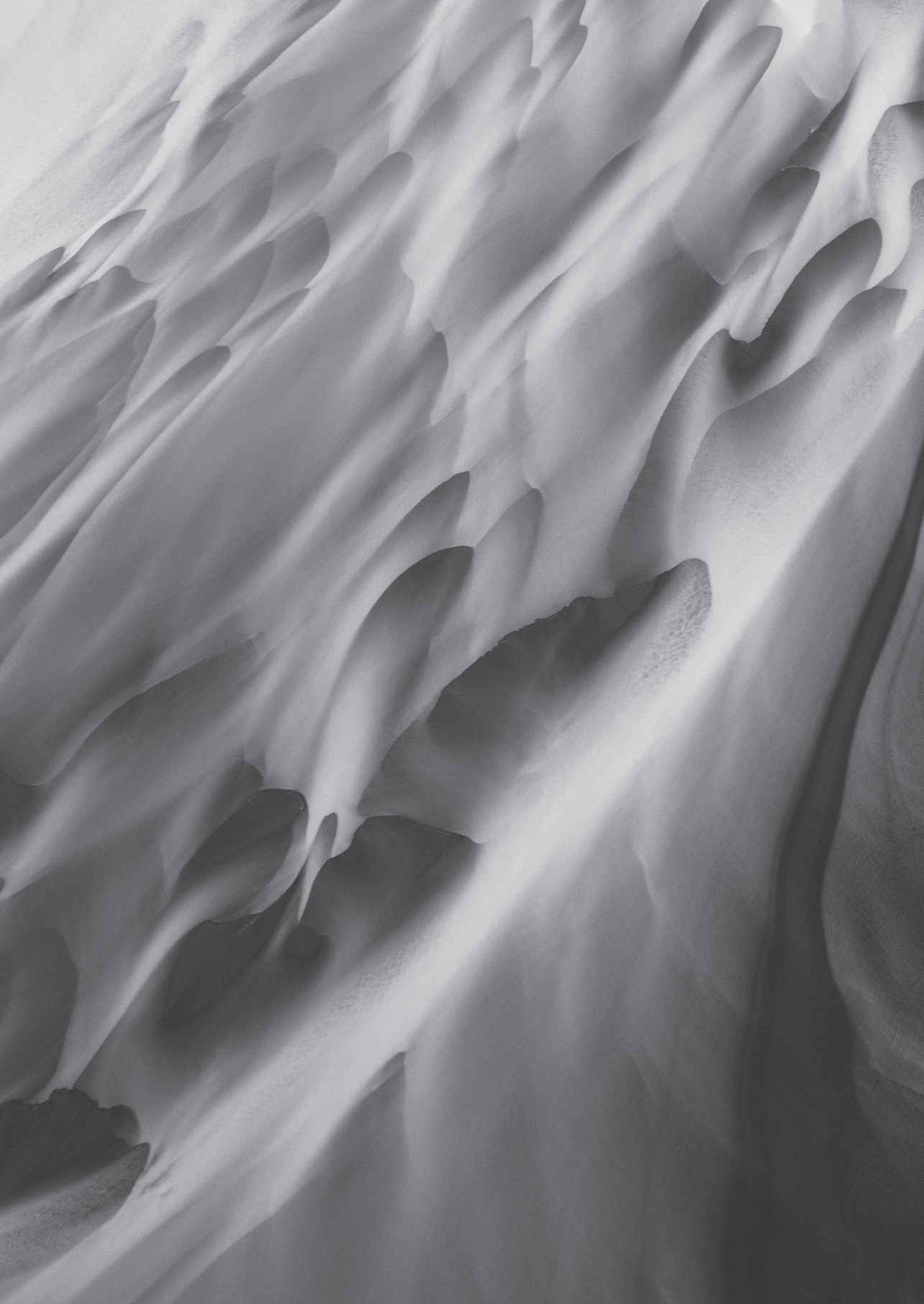
	Coronary artery bypass grafting				Percutaneous coronary intervention			
	n	Expected	Observed	O/E	n	Expected	Observed	O/E
Entire population	923	0.76	1.30	1.70	935	0.77	0.64	0.83
Quintile1	184	0.27	0.54	1.99	187	0.26	0	0
Quintile 2	185	0.45	1.62	3.62	187	0.44	0.53	1.20
Quintile 3	185	0.62	1.08	1.75	187	0.60	0	0
Quintile 4	185	0.88	0.54	0.62	187	0.83	0.53	0.64
Quintile 5	184	1.60	2.72	1.70	187	1.71	2.14	1.25

O/E: observed to expected ratio

Supplementary Table 5. STS mean predicted risk of renal failure, observed renal failure percentages, and the observed/expected renal failure ratios for the as-treated CABG versus PCI patients.

	Coronary artery bypass grafting				Percutaneous coronary intervention			
	n	Expected	Observed	O/E	n	Expected	Observed	O/E
Entire population	923	1.95	2.60	1.34	935	1.95	0.64	0.33
Quintile1	184	0.48	0	0	187	0.45	0.53	1.18
Quintile 2	185	0.83	1.08	1.30	187	0.79	1.07	1.35
Quintile 3	185	1.26	1.62	1.29	187	1.18	0	0
Quintile 4	185	1.97	0.54	0.27	187	1.92	0	0
Quintile 5	184	5.20	9.78	1.88	187	5.41	1.60	0.30

O/E: observed to expected ratio.



Chapter 3

Impact of left ventricular ejection fraction on clinical outcomes after left main coronary artery revascularisation: results from the randomized EXCEL trial

Daniel J.F.M. Thuijs, Milan Milojevic, Gregg W. Stone, John D. Puskas, Patrick W. Serruys, Joseph F. Sabik 3rd, Ovidiu Dressler, Aaron Crowley, Stuart J. Head, A. Pieter Kappetein

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ABSTRACT

Aims

To evaluate the impact of left ventricular ejection fraction (LVEF) on 3-year outcomes in patients with left main coronary artery disease (LMCAD) undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the EXCEL trial.

Methods and results

The EXCEL trial randomized patients with LMCAD to PCI with everolimus-eluting stents (n = 948) or CABG (n = 957). Among 1804 patients with known baseline LVEF, 74 (4.1%) had LVEF <40% [heart failure with reduced ejection fraction (HFrEF)], 152 (8.4%) LVEF 40-49% [heart failure with mid-range ejection fraction (HFmrEF)] and 1578 (87.5%) LVEF ≥50% (heart failure with preserved ejection fraction). Patients with HFrEF vs. HFmrEF vs. preserved LVEF experienced a longer postoperative hospital stay (9.0 vs. 7.0 vs. 6.0 days, P = 0.02) with greater peri-procedural complications after CABG, while hospital stay after PCI was unaffected by LVEF (1 .5 vs. 2.0 vs. 1 .0 days, P = 0.20). The composite primary endpoint of death, stroke, or myocardial infarction at 3years was 29.3% (PCI) vs. 27.6% (CABG) in patients with HFrEF, 1 6.2% vs. 15.0% in patients with HFmrEF, and 1 4.5% vs. 1 4.6% in those with preserved LVEF, respectively ($P_{interaction}$ = 0.90). Smoothing spline analysis demonstrated that the 3-year risk of all-cause death increased when LVEF decreased, both in patients undergoing CABG and PCI.

Conclusion

In the EXCEL trial, the composite rate of death, stroke or myocardial infarction at 3years was significantly higher in patients with HFrEF compared with HFmrEF or preserved LVEF, driven by an increased rate of all-cause death. No significant differences after PCI vs. CABG were observed among patients with HFrEF, HFmrEF and preserved LVEF. Longer-term follow-up could provide important insights on differences in clinical outcomes that might emerge over time.

Keywords

Coronary artery bypass grafting, Percutaneous coronary intervention, Left main coronary artery disease, Left ventricular ejection fraction, Left ventricular function, Heart failure with reduced ejection fraction

INTRODUCTION

Coronary artery bypass surgery is generally recommended for patients with extensive multivessel coronary artery disease (CAD) and severely impaired left ventricular ejection fraction (LVEF) (<35%).[1, 2] However, whether coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) is preferred in patients with left main CAD (LMCAD) and impaired LVEF (<50%) is unclear. Whereas randomized trials of patients with impaired LVEF undergoing CABG vs. medical therapy have been performed,[3] most trials comparing PCI with CABG have excluded patients with severely impaired LVEF (≤35%). Insights related to myocardial revascularisation in patients with impaired LVEF are thus mainly limited to observational studies. A recent systematic review of mainly observational studies (*n* = 16 191), compared myocardial revascularisation with medical therapy and reported an overall survival benefit of CABG over PCI in 8782 patients with LVEF ≤40% [hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.75–0.90].[4] However, the results varied widely between the individual studies (I^2 = 47%), possibly in part because follow-up ranged from 12–180 months. Moreover, only a limited number of patients with LMCAD and impaired LVEF was included in the analysis.

In the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main revascularisation trial, PCI with drug-eluting stents was shown to be an acceptable alternative to CABG in selected patients with LMCAD at 3-year follow-up.[5–7] The current pre-specified EXCEL sub-study aims to estimate the impact of LVEF, defined according to the European Society of Cardiology heart failure terminology,[8] on 3-year outcomes and evaluates differences in treatment effect of PCI with everolimus-eluting stents vs. CABG according to LVEF in patients with LMCAD in the EXCEL trial.

METHODS

Study design

The design of the EXCEL trial and the main outcomes have been reported previously.[9,10] In brief, 1905 patients with LMCAD and a site-determined SYNTAX score of ≤32 were randomized to PCI with everolimus-eluting stents (*n* = 948) and CABG (*n* = 957). Among those, baseline data on LVEF were available for 1804 patients (94.7%) and were assessed within 14 days after randomization. In 226 out of 1804 patients (12.5%) LVEF was <50%. These 226 patients were classified according to the European Society of Cardiology heart failure terminology; heart failure with reduced ejection

fraction (HFrEF; LVEF <40%) and heart failure with mid-range ejection fraction (HFmrEF; LVEF 40–49%). The HFrEF group consisted of 74 patients, and of those 43 were randomized to PCI and 31 to CABG. There were 152 patients in the HFmrEF group, of which 68 were randomized to PCI and 84 to CABG. LVEF was preserved (≥50%) in 1578 out of 1804 patients (87.5%), of whom 782 were randomized to PCI and 796 to CABG. The aim of the present pre-specified analysis was to evaluate the association of LVEF on 3-year clinical outcomes among patients with LMCAD undergoing PCI or CABG.

All patients reached 3-year follow-up at the time of this post-hoc analysis. An independent clinical events committee monitored and adjudicated adverse events. Informed consent was signed by all patients prior to randomization. The EXCEL trial complies with the Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01205776).

Endpoints

The primary endpoint consisted of the composite rate of all-cause death, stroke, or myocardial infarction (MI),[11] at 3years in subgroups of patients with HFrEF, HFmrEF and preserved LVEF, randomized to either PCI or CABG. Secondary powered endpoints included the primary endpoint measure at 30 days and the composite rate of all-cause death, stroke, MI, or ischaemia-driven revascularisation at 3 years in subgroup of patients with HFrEF, HFmrEF and preserved LVEF, randomized to PCI or CABG. Additional endpoints consisted of the individual components of the primary and secondary endpoints at 3 years and 30 days.[9,10]

Statistical analyses

All analyses were performed according to the intention-to-treat principle. Discrete variables were expressed as percentages with frequencies and compared with the χ^2 test or Fisher exact test when the expected frequency in any cell was <5. Continuous variables were summarized as mean ± standard deviation and were compared by independent samples *t*-test if normally distributed, or the Wilcoxon rank-sum test when non-normally distributed. Event rates up to 3years were estimated according to the Kaplan–Meier method, and differences between baseline LVEF subgroups (HFrEF, HFmrEF, and preserved), and PCI vs. CABG, were assessed using the log-rank test. Any differences in baseline characteristics between subgroups of patients with HFrEF, HFmrEF and preserved LVEF were adjusted using a multivariable Cox proportional hazard model, correcting for pre-specified important clinical and statistical variables. The association of LVEF as a continuous variable on the 3-year hazard of all-cause death was analysed by smoothing spline analysis with a linear

Cox proportional hazards regression model. Baseline characteristics of patients with and without known baseline LVEF were compared to check for potential attrition bias. All reported *P*-values are 2-sided, and $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

The baseline characteristics of the overall cohort of patients classified as HFrEF (*n* = 74), HFmrEF (*n* = 152) and those with preserved LVEF (*n* = 1578) are provided in Table 1. LVEF was assessed by cardiac ultrasound in 1051 patients (58.3%) and contrast left ventriculography in 71 5 patients (39.6%). Magnetic resonance or nuclear imaging were used in 38 patients (2.1%). Mean LVEF was 31.6% vs. 43.6% vs. 59.6% in patients with HFrEF vs. HFmrEF vs. preserved LVEF, respectively (*P* = <0.001). Patients with HFrEF and HFmrEF vs. preserved LVEF had a significantly worse cardiovascular risk profile and had a higher pre-operative risk reflected by increased predicted risk of mortality STS risk scores (1.11 vs. 0.96 vs. 0.86, respectively; *P* = 0.02). More patients with HFrEF had a high SYNTAX score (≥33, core laboratory analysis) compared to those with HFmrEF and preserved LVEF (37.5% vs. 21.5% vs. 23.8%, respectively; *P* = 0.02).

Table 1. Baseline characteristics according to left ventricular ejection fraction

Characteristics % (n/N)	LVEF <40% (HFrEF) (*n* = 74)	LVEF 40–49% (HFmrEF) (*n* = 152)	Preserved LVEF ≥50% (*n* = 1578)	*P*-value
Age (years)	67.0 ± 9.3	66.7 ± 9.3	65.9 ± 9.6	0.42
Female sex	21/74 (28.4)	20/152 (13.2)	380/1578 (24.1)	0.006
LVEF (%)	31.6 ± 4.2	43.6 ± 2.6	59.6 ± 6.6	<0.001
CAD risk factors				
Hypertension[a]	54/74 (73.0)	112/152 (73.7)	1169/1578 (74.1)	0.97
Hyperlipidaemia	45/74 (60.8)	100/151 (66.2)	1116/1577 (70.8)	0.11
Diabetes mellitus[a]	24/74 (32.4)	57/152 (37.5)	449/1578 (28.5)	0.05
Current or former smoker	53/74 (71.6)	103/151 (68.2)	962/1566 (61.4)	0.06
Family history of CAD	45/64 (70.3)	92/125 (73.6)	868/1323 (65.6)	0.16
NYHA class, known	23/74 (31.1)	23/152 (15.1)	73/1573 (4.6)	<0.001
I	4/74 (5.4)	3/152 (2.0)	16/1573 (1.0)	0.003
II	6/74 (8.1)	15/152 (9.9)	33/1573 (2.1)	<0.001
III	12/74 (16.2)	5/152 (3.3)	23/1573 (1.5)	<0.001
IV	1/74 (1.4)	0/152 (0.0)	2/1573 (0.1)	0.04

Table 1. Baseline characteristics according to left ventricular ejection fraction (*continued*)

Characteristics % (n/N)	LVEF <40% (HFrEF) (*n* = 74)	LVEF 40–49% (HFmrEF) (*n* = 152)	Preserved LVEF ≥50% (*n* = 1578)	*P*-value
Pre-operative risk factors				
History of stroke	6/74 (8.1)	8/152 (5.3)	50/1577 (3.2)	0.04
History of TIA	2/74 (2.7)	4/151 (2.6)	47/1569 (3.0)	0.96
Recent myocardial infarction[b]	18/74 (24.3)	34/151 (22.5)	219/1574 (13.9)	0.001
Chronic kidney disease[c]	24/73 (32.9)	39/149 (26.2)	231/1550 (14.9)	<0.001
Dialysis	0/74 (0.0)	2/152 (1.3)	3/1578 (0.2)	0.04
Peripheral vascular disease	14/72 (19.4)	23/152 (15.1)	133/1572 (8.5)	0.004
Chronic obstructive pulmonary disease	14/74 (18.9)	17/152 (11.2)	113/1575 (7.2)	0.004
History of carotid artery disease	13/74 (17.6)	12/150 (8.0)	125/1574 (7.9)	0.01
Body mass index (kg/m^2)	28.9 ± 6.4	28.7 ± 4.9	28.7 ± 4.9	0.93
< 20: cachectic	2/74 (2.7)	2/152 (1.3)	24/1578 (1.52)	0.52
> 30: obese	25/74 (33.8)	47/152 (30.9)	514/1578 (32.6)	0.85
History of anaemia[d]	8/74 (10.8)	23/152 (15.1)	146/1572 (9.3)	0.07
Lesions per patient	2.7 ± 1.5 (42)	2.9 ± 1.5 (66)	2.5 ± 1.3 (773)	0.051
Diffuse disease or small vessels	4/73 (5.5)	18/146 (12.3)	85/1555 (5.5)	0.004
Critical pre-operative state[e] STS risk scores				
PROM score	1.11 ± 1.0	0.96 ± 0.93	0.86 ± 0.78	0.02
Stroke score	0.97 ± 0.82	0.82 ± 0.61	0.75 ± 0.56	0.004
Reop. score	4.00 ± 1.63	3.64 ± 1.41	3.51 ± 1.34	0.007
SYNTAX score (site-assessed)	21.0 ± 5.7	22.4 ± 5.7	20.4 ± 6.2 (1576)	0.004
Low (≤22)	41/74 (55.4)	77/152 (50.7)	967/1576 (61.4)	0.03
Intermediate (23–32)	33/74 (44.6)	75/152 (49.3)	609/1576 (38.6)	0.03
High (≥33)	0/74 (0.0)	0/152 (0.0)	0/1576 (0.0)	–
SYNTAX score (core laboratory-assessed)	28.4 ± 9.7	27.6 ± 9.2	26.3 ± 9.3 (1526)	0.06
Low (≤22)	24/72 (33.3)	37/144 (25.7)	563/1526 (36.9)	0.03
Intermediate (23–32)	21/72 (29.2)	76/144 (52.8)	600/1526 (39.3)	0.001
High (≥33)	27/72 (37.5)	31/144 (21.5)	363/1526 (23.8)	0.021

Values are mean ± standard deviation, or *n* (%).

CAD, coronary artery disease; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association heart failure classification; PROM, Predicted Risk Of Mortality; STS, Society of Thoracic Surgeons; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TIA, transient ischaemic attack.

[a] Medically treated.

[b] Within 7 days of randomization.

[c] Estimated glomerular filtration rate < 60 mL/min.

[d] World Health Organization criteria: Hematocrit <13 g/dL (male) and < 12 g/dL (female).

[e] Ventricular tachycardia, ventricular fibrillation, or aborted sudden death; preoperative cardiac massage; preoperative ventilation before anesthetic room; preoperative inotropes or intra-aortic balloon pump; preoperative acute renal failure (anuria or oliguria <10 mL/h).

The specific cardiovascular risk profile of patients with HFrEF, HFmrEF and preserved LVEF randomized to PCI vs. CABG are reported in online supplementary Table S1. No differences between baseline characteristics among those patients with vs. those without known baseline LVEF were identified (online supplementary Table S2).

Procedural characteristics

Surgical techniques used for CABG were similar among patients with HFrEF, HFmrEF and preserved LVEF (Table 2). Off-pump CABG was performed in 35.7% of patients (n = 10/28) with HFrEF, in 28.4% of patients (n = 23/81) with HFmrEF and in 29.1% of patients (n = 225/774) with preserved LVEF. Bilateral internal thoracic arteries were used less frequently in patients with HFrEF (14.3%; n = 4/28) vs. in those with HFmrEF (31.3%; n = 25/80) and preserved LVEF (28.4%; n = 21 9/771). The number of distal anastomoses did not differ among patients with HFrEF, HFmrEF and preserved LVEF. The duration of the PCI procedure was similar among patients with HFrEF, HFmrEF and preserved LVEF (Table 2), while the number of implanted stents and the total stent length differed significantly between patients with HFrEF, HFmrEF and preserved LVEF.

After CABG, patients with HFrEF vs. HFmrEF vs. preserved LVEF had a longer post-operative hospital stay (median 9.0 vs. 7.0 vs. 6.0, P = 0.02), and more often experienced renal failure and arrhythmias (Table 2). Following PCI, no differences were identified in hospital stay, however patients with HFrEF more often had post-operative renal failure. No statistical differences were noted in medical treatment at the time of discharge after CABG or PCI according to LVEF status.

Thirty-day outcomes

Overall, the event rates for the primary endpoint, as well as for the individual endpoints, were relatively low. The composite endpoint of death, stroke, or MI occurred more frequently in patients with preserved LVEF that underwent CABG compared with those that underwent PCI (7.9% vs. 5.1%; HR 0.65, 95% CI 0.44–0.97; online supplementary Table S3). No treatment-by-subgroup interaction was identified between LVEF status (HFrEF, HFmrEF and preserved LVEF) and revascularisation strategy (PCI vs. CABG) among any of the clinical endpoints.

Three-year outcomes

The composite of death, stroke, or MI was 28.3% vs. 15.7% vs. 14.5% according to HFrEF, HFmrEF and preserved LVEF status (P = 0.02) (Figure 1A). All-cause death occurred in 19.5% vs. 9.6% vs. 6.2%, respectively (P < 0.001) (Figure 1B). Smoothing spline analysis showed a gradually increasing risk of all-cause death with decreasing

Table 2. Procedural characteristics and discharge medication according to left ventricular ejection fraction and revascularisation assignment

	CABG (*n* = 911)				PCI (*n* = 893)			
	LVEF <40% (HFrEF) (*n* = 31)	LVEF 40–49% (HFmrEF) (*n* = 84)	Preserved LVEF ≥50% (*n* = 796)	*P*-value	LVEF <40% (HFrEF) (*n* = 43)	LVEF 40–49% (HFmrEF) (*n* = 68)	Preserved LVEF ≥50% (*n* = 782)	*P*-value
Assigned treatment received	28/31 (90.3)	81/84 (96.4)	774/796 (97.2)	0.098	42/43 (97.7)	66/68 (97.1)	773/782 (98.9)	0.22
Procedure duration[a] (min)	231 [215–305]	239 [200–291]	235 [195–280]	0.39	66 [51–101]	83 [65–109]	73 [51–106]	0.59
Bypass time (min)	80 [59–87]	73 [62–94]	74 [57–97]	0.77	–	–	–	–
Off–pump CABG	10/28 (35.7)	23/81 (28.4)	225/774 (29.1)	0.74	–	–	–	–
BITAs used	4/28 (14.3)	25/80 (31.3)	219/771 (28.4)	0.22	–	–	–	–
No. of distal anastomoses	2.5 ± 0.6	2.6 ± 0.8	2.7 ± 0.8	0.83	–	–	–	
No. of grafts used	3.0 [2.0–3.0]	2.0 [2.0–3.0]	2.0 [2.0–3.0]	0.32	–	–	–	–
No. of stents implanted	–	–	–	–	2.0 [1.0–4.0]	3.0 [2.0–3.0]	2.0 [1.0–3.0]	0.004
Total stent length (mm)	–	–	–	–	35.0 [26.0–76.0]	52.0 [30.0–84.0]	38.0 [23.0–61.0]	0.003
Intubation > 48 h	2/29 (6.9)	5/82 (6.1)	21/787 (2.7)	0.12	1/42 (2.4)	0/67 (0.0)	3/778 (0.4)	0.15
Renal failure[b]	4/29 (13.8)	4/82 (4.9)	15/787 (1.9)	0.001	2/42 (4.8)	0/67 (0.0)	4/778 (0.5)	0.004
Major arrhythmia	9/29 (31.0)	17/82 (20.7)	108/787 (13.7)	0.011	1/42 (2.4)	1/67 (1.5)	14/778 (1.8)	0.94
Post-operative hospital stay (days)	9.0 [5.0–13.0]	7.0 [5.0–10.0]	6.0 [5.0–9.0]	0.02	1.5 [1.0–3.0]	2.0 [1.0–3.0]	1.0 [1.0–2.0]	0.20
Discharge medications								
Aspirin	26/27 (96.3)	79/79 (100.0)	752/760 (98.9)	0.26	42/42 (100.0)	66/66 (100.0)	760/766 (99.2)	0.65
$P2Y_{12}$ inhibitor	7/27 (25.9)	22/79 (27.8)	259/765 (33.9)	0.40	42/42 (100.0)	65/66 (98.5)	754/769 (98.0)	0.64
DAPT	7/27 (25.9)	22/79 (27.8)	254/765 (33.2)	0.48	42/42 (100.0)	65/66 (98.5)	748/769 (97.3)	0.47
Statin	25/27 (92.6)	70/79 (88.6)	709/765 (92.7)	0.43	40/42 (95.2)	66/66 (100.0)	741/769 (96.4)	0.26
Beta-blocker	26/27 (96.3)	74/79 (93.7)	704/765 (92.0)	0.64	40/42 (95.2)	57/66 (86.4)	634/769 (82.4)	0.08
ACE-inhibitor or ARB	12/27 (44.4)	37/79 (46.8)	311/765 (40.7)	0.54	26/42 (61.9)	39/66 (59.1)	428/769 (55.7)	0.65
Calcium-channel blockers	0/27 (0.0)	9/79 (11.4)	53/765 (6.9)	0.12	0/42 (0.0)	1/66 (1.5)	48/769 (6.2)	0.07
Diuretics	7/27 (25.9)	18/79 (22.8)	185/765 (24.2)	0.94	2/42 (4.8)	2/66 (3.0)	26/769 (3.4)	0.88

Values are *n* (%), median [interquartile range], or mean ± standard deviation.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BITA, bilateral internal thoracic artery; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

[a] Time from start of anaesthesia to procedure end (e.g. for CABG this is the time of skin closure).

[b] Serum creatinine increase by ≥1 mg/dL from baseline or need for dialysis.

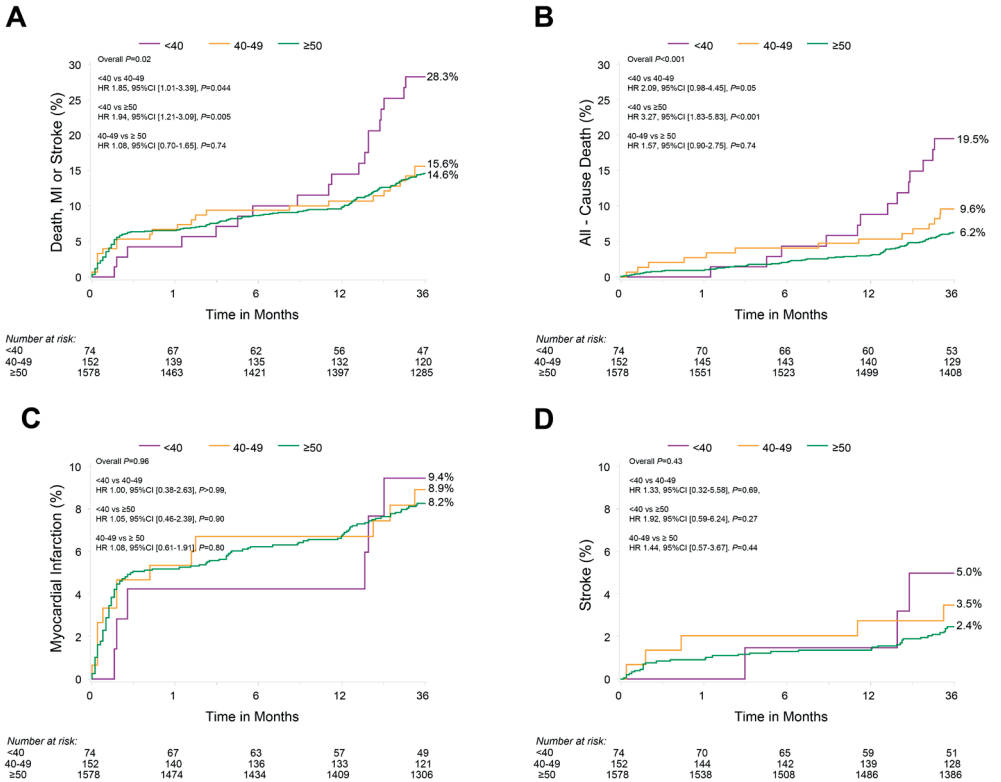

Figure 1. Three-year clinical endpoints in the overall cohort of patients with heart failure with reduced, mid-range and preserved left ventricular ejection fraction. Kaplan–Meier estimates of (*A*) the composite primary endpoint of all-cause death, stroke, or myocardial infarction (MI) and individual components of the composite primary endpoint; all-cause death (*B*), MI (*C*) and stroke (*D*) in pre-specified subgroups of patients with heart failure with reduced, mid-range (orange curve) and preserved left ventricular ejection fraction. *P*-values were generated by the log-rank test. CI, confidence interval; HR, hazard ratio.

LVEF below 50% after PCI (Figure 2) (HR 1.15, 95% CI 0.95–1.39) and CABG (HR 1.90, 95% CI 1.05–3.43). Patients with HFrEF, HFmrEF and preserved LVEF had comparable rates of stroke and MI (Figure 1C and D).

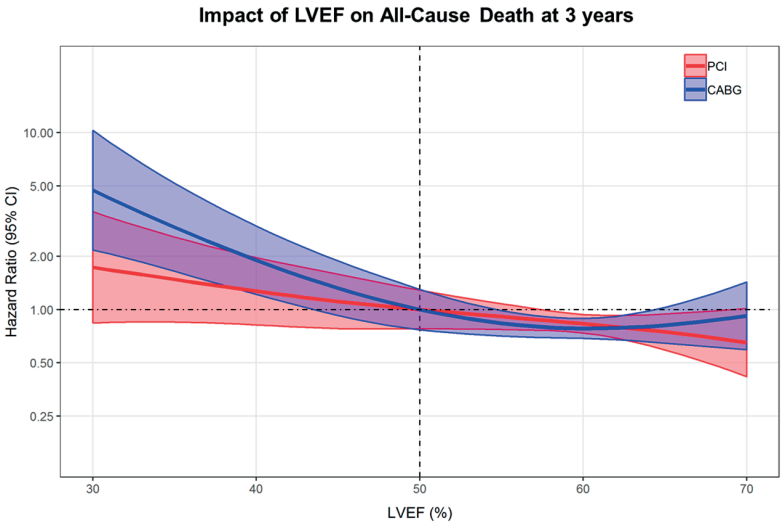

Figure 2. The influence of Left Ventricular Ejection Fraction (LVEF) on all-cause death at 3 years in patients undergoing left main coronary artery revascularisation by either Percutaneous Coronary Intervention (PCI) versus Coronary Artery Bypass Grafting (CABG). CI, confidence interval.

The rates of the 3-year composite primary endpoint were similar between PCI and CABG across groups of patients with HFrEF (29.3% after PCI vs. 27.6% after CABG: *P* = 0.90), those with HFmrEF (16.2% vs. 15.0%; *P* = 0.93) and preserved LVEF (14.5% vs. 14.6%; *P* = 0.95) (Table 3 and Figure 3). The individual rates of all-cause death, stroke, MI and ischaemia-driven revascularisation were not statistically different between PCI and CABG in patients with HFrEF or HFmrEF. Any repeat revascularisation occurred more often after PCI vs. CABG in those patients with preserved LVEF (HR 1.68, 95% CI 1.22–2.30), driven by increased rates of ischaemia-driven revascularisation. No treatment-by-subgroup interaction existed according to baseline LVEF and revascularisation strategy. Adjusted outcomes from the full multivariable adjusted Cox proportional hazard model were similar to unadjusted outcomes (Table 3).

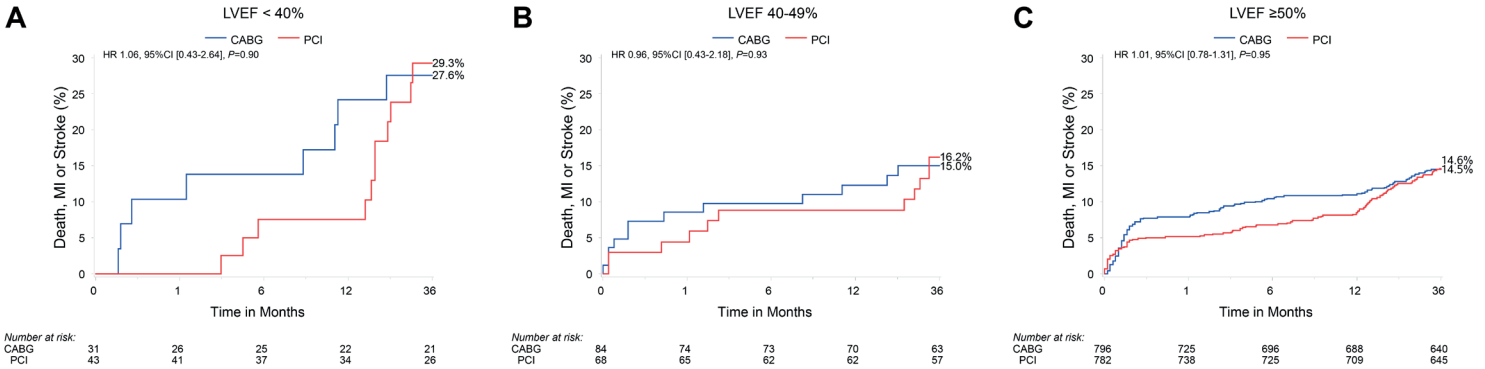

Figure 3. Three-year primary endpoint after percutaneous coronary intervention (PCI) vs. coronary artery bypass grafting (CABG) in patients with heart failure with reduced, mid-range a d preserved left ventricular ejection fraction (LVEF). Kaplan–Meier estimates of the composite primary endpoint of all-cause death, stroke, or myocardial infarction (MI) after PCI vs. CABG in patients with heart failure with reduced (*A*), mid-range (*B*) and preserved LVEF (*C*). *P*-values were generated by the log-rank test. CI, confidence interval; HR, hazard ratio.

Table 3. Three-year unadjusted and adjusted clinical outcomes stratified according to left ventricular ejection fraction status and revascularisation strategy

Clinical outcomes	PCI frequency, *n* (%)	CABG frequency, *n* (%)	Unadjusted HR (95% CI), *P*-value	$P_{interaction}$	Adjusted HR (95% CI)
Death, stroke or MI					
HFrEF	11 (29.3)	8 (27.6)	1.04 (0.46–2.35), 0.90		1.05 (0.42–2.61)
HFmrEF	11 (16.2)	12 (15.0)	0.96 (0.38–2.38), 0.92	0.90	1.06 (0.40–2.80)
Preserved LVEF	113 (14.6)	113 (14.5)	0.99 (0.76–1.28), 0.89		1.05 (0.79–1.38)
Death, stroke, MI or IDR					
HFrEF	12 (31.9)	9 (31.0)	1.22 (0.59–2.52), 0.82		1.18 (0.53–2.66)
HFmrEF	15 (22.1)	14 (17.4)	0.92 (0.39–2.19), 0.59	0.78	1.03 (0.41–2.56)
Preserved LVEF	173 (22.4)	147 (18.9)	1.18 (0.95–1.47), 0.16		1.24 (0.98–1.56)
All-cause death					
HFrEF	7 (18.6)	6 (20.7)	0.63 (0.21–1.87), 0.78		0.53 (0.16–1.81)
HFmrEF	5 (7.4)	9 (11.5)	0.85 (0.29–2.54), 0.40	0.20	0.77 (0.23–2.55)
Preserved LVEF	57 (7.4)	39 (5.0)	1.47 (0.98–2.20), 0.08		1.50 (0.98–2.31)
Cardiovascular death					
HFrEF	5 (13.5)	5 (17.8)	0.38 (0.08–1.88), 0.62		0.15 (0.02–1.28)
HFmrEF	2 (3.0)	6 (7.8)	0.73 (0.21–2.51), 0.22	0.26	0.70 (0.18–2.81)
Preserved LVEF	29 (3.8)	23 (3.0)	1.27 (0.73–2.19), 0.40		1.40 (0.79–2.48)
Stroke					
HFrEF	2 (5.5)	1 (4.2)	0.75 (0.13–4.49), 0.74		1.43 (0.19–10.69)
HFmrEF	2 (3.0)	3 (3.8)	1.49 (0.13–16.39), 0.77	0.49	-
Preserved LVEF	14 (1.9)	23 (3.0)	0.61 (0.31–1.19), 0.14		0.67 (0.34–1.32)
MI					
HFrEF	3 (8.9)	3 (10.3)	1.00 (0.34–2.97), 0.62		0.95 (0.29–3.19)
HFmrEF	6 (9.0)	7 (8.7)	0.69 (0.14–3.41), 0.99	0.78	1.02 (0.17–6.29)
Preserved LVEF	62 (8.1)	65 (8.4)	0.95 (0.67–1.35), 0.79		0.99 (0.69–1.44)
Repeat revascularisation any					
HFrEF	4 (11.9)	2 (7.5)	2.30 (0.58–9.19), 0.68		1.91 (0.45–8.10)
HFmrEF	6 (9.3)	3 (3.8)	1.43 (0.26–7.82), 0.37	0.96	2.77 (0.31–25.02)
Preserved LVEF	100 (13.2)	61 (8.1)	1.68 (1.22–2.30), 0.001		1.72 (1.23–2.39)
Ischaemia-driven revascularisation					
HFrEF	4 (11.9)	2 (7.5)	2.30 (0.57–9.18), 0.68		1.86 (0.44–7.88)
HFmrEF	6 (9.3)	3 (3.8)	1.43 (0.26–7.82), 0.37	0.95	2.82 (0.31–25.56)
Preserved LVEF	98 (12.9)	60 (8.0)	1.67 (1.21–2.30), 0.002		1.72 (1.23–2.40)

CABG, coronary artery bypass grafting; CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IDR, ischaemia-driven revascularisation LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

The event rates are Kaplan–Meier estimates (*n* events) with unadjusted and adjusted HR and 95% CI. A full multivariable Cox proportional hazards model using was constructed to provide adjusted outcomes for the primary and secondary endpoints. Significance levels of 0.10 for both addition and removal from the model were used. Adjusted models include the following covariates: age, sex (female), body mass index >30 kg/m^2, medically treated hypertension, hyperlipidaemia and diabetes, history of MI, history of stroke or transient ischaemic attack, peripheral vascular disease, carotid artery disease, chronic obstructive pulmonary disease, creatinine >200 µmol/L, recent MI, history of anaemia, diffuse or small vessel disease, LVEF (as continuous variable), unstable angina, SYNTAX score (as continuous variable), New York Heart Association class < II, and revascularisation strategy (PCI vs. CABG).

DISCUSSION

In the current pre-specified sub-study from the EXEL trial, the largest randomized study to date comparing PCI vs. CABG in selected patients with LMCAD, the composite rate of death, stroke, or MI at 3-year follow-up was significantly higher in patients with impaired (<50%; *n* = 74) vs. preserved LVEF (≥50%; *n* = 1730), driven by an increased rate of all-cause death in those with HFrEF (*n* = 74, LVEF<40%). Mortality furthermore progressively increased with decreasing LVEF. Nonetheless, baseline LVEF did not influence the relative 30-day or 3-year treatment outcomes in patients with LMCAD randomly allocated to PCI vs. CABG. Since data on the influence of HFrEF and HFmrEF on clinical outcomes after PCI and CABG are limited, especially in those patients with left main disease, a strength of the present study is that it provides important insights into clinical outcomes during 3-year follow-up in this high-risk patient population. These insights can aid clinical decision making in determining the optimal treatment strategy in such a specific patient population requiring revascularisation.

In the overall cohort, patients with HFrEF or HFmrEF had a significantly more complex cardiovascular risk profile, compared with those with preserved LVEF. The detrimental cardiovascular risk profile especially in patients with HFrEF and LMCAD, in concert with less viable myocardium, likely drives the increased all-cause death rate in this specific subgroup.[12,13] While no significant interactions were noted between clinical outcomes 3 years after PCI and CABG as a function of LVEF, patients with impaired LVEF (HFrEF and HFmrEF) experienced a longer post-operative hospital stay after CABG due to more frequent post-operative arrhythmias and renal failure. In contrast, post-PCI complications and length of stay were not significantly increased in patients with impaired LVEF. The clinical outcomes in patients with HFmrEF were essentially similar to the outcomes in patients with preserved LVEF; findings that contribute to the better understanding of the impact of heart failure and the preferred treatment modalities in those patients with LMCAD and LVEF 40–49% and >50%.[14,15] Moreover, all peri-procedural outcomes should be considered along with the potential short- and long-term clinical benefits of both revascularisation strategies in patients with impaired LVEF during structured multidisciplinary heart team meetings.

No treatment interactions were observed between PCI and CABG according to baseline LVEF status for 3-year outcomes. Nonetheless, impaired LVEF (<50%) was strongly associated with 3-year all-cause death in the overall cohort. To date, conflicting evidence has been published on the preferred revascularisation modality

in patients with CAD and impaired LVEF, with limited randomized data to provide guidance. The observational CREDO-Kyoto PCI/CABG Registry Cohort 2 (LVEF ≤50% vs. LVEF >50%) reported that PCI in patients with impaired LVEF was associated with higher rates of all-cause death after 5 years compared to CABG (33.2% vs. 23.4%; $P < 0.01$).[16] The observational, propensity-matched analysis by Nagendran *et al.*[17] ($n = 1738$) showed lower rates of major adverse cardiac and cerebrovascular events and improved 5-year survival with CABG compared with PCI in patients with diabetes and impaired LVEF (35–49% and <35%). Nonetheless, the largest pooled analysis of individual patient-level data from 11 randomized trials found no interaction for mortality between treatment strategy (PCI vs. CABG) and different LVEF cut-off values (<30%, 30–49% and ≥50%; $P_{interaction} = 0.65$).[18]

Finally, in the present study the rate of the composite of death, stroke, or MI at 3 years was significantly higher in patients with HFrEF (28.3%) compared with those patients with HFmrEF (15.7%) or preserved LVEF (14.5%) ($P = 0.02$) (Figure 1A). This finding was driven by an increased rate of all-cause death and cardiovascular death in those patients whom are at higher-risk for adverse events (e.g. patients with HFrEF). Moreover, in a smoothing spline analysis, the risk of mortality continued to increase when LVEF decreased below 50%. Nonetheless, no significant differences in clinical outcomes were found between CABG or PCI in patients with LVEF <40% at 3-year follow-up. The propensity-matched analysis by Shah *et al.*[19] ($n = 134$) reported that patients with coronary artery disease and LVEF <30% experienced an increased risk of mortality when undergoing PCI vs. CABG at 8-year follow-up (multivariable adjusted HR 3.29, 95% CI 1.78-6.10; $P < 0.001$). However, only 32% of patients in the study by Shah *et al.* had LMCAD, with the majority having three-vessel disease. Longer-term follow-up from the EXCEL trial is required to determine if differences in survival between the PCI and CABG groups might emerge over time.

Limitations

Although the present analysis was pre-specified, the number of patients with impaired LVEF was modest, especially those with HFrEF ($n = 74$), limiting statistical interaction testing. Furthermore, the EXCEL trial excluded patients with high site-assessed SYNTAX scores (>32), and thus the present results might not apply to the particularly high-risk group with more complex CAD in whom CABG is considered standard of care. Finally, patient follow-up in the EXCEL trial is prolonged up to 5 years; however, even this follow-up duration may not be long enough to determine a potential benefit of either revascularisation strategy.

CONCLUSIONS

At 3-year follow-up in the EXCEL trial, the composite rate of death, stroke, or MI was significantly higher in patients with HFrEF compared with HFmrEF or preserved LVEF, driven by an increased rate of all-cause death. No significant differences in clinical outcomes after PCI vs. CABG were observed among patients with HFrEF, HFmrEF and preserved LVEF. Prolonged follow-up could provide important insights on differences in clinical outcomes that might emerge over time.

Additional supporting information may be found online in the Supporting Information section and at the end of the article.

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Conflict of interest: J.D.P.: consultant – Medtronic. P.W.S.: consultant – Abbott, Biosensors, Medtronic, Micell Technologies, SINOMED, Philips/Volcano, Xeltis, HeartFlow. J.F.S.: consultant – Medtronic, Edwards, and Sorin. Advisory board – Medtronic Cardiac Surgery. S.J.H.: employee – Medtronic. A.P.K.: employee – Medtronic. The other authors declare to have no conflicts of interest.

REFERENCES

1. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2019;55:4–90.
2. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014; 64: 1929–1949.
3. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374:1511–1520.
4. Wolff G, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, Devito F, Zito A, Occhipinti M, Castiglioni B, Calveri G, Maisano F, Ciccone MM, De Servi S, Navarese EP. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis. Circ Heart Fail 2017;10:e003255.
5. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol 2011;58:1426–1432.
6. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. Circulation 2014;129:2388–2394.
7. Cavalcante R, Sotomi Y, Lee CW, Ahn JM, Farooq V, Tateishi H, Tenekecioglu E, Zeng Y, Suwannasom P, Collet C, Albuquerque FN, Onuma Y, Park SJ, Serruys PW. Outcomes after percutaneous coronary intervention or bypass surgery in patients with unprotected left main disease. J Am Coll Cardiol 2016;68:999–1009.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoy-annopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
9. Kappetein AP, Serruys PW, Sabik JF, Leon MB, Taggart DP, Morice MC, Gersh BJ, Pocock SJ, Cohen DJ, Wallentin L, Ben-Yehuda O, van Es GA, Simonton CA, Stone GW. Design

and rationale for a randomised comparison of everolimus-eluting stents and coronary artery bypass graft surgery in selected patients with left main coronary artery disease: the EXCEL trial. EuroIntervention 2016; 12: 861–872.

10. Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogats G, Mansour S, Noiseux N, Sabate M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Page P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016; 375: 2223–2235.
11. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol 2013;62:1563–1570.
12. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, Drozdz J, Farsky PS, Feldman AM, Doenst T, Michler RE, Berman DS, Nicolau JC, Pellikka PA, Wrobel K, Alotti N, Asch FM, Favaloro LE, She L, Velazquez EJ, Jones RH, Panza JA; STICH Trial Investigators. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med 2011;364:1617–1625.
13. Curtis JP, Sokol SI, Wang Y, Rathore SS, Ko DT, Jadbabaie F, Portnay EL, Marshalko SJ, Radford MJ, Krumholz HM. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol 2003; 42: 736–742.
14. Nauta JF, Hummel YM, van Melle JP, van der Meer P, Lam CS, Ponikowski P, Voors AA. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? Eur J Heart Fail 2017;19:1569–1573.
15. Solomon SD, McMurray JJ, Anand IS, Ge J, Lam CS, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veld-huisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dungen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609–1620.
16. Marui A, Kimura T, Nishiwaki N, Mitsudo K, Komiya T, Hanyu M, Shiomi H, Tanaka S, Sakata R. Comparison of five-year outcomes of coronary artery bypass grafting versus percutaneous coronary intervention in patients with left ventricular ejection fractions ≤50% versus >50% (from the CREDO-Kyoto PCI/CABG Registry Cohort-2). Am J Cardiol 2014;114:988–996.
17. Nagendran J, Bozso SJ, Norris CM, McAlister FA, Appoo JJ, Moon MC, Freed DH, Nagendran J. Coronary artery bypass surgery improves outcomes in patients with diabetes and left ventricular dysfunction. J Am Coll Cardiol 2018;71:819–827.
18. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Makikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF 3rd, Stables RH, Stone GW, Serruys PW, Kappetein AP. Mortality after coronary artery bypass grafting

versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391:939–948.
19. Shah S, Benedetto U, Caputo M, Angelini GD, Vohra HA. Comparison of the survival between coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with poor left ventricular function (ejection fraction <30%): a propensity-matched analysis. Eur J Cardiothorac Surg 2019;55:238–246.

SUPPLEMENTARY INFORMATION

Table S1.
Baseline characteristics according to left ventricular ejection fraction and revascularisation assignment

Table S2.
Baseline characteristics for those patients with versus without known baseline LVEF

Table S3.
Thirty-dayclinical outcomes according to left ventricular ejection fraction and revascularisation assignment

SUPPLEMENTAL MATERIALS

Table S1. Baseline Characteristics According to Left Ventricular Ejection Fraction and Revascularization Assignment

	Percutaneous Coronary Intervention				Coronary Artery Bypass Grafting			
	HFrEF LVEF <40% (n=43)	HFmrEF LVEF 40-49% (n=68)	Preserved LVEF ≥50% (n=782)	p Value	HFrEF LVEF <40% (n=31)	HFmrEF LVEF 40-49% (n=84)	Preserved LVEF ≥50% (n=796)	p value
Age, years	65.0 ± 9.0 (43)	67.4 ± 9.4 (68)	66.0 ± 9.7 (782)	0.38	69.8 ± 9.0 (31)	66.1 ± 9.3 (84)	65.8 ± 9.5 (796)	0.07
Sex, female	16/43 (37.2%)	8/68 (11.8%)	192/782 (24.6%)	0.008	5/31 (16.1%)	12/84 (14.3%)	188/796 (23.6%)	0.10
LVEF, % (mean)	31.0 ± 4.6 (43)	43.5 ± 2.8 (68)	59.6 ± 6.6 (782)	<0.0001	31/31 (100.0%)	84/84 (100.0%)	795/796 (99.9%)	0.93
LVEF diagnostic modalities								
Echocardiography	29/43 (67.4%)	41/68 (60.3%)	448/782 (57.3%)	0.39	17/31 (54.8%)	63/84 (75.0%)	453/795 (57.0%)	0.006
Left ventriculography	13/43 (30.2%)	23/68 (33.8%)	321/782 (41.0%)	0.21	11/31 (35.5%)	19/84 (22.6%)	328/795 (41.3%)	0.004
Magnetic resonance imaging	1/43 (2.3%)	0/68 (0.0%)	3/782 (0.4%)	0.15	3/31 (9.7%)	0/84 (0.0%)	2/795 (0.3%)	<0.001
MUGA scan	0/43 (0.0%)	1/68 (1.5%)	3/782 (0.4%)	0.39	0/31 (0.0%)	1/84 (1.2%)	4/795 (0.5%)	0.66
Nuclear test	0/43 (0.0%)	2/68 (2.9%)	7/782 (0.9%)	0.21	0/31 (0.0%)	1/84 (1.2%)	7/795 (0.9%)	0.83
CAD risk factors								
Hypertension*	31/43 (72.1%)	50/68 (73.5%)	586/782 (74.9%)	0.89	23/31 (74.2%)	62/84 (73.8%)	583/796 (73.2%)	0.99
Hyperlipidaemia	16/43 (37.2%)	8/68 (11.8%)	192/782 (24.6%)	0.33	17/31 (54.8%)	56/83 (67.5%)	556/796 (69.8%)	0.20
Diabetes mellitus*	14/43 (32.6%)	26/68 (38.2%)	232/782 (29.7%)	0.32	10/31 (32.3%)	31/84 (36.9%)	217/796 (27.3%)	0.16
Current or former smoker	19/43 (44.2%)	19/67 (28.4%)	175/778 (22.5%)	0.004	12/31 (38.7%)	18/84 (21.4%)	152/789 (19.3%)	0.03
Family history of CAD	19/33 (57.6%)	40/55 (72.7%)	438/652 (67.2%)	0.34	26/31 (83.9%)	52/70 (74.3%)	430/671 (64.1%)	0.02
NYHA Classification								
I	3/43 (7.0%)	3/68 (4.4%)	10/780 (1.3%)	0.006	1/31 (3.2%)	0/84 (0.0%)	6/793 (0.8%)	0.21
II	1/43 (2.3%)	4/68 (5.9%)	17/780 (2.2%)	0.17	5/31 (16.1%)	11/84 (13.1%)	16/793 (2.0%)	<0.0001
III	9/43 (20.9%)	1/68 (1.5%)	13/780 (1.7%)	<0.0001	3/31 (9.7%)	4/84 (4.8%)	10/793 (1.3%)	0.0004

Table S1. Baseline Characteristics According to Left Ventricular Ejection Fraction and Revascularization Assignment (continued)

	Percutaneous Coronary Intervention				Coronary Artery Bypass Grafting			
	HFrEF LVEF <40% (n=43)	HFmrEF LVEF 40-49% (n=68)	Preserved LVEF ≥50% (n=782)	p Value	HFrEF LVEF <40% (n=31)	HFmrEF LVEF 40-49% (n=84)	Preserved LVEF ≥50% (n=796)	p value
IV	0/43 (0.0%)	0/68 (0.0%)	1/780 (0.1%)	0.93	1/31 (3.2%)	0/84 (0.0%)	1/793 (0.1%)	0.0013
Preoperative risk factors								
History of stroke	1/43 (2.3%)	4/68 (5.9%)	24/781 (3.1%)	0.43	5/31 (16.1%)	4/84 (4.8%)	26/796 (3.3%)	0.001
History of TIA	1/43 (2.3%)	1/68 (1.5%)	18/777 (2.3%)	0.90	1/31 (3.2%)	3/83 (3.6%)	29/792 (3.7%)	0.99
Recent myocardial infarction†	13/43 (30.2%)	15/67 (22.4%)	101/771 (13.1%)	0.0015	5/31 (16.1%)	16/84 (19.0%)	109/793 (13.7%)	0.40
Chronic kidney disease‡	14/42 (33.3%)	20/67 (29.9%)	124/770 (16.1%)	0.0006	10/31 (32.3%)	19/82 (23.2%)	107/780 (13.7%)	0.0021
Dialysis	0/43 (0.0%)	0/68 (0.0%)	2/782 (0.3%)	0.87	0/31 (0.0%)	2/84 (2.4%)	1/796 (0.1%)	0.003
Peripheral vascular disease	11/43 (25.6%)	8/68 (11.8%)	71/779 (9.1%)	0.002	3/29 (10.3%)	15/84 (17.9%)	62/793 (7.8%)	0.008
Chronic obstructive pulmonary disease	8/43 (18.6%)	6/68 (8.8%)	50/781 (6.4%)	0.009	6/31 (19.4%)	11/84 (13.1%)	63/794 (7.9%)	0.03
History of carotid artery disease	7/43 (16.3%)	3/67 (4.5%)	61/780 (7.8%)	0.08	6/31 (19.4%)	9/83 (10.8%)	64/794 (8.1%)	0.07
History of anemia§	5/43 (11.6%)	11/68 (16.2%)	78/778 (10.0%)	0.28	3/31 (9.7%)	12/84 (14.3%)	68/794 (8.6%)	0.22
Body mass index, kg/m^2	28.7 ± 7.0 (43)	28.6 ± 4.6 (68)	28.6 ± 4.9 (782)	0.97	29.1 ± 5.6 (31)	28.8 ± 5.1 (84)	28.8 ± 4.9 (796)	0.95
<20 (cachectic)	1/43 (2.3%)	1/68 (1.5%)	15/782 (1.9%)	0.14*	1/31 (3.2%)	1/84 (1.2%)	9/796 (1.1%)	0.37*
>30 (obese)	14/43 (32.6%)	19/68 (27.9%)	255/182 (32.6%)	0.73	11/31 (35.5%)	28/84 (33.3%)	259/796 (32.5%)	0.94
Lesions per patient	2.7 ± 1.5 (42)	2.9 ± 1.5 (66)	2.5 ± 1.3 (773)	0.051	—	—	—	—
Diffuse disease or small vessels	1/42 (2.4%)	11/65 (16.9%)	50/769 (6.5%)	0.003	3/31 (9.7%)	7/81 (8.6%)	35/786 (4.5%)	0.12
Critical preoperative state‖	1/43 (2.3%)	0/68 (0.0%)	7/782 (0.9%)	0.45	2/31 (6.5%)	1/84 (1.2%)	16/795 (2.0%)	0.20
STS risk scores								
PROM score	1.06 ± 0.95	1.00 ± 0.82	0.86 ± 0.79	0.007	1.19 ± 1.07	0.93 ± 1.03	0.86 ± 0.78	0.31
Stroke score	0.98 ± 0.89	0.88 ± 0.65	3.80 ± 1.38	0.005	0.95 ± 0.74	0.77 ± 0.58	0.77 ± 0.56	0.66
Reop. score	3.97 ± 1.53	0.74 ± 0.55	3.48 ± 1.36	0.005	4.05 ± 1.79	3.50 ± 1.44	3.54 ± 1.32	0.23

Table S1. Baseline Characteristics According to Left Ventricular Ejection Fraction and Revascularization Assignment (continued)

	Percutaneous Coronary Intervention				Coronary Artery Bypass Grafting			
	HFrEF LVEF <40% (n=43)	HFmrEF LVEF 40-49% (n=68)	Preserved LVEF ≥50% (n=782)	p Value	HFrEF LVEF <40% (n=31)	HFmrEF LVEF 40-49% (n=84)	Preserved LVEF ≥50% (n=796)	p value
SYNTAX score (site-assessed)	21.4 ± 5.6 (43)	22.7 ± 6.0 (68)	20.4 ± 6.3 (780)	0.01	20.5 ± 6.0 (31)	22.3 ± 5.5 (84)	20.3 ± 6.2 (796)	0.02
Low (≤22)	23/43 (53.5%)	31/68 (45.6%)	474/780 (60.8%)	0.04	18/31 (58.1%)	46/84 (54.8%)	493/796 (61.9%)	0.41
Intermediate (23-32)	20/43 (46.5%)	37/68 (54.4%)	306/780 (39.2%)	0.04	13/31 (41.9%)	38/84 (45.2%)	303/796 (38.1%)	0.41
High (≥33)	0/43 (0.0%)	0/68 (0.0%)	0/780 (0.0%)	—	0/31 (0.0%)	0/84 (0.0%)	0/796 (0.0%)	—
SYNTAX score (core laboratory-assessed)	30.7 ± 9.1 (42)	27.9 ± 8.4 (62)	26.6 ± 8.8 (757)	0.01	25.3 ± 9.8 (30)	27.4 ± 9.8 (82)	26.0 ± 9.8 (769)	0.45
Low (≤22)	10/42 (23.8%)	13/62 (21.0%)	258/757 (34.1%)	0.049	14/30 (46.7%)	24/82 (29.3%)	305/769 (39.7%)	0.13
Intermediate (23-32)	11/42 (26.2%)	35/62 (56.5%)	321/757 (42.4%)	0.009	10/30 (33.3%)	41/82 (50.0%)	279/769 (36.3%)	0.046
High (≥33)	21/42 (50.0%)	14/62 (22.6%)	178/757 (23.5%)	0.0005	6/30 (20.0%)	17/82 (20.7%)	185/769 (24.1%)	0.71

Values are mean ± standard deviation or % (n/N). *Medically treated; †within 7 days of randomization; ‡estimated glomerular filtration rate<60 mL/min; §World Health Organization criteria: Hematocrit at initial presentation: <13 g/dL (male) and <12 g/dL (female); CAD = coronary artery disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association heart failure classification; PROM = Predicted Risk Of Mortality; STS = Society of Thoracic Surgeons; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

Table S2. Baseline Characteristics For Those Patients With versus Without Known Baseline LVEF

	With Available Baseline LVEF (n=1804)	Without Available Baseline LVEF (n=101)	p Value
Age, years	66.0 ± 9.5	65.1 ± 10.4	0.31
Sex, female	421/1804 (23.3%)	20/101 (19.8%)	0.41
LVEF, % (mean)	57.1 ± 9.3	—	—
LVEF diagnostic modalities			
Echocardiography	1051/1803 (58.3%)	16/45 (35.6%)	0.002
Left ventriculography	715/1803 (39.7%)	29/45 (64.4%)	0.0008
Magnetic resonance imaging	9/1803 (0.5%)	0/45 (0.0%)	>0.99
MUGA scan	9/1803 (0.5%)	0/45 (0.0%)	>0.99
Nuclear test	17/1803 (0.9%)	0/45 (0.0%)	>0.99
CAD risk factors			
Hypertension*	1335/1804 (74.0%)	71/100 (71.0%)	0.51
Hyperlipidaemia	1261/1802 (70.0%)	70/99 (70.7%)	0.88
Diabetes mellitus*	530/1804 (29.4%)	24/100 (24.0%)	0.25
Current or former smoker	395/1792 (22.0%)	21/100 (21.0%)	0.81
Family history of CAD	1005/1512 (66.5%)	47/80 (58.8%)	0.16
NYHA classification			
I	23/1799 (1.3%)	0/99 (0.0%)	0.63
II	54/1799 (3.0%)	4/99 (4.0%)	0.54
III	40/1799 (2.2%)	3/99 (3.0%)	0.49
IV	3/1799 (0.2%)	0/99 (0.0%)	>0.99
Preoperative risk factors			
History of stroke	64/1803 (3.5%)	5/100 (5.0%)	0.41
History of TIA	53/1794 (3.0%)	4/99 (4.0%)	0.54

Table S2. Baseline Characteristics For Those Patients With versus Without Known Baseline LVEF (continued)

	With Available Baseline LVEF (n=1804)	Without Available Baseline LVEF (n=101)	p Value
Recent myocardial infarction†	259/1789 (14.5%)	10/99 (10.1%)	0.23
Chronic kidney disease‡	294/1772 (16.6%)	14/97 (14.4%)	0.58
Dialysis	5/1804 (0.3%)	0/100 (0.0%)	1.00
Peripheral vascular disease	170/1796 (9.5%)	11/100 (11.0%)	0.61
Chronic obstructive pulmonary disease	144/1801 (8.0%)	4/100 (4.0%)	0.15
History of carotid artery disease	150/1798 (8.3%)	6/98 (6.1%)	0.44
History of anemia§	177/1798 (9.8%)	6/100 (6.0%)	0.20
Body mass index kg/m^2	28.7 ± 5.0	28.4 ± 4.5	0.60
<20 (cachectic)	28/1804 (1.6%)	1/100 (1.0%)	0.34*
>30 (obese)	586/1804 (32.5%)	32/100 (32.0%)	0.92
Lesions per patient	2.6 ± 1.3	2.4 ± 1.2	0.29
Diffuse disease or small vessels	107/1774 (6.0%)	6/96 (6.3%)	0.93
Critical preoperative state‖	27/1803 (1.5%)	2/100 (2.0%)	0.66
STS risk scores	N = 1757	N = 101	
PROM score	0.88 ± 0.81	0.85 ± 1.10	0.76
Stroke score	0.77 ± 0.58	0.71 ± 0.56	0.36
Reop. score	0.71 ± 0.56	3.43 ± 1.57	0.43
SYNTAX score (site-assessed)	20.6 ± 6.2	20.1 ± 6.0	0.41
Low (≤22)	1085/1802 (60.2%)	64/99 (64.6%)	0.38
Intermediate (23-32)	717/1802 (39.8%)	35/99 (35.4%)	0.38
High (≥33)	0/1802 (0.0%)	0/99 (0.0%)	—
SYNTAX score (core laboratory-assessed)	26.5 ± 9.3	26.1 ± 8.9	0.70

Table S2. Baseline Characteristics For Those Patients With versus Without Known Baseline LVEF (continued)

	With Available Baseline LVEF (n=1804)	Without Available Baseline LVEF (n=101)	p Value
Low (≤22)	26.5 ± 9.3	26.1 ± 8.9	0.82
Intermediate (23-32)	26.5 ± 9.3	26.1 ± 8.9	0.72
High (≥33)	26.5 ± 9.3	26.1 ± 8.9	0.88

Values are mean ± standard deviation or % (n/N). *Medically treated; †within 7 days of randomization; ‡estimated glomerular filtration rate<60 mL/min; §World Health Organization criteria: Hematocrit at initial presentation: <13 g/dL (male) and <12 g/dL (female); CAD = coronary artery disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association heart failure classification; PROM = Predicted Risk Of Mortality; STS = Society of Thoracic Surgeons; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

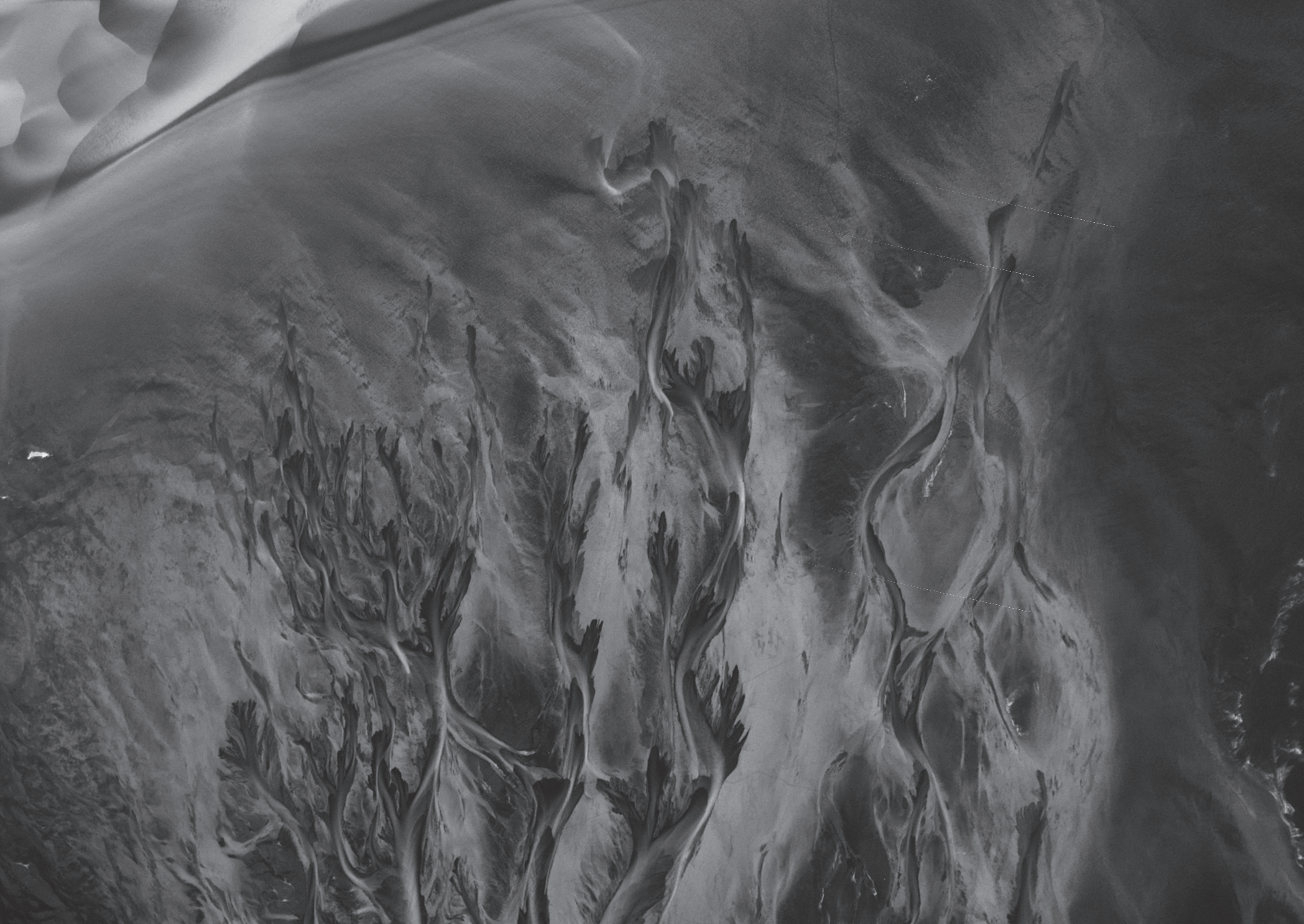
Table S3. Thirty-Day Clinical Outcomes According to Left Ventricular Ejection Fraction and Revascularization Assignment

Clinical Outcomes	PCI frequency n (%)	CABG frequency n (%)	p value	Unadjusted HR (95% CI)	*p* for interaction	Adjusted HR (95% CI)
Death, stroke or MI						
HFrEF	0. (0.0%)	3 (10.3%)	0.03	N/A	0.94	N/A
HFmrEF	3 (4.4%)	7 (8.5%)	0.31	0.51 (0.13-1.96)		0.39 (0.08-1.99)
Preserved LVEF	40 (5.1%)	62 (7.9%)	0.03	0.65 (0.44-0.97)		0.64 (0.42-0.98)
Death, stroke, MI or IDR						
HFrEF	0 (0.0%)	3 (10.3%)	0.03	N/A	0.97	N/A
HFmrEF	3 (4.4%)	7 (8.5%)	0.31	0.51 (0.13-1.96)		0.38 (0.08-1.95)
Preserved LVEF	40 (5.1%)	67 (8.5%)	0.01	0.6 (0.41-0.89)		0.58 (0.38-0.89)
All-cause death						
HFrEF	0 (0.0%)	0 (0.0%)	N/A	N/A	0.76	N/A
HFmrEF	1 (1.5%)	3 (3.7%)	0.41	0.4 (0.04-3.81)		0.47 (0.04-4.88)
Preserved LVEF	7 (0.9%)	7 (0.9%)	0.98	1.01 (0.36-2.89)		1.24 (0.41-3.73)
Cardiovascular death						
HFrEF	0 (0.0%)	0 (0.0%)	N/A	N/A	0.70	N/A
HFmrEF	1 (1.5%)	3 (3.7%)	0.41	0.4 (0.04-3.81)		0.49 (0.05-5.17)
Preserved LVEF	7 (0.9%)	6 (0.8%)	0.76	1.18 (0.40-3.52)		1.51 (0.47-4.83)
Stroke						
HFrEF	0 (0.0%)	0 (0.0%)	N/A	N/A	>0.99	N/A
HFmrEF	1 (1.5%)	2 (2.5%)	0.66	0.59 (0.05-6.49)		0.44 (0.03-5.60)
Preserved LVEF	5 (0.6%)	9 (1.1%)	0.29	0.56 (0.19-1.67)		0.58 (0.18-1.81)

Table S3. Thirty-Day Clinical Outcomes According to Left Ventricular Ejection Fraction and Revascularization Assignment (continued)

Clinical Outcomes	PCI frequency n (%)	CABG frequency n (%)	p value	Unadjusted HR (95% CI)	*p* for interaction	Adjusted HR (95% CI)
Myocardial Infarction						
HFrEF	0 (0.0%)	3 (10.3%)	0.03	N/A	>0.99	N/A
HFmrEF	3 (4.4%)	5 (6.1%)	0.65	0.72 (0.17-3.00)		0.64 (0.11-3.62)
Preserved LVEF	5 (0.6%)	9 (1.1%)	0.29	0.56 (0.19-1.67)		0.64 (0.39-1.04)
Repeat revascularization, any						
HFrEF	0 (0.0%)	1 (3.4%)	0.23	N/A	>0.99	N/A
HFmrEF	0 (0.0%)	0 (0.0%)	N/A	N/A		N/A
Preserved LVEF	7 (0.9%)	12 (1.5%)	0.26	0.59 (0.23-1.50)		0.48 (0.18-1.31)
Ischemia-driven revascularization						
HFrEF	0 (0.0%)	1 (3.4%)	0.23	N/A	>0.99	N/A
HFmrEF	0 (0.0%)	0 (0.0%)	N/A	N/A		N/A
Preserved LVEF	6 (0.8%)	12 (1.5%)	0.16	0.51 (0.19-1.35)		0.41 (0.14-1.19)

Values are Kaplan-Meier time-to-first event estimates expressed as % (n). CABG = coronary artery bypass grafting; IDR = ischemia-driven revascularization; MI = myocardial infarction; PCI = percutaneous coronary intervention.). Unadjusted and adjusted hazard ratios with 95% confidence intervals were computed with a full Cox proportional hazards model. *Composite rate of death, stroke, myocardial infarction, TIMI major or minor bleeding, transfusion ≥2 units of blood, major arrhythmia (supraventricular tachycardia requiring cardioversion, ventricular tachycardia or fibrillation requiring treatment, or bradyarrhythmia requiring temporary or permanent pacemaker, ischemia-driven revascularization, any unplanned surgery or therapeutic radiologic procedure, renal failure (serum creatinine increase by ≥0.5 mg/dL from baseline or need for dialysis, sternal wound dehiscence, infection requiring antibiotics, or prolonged intubation (>48 hours). N/A= not applicable due to the low number of events.



Chapter 4

Outcomes following surgical revascularisation with single versus bilateral internal thoracic arterial grafts in patients with left main coronary artery disease undergoing coronary artery bypass grafting: insights from the EXCEL trial

Daniel J.F.M. Thuijs, Stuart J. Head, Gregg W. Stone, John D. Puskas, David P. Taggart, Patrick W. Serruys, Ovidiu Dressler, Patrick W. Serruys, Aaron Crowley, W. Morris Brown III, Ferenc Horkay, Piet W. Boonstra, Gabor Bogats, Nicolas Noiseux, Joseph F. Sabik III, A. Pieter Kappetein

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ABSTRACT

Objectives

Observational data suggest that the use of a single internal thoracic artery (SITA) may result in inferior outcomes compared with bilateral internal thoracic artery (BITA) use for coronary artery bypass grafting (CABG)—a finding not yet supported by randomized trial outcomes. However, the optimal number of internal thoracic artery grafts in patients with left main coronary artery disease has not been investigated.

Methods

The EXCEL trial randomized 1905 patients with left main coronary artery disease to percutaneous coronary intervention with everolimus-eluting stents versus CABG. Among the 905 patients undergoing CABG, 688 (76.0%) received SITA and 217 (24.0%) received BITA. Differences in clinical event rates were estimated using the Kaplan-Meier method and compared with the log-rank test. Multivariable Cox regression was used to adjust for differences in baseline covariates.

Results

Compared to SITA, patients treated with BITA were younger (66.1 ± 9.5 vs 64.5 ± 9.3 years, $P = 0.020$), were less likely female (24.3% vs 14.3%, $P = 0.002$) and diabetic (28.8% vs 15.2%, $P < 0.001$), and had a lower prevalence of peripheral vessel disease (10.2% vs 5.5%, $P = 0.040$). The unadjusted 3-year composite primary endpoint of death, stroke or myocardial infarction (MI) occurred in 15.6% of SITA vs 11.6% of BITA patients ($P = 0.17$). The SITA group tended to have a higher 3-year rate of all-cause death compared with the BITA group (6.7% vs 3.3%; $P = 0.070$). Stroke, MI and ischaemia-driven revascularisation outcomes were not significantly different between groups. After adjusting for baseline differences, neither the composite of death, stroke or MI [hazard ratio (HR) 1.12, 95% confidence interval (CI) 0.71–1.78; $P = 0.62$] nor mortality (HR 1.36, 95% CI 0.60–3.12; $P = 0.46$) was significantly higher with SITA. The rehospitalization rate after 3 years was higher in the SITA group (35.8% vs 26.0%, P = 0.008), a difference which was no longer present after multivariable adjustment (HR 1.27, 95% CI 0.93-1.74; P=0.13). Sternal wound dehiscence within 30days did not occur more often in the BITA group compared to the SITA group (1.8% vs 2.2%, P>0.99).

Conclusions

In the EXCEL trial, there were no clinical differences at 3years between SITA or BITA revascularisation in patients with left main coronary artery disease.

Keywords

Coronary artery bypass grafting, Left main coronary artery disease, Bilateral internal thoracic artery, Mortality, Sternal, wound infection, EXCEL

INTRODUCTION

According to European and North American guidelines, coronary artery bypass grafting (CABG) is the treatment of choice for most patients with complex coronary artery disease.[1–4] However, with improvements in stent technology and advances in medical therapy, contemporary randomized trials have shown that percutaneous coronary intervention (PCI) with drug-eluting stents is an alternative for selected patients with left main coronary artery disease (LMCAD).[5–54]

In complex revascularisation procedures, the choice of techniques for both PCI and CABG may substantially affect clinical outcomes. In this regard, whether CABG should be performed using multiple arterial grafts or with the use of a single internal thoracic artery (SITA) in combination with saphenous vein grafts is still a matter of debate.[54–58] Pooled analyses of observational studies suggest that the use of multiple internal thoracic artery grafts results in better long-term outcomes with decreased mortality and lower rates of repeat revascularisation and myocardial infarction (MI).[54, 58–64] However, randomized trials have not yet demonstrated improved survival with the use of the bilateral internal thoracic artery (BITA).[64] Moreover, sternal wound infection and dehiscence may be increased with the use of BITA (especially in diabetic patients), resulting in low adoption rates of BITA for coronary revascularisation.[64, 64]

The EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial demonstrated that PCI was non-inferior to CABG for the composite endpoint of death, stroke or MI in patients with LMCAD and low or intermediate Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) scores.[64] The aim of the present analysis was to evaluate the safety and effectiveness of CABG with SITA versus BITA in patients with LMCAD in the EXCEL trial.[64]

METHODS

Study design

The design of the EXCEL trial has been reported previously.[68] In the EXCEL study, 1905 LMCAD patients with a SYNTAX score of 32 or lower were randomized between PCI (n = 948) and CABG (n = 957). Of the 957 randomized CABG patients, 17 patients did not undergo revascularisation. CABG was the first procedure in 923 patients and PCI in 17 patients. Eleven CABG patients (1.1%) underwent coronary revascularisa-

tion with venous grafts only. Information on the use of conduit was unavailable in 7 patients (0.7%). This *post hoc* analysis was therefore performed on the remaining 905 CABG patients in whom 1 or 2 internal thoracic artery grafts were used. Follow-up is ongoing over a period of 5years. At the time of the present report, all the patients had reached the 3-year follow-up. Adverse events were monitored and adjudicated by an independent clinical events committee. The study was performed under the supervision of the US Food and Drug Administration and by local ethics committees, and it is consistent with the Declaration of Helsinki. All the patients signed informed consent prior to the randomization.

Endpoints

The primary endpoint was the composite of all-cause death, stroke or MI at 3years. Major secondary endpoints were the primary endpoint at 30days and the composite of all-cause death, stroke, MI or ischaemia-driven revascularisation at 3 years. Additional endpoints included the components of the primary and secondary endpoints, sternal wound dehiscence, unplanned hospitalization and bleeding complications according to the Bleeding Academic Research Consortium (BARC) scale.[69]
The definitions of these endpoints have been described previously.[64, 68]

Coronary artery bypass grafting techniques

The goal of CABG was complete anatomical revascularisation of all the vessels with a diameter of 1.5 mm or larger and with an angiographic diameter stenosis of 50% or more. Although the configuration of bypass grafts was left to the discretion of the individual surgeon, the use of arterial grafts was strongly recommended. CABG could be performed with or without the support of cardiopulmonary bypass, depending on the expertise of the centre.

Statistical analyses

This *post hoc* analysis was performed in the SITA versus BITA as-treated cohorts. Discrete variables were expressed as percentages with frequencies, and they were compared by the χ^2 test or the Fisher's exact test when the expected frequency in any cell is <5. Continuous variables were summarized as mean ± SD, and they were compared by independent samples t-test if normally distributed or the Wilcoxon rank-sum test if non-normally distributed. The unadjusted cumulative event rates up to 3 years were estimated according to the Kaplan-Meier method, and differences between SITA and BITA were assessed using the log-rank test. Adjusted comparisons between SITA and BITA for the prespecified primary and secondary endpoints were performed by the complete-case multivariable Cox regression analysis accounting for the following covariates based on clinical relevance and a P-value <0.20 [70] in

univariable analyses: age, sex, body mass index >30kg/m^2 (e.g. obese), prior MI, medically treated hypertension, prior stroke or transient ischaemic attack, critical preoperative state, prior anaemia, diabetes mellitus, peripheral vascular disease, history of carotid artery disease and SYNTAX score (as a continuous variable). Patients who were missing any 1 of the covariates were not included in the multivariable model. We assessed the validity of the proportional hazards assumption by testing a time-dependent interaction between SITA versus BITA and survival time. There was no evidence that the proportionality assumption was violated. The complete Cox Regression model on the primary outcome (death, stroke or MI) is presented in **Supplementary Material**, **Table S1.**[20]

To account for missing data, we conducted separate sensitivity analyses using multiple imputations and generated 40 imputed datasets. The imputation models included the same set of covariates from our multivariable Cox regression models. All statistical tests were 2-sided, and P<0.05 was considered as statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

Among the 905 study patients undergoing CABG, 688 (76.0%) underwent SITA and 217 (24.0%) underwent BITA. In the SITA group, 10 patients withdrew consent (1.5%) and 23 patients were lost to follow-up (3.3%), whereas in the BITA group 3 patients withdrew consent (1.4%) and 4 patients were lost to follow-up (1.8%). Compared to patients treated with SITA, those receiving BITA were younger, were less commonly female, had less medically treated diabetes and peripheral vascular disease, and presented less frequently with a critical preoperative state (Table **1**). Anatomic complexity, as assessed by the SYNTAX score reported on-site, was similar between the 2 groups.

Table 1. Baseline characteristics: reported on-site

Characteristics, % (n/N)	SITA (N = 688)	BITA (N = 217)	P-value
Age (years)	66.1 ± 9.5	64.5 ± 9.3	0.020
Female sex	24.3(167)	14.3 (31)	0.002
CAD risk factors			
Medically treated hypertension	76 (523)	67.3 (146)	0.010
Hyperlipidaemia	69.5 (477/68)	67.7 (147)	0.62
Medically treated diabetes mellitus	28.8 (198)	15.2 (33)	<0.001
Cigarette use	63.2 (431/682)	62.0 (134/216)	0.76
Family history of CAD	63.7 (369/579)	67.4 (124/184)	0.37

Table 1. Baseline characteristics: reported on-site (*continued*)

Characteristics, % (n/N)	SITA (N = 688)	BITA (N = 217)	P-value
Preoperative risk factors			
Prior stroke or TIA	8.0(55)	4.6 (10)	0.090
Prior myocardial infarction[a]	15.2(104/685)	11.5 (25)	0.18
Dialysis	0.4 (3)	0.0 (0)	>0.99
PVD	10.2 (70/684)	5.5 (12)	0.040
Congestive heart failure	6.6 (45/685)	5.1 (11)	0.42
COPD	9.2 (63/687)	6.0 (13/216)	0.15
Carotid artery disease history	9.8 (67/685)	4.6 (10)	0.020
BMI (kg/m^2)	29.0 ± 5.1	28.2 ± 4.1	0.24
<20: cachectic	1.2 (8)	0.9 (2)	0.99
>30: obese	34.5 (237)	28.1 (61)	0.080
Critical preoperative state[b]	2.6 (18)	0(0)	0.010
Prior history of anaemia	10.6 (73/686)	3.7(8)	0.002
Coronary dominance			
Right	91.7 (626/683)	85.1 (177/208)	0.006
Left	8.3 (57/683)	14.9 (31/208)	0.006
LM stenosis locations			
Ostial	38.4 (264)	31.3 (68)	0.060
Mid	19.2(132)	16.1 (35)	0.31
Distal	50.9 (350)	54.8 (119)	0.31
Bifurcation	30.7 (211)	35.9 (78)	0.15
LM stenosis degree (%)			
0–<50	0.4 (3/686)	0.5 (1)	>0.99
≥50–<70	16.2 (111/686)	18.9 (41)	0.35
≥70	83.4 (572/686)	80.6 (175)	0.35
Total SYNTAX score, mean ± SD (*N*)	20.4 ± 6.3 (687)	20.7 ± 5.6 (217)	0.39
LVEF (%), mean ± SD (*N*)	57.0 ± 8.8 (663)	59.0 ± 9.6 (202)	0.0006

Values are shown as mean ± SD or frequencies in % (*n*), unless otherwise noted. The number of patients in each group is provided as SITA (*N* = 688) and BITA (*N* = 217), unless otherwise noted.

[a] Prior myocardial infarction within 2 months.

[b] Clinical preoperative state: ventricular tachycardia, ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or IABP and preoperative acute renal failure (anuria or oliguria <10 ml/h).

BITA: bilateral internal thoracic artery; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; IABP: intra aortic balloon pump; LM: left main; LVEF: left ventricular ejection fraction; PVD: peripheral vascular disease; SD: standard deviation; SITA: single internal thoracic artery; SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TIA: transient ischaemic attack.

Surgical characteristics

No differences were observed between the SITA and BITA groups with respect to the average number of vessels bypassed per patient or the number of conduits per patients. BITA patients had more distal anastomosis to the ramus circumflex artery yet similar rates were observed for the left anterior descending and right coronary artery (Table 2). Total arterial revascularisation was performed in 12.5% of patients

Table 2. Surgical characteristics

Characteristics	SITA (N = 688)	BITA (N = 217)	P-value
Average number of conduits per patient (arterial or venous), *n* ± SD	2.6 ± 0.8	2.6 ± 0.7	0.58
Number of vessels bypassed per patient, *n* ± SD	2.2 ± 0.6	2.3 ± 0.5	0.47
Site of distal anastomosis			
LAD	98.4 (676/687)	100.0 (217)	0.080
LCx	87.2 (599/687)	93.1 (202)	0.020
RCA	38.6 (265/687)	35.5 (77)	0.41
LAD and LCx	86.0 (591/687)	93.1 (202)	0.006
Off-pump CABG	28.6 (197)	34.1 (74)	0.13
Cardioplegia			
Crystalloid	29.9 (146/489)	23.8 (34/143)	0.16
Blood	66.9 (327/489)	71.3 (102/143)	0.32
Any blood product transfusion	4.4 (30)	2.3 (5)	0.17
Bypass duration time, min ± SD	81.6 ± 44.6	87.2 ± 44.4	0.040
Cross-clamp duration, min ± SD	52.4 ± 25.9	62.1 ± 29.2	<0.001
Duration of procedure, min ± SD (*skin-to-skin time*)	188.2 ± 62.2	218.1 ± 68.9	<0.001
ITAs used			
LITA	98.7 (679)	100.0 (217)	0.12
In situ	94.4 (641/679)	92.6 (201/217)	0.34
Free	5.7 (39/679)	8.3 (18/217)	0.18
RITA	1.3 (9)	100.0 (217)	<0.0001
In situ	77.8 (7/9)	66.4 (144/217)	0.72
Free	22.2 (2/9)	33.6 (73/217)	0.72
Use of (any) radial artery	6.4 (44)	5.1 (11)	0.48
revascularisation with only arterial grafts	12.5 (86)	65.0 (141)	<0.001
Other surgical procedures performed[a]	1.9 (13)	1.8 (4)	>0.99
Intubation >48 h	2.9 (20)	2.3 (5)	0.64
Postoperative hospital duration (days)	8.1 ± 6.7	8.8 ± 8.0	0.19
Medications at discharge			
Aspirin	99.3 (672/677)	98.1 (208/212)	0.23
ACE-inhibitor or ARB	41.9 (285/680)	43.5 (93/214)	0.69
Beta blocker	93.1 (633/680)	91.6 (196/214)	0.46
Calcium channel antagonists	7.9 (54/680)	4.7 (10/214)	0.11
Statin	92.8 (631/680)	92.5 (198/214)	0.89
Any P2Y12 inhibitors	35.0 (238/680)	26.2 (56/214)	0.020
Clopidogrel	34.4 (234/680)	24.8 (53/214)	0.008
Ticagrelor	0.0 (0/680)	0.9 (2/214)	0.060
Prasugrel	0.6 (4/680)	0.0 (0/214)	0.58

Values are shown as mean ± SD or frequencies in % (*n*), unless otherwise noted. The number of patients in each group is provided as SITA (*N* = 688) and BITA (*N* = 217), unless otherwise noted.

[a] Aortic valve surgery, mitral valve surgery, tricuspid valve surgery and atrial appendage closure.

ACE: Angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; BITA: bilateral internal thoracic artery; CABG: coronary artery bypass grafting; ITA: internal thoracic artery; LAD: left anterior descending; LCx: ramus circumflex (circumflex artery); LITA: left internal thoracic artery; RCA: right coronary artery; RITA: right internal thoracic artery; SD: standard deviation; SITA: single internal thoracic artery; Skin-to-skin time: the time between the first incision until the final closing of the sternotomy wound.

in the SITA group vs 65.0% in the BITA group (P < 0.001). Radial artery grafts were used infrequently in each group.

Usage of off-pump surgery was similar between the 2 groups. Patients treated with SITA compared with BITA had shorter procedure duration times, total bypass duration times and shorter cross-clamp times (Table **2**). The postoperative hospital stay was similar in both groups.

Clinical outcomes

The 30-day clinical outcomes, including the composite rate of death, stroke or MI and ischaemia-driven repeat revascularisation, were not significantly different between the 2 groups (Table **3**). The rate of sternal wound dehiscence was comparable with SITA and BITA revascularisation (2.2% vs 1.8%, respectively; *P* > 0.99).

Table 3. Unadjusted 30-day clinical outcomes

Endpoints	SITA (N = 688), % (n)	BITA (N = 217), % (n)	Hazard ratio (95% confidence interval)	P-value
Death, stroke or MI	7.8 (54)	7.8 (17)	1.00 (0.58–1.73)	>0.99
All-cause death	0.9 (6)	1.4 (3)	0.63 (0.16–2.51)	0.51
Cardiovascular	0.9 (6)	0.9 (2)	0.94 (0.19–4.66)	0.94
Non-cardiovascular	0.0 (0)	0.5 (1)		
Stroke	1.5 (10)	0.9 (2)	1.66 (0.34–7.16)	0.56
MI	6.1 (42)	6.5 (14)	0.95 (0.52–1.73)	0.86
Ischaemia-driven revascularisation	1.3 (9)	0.9 (2)	1.41 (0.31–6.54)	0.66
Major bleeding (BARC 3–5)	9.0 (62)	8.3 (18)	1.09 (0.65–1.85)	0.74
Sternal wound dehiscence[a]	2.2 (15)	1.8(4)	1.18 (0.40–3.53)	>0.99

Rates are the Kaplan–Meier estimates (*n* events).
[a] Reported on-site.
BARC: Bleeding Academic Research Consortium; BITA: bilateral internal thoracic artery; MI: myocardial infarction; SITA: single internal thoracic artery.

At 3-year follow-up, the unadjusted rate of the primary composite endpoint of all-cause death, stroke or MI occurred in 15.6% of patients in the SITA group vs 11.6% in the BITA group (P = 0.17, Fig. **1** A and Table **4**). There was a trend towards a higher rate of all-cause death with SITA versus BITA: 6.7% vs 3.3% (Fig. **1**B), respectively (*P* = 0.070). There were no significant differences in the 3-year rates of stroke, (Fig. **1**C and D) MI, ischaemia-driven revascularisation or major bleeding complications (BARC Class 3–5) between the (Fig. **2**A and B) groups. At 3 years, SITA patients had a significantly higher rate of unplanned hospitalization compared to BITA patients (35.8% vs 26.0%, *P* = 0.008, Fig. **2**C and Table **4**). In the SITA group, 20.1% of the

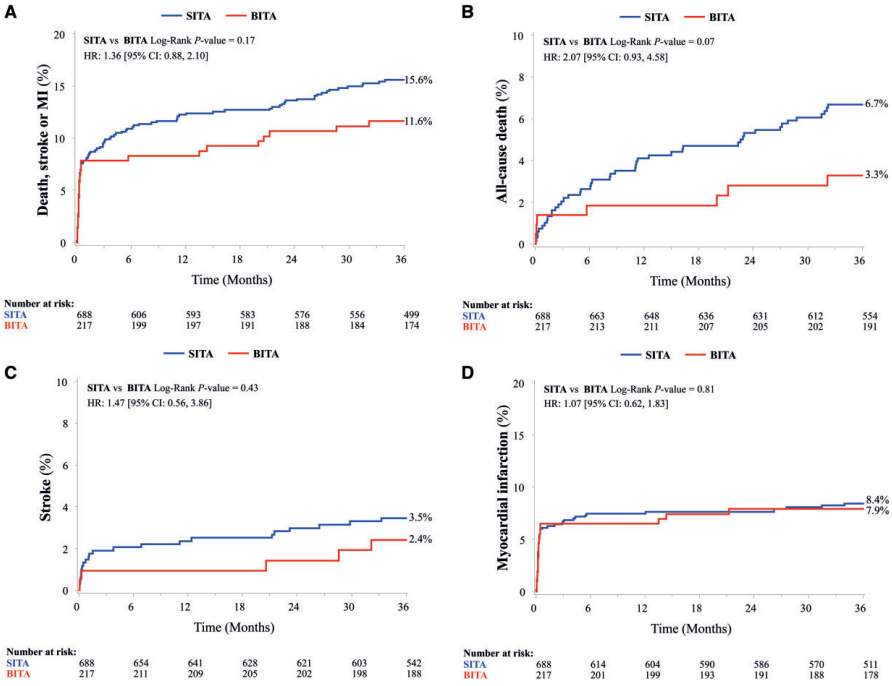

Figure 1. Kaplan–Meier curves on 3-year primary endpoints. Statistical significance is calculated with the log-rank test, and HRs with a 95% CI are provided. (A) Death, stroke or MI. (B) All-cause death. (C) Stroke. (D) MI. SITA is represented by the blue line, and BITA is represented by the red line. BITA: bilateral internal thoracic artery; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; SITA: single internal thoracic artery.

patients had a cardiovascular indication for unplanned admission compared to 13.8% of the patients in the BITA group ($P = 0.04$). After adjustment for differences in baseline covariates by multivariable Cox regression, none of the rates of the primary or secondary clinical outcomes were significantly different between the SITA and BITA groups (Table 4). Adjusted associations were consistent after multiple imputations of missing data (**Supplementary Material**, **Table S2**).

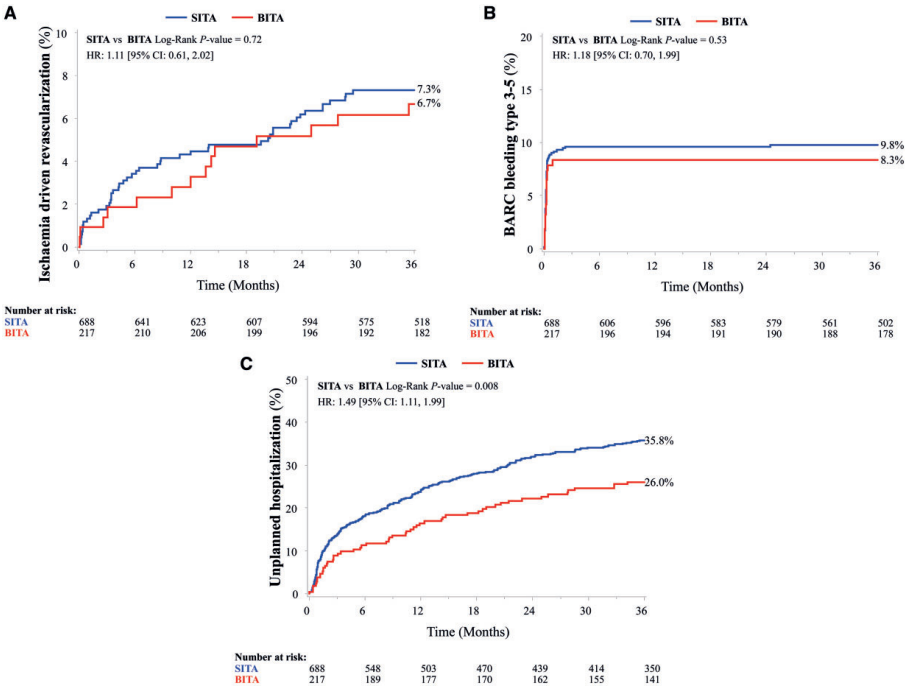

Figure 2. Kaplan–Meier curves on 3-year secondary endpoints. Statistical significance is calculated with the log-rank test, and HRs with a 95% CI are provided. (**A**) Ischaemia-driven revascularisation (**B**) BARC bleeding type 3–5. (**C**) Unplanned hospitalization. SITA is represented by the blue line, and BITA is represented by the red line. BITA: bilateral internal thoracic artery; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; SITA: single internal thoracic artery.

Table 4. Unadjusted and adjusted 3-year clinical outcomes

Endpoints	SITA (N = 688), % (n)	BITA (N = 217), % (n)	Unadjusted hazard ratio (95% CI)	Unadjusted P-value	Adjusted hazard ratio (95% CI)	Adjusted P-value
Death, stroke or MI	15.6 (106)	11.6 (25)	1.36 (0.88–2.10)	0.17	1.12 (0.71–1.78)	0.62
All-cause death	6.7 (45)	3.3 (7)	2.07 (0.93–4.58)	0.07	1.36 (0.60–3.12)	0.46
Cardiovascular	4.2 (28)	2.4 (5)	1.80 (0.69–4.65)	0.22	1.14 (0.42–3.06)	0.80
Non-cardiovascular	2.6 (17)	0.9 (2)	2.74 (0.63–11.86)	0.16	1.93 (0.43–8.77)	0.39
Stroke	3.5 (23)	2.4 (5)	1.47 (0.56–3.86)	0.43	0.88 (0.32–2.43)	0.80
MI	8.4 (57)	7.9 (17)	1.07 (0.62–1.83)	0.81	1.04 (0.58–1.85)	0.90
Ischaemia-driven revascularisation	7.3 (48)	6.7 (14)	1.11 (0.61–2.02)	0.72	1.02 (0.54–1.93)	0.96
Major bleeding (BARC 3–5)	9.8 (67)	8.3 (18)	1.18 (0.70–1.99)	0.53	1.12 (0.64–1.94)	0.39
Unplanned hospitalization	35.8 (238)	26.0 (55)	1.49 (1.11–1.99)	0.008	1.27 (0.93–1.74)	0.13

Rates are the Kaplan-Meier estimates
(*n* events).
BARC: Bleeding Academic Research Consortium; BITA: bilateral internal thoracic artery; CI: confidence interval; MI: myocardial infarction; SITA: single internal thoracic artery.

DISCUSSION

Due to the absence of significant differences in the postoperative outcomes such as all-cause death, stroke, MI or sternal wound dehiscence between BITA and SITA surgical revascularisation in patients with LMCAD and low to intermediate SYNTAX scores, one can conclude that the use of BITA was equally safe compared to the use of SITA at the 3-year follow-up.

A potential reason for the less frequent use of BITA could be the risk of competitive coronary flow on arterial grafts. Sabik *et al.* [71] showed that when the degree of preoperative proximal stenosis decreases to below mild (<40%), the risk of competitive coronary flow for arterial grafts increases and thereby compromising graft patency. Yet, in the current study, over 99% of both SITA and BITA patients had a moderate-to-severe left main coronary artery stenosis, of whom over 80% had a severe (≥70%) left main stenosis (Table **1**). Furthermore, patients undergoing BITA compared to SITA were younger and had fewer comorbidities, possibly due to the selection bias of BITA

patients having a more favourable life-expectancy and better clinical status. This resulted in less favourable 3-year outcomes in unadjusted analyses. However, after multivariable adjustment for these covariates, event-free survival and the individual rates of adverse events, including all-cause death, were comparable with both types of revascularisation. Specifically, no significant differences were observed for the individual endpoints of death, stroke, MI, ischaemia-driven repeat revascularisation, unplanned hospitalization, bleeding complications or sternal wound dehiscence.

The EXCEL trial recommended performing total arterial coronary revascularisation in an effort to ensure complete revascularisation with the highest possible graft patency rates.[54] The most commonly used grafts were the internal thoracic arteries, which were used in 99.0% of patients. Radial artery grafts were used in only 5.1% of patients in the BITA group and 6.4% of patients in the SITA group, and the gastroepiploic artery was not used at all. Despite the protocol recommendations and inclusion of highly skilled sites in the EXCEL trial, only 24.0% of patients underwent BITA, and complete arterial revascularisation was achieved in only 25.1% of all patients. The results of this study thus demonstrate that bilateral arterial grafts and complete arterial revascularisation are not frequently used in contemporary surgical practice.

Intubation and duration of the initial hospitalization were not prolonged in the BITA group. Although the use of BITA prolonged the procedure compared with SITA, the use of BITA was reassuringly safe with nearly identical 2% rates of sternal wound dehiscence in both the groups. Nonetheless, there were no significant differences in 30-day or 3-year clinical outcomes between patients treated with SITA and BITA. The higher rate of unplanned hospitalizations in the SITA group was likely due to the higher prevalence of comorbidities as this risk was no longer present after the adjustment for clinically relevant covariates. Similarly, the ART trial (n = 3102), the largest randomized trial to date with 10-year survival as a primary endpoint, did not demonstrate a difference in mortality or other adverse events in the interim analysis at 5 years with BITA compared with SITA,[64] and the sternal wound complication rate was slightly higher in the BITA group (3.5% vs 1.9%). However, the 3- to 5-year follow-up from the EXCEL and ART trials may be too short for the benefits of BITA to emerge. In a meta-analysis of observational studies, Yi *et al.* [72] reported a survival benefit of BITA compared with SITA when follow-up was extended to ≥9 years. The observational study from the Cleveland Clinic by Lytle *et al.* [73] followed patients up to 20 years and showed that BITA and SITA survival curves only started to diverge in favour of BITA revascularisation at 10-year follow-up. CABG with BITA revascularisation may therefore be encouraged, considering the outcomes of current study with

respect to the unequivocal long-term survival benefits of BITA, which is reported by observational studies and meta-analysis.[72, 73]

It is noteworthy that in the current study, 26.3% of the 707 male patients and 15.6% of the 198 female patients received BITA revascularisation. While the reasons for the lower rates of BITA use in women are not immediately apparent, these rates are similar to previous studies [75] and emphasize the need for future research in women undergoing cardiac surgery.[25, 74]

In addition to longer-term follow-up from the EXCEL and ART trials, insights into the outcomes of BITA compared to SITA will be gained from the recently initiated ROMA trial, in which more than 4000 patients undergoing CABG were randomized into two groups receiving either single or multiple arterial grafts, with follow-up planned for up to 10 years.[76]

Limitations

The present study with 905 patients is modest in size, but nonetheless represents the largest analysis to date on the use of BITA versus SITA in patients with LMCAD undergoing surgical revascularisation. The BITA and SITA groups were not randomized, and patients in the BITA group had fewer comorbidities, requiring multivariable adjustment. However, we cannot exclude the role of unmeasured confounders, and thus these results should be considered hypothesis-generating. The reasons for performing BITA versus SITA were not prospectively collected. Further insights may be obtained with longer-term follow-up from the EXCEL trial (presently planned for 5 years). Finally, EXCEL excluded patients with high anatomic SYNTAX scores assessed by local heart teams (e.g. SYNTAX score >33), and thus the results do not apply to patients with highly complex LMCAD. The recently published systematic review by Head *et al.* [78] showed a larger survival benefit of CABG over PCI in patients with intermediate to complex multi-vessel disease (SYNTAX score ≥ 23), which was not found in complex LMCAD patients.

CONCLUSIONS

In the EXCEL trial, CABG with SITA versus BITA revascularisation for patients with LMCAD resulted in no significant differences in the rate of the primary composite endpoint of death, stroke or MI at 3years, or in any of the individual endpoints at 30days or 3 years, including bleeding complications, ischaemia-driven revascularisation or unplanned hospitalization. As there were also no differences in sternal

wound dehiscence rates between SITA and BITA revascularisation, the use of BITA can be considered safe. Longer-term follow-up (for ≥10 years) should be performed to completely characterize the potential impact of SITA versus BITA revascularisation on long-term outcomes after CABG in high-risk patients with LMCAD.

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REFERENCES

1. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014; 64:1929–49.
2. Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardiothorac Surg 2014;46:517–92.
3. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146–54.
4. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190–7.
5. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol 2011;58:1426–32.
6. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. Circulation 2014;129:2388–94.
7. Cavalcante R, Sotomi Y, Lee CW, Ahn JM, Farooq V, Tateishi H et al. Outcomes after percutaneous coronary intervention or bypass surgery in patients with unprotected left main disease. J Am Coll Cardiol 2016;68:999–1009.
8. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet 2001;358:870–5.
9. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R et al. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117:855–72.
10. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1–6.
11. Aldea GS, Bakaeen FG, Pal J, Fremes S, Head SJ, Sabik J et al. The Society of Thoracic Surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting. Ann Thorac Surg 2016;101:801–9.

12. Rizzoli G, Schiavon L, Bellini P. Does the use of bilateral internal mammary artery (IMA) grafts provide incremental benefit relative to the use of a single IMA graft? A meta-analysis approach. Eur J Cardiothorac Surg 2002;22:781–6.
13. Kieser TM, Lewin AM, Graham MM, Martin BJ, Galbraith PD, Rabi DM et al. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. Ann Thorac Surg 2011;92:1269–75; discussion 75-6.
14. Taggart DP, Altman DG, Gray AM, Lees B, Nugara F, Yu LM et al. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). Eur Heart J 2010;31:2470–81.
15. Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U et al. Randomized trial of bilateral versus single internal-thoracic-artery grafts. N Engl J Med 2016;375:2540–9.
16. Toumpoulis IK, Theakos N, Dunning J. Does bilateral internal thoracic artery harvest increase the risk of mediastinitis? Interact CardioVasc Thorac Surg 2007;6:787–91.
17. Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223–35.
18. Kappetein AP, Serruys PW, Sabik JF, Leon MB, Taggart DP, Morice MC et al. Design and rationale for a randomised comparison of everolimus- eluting stents and coronary artery bypass graft surgery in selected patients with left main coronary artery disease: the EXCEL trial. EuroIntervention 2016;12:861–72.
19. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.
20. Hickey GL, Dunning J, Seifert B, Sodeck G, Carr MJ, Burger HU et al. Statistical and data reporting guidelines for the *European Journal of Cardio-Thoracic Surgery and the Interactive CardioVascular and Thoracic Surgery*. Eur J Cardiothorac Surg 2015;48:180–93.
21. Sabik JF 3rd, Lytle BW, Blackstone EH, Khan M, Houghtaling PL, Cosgrove DM. Does competitive flow reduce internal thoracic artery graft patency? Ann Thorac Surg 2003;76:1490–6. discussion 97.
22. Yi G, Shine B, Rehman SM, Altman DG, Taggart DP. Effect of bilateral internal mammary artery grafts on long-term survival: a meta-analysis approach. Circulation 2014;130:539–45.
23. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. Ann Thorac Surg 2004;78:2005–12; discussion 12–14.
24. Schwann TA, Tatoulis J, Puskas J, Bonnell M, Taggart D, Kurlansky P et al. Worldwide trends in multi-arterial coronary artery bypass grafting surgery 2004-2014: a tale of 2 continents. Semin Thorac Cardiovasc Surg 2017;29:273–80.
25. Vaina S, Milkas A, Crysohoou C, Stefanadis C. Coronary artery disease in women: from the Yentl syndrome to contemporary treatment. World J Cardiol 2015;7:10–18.
26. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting reverses the negative influence of gender on outcomes of coronary artery bypass grafting surgery. Eur J Cardiothorac Surg 2013;44:54–63.
27. Gaudino M, Alexander JH, Bakaeen FG, Ballman K, Barili F, Calafiore AM et al. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. Eur J Cardiothorac Surg 2017;52:1031–40.

28. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391: 939–48.

SUPPLEMENTARY MATERIAL

Supplementary material is also available at *EJCTS* online.

SUPPLEMENTARY MATERIAL

Table S1. Full Cox Regression model on the primary outcome (death, stroke or MI).

Variable	Hazard ratio [95% CI]	*P*-value
SITA vs BITA	1.12 [0.71 – 1.78]	0.62
Age, per 5 years	1.03 [0.84 – 1.26]	0.77
Sex, male vs female	1.04 [0.67 – 1.61]	0.86
BMI, >30 vs ≤30 kg/m^2	0.98 [0.67 – 1.46]	0.98
Prior MI	1.02 [0.64 – 1.63]	0.93
Medically-treated hypertension	1.31 [0.82 – 2.08]	0.25
Prior stroke or TIA	1.14 [0.60 – 2.16]	0.69
Critical preoperative state	0.76 [0.18 – 3.15]	0.71
Diabetes mellitus	1.29 [0.87 – 1.91]	0.21
Peripheral vascular disease	0.45 [0.22 – 0.94]	0.03
COPD	2.51 [1.54 – 4.09]	<0.001
Prior anemia	1.52 [0.89 – 2.61]	0.13
History of carotid artery disease	1.69 [0.93 – 3.06]	0.08
SYNTAX score, per 5 units	1.02 [0.93 – 1.12]	0.66

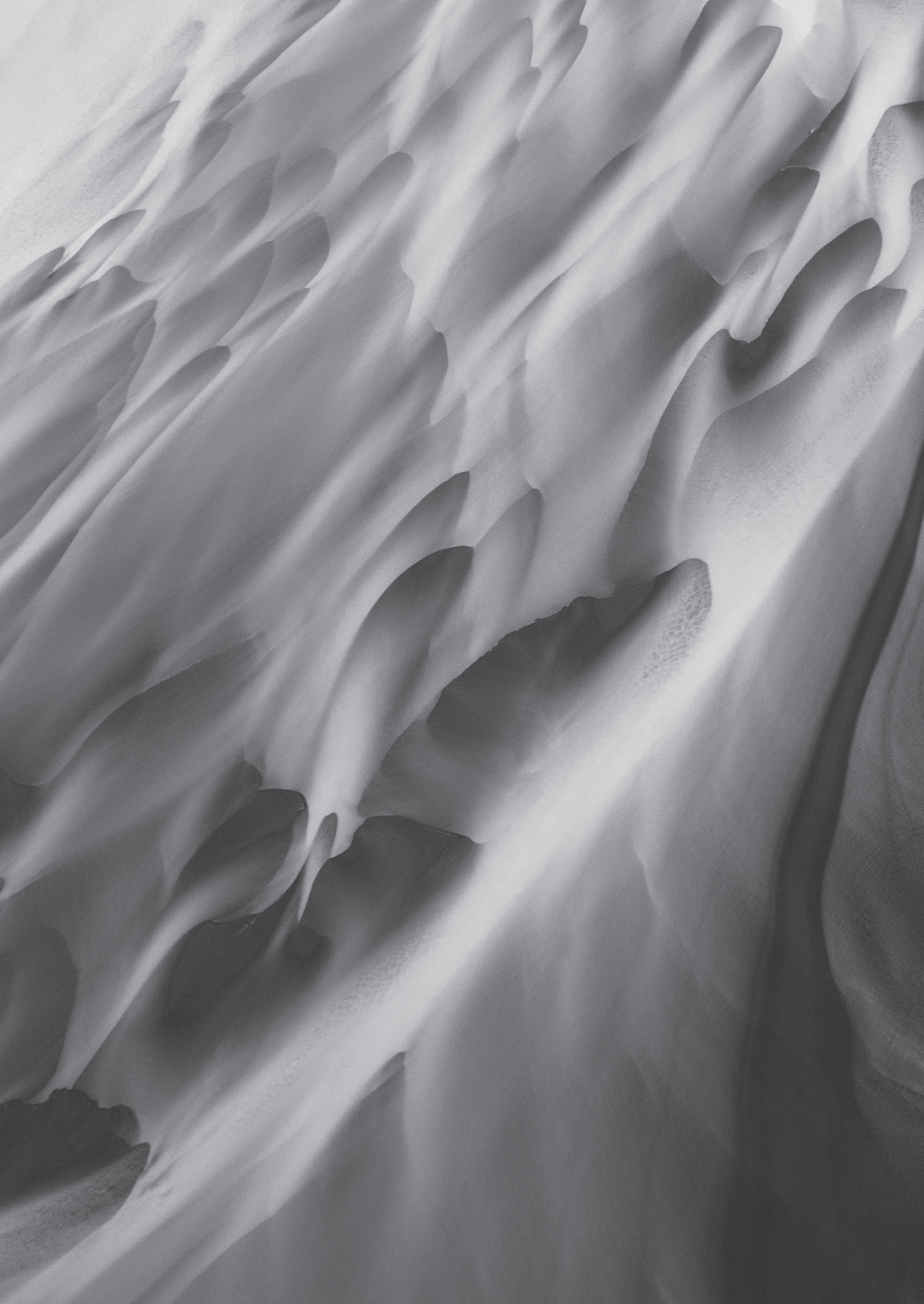
Here, the full Cox Regression Model on the primary outcome (death, stroke or MI) is reported according to the EJCTS Statistical and Data Reporting Guideline.[20] Of note, there were no changes to the treatment effect inferences when "critical preoperative state" and "peripheral vascular disease" were eliminated from the model. A BMI of > 30 is classified as obese.

Abbreviations used: SITA: single internal thoracic artery, BITA: bilateral internal thoracic artery, BMI: Body Mass Index, MI: myocardial infarction, TIA: transient ischemic attack, COPD: chronic obstructive pulmonary disease, SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

Table S2. Multivariable adjusted three-year clinical outcomes after multiple imputations.

Endpoint	Hazard ratio [95% CI] (adjusted)	Adjusted *P*-value
Death, stroke or MI	1.22 [0.77 – 1.93]	0.40
All-cause death	1.52 [0.66 – 3.49]	0.32
Cardiovascular	1.34 [0.49 – 3.66]	0.57
Non-cardiovascular	1.99 [0.47 – 8.44]	0.35
Stroke	1.14 [0.40 – 3.23]	0.80
MI	1.09 [0.62 – 1.94]	0.76
Ischemia-driven revascularization	0.99 [0.53 – 1.86]	0.99
Major bleeding (BARC 3-5)	1.08 [0.64 – 1.83]	0.78
Unplanned hospitalization	1.28 [0.95 – 1.73]	0.11

Hazard ratios with 95% confidence intervals, for SITA versus BITA, were calculated after adjustment for differences in baseline covariates by multivariable Cox regression and multiple imputations.
Abbreviations used: SITA: single internal thoracic artery, BITA: bilateral internal thoracic artery, MI: myocardial infarction, BARC: Bleeding Academic Research Consortium.



Chapter 5

Critical appraisal of a decade of left main revascularisation meta-analyses

Christiaan F.J. Antonides*, Daniel J.F.M. Thuijs*, Edris A.F. Mahtab, Mattie J. Lenzen, A. Pieter Kappetein, Ad J.J.C. Bogers, Stuart J. Head

* both authors contributed equally

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ABSTRACT

Background

The optimal revascularisation strategy for patients with left-main coronary artery disease (LMCAD) is a compelling topic. After the publication of recent trials, numerous meta-analyses on percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) were published. This study reviewed the extent of meta-analyses on PCI versus CABG in LMCAD.

Methods and Results

A systematic search in online databases was performed to identify meta-analyses on PCI versus CABG in LMCAD. Meta-analyses that reported associations between revascularisation and clinical outcomes were included.. Study outcomes were reported according to descriptive statistics, without pooling study outcomes. Fifty-one meta-analyses were included. Of those, 33 became available after EXCEL and NOBLE trial publication. The composite of major adverse cardiac (and cerebrovascular) events were reported in 41, and 49 reported all-cause mortality. Results varied, depending on (i) randomized versus observational data, or a combination of both, (ii) methodology and effect-measures to report treatment-differences, (iii) varying sample sizes, and (iv) the year of publication.

Conclusions

The number of meta-analyses on PCI versus CABG in patients with LMCAD, is disproportionate and urges the need for quality over quantity. To ensure high-quality publications, we call on all authors, editors and reviewers to appraise the evidence already available and join forces to conduct individual patient data pooled analyses instead.

Keywords

Coronary artery bypass; percutaneous coronary intervention; left main, meta-analyses; MACCE; all-cause mortality

INTRODUCTION

Meta-analyses are systematic reviews that pool study-outcomes to increase statistical power and provide a higher level of evidence than is often possible with single studies. Therefore, meta-analyses are frequently consulted by healthcare professionals and inform medical guidelines.[1]

The number of meta-analyses increased substantially in the field of cardiovascular medicine and determining the optimal strategy for patients with left main coronary artery disease (LMCAD) remains a fiercely debated subject. Over the past decades, numerous randomized studies assessed clinical outcomes after percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) in patients with LMCAD.[2-6] Two randomized controlled trials (RCTs) that contributed considerably to the evidence are the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main revascularisation and NOBLE (Nordic Baltic British left main revascularisation trials.[7, 8] Additionally, several non-randomized observational studies have reported results of CABG versus PCI. Pooling of observational data with randomized studies may lead to inter-study variability related to study design, sample size, baseline characteristics and outcomes, making it challenging to adequately appraise all scientific evidence available.

A meta-analysis, if performed correctly, can be helpful. However, an excess of meta-analyses, as was noticed over the recent decade, could lead to overlapping and redundant outcomes.[9] Therefore, this study critically appraised the extent of potential overlap and shortcomings by systematically reviewing the contemporaneous published meta-analyses on PCI versus CABG in LMCAD, with a special focus on those published after the EXCEL and NOBLE publications.

METHODS

Search strategy

On November 7th, 2018, a systematic literature search, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline[10] (Supplementary Appendix), was performed in Embase, Medline Ovid and Cochrane databases to identify meta-analyses on PCI versus CABG in LMCAD. The search contained the following key words or synonyms: “left main coronary artery disease”, “percutaneous coronary intervention”, “coronary artery bypass grafting” and “meta-analysis”. A detailed search strategy is reported in the Supplementary Appendix.

Meta-analyses comparing revascularisation strategies for LMCAD, by PCI with any stent(s) versus CABG, and reported clinical outcomes were included. Titles and abstracts were first screened for inclusion. When eligible, full-text English articles were subsequently reviewed independently by two authors (CA and DT). Predefined exclusion criteria were: (i) conference abstracts, (ii) absence of a LMCAD population, (iii) subgroups of patients with LMCAD, (iv) absence of effect estimates, (vi) individual patient pooled analyses or (vii) systematic reviews. Incongruities were resolved by agreement between two authors (CA and DT).

Data extraction

The following study details were extracted: year of publication, authors, journal, number of patients (total, CABG, and PCI) and the number of included individual randomized controlled trials (RCTs) and observational studies. Postoperative outcomes with an effect estimate (hazard, odds, risk ratios or incidence rate ratios) were extracted, along with the model used for analysis (fixed or random effects model). "Combined long-term follow-up" is defined as meta-analyses reporting a pooled event-rate at follow-up with varying durations (e.g. combination of 1, 3 and 5-year follow-up data).

Clinical outcomes that were extracted included major adverse cardiac (and cerebrovascular) events (MAC(C)E), according to the definitions used by the individual included meta-analyses, such as (i) death, stroke or myocardial infarction (MI) or as (ii) death, stroke, MI or any form of repeat revascularisation (for example; target-vessel revascularisation or ischemia-driven revascularisation All-cause mortality rates were also extracted.

Study outcomes

The primary endpoint consisted of a summary of MAC(C)E and all-cause mortality outcomes at combined long-term follow-up reported by meta-analyses published after EXCEL and NOBLE. Additionally, a summary of MAC(C)E and all-cause mortality outcomes at 1-year and combined long-term follow-up was provided for all included meta-analyses. The present report had no intention to determine which revascularisation strategy would be preferable for patients with LMCAD and rather focused on providing an overview of the currently available literature. Therefore, pooled outcomes of treatment effects are not provided.

Statistical analyses

Results are reported according to descriptive methods. All risk estimates reported, reflect a "PCI versus CABG" comparison. When an included meta-analysis reported

"CABG versus PCI" risk estimates, these were recalculated to represent "PCI versus CABG" comparisons. Forest plots were used to visualize the spread of varying study outcomes for MAC(C)E and all-cause mortality. Plots were constructed with Prism 8 (GraphPad Software, San Diego, CA, USA).

RESULTS

Study selection

The systematic search resulted in 402 articles. After excluding duplicates, screening titles and abstracts, 128 articles remained for full text reading (Figure 1). Of these, 77 were excluded based on the pre-specified criteria. Finally, 51 meta-analyses were included in the present study, of which 33 were published after EXCEL and NOBLE (Table 1 and Supplementary Appendix Table S1).[11-61]

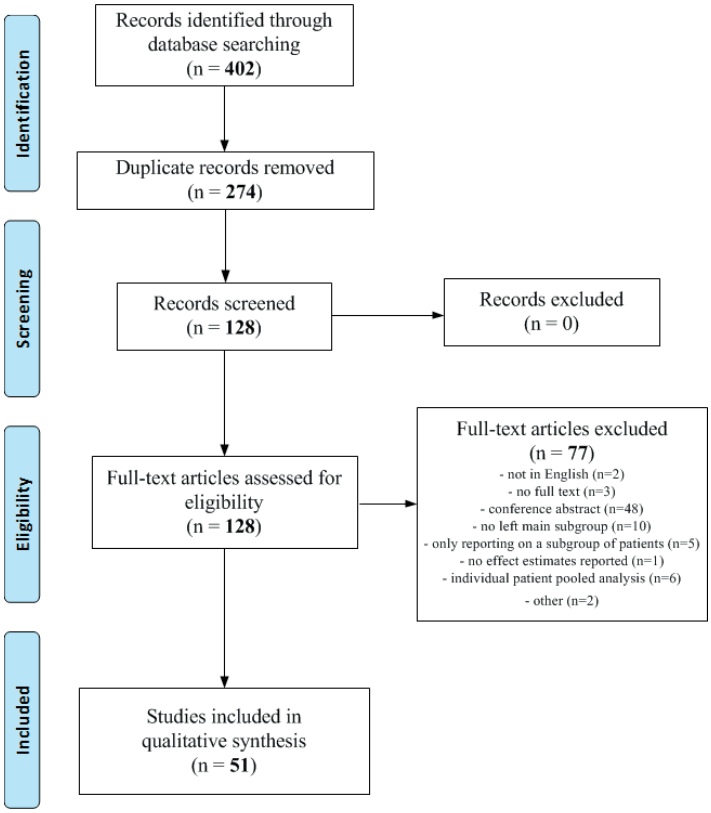

Figure 1. Flowchart of the comprehensive systematic search for meta-analyses PCI versus CABG in LMACD.

Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, LMCAD: left main coronary artery disease.

Table 1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51).

					Follow up duration					
Year	Author	Journal	PCI (n)	CABG (n)	≤30d	1y	3y	≥5y	Combined	MAC(C)E†
2018	Ali[52]	Medicine (Baltimore)	10424	11408	X	-	-	-	X	Stroke, death, MI or revascularisation
2018	Benedetto[53]	J Thorac Cardiovasc Surg	*	*	-	-	-	-	X	Death, MI or stroke
2018	Bertaina[54]	J Cardiovasc Med (Hagerstown)	8501	10813	-	-	-	-	X	Death, MI, definite or probable ST, TVR
2018	Cui[55]	J Geriatr Cardiol	6333	7797	-	-	-	-	X	Death, MI or stroke
2018	Khan[56]	Heart Lung Circul	2349	2351	X	X	-	X	-	MI, stroke, death or TVR
2018	Kodumuri[57]	Am J Cardiol	5017	5267	-	-	-	-	X	Death, MI, stroke or RR
2018	Moore[58]	Heart Lung Circul	2197	2197	-	-	-	-	X	Death, MI or CVA
2018	Rahouma[59]	Ann. cardiothorac. surg.	2349	2351	-	-	-	-	X	Death, MI, stroke or RR
2018	Takagi[60]	Catheter Cardiovasc Interventions	6009	6378	-	-	-	-	X	Death, MI and RRV (with/without stroke)
2018	Verdoia[61]	Angiology	2297	2298	-	-	-	-	X	Major Adverse Cardiovascular Events*
2017	Bajaj[30]	Eur Heart J Qual Care Clin Outcomes	2349	2351	-	X	-	-	X	Death, stroke, MI or RR
2017	Chang[31]	Ann Thorac Surg	*	*	X	X	-	-	X	Death, stroke, MI or TVR
2017	DeRosa[32]	BMC Cardiovasc Disord	2249	2250	-	-	-	-	X	Death, stroke, MI or RR
2017	Gao[33]	Oncotarget	2297	2298	-	X	-	-	X	Death, stroke, MI or RR
2017	Garg[34]	Am J Cardiol	2297	2298	-	-	-	-	X	*
2017	Giacoppo[35]	JAMA Cardiol	2197	2197	-	-	-	-	X	Death, stroke or MI
2017	Khan[36]	Am J Cardiol	2349	2351	-	X	-	-	X	Death, MI, stroke or RR
2017	Khan[37]	Am J Cardiol	3197	3340	-	-	-	X	-	Death, nonfatal MI, stroke or RR
2017	Laukkanen[38]	Open Heart	2149	2351	X	X	-	-	X	Death, MI, CVA or stroke, or TVR
2017	Mahmoud[39]	Catheter Cardiovasc Interventions	2349	2351	X	X	-	-	X	Death, MI, stroke or revascularisation
2017	Palmerini[40]	Am Heart J	2347	2339	X	-	-	-	X	Death, stroke, MI or UR

Rct (N)	Obs (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
5	24	X	-	X	X	X	X	OR		1.22 (0.95-1.56)		0.83 (0.60-1.15)
6	-	X	X	X	X	X	X	IRR		0.99 (0.70-1.40)		
6	20	X	X	X	X	X	X	OR		1.10 (1.07-1.14)		0.94 (0.89-1.00)
4	12	X	-	-	X	X	X	HR		0.94 (0.86-1.03)		1.11 (0.92-1.32)
6	-	X	X	X	X	X	X	RR	1.15 (0.92-1.45)		0.67 (0.43-1.06)	
4	8	X	-	-	X	X	X	OR		1.23 (1.01-1.51)		0.97 (0.74-1.26)
4	-	X	-	-	X	X	X	OR		1.37 (1.18-1.58)		1.08 (0.86-1.35)
6	-	X	X	X	X	X	X	IRR		1.328 (1.114-1.582)		0.947 (0.711-1.262)
5	17	X	-	X	X	X	X	HR		1.42 (1.28-1.58)		1.03 (0.90-1.18)
5	-	X	-	X	X	X	X	OR		1.16 (0.98-1.37)		0.88 (0.60-1.29)
6	-	X	X	X	X	X	X	RR	1.17 (0.94-1.44)	1.21 (1.05-1.40)	0.68 (0.44-1.06)	0.98 (0.78-1.25)
5	-	X	X	X	X	-	-	RR	1.20 (0.94-1.54)	1.25 (1.05-1.49)	0.66 (0.38-1.15)	0.81 (0.62-1.08)
5	-	X	X	-	X	X	X	OR		1.33 (1.12-1.58)		1.04 (0.82-1.32)
5	-	X	-	X	X	X	X	RR	1.15 (0.92-1.44)	1.26 (1.11-1.44)	0.70 (0.45-1.09)	1.05 (0.85-1.31)
5	-	X	-	X	X	X	X	OR				1.01 (0.76-1.34)
4	-	X	-	-	X	X	X	HR		1.06 (0.85-1.32)		1.04 (0.81-1.33)
6	-	X	X	X	X	X	X	HR	1.03 (0.69-1.52)	1.16 (0.95-1.43)	0.71 (0.47-1.06)	1.03 (0.80-1.33)
4	5	X	-	-	X	X	X	OR				
6	-	X	X	X	X	X	X	HR	1.16 (0.94-1.44)	1.27 (1.12-1.44)	0.66 (0.42-1.04)	1.04 (0.81-1.33)
6	-	X	X	X	X	X	X	RR	1.21 (0.97-1.51)	1.19 (1.01-1.41)	0.76 (0.45-1.30)	0.94 (0.73-1.22)
6	-	X	X	X	X	X	X	OR		1.27 (1.12-1.45)		0.99 (0.76-1.30)

Table 1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51). (*continued*)

					Follow up duration					
Year	Author	Journal	PCI (n)	CABG (n)	≤30d	1y	3y	≥5y	Combined	MAC(C)E†
2017	Putzu[41]	Int J Cardiol	*	*	X	X	-	-	X	Death, stroke or MI*
2017	Qian[42]	Am J Cardiol	2297	2298	-	X	-	-	X	Study specific definitions of MACCE†
2017	Sá[39]	Braz J Cardiovasc Surg	2297	2298	-	X	-	-	-	Death, MI, stroke or TVR
2017	Sardar[44]	Am J Cardiol	2303	2309	-	X	-	-	X	Death, stroke,MI or any revascularisation
2017	Shah[45]	Am J Cardiol	2349	2351	-	X	X	X	X	Death, recurrent MI, RR and stroke
2017	Sharma[46]	Cardiovasc Ther	2349	2351	X	X	X	X	X	Death, MI, stroke or revascularisation
2017	Spinthakis[47]	Int J Cardiol	2297	2298	-	X	X	X	-	-
2017	Testa[48]	PLoS ONE	2347	2339	-	X	-	-	X	Death, stroke or MI
2017	Upadhaya[49]	J Card Surg	2297	2298	-	-	-	-	X	Study specific definitions of MACCE†
2017	Ye[50]	Medicine (Baltimore)	2349	2351	-	-	-	-	X	Death, MI, stroke and revascularisation
2017	Zhang[51]	BMC Med	10406	12081	-	-	-	-	X	Death, MI, stroke or RR
2016	Nerlekar[29]	Circ Cardiovasc Interventions	2297	2297	-	X	-	-	X	Death, MI, stroke, or RR

Overview of characteristics on PCI versus CABG in LMCAD published by meta-analysis published after EXCEL and NOBLE trial.

Risk estimates representing CABG versus PCI, provided by included meta-analyses, were recalculated to represent PCI versus CABG risk estimates. X = **YES** , - = **NO**. *this specific outcome was not specified in this meta-analysis. †MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. #the correct reference was missing in the original meta-analysis.

Abbreviations used: CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, PCI: percutaneous coronary intervention, LMCAD: left main coronary artery disease, RCTs: randomized controlled trials, Obs.: Observational, Ref.: reference, LA: longest available follow-up, MI; myocardial revascularisation, RR/RRV; repeat revascularisation, TVR: target vessel revascularisation, ST; stent thrombosis, OR: odds ratio, HR: hazard ratio, RR: risk ratio, IRR: incidence rate ratio, UR: unplanned revascularisation.

Rct (N)	Obs (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
5	-	X	-	X	X	X	X	OR			0.69 (0.44-1.10)	1.08 (0.86-1.35)
5	-	X	-	X	X	X	X	RR	1.14 (0.91-1.42)	1.27 (1.13-1.43)	0.78 (0.56-1.08)	1.05 (0.83-1.34)
5	-	X	-	X	X	X	X	RR	1.05 (0.82-1.36)		1.03 (0.80-1.32)	
5	-	X	-	X	X	X	X	OR	0.73 (0.52-1.01)	1.36 (1.18-1.57)	0.71 (0.44-1.12)	1.03 (0.79-1.35)
6	-	X	X	X	X	X	X	RR	1.15 (0.91-1.44)	1.20 (1.03-1.41)	0.68 (0.44-1.06)	0.98 (0.78-1.25)
6	-	X	X	X	X	X	X	OR	1.15 (0.88-1.51)	1.36 (1.18-1.58)	0.67 (0.43-1.06)	1.06 (0.82-1.38)
5	-	X	-	X	X	X	X	OR			0.70 (0.44-1.12)	
6	-	X	X	X	X	X	X	OR	1.02 (0.76-1.36)	1.02 (0.76-1.38)	0.81 (0.63-1.03)	1.00 (0.77-1.31)
5	-	X	-	X	X	X	X	OR		1.36 (1.18-1.58)		1.03 (0.78-1.35)
6	-	X	X	X	X	X	X	RR		1.21 (1.05-1.40)		0.98 (0.78-1.25)
6	22	X	X	X	X	X	X	HR		1.42 (1.14-1.77)		1.05 (0.92-1.20)
5	-	X	-	X	X	X	X	OR	1.14 (0.86-1.49)	1.36 (1.18-1.58)		1.03 (0.78-1.35)

Published meta-analyses

The number of published meta-analyses increased over the past decade, especially after the publication of the randomized EXCEL and NOBLE trials (Figure 2).[7, 8] Several journals published more than one meta-analysis, with one journal publishing 10 meta-analyses on PCI versus CABG for LMCAD. Meta-analyses predominantly reported risk estimates according to odds, risk or hazard ratios.

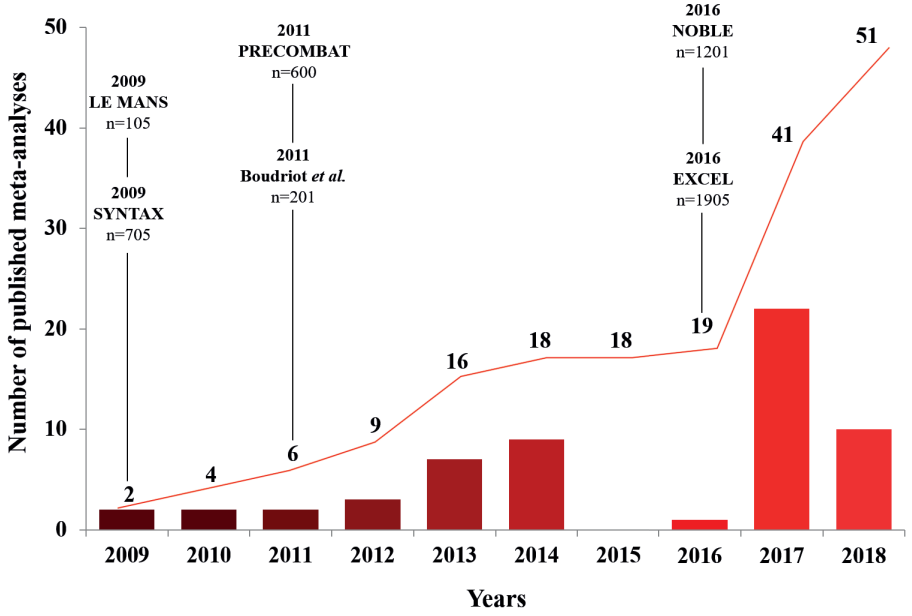

Figure 2. Representation of published randomized clinical trials and meta-analyses on PCI versus CABG in LMCAD over the past decade. The red bars represent the amount of published meta-analyses per year. The red curve represents the cumulative amount of published meta-analyses over the past decade. The main randomized studies that published data on PCI versus CABG in LMCAD are indicated by black lines and names with the intention-to-treat sample sizes.

Meta-analyses after EXCEL and NOBLE

Thirty-three meta-analyses were published after EXCEL and NOBLE. Of these, 32 included EXCEL and NOBLE in addition to results from 3 or 4 other RCTs in their analysis. MAC(C)E outcomes, at combined long-term follow-up, were reported by 26 studies (Table 1, Figure 3), while 27 meta-analyses reported all-cause mortality at combined long-term follow-up (Table 1, Figure 4).

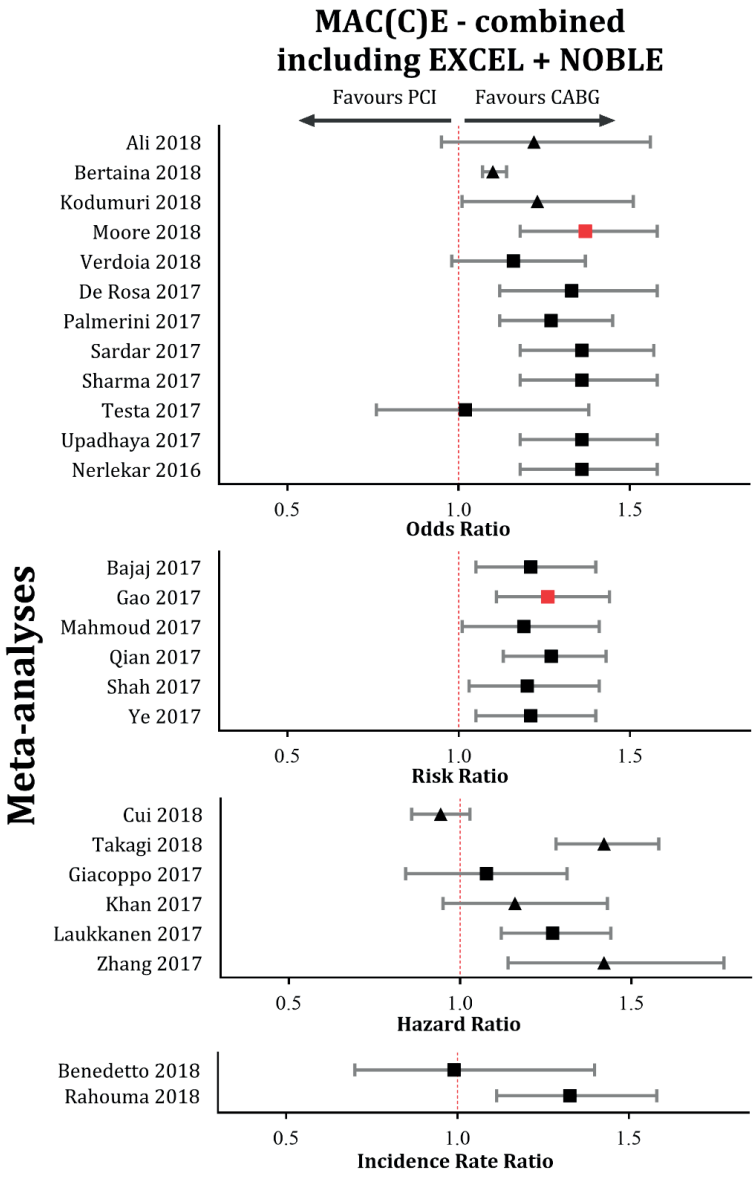

Figure 3. Forest plot representation of MAC(C)E outcomes, at longest follow-up available, reported by those meta-analyses published after the NOBLE and EXCEL trials. Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses.

Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

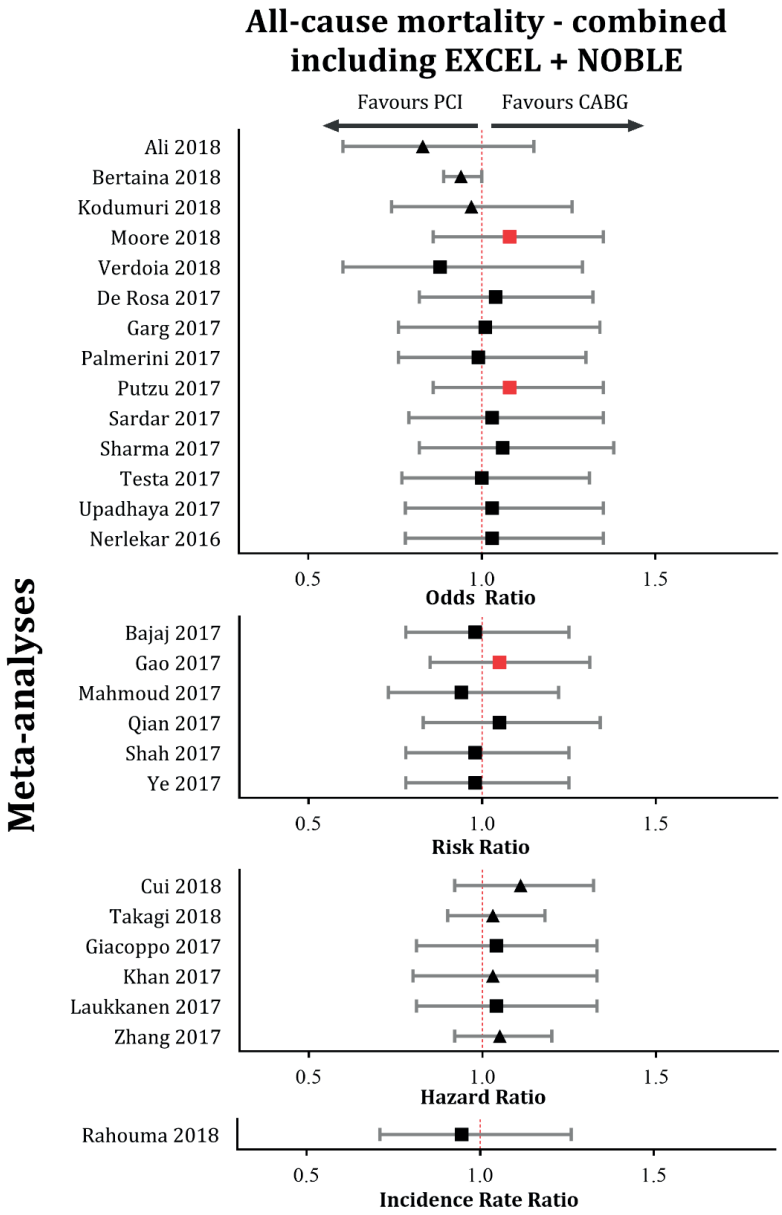

Figure 4. Forest plot representation of all-cause mortality outcomes, at longest follow-up available, reported by those meta-analyses published after the NOBLE and EXCEL trials. Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses.

Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

Meta-analyses that included the same RCTs (SYNTAX, Boudriot *et al.*, PRECOMBAT, EXCEL, NOBLE with/without LE MANS) reported varying sample sizes, ranging from 4594 to 4700 patients, while the overall intention-to-treat population consists of 4595 patients (5 RCTs) and 4700 (5 RCTs plus LE MANS, respectively) (Table 1). Eleven meta-analyses reported MAC(C)E risk estimates at combined long-term follow-up varying from 0.99 (95%CI: 0.70-1.40) to 1.36 (95%CI: 1.18-1.58), although the composite of MAC(C)E differed among trials. MAC(C)E-specific definitions used by the various trials are reported in the Supplementary Appendix (Table S2). Ten meta-analyses reported risk estimates of all-cause mortality at combined long-term follow-up, varying from 0.94 (95%CI: 0.73-1.22) to 1.06 (95%CI:0.82-1.38). Two meta-analyses that also included observational data reported similar outcomes as compared studies only including RCTs.[51, 54]

Published meta-analyses over the past decade

Since 2009, 41 meta-analyses reported MAC(C)E outcomes (Table S1). Of those, 33 reported outcomes at combined long-term follow-up (Figure S1) and 22 reported outcomes at 1-year (Table 1, Figure S2). All-cause mortality, at combined long-term follow-up, was reported by 38 meta-analyses (Table S1, Figure S3). Twenty-seven studies reported all-cause mortality at 1-year (Figure S4). Meta-analyses that only included RCTs reported similar all-cause death outcomes compared with those including also observational data.

DISCUSSION

Fifty-one meta-analyses covering the exact same topic were identified, and of these, 33 emerged over the past three years after the publications of the randomized EXCEL and NOBLE trials. Sixteen meta-analyses were published from 2009 to 2013 and this number more than doubled (n=35) from 2014 to 2018. While this study did not perform a meta-analysis of meta-analyses and had no intention on determining the preferred revascularisation strategy for LMCAD, it systematically reviewed the abundancy of meta-analyses on PCI versus CABG in LMCAD over the past decade. Interestingly, the reported outcomes differed between meta-analyses due to several methodological reasons. Although meta-analyses (should) aim to present the highest level of evidence, there are multiple shortcomings which are summarized below.[9, 62, 63]

There were methodological limitations in the design of many meta-analyses. The reported sample-sizes varied without explanation. Several studies combined the in-

tention-to-treat populations with as-treated populations. Many (n=38) meta-analyses report all-cause mortality at long-term follow-up, while the duration of follow-up differed significantly between trials. The SYNTAX trial for instance, reported 5-year follow-up, while EXCEL reported 3-year follow-up. Inclusion of studies with different follow-up durations could result in an under- or overestimation of the outcome, as it is well known that risk differences of MI and repeat revascularisation diverge over time, favoring CABG.[2, 7, 8, 64, 65] This is most evident in the landmark analysis of the EXCEL trial for the composite endpoint of death, stroke or MI: 0-30 days (HR: 0.61 (95% CI: 0.42-0.88)) versus >30 days -3 year (HR: 1.44 (95% CI: 1.06-1.96)).[7, 66]

Additionally, the statistical models used in the meta-analyses differed. Besides reporting various effect-measures, meta-analyses either used a random-effect or a fixed-effect model. A fixed-effect model assumes that the treatment-effect is similar across studies, while a random-effect model accounts for differences in treatment effect, study populations or follow-up length.[67] Some of the meta-analyses that included SYNTAX, Boudriot *et al.*, PRECOMBAT, EXCEL and NOBLE used a random-effect model while others used a fixed-effect model. Moreover, meta-analyses that included observational studies, with substantial variations in follow-up time and patients baseline characteristics, used a fixed-effect model.

Finally, composite outcomes with different definitions were pooled. The definitions of MAC(C)E differed among SYNTAX[65], EXCEL[7], and NOBLE (Table S2)[8], but some meta-analyses did not take into account these differences in the composite endpoints. This, however, is crucial information for both patient and physicians when deciding on the preferred treatment.

To diminish the overlap in future meta-analyses, it is recommended to register the rationale and protocol of a new meta-analysis at an online registration platform.[68] Finally, a preferable alternative for performing a meta-analysis is to conduct an individual patient data pooled analysis.[69, 70] Pooling individual patient data overcomes the different methods of reporting and analyzing data by individual studies. It has the advantage to use all available raw patients characteristics, account for missing variables, use accurate follow-up data and a standardized statistical method for analysis.[69]

CONCLUSION

The present study identified 51 meta-analyses covering the exact same topic of PCI versus CABG revascularisation in patients with LMCAD. With the publications of longer-term follow-up of the SYNTAX and EXCEL trials, one could anticipate another surge of meta-analyses. To ensure high quality studies and reduce overlapping publications, we call on all authors, editors and reviewers to critically appraise the evidence already available and use online meta-analyses registration platforms to avoid potential overlap. Collaborating and focusing research capacities, by conducting individual patient data pooled analyses could enable us to work more efficiently and ensure reporting the highest quality of available evidence.

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CONFLICT OF INTEREST

Dr. Kappetein and dr. Head report to work as employees of Medtronic, outside the submitted work. All other authors declare no competing interests relevant to this publication.

REFERENCES

1. Evidence-Based Medicine Working G. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992;**268**:2420-5.
2. Morice MC, Serruys PW, Kappetein AP. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. Circulation 2014;**129**:2388-94.
3. Buszman PE, Buszman PP, Kiesz RS. Early and long-term results of unprotected left main coronary artery stenting: the LE MANS (Left Main Coronary Artery Stenting) registry. J Am Coll Cardiol 2009;**54**:1500-11.
4. Ahn JM, Roh JH, Kim YH. Randomized Trial of Stents Versus Bypass Surgery for Left Main Coronary Artery Disease: 5-Year Outcomes of the PRECOMBAT Study. J Am Coll Cardiol 2015;**65**:2198-206.
5. Boudriot E, Thiele H, Walther T. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol 2011;**57**:538-45.
6. Park S-J, Ahn J-M, Kim Y-H. Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease. New England Journal of Medicine 2015;**372**:1204-1212.
7. Stone GW, Sabik JF, Serruys PW. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. N Engl J Med 2016;**375**:2223-2235.
8. Makikallio T, Holm NR, Lindsay M. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. Lancet 2016;**388**:2743-2752.
9. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. BMJ 2013;**347**:f4501.
10. Moher D, Liberati A, Tetzlaff J. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med 2009;**3**:e123-30.
11. Naik H, White AJ, Chakravarty T. A Meta-Analysis of 3,773 Patients Treated With Percutaneous Coronary Intervention or Surgery for Unprotected Left Main Coronary Artery Stenosis. JACC Cardiovasc Interventions 2009;**2**:739-747.
12. Takagi H, Kawai N, Umemoto T. Stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: A meta-analysis of comparative studies. J Thorac Cardiovasc Surg 2009;**137**:e54-e57.
13. Lee MS, Yang T, Dhoot J. Meta-Analysis of Clinical Studies Comparing Coronary Artery Bypass Grafting With Percutaneous Coronary Intervention and Drug-Eluting Stents in Patients With Unprotected Left Main Coronary Artery Narrowings. Am J Cardiol 2010;**105**:1070-1075.
14. Takagi H, Matsui M, Umemoto T. Increased late mortality with percutaneous stenting for unprotected left main coronary artery stenosis relative to coronary artery bypass grafting: A meta-analysis of observational studies. J Thorac Cardiovasc Surg 2010;**139**:1351-1353.
15. Capodanno D, Stone GW, Morice MC. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol 2011;**58**:1426-32.

16. Zheng S, Zheng Z, Hou J. Comparison between drug-eluting stents and coronary artery bypass grafting for unprotected left main coronary artery disease: A meta-analysis of two randomized trials and thirteen observational studies. Cardiology 2011;**118**:22-32.
17. Jang JS, Choi KN, Jin HY. Meta-analysis of three randomized trials and nine observational studies comparing drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery disease. Am J Cardiol 2012;**110**:1411-1418.
18. Jiang WB, Zhao W, Huang H. Meta-analysis of effectiveness of first-generation drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary disease. Am J Cardiol 2012;**110**:1764-1772.
19. Kajimoto K, Miyauchi K, Yamamoto T. Meta-analysis of randomized controlled trials on the treatment of unprotected left main coronary artery disease: One-year outcomes with coronary artery bypass grafting versus percutaneous coronary artery intervention with drug-eluting stent. J Card Surg 2012;**27**:152-157.
20. Alam M, Huang HD, Shahzad SA. Percutaneous coronary intervention vs. coronary artery bypass graft surgery for unprotected left main coronary artery disease in the drug-eluting stents era - An aggregate data meta-analysis of 11,148 patients. Circ J 2013;**77**:372-382.
21. Athappan G, Patvardhan E, Tuzcu ME. Left main coronary artery stenosis: A meta-analysis of drug-eluting stents versus coronary artery bypass grafting. JACC Cardiovasc Interventions 2013;**6**:1219-1230.
22. Bittl JA, He Y, Jacobs AK. Bayesian Methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. Circulation 2013;**127**:2177-2185.
23. Cao C, Manganas C, Bannon P. Drug-eluting stents versus coronary artery bypass graft surgery in left main coronary artery disease: A meta-analysis of early outcomes from randomized and nonrandomized studies. J Thorac Cardiovasc Surg 2013;**145**:738-747.
24. Desch S, Boudriot E, Rastan A. Bypass surgery versus percutaneous coronary intervention for the treatment of unprotected left main disease: A meta-analysis of randomized controlled trials. Herz 2013;**38**:48-56.
25. Li Q, Zhang Z, Yin RX. Drug-eluting stents or coronary artery bypass grafting for unprotected left main coronary artery disease: a meta-analysis of four randomized trials and seventeen observational studies Review. Trials 2013;**14**:133.
26. Sá MP, Soares AM, Lustosa PC. Meta-analysis of 5,674 patients treated with percutaneous coronary intervention and drug-eluting stents or coronary artery bypass graft surgery for unprotected left main coronary artery stenosis. Eur J Cardiothorac Surg 2013;**43**:73-80.
27. Al Ali J, Franck C, Filion KB. Coronary artery bypass graft surgery versus percutaneous coronary intervention with first-generation drug-eluting stents: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv 2014;**7**:497-506.
28. Benedetto U, Ng C, Smith R. Coronary artery bypass grafting is superior to first-generation drug-eluting stents for unprotected left main coronary artery disease: An updated meta-analysis of 4 randomized, controlled trials. J Thorac Cardiovasc Surg 2014;**148**:2430-2432.
29. Nerlekar N, Ha FJ, Verma KP. Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interventions 2016;**9**.

30. Bajaj NS, Patel N, Kalra R. Percutaneous coronary intervention vs. coronary artery bypass grafting for left main revascularization: An updated meta-analysis. Eur Heart J Qual Care Clin Outcomes 2017;**3**:173-182.
31. Chang YS, Wang JX, Chang DW. Outcomes of Coronary Artery Bypass and Stents for Unprotected Left Main Coronary Stenosis. Ann Thorac Surg 2017;**104**:630-637.
32. De Rosa S, Polimeni A, Sabatino J. Long-term outcomes of coronary artery bypass grafting versus stent-PCI for unprotected left main disease: a meta-analysis Review. BMC Cardiovasc Disord 2017;**17**:240.
33. Gao L, Liu Y, Sun Z. Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass graft surgery in left main coronary artery disease an updated meta-analysis of randomized clinical trials. Oncotarget 2017;**8**:66449-66457.
34. Garg A, Rao SV, Agrawal S. Meta-Analysis of Randomized Controlled Trials of Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease. Am J Cardiol 2017;**119**:1942-1948.
35. Giacoppo D, Colleran R, Cassese S. Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients With Left Main Coronary Artery Stenosis: A Systematic Review and Meta-analysis. JAMA Cardiol 2017;**2**:1079-1088.
36. Khan AR, Golwala H, Tripathi A. Meta-analysis of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease. Am J Cardiol 2017;**119**:1949-1956.
37. Khan MR, Kayani WT, Ahmad W. Meta-Analysis of Comparison of 5-Year Outcomes of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients With Unprotected Left Main Coronary Artery in the Era of Drug-eluting Stents. Am J Cardiol 2017;**120**:1514-1520.
38. Laukkanen JA, Kunutsor SK, Niemela M. All-cause mortality and major cardiovascular outcomes comparing percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: a meta-analysis of short-term and long-term randomised trials. Open Heart 2017;**4**:e000638.
39. Mahmoud AN, Elgendy IY, Mentias A. Percutaneous coronary intervention or coronary artery bypass grafting for unprotected left main coronary artery disease. Catheter Cardiovasc Interventions 2017;**90**:541-552.
40. Palmerini T, Serruys P, Kappetein AP. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: A meta-analysis of 6 randomized trials and 4,686 patients. Am Heart J 2017;**190**:54-63.
41. Putzu A, Gallo M, Martino EA. Coronary artery bypass graft surgery versus percutaneous coronary intervention with drug-eluting stents for left main coronary artery disease: A meta-analysis of randomized trials. Int J Cardiol 2017;**241**:142-148.
42. Qian C, Feng H, Cao J. Meta-Analysis of Randomized Control Trials Comparing Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Significant Left Main Coronary Narrowing. Am J Cardiol 2017;**119**:1338-1343.
43. Sá MPBO, Soares AF, Miranda RGA. CABG Surgery Remains the best Option for Patients with Left Main Coronary Disease in Comparison with PCI-DES: Meta-Analysis of Randomized Controlled Trials. Braz J Cardiovasc Surg 2017;**32**:408-416.

44. Sardar P, Giri J, Elmariah S. Meta-Analysis of Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Coronary Narrowing. Am J Cardiol 2017;**119**:1746-1752.
45. Shah R, Morsy MS, Weiman DS. Meta-Analysis Comparing Coronary Artery Bypass Grafting to Drug-Eluting Stents and to Medical Therapy Alone for Left Main Coronary Artery Disease. Am J Cardiol 2017;**120**:63-68.
46. Sharma SP, Dahal K, Khatra J. Percutaneous coronary intervention vs coronary artery bypass grafting for left main coronary artery disease? A systematic review and meta-analysis of randomized controlled trials. Cardiovasc Ther 2017;**35**.
47. Spinthakis N, Farag M, Gorog DA. Percutaneous coronary intervention with drug-eluting stent versus coronary artery bypass grafting: A meta-analysis of patients with left main coronary artery disease. Int J Cardiol 2017;**249**:101-106.
48. Testa L, Latib A, Bollati M. Unprotected left main revascularization: Percutaneous coronary intervention versus coronary artery bypass. An updated systematic review and meta-analysis of randomised controlled trials. PLoS ONE 2017;**12**.
49. Upadhaya S, Baniya R, Madala S. Drug-eluting stent placement versus coronary artery bypass surgery for unprotected left main coronary artery disease: A meta-analysis of randomized controlled trials. J Card Surg 2017;**32**:70-79.
50. Ye Y, Yang M, Zhang S. Percutaneous coronary intervention versus cardiac bypass surgery for left main coronary artery disease: A trial sequential analysis. Medicine (Baltimore) 2017;**96**:e8115.
51. Zhang XL, Zhu QQ, Yang JJ. Percutaneous intervention versus coronary artery bypass graft surgery in left main coronary artery stenosis: a systematic review and meta-analysis Review. BMC Med 2017;**15**:84.
52. Ali WE, Vaidya SR, Ejeh SU. Meta-analysis study comparing percutaneous coronary intervention/drug eluting stent versus coronary artery bypass surgery of unprotected left main coronary artery disease: Clinical outcomes during short-term versus long-term (> 1 year) follow-up. Medicine (Baltimore) 2018;**97**:e9909.
53. Benedetto U, Taggart DP, Sousa-Uva M. New-generation stents compared with coronary bypass surgery for unprotected left main disease: A word of caution. J Thorac Cardiovasc Surg 2018;**155**:2013-2019.e2016.
54. Bertaina M, De Filippo O, Iannaccone M. Percutaneous coronary intervention or coronary artery bypass graft in left main coronary artery disease: a comprehensive meta-analysis of adjusted observational studies and randomized controlled trials. J Cardiovasc Med (Hagerstown) 2018;**19**:554-563.
55. Cui KY, Lyu SZ, Song XT. Long term outcomes of drug-eluting stent versus coronary artery bypass grafting for left main coronary artery disease: A meta-analysis. J Geriatr Cardiol 2018;**15**:162-172.
56. Khan SU, Rahman H, Arshad A. Percutaneous Coronary Intervention Versus Surgery in Left Main Stenosis–A Meta-Analysis and Systematic Review of Randomised Controlled Trials. Heart Lung Circul 2018;**27**:138-146.
57. Kodumuri V, Balasubramanian S, Vij A. A Meta-Analysis Comparing Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Disease. Am J Cardiol 2018;**121**:924-933.

58. Moore P, Burrage M, Garrahy P. Drug-Eluting Stents Versus Coronary Artery Bypass Grafts for Left Main Coronary Disease: A Meta-Analysis and Review of Randomised Controlled Trials. Heart Lung Circul 2018;**27**:1437-1445.
59. Rahouma M, Abouarab A, Di Franco A. Percutaneous coronary intervention versus coronary bypass surgery for unprotected left main disease: a meta-analysis of randomized controlled trials. Ann. cardiothorac. surg. 2018;**7**:454-462.
60. Takagi H, Ando T, Umemoto T. Drug-eluting stents versus coronary artery bypass grafting for left-main coronary artery disease. Catheter Cardiovasc Interventions 2018;**91**:697-709.
61. Verdoia M, Barbieri L, Kedhi E. Percutaneous Versus Surgical Revascularization for Left Main or Multivessel Coronary Artery Disease: Results From a Large-Scale Meta-Analysis in the Era of Drug-Eluting Stents. Angiology 2018;**69**:812-824.
62. Higgins J, Thompson S, Deeks J. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. J Health Serv Res Policy 2002;**7**:51-61.
63. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. Milbank Q 2016;**94**:485-514.
64. Mohr FW, Morice MC, Kappetein AP. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;**381**:629-38.
65. Serruys P, Morice M, Kappetein A. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;**360**:961-72.
66. Ruel M, Falk V, Farkouh ME. Myocardial Revascularization Trials. Circulation 2018;**138**:2943-2951.
67. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;**342**:d549.
68. *PROSPERO*. https://www.crd.york.ac.uk/PROSPERO/.
69. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;**340**:c221.
70. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. Eur Heart J 2014;**35**:3336-45.

SUPPLEMENTARY MATERIALS

Detailed description of the used search terms

The following search terms was used in the **Embase database**: "('percutaneous coronary intervention'/exp OR 'stent'/exp OR 'coronary stenting'/exp OR ((percutan* NEAR/6 (interven* OR approach* OR revascul*)) OR stent* OR pci):ab,ti) AND ('coronary artery bypass graft'/exp OR 'coronary artery bypass surgery'/de OR 'bypass surgery'/de OR 'coronary artery surgery'/de OR 'off pump coronary surgery'/de OR 'heart muscle revascularisation'/de OR (revascularisation/de AND surgery/de) OR (bypass* OR shunt* OR graft* OR cabg OR (revascular* NEAR/3 (surg* OR myocard* OR muscl*))):ab,ti) AND ('left coronary artery'/de OR ((left NEAR/3 (coronar* OR main*)) OR lmca OR ulcma):ab,ti) AND ('meta analysis'/exp OR 'meta analysis (topic)'/de OR 'systematic review'/de OR 'systematic review (topic)'/de OR (((meta OR pooled) NEAR/3 analys*) OR metaanalys* OR (systematic* NEAR/3 review*)):ab,ti)".

The search term for the **Medline Ovid database** was as follows: "(exp Percutaneous Coronary Intervention/ OR exp Stents/ OR ((percutan* ADJ6 (interven* OR approach* OR revascul*)) OR stent* OR pci).ab,ti.) AND (exp Coronary Artery Bypass/ OR Myocardial Revascularization/ OR (bypass* OR shunt* OR graft* OR cabg OR (revascular* ADJ3 (surg* OR myocard* OR muscl*))).ab,ti.) AND (((left ADJ3 (coronar* OR main*)) OR lmca OR ulcma).ab,ti.) AND (Meta-Analysis as Topic/ OR Meta-Analysis / OR (((meta OR pooled) ADJ3 analys*) OR metaanalys* OR (systematic* ADJ3 review*)).ab,ti.)".

Finally, the following search term was used for the **Cochrane database**: "(((percutan* NEAR/6 (interven* OR approach* OR revascul*)) OR stent* OR pci):ab,ti) AND ((bypass* OR shunt* OR graft* OR cabg OR (revascular* NEAR/3 (surg* OR myocard* OR muscl*))):ab,ti) AND (((left NEAR/3 (coronar* OR main*)) OR lmca OR ulcma):ab,ti)

SUPPLEMENTAL TABLE

Table S1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51).

						Follow up duration					
Year	Author	Journal	Total patients (n)	PCI (N)	CABG (N)	≤30d	1y	3y	≥5y	Combined	MAC(C)E†
2018	Ali *et al.*[1]	Medicine (Baltimore)	21832	10424	11408	X	-	-	-	X	Stroke, death, MI or revascularisation
2018	Benedetto *et al.*[2]	J Thorac Cardiovasc Surg	4654	*	*	-	-	-	-	X	Death, MI or stroke
2018	Bertaina *et al.*[3]	J Cardiovasc Med (Hagerstown)	19314	8501	10813	-	-	-	-	X	Death, MI, definite or probable ST, TVR
2018	Cui *et al.*[4]	J Geriatr Cardiol	14130	6333	7797	-	-	-	-	X	Death, MI or stroke
2018	Khan *et al.*[5]	Heart Lung Circul	4700	2349	2351	X	X	-	X	-	MI, stroke, death or TVR
2018	Kodumuri *et al.*[6]	Am J Cardiol	10284	5017	5267	-	-	-	-	X	Death, MI, stroke or RR
2018	Moore *et al.*[7]	Heart Lung Circul	4404	2197	2197	-	-	-	-	X	Death, MI or CVA
2018	Rahouma *et al.*[8]	Ann. cardiothorac. surg.	4700	2349	2351	-	-	-	-	X	Death, MI, stroke or RR
2018	Takagi *et al.*[9]	Catheter Cardiovasc Interventions	12387	6009	6378	-	-	-	-	X	Death, MI and RRV (with/ without stroke)
2018	Verdoia *et al.*[10]	Angiology	4595	2297	2298	-	-	-	-	X	Major Adverse Cardiovascular Events*
2017	Bajaj *et al.*[11]	Eur Heart J Qual Care Clin Outcomes	4700	2349	2351	-	X	-	-	X	Death, stroke, MI or RR
2017	Chang *et al.*[12]	Ann Thorac Surg	2343	*	*	X	X	-	-	X	Death, stroke, MI or TVR
2017	De Rosa *et al.*[13]	BMC Cardiovasc Disord	4499	2249	2250	-	-	-	-	X	Death, stroke, MI or RR
2017	Gao *et al.*[14]	Oncotarget	4595	2297	2298	-	X	-	-	X	Death, stroke, MI or RR
2017	Garg *et al.*[15]	Am J Cardiol	4595	2297	2298	-	-	-	-	X	*
2017	Giacoppo *et al.*[16]	JAMA Cardiol	4394	2197	2197	-	-	-	-	X	Death, stroke or MI
2017	Khan *et al.*[17]	Am J Cardiol	4700	2349	2351	-	X	-	-	X	Death, MI, stroke or RR
2017	Khan *et al.*[18]	Am J Cardiol	6637	3197	3340	-	-	-	X	-	Death, nonfatal MI, stroke or RR

Rct. (N)	Obs. (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E†		All-cause mortality	
									1 year	Combined	1 Year	Combined
5	24	X	-	X	X	X	X	OR	-	1.22 (0.95-1.56)	-	0.83 (0.60-1.15)
6	-	X	X	X	X	X	X	IRR	-	0.99 (0.70-1.40)		-
6	20	X	X	X	X	X	X	OR	-	1.10 (1.07-1.14)	-	0.94 (0.89-1.00)
4	12	X	-	-	X	X	X	HR	-	0.94 (0.86-1.03)	-	1.11 (0.92-1.32)
6	-	X	X	X	X	X	X	RR	1.15 (0.92-1.45)	-	0.67 (0.43-1.06)	-
4	8	X	-	-	X	X	X	OR	-	1.23 (1.01-1.51)	-	0.97 (0.74-1.26)
4	-	X	-	-	X	X	X	OR	-	1.37 (1.18-1.58)	-	1.08 (0.86-1.35)
6	-	X	X	X	X	X	X	IRR	-	1.328 (1.114-1.582)	-	0.947 (0.711-1.262)
5	17	X	-	X	X	X	X	HR	-	1.42 (1.28-1.58)	-	1.03 (0.90-1.18)
5	-	X	-	X	X	X	X	OR	-	1.16 (0.98-1.37)	-	0.88 (0.60-1.29)
6	-	X	X	X	X	X	X	RR	1.17 (0.94-1.44)	1.21 (1.05-1.40)	0.68 (0.44-1.06)	0.98 (0.78-1.25)
5	-	X	X	X	X	-	-	RR	1.20 (0.94-1.54)	1.25 (1.05-1.49)	0.66 (0.38-1.15)	0.81 (0.62-1.08)
5	-	X	X	-	X	X	X	OR		1.33 (1.12-1.58)		1.04 (0.82-1.32)
5	-	X	-	X	X	X	X	RR	1.15 (0.92-1.44)	1.26 (1.11-1.44)	0.70 (0.45-1.09)	1.05 (0.85-1.31)
5	-	X	-	X	X	X	X	OR	-	-	-	1.01 (0.76-1.34)
4	-	X	-	-	X	X	X	HR	-	1.06 (0.85-1.32)	-	1.04 (0.81-1.33)
6	-	X	X	X	X	X	X	HR	1.03 (0.69-1.52)	1.16 (0.95-1.43)	0.71 (0.47-1.06)	1.03 (0.80-1.33)
4	5	X	-	-	X	X	X	OR	-	-	-	-

Table S1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51). (*continued*)

						Follow up duration					
Year	Author	Journal	Total patients (n)	PCI (N)	CABG (N)	≤30d	1y	3y	≥5y	Combined	MAC(C)E†
2017	Laukkanen *et al.*[19]	Open Heart	4700	2149	2351	X	X	-	-	X	Death, MI, CVA or stroke, or TVR
2017	Mahmoud *et al.*[20]	Catheter Cardiovasc Interventions	4700	2349	2351	X	X	-	-	X	Death, MI, stroke or revascularisation
2017	Palmerini *et al.*[21]	Am Heart J	4686	2347	2339	X	-	-	-	X	Death, stroke, MI or UR
2017	Putzu *et al.*[22]	Int J Cardiol	4595	*	*	X	X	-	-	X	Death, stroke or MI*
2017	Qian *et al.*[23]	Am J Cardiol	4595	2297	2298	-	X	-	-	X	Study specific definitions of MACCE†
2017	Sá *et al.*[24]	Braz J Cardiovasc Surg	4595	2297	2298	-	X	-	-	-	Death, MI, stroke or TVR
2017	Sardar *et al.*[25]	Am J Cardiol	4612	2303	2309	-	X	-	-	X	Death, stroke,MI or any revascularisation
2017	Shah *et al.*[26]	Am J Cardiol	4700	2349	2351	-	X	X	X	X	Death, recurrent MI, RR and stroke
2017	Sharma *et al.*[27]	Cardiovasc Ther	4700	2349	2351	X	X	X	X	X	Death, MI, stroke or revascularisation
2017	Spinthakis *et al.*[28]	Int J Cardiol	4595	2297	2298	-	X	X	X	-	-
2017	Testa *et al.*[29]	PLoS ONE	4686	2347	2339	-	X	-	-	X	Death, stroke or MI
2017	Upadhaya *et al.*[30]	J Card Surg	4595	2297	2298	-	-	-	-	X	Study specific definitions of MACCE†
2017	Ye *et al.*[31]	Medicine (Baltimore)	4700	2349	2351	-	-	-	-	X	Death, MI, stroke and revascularisation
2017	Zhang *et al.*[32]	BMC Med	22487	10406	12081	-	-	-	-	X	Death, MI, stroke or RR
2016	Nerlekar *et al.*[33]	Circ Cardiovasc Interventions	4594	2297	2297	-	X	-	-	X	Death, MI, stroke, or RR
2014	Al Ali *et al.*[34]	JACC Cardiovasc Interv	1506	757	749	-	-	-	-	X	-
2014	Benedetto *et al.*[35]	J Thorac Cardiovasc Surg	1611	809	802	-	-	-	-	X	*

Rct. (N)	Obs. (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
6	-	X	X	X	X	X	X	HR	1.16 (0.94-1.44)	1.27 (1.12-1.44)	0.66 (0.42-1.04)	1.04 (0.81-1.33)
6	-	X	X	X	X	X	X	RR	1.21 (0.97-1.51)	1.19 (1.01-1.41)	0.76 (0.45-1.30)	0.94 (0.73-1.22)
6	-	X	X	X	X	X	X	OR	-	1.27 (1.12-1.45)	-	0.99 (0.76-1.30)
5	-	X	-	X	X	X	X	OR	-	-	0.69 (0.44-1.10)	1.08 (0.86-1.35)
5	-	X	-	X	X	X	X	RR	1.14 (0.91-1.42)	1.27 (1.13-1.43)	0.78 (0.56-1.08)	1.05 (0.83-1.34)
5	-	X	-	X	X	X	X	RR	1.05 (0.82-1.36)	-	1.03 (0.80-1.32)	-
5	-	X	-	X	X	X	X	OR	0.73 (0.52-1.01)	1.36 (1.18-1.57)	0.71 (0.44-1.12)	1.03 (0.79-1.35)
6	-	X	X	X	X	X	X	RR	1.15 (0.91-1.44)	1.20 (1.03-1.41)	0.68 (0.44-1.06)	0.98 (0.78-1.25)
6	-	X	X	X	X	X	X	OR	1.15 (0.88-1.51)	1.36 (1.18-1.58)	0.67 (0.43-1.06)	1.06 (0.82-1.38)
5	-	X	-	X	X	X	X	OR	-	-	0.70 (0.44-1.12)	-
6	-	X	X	X	X	X	X	OR	1.02 (0.76-1.36)	1.02 (0.76-1.38)	0.81 (0.63-1.03)	1.00 (0.77-1.31)
5	-	X	-	X	X	X	X	OR	-	1.36 (1.18-1.58)	-	1.03 (0.78-1.35)
6	-	X	X	X	X	X	X	RR	-	1.21 (1.05-1.40)	-	0.98 (0.78-1.25)
6	22	X	X	X	X	X	X	HR	-	1.42 (1.14-1.77)	-	1.05 (0.92-1.20)
5	-	X	-	X	X	X	X	OR	1.14 (0.86-1.49)	1.36 (1.18-1.58)	-	1.03 (0.78-1.35)
3	-	X	-	X	X	-	-	OR	-	-	-	1.08 (0.75-1.57)
4	-	X	X	X	X	-	-	OR	-	1.39 (1.09-1.77)	-	0.79 (0.54-1.15)

Table S1. Study characteristics and outcomes by the included meta-analyses on PCI versus CABG in LMCAD (n=51). (*continued*)

						Follow up duration					
Year	**Author**	**Journal**	**Total patients (n)**	**PCI (N)**	**CABG (N)**	**≤30d**	**1y**	**3y**	**≥5y**	**Combined**	**MAC(C)E†**
2013	Alam *et al.*[36]	Circ J	11148	4814	6334	X	X	-	X	-	Death, stroke, MI or RR
2013	Athappan *et al.*[37]	JACC Cardiovasc Interventions	14203	7055	7148	-	X	X	X	-	Death, stroke or nonfatal MI
2013	Bittl *et al.*[38]	Circulation	4574	2059	2515	-	X	X	-	-	-
2013	Cao *et al.*[39]	J Thorac Cardiovasc Surg	5628	2490	3138	X	X	-	-	X	Death, stroke, MI or RR
2013	Desch *et al.*[40]	Herz	1611	809	802	-	-	-	-	X	Death, stroke, MI or RR
2013	Li *et al.*[41]	Trials	8413	3682	4731	X	X	-	-	X	Death, MI or cerebrovascular events
2013	Sá *et al.*[42]	Eur J Cardiothorac Surg	5674	2331	3343	-	X	-	-	-	Death, stroke, MI or TVR
2012	Jang *et al.*[43]	Am J Cardiol	5079	2107	2972	-	X	-	-	-	Death, stroke, MI or TVR
2012	Jiang *et al.*[44]	Am J Cardiol	7230	2696	4534	-	-	-	-	X	Death, stroke, MI or TVR
2012	Kajimoto *et al.*[45]	J Card Surg	2601	1303	1298	-	X	-	-	-	Death, stroke, MI or TVR
2011	Capodanno *et al.*[46]	J Am Coll Cardiol	1611	809	802	-	X	-	-	-	Death, stroke, MI or TVR
2011	Zheng *et al.*[47]	Cardiology	5479	2351	3128	X	X	X	X	X	Death, stroke or MI
2010	Lee *et al.*[48]	Am J Cardiol	2905	1236	1669	-	X	-	-	-	-
2010	Takagi *et al.*[49]	J Thorac Cardiovasc Surg	2841	1198	1643	-	-	-	-	X	-
2009	Naik *et al.*[50]	JACC Cardiovasc Interventions	3773	1659	2114	-	X	X	-	-	Death, stroke or MI
2009	Takagi *et al.*[51]	J Thorac Cardiovasc Surg	2181	1006	1175	-	-	-	-	X	Death, stroke, MI or RR

Overview of characteristics reported by all included meta-analyses on PCI versus CABG in LMCAD. Meta-analyses that were published after the EXCEL and NOBLE trials are highlighted in green. Those meta-analyses that were published prior to the EXCEL and NOBLE publications are highlighted in red.
Risk estimates representing CABG versus PCI, provided by included meta-analyses, were recalculated to represent PCI versus CABG risk estimates. X = **YES** , - = **NO**. *this specific outcome was not specified in this meta-analysis. †MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. #the correct reference was missing in the original meta-analysis.
Abbreviations used: CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, PCI: percutaneous coronary intervention, LMCAD: left main coronary artery disease, RCTs: randomized controlled trials, Obs.: Observational, Ref.: reference, LA: longest available follow-up, MI; myocardial revascularisation, RR/RRV; repeat revascularisation, TVR: target vessel revascularisation, ST; stent thrombosis, OR: odds ratio, HR: hazard ratio, RR: risk ratio, IRR: incidence rate ratio, UR: unplanned revascularisation.

Rct. (N)	Obs. (N)	SYNTAX	LE MANS	Boudriot	PRECOMBAT	NOBLE	EXCEL	Risk estimates	MAC(C)E† 1 year	MAC(C)E† Combined	All-cause mortality 1 Year	All-cause mortality Combined
4	23	X	X	X	X	-	-	OR	1.22 (0.94-1.58)	1.30 (1.10-1.55)	0.69 (0.49-0.97)	0.87 (0.71-1.08)
3	21	X	-	X	X	-	-	OR	0.938 (0.659-1.337)	-	0.792 (0.528-1.193)	-
4	8	X	X	X	X	-	-	OR	-	-	1.00 (0.72-1.40)	-
3	11	X	X	X	-	-	-	RR	1.53 (1.23-1.89)	1.57 (1.29-1.89)	0.71 (0.54-0.95)	0.84 (0.70-1.02)
4	-	X	X	X	X	-	-	RR	-	-	0.34 (0.09-1.24)	0.74 (0.46-1.19)
3	17	X	-	X	X	-	-	RR	-	-	0.80 (0.63-1.02)	0.79 (0.71-0.87)
3	13	X	-	X	X	-	-	OR	1.607	-	0.691	-
3	9	X	-	X	X	-	-	OR	0.70 (0.49-1.00)	-	0.68 (0.45-1.02)	-
-	25	-	-	-	-	-	-	RR	-	1.22 (0.89-1.68)	-	0.72 (0.52-1.00)
3	-	X	-	X	X	-	-	OR	-	1.81 (1.43-2.33)	-	1.09 (0.71-1.67)
4	-	X	X	X	X	-	-	OR	1.276 (0.950-1.715)	-	0.741 (0.427-1.284)	-
2	13	X	-	X	-	-	-	OR	0.95 (0.63-1.43)		0.71 (0.50-1.03)	
2	6	X	-	X	-	-	-	OR			1,40 (0.81-2.39)	
-	7	-	-	-	-	-	-	HR				1.35 (1.04-1.75)
2	8	X	X	-	-	-	-	OR	0.84 (0.57-1.22)		1.00 (0.70-1.41)	
1	5	-	X	-	-	-	-	RR		0.68 (0.32-1.46)		0.99 (0.69-1.43)

Table S2. MAC(C)E definitions used by the six included randomized trials.

Randomized Controlled Trial	Years of inclusion	Patients randomly allocated to:		MAC(C)E definition
		PCI	CABG	
SYNTAX	2005-2007	357	348	death from any cause, stroke, myocardial infarction, or repeat revascularisation
LE MANS	1997-2008	52	53	any cause, myocardial infarction, stroke, target lesion revascularisation (TLR), or acute stent thrombosis
Boudriot *et al.*	2003-2009	100	101	death from any cause, myocardial infarction, and the need for repeat revascularisation
PRECOMBAT	2004-2009	300	300	death from any cause, myocardial infarction, stroke, and ischemia-driven target-vessel revascularisation
EXCEL	2010-2014	948	957	death, stroke, or myocardial infarction
NOBLE	2008-2015	598	603	death from any cause, non-procedural myocardial infarction, repeat revascularisation or stroke

The MAC(C)E-specific definitions of the major randomized controlled trials are reported in the current table.

SUPPLEMENTAL FIGURES

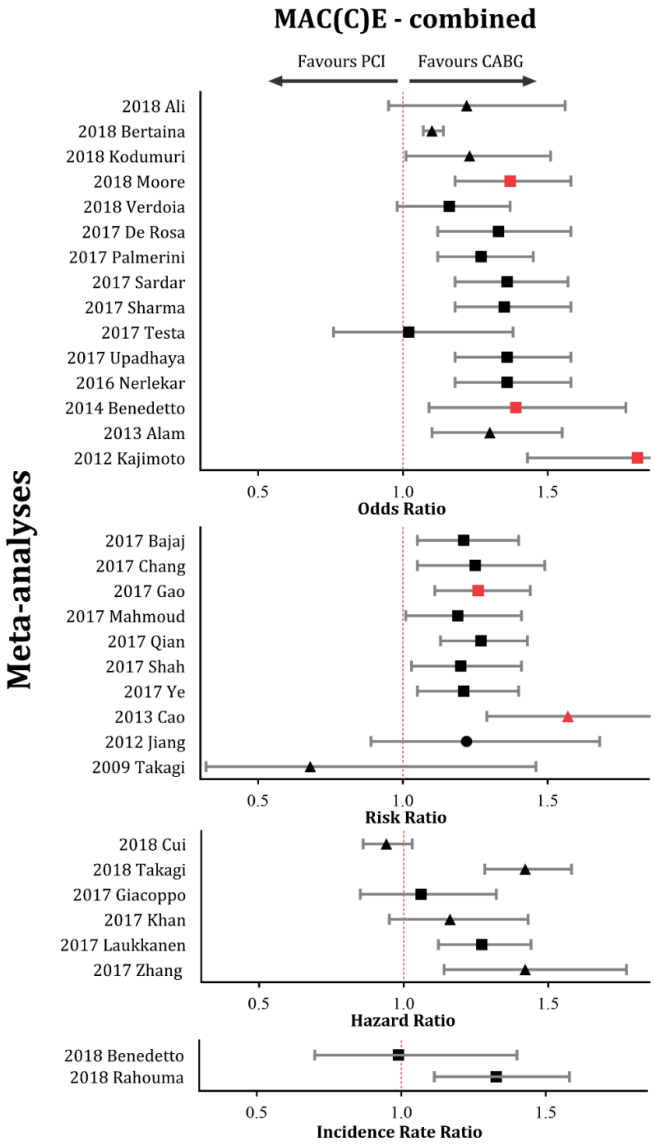

Figure S1. Forest plot representation of MAC(C)E outcomes, at longest follow-up available, reported by all included meta-analyses.
Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies, circle: only observational. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

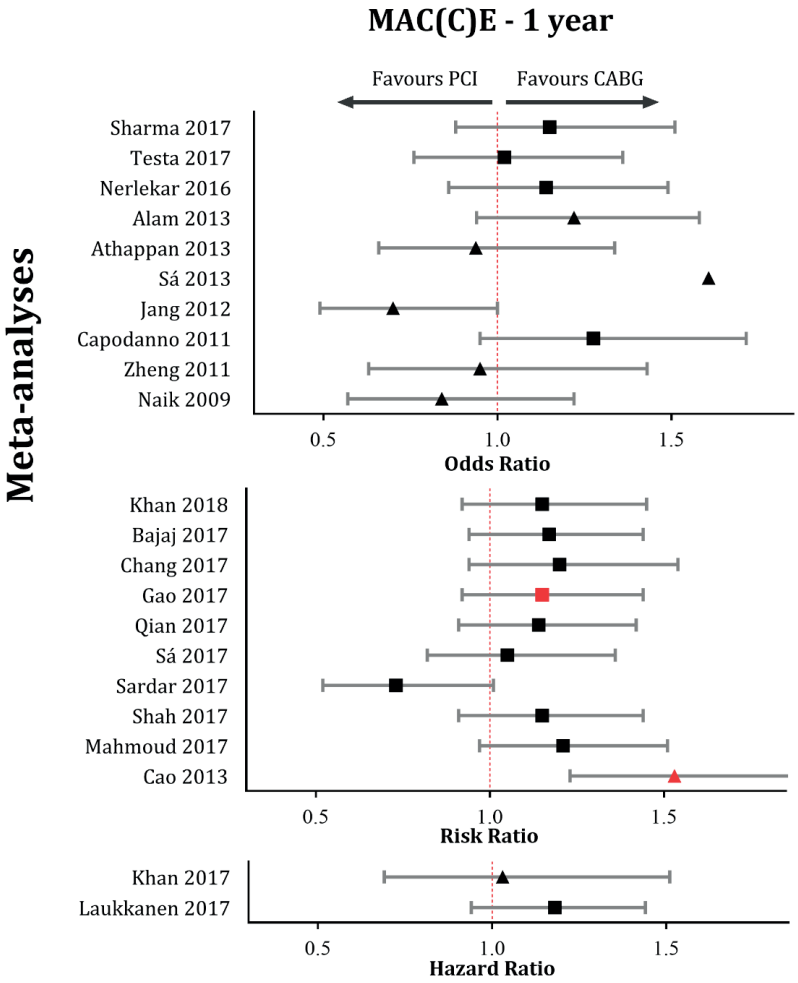

Figure S2. Supplemental Material. Forest plot representation of MAC(C)E outcomes, at 1 year, reported by all included meta-analyses.

Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses. MAC(C)E was defined according to the study-specific definition used by the included meta-analysis. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

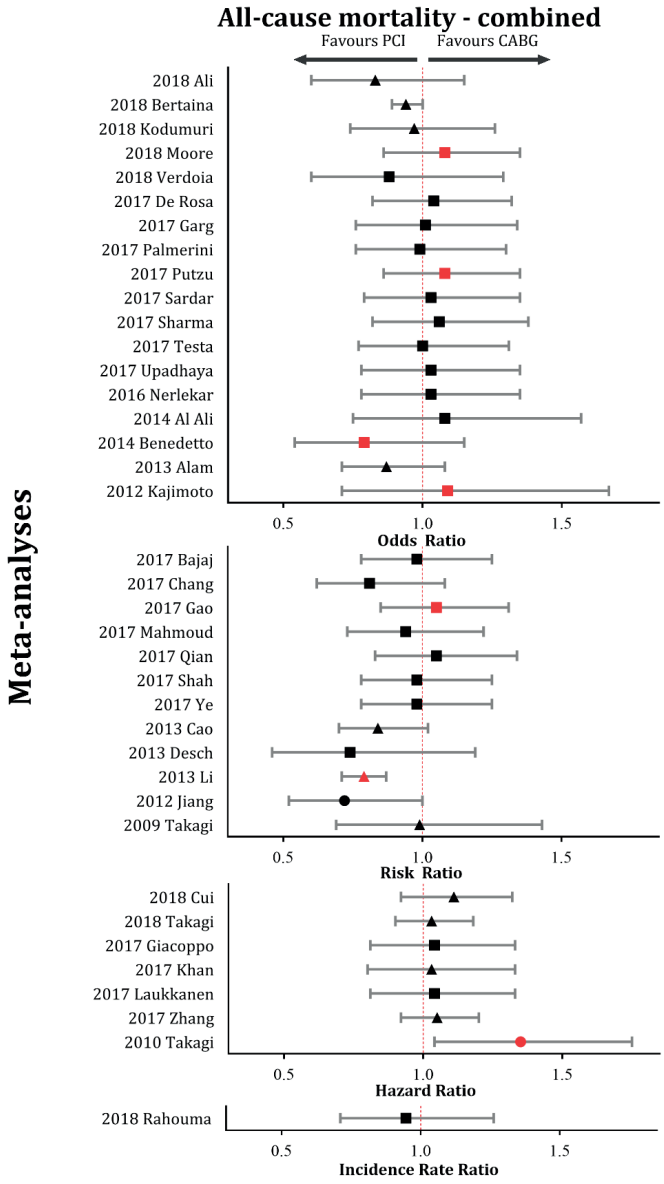

Figure S3. Forest plot representation of all-cause mortality outcomes, at combined long-term follow-up, reported by all included meta-analyses.
Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies, circle: only observational. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

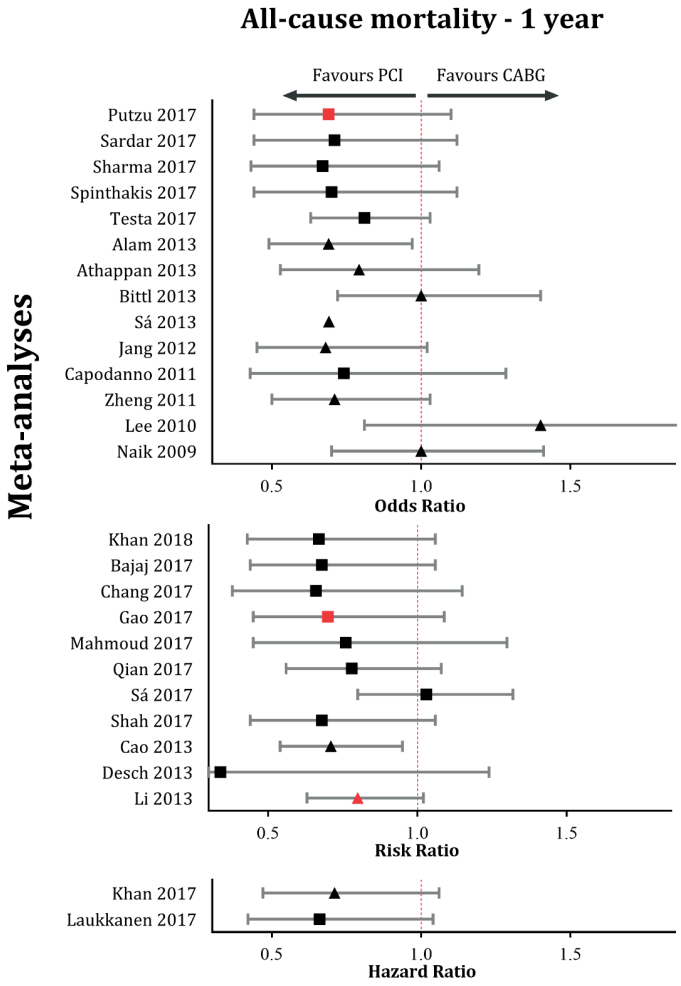

Figure S4. Supplemental Material. Forest plot representation of all-cause mortality outcomes, at 1 year, reported by all included meta-analyses.

Risk estimates represent PCI versus CABG comparisons and were categorized according to: odds, risk, hazard and incidence rate ratios. Legend of shapes used: square: only randomized controlled trials, triangle: randomized controlled trials plus observational studies. Size of a shape does not represent the study sample size nor the weight of a specific study. Black represents random-effect meta-analyses, red fixed-effect meta-analyses. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

SUPPLEMANTARY REFERENCES TABLE S1

1. Ali WE, Vaidya SR, Ejeh SU, Okoroafor KU. Meta-analysis study comparing percutaneous coronary intervention/drug eluting stent versus coronary artery bypass surgery of unprotected left main coronary artery disease: Clinical outcomes during short-term versus long-term (> 1 year) follow-up. Medicine (Baltimore) 2018;**97**(7):e9909.
2. Benedetto U, Taggart DP, Sousa-Uva M, Biondi-Zoccai G, Di Franco A, Ohmes LB, Rahouma M, Kamel M, Caputo M, Girardi LN, Angelini GD, Gaudino M. New-generation stents compared with coronary bypass surgery for unprotected left main disease: A word of caution. J Thorac Cardiovasc Surg 2018;**155**(5):2013-2019.e2016.
3. Bertaina M, De Filippo O, Iannaccone M, Colombo A, Stone G, Serruys P, Mancone M, Omede P, Conrotto F, Pennone M, Kimura T, Kawamoto H, Zoccai GB, Sheiban I, Templin C, Benedetto U, Cavalcante R, D'Amico M, Gaudino M, Moretti C, Gaita F, D'Ascenzo F. Percutaneous coronary intervention or coronary artery bypass graft in left main coronary artery disease: a comprehensive meta-analysis of adjusted observational studies and randomized controlled trials. J Cardiovasc Med (Hagerstown) 2018;**19**(10):554-563.
4. Cui KY, Lyu SZ, Song XT, Yuan F, Xu F, Zhang M, Zhang MD, Wang W, Zhang DF, Dai J, Tian JF, Wang YL. Long term outcomes of drug-eluting stent versus coronary artery bypass grafting for left main coronary artery disease: A meta-analysis. J Geriatr Cardiol 2018;**15**(2):162-172.
5. Khan SU, Rahman H, Arshad A, Khan MU, Lekkala M, Yang T, Mishra A, Kaluski E. Percutaneous Coronary Intervention Versus Surgery in Left Main Stenosis–A Meta-Analysis and Systematic Review of Randomised Controlled Trials. Heart Lung Circul 2018;**27**(2):138-146.
6. Kodumuri V, Balasubramanian S, Vij A, Siddamsetti S, Sethi A, Khalafallah R, Khosla S. A Meta-Analysis Comparing Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Disease. Am J Cardiol 2018;**121**(8):924-933.
7. Moore P, Burrage M, Garrahy P, Lim R, McCann A, Camuglia A. Drug-Eluting Stents Versus Coronary Artery Bypass Grafts for Left Main Coronary Disease: A Meta-Analysis and Review of Randomised Controlled Trials. Heart Lung Circul 2018;**27**(12):1437-1445.
8. Rahouma M, Abouarab A, Di Franco A, Leonard JR, Lau C, Kamel M, Ohmes LB, Girardi LN, Gaudino M. Percutaneous coronary intervention versus coronary bypass surgery for unprotected left main disease: a meta-analysis of randomized controlled trials. Ann. cardiothorac. surg. 2018;**7**(4):454-462.
9. Takagi H, Ando T, Umemoto T. Drug-eluting stents versus coronary artery bypass grafting for left-main coronary artery disease. Catheter Cardiovasc Interventions 2018;**91**(4):697-709.
10. Verdoia M, Barbieri L, Kedhi E, Suryapranata H, De Luca G. Percutaneous Versus Surgical Revascularization for Left Main or Multivessel Coronary Artery Disease: Results From a Large-Scale Meta-Analysis in the Era of Drug-Eluting Stents. Angiology 2018;**69**(9):812-824.
11. Bajaj NS, Patel N, Kalra R, Marogil P, Bhardwaj A, Arora G, Arora P. Percutaneous coronary intervention vs. coronary artery bypass grafting for left main revascularization: An updated meta-analysis. Eur Heart J Qual Care Clin Outcomes 2017;**3**(3):173-182.

12. Chang YS, Wang JX, Chang DW. Outcomes of Coronary Artery Bypass and Stents for Unprotected Left Main Coronary Stenosis. Ann Thorac Surg 2017;**104**(2):630-637.
13. De Rosa S, Polimeni A, Sabatino J, Indolfi C. Long-term outcomes of coronary artery bypass grafting versus stent-PCI for unprotected left main disease: a meta-analysis Review. BMC Cardiovasc Disord 2017;**17**(1):240.
14. Gao L, Liu Y, Sun Z, Wang Y, Cao F, Chen Y. Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass graft surgery in left main coronary artery disease an updated meta-analysis of randomized clinical trials. Oncotarget 2017;**8**(39):66449-66457.
15. Garg A, Rao SV, Agrawal S, Theodoropoulos K, Mennuni M, Sharma A, Garg L, Ferrante G, Meelu OA, Sargsyan D, Reimers B, Cohen M, Kostis JB, Stefanini GG. Meta-Analysis of Randomized Controlled Trials of Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease. Am J Cardiol 2017;**119**(12):1942-1948.
16. Giacoppo D, Colleran R, Cassese S, Frangieh AH, Wiebe J, Joner M, Schunkert H, Kastrati A, Byrne RA. Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients With Left Main Coronary Artery Stenosis: A Systematic Review and Meta-analysis. JAMA Cardiol 2017;**2**(10):1079-1088.
17. Khan AR, Golwala H, Tripathi A, Riaz H, Kumar A, Flaherty MP, Bhatt DL. Meta-analysis of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease. Am J Cardiol 2017;**119**(12):1949-1956.
18. Khan MR, Kayani WT, Ahmad W, Hira RS, Virani SS, Hamzeh I, Jneid H, Lakkis N, Alam M. Meta-Analysis of Comparison of 5-Year Outcomes of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients With Unprotected Left Main Coronary Artery in the Era of Drug-eluting Stents. Am J Cardiol 2017;**120**(9):1514-1520.
19. Laukkanen JA, Kunutsor SK, Niemela M, Kervinen K, Thuesen L, Makikallio TH. All-cause mortality and major cardiovascular outcomes comparing percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: a meta-analysis of short-term and long-term randomised trials. Open Heart 2017;**4**(2):e000638.
20. Mahmoud AN, Elgendy IY, Mentias A, Saad M, Ibrahim W, Mojadidi MK, Nairooz R, Eshtehardi P, David Anderson R, Samady H. Percutaneous coronary intervention or coronary artery bypass grafting for unprotected left main coronary artery disease. Catheter Cardiovasc Interventions 2017;**90**(4):541-552.
21. Palmerini T, Serruys P, Kappetein AP, Genereux P, Riva DD, Reggiani LB, Christiansen E, Holm NR, Thuesen L, Makikallio T, Morice MC, Ahn JM, Park SJ, Thiele H, Boudriot E, Sabatino M, Romanello M, Biondi-Zoccai G, Cavalcante R, Sabik JF, Stone GW. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: A meta-analysis of 6 randomized trials and 4,686 patients. Am Heart J 2017;**190**:54-63.
22. Putzu A, Gallo M, Martino EA, Ferrari E, Pedrazzini G, Moccetti T, Cassina T. Coronary artery bypass graft surgery versus percutaneous coronary intervention with drug-eluting stents for left main coronary artery disease: A meta-analysis of randomized trials. Int J Cardiol 2017;**241**:142-148.

23. Qian C, Feng H, Cao J, Wei B, Wang Y. Meta-Analysis of Randomized Control Trials Comparing Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Significant Left Main Coronary Narrowing. Am J Cardiol 2017;**119**(9):1338-1343.
24. Sá MPBO, Soares AF, Miranda RGA, Araújo ML, Menezes AM, Silva FPV, Lima RC. CABG Surgery Remains the best Option for Patients with Left Main Coronary Disease in Comparison with PCI-DES: Meta-Analysis of Randomized Controlled Trials. Brazilian journal of cardiovascular surgery 2017;**32**(5):408-416.
25. Sardar P, Giri J, Elmariah S, Chatterjee S, Kolte D, Kundu A, Nairooz R, Aronow WS, Owan T, Mukherjee D, Feldman DN, Abbott JD. Meta-Analysis of Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Coronary Narrowing. Am J Cardiol 2017;**119**(11):1746-1752.
26. Shah R, Morsy MS, Weiman DS, Vetrovec GW. Meta-Analysis Comparing Coronary Artery Bypass Grafting to Drug-Eluting Stents and to Medical Therapy Alone for Left Main Coronary Artery Disease. Am J Cardiol 2017;**120**(1):63-68.
27. Sharma SP, Dahal K, Khatra J, Rosenfeld A, Lee J. Percutaneous coronary intervention vs coronary artery bypass grafting for left main coronary artery disease? A systematic review and meta-analysis of randomized controlled trials. Cardiovasc Ther 2017;**35**(3).
28. Spinthakis N, Farag M, Gorog DA, Prasad A, Mahmood H, Gue Y, Wellsted D, Nabhan A, Srinivasan M. Percutaneous coronary intervention with drug-eluting stent versus coronary artery bypass grafting: A meta-analysis of patients with left main coronary artery disease. Int J Cardiol 2017;**249**:101-106.
29. Testa L, Latib A, Bollati M, Montone RA, Colombo A, Crea F, Bedogni F. Unprotected left main revascularization: Percutaneous coronary intervention versus coronary artery bypass. An updated systematic review and meta-analysis of randomised controlled trials. PLoS ONE 2017;**12**(6).
30. Upadhaya S, Baniya R, Madala S, Subedi SK, Khan J, Velagapudi RK, Bachuwa G. Drug-eluting stent placement versus coronary artery bypass surgery for unprotected left main coronary artery disease: A meta-analysis of randomized controlled trials. J Card Surg 2017;**32**(2):70-79.
31. Ye Y, Yang M, Zhang S, Zeng Y. Percutaneous coronary intervention versus cardiac bypass surgery for left main coronary artery disease: A trial sequential analysis. Medicine (Baltimore) 2017;**96**(41):e8115.
32. Zhang XL, Zhu QQ, Yang JJ, Chen YH, Li Y, Zhu SH, Xie J, Wang L, Kang LN, Xu B. Percutaneous intervention versus coronary artery bypass graft surgery in left main coronary artery stenosis: a systematic review and meta-analysis Review. BMC Med 2017;**15**(1):84.
33. Nerlekar N, Ha FJ, Verma KP, Bennett MR, Cameron JD, Meredith IT, Brown AJ. Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interventions 2016;**9**(12).
34. Al Ali J, Franck C, Filion KB, Eisenberg MJ. Coronary artery bypass graft surgery versus percutaneous coronary intervention with first-generation drug-eluting stents: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv 2014;**7**(5):497-506.
35. Benedetto U, Ng C, Smith R, Raja SG. Coronary artery bypass grafting is superior to first-generation drug-eluting stents for unprotected left main coronary artery disease: An updated meta-analysis of 4 randomized, controlled trials. J Thorac Cardiovasc Surg 2014;**148**(5):2430-2432.

36. Alam M, Huang HD, Shahzad SA, Kar B, Virani SS, Rogers PA, Paniagua D, Bozkurt B, Palacios I, Kleiman NS, Jneid H. Percutaneous coronary intervention vs. coronary artery bypass graft surgery for unprotected left main coronary artery disease in the drug-eluting stents era - An aggregate data meta-analysis of 11,148 patients. Circ J 2013;**77**(2):372-382.
37. Athappan G, Patvardhan E, Tuzcu ME, Ellis S, Whitlow P, Kapadia SR. Left main coronary artery stenosis: A meta-analysis of drug-eluting stents versus coronary artery bypass grafting. JACC Cardiovasc Interventions 2013;**6**(12):1219-1230.
38. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SLT. Bayesian Methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. Circulation 2013;**127**(22):2177-2185.
39. Cao C, Manganas C, Bannon P, Vallely M, Yan TD. Drug-eluting stents versus coronary artery bypass graft surgery in left main coronary artery disease: A meta-analysis of early outcomes from randomized and nonrandomized studies. J Thorac Cardiovasc Surg 2013;**145**(3):738-747.
40. Desch S, Boudriot E, Rastan A, Buszman PE, Bochenek A, Mohr FW, Schuler G, Thiele H. Bypass surgery versus percutaneous coronary intervention for the treatment of unprotected left main disease: A meta-analysis of randomized controlled trials. Herz 2013;**38**(1):48-56.
41. Li Q, Zhang Z, Yin RX. Drug-eluting stents or coronary artery bypass grafting for unprotected left main coronary artery disease: a meta-analysis of four randomized trials and seventeen observational studies Review. Trials 2013;**14**:133.
42. Sá MP, Soares AM, Lustosa PC, Martins WN, Browne F, Ferraz PE, Vasconcelos FP, Lima RC. Meta-analysis of 5,674 patients treated with percutaneous coronary intervention and drug-eluting stents or coronary artery bypass graft surgery for unprotected left main coronary artery stenosis. Eur J Cardiothorac Surg 2013;**43**(1):73-80.
43. Jang JS, Choi KN, Jin HY, Seo JS, Yang TH, Kim DK, Kim DS, Urm SH, Chun JH, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Meta-analysis of three randomized trials and nine observational studies comparing drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery disease. Am J Cardiol 2012;**110**(10):1411-1418.
44. Jiang WB, Zhao W, Huang H, Li CL, Zhang JH, Wang Y, Fu GS. Meta-analysis of effectiveness of first-generation drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary disease. Am J Cardiol 2012;**110**(12):1764-1772.
45. Kajimoto K, Miyauchi K, Yamamoto T, Daida H, Amano A. Meta-analysis of randomized controlled trials on the treatment of unprotected left main coronary artery disease: One-year outcomes with coronary artery bypass grafting versus percutaneous coronary artery intervention with drug-eluting stent. J Card Surg 2012;**27**(2):152-157.
46. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol 2011;**58**(14):1426-32.
47. Zheng S, Zheng Z, Hou J, Hu S. Comparison between drug-eluting stents and coronary artery bypass grafting for unprotected left main coronary artery disease: A meta-analysis of two randomized trials and thirteen observational studies. Cardiology 2011;**118**(1):22-32.

48. Lee MS, Yang T, Dhoot J, Liao H. Meta-Analysis of Clinical Studies Comparing Coronary Artery Bypass Grafting With Percutaneous Coronary Intervention and Drug-Eluting Stents in Patients With Unprotected Left Main Coronary Artery Narrowings. Am J Cardiol 2010;**105**(8):1070-1075.
49. Takagi H, Matsui M, Umemoto T. Increased late mortality with percutaneous stenting for unprotected left main coronary artery stenosis relative to coronary artery bypass grafting: A meta-analysis of observational studies. J Thorac Cardiovasc Surg 2010;**139**(5):1351-1353.
50. Naik H, White AJ, Chakravarty T, Forrester J, Fontana G, Kar S, Shah PK, Weiss RE, Makkar R. A Meta-Analysis of 3,773 Patients Treated With Percutaneous Coronary Intervention or Surgery for Unprotected Left Main Coronary Artery Stenosis. JACC Cardiovasc Interventions 2009;**2**(8):739-747.
51. Takagi H, Kawai N, Umemoto T. Stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: A meta-analysis of comparative studies. J Thorac Cardiovasc Surg 2009;**137**(1):e54-e57.

Chapter 6

Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial

Daniel J.F.M. Thuijs, A. Pieter Kappetein, Patrick W. Serruys, Friedrich-Wilhelm Mohr, Marie-Claude Morice, Michael J. Mack, David R. Holmes Jr, Nick Curzen, Piroze Davierwala, Thilo Noack, Milan Milojevic, Keith D Dawkins, Bruno R da Costa, Peter Juni, Stuart J. Head

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ABSTRACT

Background

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial was a non-inferiority trial that compared percutaneous coronary intervention (PCI) using first-generation paclitaxel-eluting stents with coronary artery bypass grafting (CABG) in patients with de-novo three-vessel and left main coronary artery disease, and reported results up to 5 years. We now report 10-year all-cause death results.

Methods

The SYNTAX Extended Survival (SYNTAXES) study is an investigator-driven extension of follow-up of a multicentre, randomised controlled trial done in 85 hospitals across 18 North American and European countries. Patients with de-novo three-vessel and left main coronary artery disease were randomly assigned (1:1) to the PCI group or CABG group. Patients with a history of PCI or CABG, acute myocardial infarction, or an indication for concomitant cardiac surgery were excluded. The primary endpoint of the SYNTAXES study was 10-year all-cause death, which was assessed according to the intention-to-treat principle. Prespecified subgroup analyses were performed according to the presence or absence of left main coronary artery disease and diabetes, and according to coronary complexity defined by core laboratory SYNTAX score tertiles. This study is registered with ClinicalTrials.gov, NCT03417050.

Findings

From March, 2005, to April, 2007, 1800 patients were randomly assigned to the PCI (n=903) or CABG (n=897) group. Vital status information at 10 years was complete for 841 (93%) patients in the PCI group and 848 (95%) patients in the CABG group. At 10 years, 248 (28%) patients had died after PCI and 212 (24%) after CABG (hazard ratio 1-19 [95% CI 0.99-1.43], p =0.066). Among patients with three-vessel disease, 153 (28%) of 546 had died after PCI versus 114 (21%) of 549 after CABG (hazard ratio 1.42 [95% CI 1-11-1-81]), and among patients with left main coronary artery disease, 95 (27%) of357 had died after PCI versus 98 (28%) of348 after CABG (0.92 [0.69–1.22], $p_{interaction}$=0.023). There was no treatment-by-subgroup interaction with diabetes ($p_{interaction}$=0.60) and no linear trend across SYNTAX score tertiles (p_{trend}=0.20).

Interpretation

At 10 years, no significant difference existed in all-cause death between PCI using first-generation paclitaxel-eluting stents and CABG. However, CABG provided a significant survival benefit in patients with three-vessel disease, but not in patients with left main coronary artery disease.

Funding

German Foundation of Heart Research (SYNTAXES study, 5–10-year follow-up) and Boston Scientific Corporation (SYNTAX study, 0-5-year follow-up).

INTRODUCTION

Several randomised trials[1-8] have compared coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) with simple balloon angioplasty, bare metal stents, or drug-eluting stents for the treatment of multivessel or left main coronary artery disease, but no significant differences in survival were demonstrated. Results from a pooled analysis of individual patient data[9] from 11 trials and 11 518 patients suggested that all-cause death was significantly lower after CABG versus PCI at 5-year follow-up (9.2% *vs* 11.2%: hazard ratio [HR] 1.20 [95% CI 1.06–1-37], p=0.0038). However, the mean age of the patient population was 65 years, and thus the overall life expectancy of most patients exceeded this follow-up time. Longer-term follow-up beyond 5 years is required to determine the relative effectiveness of PCI versus CABG. The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial compared PCI with paclitaxel-eluting stents versus CABG in 1800 patients with de-novo three-vessel disease and left main coronary artery disease, and reported similar survival among patients in the PCI and CABG groups after 5 years of follow-up (13-9% all-cause death in the PCI group *vs* 11.4% all-cause death in the CABG group, p=0.10).[5,10,11] This study, the SYNTAX Extended Survival (SYNTAXES) study, examined all-cause death after 10 years of follow-up in patients randomly assigned to PCI or CABG in the SYNTAX trial.

Research in context

Evidence before this study

We searched PubMed for articles published in English between database inception and July 24, 2019, with the following search terms: "percutaneous coronary intervention", "stents", "coronary artery bypass grafting", and "random*". Randomised controlled trials and meta-analyses comparing percutaneous coronary intervention (PCI) using stents versus coronary artery bypass grafting (CABG) in patients with three-vessel or left main coronary artery disease were included. An individual patient data meta-analysis reported that mortality outcomes favoured CABG over PCI at 5-year follow-up in patients with multivessel disease, particularly those with diabetes and more complex coronary artery disease, whereas no significant difference was identified in patients with left main coronary artery disease. It was concluded that longer-term follow-up would be required to better define mortality differences between revascularisation strategies. In our search, we only found two randomised controlled trials reporting survival outcomes at 10 years after PCI versus CABG. In the MASS II trial, patients with multivessel disease had a 10-year all-cause death rate of 24.9% after PCI versus 25-1% after CABG (p=0.089). However, PCI was done

with bare metal stents and about 40% of patients had two-vessel disease, and no patients with left main coronary artery disease were included. In the LE MANS trial, which included only patients with left main coronary artery disease (n=105), 10-year all-cause death was 21.6% after PCI versus 30^2% after CABG (p=0.41). However, the sample size was small and only 35% of PCI procedures were performed with (first-generation) drug-eluting stents. The search did not identify studies reporting outcomes in patients with de-novo three-vessel and left main coronary artery disease randomly assigned to PCI with drug-eluting stents or CABG.

Added value of this study

The current study is the first randomised trial that reports complete 10-year data on all-cause death in patients with de-novo three-vessel and left main coronary artery disease after PCI with drug-eluting stents versus CABG. It provides important insights into the relative effectiveness of PCI versus CABG regarding the most robust and clinically relevant outcome—all-cause death. At 10 years, no significant difference was found in all-cause death between PCI using first-generation paclitaxel-eluting stents and CABG. However, CABG provided a significant survival benefit in patients with three-vessel disease, but not in patients with left main coronary artery disease. These findings can aid decision making for patients with coronary artery disease who require PCI or CABG, accounting for differences in cardiovascular risk factors, coronary lesion complexity (eg, SYNTAX score), and the presence of three-vessel or left main coronary artery disease.

Implications of all the available evidence

Patients with complex, three-vessel coronary artery disease who require revascularisation should undergo CABG as it results in significantly lower all-cause death than PCI. In selected patients with left main coronary artery disease, PCI is a suitable alternative to CABG and provides similar 10-year survival.

METHODS

Study design and patients

The SYNTAX trial (NCT00114972) was a multicentre, randomised controlled trial done in 85 hospitals across 18 North American and European countries, with the aim of assessing non-inferiority of PCI with paclitaxel- eluting stents versus CABG in patients with de-novo three-vessel disease and left main coronary artery disease for the primary endpoint of major adverse cardiac or cerebrovascular events at 1 year. The rationale, design, and 1-year primary endpoint results of the SYNTAX trial

have been published previously, as well as results at prolonged 3-year and 5-year follow-ups.[1,5,12]

The SYNTAX trial completed follow-up at 5 years and was reinitiated as the SYNTAXES study to evaluate survival up to 10 years (the protocol and CONSORT checklist are available in the appendix pp 26–58). Patients aged 21 years or older with de-novo three-vessel disease and left main coronary artery disease were enrolled with the following exclusion criteria: a history of PCI or CABG, acute myocardial infarction, or an indication for concomitant cardiac surgery (see appendix pp 56–58 for the complete list of inclusion and exclusion criteria).

The SYNTAXES study is registered at ClinicalTrials.gov as an investigator-driven extension of follow-up of the SYNTAX trial. Medical Ethical Committee approval for this study was granted at the institution of the principal investigators (Erasmus University Medical Centre, Rotterdam, Netherlands, reference: MEC-2016-716). Informed consent to obtain information on 10-year vital status was waived, and follow-up was performed in accordance with local law and regulations of each participating site and complied with the Declaration of Helsinki. Survival data were obtained by (electronic) health-care record review and national death registry checks.

Randomisation and masking

Randomisation and masking for the SYNTAXES study was the same as for the SYNTAX study. Briefly, patients who were assessed as equally suitable for CABG or PCI were randomly assigned (1:1) to one of the two treatments, as described in detail in previous publications.[1,5,12]

Procedures

Procedures were done according to local practice with the intention to accomplish complete revascularisation of any vessel at least 1.5 mm in diameter with stenosis of 50% or more, identified during pre-procedural heart team meetings.[1] CABG could be performed with or without cardiopulmonary bypass and the use of arterial grafts was strongly recommended yet not mandatory. PCI could be performed using a radial, femoral, or brachial approach. Staged PCI procedures were allowed when performed within 72 h of the initial treatment and during the same hospital stay. Every patient was prescribed life-long aspirin, and adherence to contemporaneous guideline- directed medical treatment was highly recommended.[13]

Outcomes

The prespecified primary endpoint of the SYNTAXES study was all-cause death at 10 years in patients randomly assigned to PCI with drug-eluting stents versus CABG. The secondary endpoint was all-cause death at maximum available follow-up in patients randomly assigned to PCI with drug-eluting stents versus CABG.

The left main coronary artery disease subgroup consisted of patients with any left main disease, either isolated, or in combination with single-vessel, two-vessel, or three-vessel coronary artery disease. The three-vessel disease subgroup consisted of patients with coronary artery disease involving all three vessels in the absence of left main coronary artery disease.[5,12] The anatomical complexity of coronary artery disease was graded according to the SYNTAX score during prerandomisation heart team meetings, with higher SYNTAX scores indicating more complex coronary artery disease.[14] SYNTAX scores, according to core laboratory analyses, were defined according to tertiles, with scores of 22 or lower defined as low, 23–32 as intermediate, and 33 or higher as high.[1,6] The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was used to assess operative risk. Diabetes was defined as patients requiring treatment with oral hypoglycaemic agents or insulin. Incomplete revascularisation was determined post-procedurally by correlating the revascularised lesions to those lesions identified during the preoperative heart team meeting.

Statistical analysis

The sample size of the SYNTAXES study was based on the sample size considerations for the original trial, which was powered for a non-inferiority comparison of major adverse cardiac and cerebrovascular events at 12 months between PCI and CABG (a complete description of the sample size calculation is provided in the appendix p 6).[1] Sample sizes were calculated for each of the left main coronary artery disease and three-vessel disease subgroups and overall. After allowing for an expected attrition rate of 3.5%, the overall sample size of 1800 patients (900 per group) resulted in 96% power to detect non-inferiority at a noninferiority margin of 6.6% and a one-sided a level of 5%.

All analyses were according to the intention-to-treat principle. Patients with missing follow-up data were included in the analysis and censored at the time they were lost to follow-up or at 5 years if their recruiting hospital did not participate in the 10-year follow-up. We analysed the primary endpoint of 10-year all-cause death using Kaplan-Meier curves, with a log-rank p value to test between-group differences at a two-sided a value of 0.05. We used Cox proportional hazards models to estimate HRs with 95% CIs comparing PCI with CABG. We did landmark analyses in the overall

population and in prespecified subgroups, setting the landmark point at 5 years to distinguish the results of the 5-year analysis in the SYNTAX trial from the extended follow-up in the SYNTAXES study. Landmark analyses were accompanied by a test for interaction between treatment effect and time (first 5 years versus subsequent period). We did a sensitivity analysis of the primary endpoint using a multivariable Cox model with stepwise forward selection of covariates. Prespecified subgroup analyses were done in a hierarchical manner. For the primary subgroup analysis according to the presence or absence of left main coronary artery disease, we used a prespecified Bonferroni correction, which allowed for the treatment-by-subgroup interaction to be tested at a two-sided a value of 0.025 (0.05/2) in addition to comparing the primary endpoint between PCI and CABG in the overall population. For the secondary subgroup analyses according to presence or absence of diabetes and complexity of coronary artery disease defined by ordered SYNTAX score tertiles, we used an additional Bonferroni correction, which allowed for the interaction and the trend of log HRs across ordered SYNTAX score tertiles to be tested at a two-sided a value of 0.0125 (0.05/4). As this approach allow.05, without requiring a significant test of the primary endpoint at the prespecified a level before proceeding with treatment-by- subgroup interaction tests, it mitigated the inflation of the type I error rate considerably when performing multiple subgroup analyses, but did not fully control it. Prespecified subgroup analyses of the primary endpoint by age, sex, and ordered SYNTAX score tertiles in left main coronary artery disease and three-vessel disease subgroups were considered exploratory. Additional post- hoc exploratory analyses in the left main coronary artery disease subgroup were performed according to the presence or absence of additional vessel disease (ie, isolated left main coronary artery disease, or left main coronary artery disease in combination with one-vessel, two-vessel, or three-vessel disease). All subgroup analyses were done in unadjusted and adjusted manners (the statistical analysis plan is available in the appendix pp 59–66). The secondary endpoint of all-cause death at maximum follow-up was analysed identically, including post-hoc subgroup analyses. Baseline characteristics of patients with and without availability of 10-year follow-up were compared to address the potential for attrition bias. Analyses were performed using Stata, version 15, and SPSS Statistics software, version 24.This study is registered with ClinicalTrials.gov, NCT03417050.

Role of the funding source

The funders had no role in the SYNTAXES study design, data collection, data analyses, interpretation of the data, or writing of the report. The corresponding author, and APK, MM, BRdC, PJ, and SJH, had full access to the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

From March, 2005, to April, 2007, 1800 patients were randomly assigned to undergo PCI with paclitaxel- eluting stents (n=903) or CABG (n=897: figure 1). Clinical and angiographic characteristics were well matched between groups (table 1). Further details about the procedural characteristics of the patients included in this study have been published previously[1,5] and are included in the appendix (p 8).

Information on 10-year survival was collected between March 1, 2017, and June 17, 2019. Two hospitals, which included five patients, elected not to participate in the SYNTAXES study. Information on vital status at 10-year follow-up was complete in 841 (93%) patients in the PCI group and 848 (95%) patients in the CABG group. Baseline characteristics of patients with versus without vital status at 10 years are provided in the appendix (p 9). The median duration of follow-up was 11-2 years (IQR 7.7–12.1) overall and 11-9 years (11.2–12.3) in survivors.

Table 1. Baseline clinical and angiographic characteristics

	PCI group (n=903)	CABG group (n=897)
Age, years	65.2 (9-7)	65'0 (9-8)
Sex		
Women	213 (24%)	189 (21%)
Men	690 (76%)	708 (79%)
Body-mass index, kg/m^2	28.1 (4.8)	27.9 (4-5)
Diabetes		
Requiring oral medications or insulin	231 (26%)	221 (25%)
Requiring insulin	89 (10%)	93 (10%)
Metabolic syndrome	339/737 (46%)	317/696 (46%)
Ever smoked	167 (18%)	196/890 (22%)
Previous myocardial infarction	285/893 (32%)	300/887 (34%)
Previous stroke	35/899 (4%)	43/890 (5%)
Previous transient ischaemic attack	39/901 (4%)	45/888 (5%)
Hypertension (≥130/85 mm Hg)	622 (69%)	574 (64%)
Congestive heart failure	36/898 (4%)	47/880 (5%)
Previous carotid artery disease	73 (8%)	75 (8%)
Hyperlipidaemia	705/896 (79%)	686/889 (77%)

Table 1. Baseline clinical and angiographic characteristics (*continued*)

	PCI group (n=903)	CABG group (n=897)
Angina		
Stable	514 (57%)	513 (57%)
Unstable	262 (29%)	251 (28%)
Ejection fraction <30%	12/891 (1%)	22/875 (3%)
EuroSCORE value	3.8 (2.6)	3.8 (2.7)
Parsonnet score	8.5 (7.0)	8.4 (6.8)
SYNTAX score*	28.4 (11.5)	29.1 (11.4)
Number of lesions	4-3 (1-8)	4.4(1.8)
Total occlusion	217/897 (24%)	198/897 (22%)
Bifurcation lesion	649/897 (72%)	651/890 (73%)
Three-vessel disease	546 (60%)	549 (61%)
Left main coronary artery disease, any	357 (40%)	348 (39%)
Isolated	42/357 (12%)	49/348 (14%)
Plus one-vessel disease	67/357 (19%)	71/348 (20%)
Plus two-vessel disease	112/357 (31%)	106/348 (30%)
Plus three-vessel disease	136/357 (38%)	122/348 (35%)

Data are mean (SD), n (%), or n/N (%), unless otherwise noted. Percentages might not sum to 100% as a result of rounding. Data are reported according to the intention-to-treat principle. CABG=coronary artery bypass grafting. EuroSCORE=European System for Cardiac Operative Risk Evaluation. PCI=percutaneous coronary intervention. *SYNTAX scores are reported according to core laboratory analysed data.

The primary endpoint of all-cause death at 10 years occurred in 248 (28%) of 903 patients after PCI and 212 (24%) of 897 patients after CABG (HR 1-19 [95% CI 0-99-1-43, p=0.066; figure 2A). Landmark analysis between 5-year and 10-year follow-up identified that allcause death occurred in 122 (14%) patients after PCI and in 107 (12%) patients after CABG (HR 1.17 [95% CI 0.91–1.52]; figure 2B). At maximum follow-up, PCI was associated with higher all-cause death than was CABG (303 [34%] *vs* 265 [29%], HR 1-18 [95% CI 1-00-1-39]; appendix p 15).

There was a treatment-by-subgroup interaction according to presence or absence of left main coronary artery disease ($p_{interaction}$=0.023). In the three-vessel disease subgroup, all-cause death at 10 years occurred in 153 (28%) of 546 patients after PCI compared with 114 (21%) of 549 patients after CABG (HR 1-42 [95% CI 1.11–1.81]; figure 3A). In the left main coronary artery disease subgroup, all-cause death at 10 years occurred in 95 (27%) of 357 patients after PCI versus 98 (28%) of 348 patients after CABG (HR 0.92 [95% CI 0.69–1.22]; figures 3B, 4). There was no treatment-by-subgroup interaction according to diabetes status ($p_{interation}$=0.60; figures 3C, 3D, 4) and ordered SYNTAX score tertiles (p_{trend}=0.20; figures 4, 5). Results were similar

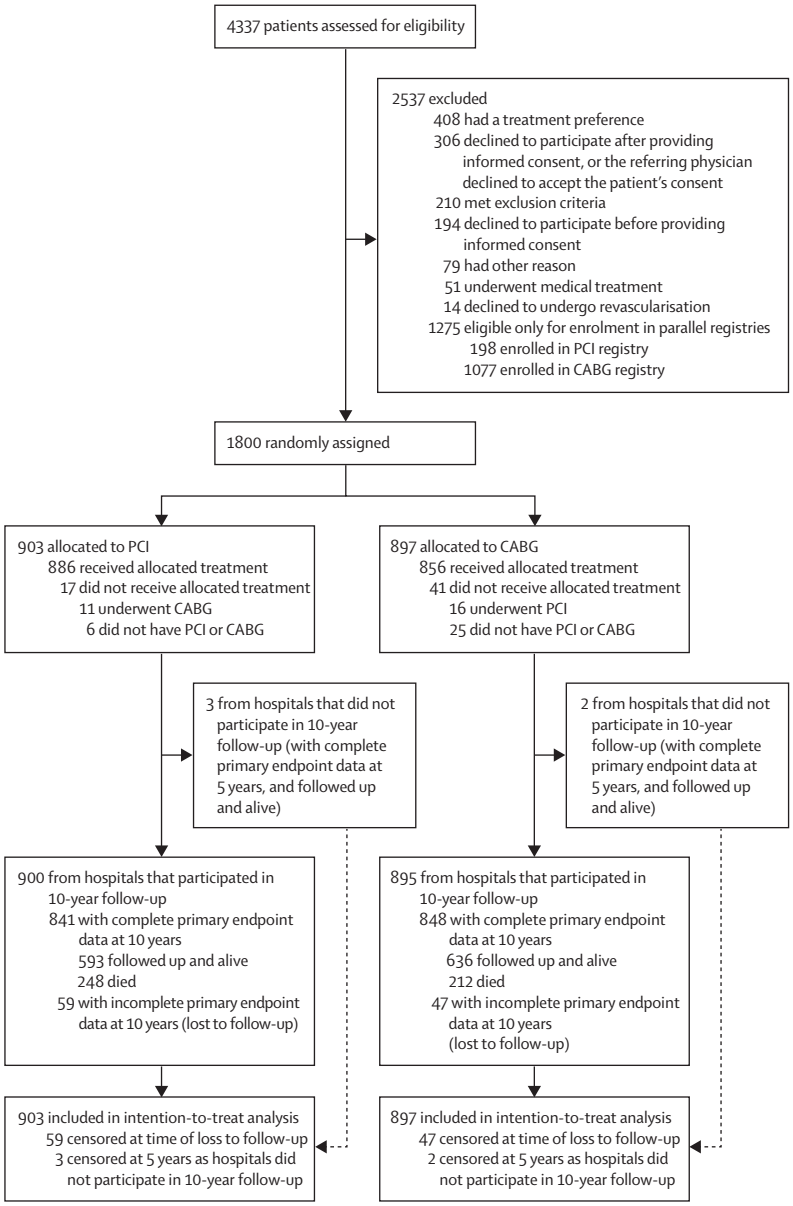

Figure 1. Trial profile Patient flow through the SYNTAX trial (0–5 years of follow-up) and the SYNTAX Extended Survival study (up to 10 years of follow-up). CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention.

in adjusted subgroup analyses at 10 years and in subgroup analyses at maximum follow-up (appendix pp 16–24). Additional exploratory analyses and the prespecified sensitivity analysis are provided in the appendix (pp 11–14, 25).

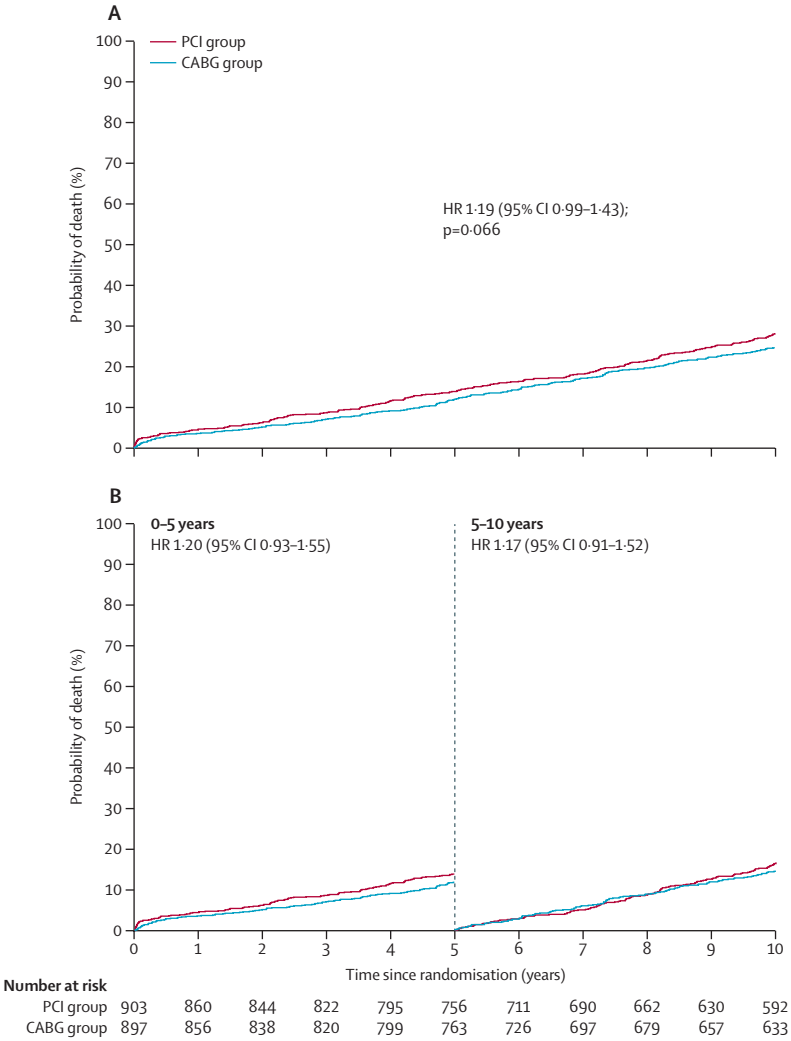

Figure 2. Kaplan-Meier curves for primary analysis of 10-year all-cause death (intention-to-treat population) The probability of all-cause death in PCI versus CABG up to 10 years of follow-up (A) and landmark analysis according to a landmark point at 5 years (B). Because the widths of 95% CIs were not adjusted for multiple comparisons in the landmark analysis, these intervals should not be used for inference about between-group differences. CABG=coronary artery bypass grafting. HR=hazard ratio. PCI=percutaneous coronary intervention.

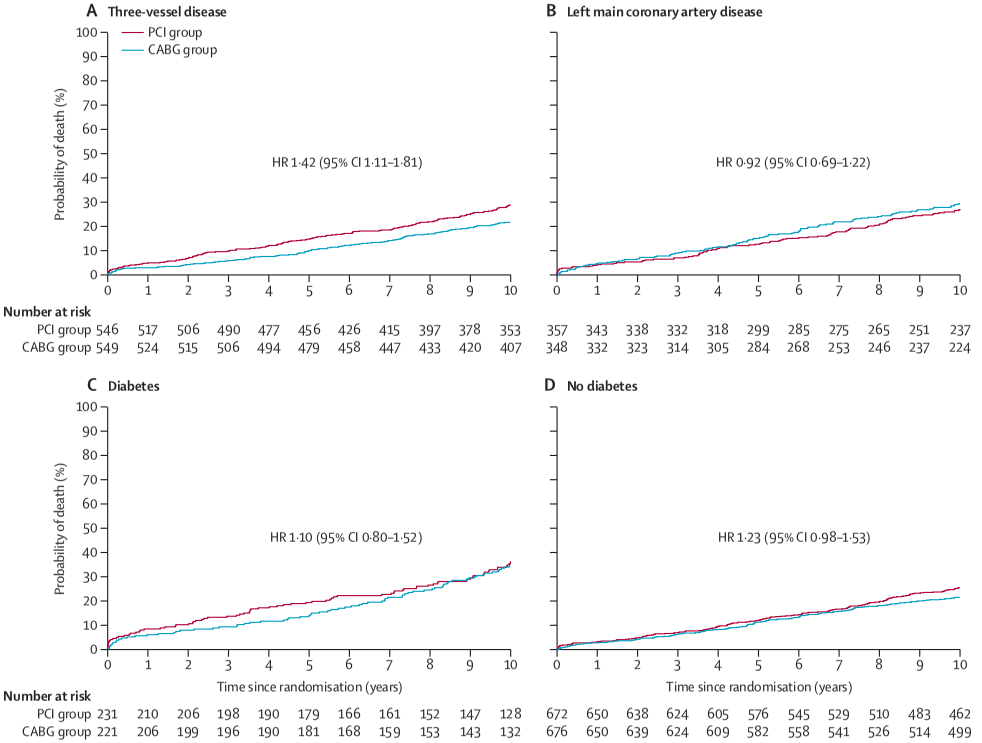

Figure 3. Kaplan-Meier curves for prespecified subgroup analysis of 10-year all-cause death (intention-to-treat population) The probability of all-cause death in PCI versus CABG up to 10 years of follow-up in prespecified subgroups of patients with three-vessel disease (A), with left main coronary artery disease (B), with diabetes (C), and without diabetes (D). p value for interaction for three-vessel disease versus left main coronary artery disease was 0-023, and p value for interaction for diabetes versus no diabetes was 0^60. Because the widths of 95% CIs were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. CABG=coronary artery bypass grafting. HR=hazard ratio. PCI=percutaneous coronary intervention.

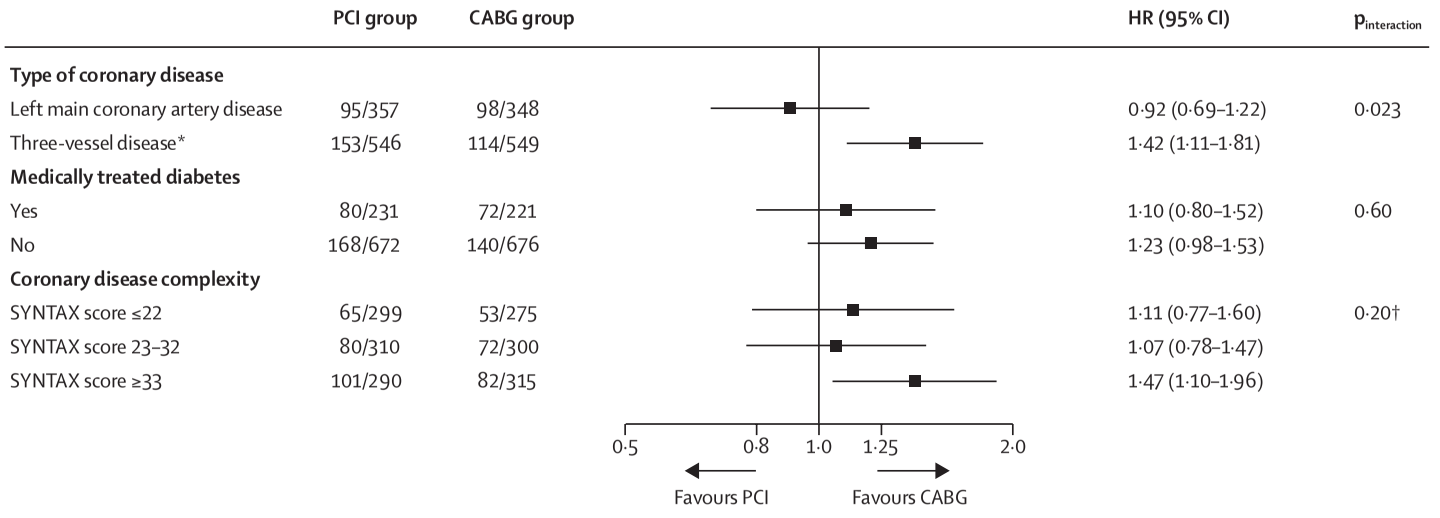

Figure 4. Forest plot of prespecified subgroup analyses of 10-year all-cause death (intention-to-treat population) All-cause death after PCI versus CABG at 10-year follow-up in prespecified unadjusted subgroup analyses according to baseline characteristics. Because the widths of 95% CIs were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. CABG=coronary artery bypass grafting. HR=hazard ratio. PCI=percutaneous coronary intervention. *Patients with coronary artery disease involving all three vessels in the absence of left main coronary artery disease. †p value for trend of log HRs across SYNTAX score tertiles for subgroup analysis according to lesion complexity.

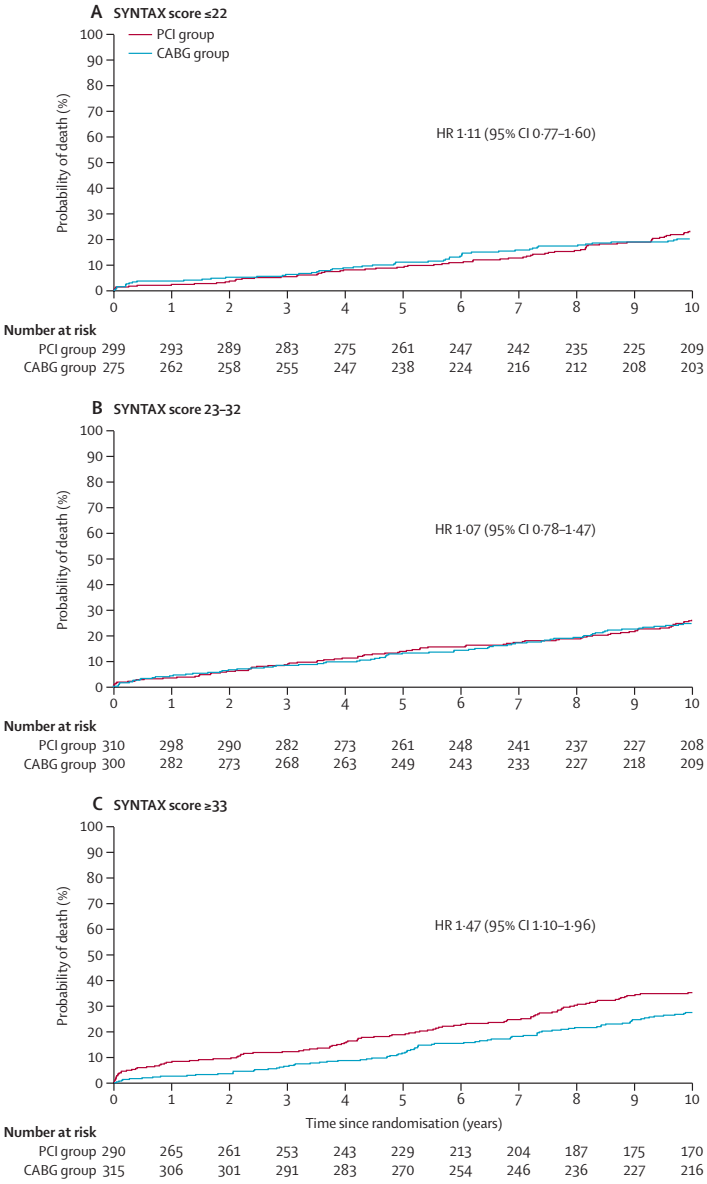

Figure 5. Kaplan-Meier curves for 10-year all-cause death in prespecified SYNTAX score tertile subgroups (intention-to-treat population) The probability of all-cause death in PCI versus CABG up to 10 years of follow-up in prespecified subgroups of patients with low SYNTAX scores (≤22; A), intermediate SYNTAX scores (23–32; B), and high SYNTAX scores (≥33; C). p value for trend was 030. SYNTAX scores were reported according to core laboratory analysed data. Because the widths of 95% CIs were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. CABG=coronary artery bypass grafting. HR=hazard ratio. PCI=percutaneous coronary intervention.

DISCUSSION

The SYNTAX trial reported similar survival in patients with de-novo three-vessel and left main coronary artery disease randomly assigned to PCI with paclitaxel-eluting stents versus CABG after 5 years of follow-up. The SYNTAXES study is the first study to assess 10-year survival after PCI with drug-eluting stents versus CABG.At 10-year follow-up, the proportions of all-cause deaths between PCI and CABG were similar. Prespecified subgroup analyses identified that CABG resulted in significantly lower all-cause death than did PCI in patients with three-vessel disease, whereas no significant difference between PCI and CABG was identified in patients with left main coronary artery disease. The current study provides unique long-term insights into survival after PCI versus CABG by extending follow-up to 10 years, which could aid in decision making in determining the optimal revascularisation strategy for patients with coronary artery disease. Moreover, the primary endpoint of all-cause death focuses on the most robust endpoint that is clinically relevant for both patients and physicians. In addition, follow-up at 10 years was complete for 94% of randomly assigned patients and equally distributed between CABG and PCI.

In the SYNTAX trial, PCI was performed with first- generation drug-eluting stents that are no longer available. Newer-generation drug-eluting stents have been shown to be associated with significantly improved mid-term (up to 3 years of follow-up) outcomes, including reduction of all-cause death.[15] Moreover, the larger adoption of fractional-flow reserve instead of solely angiography-guided interventions, in combination with the application of intravascular ultrasound, has resulted in improved outcomes after PCI.[16,17] Indeed, the SYNTAX II study[18] demonstrated that these developments were associated with significant reductions in adverse events during follow-up. Despite these improvements, most recent randomised trials have shown that CABG remained consistently associated with lower rates of repeat revascularisation at mid-term followup compared with PCI, regardless of which type of stent was used.[2,4] Longer-term follow-up of trials comparing contemporaneous PCI with CABG are therefore warranted to determine the relative effectiveness of PCI versus CABG.

According to our prespecified subgroup analyses, patients with more complex coronary disease (eg, three-vessel disease and those with higher SYNTAX scores) continued to derive a benefit of CABG over PCI beyond the 5-year follow-up. These results underscore the long-term impact of CABG over PCI that might be attributable to two factors. First, coronary bypass surgery offers the advantage of overcoming the overall burden of complex and diffuse atherosclerotic disease by constructing the anastomosis distal to diseased segments, whereas PCI only treats significant

flow-limiting lesions without protecting the distally diseased vessels. Second, CABG is associated with a higher rate of complete revascularisation than achieved with PCI.[19-21] Particularly in patients with diffuse and complex coronary disease, PCI can be technically challenging and more frequently results in incomplete revascularisation. More incomplete revascularisation is associated with an increased risk of death at 5-year follow-up, whereas minimal incomplete revascularisation is not.[22,23] In patients with low coronary disease complexity for which complete revascularisation with PCI is achievable, PCI is a suitable alternative to CABG.[24] Finally, adherence to guideline-directed medical therapy after revascularisation is important to adequately treat any progression of coronary artery disease.

The FREEDOM Follow-On study[25] found significantly fewer deaths with CABG versus PCI at a median followup of 7-5 years in patients with multivessel disease. Typically, patients with diabetes, who have more complex and progressive coronary disease, also benefit from CABG compared with PCI.[6] The current study, however, found no survival difference between PCI and CABG in patients with diabetes at 10 years. This finding could be due to chance related to the smaller sample size (n=452) as compared with the FREEDOM trial (n=1900). The length of follow-up could also have affected the difference in results of the FREEDOM study (median 7.5 years) and the current study (median 11-2 years), because in our analysis the Kaplan-Meier curves converged further with follow-up prolonging after 7–8 years. Moreover, the inclusion of patients with left main coronary artery disease in the current study could have had an effect on the relative benefit of CABG over PCI in the overall diabetic cohort. In the recent pooled analysis of PCI versus CABG randomised trials, diabetes was an effect modifier in patients with multivessel disease but not in patients with left main coronary artery disease.[9]

Results at the 5-year follow-up provided promising survival outcomes of PCI versus CABG in patients with left main coronary artery disease and was corroborated in the pooled analysis of trials.[9] It is reassuring that PCI resulted in a similar number of deaths at 10 years compared with CABG, as shown in the current analysis. The LE MANS trial[26] also reported similar survival outcomes at 10 years in patients randomly assigned to CABG or PCI with bare metal stents or first- generation drug-eluting stents, but in a smaller cohort (n=105). Similarly, the observational MAIN-COMPARE study[27] (n=2240) found no survival difference between PCI with bare metal stents or drug-eluting stents and CABG at 10-year follow-up. PCI for a focal left main lesion—ie, large in diameter with high flow—results in better stent patency and is therefore a suitable alternative to CABG in selected patients with left main coronary artery disease. Nevertheless, 56% of patients with left main coronary artery disease

who underwent PCI in the SYNTAX trial had a distal left main lesion.[28] Moreover, in the EXCEL trial,[4] 80.5% of patients had a distal lesion that involved a bifurcation or trifurcation lesion, and subgroup analyses according to the presence or absence of a distal bifurcation or trifurcation lesion found no significant interaction. These data suggest that PCI can be an alternative to CABG not only in patients with relatively non-complex left main lesions, but also in patients with more complex disease, as also demonstrated in our analyses according to SYNTAX scores. The NOBLE[3] and EXCEL[4] trials might provide important additional insights in long-term outcomes after PCI with second-generation stents versus CABG if follow-up is prolonged to 10 years.

Despite the fact that the SYNTAX score was originally intended to predict major adverse cardiac and cerebrovascular events at the 1-year follow-up,[14] the recent pooled analysis of randomised trials suggested an interaction between SYNTAX score tertiles and death, particularly in patients with multivessel disease and less so in patients with left main coronary artery disease.[9,29] In patients with left main coronary artery disease, we confirmed the absence of an association between the SYNTAX score and 10-year all-cause death. However, although in the current study the interaction test was negative, the visual interpretation of the interaction in patients with three-vessel disease indicates that patients with advanced coronary artery disease, as reflected by increasing SYNTAX scores, have a benefit with CABG over PCI. Indeed, in the subgroup of patients with three-vessel disease and a high SYNTAX score, PCI resulted in higher 10-year all-cause death than did CABG (HR 1.91 [95% CI 1.25–2.92]; appendix p 21), indicating a significant survival benefit of CABG over PCI. This hypothesis is further corroborated by the reasons for exclusion from randomisation in the SYNTAX trial; the majority of patients were referred to CABG for having very complex coronary artery disease (mean SYNTAX score was 37.8).[30]

At maximum follow-up, CABG appeared to be associated with a borderline survival benefit compared with PCI. It is important to note that the HR was similar at 10-year and maximum follow-up, but with additional deaths the statistical power was increased at maximum follow-up. The differences in survival outcomes between PCI and CABG at maximum follow-up were identified only in patients with three-vessel disease but not left main coronary artery disease, similar to the 10-year findings. Because of the limited number of patients at risk at maximum follow-up, these results should be interpreted as hypothesis-generating and could be used for sample size calculation in randomised controlled trials comparing PCI with CABG.

Additional limitations should be considered. First, the endpoint was all-cause death only. Although causes of death could have provided additional insights into mechanisms of death that could potentially be related to the revascularisation strategy, it was not feasible to collect those data.[31] Second, additional outcomes, such as myocardial infarction, stroke, stent thrombosis, and graft occlusion, were not assessed but are important to consider when choosing the most appropriate revascularisation strategy.

In conclusion, no significant differences in all-cause death emerged between PCI with first-generation paclitaxel-eluting stents and CABG at 10 years. Nonetheless, in patients with three-vessel disease, CABG provided a significant survival benefit over PCI, whereas no treatment differences were identified in patients with left main coronary artery disease. The decision to opt for PCI or CABG in patients with three-vessel disease or left main coronary artery disease should be put forward by a multidisciplinary heart team that takes into consideration the presence or absence of mortality differences in patient subgroups. In addition, the overall coronary lesion complexity (eg, SYNTAX score), and other cardiovascular risk factors of an individual patient, such as diabetes and additional comorbidities, together with a patient's preference, should be included in the discussion.

Contributors

DJFMT, APK, PWS, F-WM, M-CM, MJM, DRH, NC, PD, KDD, and SJH designed the SYNTAX trial or SYNTAXES study, enrolled patients, or collected the data. DJFMT, APK, PWS, MM, BRdC, PJ, and SJH analysed and interpreted the data. BRdC and MM were the study statisticians. The analyses were performed in twofold, with one team led by PJ and one team led by SJH and DJFMT, to ensure validity of analyses. DJFMT participated in the study design and oversaw data collection and verification. DJFMT, APK, PJ, and SJH drafted the report, which was critically reviewed by all authors. All authors approved the final version of the manuscript for submission.

Declaration of interests

APK is Chief Medical Officer, Vice President at Medtronic. PWS reports personal consultancy fees from Abbott Laboratories, Biosensors, Cardialysis, Medtronic, Micell, Sino Medical Sciences Technology, Philips/Volcano, Xeltis, and Heartflow. MJM reports non-financial support from Edwards Lifesciences, Medtronic, and Abbott, outside the submitted work. NC reports grants from Boston Scientific Corporation, Haemonetics, and HeartFlow; personal fees from Boston Scientific Corporation, Abbott, Haemonetics, and Heartflow; education grant from Volcano Phillips; and non-financial support from Haemonetics, Heartflow, Biosensors, and Edwards,

outside the submitted work. KDD is the chief medical officer of Shockwave Medical Inc and 4Tech Cardio Ireland, and is also on the Board of Directors of Avicena LLC, JenaValve Technology Inc, and InnovHeart srl, and is a senior adviser to Conformal Medical Inc. PJ reports grants from Canadian Institutes of Health Research, AstraZeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company, outside the submitted work; reports honoraria to the institution for participation in advisory boards from Amgen unrelated to the submitted work, but has not received personal payments by any pharmaceutical company or device manufacturer; serves as unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St Jude Medical, and The Medicines Company; and is a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases funded by the Canadian Institutes of Health Research. SJH is Global Clinical Evidence Director at Medtronic. All other authors declare no competing interests.

Data sharing

The SYNTAX Extended Survival study hereby declares that no data will be made available to others.

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REFERENCES

1 Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360:** 961–72.

2 Park SJ, Ahn JM, Kim YH, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med* 2015; **372:** 1204–12.

3 Makikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet* 2016; **388:** 2743–52.

4 Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med* 2016; **375:** 2223–35.

5 Mohr FW, Morice M-C, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013; 381: 629–38.

6 Sousa-Uva M, Neumann F-J, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg* 2019; **55:** 4–90.

7 Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/ AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014; **64:** 1929–49.

8 Hueb W, Lopes N, Gersh BJ, et al. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2010; **122:** 949–57.

9 Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet* 2018; **391:** 939–48.

10 Morice MC, Serruys PW, Kappetein AP, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation* 2014; **129:** 2388–94.

11 Head SJ, Davierwala PM, Serruys PW, et al. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J* 2014; **35:** 2821–30.

12 Ong AT, Serruys PW, Mohr FW, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J* 2006; **151:** 1194–204.

13 King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 Focused Update of the ACC/AHA/ SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI

2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation* 2008; **117:** 261–95.

14 Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005; **1:** 219–27.

15 Stefanini GG, Baber U, Windecker S, et al. Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. *Lancet* 2013; **382:** 1879–88.

16 Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360:** 213–24.

17 Zhang YJ, Pang S, Chen XY, et al. Comparison of intravascular ultrasound guided versus angiography guided drug eluting stent implantation: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2015; **15:** 153.

18 Serruys PW, Kogame N, Katagiri Y, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study. *EuroIntervention* 2019; **15:** e244–52.

19 Doenst T, Haverich A, Serruys P, et al. PCI and CABG for treating stable coronary artery disease: JACC review topic of the week. *J Am Coll Cardiol* 2019; **73:** 964–76.

20 Gersh BJ, Frye RL. Methods of coronary revascularization—things may not be as they seem. *N Engl J Med* 2005; 352: 2235–37.

21 Head SJ, Mack MJ, Holmes DR Jr, et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg* 2012; **41:** 535–41.

22 Garcia S, Sandoval Y, Roukoz H, et al. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol* 2013; **62**: 1421–31.

23 Farooq V, Serruys PW, Bourantas CV, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 2013; **128:** 141–51.

24 Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. *N Engl J Med* 2015; **372:** 1213–22.

25 Farkouh ME, Domanski M, Dangas GD, et al. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM Follow-On study. *J Am Coll Cardiol* 2019; **73:** 629–38.

26 Buszman PE, Buszman PP, Banasiewicz-Szkrobka I, et al. Left main stenting in comparison with surgical revascularization: 10-year outcomes of the (left main coronary artery stenting) LE MANS trial. *JACC Cardiovasc Interv* 2016; **9:** 318–27.

27 Park DW, Ahn JM, Yun SC, et al. 10-year outcomes of stents versus coronary artery bypass grafting for left main coronary artery disease. *J Am Coll Cardiol* 2018; **72:** 2813–22.

28 Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation* 2010; **121:** 2645–53.

29 Head SJ, Papageorgiou G, Milojevic M, Stone GW, Kappetein AP. Interpretation of results of pooled analysis of individual patient data—authors' reply. *Lancet* 2018; **392:** 818.
30 Head SJ, Holmes DR Jr, Mack MJ, et al. Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries. *JACC Cardiovasc Interv* 2012; **5:** 618-25.
31 Milojevic M, Head SJ, Parasca CA, et al. Causes of death following PCI versus CABG in complex CAD: 5-year follow-up of SYNTAX. *J Am Coll Cardiol* 2016; **67:** 42–55.

SUPPLEMENTARY APPENDIX

Ten-Year Survival After Percutaneous Coronary Intervention versus Coronary Artery Bypass Grafting in Patient with Three-Vessel and Left Main Coronary Artery Disease: A Multicentre, Randomized Controlled Trial

The SYNTAX Extended Survival (SYNTAXES) study

Daniel J.F.M. Thuijs, MD; Prof. A. Pieter Kappetein, Ph.D.; Prof. Patrick W. Serruys, Ph.D.; Prof. Friedrich- Wilhelm Mohr, Ph.D.; Marie-Claude Morice, Ph.D.;Michael J. Mack, Ph.D.; David R. Holmes Jr., MD; Prof. Nick Curzen, Ph.D.; Piroze Davierwala, MD; Thilo Noack, MD; Milan Milojevic, Ph.D.; Keith D. Dawkins, MD; Bruno R. da Costa, Ph.D; Prof. Peter Jüni, MD; Stuart J. Head, Ph.D.; for the SYNTAX Extended Survival Investigators

This appendix has been provided by the authors to give readers additional information about their work.

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I. SYNTAX EXTENDED SURVIVAL STUDY ORGANIZATION, PARTICIPATING SITES AND LOCAL INVESTIGATORS

SYNTAX Extended Survival Principal Investigators:

dr. Stuart J. Head, MD PhD, Erasmus MC, Rotterdam, The Netherlands

dr. Piroze M. Davierwala, MD, German Heart Center, Leipzig, Germany

Prof. dr. Friedrich-Wilhelm Mohr, MD PhD, German Heart Center, Leipzig, Germany

Prof. dr. Patrick W.J.C. Serruys, MD PhD, Imperial College London, United Kingdom

dr. Michael J. Mack, MD, Baylor Scott & White Health, Plano, TX, United States

dr. David R. Holmes Jr, MD, Mayo Clinic, Rochester, MN, United States

dr. Marie-Claude Morice, MD, ICPS Ramsay-Générale de Santé, Massy, France

Prof. dr. A. Pieter Kappetein, MD PhD, Erasmus MC, Rotterdam, The Netherlands

SYNTAX Extended Survival Chief Investigator/Study director:

Daniel J.F.M. Thuijs, MD, Erasmus MC, Rotterdam, The Netherlands

**SYNTAX Extended Survival Participating sites with Local Chief Investigators:*

1. Aalst, Onze Lieve Vrouw Ziekenhuis (OLVZ), Belgium: Filip Casselman, Bernard de Bruyne
2. Aarhus, Aarhus Universitets hospital, Denmark: Evald Høj Christiansen
3. Alicante, Hospital General de Alicante, Spain: Juan M. Ruiz-Nodar
4. Antwerp, ZNA Middelheim, Belgium: Paul Vermeersch
5. Bad Oeynhausen, Universitätsklinikum der Ruhr-Universität Bochum, Germany: Werner Schultz
6. Barcelona, Hospital Clínic de Barcelona, Spain: Manel Sabaté
7. Bergamo, Ospedale Papa Giovanni di Bergamo, Italy; Giulio Guagliumi
8. Berlin, Charité - Universitätsmedizin Berlin, Germany: Herko Grubitzsch, Karl Stangl
9. Bordeaux, Clinique ST Augustin, France: Olivier Darremont
10. Breda, Amphia Ziekenhuis, The Netherlands: M. Bentala, Peter den Heijer
11. Budapest, Cardiovascular Center of the Semmelweis University, Hungary: Istvan Preda
12. Dallas, Baylor University Medical Centre, TX, USA: Robert Stoler
13. Dallas, Medical City Dallas Hospital, TX, USA: Michael J. Mack
14. Debrecen, University of Debrecen, Hungary: Tamás Szerafin
15. Denver, UCH Denver Colorado, USA: John K. Buckner and Myles S. Guber
16. Eindhoven, Catharina Ziekenhuis, The Netherlands: Niels Verberkmoes, Ferdi Akca
17. Evanston, Northshore University HealthSystem, IL, USA: Ted Feldman
18. Freiburg, Heart Center, University of Freiburg, Germany: Friedhelm Beyersdorf
19. Gent, Universitair Ziekenhuis Gent, Belgium: Benny Drieghe
20. Glasgow, Golden Jubilee National Hospital, Clydebank, UK: Keith Oldroyd, Geoff Berg
21. Gothenborg, Sahlgrenska University Hospital, Sweden; Anders Jeppsson
22. Grand Blanc, Genesys Regional Medical Center, Grand Blanc, MI, USA: Kimberly Barber
23. Grand Rapids, Spectrum Health Hospitals Cook Research Department, MI, USA; Kevin Wolschleger, John Heiser
24. Groningen, Universitair Medisch Centrum Groningen, The Netherlands: Pim van der Harst, Massimo A. Mariani
25. Hamburg, University Heart Center Hamburg, Germany: Hermann Reichenspurner
26. Helsinki, University of Helsinki Meilahti Hospital, Finland: Christoffer Stark, Mika Laine

27. Honolulu, Kaiser Permanente, HI, USA: Paul C. Ho and John C. Chen
28. Hyannis, Cape Cod Hospital, MA, USA: Richard Zelman
29. Iowa, University of Iowa Hospitals & Clinics, IA, USA: Phillip A. Horwitz MD,
30. Katowice, Centrum Badawczo-Rozwojowe, American Heart of Poland, Poland: Agata Krauze, Andrzej Bochenek
31. Kiel, Universitätsklinikum Campus Kiel, Germany: Christina Grothusen
32. Krakow, John Paul II Hospital, Poland: Dariusz Dudek
33. Langhorne, St. Mary Medical Center, PA, USA: George Heyrich
34. Leipzig, Heart Center, University of Leipzig, Germany: Piroze Davierwala, Thilo Noack
35. Liege, University Hospital of Liege, Belgium: Victor LeGrand, Philippe Kolh
36. Lisbon, Hospital de Santa Marta, Portugal: Pedro Coelho
37. Lubeck, University Medical Center Schleswig-Holstein, Campus Lübeck, Germany: Stephan Ensminger, Boris Nasseri
38. Lund, Skånes Universitetssjukvård, Sweden: Richard Ingemansson, Goran Olivecrona
39. Madrid, Hospital Clinico San Carlos, Spain: Javier Escaned, Reddy Guera
40. Massa, Fondazione CNR/Regione Toscana per la Ricerca Medica e di Sanità Pubblica-Ospedale del Cuore G.Pasquinucci, Italy: Sergio Berti
41. Massy, Cardiovascular Institute Paris-Sud (ICPS), Hopital privé Jacques Cartier, Ramsay, Générale de Santé Massy, France : Marie-Claude Morice
42. Milan, San Raffaele Hospital, Milan, Italy: Alaide Chieffo
43. Minneapolis, Minneapolis Heart Institute Foundation, MN, USA: Nicholas Burke, Michael Mooney
44. Mirano, Ospedale di Mirano, Italy: Alvise Spolaor
45. Munich, Klinikum der Universität München, Campus Großhadern, Germany; Christian Hagl, Michael Näbauer
46. Nieuwegein, Sint-Antonius Ziekenhuis, The Netherlands: Maarten Jan Suttorp
47. Norfolk, Sentara Cardiovascular Research Institute, Norfolk, VA, USA: Ronald A. Stine
48. Oklahoma, Oklahoma Cardiovascular Research Group, OK, USA: Thomas McGarry, Scott Lucas
49. Olso, Oslo universitetssykehus HF, Norway: Knut Endresen
50. Orlando, Florida Hospital Cardiovascular Research, Florida, USA: Andrew Taussig, Kevin Accola
51. Pavia, IRCCS Policlinico San Matteo, Italy: Umberto Canosi
52. Pecs, University Hospital of Pecs, Hungary: Ivan Horvath
53. Petoskey, Cardiac & Vascular Research Center of Northern Michigan, Michigan, USA, Louis Cannon, John D. Talbott, Chris W. Akins

54. Portland, Maine Medical Center, ME, USA: Robert Kramer
55. Prague, Interni Klinika VFN, Czech Republic: Michael Aschermann
56. Raleigh, WakeMed Health & Hospitals, Raleigh, NC, USA; William Killinger
57. Riga, Latvian Centre of Cardiology, Latvia: Inga Narbute
58. Rochester, Mayo Clinic, MN, USA: David R. Holmes Jr.
59. Rome, Catholic University of the Sacred Heart, Italy: Francesco Burzotta
60. Rotterdam, Erasmus University Medical Centre, The Netherlands: Ad J.J.C. Bogers, Felix Zijlstra
61. Rouen, Centre Hôpital Universitaire Rouen, Hôpital Charles Nicolle, France: Helene Eltchaninoff
62. Rouen, Clinique Saint-Hilaire Rouen, France: Jacques Berland
63. Rozanno, Instituto Clinico Humanitas, Italy: Giulio Stefanini
64. Salamanca, Hospital Clinico Salamanca, Spain: Ignacio Cruz Gonzalez
65. Salzburg, Dept. of Cardiology, Paracelsus Medical University Salzburg, Austria: Uta Hoppe
66. San Antonio, San Antonio Endovascular and Heart Inst., TX, USA: Radoslaw Stefan Kiesz, Bartlomiej Gora
67. Stockholm, Karolinska University Hospital, Sweden: Anders Ahlsson, Matthias Corbascio
68. Stonybrook, Stony Brook University, NY, USA: Thomas V. Bilfinger
69. Toulouse, Centre Hôpital Universitaire Rangueil, France: Didier Carrie
70. Toulouse, Groupe CardioVasculaire Interventionnel, Clinique Pasteur, France: Didier Tchétché
71. Trier, Krankenhaus der Barmherzigen Bruder Trier, Germany: Karl-Eugen Hauptman
72. Uppsala, University Hospital Uppsala, Sweden: Elisabeth Stahle, Stefan James
73. Vienna, Allgemeines Krankenhaus AKH, Austria: Sigrid Sandner, Günther Laufer, Irene Lang
74. Warsaw, Institute of Cardiology, Poland: Adam Witkowski
75. Washington, Medstar Heart and Vascular Institute, DC, USA; Vinod Thourani
76. Zwolle, Isala Zwolle, The Netherlands: Harry Suryapranata
77. London, Guys and St Thomas, UK Simon Redwood
78. London, Barts, UK: Charles Knight
79. London, King's College, UK: Philip MacCarthy
80. Southampton, University Hospital Southampton NHS FT, UK: Nick Curzen
81. Brighton, Brighton and Sussex University Hospitals NHS Trust, UK: Adam de Belder
82. Oxford, John Radcliffe Hospital, UK: Adrian Banning

83. Leicester, University Hospitals of Leicester NHS Trust Glenfield Hospital, UK: Anthony Gershlick
84. Rockford, St. Anthony's Medical Center, IL, USA: Robert Minor (elected not to participate in SYNTAX Extended Survival, yet did contribute to the SYNTAX trial)
85. Sacramento, Mercy General, CA, USA: Michael Chang (elected not to participate in SYNTAX Extended Survival, yet did contribute to the SYNTAX trial)

II. SAMPLE SIZE CALCULATION

The sample size of the SYNTAX Extended Survival study was based on the sample size considerations for the original trial. The original SYNTAX trial was powered for a noninferiority comparison of major adverse cardiac and cerebrovascular events (MACCE) at 12 months between CABG and PCI. The trial was powered separately for patients with 3VD and patients with LMCAD, so that each would have 80% power for a non-inferiority comparison of MACCE between PCI and CABG. For the subgroup of patients with 3VD only, the expected MACCE rates were 12% for both CABG and PCI. With a noninferiority margin of 5% and a one-sided alpha of 5%, 1050 patients were needed to have 80% power for the analysis. After allowing for an expected attrition rate of 3.5%, 1090 patients (545 per group) were needed for the 3VD comparison. For the subgroup of patients with LMCAD, the expected MACCE rates were 15% for CABG and 17% for PCI. With a noninferiority margin of 9% and a one-sided alpha of 5%, 684 patients were needed to have 80% power for the analysis. After allowing for an expected attrition rate of 3.5%, 710 patients (355 per group) were needed for the LMCAD comparison. After allowing for an expected attrition rate of 3.5%, the overall sample size of 1800 patients (900 per group) resulted in 96% power to detect noninferiority at a noninferiority margin of 6.6% (weighted average of 5.0% for the 3VD subgroup and 9.0% for LMCAD subgroup) and a one-sided alpha of 5%.

III. EXPLORATORY ANALYSES AND PRE-SPECIFIED SENSITIVITY ANALYSIS

Results from additional exploratory analyses and sensitivity analyses are provided below in Table 2 to Table 5, and in Figures S4 to S10.

IV. SUPPLEMENTARY TABLES

Table S1. Procedural characteristics of the randomized SYNTAX patients.

Characteristics	PCI (n = 903)	CABG (n = 897)
Revascularization presentation – no. (%)		
Urgent	4.1 (37/896)	3.8 (33/870)
Emergent	1.8 (16/896)	3.9 (34/870)
Elective	94.1 (843/896)	92.3 (803/870)
Off-pump surgery – no. (%)	-	15.0 (128/853)
Graft revascularization – no. (%)		
≥ 1 arterial graft	-	97.3 (831/854)
Bilateral internal thoracic arteries	-	27.6 (236/854)
Complete arterial revascularization	-	18.9 (161/854)
Venous graft only	-	2.6 (22/854)
Grafts per patient – mean ± SD	-	2.8 ± 0.7
Distal anastomoses – mean ± SD	-	3.2 ± 0.9
Staged procedure – (%)	14.1 (125/885)	-
Bi/trifurcation lesions treated – no. (%)	24.8 (790/3180)	-
Lesions treated - mean ± SD	3.6 ± 1.6	-
Stents implanted - mean ± SD	4.6 ± 2.3	-
Total length implanted - mean ± SD, mm	86.1 ± 47.9	-
Range, mm	8.0 – 324.0	-
Long stenting (>100 mm) – no. (%)	33.2 (291/877)	-
Complete revascularization[#] – no. %	56.7 (508/896)	63.2 (550/870)
Post procedural hospital stay[#] – days	3.4 ± 4.5	9.5 ± 8.0

Supplementary Appendix Table S1. Values are shown as mean ± SD (standard deviation) or frequencies in percentages and (n), unless otherwise noted. [#]Both differed significantly between PCI versus CABG (P=0.005). Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

Table S2. Baseline Clinical and Angiographic Characteristics of the patients with and without vital status up to 10-year follow-up.

Characteristics	With 10-year follow-up (n=1689)	Without 10-year follow-up (n=111)	P-value
Age (years)	65.1 ± 9.7	65.1 ± 9.6	0.23
Female sex – no. (%)	370 (21.9)	32 (28.8)	0.09
Body mass index (kg/m2) - mean ± SD	28.0 ± 4.6	29.0 ± 5.1	0.32
Diabetes – no. (%)			
Requiring oral medications or insulin	417 (24.6)	35 (31.5)	0.11
Requiring insulin	173 (10.2)	13 (11.7)	0.62
Metabolic syndrome – no. (%)	615 (45.7)	41 (46.6)	0.87
Prior nicotine abuse – no. (%)	1090 (64.8)	71 (64.5)	0.96
Prior myocardial infarction – no. (%)	556/1673 (33.2)	29/107 (27.1)	0.19
Prior stroke – no. (%)	75/1679 (4.5)	3/110 (2.7)	0.39
Prior transient ischemic attack – no. (%)	82/1679 (4.9)	2/110 (1.8)	0.14
Hypertension (≥130/85mmHg) – no. (%)	1109 (65.7)	87 (78.4)	0.006
Congestive heart failure – no. (%)	82/1673 (4.9)	1/105 (1.0)	0.06
Prior carotid artery disease – no. (%)	137 (8.1)	11 (9.9)	0.50
Hyperlipidaemia – no. (%)	1314/1674 (78.5)	77 (69.4)	0.03
Angina – no. (%)			
Stable	969 (57.4)	58 (52.3)	0.29
Unstable	478 (28.3)	35 (31.5)	0.47
Ejection fraction <30% – no. (%)	29/1661 (1.7)	3 (2.7)	0.46
EuroSCORE value - mean ± SD	3.8 ± 4.6	3.5 ± 2.9	0.06
Parsonnet score - mean ± SD	8.5 ± 7.0	8.4 ± 5.7	0.07
SYNTAX score∞ – mean ± SD	28.8 ± 11.4	27.5 ± 11.6	0.76
No. of lesions – mean ± SD	4.0 ± 1.7	4.1 ± 7.8	0.38
Total occlusion – no. (%)	387/1676 (23.1)	28 (25.2)	0.61
Bifurcation lesion – no. (%)	1221/1676 (72.9)	79 (71.2)	0.70
Three-vessel disease	1029 (60.9)	66 (59.5)	0.76
Left main disease, any	660 (39.1)	45 (40.5)	0.76

Table S2. This table reports the baseline characteristics of those patients with 10-year all-cause death follow-up (PCI n=841, CABG n=848) versus those without 10-year follow-up (PCI n=62; including 3 patients from not-participating SYNTAXES sites, CABG n=49; including 2 patients from not-participating SYNTAXES sites). Values are shown as mean ± SD (standard deviation) or frequencies in percentages and (n), unless otherwise noted. ∞SYNTAX scores reported according to core-lab analysed data. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention.

Table S3. Landmark analysis for the overall cohort and according to pre-specified subgroups of patients with three-vessel disease, left main coronary artery disease, diabetes, without diabetes and according to SYNTAX score tertiles.

Time period of landmark analysis	HR (95% CI)	P for interaction
All patients		0.99
0-5 years	1.20 (0.93 to 1.55)	
>5-10 years	1.17 (0.91 to 1.52)	
Three-vessel disease		0.59
0-5 years	1.52 (1.08 to 2.14)	
>5-10 years	1.33 (0.95 to 1.87)	
Left main coronary artery disease		0.58
0-5 years	0.85 (0.57 to 1.27)	
>5-10 years	1.00 (0.67 to 1.49)	
Diabetes		0.082
0-5 years	1.48 (0.93 to 2.34)	
>5-10 years	0.83 (0.53 to 1.31)	
No diabetes		0.23
0-5 years	1.07 (0.78 to 1.46)	
>5-10 years	1.41 (1.02 to 1.95)	
Syntax score 0-22		0.097
0-5 years	0.81 (0.48 to 1.36)	
>5-10 years	1.51 (0.90 to 2.54)	
Syntax score 23-32		0.92
0-5 years	1.05 (0.68 to 1.62)	
>5-10 years	1.09 (0.68 to 1.74)	
Syntax score ≥33		0.23
0-5 years	1.76 (1.16 to 2.67)	
>5-10 years	1.23 (0.82 to 1.85)	

Table S3. HR: hazard ratio; CI: confidence interval. A HR below 1 favours Percutaneous Coronary Intervention, and above 1 favours Coronary Artery Bypass Graft. The p-values for interaction are for the time-by-treatment interactions based on a cut-off at 5 years to distinguish between the period up to 5 years and the subsequent follow-up up to 10 years.

Table S4. Multivariable Cox proportional hazard model – Sensitivity analysis

Characteristics	HR (95% CI)	P for interaction
Overall cohort	1.24 (1.02 – 1.48)	
Type of Coronary Artery Disease		0.022
Left Main Disease	0.96 (0.72 – 1.27)	
Three-Vessel Disease	1.48 (1.16 – 1.89)	

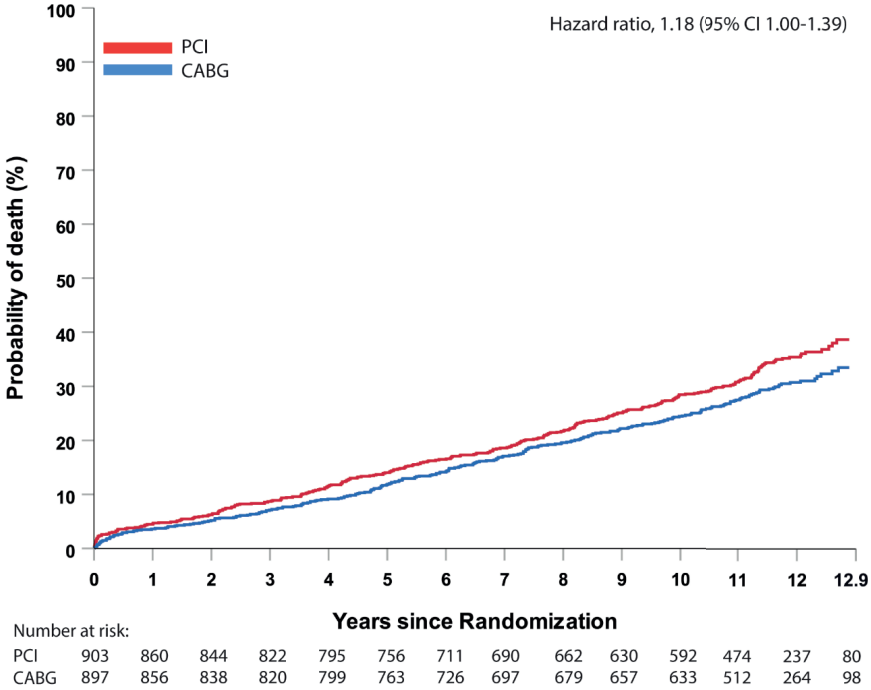
Supplementary Appendix Table S4. The model included all 1800 randomized patients and was constructed using stepwise forward selection. Significance levels of 0.10 for both addition and removal from the model were used, considering all baseline variables listed Table 1 and forcing the allocated treatment and the variables used for stratification of randomization (LMCAD and diabetes) into the model. Subgroup specific estimates of the hazard ratios of the primary endpoint in the LMCAD and 3VD subgroups were derived by appropriate linear combinations of coefficients representing treatment and the interaction between treatment and subgroup (LMCAD versus 3VD). Abbreviations used: CI; confidence interval, HR; hazard ratio.

Table S5. Multivariable Cox proportional hazard model – Included Variables.

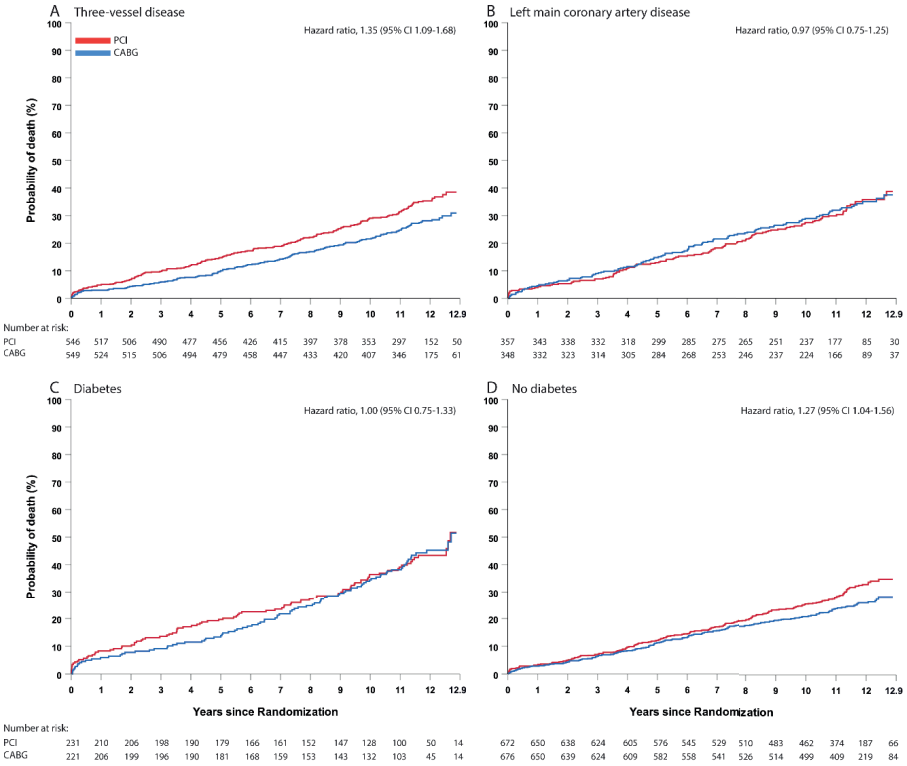
Characteristics	HR (95% CI)
Allocated treatment (PCI versus CABG)	1.23 (1.02 – 1.48)
Age, years	1.04 (1.03 – 1.05)
Bifurcation lesion	1.18 (0.95 – 1.47)
Congestive heart failure	1.34 (1.15 – 1.56)
Diabetes	1.40 (1.14 – 1.72)
EuroSCORE	1.16 (1.11 – 1.21)
Left Main Disease	1.14 (0.94 – 1.37)
Metabolic syndrome	1.39 (1.13 – 1.71)
Nicotine abuse at time of enrolment	1.46 (1.20 – 1.79)

Supplementary Appendix Table S5. The model included all 1800 randomized patients and was constructed using stepwise forward selection. This table represents the individual variables, with hazard ratios and 95% confidence intervals, that were included in the final model. Abbreviations used: CI; confidence interval, HR; hazard ratio.

V. SUPPLEMENTARY FIGURES



Supplementary Appendix Figure S1. All-cause death at maximum follow-up of patients randomized to PCI versus CABG (intention-to-treat population). Kaplan-Meier curves describing the probability of death in PCI versus CABG up to 12.9 years of follow-up. Curves were truncated at 12.9 years when only 10% of patients were at risk to avoid visual misinterpretation. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, PCI; percutaneous coronary intervention.



Supplementary Appendix Figure S2. All-cause death at maximum follow-up of patients randomized to PCI versus CABG with 3VD, LMCAD, diabetes and without diabetes (intention-to-treat population). Kaplan-Meier curves describing the probability of death in PCI versus CABG up to 12.9 years of follow-up in pre-specified subgroups of patients with three-vessel disease (Panel A), left main coronary artery disease (Panel B), with diabetes (Panel C) and without diabetes (Panel D). Curves were truncated at 12.9 years when only 10% of patients were at risk to avoid visual misinterpretation. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, PCI; percutaneous coronary intervention.

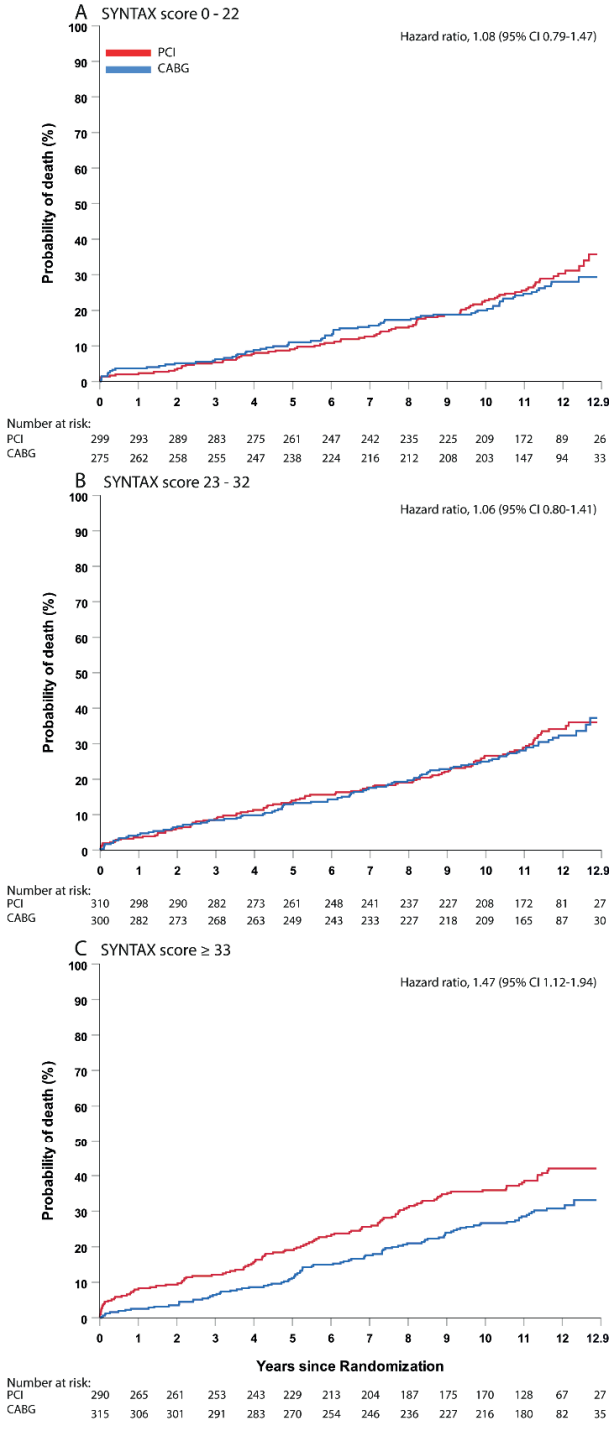
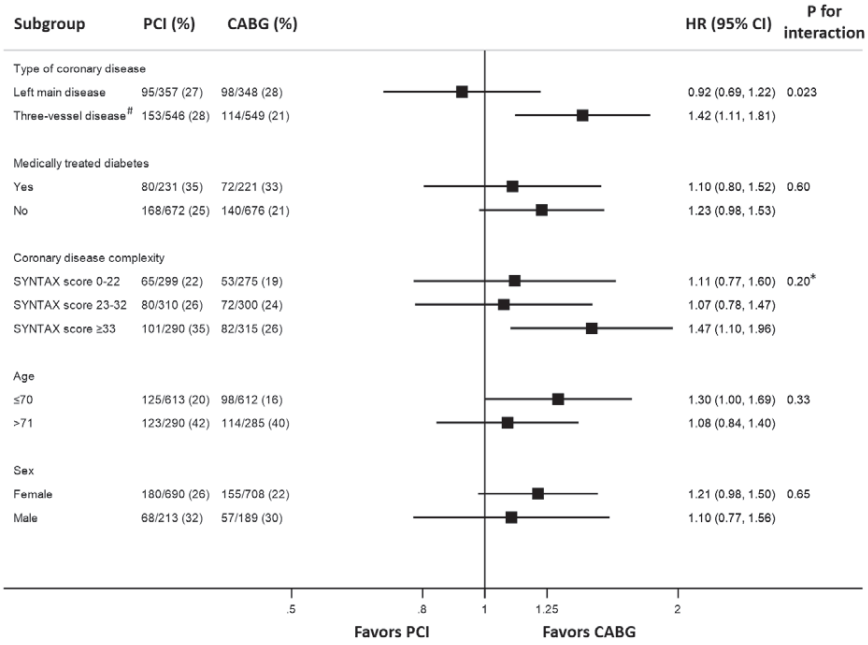
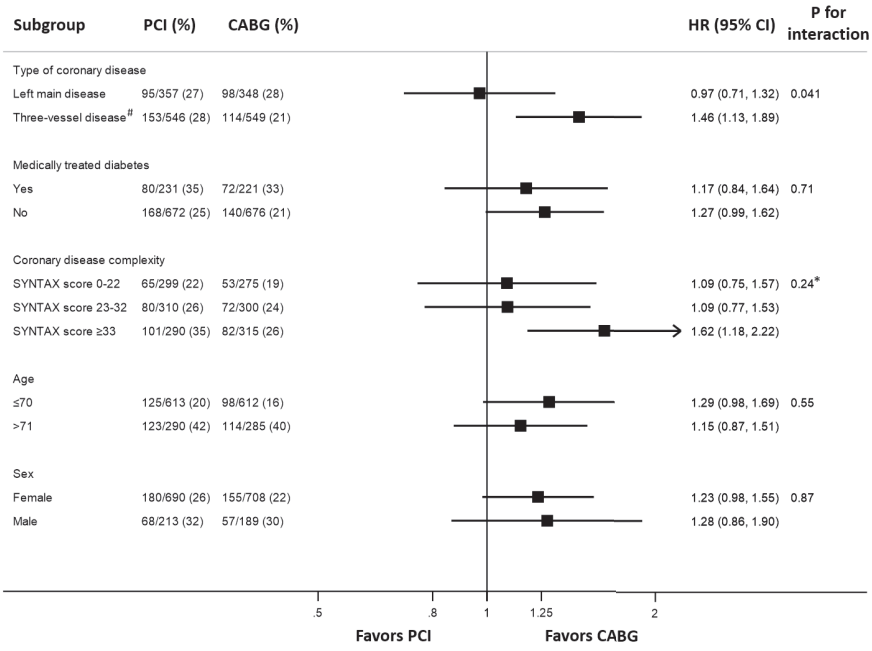


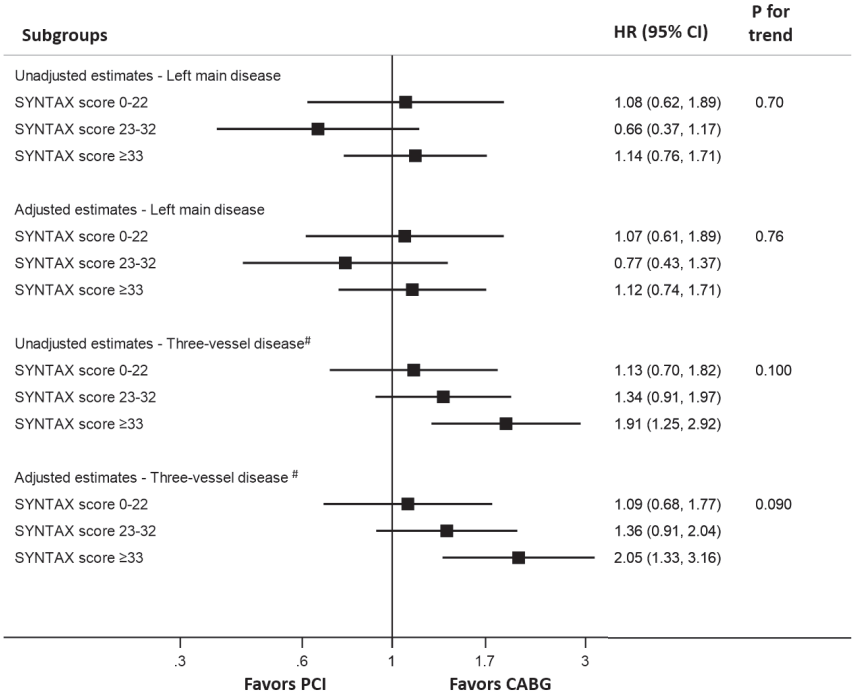
Figure S3. All-cause death at maximum follow-up of patients randomized to PCI versus CABG with low, intermediate and high SYNTAX scores (intention-to-treat population). Kaplan-Meier curves describing the probability of death in PCI versus CABG up to 12.9 years of follow-up in pre-specified subgroups of patients with low SYNTAX scores (0-22; panel A), intermediate SYNTAX scores (23-32; Panel B), and high SYNTAX scores (≥33; Panel C). SYNTAX scores were reported according to core-lab analysed data. Curves were truncated at 12.9 years when only 10% of patients were at risk to avoid visual misinterpretation. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, PCI; percutaneous coronary intervention.



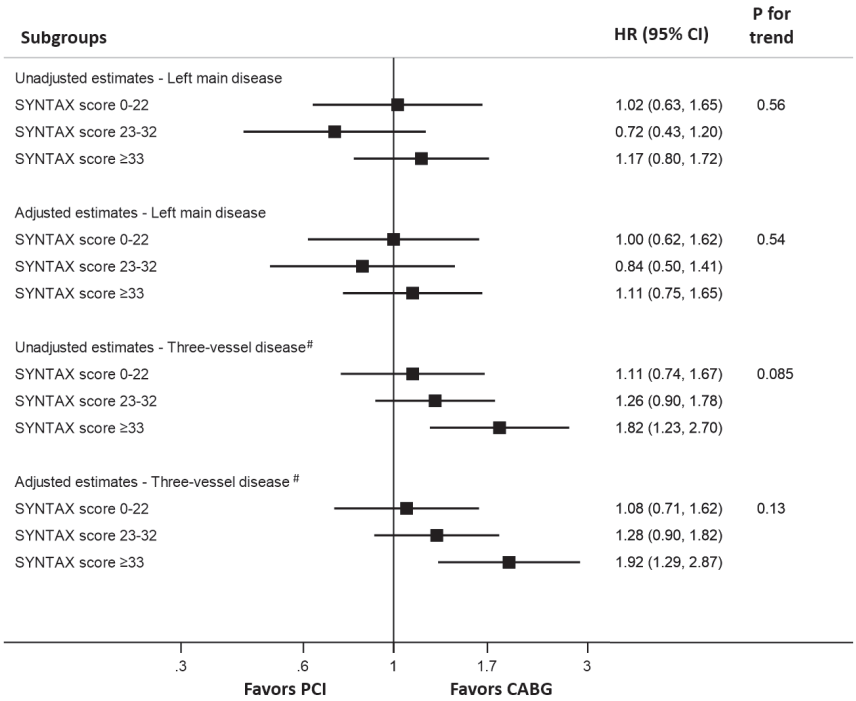
Supplementary Appendix Figure S4. Unadjusted subgroup analyses on 10-year all-cause death in patients randomized to PCI and CABG (intention-to-treat population). All-cause death after PCI versus CABG during 10-year follow-up in pre-specified unadjusted subgroup analyses according to baseline characteristics. Outcomes according to age and sex were considered exploratory. *P value for trend of log HRs across SYNTAX tertiles for subgroup analysis according to lesion complexity. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. #Patients with coronary artery disease involving all three vessels in the absence of left main disease. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, HR; hazard ratio, PCI; percutaneous coronary intervention.



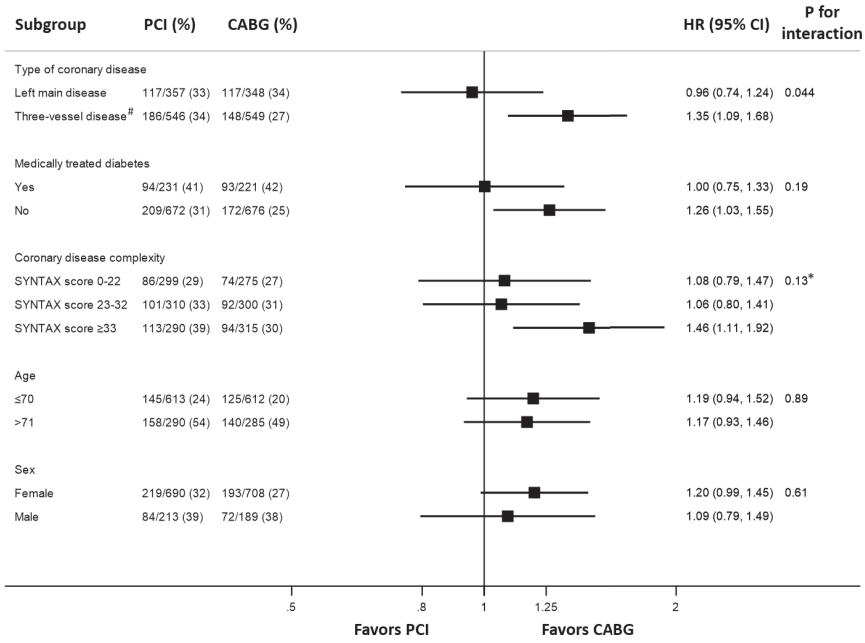
Supplementary Appendix Figure S5. Adjusted subgroup analyses on 10-year all-cause death in patients randomized to PCI and CABG (intention-to-treat population). All-cause death after PCI versus CABG during 10-year follow-up in pre-specified adjusted subgroup analyses according to baseline characteristics. *P value for trend of log HRs across SYNTAX tertiles for subgroup analysis according to lesion complexity. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. #Patients with coronary artery disease involving all three vessels in the absence of left main disease. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, HR; hazard ratio, PCI; percutaneous coronary intervention.



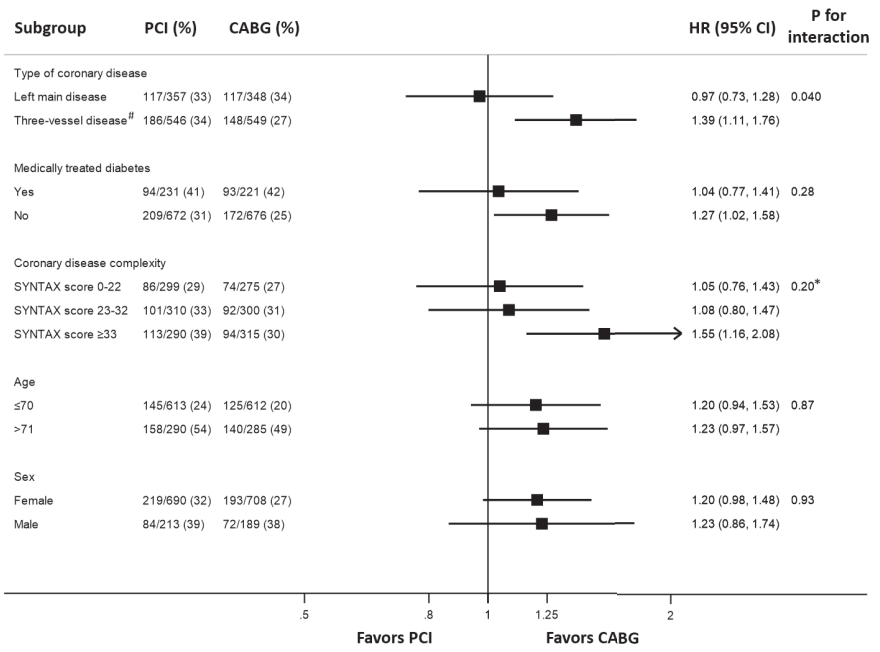
Supplementary Appendix Figure S6. Subgroup analyses according to SYNTAX score tertiles in 3VD and LMCAD subgroups at 10 year follow-up (intention-to-treat population). PCI versus CABG 10-year all-cause death (unadjusted and adjusted) hazard ratios in the overall cohort and pre-specified subgroups of patients 3VD and LMCAD according to low SYNTAX scores (0-22), intermediate SYNTAX scores (23-32) and high SYNTAX scores (≥33). #Patients with coronary artery disease involving all three vessels in the absence of left main disease. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, HR; hazard ratio, PCI; percutaneous coronary intervention.



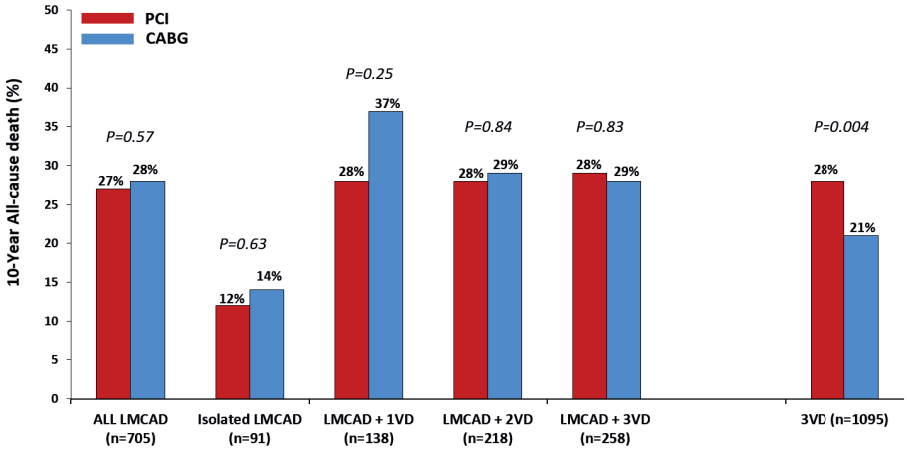
Supplementary Appendix Figure S7. Subgroup analyses according to SYNTAX score tertiles in 3VD and LMCAD subgroups at maximum follow-up (intention-to-treat population). PCI versus CABG 10-year all-cause death (unadjusted and adjusted) hazard ratios in the overall cohort and pre-specified subgroups of patients 3VD and LMCAD according to low SYNTAX scores (0-22), intermediate SYNTAX scores (23-32) and high SYNTAX scores (≥33). Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. #Patients with coronary artery disease involving all three vessels in the absence of left main disease. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, HR; hazard ratio, PCI; percutaneous coronary intervention.



Supplementary Appendix Figure S8. Unadjusted subgroup analyses at maximum follow-up in patients randomized to PCI and CABG (intention-to-treat population). All-cause death after PCI versus CABG during maximum follow-up in pre-specified adjusted subgroup analyses according to baseline characteristics. *P value for trend of log HRs across SYNTAX tertiles for subgroup analysis according to lesion complexity. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. #Patients with coronary artery disease involving all three vessels in the absence of left main disease. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, HR; hazard ratio, PCI; percutaneous coronary intervention.



Supplementary Appendix Figure S9. Adjusted subgroup analyses at maximum follow-up in patients randomized to PCI and CABG (intention-to-treat population). All-cause death after PCI versus CABG during maximum follow-up in pre-specified adjusted subgroup analyses according to baseline characteristics. *P value for trend of log HRs across SYNTAX tertiles for subgroup analysis according to lesion complexity. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about between-group differences. #Patients with coronary artery disease involving all three vessels in the absence of left main disease. Abbreviations used: CABG; coronary artery bypass grafting, CI; confidence interval, HR; hazard ratio, PCI; percutaneous coronary intervention.



Supplementary Appendix Figure S10. PCI versus CABG 10-year all-cause death outcomes between PCI and CABG in pre-specified subgroups of patients three-vessel and left main coronary artery disease; with any additional coronary artery disease (intention-to-treat population). All LMCAD (PCI n=357, CABG n=348), isolated (PCI n=42, CABG n=49), LMCAD + 1VD (PCI n=67, CABG n=71), LMCAD + 2VD (PCI n=112, CABG n=106), LMCAD + 3VD (PCI n=136, CABG n=122), 3VD (PCI n=546, CABG n=549). P values, to determine potential differences between PCI versus CABG, were derived from a log rank test. Abbreviations used: CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, LMCAD: left main coronary artery disease, 1VD: one-vessel disease, 2VD: two-vessel disease, 3VD: three-vessel disease.

Chapter 7

Risk Profile and 10-Year Survival in the SYNTAX Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting Nested Registries

Mohanad Hamandi, Karim Al-Azizi, Daniel J.F.M. Thuijs, Jasjit K. Banwait, Patrick W. Serruys MD, Friedrich-Wilhelm Mohr, Piroze Davierwala, David R. Holmes Jr, Marie-Claude Morice, A. Pieter Kappetein, Stuart J. Head, for the SYNTAX Extended Survival Investigators

Submitted

ABSTRACT

Objectives

To report the risk profile and 10-year survival of patients deemed ineligible for randomization and therefore enrolled in coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) nested-registries.

Background

The SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial was a randomized study of patients with stable *de novo* three vessel (3VD) and/or left main coronary artery disease (LMCAD) eligible for CABG and PCI. Patients ineligible for randomization were entered into a PCI or CABG nested-registry.

Methods

This study is a prespecified subgroup analysis of the SYNTAX Extended Survival (SYNTAXES) study. Patients from the PCI and CABG nested-registries were followed to determine 10-year all-cause death (primary endpoint). Prespecified sub-analyses were performed for 3VD versus LMCAD, diabetes versus no diabetes, and among SYNTAX score tertiles.

Results

Ten-year all-cause death was 51.6% (99/192) in the PCI-registry and 25.9% (167/644) in the CABG-registry. In the PCI registry, 10-year all-cause death was 44.4% and 62.0% among 3VD and LMCAD patients, respectively (HR 0.56 [95% CI 0.37–0.83]; p=0.003). Diabetes did not affect 10-year all-cause death, while low versus high SYNTAX score did (34.1% vs. 63.4%, respectively) (HR 1·53 [95% CI 1.18–2.002]; p = 0.006). In the CABG-registry, all-cause death was not different according to 3VD, LMCAD, or SYNTAX score tertile. All-cause death occurred in 40.3% vs. 19.9% of patients with versus without diabetes (HR 2.44 [95% CI 1.80–3.31]; p < 0.001).

Conclusion

Patients in the CABG-registry showed excellent 10-year survival (all-cause death 25.9%). However, patients in the PCI-registry showed poor 10-year survival with an all-cause death rate exceeding 50%. Decisions on treatment strategies require a case-based heart team approach, weighing different aspects of comorbidities and treatment options.

Condensed Abstract:

The SYNTAX trial was an all-comer randomized study of patients with stable *de novo* three vessel and/or left main CAD eligible for either CABG or PCI by a heart team. We report 10-year survival of PCI-registry patients ineligible for CABG due to the presence of significant comorbidities increasing surgical risk, and CABG registry patients ineligible for PCI due to too extensive CAD. Ten-year all-cause death was 25.9% (167/644) and 51.6% (99/192) in the CABG- and PCI-registries, respectively. These results underline that long-term survival is impacted by cardiovascular risk factors and provide "real-world" insight regarding the interaction between CABG and PCI in high-risk CAD patients.

Keywords

SYNTAX; PCI; CABG; Extended Survival

INTRODUCTION

Coronary artery bypass grafting (CABG) has been considered the preferred treatment for stable multi-vessel and/or left main coronary artery disease (LMCAD) (1). Since the introduction of percutaneous coronary intervention (PCI), various randomized clinical trials have been conducted comparing PCI outcomes with those of CABG in this patient population (2-5). However, the randomized patients from these trials are considered highly-selected patients and may not adequately represent "real-world" patients with coronary artery disease regularly treated by cardiologists and cardiothoracic surgeons.

The SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial was an all-comer randomized study that enrolled patients with stable *de novo* three vessel disease and/or left main CAD (CAD) deemed eligible by the heart team for either CABG or PCI. A major strength and novelty of the SYNTAX trial was that patients were excluded from randomization and entered into nested registries when significant comorbidities were present creating an increased surgical risk in the judgement of the heart team (e.g., the PCI-registry with CABG ineligible patients). Furthermore, patients were entered into a CABG-registry if the complexity of the CAD was deemed too extensive for optimal PCI outcomes (e.g., PCI ineligible patients) (6,7).

The SYNTAX trial reported clinical outcomes with up to 5-years follow-up, and The SYNTAX Extended Survival (SYNTAXES) study provided unique long-term data on all-cause death up to 10 years of follow-up (8,9). The present study reports the risk profiles and 10-year survival of those patients deemed ineligible for randomization and enrolled in the SYNTAX CABG and PCI nested-registries.

METHODS

Study Design and Patients

The present study is a prespecified subgroup analysis of the SYNTAXES study (NCT03417050), an investigator-driven extension of follow-up up to 10 years of the original SYNTAX trial (NCT00114972). The SYNTAX trial was a multicenter randomized controlled trial performed in 85 centers across 18 North-American and European countries. The trial design and rationale have been described previously (6,7). In summary, patients with stable *de novo* three-vessel disease (3VD) and/or LMCAD were screened for enrollment by the local heart team. During a multidisciplinary heart team discussion (consisting of a cardiothoracic surgeon, an interventional

cardiologist and a non-interventional cardiologist), a consensus was reached on whether both PCI with a first-generation paclitaxel drug-eluting stents and CABG would result in clinical equipoise, allowing the patient to be randomized for either treatment. Patients found ineligible to be randomized were included in nested CABG (PCI-ineligible patients) and PCI (CABG-ineligible patients) registries. (6,7). A random group of patients from the CABG registry (60%; n=649) and all PCI registry patients (100%; n=198) were selected to be followed-up (6,10).

Medical Ethical Committee approval for this study was granted at the institution of the principal investigators (Erasmus University Medical Centre, Rotterdam, Netherlands, reference: MEC-2016-716). The study protocol is consistent with the International Conference on Harmonization Guidance of Industry E6 Good Clinical Practice and the Declaration of Helsinki. Informed consent to obtain information on 10-year vital status was waived, and follow-up was performed in accordance with local law and regulations of each participating site. Survival data was obtained from electronic medical records or by query of national death registries.

Endpoints

The primary endpoint of this study was all-cause death at 10-year follow-up in patients entered into the PCI and CABG nested-registries. Prespecified sub-analyses for 10-year all-cause death were performed in subgroups of patients with 3VD versus LMCAD, the presence versus absence of diabetes, and according to coronary artery disease complexity defined by SYNTAX score tertiles (low; 0-22, intermediate; 23-32, and high; ≥33).

Definitions

The LMCAD subgroup consisted of patients in which the disease was either isolated or combined with single-vessel, two-vessel, or three-vessel CAD. The 3VD subgroup consisted of patients with CAD involving all three vessels in the absence of LMCAD. SYNTAX scores representing the extensiveness and complexity of CAD based on visual interpretation of the coronary angiogram assessed during heart team meetings were defined according to the classical tertiles; scores of 22 or lower defined as low, 23–32 as intermediate, and 33 or higher as high. Diabetes was defined as patients requiring treatment with oral agents or insulin (6,7,10). The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was used to assess operative risk.

Statistical Analysis

The analyses were performed according to the as-treated principle. Patient characteristics were presented according to descriptive statistics and reported as proportions (%, count/sample size) or mean ± SD.

Sub-analyses were performed for LMCAD and 3VD, with or without diabetes, and SYNTAX score tertile. Kaplan-Meier curves were generated to measure the probability of all-cause death for patients entered in the PCI and CABG nested-registries (primary endpoint), as well as for prespecified subgroups (3VD, LMCAD, diabetes, no diabetes, and SYNTAX score tertiles; secondary endpoint). Patients with missing vital status were included in the time to event Kaplan Meier analysis and censored at the time of "lost to follow-up." Statistical comparison was performed by overall and pairwise log-rank testing with Benjamini-Hochberg correction, with a 2-sided p-value of 0.05 or less considered statistically significant. Cox proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for sub-group comparisons. Analyses were performed with R, version 3.5.0 or higher (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From March 2005 through April 2007, 198 patients were included in the PCI and 1,077 patients in the CABG registries. Of the 198 patients in the PCI registry, 192 were treated with PCI, four patients were treated medically, one underwent CABG, and one patient withdrew consent. From the 1,077 patients in the CABG registry, 649 were randomly selected to be followed-up, and of which, 644 were treated with CABG, three did not receive treatment, and two were managed medically. Another nine patients were lost to follow-up, and three patients withdrew consent. Follow-up at 10 years was complete in 100% (192/192) of as-treated PCI Registry and in 100% (644/644) of the randomly selected as-treated CABG Registry patients.

Patients included in the PCI registry were deemed either high-risk for CABG (70.7%), had no graft material for anastomosis (9.1%), refused CABG (5.6%), had small or poor quality of distal vessels (1.5%), or were excluded from randomization because of other reasons (13.1%). Reasons for inclusion in the CABG registry included complex coronary anatomy not ideal for PCI (70.9%), chronic total occlusion untreatable with PCI (22.0%), inability to take antiplatelet medication (0.9%), refusal to undergo PCI (0.5%), or other reasons (5.7%).

Patient Characteristics

The baseline characteristics of patients entered into the nested CABG and PCI-registries have been reported previously (10). In brief, compared to the randomized trial, PCI registry patients were older and at higher operative risk. Those in the CABG registry showed similar age and operative risk compared to the randomized

patients (Table 1). For both cohorts, coronary lesion complexity was higher in registry patients compared to the randomized patients.

Table 1. Baseline demographics and lesion characteristics in the registry and trial patients

Characteristics	Registry		Trial	
	PCI (n=192)	CABG (n=644)	PCI (n=903)	CABG (n=897)
Age, yrs.	71.2 ± 10.4 (192)	65.7 ± 9.4 (644)	65.2 ± 9.7	65.0 ± 9.8
Male	70.3% (135/192)	80.7% (520/644)	76.4% (690/903)	78.9% (708/897)
Comorbid risk factors				
Body mass index (kg/m^2)	28.0 ± 5.5 (191)	28.0 ± 4.6 (643)	28.1 ± 4.8	27.9 ± 4.5
Diabetes				
Any	35.4% (68/192)	29.7% (191/644)	25.6% (231/903)	24.6% (221/897)
Requiring insulin	15.1% (29/192)	9.2% (59/644)	9.9% (89/903)	10.4% (93/897)
Blood pressure ≥130/85 mm Hg	69.8% (134/192)	68.5% (441/644)	68.9% (622/903)	64.0% (574/897)
Hyperlipidemia	67.5% (129/191)	76.4% (480/628)	78.7% (705/896)	77.2% (686/889)
Cardiovascular history				
Smoking status	11.2% (21/188)	21.9% (140/639)	18.5 % (167/903)	22.0% (196/890)
Previous myocardial infarction	40.4% (76/188)	33.5% (211/629)	31.9% (285/893)	33.8% (300/887)
Previous stroke	7.8% (15/192)	5.5% (35/639)	3.9% (35/899)	4.8% (43/890)
Previous transient ischemic attack	7.9% (15/191)	5.6% (36/638)	4.3% (39/901)	5.1% (45/888)
Congestive heart failure	9.7% (18/186)	5.5% (35/633)	4.0% (36/898)	5.3% (47/880)
Carotid artery disease	10.4% (20/192)	12.3% (79/644)	8.1% (73/903)	8.4% (75/897)
Angina				
Stable	46.4% (89/192)	62.9% (405/644)	56.9% (514/903)	57.2% (513/897)
Unstable	38.0% (73/192)	21.6% (139/644)	29.0% (262/903)	28.0% (251/897)
Ejection fraction <30%	5.7% (11/192)	4.5% (29/644)	1.3% (12/891)	2.5% (22/875)
Additive EuroSCORE	5.8 ± 3.1 (192)	3.9 ± 2.7 (644)	3.8 ± 2.6 (903)	3.8 ± 2.7 (897)
Parsonnet score	14.4 ± 9.5 (192)	9.0 ± 7.1 (644)	8.5 ± 7.0 (903)	8.4 ± 6.8 (897)
Lesion complexity				
SYNTAX score	31.6 ± 12.3 (189)	37.8 ± 13.3 (632)	28.4 ± 11.5 (903)	29.1 ± 11.4 (897)
Total occlusion	36.5% (69/189)	56.4% (356/631)	24.2% (217/897)	22.1% (198/897)
Lesion characteristics				
Number of lesions	4.8 ± 1.9 (192)	3.9 ± 1.6 (644)	4.3 ± 1.8 (903)	4.4 ± 1.8 (897)
Left main coronary artery disease, any	41.1% (79/192)	47.5% (306/644)	39.5% (357/903)	38.8% (348/897)
Isolated	13.9% (11/79)	3.3% (10/306)	11.8% (42/357)	14.1% (49/348)
Plus one-vessel disease	19.0% (15/79)	11.4% (35/306)	18.8% (67/357)	20.4% (71/348)
Plus two-vessel disease	32.9% (26/79)	21.9% (67/306)	31.4% (112/357)	30.5% (106/348)
Plus three-vessel disease	34.2% (27/79)	63.4% (194/306)	38.1% (136/357)	35.1% (122/348)
Three-vessel disease only	56.8% (108/192)	51.6% (332/644)	60.5% (546/903)	61.2% (549/897)

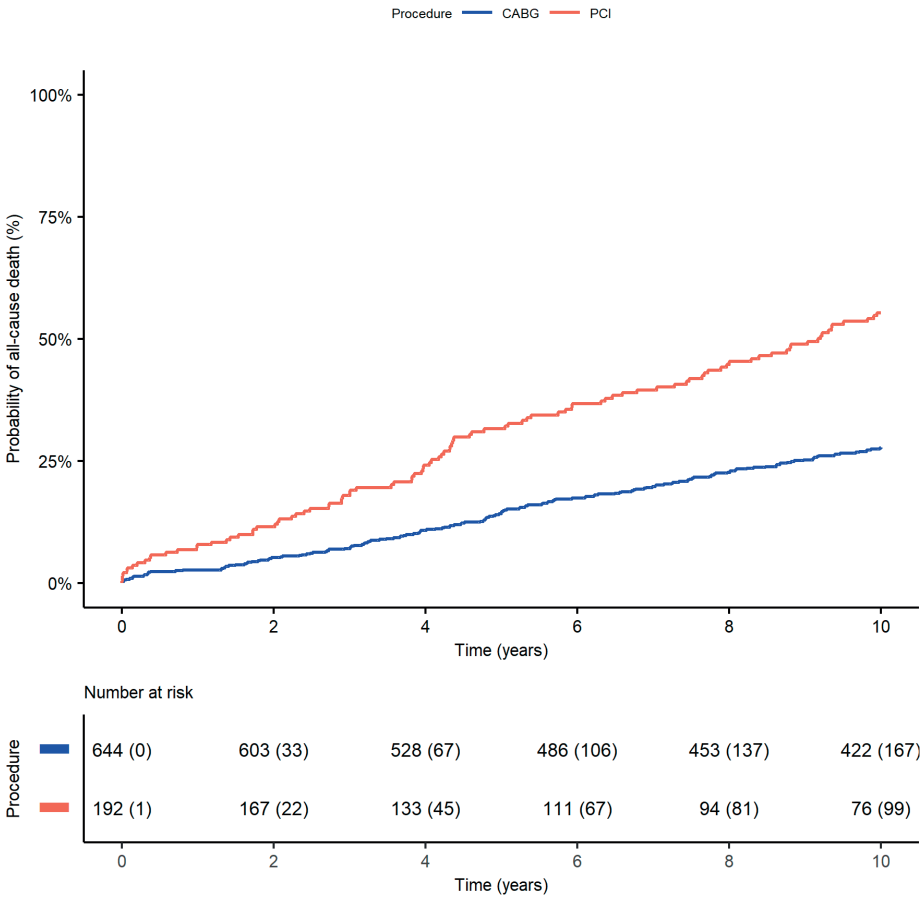
Values are mean SD (N) or % (n/N)), unless otherwise noted. Percentages might not sum to 100% as a result of rounding

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SYNTAX = Synergy between PCI with TAXUS and Cardiac Surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

Primary endpoint

PCI Registry

The primary endpoint of all-cause death at 10 years occurred in 51.6% (99/192) of patients entered into the PCI nested-registry (Central Illustration) compared to 27% (244/903) in the PCI arm of the randomized trial.



Central Illustration. Kaplan-Meier curves for primary analysis of 10-year all-cause death in coronary artery bypass grafting (CABG in blue) and percutaneous coronary intervention (PCI in red) registries, respectively.

Ten-year all-cause death was significantly lower for patients with 3VD as compared to those with LMCAD (44% (48/108) vs. 62% (49/79), respectively; HR 0.56 [95% CI 0.37–0.83]; p = 0.003) (Figure 1A).

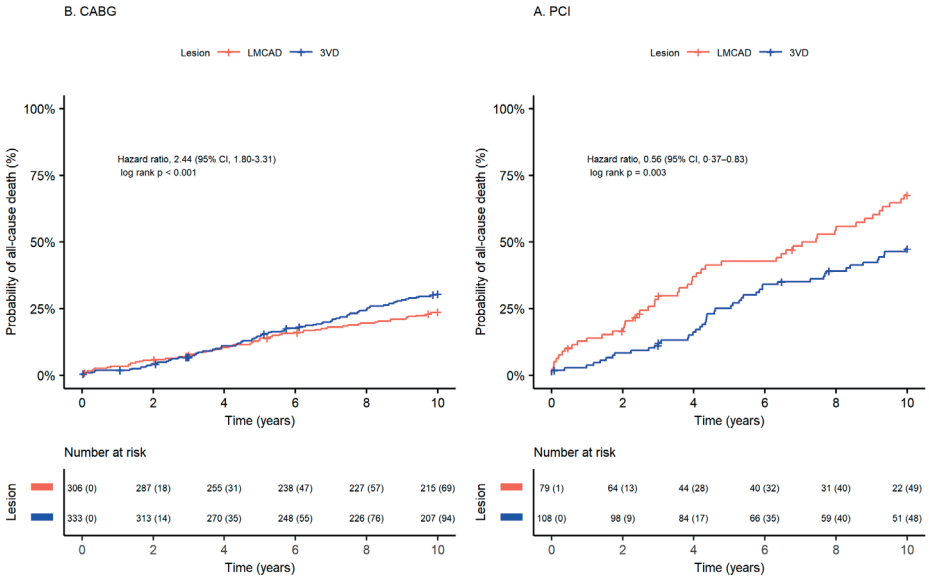


Figure 1. Kaplan-Meier curves of the three-vessel disease vs. left main disease analysis of 10-year all-cause death in (A) percutaneous coronary intervention (PCI) and (B) coronary artery bypass grafting (CABG) registries, respectively.

Among PCI patients with or without diabetes, the 10-year all-cause death occurred in 52.9% (36/68) and 50.8% (63/124), respectively (HR 1.15 [95% CI 0.76–1.74]; p = 0.49; Figure 2A).

All cause death at 10 years was 34.1% (15/44) for patients with a low SYNTAX score (<22; n=44; mean 16.5 ± 5.1), 50.8% (32/63) for patient with intermediate SYNTAX score (23-32; n=63; mean 27.7 ± 2.8), and 63.4% (52/82) in patients with high SYNTAX score (>33; n=82; mean 42.4 ± 9.2) (HR 1·53 [95% CI 1.18–2.002]; p = 0.006; Figure 3A). There was no significant difference in all-cause death between low- and intermediate-SYNTAX score groups (p = 0.11) or intermediate- and high-SYNTAX score groups (p = 0.11). However, a significant difference was observed between the low- and high-score groups (p = 0.006). Incomplete revascularisation was 63.5% (122/192).

CABG Registry

The primary endpoint of all-cause death at 10 years occurred in 25.9% (167/644) of patients after CABG (Central Illustration). This compared to 24% (211/897) 10-year all-cause death in the CABG arm of the randomized trial.

The 10-year all-cause death was 28.3% (94/332) in 3VD as compared to 22.5% (69/306) in LMCAD patients (HR 1.31 [95% CI 0.96–1.78]; p = 0.09) (Figure 1B). Sub-group

analysis revealed a significant difference in 10-year all-cause death for 40.3% (77/191) patients with versus without diabetes (19.9% (90/453); HR 2.44 [95% CI 1.80–3.31]; p < 0.001; Figure 2B).

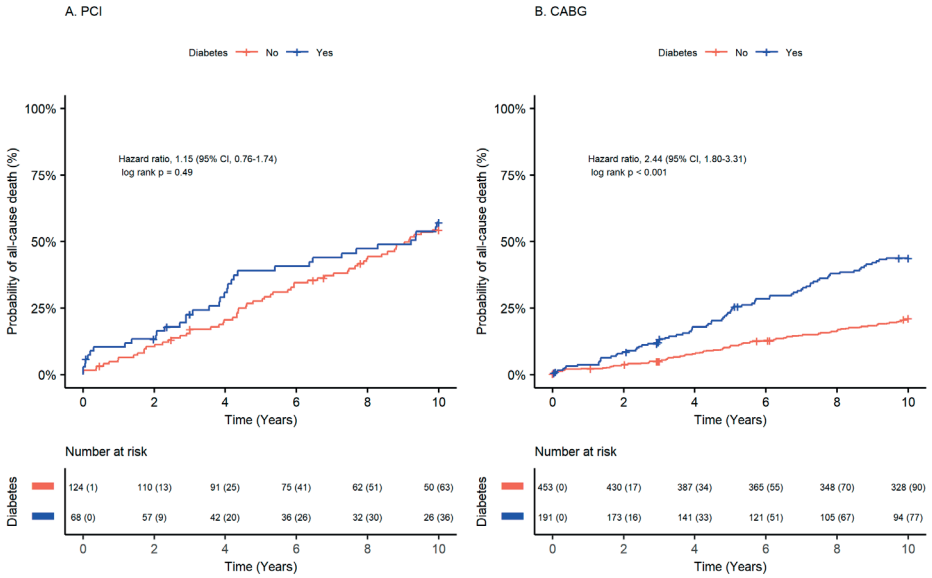


Figure 2. Kaplan-Meier curves of the diabetes vs. no diabetes analysis of 10-year all-cause death in (A) PCI and (B) CABG registries, respectively. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

All-cause death at 10 years was 17.7% (12/68) in low SYNTAX score patients (<22; n=68; mean 16.8 ± 4.1), 24.2% (39/161) in intermediate SYNTAX score patients (23-32; n=161; mean 28.2 ± 2.7), and 28.0% (113/403) in high SYNTAX score patients (>33; n=403; mean 45.2 ± 10.1; HR 1·27 [95% CI 0·99–1·62]; p = 0.16; Figure 3B). The difference in all-cause death was not statistically significant between the different score tertiles. Incomplete revascularisation was 25.3% (163/644).

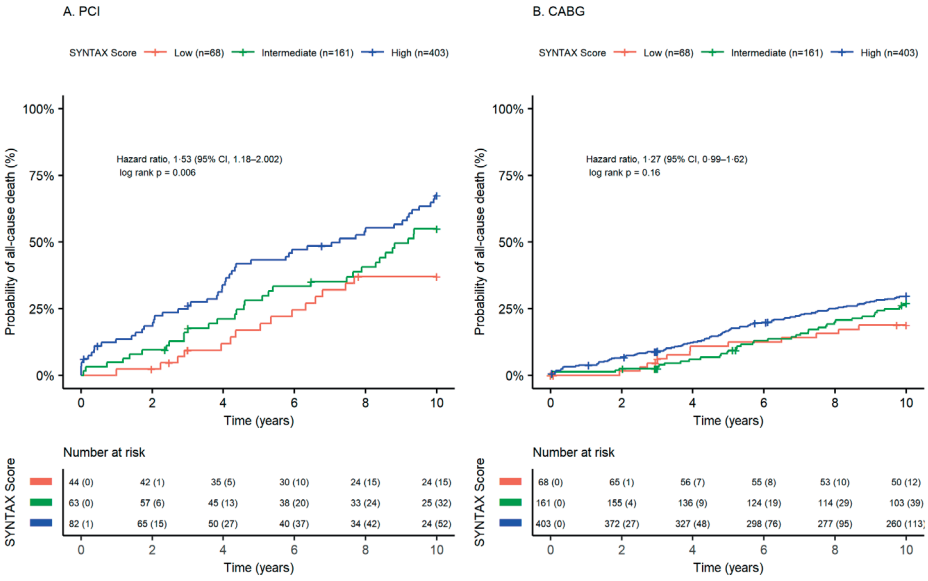


Figure 3. Kaplan-Meier curves for primary analysis of 10-year all-cause death in (A) percutaneous coronary intervention (PCI) and (B) coronary artery bypass grafting (CABG) registries, respectively, in the pre-specified SYNTAX score tertile subgroups.

DISCUSSION

The SYNTAXES study is the first to assess 10-year survival after PCI with drug-eluting stents and CABG in patients with *de novo* three-vessel and/or left main disease (8). The SYNTAX trial only randomized patients in whom both PCI and CABG would lead to clinical equipoise and entered all patients ineligible for randomization into nested-registries (7). There were 6.4% (198/3075) of all-comers with 3VD or LMCAD considered ineligible to undergo surgical revascularisation mainly due to systemic factors including frailty and comorbidities, and more than one-third, 35% (1077/3075), were deemed poor candidates for PCI, mainly due to the extent, diffuse nature and complexity of their coronary disease (7,10). This study provides important long-term insight into survival after PCI and CABG by extending follow-up to 10 years for complex patients with coronary artery disease deemed appropriate for only one revascularisation strategy.

At 10-year follow-up, the primary endpoint of all-cause death occurred in 25.9% of patients entered in the CABG-registry, and 51.6% of patients entered in the PCI-registry. In comparison, 10-year all-cause death in the SYNTAX trial was 23.5% (211/897) in CABG patients and 27.0% (244/903) in PCI patients (HR 1.17 [95% CI

0.97–1.41, p=0.09]) (8). This shows that patients who were deemed suitable for CABG had excellent 10-year survival both in the registry as in the randomized-arm of the SYNTAX trial. However, patients that were found unsuitable to undergo CABG and were entered into the PCI nested-registry showed a much worse 10-year survival prognosis compared to the PCI randomized-arm of the trial. The possible explanation could be the older age, significant comorbidities, and frailty among PCI-registry patients. It is important to note that more patients with depressed left ventricular ejection fraction (<30%) were included in the PCI nested-registry than in the PCI arm of the SYNTAX trial (5.7% vs 1.3%), which may be linked to worse outcomes. In our study, the high-risk profile of patients due to extensive comorbidities dictated treatment strategy and thereby allocated those patients to the PCI registry rather than the CABG registry.

Patients with LMCAD had significantly higher all-cause death compared with 3VD patients within the PCI registry (Table 2). Patients stratified by the type of coronary artery disease within the CABG registry had similar all-cause death rates (Table 2). The LMCAD cohort in the PCI registry had 25.3% (20/79) chronic total occlusions and 12.7% (10/79) trifurcation lesions, which may explain the high incomplete revascularisation rate of 63% (122/192). Moreover, 36.9% (45/122) of patients with incomplete revascularisation in the PCI registry had left main coronary disease.

It is important to note that there have been significant improvements in PCI techniques since the SYNTAX and SYNTAXES PCI registry enrollment. This was well demonstrated in the SYNTAX II study that incorporated physiologic assessment. Physiologic assessment was performed in 75.5% of the lesions, leading to treatment deferral of 24.5% of the stenoses (11). Furthermore, post-implantation intravascular ultrasound was performed in 76.4% of the lesions leading to stent optimization and post-dilation in 30.2% of the stented lesions (12). Additionally, the advances and improvements in techniques addressing chronic total occlusion have been associated with improved procedural outcomes (12). Intravascular ultrasound (IVUS) is also used to optimize LM PCI in current daily practice and has been recommended by multiple society guidelines (13).

In the CABG registry, patients with 3VD 10-year all-cause death occurred in 28.2% (94/332) of patients compared to 20.6% (113/549) in the randomized CABG cohort. Furthermore, CABG registry patients in the LMCAD subgroup had better long-term outcomes compared to the trial patients, as demonstrated by an all-cause death of 22.5% (69/306) compared to 28.2% (98/348), respectively.

Table 2. Outcomes in the PCI and CABG registry

Outcomes	PCI	CABG
Overall		
10-year all-cause mortality	51.6% (99/192)	25.9% (167/644)
SYNTAX score ≥33	43.4% (82/189)	63.8% (403/632)
SYNTAX score 23-32	33.3% (63/189)	25.5% (161/632)
SYNTAX score ≤22	23.3% (44/189)	10.8% (68/632)
Chronic total occlusion	36.5% (69/189)	56.4% (356/631)
Incomplete revascularisation	63.5% (122/192)	25.3% (163/644)
Left main coronary artery disease		
Overall 10-year all-cause mortality	62.0% (49/79)	22.5% (69/306)
SYNTAX score ≥33	47.3% (36/76)	68.2% (206/302)
SYNTAX score 23-32	26.3% (20/76)	17.5% (53/302)
SYNTAX score ≤22	26.3% (20/76)	14.2% (43/302)
Diabetes	30.4% (24/79)	25.2% (77/306)
Chronic total occlusion	25.3 % (20/79)	44.9% (135/301)
Incomplete revascularisation	57.0% (45/79)	22.9% (70/306)
Three-vessel disease		
Overall 10-year all-cause mortality	44.4% (48/108)	28.2% (94/332)
SYNTAX score ≥33	42.6% (46/108)	59.9% (194/324)
SYNTAX score 23-32	37.0% (40/108)	33.0% (107/324)
SYNTAX score ≤22	20.4% (22/108)	7.1% (23/324)
Diabetes	40.7% (44/108)	33.7% (112/332)
Chronic total occlusion	44.4% (48/108)	67.6% (219/324)
Incomplete revascularisation	68.5% (74/108)	27.7% (92/332)

Values are mean SD (N) or % (n/N)), unless otherwise noted. Percentages might not sum to 100% as a result of rounding

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SYNTAX = Synergy between PCI with TAXUS and Cardiac Surgery;

There was a stepwise increase in all-cause-death associated with higher SYNTAX scores. All-cause death between the low- and high- SYNTAX score tertiles within the PCI registry were significantly different (p =0.006), while there was no significant difference in all-cause death within the CABG registry patients stratified by the SYNTAX score tertile.

Study limitations: The present findings should be appraised in the light of some limitations. First, only 60% of the patients in the CABG Registry were followed for 10 years. Nonetheless, the selection of those included for follow-up was random, and there were no differences in baseline characteristics compared to those who were not followed-up (10). Second, the PCI registry contains a relatively small number of patients; therefore, some of the results should be interpreted with caution. Finally, explorative subgroup analyses by lesion subsets could not be performed due to the low patient number in separate groups.

CONCLUSION

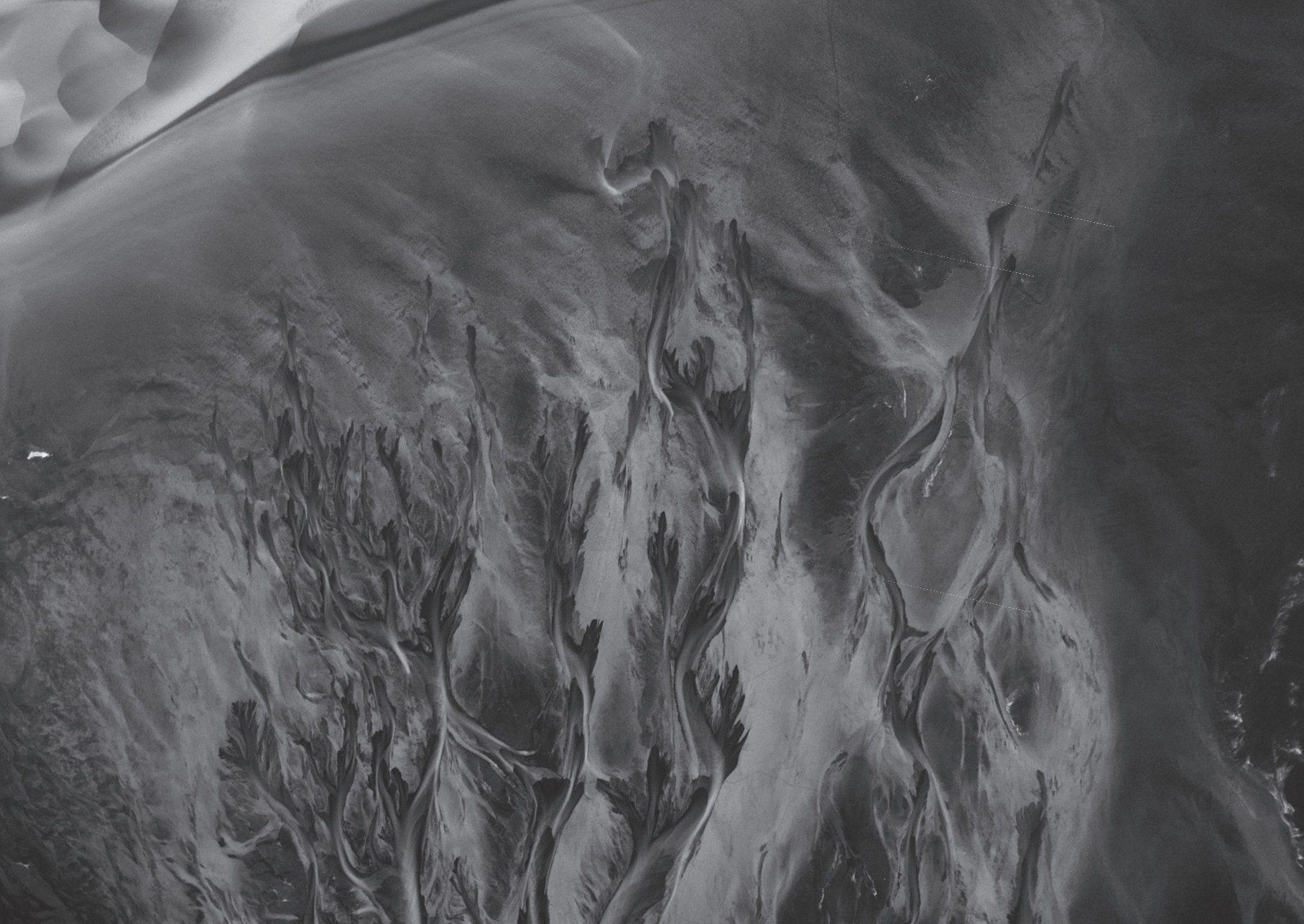
In the SYNTAX trial, patients who were deemed ineligible for PCI due to coronary disease complexity and instead enrolled in the CABG-registry showed excellent 10-year survival comparable to patients who were randomized to undergo CABG. Conversely, patients too frail to undergo CABG who were enrolled in the PCI-registry showed poor 10-year survival. Thus, patients with extensive coronary disease should ideally undergo CABG when at all feasible. Furthermore, this study shows that treatment strategy decisions should be made through a case-based heart team approach during which different aspects of comorbidities and treatment options are considered.

Abbreviations

CABG =	coronary artery bypass
CI =	confidence interval
HR =	hazard ratio
LMCAD =	left main coronary artery disease
PCI =	percutaneous coronary intervention
SYNTAX =	Synergy between PCI with TAXUS and Cardiac Surgery
SYNTAXES =	SYNTAX Extended Survival
3VD =	three-vessel disease

REFERENCES

1. Hlatky MA, Boothroyd DB, Bravata DM et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190-1197.
2. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;1:263-263.
3. Serruys PW, Ong ATL, van Herwerden LA et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005;46:575-581.
4. Rodriguez AE, Baldi J, Fernández Pereira C et al. Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). Journal Am Coll Cardiol 2005;46:582-588.
5. Hueb W, Lopes NH, Gersh BJ et al. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation 2007;115:1082-1089.
6. Ong ATL, Serruys PW, Mohr FW et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006;151:1194-1204.
7. Serruys PW, Morice M-C, Kappetein AP et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med2009;360:961-972.
8. Thuijs D, Kappetein AP, Serruys PW et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet 2019;394:1325-1334.
9. Mohr FW, Morice MC, Kappetein AP et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629-38.
10. Head SJ, Holmes DR, Jr., Mack MJ et al. Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries. JACC Cardiovasc Interv 2012;5:618-625.
11. Campos CM, Stanetic BM, Farooq V et al. Risk stratification in 3-vessel coronary artery disease: Applying the SYNTAX Score II in the Heart Team Discussion of the SYNTAX II trial. Catheter Cardiovasc Interv 2015;86:E229-38.
12. Escaned J, Collet C, Ryan N et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. Eur Heart J 2017;38:3124-3134.
13. Räber L, Mintz GS, Koskinas KC et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. Eur Heart J 2018;39:3281-3300.



Chapter 8

Long-Term Survival After CABG with Multiple Versus Single Arterial Grafts in The Randomized SYNTAX Trial

Daniel J.F.M. Thuijs*, Piroze Davierwala*, Milan Milojevic, Salil V. Deo, Thilo Noack, A. Pieter Kappetein, Patrick W. Serruys, Friedrich-Wilhelm Mohr, Marie-Claude Morice, Michael J. Mack, L. Elisabeth G.E. Ståhle, Niels J. Verberkmoes, David R. Holmes Jr., Stuart J. Head, for the SYNTAX Extended Survival Investigators

* both authors contributed equally

Submitted

ABSTRACT

Objectives

To evaluate the impact coronary artery bypass grafting (CABG) using multiple versus single arterial grafts (MAG versus SAG) on long-term survival in the SYNTAX trial.

Methods

The present analysis included the randomized and registry as-treated CABG patients (n=1509) from the SYNTAX Extended Survival study (SYNTAXES). Patients with only venous (n=42) or synthetic grafts (n=1) were excluded. The primary endpoint was all-cause death at maximum follow-up. Multi-variable Cox regression was used to adjust for differences in baseline characteristics. Sensitivity analysis using propensity matching with inverse probability for treatment weights (IPTW) was performed.

Results

Of the 1466 included patients, 465 (31.7%) received MAG and 1001 (68.3%) SAG. Patients receiving MAG were younger and at lower risk. At maximum follow-up of 12.6 years, all-cause death occurred in 23.6% of MAG and 40.0% of SAG patients (adjusted hazard ratio (HR) 0.58, 95% confidence interval (CI) [0.46-0.72], P=0.001), which was confirmed by sensitivity analysis. MAG in patients with three-vessel disease was associated with significant lower unadjusted and adjusted all-cause death at 12.6 years (adjusted HR 0.65, 95%CI [0.44-0.97], P=0.033), whereas no significance was observed following after risk-adjustment in patients with left main disease, with and without diabetes, and among SYNTAX-score tertiles.

Conclusions

In the present analysis of all-comers patients from the SYNTAX trial, MAG resulted in markedly lower all-cause death at 12.6-year follow-up, compared to a SAG strategy. Hence, the striking long-term survival benefit of MAG over SAG in the SYNTAX trial encourages a more extensive use of multiple arterial grafting.

Keywords

SYNTAX; coronary artery disease; revascularisation CABG; multiple arterial grafts; survival

INTRODUCTION

Whether coronary artery bypass grafting (CABG) should be performed with multiple arterial grafts (MAG) in patients requiring bypass surgery remains fiercely debated. Observational studies identified the long-term advantages of multiple arterial grafting compared with the use of a single arterial graft (SAG).[1-5] However, the randomized Arterial Revascularization Trial ART trial failed to show superiority of CABG with a bilateral- versus a single internal mammary artery (BITA versus SITA) in the intention-to-treat analysis. The as-treated analysis, however, showed that multiple arterial grafting resulted in a significant decrease in all-cause death (18.6%) compared with the use of a single arterial graft (23.1%; HR 0.81, 95% CI [0.68-0.95]).[6] Besides, at a 10 year follow-up, the overall patency for venous bypass grafts is considerably lower than that for arterial bypass grafts. (61% vs. 85%, respectively).[7] Therefore, assessment of all-cause death after MAG versus SAG beyond 10-year follow-up is required to adequately support the clinical utility of a multiple arterial grafting strategy in daily CABG practice. The present pre-specified sub-analysis of the SYNTAX Extended Survival study [8] aimed to evaluate the impact of multiple arterial grafts versus a single arterial graft on long-term survival (>10 years) in patients with complex coronary artery disease (CAD).

METHODS

Study design

The rationale, design and outcomes of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (NCT00114972) have been reported previously.9-13 In brief, the SYNTAX trial randomized patients with de novo three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD) to undergo either percutaneous coronary intervention (PCI) with paclitaxel-eluting stents or CABG. Patients who were ineligible for randomization were included in parallel nested registries for PCI-ineligible patients (CABG registry n=1077) and CABG-ineligible patients (PCI-registry n=198). Out of the 1077 patients in the CABG registry, 649 were randomly allocated for a long-term follow-up, of which 644 underwent CABG (as-treated).

The present analysis is a sub-study of the SYNTAX Extended Survival study (NCT03417050) and included patients from the randomized and registry cohorts of the SYNTAX trial that underwent CABG.[8] Patients who received only venous or synthetic grafts were excluded. Follow-up was performed in accordance with local

law and regulations of each participating institution and complied with the Declaration of Helsinki. The extended follow-up of the SYNTAXES study was funded by the German Heart Research Foundation (GHF; Frankfurt am Main, Germany). The sponsor had neither a role in the study design nor in the collection, analyses and interpretation of the study data, nor in the decision to publish.

Endpoints and definitions

The primary endpoint of the current study was all-cause death in patients who underwent CABG with multiple versus single arterial grafts (as-treated MAG versus SAG). Furthermore, the primary endpoint was examined in pre-specified subgroups of patients (i) with three-vessel disease, (ii) LMCAD (iii) patients with medically treated diabetes and (iv) those without diabetes, and (v) according to SYNTAX score tertiles (low: 0-22, intermediate 23-32, high≥33).

The MAG cohort consisted of patients who received two or more arterial grafts, irrespective of configuration or type of graft (internal thoracic arteries, radial artery or gastroepiploic artery). The SAG cohort consisted of patients with only one single arterial graft. LMCAD was defined as patients having any left main disease, either isolated, or with single-vessel, two-vessel or three-vessel CAD. Three-vessel disease was defined as patients with CAD involving all three vessels, in the absence of LMCAD.[9, 12] Coronary disease anatomical complexity was reported according to the SYNTAX score, with higher SYNTAX scores indicating more complex CAD.[14] SYNTAX score subgroups were defined according to the classical tertiles; low ≤22, intermediate 23-32 and high ≥33.[10, 15] The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was used to predict operative risk. Diabetes was defined as those patients requiring treatment with oral hypoglycemic agents and/or insulin. Incomplete revascularisation was determined post-procedurally by correlating all lesions requiring bypass, identified during the preoperative Heart Team meeting, to those lesions that were revascularized during the procedure.

Coronary artery bypass grafting techniques

Bypass surgery was performed with the aim to achieve complete revascularisation of all vessels with a diameter ≥ 1.5 mm or larger and with an angiographic diameter stenosis of ≥ 50% as quantified on coronary angiography and discussed during preoperative Heart Team meetings. The choice and configuration of bypass grafts, as well as the surgical technique utilized, was left at the discretion of the individual surgeon.

Statistical analyses

The current analysis was performed according to the as-treated principle. Discrete variables were expressed as percentages with frequencies, and were compared by Chi-square tests or Fisher's exact test when the expected frequency in any cell was less than 5. Continuous variables were summarized as mean ± standard deviation (SD) and were compared by independent samples t-test, if normally distributed, or the Wilcoxon rank-sum test if non-normally distributed. Unadjusted cumulative all-cause death rates were estimated according to the Kaplan–Meier method and the difference between the use of MAG and SAG was evaluated with a log-rank test. Kaplan Meier survival curves are truncated at a time-point in follow-up, when at least 10% of patients were still at risk, to avoid visual misinterpretation.[16] Exploratory analyses were performed for bilateral versus single internal thoracic artery (BITA vs SITA) and total arterial revascularisation (TAR) versus without TAR. Survival analyses for the use of MAG versus SAG were adjusted using multivariable Cox regression analysis that included the following combination of clinically and statistically relevant pre-operative variables[17]: age (as a continuous variable; per 1 year increase), sex, body mass index ≥ 30kg/m^2 , medically treated hypertension, medically treated hyperlipidemia, history of myocardial infarction (MI), unstable angina, history of stroke and/or transient ischemic attack, medically treated diabetes mellitus, peripheral vascular disease, carotid artery disease, Creatinine >200 micromole per liter, chronic obstructive pulmonary disease, left ventricular ejection fraction<50%, presence/absence of LMCAD, and SYNTAX score (as a continuous variable). To further confirm results obtained with the multi-variable Cox model, a sensitivity analysis was performed using propensity score derived weighing. Hence, the same preoperative covariates were included in a mixed model to develop a propensity score for each patient to receive MAG rather than SAG. Volume differences between MAG vs SAG among 85 centers included in the original SYNTAX study were corrected for by including this as a random effect term in the mixed model. From the propensity scores, truncated Inverse Probability Treatment Weighting (IPTW) weights (limited to 1st and 99th percentile) were calculated and included to fit a weighed Cox proportional hazards model for all-cause mortality. More information regarding the statistical methods and relevent results are presented in the Supplementary Materials. Finally, adjusted survival analyses in the pre-specified subgroups between the use of MAG versus SAG were performed by multivariable Cox regression analysis adjusting for the same preoperative variables mentioned above. Statistical tests were reported as 2-sided, and a P<0.05 was considered as statistically significant. Statistical analyses were performed with SPSS Statistics software, version 24 (IBM Corporation, Armonk, NY, USA) and R (The R Foundation for Statistical Computing, Austria).

RESULTS

Patient-flow and characteristics

The as-treated CABG cohort consisted of 1466 patients, with 465 in the MAG and 1001 the SAG group (Figure 1). Information on vital status of patients at the 10-year follow-up mark was available in 94% of all included patients. The mean age of patients who received MAG was 62.3 years versus 66.5 years in patients who received SAG (P<0.001, Table 1). Patients receiving MAG were less likely to be female and had a lower cardiovascular risk-profile. Approximately a quarter of patients had diabetes. The mean EuroSCORE was 2.9 versus 4.4 (P<0.001) and the mean SYNTAX score was 32.2 versus 33.3 (P=0.14), among MAG versus SAG patient, respectively.

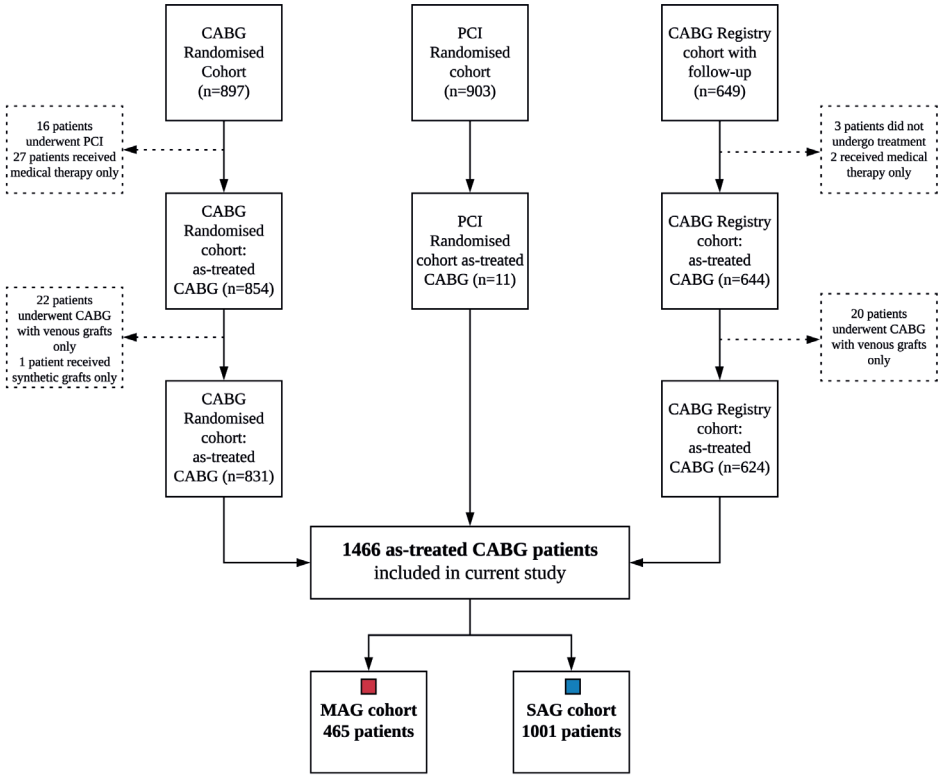


Figure 1. Flow of as-treated CABG patients through the SYNTAX trial.
Abbreviations used: CABG; coronary artery bypass grafting, MAG; multiple arterial grafting, PCI; percutaneous coronary intervention, SAG; single arterial grafting.

Table 1. Baseline demographic and clinical characteristics of patients undergoing CABG in the SYNTAX trial.

Characteristics	CABG (n = 1466)[#]		
	MAG (N=465)	SAG (N=1001)	P-value
Age (years)	62.3 ± 9.7	66.5 ± 9.2	<0.0001
Female sex – no. (%)	64 (13.8)	224 (22.4)	<0.0001
Body mass index ≥30 (kg/m^2) – no (%)	144 (31.0)	310/1000 (31.0)	0.99
Medically Treated Diabetes – no. (%)			
Oral medication or insulin	103 (22.2)	259 (25.9)	0.12
Insulin	38 (8.3)	102 (10.2)	0.22
History of nicotine abuse – no. (%)	319/462 (69.0)	657/994 (66.1)	0.27
History of Chronic Obstructive Pulmonary Disease – no. (%)	34 (7.3)	89 (8.9)	0.31
Carotid Artery disease – no. (%)	45 (9.7)	101 (10.1)	0.81
Peripheral Vascular Disease – no. (%)	49 (10.5)	128 (12.8)	0.22
Creatinine >200 micromol/L	6 (1.3)	21 (2.1)	0.29
History of myocardial infarction – no. (%)	128/457 (28.0)	351/984 (35.7)	0.004
History of stroke or TIA– no. (%)	39/464 (8.4)	94/996 (9.4)	0.52
Medically Treated Hypertension (≥130/85mmHg) – no. (%)	344/459 (74.9)	742/990 (74.9)	>0.99
Medically Treated Hyperlipidemia – no. (%)	361/459 (78.6)	751/985 (76.2)	0.31
Angina – no. (%)			
Stable	265 (57.0)	610 (60.9)	0.15
Unstable	119 (25.6)	256 (25.6)	0.99
Impaired Left Ventricular Ejection Fraction (<50%) – no. (%)[Ω]	74 (15.9)	265/996 (26.6)	<0.0001
EuroSCORE value – mean ± SD	2.9 ± 2.9	4.4 ± 4.9	<0.0001
SYNTAX score* – mean ± SD	32.2 ± 12.8	33.3 ± 13.0	0.14
No. of lesions* – mean ± SD	4.3 ± 1.7	4.4 ± 1.8	0.80
Left main[∞], any	181 (38.9)	445 (44.5)	0.046
Three-vessel[∞], without left main involvement	284 (61.1)	556 (55.5)	0.046

Values are shown as mean ± SD (standard deviation) or frequencies in percentages and (n), unless otherwise noted. [#]Data is reported according the as-treated principle based on the randomized and registry as-treated CABG patients. Ω Impaired left ventricular ejection fraction (LVEF) was defined as < 50%. *core laboratory assessment, [∞]site reported. Abbreviations used: MAG: multiple arterial grafts, SAG: single arterial graft, CABG; coronary artery bypass grafting, BMI: body mass index, TIA: transient ischemic attack.

Off-pump surgery was performed in 101 patients (21.7%) who underwent CABG with MAG versus 146 patients (14.5%) who received SAG (Table 2). Both MAG and SAG patients received an average of 2.8 conduits per patients, with 3.4 distal anastomoses per patient. BITA grafting was performed in 341 patients (73.3) who received MAG. In the SAG cohort, 995 patients (99.4%) received a single left internal thoracic artery (LITA), 2 patients a radial artery (0.2%) and 4 patients (0.4%) a single right internal thoracic artery (RITA), in addition to venous grafts. The rate of complete revascularisation was similar among patients receiving MAG (68.0%) versus SAG (69.4%).

Table 2. Surgical characteristics.

Characteristic	MAG (N = 465)	SAG (N = 1001)	P-value
Average number of conduits per patient	2.8 ± 0.7	2.8 ± 0.8	0.74
Average number of distal anastomoses per patient	3.4 ± 0.9	3.4 ± 1.0	0.75
Off-pump CABG	101 (21.7)	146 (14.5)	0.003
Grafts used*:		*	
LITA	463 (99.6)	995 (99.4)	0.68
LITA/RITA	341 (73.3)	0 (0)	<0.0001
Radial artery	192 (41.3)	2 (0.2)	<0.0001
Gastroepiploic Artery	1 (0.2)	0 (0)	0.14
Venous	245 (52.7)	985 (98.4)	<0.0001
Arterial graft to LAD	461 (99.8)	977 (98.0)	0.008
Complete revascularisation	316 (68.0)	695 (69.4)	0.57

Values are shown as mean ± SD (standard deviation) or frequencies in percentages and (n), unless otherwise noted. "*Four patients received a single right internal thoracic artery (RITA), in addition to venous graft(s) in the "single" cohort. Abbreviations used: MAG: multiple arterial grafts, SAG: single arterial graft, CABG: coronary artery bypass grafting, LAD: left anterior descending artery, LITA: left internal thoracic artery, RITA: right internal thoracic artery.

Clinical outcomes

At 12.6 years of follow-up, all-cause death occurred in 23.6% of patients who received MAG versus 40.0% of those undergoing CABG with SAG (unadjusted HR 0.65, 95% CI [0.51-0.83], P<0.001, Figure 2, graphical abstract). After correcting for preselected baseline variables, MAG remained to be associated with a significant lower all-cause death rate as compared with those undergoing CABG with SAG (adjusted HR 0.74 (95% CI [0.55-0.98], P=0.038, Table 3).

CABG with MAG was associated with lower unadjusted all-cause death rates in pre-specified subgroups of patients with 3VD and LMCAD (unadjusted HR 0.56, 95% CI [0.41-0.75]; and HR 0.60, 95% CI [0.43-0.85], respectively, P for interaction=0.73) (Figure 3A, 3B, Table 3). Furthermore, the use of MAG provided an unadjusted survival benefit in subgroups of patients with diabetes, without diabetes (Figure 3C, 3D) and in those with the least and most complex CAD (as reflected by low and high SYNTAX scores, Figure 4A-4C), compared with SAG. After multivariable adjustment the 12.6-year survival benefit of MAG over SAG remained significant in patients with 3VD (adjusted HR 0.65, 95% CI [0.44-0.97], P=0.033, Table 3), while a numerical and non-significant difference was found after adjustment in subgroup of patients with LMCAD, with and without diabetes and according to CAD complexity defined by SYNTAX score tertiles. The IPTW sensitivity analysis confirmed that MAG was associated with lower mortality [(HR 0.75, 95% CI [0.57 - 0.99], P = 0.04]; Supplemental Materials, Figure S1-S2).

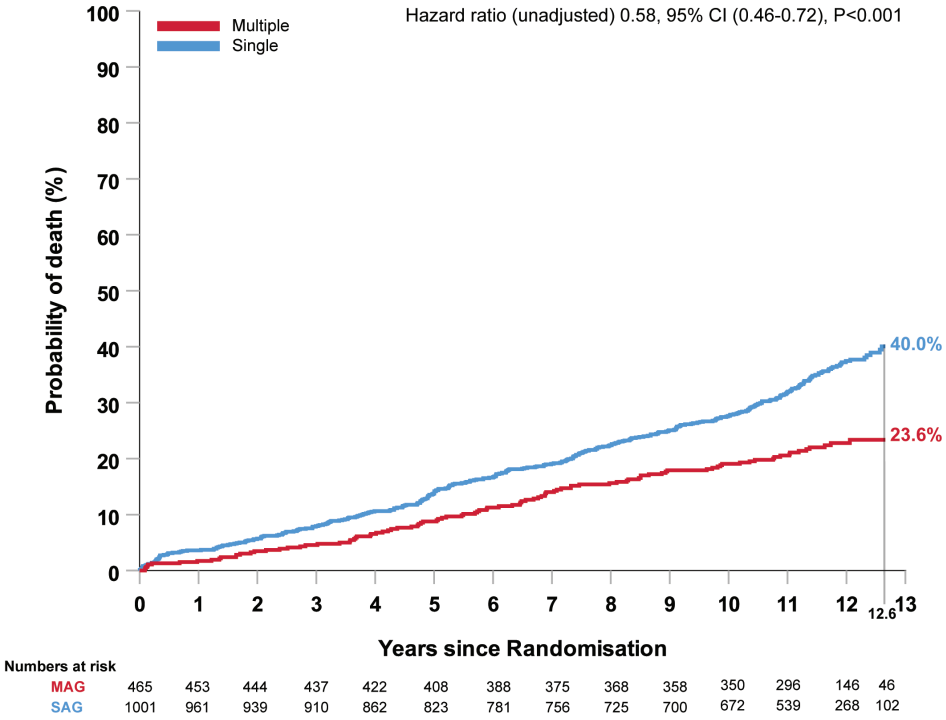


Figure 2. All-cause death of patients who underwent CABG with single versus multiple arterial grafts. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in the overall cohort of patients who underwent CABG with multiple arterial grafts (MAG; red curve) versus single (SAG; blue curve) revascularisation

Abbreviations used: HR; hazard ratio, CI; confidence interval, MAG; multiple arterial grafts, SAG; single arterial graft.

Exploratory analyses showed that CABG using bilateral internal thoracic arteries versus a single internal thoracic artery was associated with a lower rate of all-cause death at 12.6 years (BITA: 21.8% vs SITA: 40.3%; unadjusted HR 0.54, 95%CI [0.42-0.70], P<0.001 and adjusted HR 0.72, 95%CI [0.52-1.01], P=0.054, Supplementary Materials Figure S3). Of those that received SITA, only 2 patients received an additional radial artery graft (0.2%), whereas it was used in 73 patients (21.4%) undergoing BITA grafting. Total arterial revascularisation (TAR), compared with no-TAR, was associated with a significant unadjusted lower all-cause death rate at 12.6 years follow-up (unadjusted HR 0.70, 95%CI [0.55-0.93P=0.015, Supplementary Materials Figure S4). Of note, 245 patients from the no-TAR cohort underwent CABG with multiple arterial grafts. After multivariable adjustment the difference in favor of total arterial revascularisation was no longer statistically significant (adjusted HR 0.80, 95%CI [0.55-1.16], P=0.24).

Table 3. Multivariable Cox Regression model: unadjusted and adjusted outcomes (as-treated).

Cohort	MAG 12.6-year deaths (%)	SAG 12.6-year deaths (%)	Unadjusted Hazard Ratio (95% CI), P-value	*P* for interaction	Adjusted Hazard Ratio (95% CI), P-value
Overall	23.6	40.0	0.58 (0.46-0.72), *P*<0.001	-	0.74 (0.55-0.98), *P*=0.038**
Three-vessel disease	22.5	38.5	0.56 (0.41-0.75), *P*<0.001	0.73	0.65 (0.44-0.97), *P*=0.033
Left main disease	24.9	42.3	0.60 (0.43-0.85), *P*=0.004		0.85 (0.54-1.34), *P*=0.49
Diabetes	39.5	56.7	0.67 (0.46-0.97), *P*=0.036	0.43	0.73 (0.43-1.24), *P*=0.25
No diabetes	19.1	34.6	0.55 (0.42-0.73), *P*<0.001		0.76 (0.54-1.09), *P*=0.14
Coronary complexity					
SYNTAX score 0 – 22	17.5	35.3	0.47 (0.28-0.80), *P*=0.005		0.83 (0.41-1.66), *P*=0.60
SYNTAX score 23-32	28.4	41.7	0.70 (0.48-1.01), *P*=0.060		0.74 (0.44-1.24), *P*=0.25
SYNTAX score ≥ 33	23.6	41.0	0.58 (0.42-0.81), *P*=0.001	0.86	0.71 (0.47-1.09), *P*=0.11

Cox Regression Model on the primary outcome of ten-year all-cause death. Data is reported according the as-treated principle. Ω Impaired left ventricular ejection fraction (LVEF) was defined as < 50%. *core laboratory assessment, °site reported. Variables used in the full multivariable Cox regression analysis: age, sex, hypertension, hyperlipidemia, stroke or TIA, diabetes mellitus, peripheral vascular disease, carotid artery disease, chronic obstructive pulmonary disease, creatinine >200micromol/L, left ventricular ejection fraction<50% and SYNTAX score (as a continuous variable). Abbreviations used: MAG: multiple arterial grafts, SAG: single arterial graft, BMI: body mass index (kg/m^2), CABG; coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, LVEF: left ventricular ejection fraction. **This result was confirmed with a weighted Cox proportional hazards model [HR : 0.75 95% CI (0.57 - 0.99) p = 0.04].

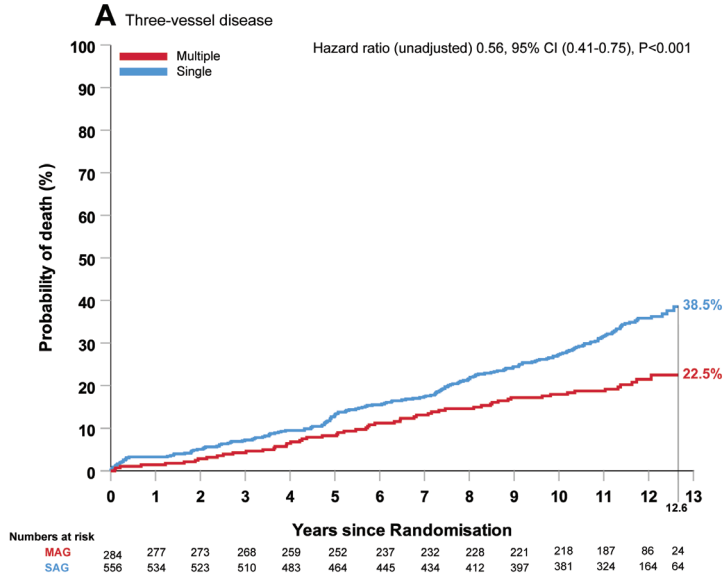


Figure 3. – PANEL A 3VD

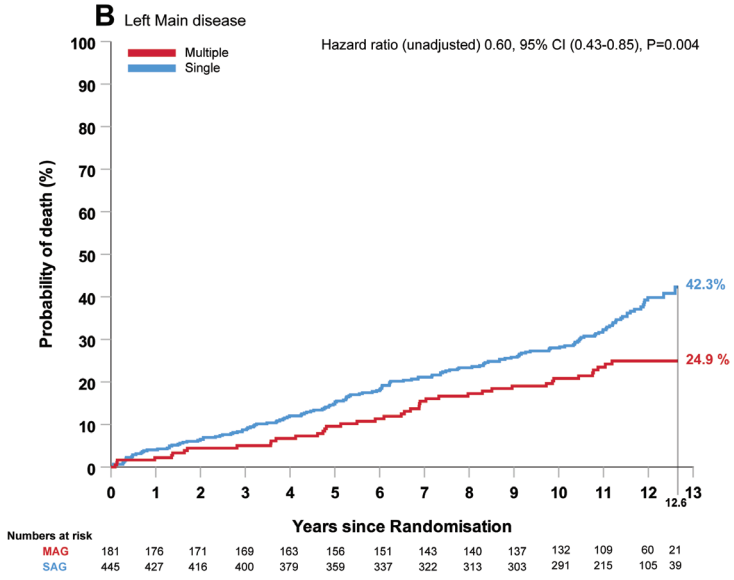


Figure 3. – PANEL B LMCAD

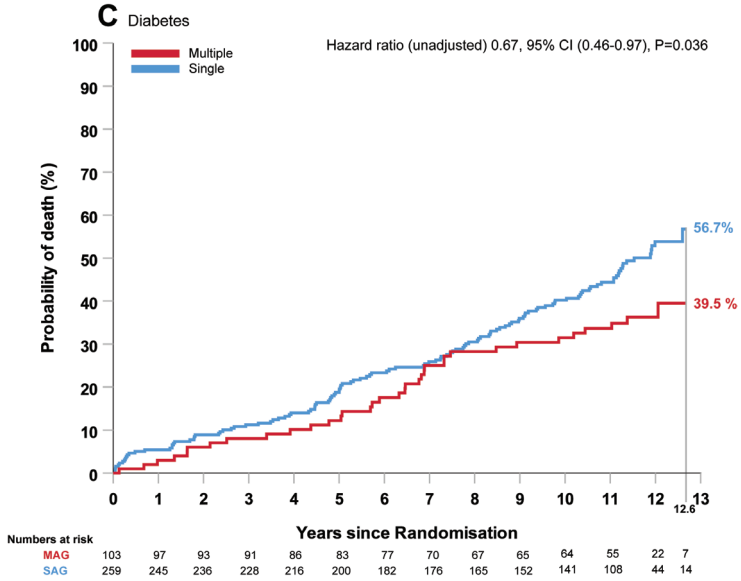


Figure 3. – PANEL C Diabetes

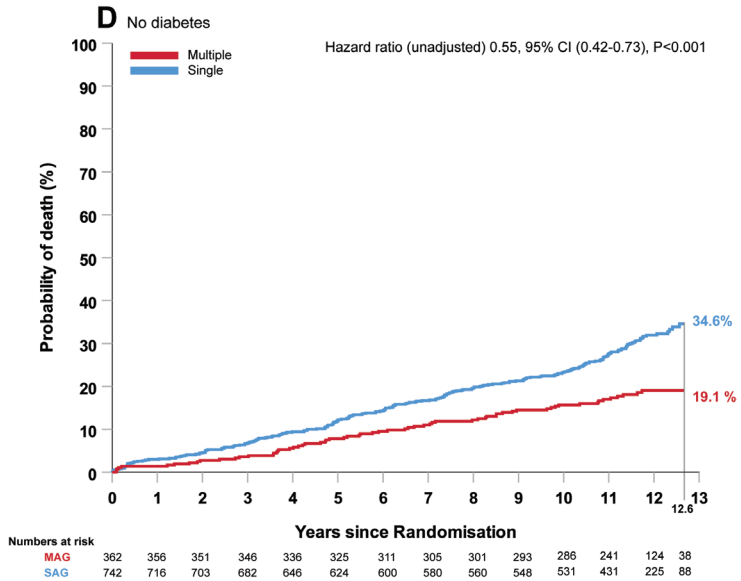


Figure 3. – PANEL D NO Diabetes

All-cause death in patients with three-vessel disease, left main disease, diabetes and no diabetes, who received multiple versus single arterial grafts. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in patients with 3VD that underwent CABG and received multiple arterial grafts (MAG; red curve) versus single (SAG; blue curve) (Panel A), those with left main disease (Panel B), medically treated diabetes (Panel C) and those without diabetes (Panel D). The widths of 95% confidence intervals were not adjusted for multiple comparisons, therefore these intervals should not be used for inference about between-group differences. Abbreviations used: HR; hazard ratio, CI; confidence interval, MAG; multiple arterial grafts, SAG; single arterial graft.

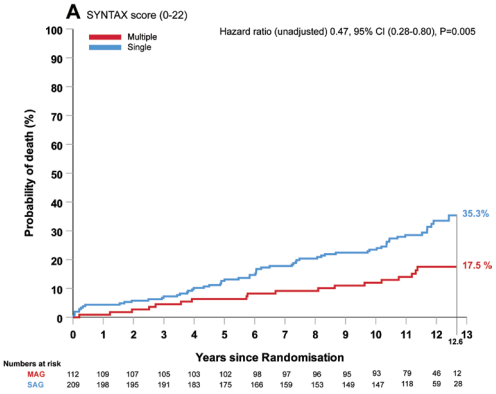


Figure 4. – PANEL A – SYNTAX score 0-22

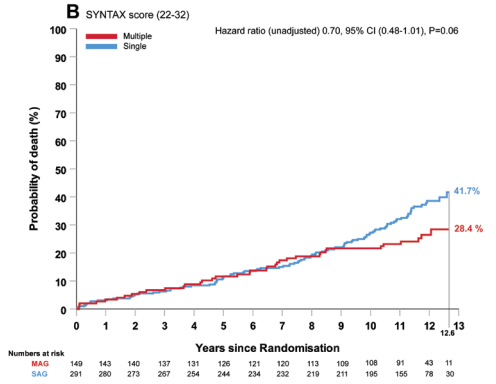


Figure 4. – PANEL B – SYNTAX score 23-32

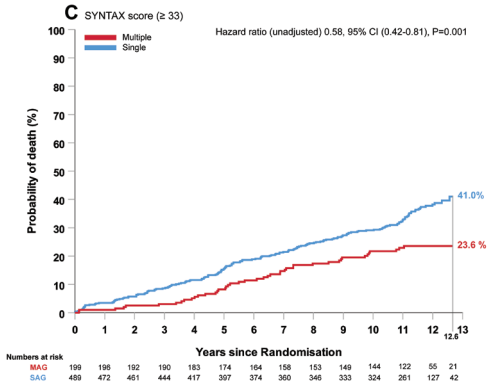
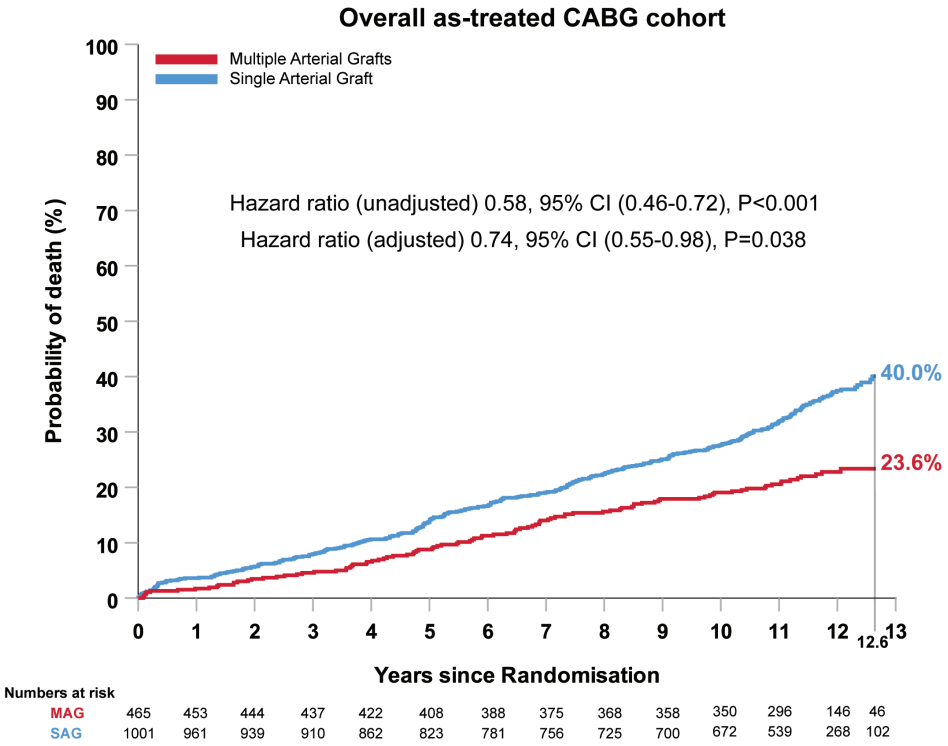


Figure 4. – PANEL C – SYNTAX score ≥33

All-cause death in patients with multiple versus single arterial grafts according to SYNTAX score tertiles. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in patients who underwent CABG and received multiple arterial grafts (MAG; red curve) versus single (SAG; blue curve) according to SYNTAX score tertiles; low (0-22; Panel A), intermediate (23-32; Panel B), and high (≥33; Panel C). The widths of 95% confidence intervals were not adjusted for multiple comparisons, therefore these intervals should not be used for inference about between-group differences. Abbreviations used: HR; hazard ratio, CI; confidence interval, MAG; multiple arterial grafts, SAG; single arterial graft.



Graphical abstract.

All-cause death of patients with multiple arterial grafts versus a single arterial graft in the as-treated CABG cohort from the SYNTAX trial. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in the overall cohort of patients who underwent CABG with multiple arterial grafts (red curve; n=465) versus a single arterial graft (blue curve; n=1001). *This result was confirmed with a weighted Cox proportional hazards model [HR : 0.75 95% CI (0.57 - 0.99) p = 0.04]. Abbreviations used: HR; hazard ratio, CI; confidence interval, MAG; multiple arterial grafts, SAG; single arterial graft.

DISCUSSION

CABG using multiple arterial grafts, compared to using a single arterial graft, was associated with lower all-cause death at 12.6 year follow-up in patients with *de novo* three-vessel and left main coronary artery disease from the SYNTAX trial. The significant survival benefit of using multiple arterial grafts remained after adjusting for differences in baseline characteristics (Graphical Abstract). This result was also confirmed with inverse probability weighed Cox regression. In pre-specified subgroups of patients with 3VD, LMCAD, those with diabetes and those without, CABG using multiple arterial grafts was associated with a significant survival benefit at 12.6-year follow-up. After adjusting for differences in baseline characteristics, MAG remained associated with a survival benefit for patients with 3VD, while no differences in all-cause death were found in patients with LMCAD and those with or without diabetes.

Although from a pathophysiological standpoint it is reasonable to expect that arterial grafts improve graft-patency and clinical outcomes compared with venous grafts, proof remains limited to observational data.[4, 7, 18-22] While the ART trial showed no difference in survival between bilateral versus single internal thoracic artery revascularisation multiple arterial grafting in the as-treated analyses demonstrated a significant survival benefit compared with a single arterial grafting strategy.(5) Some of the methodological limitations of the ART guided the design of the Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts (ROMA) trial which aims to determine the impact of using at least 2 arterial grafts to the left coronary system on 10-year survival in 4300 patients [23]; however, the first study results are unlikely to be published before 2025. Results reported in the present study are comparable to the as-treated MAG versus SAG 10-year all-cause death outcomes from the randomized ART trial (adjusted HR 0.81, 95% CI [0.68-0.95]).[6] Moreover, present data corresponds well with real-world data from large registries and single center studies that showed a significant reduction in all-cause death beyond 10year follow-up.[24, 25]

Pre-specified subgroup analysis revealed that MAG, compared with SAG, remained associated with significantly lower all-cause death in patients with 3VD, even after adjusting for differences in characteristics between groups. The adjusted, non-significant, HR in favor of MAG for patients with LMCAD (HR 0.85, 95%CI [0.54-1.34]) provides reassuring long-term insights that multiple arterial grafting is safe to perform in this specific patient population.[26]

The majority of patients with diabetes have diffuse and complex CAD. The present study found that 57% of patients with diabetes that received SAG have died during 12.6-year follow-up, versus 40% of patients who received MAG. This survival difference was associated with a significant, unadjusted, decreased risk of all-cause death in favor of MAG (HR 0.67, P=0.036). After adjusting for differences in baseline characteristics, this trend remained similar, yet was no longer significant. The propensity-matched analysis by Yamaguchi *et al.* reported decreased 12-year all-cause death rates with MAG versus SAG in patients with (35.1% vs 41.2%, P = 0.041) and without diabetes (28.6 vs 36.2%, P=0.014).[27] Furthermore, an increasing number of arterial grafts have been shown to have an incremental survival benefit in both patients with and without diabetes.[28]

Both the right internal thoracic artery and the radial artery have been associated with less adverse event and show a survival benefit compared with venous conduits.[1, 3, 21, 29] In the present study, 41% of patients in the MAG cohort received

radial arteries and almost three-quarters received bilateral internal thoracic arteries (BITA). At 12.6 years, unadjusted all-cause death rates were significantly lower for patients that received BITA versus SITA and for those that received TAR versus no-TAR. A trend towards a survival benefit with BITA and TAR, compared with the use of a single artery, remained after adjusting for clinically and statistically relevant baseline differences. The use of additional arterial grafts in 245 patients (19.9%) in the no-TAR cohort may have skewed the survival outcomes in its favor following adjustment.

The major strength of the SYNTAX trial was that all patients were discussed in a multidisciplinary heart team, consisting of a cardiac surgeon, a clinical cardiologist and an interventional cardiologist. Prior to receiving either PCI or CABG, all significantly stenosed coronary vessels were assessed and those suitable for revascularisation determined. After myocardial revascularisation completeness of revascularisation was verified based on the number of vessels revascularized compared to those deemed suitable for revascularisation prior to intervention. The rate of complete revascularisation in both treatment groups in our study was lower than observed in previous studies.[30-32] These differences most certainly reflect the variation in definitions of completeness of revascularisation used across clinical trials, yet could also be partly explained by the greater anatomical complexity of coronary artery disease in patients included in the SYNTAX trial and in the nested CABG registry (higher burden of cardiovascular risk factors and a higher SYNTAX score). Severely calcified and diffusely diseased coronary arteries and small-sized (<2 mm) vessels distal to the lesion were the most common rationale for incomplete revascularisation in the CABG cohort of the SYNTAX trial. [33] Inability to graft such vessels is usually not associated with an increased risk of adverse events, which was clearly evident after 3-year follow-up of CABG patients in the SYNTAX trial who did not undergo complete revascularisation. Additional studies with longer follow-up (≥ 10-year) are warranted to determine the influence of complete revascularisation on clinical outcomes beyond 3 years.

Strengths and limitations

The high rate of completeness of follow-up and that follow-up is extended beyond 10 years are major strengths of the current study.

Results from this study should be considered as 'hypothesis-generating', as patients were not randomly allocated to undergo multiple versus single arterial grafting. Any influence of inter-institutional variation regarding patient selection, preferred surgical techniques and surgical experience could not be adequately corrected for.

Moreover, apart from well-designed randomized studies, none of the statistical methods that adjust for confounding factors are sufficient to fully account for confounders.[34] Furthermore, the modest sample size among subgroups of patients could have influenced results after adjusting for differences in baseline characteristics. Finally, the rate of incomplete revascularisation (approximately 28%) in combination with the suboptimal use of guideline directed medical treatment in patients from the SYNTAX trial could have diminished overall long-term survival in both cohorts.[10, 35]

CONCLUSION

In the present analysis of 1466 all-comers patients from the SYNTAX trial undergoing bypass surgery, CABG using a multiple arterial grafting strategy, as compared with using a single arterial graft, resulted in markedly lower incidence of all-cause death. This survival benefit of using MAG over SAG remained significant after adjusting for differences in important preselected patient characteristics between MAG and SAG. MAG in patients with three-vessel disease was associated with a significantly lower unadjusted and adjusted rate of all-cause death, while no statistically difference was identified in subgroups of patients with LMCAD and diabetes after adjusting for differences in important baseline variables. The markedly 12.6-year survival benefit of CABG using MAG over SAG in the SYNTAX trial strongly encourages a more extensive use of multiple arterial grafting in selected patients.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

Dr. Kappetein reports to work as employee of Medtronic, outside the submitted work. Dr. Serruys reports personal consultancy fees from Abbott Laboratories, Biosensors, Cardialysis, Medtronic, Micell, Sino Medical Sciences Technology, Philips/Volcano, Xeltis and Heartflow. Dr. Mack reports non-financial support from Edwards Lifesciences, non-financial support from Medtronic and non-financial support from Abbott, outside the submitted work. Dr. Verberkmoes reports personal fees from Medtronic and personal fees from Atricure, outside the submitted work. Dr. Head reports to work as employee of Medtronic, outside the submitted work. All other authors report no potential conflict(s) of interest relevant to this publication.

Abbreviations

3VD #	three-vessel coronary artery disease
BITA #	bilateral internal thoracic artery
CABG #	coronary artery bypass grafting
CAD #	coronary artery disease
CI #	confidence interval
EuroSCORE #	The European System for Cardiac Operative Risk Evaluation
GHF #	German Heart Research Foundation
HR #	hazard ratio
IPTW #	inverse probability for treatment weights
LMCAD #	left main coronary artery disease
MAG #	multiple arterial grafting
SAG #	single arterial grafting
SITA #	single internal thoracic artery
SYNTAX #	Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery
SYNTAXES #	SYNTAX Extended Survival study
TAR #	total arterial revascularisation

REFERENCES

1. Taggart DP, D'Amico R and Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *The Lancet*. 2001;358:870-875.
2. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M and Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg*. 2010;90:101-8.
3. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD and Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. *Ann Thorac Surg*. 2004;78:2005-12; discussion 2012-4.
4. Buttar SN, Yan TD, Taggart DP and Tian DH. Long-term and short-term outcomes of using bilateral internal mammary artery grafting versus left internal mammary artery grafting: a meta-analysis. *Heart*. 2017;103:1419-1426.
5. Chikwe J, Sun E, Hannan EL, Itagaki S, Lee T, Adams DH and Egorova NN. Outcomes of Second Arterial Conduits in Patients Undergoing Multivessel Coronary Artery Bypass Graft Surgery. *J Am Coll Cardiol*. 2019;74:2238-2248.
6. Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, Gaudino M, Zamvar V, Bochenek A, Buxton B, Choong C, Clark S, Deja M, Desai J, Hasan R, Jasinski M, O'Keefe P, Moraes F, Pepper J, Seevanayagam S, Sudarshan C, Trivedi U, Wos S, Puskas J, Flather M and Arterial Revascularization Trial I. Bilateral versus Single Internal-Thoracic-Artery Grafts at 10 Years. *N Engl J Med*. 2019;380:437-446.
7. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, Henderson W and Group VACS. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol*. 2004;44:2149-56.
8. Thuijs D, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, Holmes DR, Jr., Curzen N, Davierwala P, Noack T, Milojevic M, Dawkins KD, da Costa BR, Juni P, Head SJ and Investigators SES. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019.
9. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J and Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J*. 2006;151:1194-204.
10. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW and Investigators S. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-72.
11. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW and Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J*. 2011;32:2125-34.
12. Mohr FW, Morice M-C, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Morel M-a, Dyck NV, Houle VM, Dawkins KD and Serruys PW. Coronary

artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *The Lancet*. 2013;381:629-638.

13. Parasca CA, Head SJ, Mohr FW, Mack MJ, Morice MC, Holmes DR, Jr., Feldman TE, Colombo A, Dawkins KD, Serruys PW, Kappetein AP and Investigators S. The impact of a second arterial graft on 5-year outcomes after coronary artery bypass grafting in the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery Trial and Registry. *J Thorac Cardiovasc Surg*. 2015;150:597-606 e2.
14. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW and Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219-27.
15. Sousa-Uva M, Neumann F-J, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO and Group ESCSD. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Journal of Cardio-Thoracic Surgery*. 2018:ezy289-ezy289.
16. Pocock SJ, Clayton TC and Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet*. 2002;359:1686-9.
17. Hickey GL, Dunning J, Seifert B, Sodeck G, Carr MJ, Burger HU, Beyersdorf F, Ejcts and Committees IE. Statistical and data reporting guidelines for the European Journal of Cardio-Thoracic Surgery and the Interactive CardioVascular and Thoracic Surgery. *Eur J Cardiothorac Surg*. 2015;48:180-93.
18. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM and Cosgrove DM. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg*. 1999;117:855-72.
19. Gaudino M, Rahouma M, Abouarab A, Tam DY, Di Franco A, Leonard J, Benedetto U, Iannaccone M, D'Ascenzo F, Biondi-Zoccai G, Vallely M, Girardi LN, Fremes SE and Taggart DP. Meta-Analysis Comparing Outcomes of Drug Eluting Stents Versus Single and Multiarterial Coronary Artery Bypass Grafting. *Am J Cardiol*. 2018;122:2018-2025.
20. Rocha RV, Tam DY, Karkhanis R, Nedadur R, Fang J, Tu JV, Gaudino M, Royse A and Fremes SE. Multiple Arterial Grafting Is Associated With Better Outcomes for Coronary Artery Bypass Grafting Patients. *Circulation*. 2018;138:2081-2090.
21. Schwann TA, Hashim SW, Badour S, Obeid M, Engoren M, Tranbaugh RF, Bonnell MR and Habib RH. Equipoise between radial artery and right internal thoracic artery as the second arterial conduit in left internal thoracic artery-based coronary artery bypass graft surgery: a multi-institutional studydagger. *Eur J Cardiothorac Surg*. 2016;49:188-95.
22. Taggart DP, D'Amico R and Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet*. 2001;358:870-5.
23. Gaudino M, Alexander JH, Bakaeen FG, Ballman K, Barili F, Calafiore AM, Davierwala P, Goldman S, Kappetein P, Lorusso R, Mylotte D, Pagano D, Ruel M, Schwann T, Suma H, Taggart DP, Tranbaugh RF and Fremes S. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. *Eur J Cardiothorac Surg*. 2017.

24. Pu A, Ding L, Shin J, Price J, Skarsgard P, Wong DR, Bozinovski J, Fradet G and Abel JG. Long-term Outcomes of Multiple Arterial Coronary Artery Bypass Grafting: A Population-Based Study of Patients in British Columbia, Canada. *JAMA Cardiol*. 2017;2:1187-1196.
25. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z and Daly RC. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation*. 2012;126:1023-30.
26. Thuijs D, Head SJ, Stone GW, Puskas JD, Taggart DP, Serruys PW, Dressler O, Crowley A, Brown WM, 3rd, Horkay F, Boonstra PW, Bogats G, Noiseux N, Sabik JF, 3rd and Kappetein AP. Outcomes following surgical revascularization with single versus bilateral internal thoracic arterial grafts in patients with left main coronary artery disease undergoing coronary artery bypass grafting: insights from the EXCEL trial. *Eur J Cardiothorac Surg*. 2018.
27. Yamaguchi A, Kimura N, Itoh S, Adachi K, Yuri K, Okamura H and Adachi H. Efficacy of multiple arterial coronary bypass grafting in patients with diabetes mellitus. *Eur J Cardiothorac Surg*. 2016;50:520-7.
28. Schwann TA, El Hage Sleiman AKM, Yammine MB, Tranbaugh RF, Engoren M, Bonnell MR and Habib RH. Incremental Value of Increasing Number of Arterial Grafts: The Effect of Diabetes Mellitus. *Ann Thorac Surg*. 2018;105:1737-1744.
29. Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, Hayward P, Nasso G, Moat N, Peric M, Yoo KJ, Speziale G, Girardi LN, Taggart DP and Investigators R. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. *N Engl J Med*. 2018;378:2069-2077.
30. Briguori C, Condorelli G, Airoldi F, Focaccio A, D'Andrea D, Cannavale M, Abarghouei AA, Giordano S, De Vivo F, Ricciardelli B and Colombo A. Comparison of coronary drug-eluting stents versus coronary artery bypass grafting in patients with diabetes mellitus. *Am J Cardiol*. 2007;99:779-84.
31. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurakowski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymszal J, Martin JL and Tendera M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008;51:538-45.
32. Palmerini T, Barlocco F, Santarelli A, Bacchi-Reggiani L, Savini C, Baldini E, Alessi L, Ruffini M, Di Credico G, Piovaccari G, Di Bartolomeo R, Marzocchi A, Branzi A and De Servi S. A comparison between coronary artery bypass grafting surgery and drug eluting stent for the treatment of unprotected left main coronary artery disease in elderly patients (aged > or =75 years). *Eur Heart J*. 2007;28:2714-9.
33. Head SJ, Mack MJ, Holmes DR, Jr., Mohr FW, Morice MC, Serruys PW and Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg*. 2012;41:535-41.
34. Milojevic M, Nikolic A, Jüni P and Head SJ. A statistical primer on subgroup analyses. *Interactive CardioVascular and Thoracic Surgery*. 2020.
35. Iqbal J, Zhang YJ, Holmes DR, Morice MC, Mack MJ, Kappetein AP, Feldman T, Stahle E, Escaned J, Banning AP, Gunn JP, Colombo A, Steyerberg EW, Mohr FW and Serruys PW. Optimal medical therapy improves clinical outcomes in patients undergoing revascu-

larization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. *Circulation*. 2015;131:1269-77.

SUPPLEMENTARY MATERIALS

Statistical analysis – Propensity score method:

A propensity sore adjusted weighting was performed as a sensitivity analysis to further confirm results obtained with the multi-variable Cox model. This study included 1466 patients at 84 different centers. The median number of procedures performed by each center was 16 (interquartile range 9 – 24). MAG was performed by 62 different hospitals. From all patients operated at a specific center, a median of 6 (interquartile range 2 - 10) patients in that center underwent multi-arterial grafting. In order to adjust for this large variation in grafting strategies, center volume was included in the model developed to calculate the propensity score. Centers were, therefore, grouped according to MAG into (1) low volume: 1 - 10 procedures contributed (2) moderate volume: 11 - 20 procedures contributed (3) high volume: > 20 procedures contributed (Supplement Figure 1). A generalized linear mixed model (hierarchical model) was developed with two levels; level 1 - clinical covariates as fixed effects and level 2 - grouping indicator for MAG procedure volume fit as a random intercept. The clinical covariates included in the model were: age at surgery, sex, obesity (BMI > 30), hypertension, hyperlipidemia, prior myocardial infarction, prior stroke, medically treated diabetes, PAD, COPD, smoking, chronic kidney disease, low LVEF, CAD, unstable angina, left main disease, syntax score and logistic Euroscore. Given the importance of both age and the SYNTAX score on long term survival, both these continuous variables were fit as natural splines (with 3 degrees of freedom). The logistic Euroscore was fit as a linear term in the model. The variables with observed missing proportion are as follows: obesity 0.06%, hypertension 1.15%, hyperlipidemia 1.5%, prior myocardial infarction 1.7%, prior stroke 0.4%, smoking 0.6%, SYNTAX score 1.1% and low LVEF 0.3%. As seen, missing data was very limited. Hence, the mean and mode were used to fill missing values for continuous and categorical variables respectively.

After confirming model diagnostics, fitted values derived from the model provide the marginal likelihood for each patient to receive MAG rather than SAG. A significant difference in sample sizes between groups (MAG - 465 & SAG - 1001) was observed, hence, propensity score derived weighting methods were chosen as the preferred method[1].

To obtain the adjusted association of MAG with long-term survival, the average treatment effect (ATE)/IPTW (Inverse Probability of Treatment Weight) weights were calculated for each patient. Briefly, the IPTW weights were calculated as:

1. for the treated (MAG) = 1/ps
2. For the control (SAG) = 1/(1 - ps) where ps = propensity score.

When using IPTW, patients with very low ps scores in the treated group, or very high ps scores in the control group have unusually high weights. These weights can be considered as outliers; thus, it is recommended to use either stabilized weights or truncated weights rather than the calculated IPTW raw weights [2]. We chose to use truncated weights; hence, the range of IPTW weights were limited to their 1st and 99th percentile. Any value beyond these limits were set to the 1st or 99th percentile as appropriate. To determine balance before and after weighting, standardized differences for each co-variate were compared. With the derived truncated weights, a weighted Cox proportional hazards model was fit to evaluate the marginal long-term survival benefit of MAG compared to SAG. The model fulfills the proportional hazards assumption. Results are presented as hazard ratio at the 95% confidence level.

Supplement Figures:

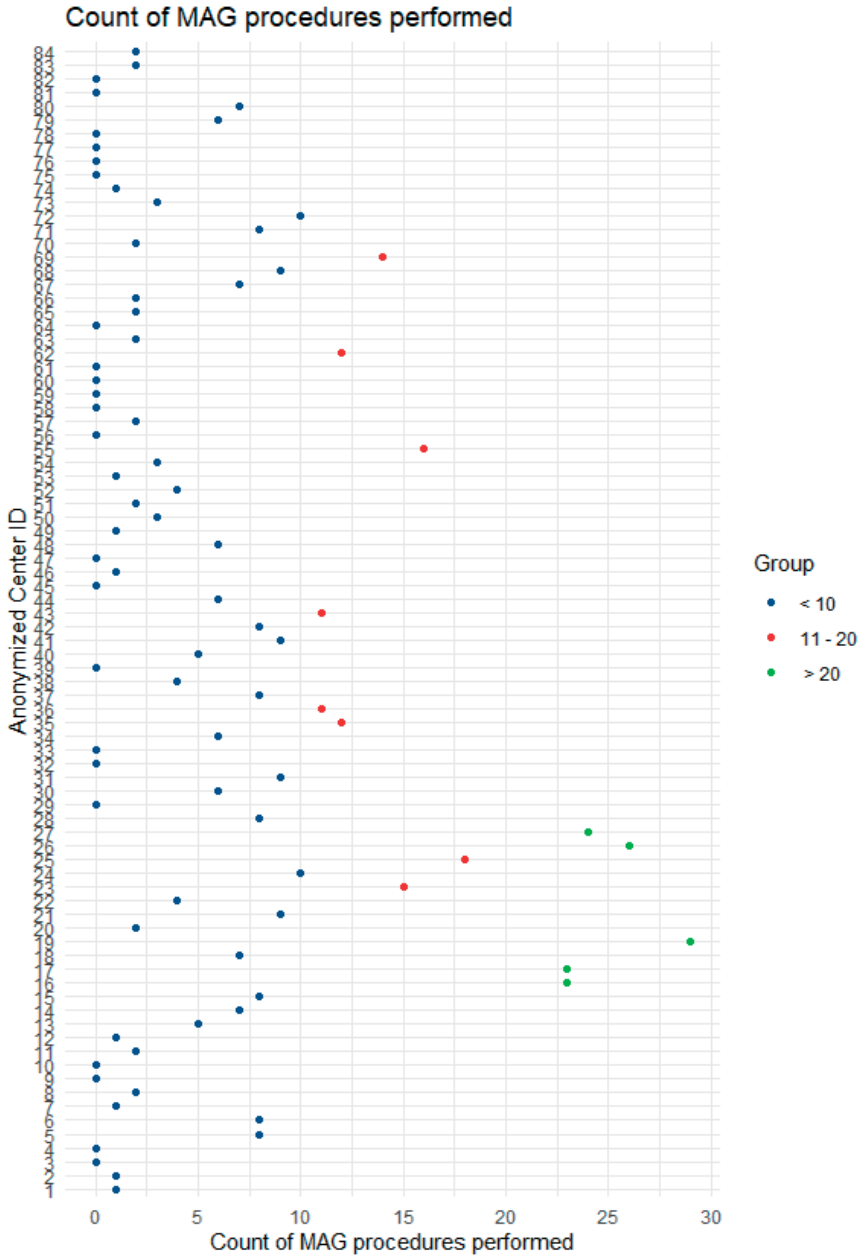


Figure S1. Total number of MAG performed at each center enrolled in the SYNTAX study. This dot chart presents the total number of MAG procedures performed at each of the 85 centers that contribute data to our study. As depicted, five centers performed more than 20 procedures each (green dots), while 8 hospitals contributed between 11 – 20 patients each (red dots).
Abbreviations used: MAG; multiple arterial grafting.

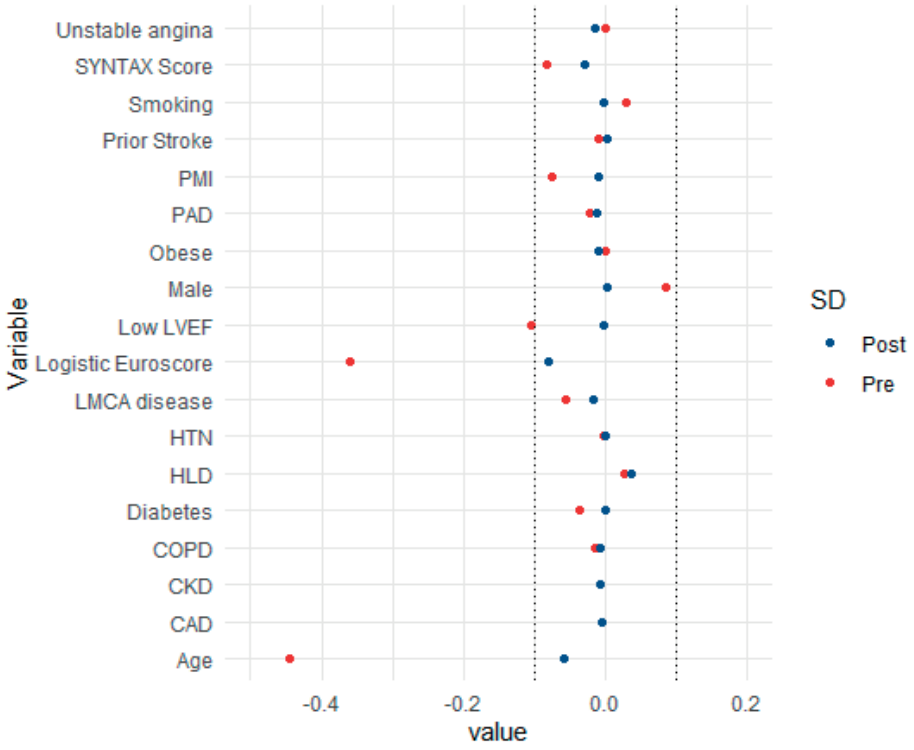


Figure S2. The standardized differences for all the variables included as fixed covariates in the mixed effects model to derive the propensity score. The standardized difference for all co-variates included in our mixed model were calculated to compute the propensity score. The red dots and blue dots depict SD pre- and post-weighting respectively. As depicted, after weighting, all variables have an absolute post-weighting SD < 0.1. Hence, one can assume that these weights are able to neutralize the imbalance in clinical co-variates between the MAG and SAG groups.
Abbreviations used: PMI ; periprocedural myocardial infarction, PAD; peripheral arterial disease, LVEF: left ventricular ejection fraction, LMCA; left main coronary artery disease, HTN; hypertension, HLD; hyperlipidemia, COPD; chronic obstructive pulmonary disease, CKD: chronic kidney disease, CAD: coronary artery disease.

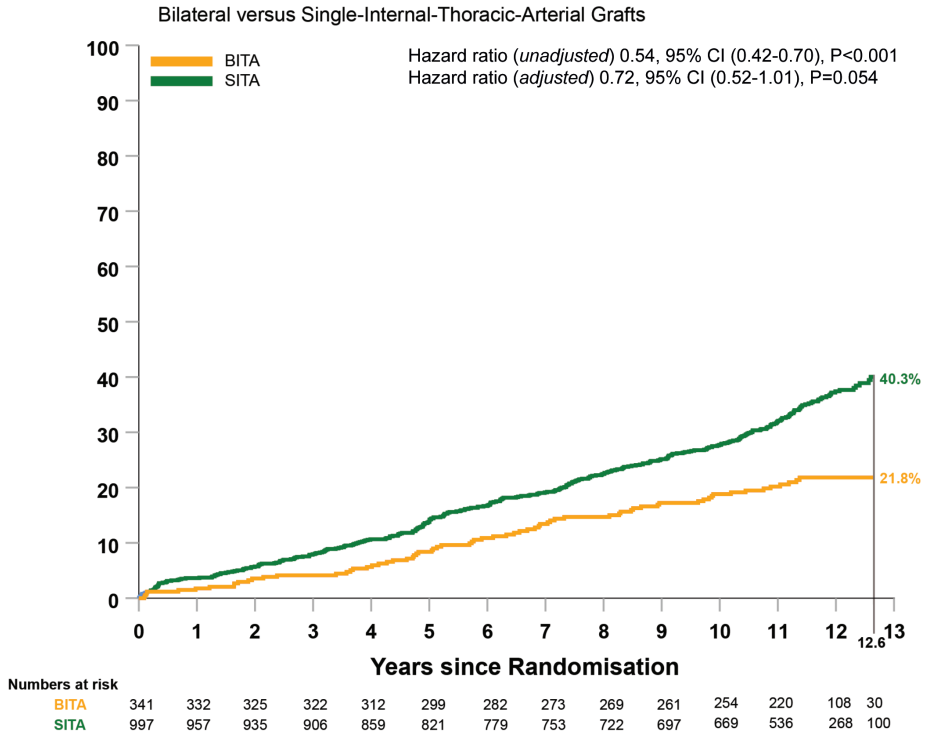


Figure S3. All-cause death in patients who received Bilateral versus Single-Internal-Thoracic-Artery revascularisation Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in patients who underwent CABG and received BITA (orange curve) versus SITA (green curve). Variables used in the full multivariable Cox regression analysis: age, sex, hypertension, hyperlipidemia, stroke or TIA, diabetes mellitus, peripheral vascular disease, carotid artery disease, chronic obstructive pulmonary disease, creatinine >200micromol/L, left ventricular ejection fraction<50% and SYNTAX score (as a continuous variable). The widths of 95% confidence intervals were not adjusted for multiple comparisons, therefore these intervals should not be used for inference about between-group differences.

Abbreviations used: BITA: bilateral-internal-thoracic-arteries, SITA: single-internal-thoracic-artery, HR; hazard ratio, CI; confidence interval.

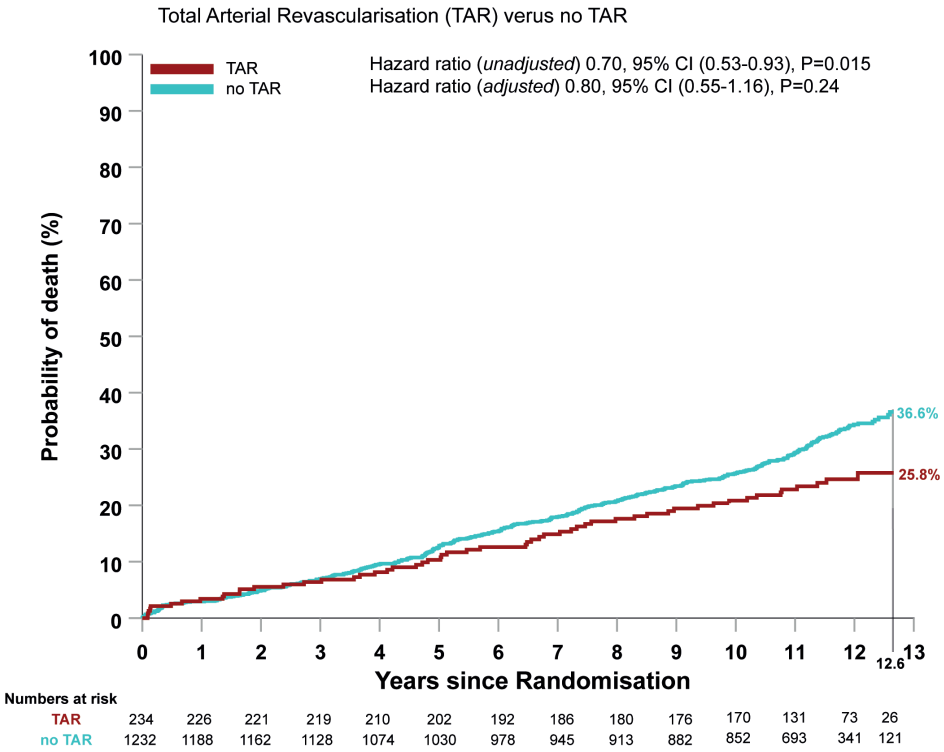


Figure S4. All-cause death in patients who received Total Arterial Revascularisation (TAR) versus no TAR. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in patients who underwent CABG and received TAR (burgundy curve) versus no TAR (turquoise curve). Variables used in the full multivariable Cox regression analysis: age, sex, hypertension, hyperlipidemia, stroke or TIA, diabetes mellitus, peripheral vascular disease, carotid artery disease, chronic obstructive pulmonary disease, creatinine >200micromol/L, left ventricular ejection fraction<50% and SYNTAX score (as a continuous variable). The widths of 95% confidence intervals were not adjusted for multiple comparisons, therefore these intervals should not be used for inference about between-group differences.

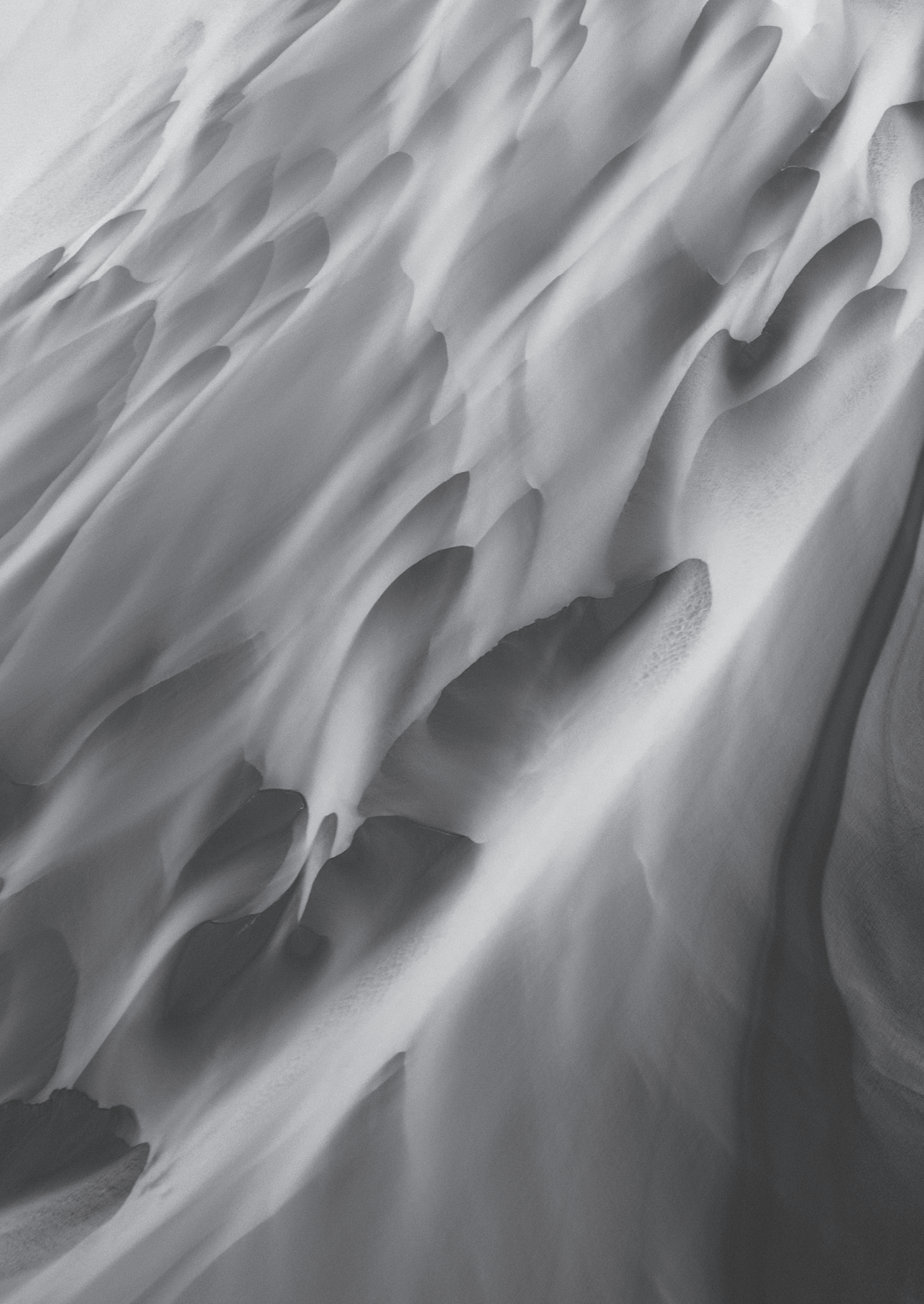
Abbreviations used: BITA: bilateral-internal-thoracic-arteries, SITA: single-internal-thoracic-artery, HR; hazard ratio, CI; confidence interval.

SUPPLEMENT REFERENCES:

1. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424. doi: 10.1080/00273171.2011.568786
2. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-3679. doi:10.1002/sim.6607

PACKAGES USED FOR ANALYSIS:

1. survival-package, A Package for Survival Analysis in R. Terry M Therneau 2020
R package version 3.2-3 https://CRAN.R-project.org/package=survival},
2. cobalt : Noah Greifer (2020). cobalt: Covariate Balance Tables and Plots.
R package version 4.2.2. https://CRAN.R-project.org/package=cobalt
3.tidvyerse - Wickham et al., (2019). Welcome to the tidyverse. Journal of Open Source Software, 4(43), 1686, https://doi.org/10.21105/joss.01686
4. splines - R Core Team (2008) R: A language and environment for statistical computing. R foundation for Statistical Computing. Vienna, Austria.
5.lme4 - Douglas Bates, Martin Maechler, Ben Bolker, Steve Walker (2015).
Fitting Linear Mixed-Effects Models using lme4. Journal of Statistical Software, 67(1). 1 - 48. doi: 10.18637/jss.v067.i01



Chapter 9

Impact of Incomplete Revascularisation on 10-year All-cause Death in Patients with Three-vessel Disease or Left Main Coronary Artery Disease: Insights from the SYNTAX Extended Survival Study

Kuniaki Takahashi, Patrick W. Serruys, Daniel J.F.M. Thuijs, A. Pieter Kappetein, Marie-Claude Morice, Friedrich-Wilhelm Mohr, Michael J. Mack, Nick Curzen, Piroze Davierwala, Milan Milojevic, Rutao Wang, Hironori Hara, Faisal Sharif, Joanna J. Wykrzykowska, Robbert J. de Winter, Yoshinobu Onuma, Stuart J. Head, David R. Holmes Jr., On behalf of the SYNTAX Extended Survival Study Investigators

Submitted

ABSTRACT

Objectives

The goal of this study was to evaluate the effect of completeness of revascularisation on 10-year all-cause death in patients with percutaneous coronary intervention (PCI) versus those undergoing coronary artery bypass grafting (CABG).

Background

The impact of incomplete (IR) versus complete revascularisation (CR) on 10-year all-cause death has not been fully investigated in patients with three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD).

Methods

The SYNTAX Extended Survival Study evaluated the vital status up to 10 years of patients who were originally enrolled in the SYNTAX trial. In the present sub-study, outcomes of the CABG CR group were compared with the CABG IR, PCI CR, and PCI IR groups. In addition, in the PCI cohort, the residual SYNTAX score (rSS) was used to quantify the extent of IR and its prognostic impact. The rSS of 0 suggests CR, whereas a rSS>0 identifies IR of variable degree.

Results

IR was more frequently observed in patients with PCI vs. CABG (56.0% vs. 35.7%). IR was more common in patients with 3VD compared with LMCAD in both PCI (58.0% vs. 52.9%) and CABG arm (41.3% vs. 27.2%). Patients undergoing PCI with CR had a similar risk of 10-year all-cause death compared with those undergoing CABG (22.0% for PCI with CR vs. 23.8% for CABG with IR vs. 23.7% for CABG with CR). In contrast, those with PCI and IR had a significantly higher risk of all-cause death at 10 years compared with CABG and CR (33.9% vs. 23.7%; adjusted hazard ratio [aHR]:1.68; 95% confidence interval [CI]:1.22-2.30; p<0.001). When patients with PCI were stratified according to the rSS, those with a rSS≤8 had a comparable risk of all-cause death at 10 years as the other terciles (22.0% for rSS=0 vs. 24.0% for rSS>0-4 vs. 28.9% for rSS>4-8), whereas a rSS> 8 had a significantly higher risk of 10-year all-cause death as compared with those undergoing PCI with CR (53.0% vs. 22.0%; aHR:3.75; 95% CI:2.33-6.05; p<0.001).

Conclusion

Incomplete revascularisation is common after PCI; the degree of incompleteness has a major impact on 10-year mortality. Patients with a rSS ≤8 after PCI had a comparable risk of 10-year all-cause death compared with those after CABG, whereas

patients with a rSS>8 after PCI had a marked increase in 10-year mortality. Further studies are needed to optimize outcomes in this high-risk population.

Keywords

Coronary artery bypass grafting; Incomplete revascularisation; Left main coronary artery disease; Percutaneous coronary intervention; residual SYNTAX score; Three-vessel disease.

INTRODUCTION

The aim of myocardial revascularisation is to relieve ischemia of patients to improve clinical outcomes including mortality [1, 2]. The nuclear sub-study of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial has shown that patients on medical therapy with >10% of reversible ischemia had an excess of 5-year mortality. In contrast, in the revascularisation group also treated with medical therapy, a reduction of residual ischemia from >10% of the myocardium to ≤ 5% by revascularisation resulted in a lower risk of mortality and myocardial infarction (MI) [2]. Although numerous randomized clinical trials have tested the efficacy and safety of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) with drug-eluting stent (DES) in patients with severe coronary artery disease (CAD) [3], the selection of the most appropriate mode of revascularisation for a given patient remains a complex process [4, 5].

The 2018 European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgery (EACTS) guidelines on myocardial revascularisation suggest that (i) the use of surgical mortality scores of STS score (class IB) or EuroSCORE II (class IIb B) to estimate in-hospital mortality, (ii) calculation of the anatomical SYNTAX score (SS) (class IB) to assess the extent and complexity of coronary artery disease (CAD) and to predict long-term morbidities and mortality after revascularisation, and (iii) expected completeness of revascularisation (class IIa B) are of paramount importance for decision-making of revascularisation strategies between CABG and PCI [6, 7]. To date, there have been several comparative studies evaluating the impact of IR vs. CR on clinical outcomes in patients with complex CAD undergoing CABG or PCI [8-16]. Among them, only the MASS II (Second Medicine, Angioplasty, or Surgery Study) has evaluated outcomes beyond 5 years, although it was conducted in the era of bare-metal stent (BMS) with a limited number of patients [12].

More recently, the SYNTAX Extended Survival (SYNTAXES) study has assessed survival prognosis at 10 years in all-comers patients with *de novo* three-vessel disease (3VD) or left main coronary artery disease (LMCAD) randomized to PCI or CABG who were originally enrolled in the SYNTAX trial [17]. The present analysis evaluates outcomes according to completeness of revascularisation in patients who underwent percutaneous or surgical revascularisation in the SYNTAXES study.

METHODS

Study design and population

The study design and the primary and final 5-year results of the SYNTAX (NCT00114972) trial have been published previously [18-20]. In summary, the SYNTAX trial was a prospective, international, multicenter, randomized controlled trial conducted at 85 centers in Europe and the United States between March 2005 and April 2007. Based on clinical judgement and consensus of heart team consisting of a cardiothoracic surgeon and interventional cardiologist at each center, all-comers patients with *de novo* 3VD or LMCAD who were anticipated to achieve a clinical equipoise between CABG and PCI were enrolled and randomized in a 1:1 fashion to either CABG (n= 897) or PCI (n= 903) with TAXUS Express paclitaxel-drug eluting stents (PES) (Boston Scientific Corporation, Marlborough, MA, USA). The SYNTAX trial (NCT00114972) completed patient follow-up up to 5 years [20], and the SYNTAXES study (NCT03417050) has evaluated vital status up to 10 years [17]. These trials were approved by the ethics committees at each investigating center, and all patients provided their written informed consent prior to participation in the SYNTAX trial.

Completeness of revascularisation

In the SYNTAX CABG arm, due to the overall lack of protocol driven angiographic follow-up after surgery, we used the surgical investigator-reported classification of either CR or IR according to the anatomical SS; the surgeons had a surgical report on the location of their bypass grafts based on the anatomical SS established by the Heart Team and concluded to be CR or IR. The definition of CR was predefined by the trial protocol [19]; investigators documented a binary outcome as to whether any lesion with more than 50% diameter stenosis in vessels ≥1.5 mm as estimated on the diagnostic angiogram during the local Heart Team conference was actually treated by the revascularisation.

In the PCI arm, we previously quantified the extent of IR by an independent core laboratory unaware of and blind to patient outcome (i.e. residual SS [rSS]) [21], which was calculated as the sum of the individual scores of coronary lesions with ≥ 50% diameter stenosis in vessel ≥ 1.5 mm but left untreated [14, 21, 22]. The rSS of 0 indicates CR, whereas a rSS > 0 indicates IR with a higher rSS representing more coronary stenoses left untreated. The ΔSS, representing the burden of disease treated with PCI, was calculated by subtraction of the rSS from the baseline anatomical SS [14, 21, 22].

Study endpoint

The pre-specified primary endpoint of the SYNTAXES trial was all-cause death at 10 years. Vital status was confirmed by electronic healthcare record review and national death registry.

Statistical analyses

All the analyses are performed according to as-treated principle [16]. The cumulative incidence of clinical adverse events up to 10 years is assessed using the Kaplan-Meier method and compared using the log-rank test. Hazard ratio (HR) with 95% confidence interval (CI) is assessed by a Cox proportional regression model. To adjust for potential confounding factors, the following variables are entered into a multivariable Cox regression model: age, sex, body mass index (BMI), medically treated diabetes mellitus, hypertension, dyslipidemia, current smoking, previous MI, previous cerebrovascular disease, chronic kidney disease (defined as creatinine clearance < 60 mL/min), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), left ventricular ejection fraction (LVEF), clinical presentation (stable or unstable angina), disease type (LMCAD or 3VD), and anatomical SS. Multivariable Cox regression model is used to compare outcomes of the CABG CR group with the CABG IR, PCI CR, and PCI IR groups. Patients with missing vital status are included in the analysis and censored at the time of lost to follow-up or at 5 years if centers decided not to participate in the SYNTAXES study with 10-year extended follow-up (only 2 centers with a total of 5 patients declined participation) [17]. Continuous variables were reported as mean ± standard deviations (SD) or median and interquartile range (IQR), and are compared using Student's *t* tests or Mann-Whitney U test, respectively. Categorical variables are reported as percentages and numbers, and are compared using Chi-square or Fisher's exact test as appropriate. All tests are two-sided and a p-value of <0.05 is considered to be statistically significant. All analyses are performed using SPSS Statistics, version 25 (IBM Corp., Armonk, 281 N.Y., USA).

RESULTS

Study population

Among 1,800 patients enrolled in the SYNTAX trial, 34 (1.9 %) patients did not undergo PCI or CABG, of whom 8 (0.4%) patients were treated medically, and the rSS was not available in 26 (1.4%) patients who underwent PCI. As a result, 1,740 (96.7%) patients were included in the present analysis (CABG, n= 865; PCI, n=875) (**Figure 1**). Overall, 54.1% achieved CR, however, patients undergoing PCI resulted in a higher

rate of IR compared with CABG (56.0% for PCI vs. 35.7% for CABG) (**Figure 2A**). In both PCI and CABG arms, patients with 3VD were more likely to had IR, compared with those with LMCAD (**Figure 2B** and **2C**).

Baseline characteristics according to the completeness of revascularisation are presented in **Table 1**. Patients undergoing PCI with IR had a higher prevalence of co-morbidities (medically treated diabetes, on insulin, hypertension, and lower LVEF).

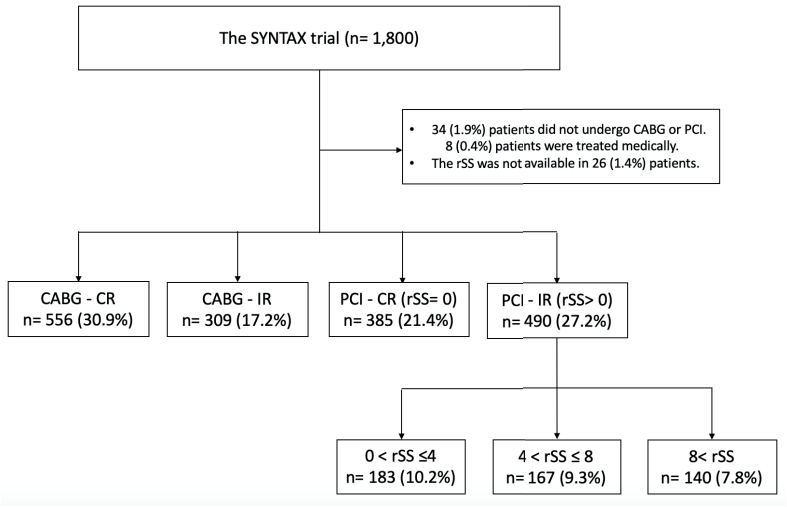


Figure 1. Patient flow diagram of the present study.
CABG: coronary artery bypass grafting; CR: complete revascularization; IR: incomplete revascularization; PCI: percutaneous coronary intervention; rSS: residual SYNTAX score.

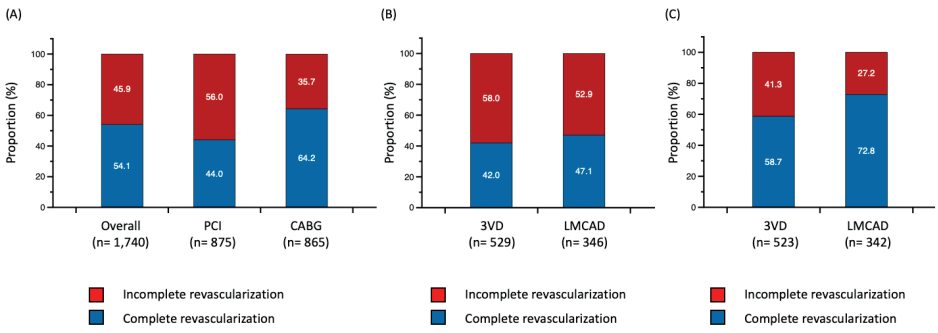


Figure 2. Proportion of completeness of revascularization in the overall population (A), PCI arm (B), and CABG arm (C).
For the PCI cohort, the completeness of revascularization was based on the Core Laboratory analysis, whereas for the CABG cohort, it was investigator-reported.
CABG: coronary artery bypass grafting; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; 3VD: three-vessel disease.

Table 1. Baseline characteristics according to completeness of revascularization.

	CABG			PCI			
	CR	IR	p-value	CR	IR	p-value	Overall p-value
Age (year)	64.6± 9.8	65.4± 9.8	0.243	64.7± 9.8	65.9± 9.5	0.060	0.115
Sex			0.755			0.026	0.048
Male	79.9 (444)	79.0 (244)		72.7 (280)	79.2 (388)		
Female	20.1 (112)	21.0 (65)		27.3 (105)	20.8 (102)		
Body mass index (kg/m^2)	28.0± 4.5	27.7± 4.2	0.317	28.1± 4.7	28.2± 4.9	0.748	0.482
Diabetes	22.7 (126)	25.2 (78)	0.392	20.5 (79)	29.8 (146)	0.002	0.008
Insulin	9.0 (50)	12.0 (37)	0.162	7.0 (27)	12.2 (60)	0.010	0.036
Metabolic syndrome	48.2 (212)	41.4 (104)	0.087	43.1 (137)	48.2 (191)	0.170	0.185
Hypertension	64 (356)	62.5 (193)	0.646	68.1 (262)	70.8 (347)	0.378	0.040
Dyslipidemia	77.5 (428)	77.3 (235)	0.938	77.9 (299)	79.6 (386)	0.537	0.836
Current smoker	23.9 (132)	19.5 (60)	0.144	20.3 (78)	16.7 (82)	0.181	0.040
Previous myocardial infarction	31 (170)	37.5 (115)	0.055	29.9 (114)	33.1 (160)	0.325	0.157
Previous cerebrovascular disease	14.2 (78)	16.2 (50)	0.412	12.3 (47)	14.3 (70)	0.386	0.528
Previous stroke	5.1 (28)	4.5 (14)	0.735	3.9 (15)	3.9 (19)	0.986	0.775
Previous transient ischemic attack	4.2 (23)	6.5 (20)	0.132	3.4 (13)	5.3 (26)	0.170	0.216
Previous carotid artery disease	7.4 (41)	10.0 (31)	0.175	7.3 (28)	9.0 (44)	0.362	0.443
Peripheral vascular disease	9.0 (50)	13.6 (42)	0.036	8.3 (32)	9.8 (48)	0.450	0.096
Chronic obstructive pulmonary disease	9.7 (54)	7.8 (24)	0.339	8.8 (34)	7.6 (37)	0.491	0.601
Chronic kidney disease	17.9 (90)	20.9 (58)	0.304	20.3 (75)	19.7 (91)	0.822	0.713
Creatinine clearance (ml/min)	86.6± 29.4	83.2± 29.3	0.128	87.2± 32.0	85.8± 38.3	0.566	0.446
Left ventricular ejection fraction	59.3± 13.5	56.7± 12.5	0.025	60.4± 12.1	58.0± 13.6	0.034	0.016
Congestive heart failure	5.1 (28)	5.6 (17)	0.777	4.2 (16)	3.7 (18)	0.726	0.553
Clinical presentation			0.062			0.216	0.181
Silent ischemia	13.5 (75)	15.5 (48)		13.8 (53)	13.9 (68)		
Stable angina	60.6 (337)	52.4 (162)		60.0 (231)	54.7 (268)		
Unstable angina	25.9 (144)	32.0 (99)		26.2 (101)	31.4 (154)		

Table 1. Baseline characteristics according to completeness of revascularization. (*continued*)

	CABG			PCI			
	CR	IR	p-value	CR	IR	p-value	Overall p-value
EuroSCORE	3.6± 2.5	4.0± 3.0	0.037	3.6± 2.7	3.9± 2.5	0.144	0.085
Parsonnet SCORE	8.1± 6.7	9.0± 7.2	0.065	8.2± 7.1	8.9± 6.8	0.133	0.101
Disease type			<0.001				<0.001
3VD	55.2 (307)	69.9 (216)		57.7 (222)	62.7 (307)		
LMCAD	44.8 (249)	30.1 (93)		42.3 (163)	37.3 (183)	0.134	
Disease type			<0.001			<0.001	<0.001
LMCAD only	7.4 (41)	1.0 (3)		8.1 (31)	1.8 (9)		
LMCAD+1VD	10.8 (60)	3.2 (10)		10.6 (41)	5.1 (25)		
LMCAD+2VD	15.1 (84)	7.5 (23)		14.0 (54)	11.2 (55)		
LMCAD+3VD	11.5 (64)	18.5 (57)		9.6 (37)	19.2 (94)		
2VD	1.4 (8)	2.9 (9)		2.9 (11)	1.0 (5)		
3VD	53.8 (299)	66.9 (206)		54.8 (211)	61.6 (302)		
SYNTAX score	27.9± 11.0	31.2± 11.6	<0.001	23.6± 10.0	32.2± 11.0	<0.001	<0.001
Low (0-22)	35.4 (196)	22.9 (70)	<0.001	50.4 (193)	19.5 (95)	<0.001	<0.001
Intermediate (23-32)	33.2 (184)	35.3 (108)	0.537	33.7 (129)	35.7 (174)	0.544	0.830
High (>32)	31.4 (174)	41.8 (128)	0.002	15.9 (61)	44.9 (219)	<0.001	<0.001
Optimal medical therapy at discharge	32.6 (181)	31.7 (98)	0.800	46.5 (179)	54.1 (265)	0.026	<0.001
Any antiplatelet therapy	92.4 (514)	90.0 (278)	0.209	99.2 (382)	98.6 (483)	0.370	<0.001
Aspirin	89.0 (495)	87.1 (269)	0.386	96.1 (370)	96.7 (474)	0.616	<0.001
Thienopyridine	16.9 (94)	20.4 (63)	0.203	98.7 (380)	96.7 (474)	0.059	<0.001
Statin	76.1 (423)	72.2 (223)	0.205	85.2 (328)	87.8 (430)	0.269	<0.001
Beta blocker	79.9 (444)	77.3 (239)	0.385	81.3 (313)	80.8 (396)	0.857	0.577
ACEi or ARB	48.6 (270)	53.4 (165)	0.173	63.4 (244)	70.2 (344)	0.033	<0.001

Data are presented as mean ± standard deviation or percentage (number).
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CABG: coronary artery bypass grafting; CAD: coronary artery disease; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; 3VD: three-vessel disease.

In terms of extent and complexity of CAD, patients with IR more commonly had 3VD and a higher anatomical SS. In patients undergoing PCI, those with IR more frequently had complex lesions (total occlusion [TO], bifurcation, diffuse or small vessel disease, heavy calcification, severe tortuosity, and long lesions [defined as lesions with > 20mm]), resulting in a higher rSS (2.1± 3.4 for CR vs. 7.0± 8.0 for IR) (**Table 2**).

In patients undergoing CABG, those with CR received more grafts for less complex CAD, as reflected by a lower anatomical SS (27.9± 11.0 for CR vs. 31.2± 11.6 for IR; p< 0.001), and fewer TO (19.5% for CR vs. 27.1% for IR; p= 0.010) (**Table 2**).

Table 2. Procedural characteristics according to completeness of revascularization.

	CABG			PCI			
	CR	IR	p-value	CR	IR	p-value	Overall p-value
Number of lesions	4.1± 1.7	4.9± 1.7	<0.001	3.7± 1.7	4.8± 1.7	<0.001	<0.001
Any TO	19.5 (108)	27.1 (83)	0.010	12.3 (47)	33.4 (163)	<0.001	<0.001
1TO	17.3 (96)	24.8 (76)		12.1 (46)	29.9 (146)		
2TO	2.2 (12)	2.3 (7)		0.3 (1)	3.5 (17)		
Any bifurcation	72.2 (400)	75.2 (230)	0.348	62.7 (239)	79.9 (390)	<0.001	<0.001
Diffuse or small vessel disease	-	-	-	18.4 (71)	25.3 (124)	0.015	
Any aorto-ostial lesion	-	-	-	17.1 (65)	13.1 (64)	0.105	
Any angiographically visible thrombus	-	-	-	2.6 (10)	2.5 (12)	0.877	
Any heavy calcification	-	-	-	42.8 (163)	54.1 (264)	<0.001	
Any severe tortuosity	-	-	-	55.9 (213)	74.2 (362)	<0.001	
Any lesion length > 20 mm	-	-	-	46.2 (176)	64.1 (313)	<0.001	
Left arterial dominance	-	-	-	16.9 (65)	19.0 (93)	<0.001	
Number of stents implanted	-	-	-	4.5± 2.4	4.7± 2.1	0.228	-
Total stent length per patient	-	-	-	86± 51.8	86.5± 44.6	0.900	-
Off pump CABG	14.9 (83)	15.3 (47)	0.896	-	-	-	
Use of LIMA graft	86.3 (480)	85.4 (264)	0.716	-	-	-	
Number of total conduits	2.8± 0.7	2.6± 0.7	<0.001	-	-	-	-
Number of arterial conduits	1.4± 0.7	1.4± 0.6	0.777	-	-	-	-
Number of venous conduits	1.5± 0.9	1.2± 0.9	<0.001	-	-	-	-

Data are presented as mean ± standard deviation or percentage (number).
CABG: coronary artery bypass grafting; CAD: coronary artery disease; LIMA: left internal mammary artery; PCI: percutaneous coronary intervention; TO: total occlusion.

In the SYNTAX trial enrolling patients from 2005 to 2007, approximately half of patients undergoing PCI received optimal medical therapy (OMT) [23], defined as the combination of at least one antiplatelet therapy, statin, βblocker, and angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker at discharge, and the rate of OMT was significantly higher in patients with PCI and IR vs. CR (54.1% vs.

46.5%; p= 0.026). In contrast, only one third of patients undergoing CABG received OMT at discharge, and a rate of OMT was similar between patients with IR and CR in the CABG cohort (31.7% vs. 32.6%; p= 0.800) (**Table 1**).

Outcomes according to completeness of revascularisation in patients undergoing PCI or CABG

The median duration of follow-up after randomization was 11.2 years (interquartile range 8.0 to 12.1 years). All-cause death occurred in 442 (25.4%) of patients at 10 years and 549 (31.6%) at maximum follow-up of 12.7 years. The crude rates of 10-year all-cause death was 23.7% in patients with CABG and CR, 23.8% with CABG and IR, 22.0% with PCI and CR, and 33.9% with PCI and IR (p< 0.001) (**Figure 3A** and **Table 3**). Notably, patients undergoing PCI who achieved CR had a similar risk of all-cause death at 10 years to those undergoing CABG (**Figure 3A** and **Table 3**). After adjustment for baseline characteristics, the risk of all-cause death remained significantly higher in patients undergoing PCI with IR, compared with those undergoing CABG with CR (adjusted HR: 1.68; 95% CI: 1.22 to 2.30; p< 0.001) (**Table 3**).

The stratified analysis according to disease type (3VD or LMCAD) yielded similar results in patients with 3VD (**Figure 3B** and **Table 3**). Specifically, the crude rates of 10-year all-cause death was 20.4% in patients with CABG and CR, 20.7% with CABG and IR, 24.3% with PCI and CR, and 33.1% with PCI and IR (p< 0.001). In contrast, patients with LMCAD who underwent PCI with CR had a lower adjusted risk of 10-year all-cause death as compared with CABG with CR (adjusted HR: 0.47; 95% CI: 0.26 to 0.86) (**Table 3**). This significant survival benefit at 10 years was no longer observed at a maximum follow-up (**Online Figure 1** and **Online Table 1**).

Outcomes stratified according to the rSS in patients undergoing PCI

Baseline characteristics according to the rSS are presented in **Table 4**. Patients with a higher rSS were older and more likely to be female. A higher rSS was associated with a progressive increase in co-existing comorbidities (medically treated diabetes, on insulin, PVD, CKD, and lower LVEF) and greater EuroSCORE or Parsonnet SCORE. Similarly, patients with a higher rSS had a greater anatomical SS at baseline and a higher prevalence of complex lesions (TO, diffuse or small vessel disease, heavy calcification, severe tortuosity, and lesion length). Although the number of lesions was greater in patients with a rSS of >8, the number of stents implanted and total stent length per patient were similar among the four rSS groups. Of note, a higher rSS was associated with a more frequent use of OMT at discharge (**Table 4**).

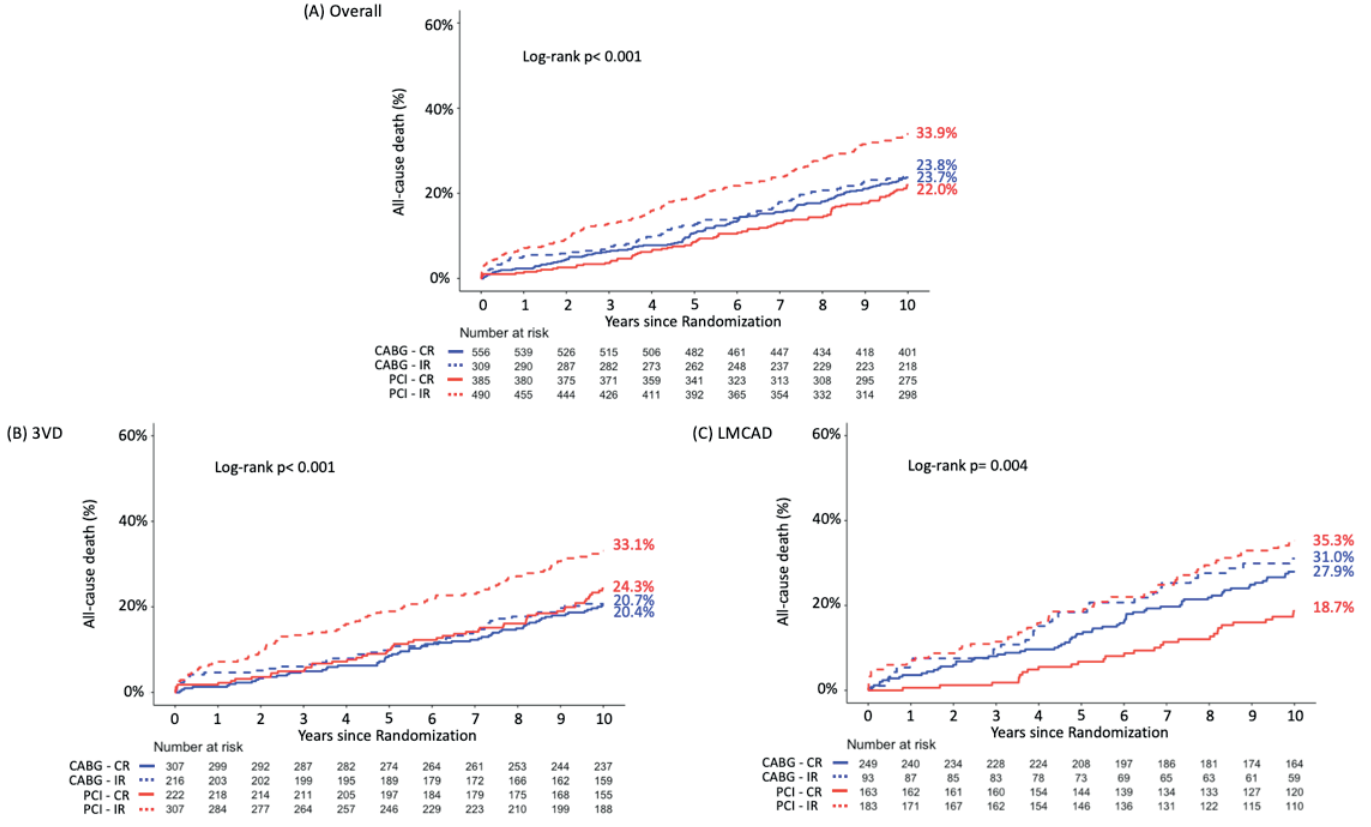


Figure 3. Kaplan-Meier curves for the primary endpoint of all-cause death up to 10 years according to randomized treatments of CABG (blue) or PCI (red) and completeness of revascularization. (A) overall population; (B) 3VD cohort; (C) LMCAD cohort.

CABG: coronary artery bypass grafting; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; 3VD: three-vessel disease, CR: complete revascularization, IR: incomplete revascularization..

Table 3. Crude and adjusted all-cause death at 10 years according to completeness of revascularization.

	Crude incidence					Adjusted HR (95% CI)				
	CABG – CR (n= 556)	CABG – IR (n= 309)	PCI – CR (n= 385)	PCI – IR (n= 490)	p-value	CABG - CR	CABG - IR	PCI - CR	PCI - IR	p-value
Overall	23.7 (128)	23.8 (71)	22.0 (81)	33.9 (162)	<0.001	1.00 (reference)	0.97 (0.66-1.42)	0.86 (0.59-1.26)	1.68 (1.22-2.30)	<0.001
3VD	20.4 (61)	20.7 (43)	24.3 (52)	33.1 (99)	<0.001	1.00 (reference)	0.99 (0.58-1.70)	1.50 (0.89-2.52)	1.92 (1.23-2.97)	0.010
LMCAD	27.9 (67)	31.0 (28)	18.7 (29)	35.3 (63)	0.004	1.00 (reference)	0.97 (0.55-1.73)	0.47 (0.26-0.86)	1.57 (0.97-2.55)	0.002

Data are presented as percentage (number of deaths).

CABG: coronary artery bypass grafting; CI: confidence interval; CR: complete revascularization; HR: hazard ratio; IR: incomplete revascularization; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Table 4. Baseline and procedural characteristics according to the residual SYNTAX score in patients treated with PCI.

	rSS= 0 (n= 385)	0 < rSS ≤ 4 (n= 183)	4 < rSS ≤ 8 (n= 167)	8< rSS (n= 140)	p-value
Age (year)	64.7± 9.8	64.8± 8.8	66.0± 9.8	67.3± 9.9	0.029
Sex					0.025
Male	72.7 (280)	81.4 (149)	82.0 (137)	72.9 (102)	
Female	27.3 (105)	18.6 (34)	18.0 (30)	27.1 (38)	
Body mass index (kg/m^2)	28.1± 4.7	28.4± 5.2	27.6± 4.6	28.6± 4.7	0.272
Diabetes	20.5 (79)	26.8 (49)	26.3 (44)	37.9 (53)	0.001
Insulin	7.0 (27)	10.9 (20)	7.2 (12)	20.0 (28)	<0.001
Metabolic syndrome	43.1 (137)	50.7 (74)	42.0 (58)	52.7 (59)	0.153
Hypertension	68.1 (262)	71.0 (130)	73.7 (123)	67.1 (94)	0.510
Dyslipidemia	77.9 (299)	75.7 (137)	80.7 (134)	83.3 (115)	0.345
Current smokers	20.3 (78)	15.3 (28)	16.2 (27)	19.3 (27)	0.442
Previous myocardial infarction	29.9 (114)	32.0 (58)	28.8 (47)	39.3 (55)	0.179
Previous cerebrovascular disease	12.3 (47)	16.9 (31)	10.8 (18)	15.0 (21)	0.296
Previous stroke	3.9 (15)	2.7 (5)	3.6 (6)	5.8 (8)	0.580
Previous transient ischemic attack	3.4 (13)	6.6 (12)	5.4 (9)	3.6 (5)	0.311
Prior carotid artery disease	7.3 (28)	10.4 (19)	7.2 (12)	9.3 (13)	0.565
Peripheral vascular disease	8.3 (32)	6.0 (11)	9.6 (16)	15.0 (21)	0.040
Chronic obstructive pulmonary disease	8.8 (34)	6.0 (11)	8.4 (14)	8.6 (12)	0.704
Chronic kidney disease	20.3 (75)	14.5 (25)	17.2 (27)	29.3 (39)	0.010
Creatinine clearance	87.2± 32.0	92.5± 48.3	83.6± 28.2	79.6± 32.4	0.011
Left ventricular ejection fraction	60.4± 12.1	59.8± 12.9	57.3± 13.9	56.4± 13.8	0.041
Congestive heart failure	4.2 (16)	2.2 (4)	4.2 (7)	5.0 (7)	0.586
Clinical presentation					0.547
Silent ischemia	13.8 (53)	12.6 (23)	15.0 (25)	14.3 (20)	
Stable angina	60.0 (231)	52.5 (96)	55.7 (93)	56.4 (79)	
Unstable angina	26.2 (101)	35.0 (64)	29.3 (49)	29.3 (41)	
EuroSCORE	3.6± 2.7	3.6± 2.4	3.8± 2.5	4.4± 2.6	0.020
Parsonnet SCORE	8.2± 7.1	7.8± 5.9	8.6± 6.8	10.8± 7.6	0.001
Disease extent					0.359
3VD	57.7 (222)	65.0 (119)	59.9 (100)	62.9 (88)	
LMCAD	42.3 (163)	35.0 (64)	40.1 (67)	37.1 (52)	
Disease extent					<0.001
LMCAD	8.1 (31)	2.2 (4)	3.0 (5)	0 (0)	
LMCAD+1VD	10.6 (41)	4.4 (8)	7.8 (13)	2.9 (4)	
LMCAD+2VD	14.0 (54)	10.9 (20)	10.8 (18)	12.1 (17)	
LMCAD+3VD	9.6 (37)	17.5 (32)	18.6 (31)	22.1 (31)	
2VD	2.9 (11)	2.2 (4)	0 (0)	0.7 (1)	
3VD	54.8 (211)	62.8 (115)	59.9 (100)	62.1 (87)	
Number of lesions	3.7± 1.7	4.7± 1.7	4.8± 1.7	5.0± 1.7	<0.001
SYNTAX score	23.6± 10.0	29.1± 10	31.7± 9.8	36.9± 11.9	<0.001
Low	50.4 (193)	27.9 (51)	17.5 (29)	10.8 (15)	<0.001
Intermediate	33.7 (129)	39.9 (73)	37.3 (62)	28.1 (39)	0.135
High	15.9 (61)	32.2 (59)	45.2 (75)	61.2 (85)	<0.001
Residual SYNTAX score	0± 0	3.0± 1.0	6.2± 1.1	15.0± 9.0	<0.001

Table 4. Baseline and procedural characteristics according to the residual SYNTAX score in patients treated with PCI. (*continued*)

	rSS= 0 (n= 385)	0 < rSS ≤ 4 (n= 183)	4 < rSS ≤ 8 (n= 167)	8< rSS (n= 140)	p-value
Δ SYNTAX score	1.5± 0.7	1.8± 0.8	2.0± 0.9	1.9± 0.9	<0.001
Number of stents	4.5± 2.4	4.9± 2.2	4.6± 2.0	4.6± 2.1	0.305
Total stent length per patient	86± 51.8	91.6± 47.8	83.9± 42.3	82.6± 42.4	0.289
Any TO	12.3 (47)	22.4 (41)	28.3 (47)	54.0 (75)	<0.001
1TO	12.1 (46)	22.4 (41)	25.3 (42)	45.3 (63)	
2TO	0.3 (1)	0 (0)	3.0 (5)	8.6 (12)	<0.001
Any bifurcation	62.7 (239)	77.6 (142)	77.7 (129)	85.6 (119)	<0.001
Diffuse or small vessel disease	18.4 (71)	26.2 (48)	20.4 (34)	30.0 (42)	0.018
Any aorto-ostial lesion	17.1 (65)	13.1 (24)	11.4 (19)	15.1 (21)	0.329
Any angiographically visible thrombus	2.6 (10)	2.2 (4)	2.4 (4)	2.9 (4)	0.981
Any heavy calcification	42.8 (163)	47.5 (87)	53 (88)	64 (89)	<0.001
Any severe tortuosity	55.9 (213)	74.9 (137)	74.7 (124)	72.7 (101)	<0.001
Left arterial dominance	16.9 (65)	19.7 (36)	19.8 (33)	17.1 (24)	0.780
Any lesion length > 20 mm	46.2 (176)	57.9 (106)	62.0 (103)	74.8 (104)	<0.001
Optimal medical therapy at discharge	46.5 (179)	50.3 (92)	52.1 (87)	61.4 (86)	0.025
Any antiplatelet therapy	99.2 (382)	100 (183)	98.8 (165)	96.4 (135)	0.020
Aspirin	96.1 (370)	98.4 (180)	95.8 (160)	95.7 (134)	0.473
Thienopyridine	98.7 (380)	100 (183)	97.6 (163)	91.4 (128)	<0.001
Statin	85.2 (328)	86.9 (159)	89.8 (150)	86.4 (121)	0.538
Beta blocker	81.3 (313)	82.0 (150)	79.6 (133)	80.7 (113)	0.952
ACEi or ARB	63.4 (244)	67.8 (124)	67.7 (113)	76.4 (107)	0.046

Data are presented as mean ± standard deviation or percentage (number).
CABG: coronary artery bypass grafting; CAD: coronary artery disease; LIMA: left internal mammary artery; LMCAD: left main coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; 3VD: three-vessel disease.

Ten-year all-cause death stratified according to the gradient of rSS are presented in **Figure 4** and **Table 5**. Compared with patients who achieved CR (i.e. rSS of 0), patients with a rSS of ≤ 8 had a comparable risk of all-cause death at 10 years (22.0% for rSS of 0 vs. 24.0% for 0< rSS≤ 4 vs. 28.9% for 4< rSS≤ 8), whereas patients with rSS of >8 had a more than 3.5-fold higher risk of 10-year all-cause death, compared with those with rSS of 0 (adjusted HR: 3.75; 95% CI: 2.33 to 6.05; p< 0.001) (**Figure 4A** and **Table 5**). These findings were largely consistent with subgroups of 3VD or LMCAD (**Figure 4B, 4C** and **Table 5**) and at maximum follow-up (**Online Figure 2** and **Online Table 2**).

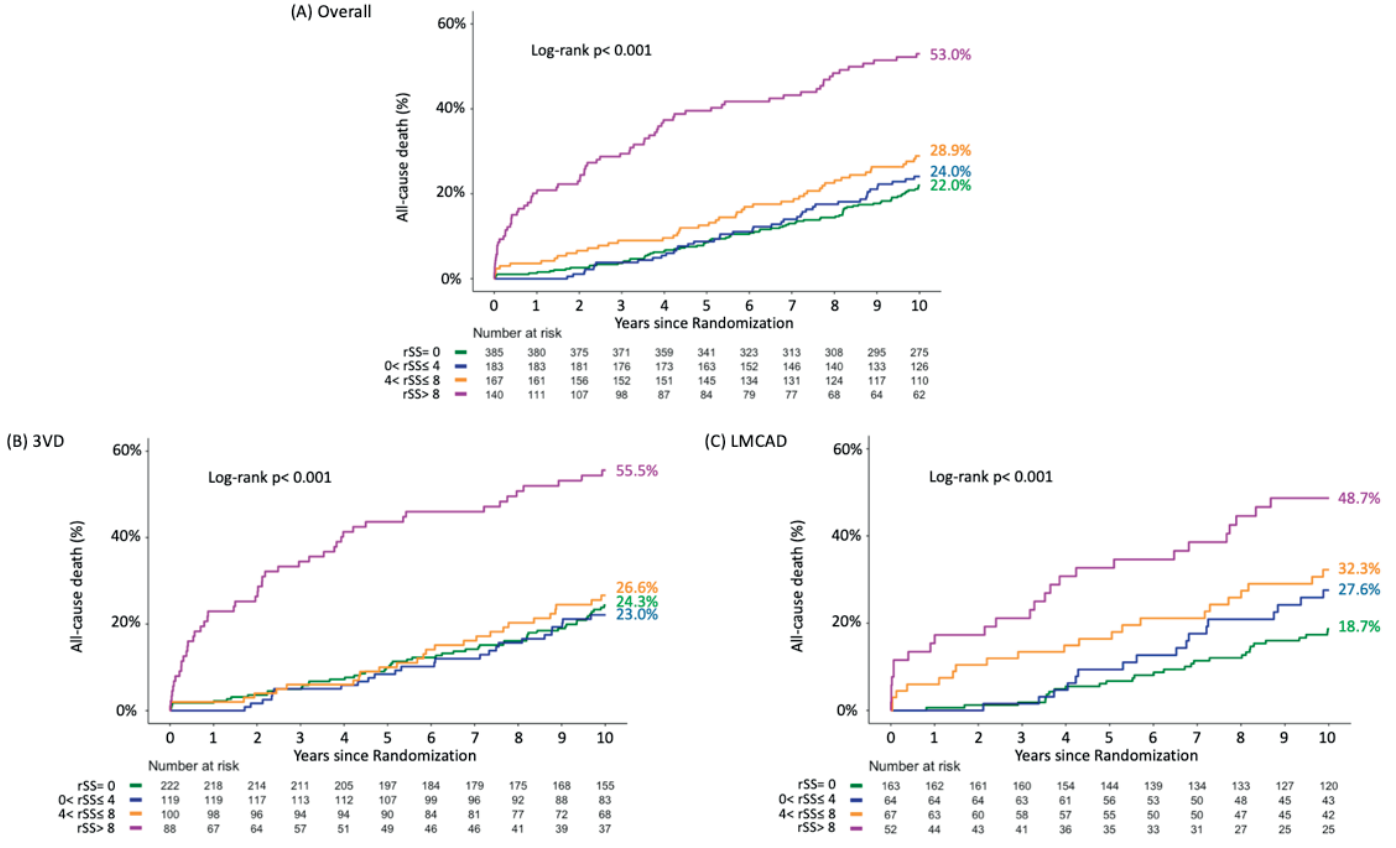


Figure 4. Kaplan-Meier curves for the primary endpoint of all-cause death up to 10 years according to the rSS in patients who underwent PCI. (A) overall population; (B) 3VD cohort; (C) LMCAD cohort.

Abbreviations are as in **Figure 3**.

Table 5. Crude and adjusted all-cause death at 10 years according to the rSS.

	Crude incidence					Adjusted HR (95% CI)				
	rSS= 0	0< rSS≤ 4	4< rSS≤ 8	8< rSS	p-value	rSS= 0	0< rSS≤ 4	4< rSS≤ 8	8< rSS	p-value
Overall	22.0 (81)	24.0 (42)	28.9 (47)	53.0 (73)	<0.001	1.00 (reference)	1.47 (0.89-2.41)	1.17 (0.69-2.00)	3.75 (2.33-6.05)	<0.001
3VD	23.0 (52)	24.3 (25)	26.6 (26)	55.5 (48)	<0.001	1.00 (reference)	0.92 (0.49-1.75)	0.61 (0.28-1.30)	3.19 (1.74-5.83)	<0.001
LMCAD	18.7 (29)	27.6 (17)	32.3 (21)	48.7 (25)	<0.001	1.00 (reference)	5.01 (2.12-11.82)	2.93 (1.26-6.82)	5.17 (2.14-12.48)	<0.001

Data are presented as percentage (number of deaths).

CI: confidence interval; HR: hazard ratio; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; rSS: residual SYNTAX score; 3VD: three-vessel disease.

DISCUSSION

The main findings of the present study can be summarized as follows.

1. IR was more frequently observed in patients with PCI when compared with CABG. Irrespective of the revascularisation strategy, patients with 3VD were more prone to have IR than those with LMCAD.
2. Patients undergoing PCI with CR had a similar risk of all-cause death at 10 years compared with those undergoing CABG. In contrast, PCI with IR resulted in a significantly higher risk of all-cause death at 10 years.
3. Although a rSS was associated with a progressive increase in clinical comorbidities and complex lesions among patients undergoing PCI, patients with a rSS of ≤ 8 had a similar risk of all-cause death compared with those with rSS of 0. However, patients with a rSS of >8 had a more than 3.5-fold higher risk of all-cause death at 10 years despite a higher rate of OMT at discharge.

Early studies in 1980s demonstrated a survival benefit of CR over IR in stable patients with multivessel disease who underwent CABG [24-26]. This clinical benefit of CR was somewhat mitigated when the internal mammary artery was grafted to the left anterior descending artery [11, 27, 28]. Nevertheless, a recent study-level meta-analysis from 28 studies between 2000 and 2013 including 83,695 patients with a median follow-up period of 4.7 years showed that CR resulted in a greater survival benefit over IR in patients with CABG (RR: 0.76; 95% CI: 0.63-0.90) [29]. Consistently, a previous analysis in the SYNTAX trial demonstrated that, CR with CABG had a lower risk of all-cause death at 4 years compared with IR (HR: 0.70; 95% CI: 0.49-0.98; p= 0.039) in all-comers 3VD or LMCAD patients consisting of randomized patients and nested registry [14]. Conversely, the present analysis confined to the randomized SYNTAX patients found that CR had a similar risk of 10-year all-cause death compared with IR. This discrepancy in the 4-year SYNTAX data [14] was likely attributable to the fact that the nested CABG registry included patients with a more complex anatomy (anatomical SS: nested CABG registry 37.8± 13.3 vs. randomized CABG 29.1±11.4, p< 0.001) and more clinical comorbidities, accounting for a significantly higher risk of all-cause death in patients undergoing CABG with IR vs. CR.

The similar advantage of CR vs. IR among PCI population has been reported during the past two decades [30-33]. A more recent study-level meta-analysis with 156,240 patients from 38 studies has shown that CR with PCI was associated with a significantly lower risk of all-cause death (OR: 0.69; 95% CI: 0.61-0.78; p< 0.001) compared with IR [34]. The present study supports those previous findings and further extended this timeframe up to 10 years, demonstrating that, IR, in contrast to CR, was associated

with a significantly increased risk of 10-year all-cause death in patients undergoing PCI (**Table 3**).

Among those studies, the completeness of revascularisation was classified as binary (i.e. complete vs. incomplete). As a result, the IR group pools together patients with any lesions left untreated regardless of its location, extent, and complexity, representing a vast heterogeneity of patients with IR. For a more accurate risk stratification, quantification of residual burden of coronary atherosclerosis after PCI, namely the rSS, was introduced in the context of moderate to high-risk acute coronary syndromes [22], showing a poorer 30-day and 1-year mortality in patients with a rSS> 8. Subsequently, the rSS was externally validated in the SYNTAX trial [21]. The present study further supports a graded spectrum of IR and identified patients with a rSS> 8 being a more than 3.5-fold higher risk of all-cause death at 10 years (**Table 5**). Incomplete revascularisation is a multifactorial phenomenon related to small vessel disease, highly calcified lesion, extreme tortuosity, extremely angulated bifurcation lesions among others, although the main identifiable reason for IR remained the presence of a TO not successfully recanalized [14]. Thus, a high residual SS post procedure is difficult to predict prior to the attempted treatment. The Japanese and European CTO score are the only established predictor of anticipated treatment failure that could be a strong and reliable deterrent for a percutaneous treatment and favor a surgical approach. Nevertheless, it remains difficult to predict a high rSS prior to the procedure prospectively, and only post procedure, is it feasible and realistic to quantify the rSS. However, if operators are unable to reduce the score below the threshold of 8, then they should be aware that their patients will be at high risk of a fatal late outcome. These patients with IR need definitely more intensive pharmacotherapy [23] and aggressive risk factor modification (e.g. smoking cessation [35]) for secondary prevention. Interestingly, the present analysis has found a progressively greater use of OMT according to the rSS, suggesting that investigators might perceive a higher risk of adverse events in patients with a higher rSS, although the rate of OMT was suboptimal with approximately two thirds of patients receiving OMT at discharge. In this regard, the recently proposed “aspirin-free strategy” may be helpful since it has shown to be associated with a significantly lower risk of bleeding events without a trade-off in ischemic risks, potentially resulting in a lower risk of mortality especially in high-risk patients [36-39].

The rSS is purely an angiographic (anatomic) index quantifying the residual burden of anatomic lesions left untreated, whereas Bech et al. first demonstrated in 1999 that “residual ischemia”, defined as FFR≤ 0.89 after PCI, was associated with a higher risk of adverse events at two years [40]. Subsequently, several studies have confirmed

that observation. Nevertheless, functional assessment of rSS is rarely performed in daily practice. Recently, the ERIS (Evolving Routine Standards of FFR Use) study demonstrated that physiology-guided PCI was performed in 7% of the total PCI volume [41]. Interestingly, even if FFR value after coronary stent implantation was suboptimal (defined as post PCI FFR≤ 0.88), in 89% of these cases, no further intervention was performed. Reasons for a low prevalence of FFR use after PCI are multifactorial; (i) physiology optimization with FFR is performed only in cases in which FFR has been used for decision making prior to the PCI; (ii) the need to administer adenosine post procedure increases the procedure time and cost and exposes the patient a second time to the side effects of the drug; (iii) a standardized threshold to perform additional procedure based on randomized trials is lacking; (iv) the difficulty to interpret the manual FFR pullback and identify the underlying causes in case of suboptimal post-PCI FFR results with the possible need for intravascular imaging in order to identify the remediable mechanistic cause.

Against this background, another index integrating anatomical and physiological information after PCI, termed the residual functional SS (rFSS), which is calculated by the sum of the rSS in vessels with FFR≤ 0.80, has been recently introduced [42]; specifically, in a pre-specified sub-study of the 3V FFR-FRIENDS (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease) registry (n= 1,136), which performed FFR measurement in all major coronary arteries post-procedure [43], patients with functional IR, defined as a rFSS≥ 1, was associated with a significantly higher risk of MACE at two years as compared to those with functional CR (i.e. rFSS of 0) [42]. However, the results should be interpreted cautiously, because the study included a lower-risk population without TO with a relatively small sample size (n=385), resulting in only 24 MACE events, most of which were ischemia-driven revascularisation [42], a less objective endpoint with respect to death or MI [44]. Nevertheless, these findings with functional assessment at post-procedure are of great interest, and further investigations are warranted including cost-effectiveness of the prediction models.

Limitation

Our findings should be interpreted in light of the following limitations. First, as discussed previously, physiological assessment pre- and post-procedure was not mandatory in the SYNTAX trial. Nevertheless, the present study provided unique information after angiographically guided PCI regarding 10-year all-cause death, which is the most robust endpoint that is clinically relevant for both patients and physicians. In addition, it has to be emphasized that the use of FFR varies significantly across countries, centres, and operators ranging from 3% to 30% of the total volume of PCI

due to equipment, reimbursement, and operator choice. Even resting indices such as instantaneous wave-free ratio have not increased the usage of physiology-guided PCI significantly [41, 45, 46]. Second, although the SYNTAX trial collected baseline information that are related to mortality and the present analysis accounted for imbalances in multivariable models, the role of unmeasured confounders cannot be excluded. Third, the SYNTAX trial was conducted between 2005 and 2007 with a default use of the first-generation DES for treatment with PCI, as well as less concerted attention to multidrug OMT, which may limit generalizability of our findings to our current practice [47]. Nevertheless, the SYNTAXES study is the first randomized data that was meticulously conducted and achieved a high follow-up rate of 93.8% for 10-year vital status (1,689 out of 1,800 enrolled patients) [17].

CONCLUSION

CR was less frequently achieved in patients undergoing PCI when compared to CABG, especially in cases with 3VD. Patients undergoing PCI with CR had a comparable risk of all-cause death at 10 years compared with those undergoing CABG. In contrast, patients undergoing PCI with IR had a significantly higher risk of all-cause death at 10 years. Patients undergoing PCI with IR represented a population with great heterogeneity of clinical and anatomic comorbidities. Patients with a rSS of ≤ 8 had a similar risk of all-cause death compared with those with CR, whereas patients with a rSS of > 8 had a more than 3.5-fold higher risk of all-cause death at 10 years despite a higher rate of OMT at discharge.

Abbreviations List

CABG: coronary artery bypass grafting
CAD: coronary artery disease
LMCAD: left main coronary artery disease
MI: myocardial infarction
PCI: percutaneous coronary intervention
3VD: three-vessel disease

REFERENCES

1. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G and Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J*. 2011;32:1012-24.
2. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE and Investigators C. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283-91.
3. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Makikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF, 3rd, Stables RH, Stone GW, Serruys PW and Kappetein AP. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391:939-948.
4. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Jr., Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW and Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639-50.
5. Kent DM, Steyerberg E and van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. *BMJ*. 2018;363:k4245.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO and Group ESCSD. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
7. Windecker S, Neumann FJ, Juni P, Sousa-Uva M and Falk V. Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:204-212.
8. Bourassa MG, Kip KE, Jacobs AK, Jones RH, Sopko G, Rosen AD, Sharaf BL, Schwartz L, Chaitman BR, Alderman EL, Holmes DR, Roubin GS, Detre KM and Frye RL. Is a strategy of intended incomplete percutaneous transluminal coronary angioplasty revascularization acceptable in nondiabetic patients who are candidates for coronary artery bypass graft surgery? The Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol*. 1999;33:1627-36.
9. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA and Arterial Revascular-

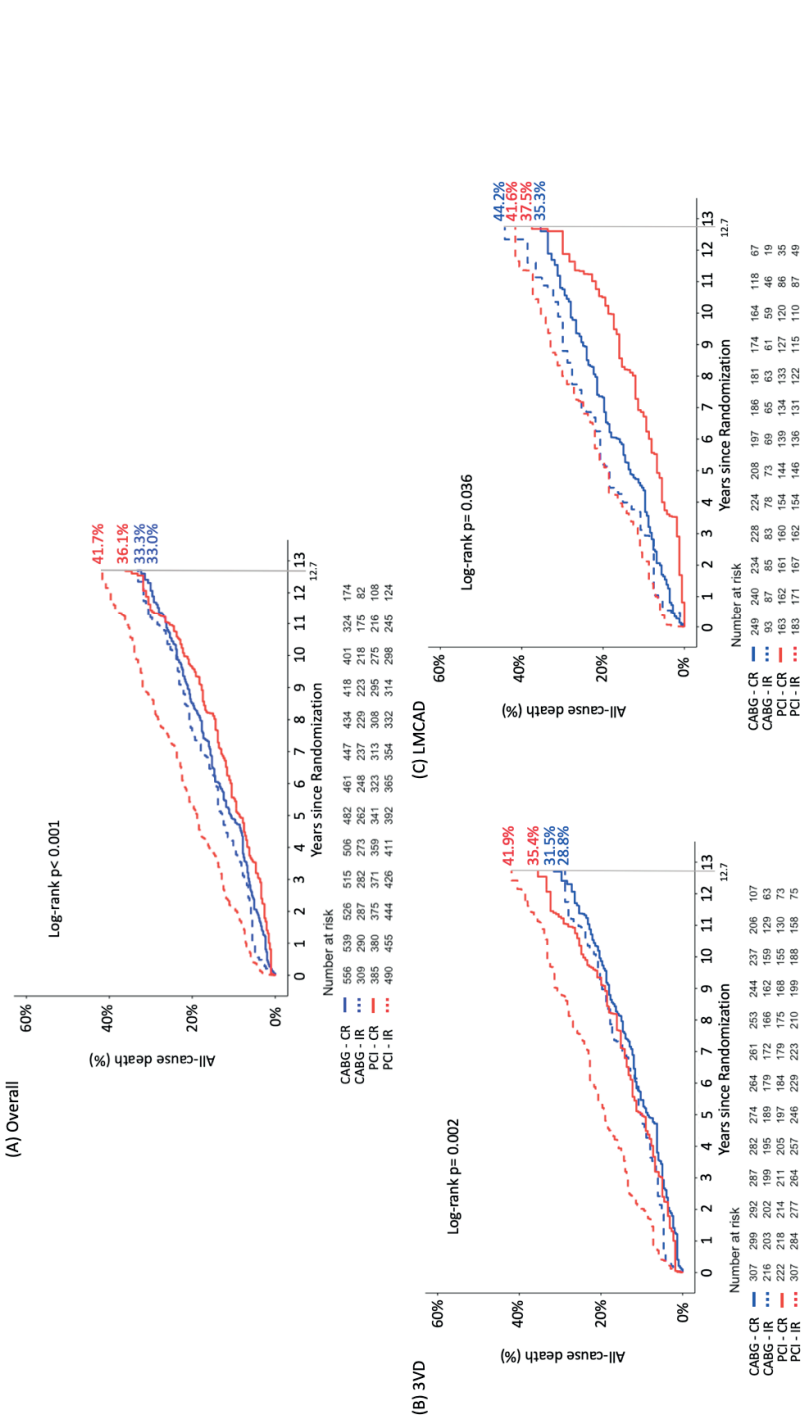
ization Therapies Study G. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344:1117-24.
10. Sarno G, Garg S, Onuma Y, Gutierrez-Chico JL, van den Brand MJ, Rensing BJ, Morel MA, Serruys PW and Investigators A-I. Impact of completeness of revascularization on the five-year outcome in percutaneous coronary intervention and coronary artery bypass graft patients (from the ARTS-II study). *Am J Cardiol*. 2010;106:1369-75.
11. Kim YH, Park DW, Lee JY, Kim WJ, Yun SC, Ahn JM, Song HG, Oh JH, Park JS, Kang SJ, Lee SW, Lee CW, Park SW and Park SJ. Impact of angiographic complete revascularization after drug-eluting stent implantation or coronary artery bypass graft surgery for multivessel coronary artery disease. *Circulation*. 2011;123:2373-81.
12. Vieira RD, Hueb W, Gersh BJ, Lima EG, Pereira AC, Rezende PC, Garzillo CL, Hueb AC, Favarato D, Soares PR, Ramires JA and Kalil Filho R. Effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease: MASS II trial. *Circulation*. 2012;126:S158-63.
13. Head SJ, Mack MJ, Holmes DR, Jr., Mohr FW, Morice MC, Serruys PW and Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2012;41:535-41.
14. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G and Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol*. 2013;61:282-94.
15. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J and Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. *N Engl J Med*. 2015;372:1213-22.
16. Ahn JM, Park DW, Lee CW, Chang M, Cavalcante R, Sotomi Y, Onuma Y, Tenekecioglu E, Han M, Lee PH, Kang SJ, Lee SW, Kim YH, Park SW, Serruys PW and Park SJ. Comparison of Stenting Versus Bypass Surgery According to the Completeness of Revascularization in Severe Coronary Artery Disease: Patient-Level Pooled Analysis of the SYNTAX, PRECOMBAT, and BEST Trials. *JACC Cardiovasc Interv*. 2017;10:1415-1424.
17. Thuijs D, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, Holmes DR, Jr., Curzen N, Davierwala P, Noack T, Milojevic M, Dawkins KD, da Costa BR, Juni P, Head SJ and Investigators SES. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019.
18. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J and Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J*. 2006;151:1194-204.
19. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW and Investigators S. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-72.

20. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Jr., Morel MA, Van Dyck N, Houle VM, Dawkins KD and Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381:629-38.
21. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP and Mohr FW. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation*. 2013;128:141-51.
22. Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW and Stone GW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol*. 2012;59:2165-74.
23. Iqbal J, Zhang YJ, Holmes DR, Morice MC, Mack MJ, Kappetein AP, Feldman T, Stahle E, Escaned J, Banning AP, Gunn JP, Colombo A, Steyerberg EW, Mohr FW and Serruys PW. Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. *Circulation*. 2015;131:1269-77.
24. Buda AJ, Macdonald IL, Anderson MJ, Strauss HD, David TE and Berman ND. Long-term results following coronary bypass operation. Importance of preoperative actors and complete revascularization. *J Thorac Cardiovasc Surg*. 1981;82:383-90.
25. Lawrie GM, Morris GC, Jr., Silvers A, Wagner WF, Baron AE, Beltangady SS, Glaeser DH and Chapman DW. The influence of residual disease after coronary bypass on the 5-year survival rate of 1274 men with coronary artery disease. *Circulation*. 1982;66:717-23.
26. Jones EL, Craver JM, Guyton RA, Bone DK, Hatcher CR, Jr. and Riechwald N. Importance of complete revascularization in performance of the coronary bypass operation. *Am J Cardiol*. 1983;51:7-12.
27. Vander Salm TJ, Kip KE, Jones RH, Schaff HV, Shemin RJ, Aldea GS and Detre KM. What constitutes optimal surgical revascularization? Answers from the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol*. 2002;39:565-72.
28. Rastan AJ, Walther T, Falk V, Kempfert J, Merk D, Lehmann S, Holzhey D and Mohr FW. Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? *Circulation*. 2009;120:S70-7.
29. Zimarino M, Ricci F, Romanello M, Di Nicola M, Corazzini A and De Caterina R. Complete myocardial revascularization confers a larger clinical benefit when performed with state-of-the-art techniques in high-risk patients with multivessel coronary artery disease: A meta-analysis of randomized and observational studies. *Catheter Cardiovasc Interv*. 2016;87:3-12.
30. Bourassa MG, Yeh W, Holubkov R, Sopko G and Detre KM. Long-term outcome of patients with incomplete vs complete revascularization after multivessel PTCA. A report from the NHLBI PTCA Registry. *Eur Heart J*. 1998;19:103-11.

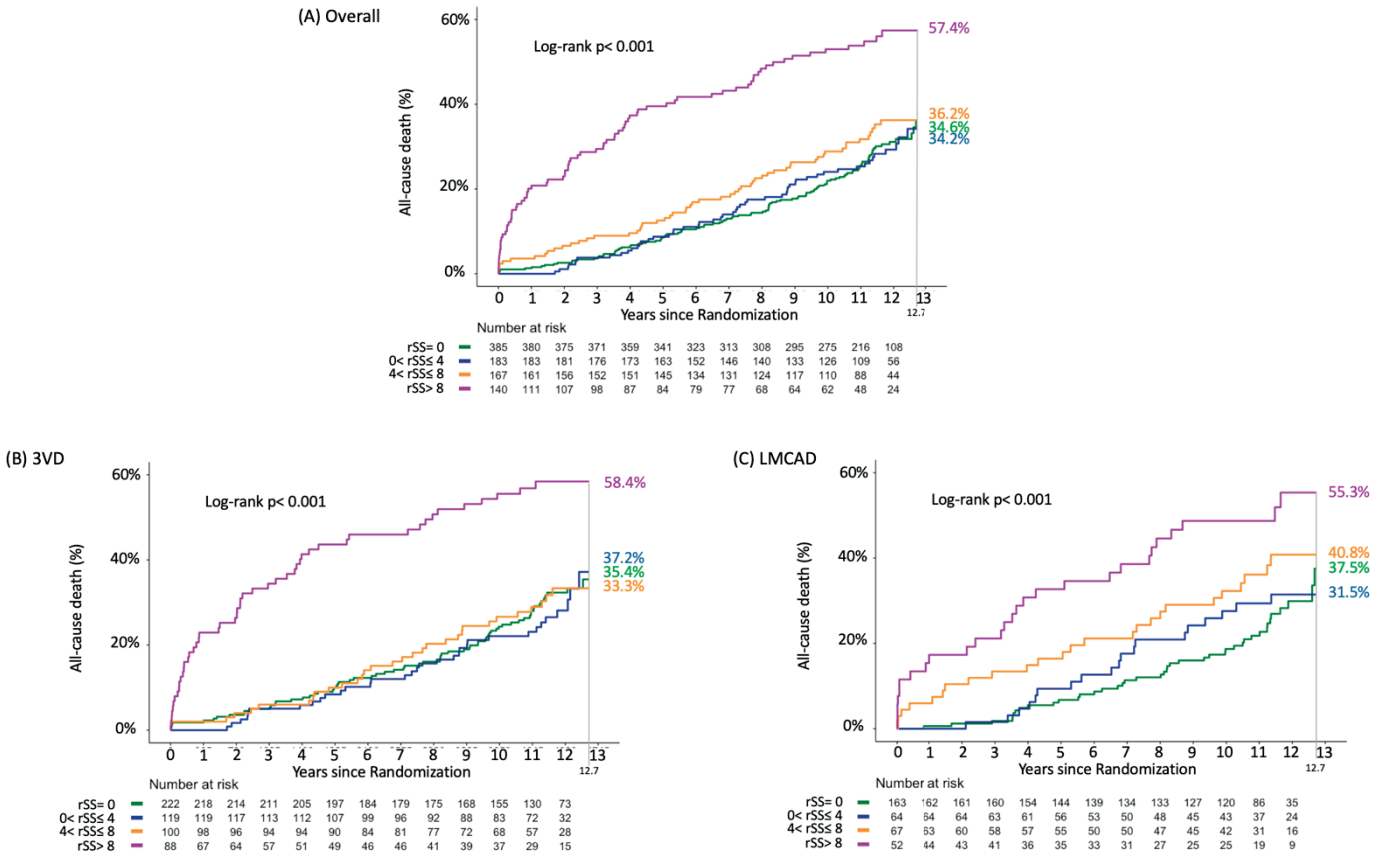
31. Hannan EL, Racz M, Holmes DR, King SB, 3rd, Walford G, Ambrose JA, Sharma S, Katz S, Clark LT and Jones RH. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation*. 2006;113:2406-12.
32. Hannan EL, Wu C, Walford G, Holmes DR, Jones RH, Sharma S and King SB, 3rd. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interv*. 2009;2:17-25.
33. Bangalore S, Guo Y, Samadashvili Z and Hannan EL. Outcomes With Complete Versus Incomplete Revascularization in Patients With Multivessel Coronary Disease Undergoing Percutaneous Coronary Intervention With Everolimus Eluting Stents. *Am J Cardiol*. 2019.
34. Nagaraja V, Ooi SY, Nolan J, Large A, De Belder M, Ludman P, Bagur R, Curzen N, Matsukage T, Yoshimachi F, Kwok CS, Berry C and Mamas MA. Impact of Incomplete Percutaneous Revascularization in Patients With Multivessel Coronary Artery Disease: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2016;5.
35. Zhang YJ, Iqbal J, van Klaveren D, Campos CM, Holmes DR, Kappetein AP, Morice MC, Banning AP, Grech ED, Bourantas CV, Onuma Y, Garcia-Garcia HM, Mack MJ, Colombo A, Mohr FW, Steyerberg EW and Serruys PW. Smoking is associated with adverse clinical outcomes in patients undergoing revascularization with PCI or CABG: the SYNTAX trial at 5-year follow-up. *J Am Coll Cardiol*. 2015;65:1107-15.
36. Serruys PW, Takahashi K, Chichareon P, Kogame N, Tomaniak M, Modolo R, Chang CC, Komiyama H, Soliman O, Wykrzykowska JJ, de Winter RJ, Ferrario M, Dominici M, Buszman P, Bolognese L, Tumscitz C, Benit E, Stoll HP, Hamm C, Steg PG, Onuma Y, Juni P, Windecker S, Vranckx P, Colombo A and Valgimigli M. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. *Eur Heart J*. 2019;40:2595-2604.
37. Takahashi K, Serruys PW, Chichareon P, Chang CC, Tomaniak M, Modolo R, Kogame N, Magro M, Chowdhary S, Eitel I, Zweiker R, Ong P, Ottesen MM, Tijssen JGP, Wykrzykowska JJ, de Winter RJ, Garg S, Stoll HP, Hamm C, Steg PG, Onuma Y, Valgimigli M, Vranckx P, Carrie D and Windecker S. Efficacy and Safety of Ticagrelor Monotherapy in Patients Undergoing Multivessel PCI. *J Am Coll Cardiol*. 2019;74:2015-2027.
38. Takahashi K, Chichareon P, Modolo R, Kogame N, Chang CC, Tomaniak M, Moschovitis A, Curzen N, Haude M, Jung W, Holmvang L, Garg S, Tijssen JGP, Wykrzykowska JJ, de Winter RJ, Hamm C, Steg PG, Stoll HP, Onuma Y, Valgimigli M, Vranckx P, Windecker S and Serruys PW. Impact of Ticagrelor Monotherapy on Two-Year Clinical Outcomes in Patients with Long Stenting: A Post Hoc Analysis of the Global Leaders Trial. *EuroIntervention*. 2019.
39. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Dzavik V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S and Gibson CM. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med*. 2019.
40. Bech GJ, Pijls NH, De Bruyne B, Peels KH, Michels HR, Bonnier HJ and Koolen JJ. Usefulness of fractional flow reserve to predict clinical outcome after balloon angioplasty. *Circulation*. 1999;99:883-8.

41. Tebaldi M, Biscaglia S, Fineschi M, Musumeci G, Marchese A, Leone AM, Rossi ML, Stefanini G, Maione A, Menozzi A, Tarantino F, Lodolini V, Gallo F, Barbato E, Tarantini G and Campo G. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. *JACC Cardiovasc Interv*. 2018;11:1482-1491.
42. Choi KH, Lee JM, Koo BK, Nam CW, Shin ES, Doh JH, Rhee TM, Hwang D, Park J, Zhang J, Kim KJ, Hu X, Wang J, Ye F, Chen S, Yang J, Chen J, Tanaka N, Yokoi H, Matsuo H, Takashima H, Shiono Y and Akasaka T. Prognostic Implication of Functional Incomplete Revascularization and Residual Functional SYNTAX Score in Patients With Coronary Artery Disease. *JACC Cardiovasc Interv*. 2018;11:237-245.
43. Lee JM, Koo BK, Shin ES, Nam CW, Doh JH, Hwang D, Park J, Kim KJ, Zhang J, Hu X, Wang J, Ahn C, Ye F, Chen S, Yang J, Chen J, Tanaka N, Yokoi H, Matsuo H, Takashima H, Shiono Y and Akasaka T. Clinical implications of three-vessel fractional flow reserve measurement in patients with coronary artery disease. *Eur Heart J*. 2018;39:945-951.
44. Lamelas P, Belardi J, Whitlock R and Stone GW. Limitations of Repeat Revascularization as an Outcome Measure: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;74:3164-3173.
45. Gotberg M, Cook CM, Sen S, Nijjer S, Escaned J and Davies JE. The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve. *J Am Coll Cardiol*. 2017;70:1379-1402.
46. Toth GG, Toth B, Johnson NP, De Vroey F, Di Serafino L, Pyxaras S, Rusinaru D, Di Gioia G, Pellicano M, Barbato E, Van Mieghem C, Heyndrickx GR, De Bruyne B and Wijns W. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. *Circ Cardiovasc Interv*. 2014;7:751-9.
47. Escaned J, Collet C, Ryan N, De Maria GL, Walsh S, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Ej West N, Piek JJ, Zaman A, Fath-Ordoubadi F, Stables RH, Appleby C, van Mieghem N, van Geuns RJ, Uren N, Zueco J, Buszman P, Iniguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, Hanratty C, Cavalcante R, Kappetein AP, Taggart DP, van Es GA, Morel MA, de Vries T, Onuma Y, Farooq V, Serruys PW and Banning AP. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J*. 2017;38:3124-3134.

SUPPLEMENTAL MATERIAL



Online Figure 1. Kaplan-Meier curves for the primary endpoint of all-cause death up to 12.7 years according to randomized treatments of CABG (blue) or PCI (red) and completeness of revascularization. (A) overall population; (B) 3VD cohort; (C) LMCAD cohort.
CABG: coronary artery bypass grafting; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; 3VD: three-vessel disease, CR: complete revascularization, IR: incomplete revascularization.



Online Figure 2. Kaplan-Meier curves for the primary endpoint of all-cause death up to 12.7 years according to the rSS in patients who underwent PCI. (A) overall population; (B) 3VD cohort; (C) LMCAD cohort.
Abbreviations are as in Figure 2.

Online Table 1. Crude and adjusted all-cause death during a maximum follow-up according to completeness of revascularization.

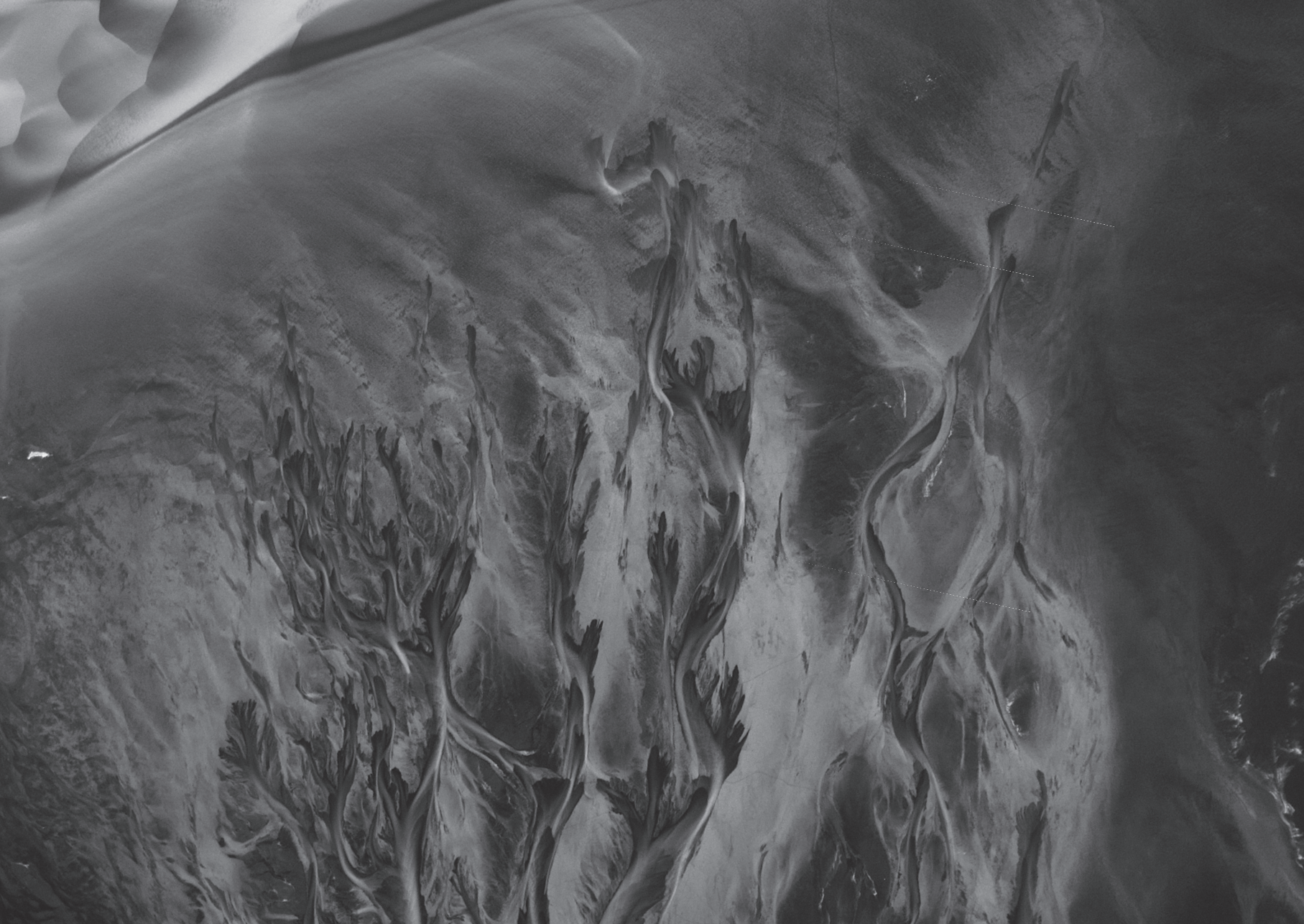
	Crude incidence					Adjusted HR (95% CI)				
	CABG – CR	CABG – IR	PCI – CR	PCI – IR	p-value	CABG - CR	CABG - IR	PCI - CR	PCI - IR	p-value
Overall	33.3 (157)	33.0 (91)	36.1 (110)	41.7 (185)	<0.001	1.00 (reference)	1.05 (0.74-1.49)	1.02 (0.73-1.43)	1.52 (1.13-2.05)	0.018
3VD	31.5 (80)	28.8 (57)	35.4 (68)	41.9 (114)	0.002	1.00 (reference)	1.06 (0.65-1.71)	1.64 (1.04-2.60)	1.66 (1.10-2.50)	0.034
LMCAD	35.3 (77)	44.2 (34)	37.5 (42)	41.6 (71)	0.036	1.00 (reference)	1.11 (0.66-1.88)	0.62 (0.37-1.04)	1.49 (0.94-2.35)	0.019

Data are presented as percentage (number of deaths).
CABG: coronary artery bypass grafting; CI: confidence interval; CR: complete revascularization; HR: hazard ratio; IR: incomplete revascularization; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Online Table 2. Crude and adjusted all-cause death during a maximum follow-up according to the rSS.

	Crude incidence					Adjusted HR (95% CI)				
	rSS= 0	0< rSS≤ 4	4< rSS≤ 8	8< rSS	p-value	rSS= 0	0< rSS≤ 4	4< rSS≤ 8	8< rSS	p-value
Overall	34.6 (110)	34.2 (52)	36.2 (56)	57.4 (77)	<0.001	1.00 (reference)	1.12 (0.71-1.77)	0.92 (0.56-1.52)	2.84 (1.83-4.41)	<0.001
3VD	35.4 (68)	37.2 (33)	33.3 (31)	58.4 (50)	<0.001	1.00 (reference)	0.74 (0.41-1.34)	0.55 (0.27-1.09)	2.46 (1.40-4.30)	<0.001
LMCAD	37.5 (42)	31.5 (19)	40.8 (25)	55.3 (27)	<0.001	1.00 (reference)	3.44 (1.58-7.48)	1.90 (0.86-4.16)	3.92 (1.79-8.59)	0.002

Data are presented as percentage (number of deaths).
CI: confidence interval; HR: hazard ratio; LMCAD: left main coronary artery disease; PCI: percutaneous coronary intervention; rSS: residual SYNTAX score; 3VD: three-vessel disease.



Chapter 10

Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation

Kuniaki Takahashi, Patrick W. Serruys, Valentin Fuster, Michael E. Farkouh, John A. Spertus, David J. Cohen, Seung-Jung Park, Duk-Woo Park, Jung-Min Ahn, A. Pieter Kappetein, Stuart J. Head, Daniel J.F.M. Thuijs, Yoshinobu Onuma, David M. Kent, Ewout W. Steyerberg, David van Klaveren, on behalf of the SYNTAXES, FREEDOM, BEST, and PRECOMBAT trial investigators

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ABSTRACT

Background

Randomised controlled trials are considered the gold standard for testing the efficacy of novel therapeutic interventions, and typically report the average treatment effect as a summary result. As the result of treatment can vary between patients, basing treatment decisions for individual patients on the overall average treatment effect could be suboptimal. We aimed to develop an individualised decision making tool to select an optimal revascularisation strategy in patients with complex coronary artery disease.

Methods

The SYNTAX Extended Survival (SYNTAXES) study is an investigator-driven extension follow-up of a multicentre, randomised controlled trial done in 85 hospitals across 18 North American and European countries between March, 2005, and April, 2007. Patients with de-novo three-vessel and left main coronary artery disease were randomly assigned (1:1) to either the percutaneous coronary intervention (PCI) group or coronary artery bypass grafting (CABG) group. The SYNTAXES study ascertained 10-year all-cause deaths. We used Cox regression to develop a clinical prognostic index for predicting death over a 10-year period, which was combined, in a second stage, with assigned treatment (PCI or CABG) and two prespecified effect-modifiers, which were selected on the basis of previous evidence: disease type (three-vessel disease or left main coronary artery disease) and anatomical SYNTAX score. We used similar techniques to develop a model to predict the 5-year risk of major adverse cardiovascular events (defined as a composite of all-cause death, non-fatal stroke, or non-fatal myocardial infarction) in patients receiving PCI or CABG. We then assessed the ability of these models to predict the risk of death or a major adverse cardiovascular event, and their differences (ie, the estimated benefit of CABG versus PCI by calculating the absolute risk difference between the two strategies) by cross-validation with the SYNTAX trial (n=1800 participants) and external validation in the pooled population (n=3380 participants) of the FREEDOM, BEST, and PRECOMBAT trials. The concordance (C)-index was used to measure discriminative ability, and calibration plots were used to assess the degree of agreement between predictions and observations.

Findings

At cross-validation, the newly developed SYNTAX score II, termed SYNTAX score II 2020, showed a helpful discriminative ability in both treatment groups for predicting 10-year all-cause deaths (C-index=0.73 [95% CI 0.69–0.76] for PCI and 0.73 [0.69–0.76]

for CABG) and 5-year major adverse cardiovascular events (C-index=0.65 [0.61–0.69] for PCI and C-index=0.71 [0.67–0.75] for CABG). At external validation, the SYNTAX score II 2020 showed helpful discrimination (C-index=0.67 [0.63–0.70] for PCI and C-index=0.62 [0.58–0.66] for CABG) and good calibration for predicting 5-year major adverse cardiovascular events. The estimated treatment benefit of CABG over PCI varied substantially among patients in the trial population, and the benefit predictions were well calibrated.

Interpretation

The SYNTAX score II 2020 for predicting 10-year deaths and 5-year major adverse cardiovascular events can help to identify individuals who will benefit from either CABG or PCI, thereby supporting heart teams, patients, and their families to select optimal revascularisation strategies.

Funding The German Heart Research Foundation and the Patient-Centered Outcomes Research Institute.

INTRODUCTION

Myocardial revascularisation is one of the most studied fields in medicine, with more than 20 randomised controlled trials testing the efficacy and safety of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) in approximately 15 000 patients to date.[1] Nevertheless, the optimal revascularisation strategy for individual patients with complex coronary artery disease is still debated. By contrast with previous randomised controlled trials, which enrolled highly selected populations, the Synergy Between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial was a landmark study comparing CABG with PCI (using first-generation drug-eluting stents) in all-comer patients with de-novo three-vessel disease or left main coronary artery disease, or both.[2–5] Following the publication of the primary results of the SYNTAX trial and subgroup analyses in 2009,3 the 2010 European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularisation introduced an algorithm based on the type (three-vessel disease or left main coronary artery disease), extent, and severity of coronary artery disease, as assessed by the anatomical SYNTAX score.[6–8] This stratification has been maintained in the 2018 version of the guidelines.[1] However, as noted in the guidelines, these subgroup analyses merely provide the heart team with an anatomical stratification of treatment recommendations, and do not consider major clinical characteristics and comorbidities.[9–11]

Conventional subgroup analyses evaluate the heterogeneity of a treatment effect by comparing groups of patients who differ in only one single variable (eg, male vs female or age <70 years vs ≥70 years) and do not account for multiple variables that might simultaneously influence outcomes (eg, young male vs old male vs young female vs old female). As such, conventional subgroup analyses do not represent the broader heterogeneity of patients who clinicians treat in daily practice.[12–19] In addition, conventional subgroup analyses usually divide the overall population into smaller groups, resulting in reduced statistical power for detecting a differential treatment effect (ie, false-negative findings) and an increased risk for false-positive findings due to multiple comparisons.[13–21] Finally, clinical interpretation of subgroup analyses is hampered by the fact that the average treatment effect is usually presented on a relative scale (eg, as odds ratios or hazard ratios [HRs]), whereas the absolute risk difference is the most important scale for clinical decision making.[15–19]

To move beyond conventional subgroup analyses, multivariable risk predictive models have been proposed to simultaneously account for multiple patient characteristics that influence treatment effects. Such an approach can readily estimate

treatment benefits on the basis of multiple individual patient characteristics, enabling personalised decision making for each patient.[13–19] We previously developed the SYNTAX score II to predict 4-year mortality in individual patients given CABG or PCI, to support more evidence-based decision making by the heart team.[11] The SYNTAX score II included eight prognostic factors and their interactions with treatment assignment. However, simulations have shown that data-driven inclusion of interactions overestimated the heterogeneity of the treatment effect.[22] In 2019, the SYNTAX Extended Survival (SYNTAXES) study reported 10-year all-cause death in patients with de-novo three-vessel disease or left main coronary artery disease, or both, who were randomly assigned to receive either CABG or PCI in the original SYNTAX trial.[23] Therefore, the aims of the present study were to redevelop the SYNTAX score II for predicting the benefit of CABG versus PCI over a 10-year period, and to externally validate the updated score (termed the SYNTAX score II 2020) for its ability to predict treatment benefit, further supporting its potential usefulness in clinical care.

Research in context

Evidence before this study

We searched PubMed on Feb 20, 2020, using the search terms "percutaneous coronary intervention", "coronary artery bypass grafting", and "score". We searched for studies on multivariable risk predictive models that had been developed for individualised decision making between percutaneous coronary intervention (PCI) and coronary artery bypass (CABG) in patients with complex coronary artery disease, published in English from database inception up to Feb 20, 2020. We identified 936 potential studies, which were checked manually. Several randomised controlled trials have been done to identify an optimal revascularisation strategy in patients with complex coronary artery disease. However, these trials report an average treatment effect as a summary result of a trial, and treatment effect has been shown to vary among individual patients. Therefore, basing treatment decisions for individual patients on the overall average treatment effect could be suboptimal. Among the 936 studies identified through the literature search, we identified only two studies that had developed a score, based on the predicted risk of long-term adverse events from CABG or PCI as a decision-making tool to guide the selection of an optimal revascularisation strategy for individual patients. One study was on the development of the original SYNTAX score II, which aimed to improve the individualised decision making process by estimating the risk difference in 4-year death between CABG and PCI in patients with three-vessel disease or left main coronary artery disease, or both. The other study developed the FREEDOM score, which estimated the 5-year

risk of having a major adverse cardiovascular event and the 1-year risk of angina in patients with diabetes and multivessel coronary artery disease.

Added value of this study

Using the SYNTAX Extended Survival (SYNTAXES) study, which reported 10-year all-cause death in patients with de-novo three-vessel disease or left main coronary artery disease, or both, who were randomly assigned to receive either CABG or PCI in the original SYNTAX trial, we redeveloped the SYNTAX score II (termed SYNTAX score II 2020), with two prespecified effect-modifiers selected on the basis of previous evidence for predicting the 10-year death risk and 5-year risk of having a major adverse cardiovascular event. The primary results of the SYNTAXES study showed that there was no significant difference in 10-year all-cause death between the PCI group and the CABG group. However, the SYNTAX score II 2020 disentangled the results of this pivotal study and identified patients who gained the most benefit from CABG over PCI, or vice versa, in terms of 10-year all-cause mortality.

Implications of all the available evidence

The SYNTAX score II 2020 provides individuals with a predicted treatment benefit of CABG over PCI, in terms of the 10-year death risk and 5-year risk of having a major adverse cardiovascular event, based on key angiographic and clinical variables obtained at the time of decision making. This model enables more individualised and patient-centred care to be delivered during multidisciplinary heart team discussions for patients and their families.

METHODS

Study design and participants

The study design, and the primary and final 5-year results of the SYNTAX trial (NCT00114972), have been reported previously.[2–5] In brief, the SYNTAX trial is an international, multicentre, randomised controlled trial done in 85 centres across 18 North American and European countries between March, 2005, and April, 2007. Based on clinical judgment and consensus of a heart team (consisting of a cardiothoracic surgeon and interventional cardiologist) at each centre, all patients with three-vessel disease or left main coronary artery disease who were considered to achieve a clinical equipoise between CABG and PCI were randomly assigned (1:1) to either the CABG group (n=897) or the PCI group (n=903), with paclitaxel-eluting stents. The SYNTAX trial completed patient follow-up at 5 years,[5] and the SYNTAXES study (NCT03417050) ascertained all-cause deaths at 10 years.[23]

No randomised trials with 10-year follow-up data in patients with three-vessel disease or left main coronary artery disease, or both (ie, a SYNTAX-like population), are available, thus precluding external validation of the SYNTAX score II 2020 model. However, we extracted patient-level data from three trials involving patients with multivessel disease or left main coronary artery disease treated with PCI and CABG to externally validate the SYNTAX score II 2020 model for predicting 5-year all-cause deaths and 5-year major adverse cardiovascular events, defined as a composite of all-cause death, non-fatal stroke, or non-fatal myocardial infarction. These trials included the Future Revascularisation Evaluation in Patients with Diabetes Mellites: Optimal Management of Multivessel Disease trial (FREEDOM; NCT00086450),[24] the Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease trial (BEST; NCT00997828), and the BYPASS Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease trial (PRECOMBAT; NCT00422968).

The study design, and the primary and final 5-year follow-up results of the FREEDOM trial have been published previously.[24] Briefly, the FREEDOM trial, which was done at 140 international centres between 2005 and 2010, randomly assigned (1:1) 1900 patients with diabetes and multivessel disease to either the CABG group (n=947) or the PCI group (n=953), in which patients received first-generation drug-eluting stents.[24] The FREEDOM trial has reported the primary results at 5 years of follow-up.[24] In 2019, an extended follow-up report of the trial was published, which presents all-cause mortality at 8 years in approximately half of the original trial cohort.[25]

The BEST trial is a multicentre randomised trial done at 27 centres in Asia (South Korea, China, Malaysia, and Thailand) between July, 2008, and September, 2013, that randomly assigned (1:1) 880 patients with multivessel disease to either the CABG group (n=442) or the PCI group (n=438), in which patients received everolimus-eluting stents.[26] The BEST trial has completed patient follow-up for up to 5 years, with 10-year follow-up ongoing.

The PRECOMBAT trial is a multicentre randomised trial, done at 13 centres in Korea between April, 2004, and August, 2009, which randomly assigned (1:1) 600 patients with left main coronary artery disease to either the CABG group (n=300) or the PCI group (n=300), in which patients received a sirolimus-eluting stent.[27,28] The 10-year follow-up results from the PRECOMBAT trial were published in 2020.[29]

All randomised trials included in this study were approved by the ethics committees at each investigating centre, and all patients provided written informed consent before participating in the trial.

Procedures

We contacted the principal investigators of the included trials to request the patient-level data for the external validation of the SYNTAX score II 2020. Data on three randomised trials (FREEDOM, BEST, and PRECOMBAT) were already available, and two investigators (KT and DvK) independently checked the data and compared them with the original publications for completeness and consistency. The principal investigators of these trials were contacted if queries arose during the data checks. A clinical event committee masked to randomisation adjudicated all clinical adverse events of each study. Unless specified, previously reported definitions in each study were used for variables.

We extracted data on age, sex, body-mass index, smoking status (ie, whether they smoked at the time of enrolment), creatinine clearance (according to the Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] formula), and left ventricular ejection fraction, whether they had chronic obstructive pulmonary disease (COPD), peripheral vascular disease, medically treated diabetes, or had received insulin therapy, and whether they had a history of myocardial infarction or stroke.

We developed a predictive model for the prespecified primary endpoint of the SYNTAXES study, 10-year all-cause death, which is the most robust endpoint for both patients and physicians. In addition, we developed a predictive model for 5-year major adverse cardiovascular events, because patients valued stroke or myocardial infarction as an equally or even more important endpoint than death, and they valued other endpoints (eg, repeat revascularisation or readmission to hospital) as substantially less important.[30]

Statistical analysis

In the original SYNTAX trial, results for most of the baseline variables were available for more than 98% of the trial population, whereas data on left ventricular ejection fraction was 98.4% complete as a categorical variable (defined as good [≥50%], moderate [30–49%], and poor [<30%]), and 62.6% complete as continuous variable. Data on serum creatinine was 91% complete. During the development of the original SYNTAX score II, the Cockcroft-Gault formula was used to calculate creatinine clearance.[11] This formula is no longer recommended for clinical use, as it does not adjust for body surface area and overestimates creatinine clearance.[31] We therefore used

the CKD-EPI formula to estimate creatinine clearance, as endorsed by consensus guidelines.[32–34] Similar to the development of the original SYNTAX score II, multiple imputation (20 times) of missing values was done, based on the correlation between all potential predictors, to make efficient use of the available data without introducing bias under the missing at random assumption.[35,36]

Following the recommendations of the Predictive Approaches to Treatment effect Heterogeneity statement,[18,19] published in 2019, we first used Cox regression for the SYNTAXES study data (n=1800 participants) to develop a clinical prognostic index for predicting 10-year all-cause deaths, while masked to treatment assignment.[37] Since the ultimate goal of model development was to inform the choice of a revascularisation strategy, only variables available at the time of decision making were included. Candidate variables were selected a priori on the basis of published data and clinical experience. We then fitted a Cox model, which included treatment assignment, the prognostic index, and two prespecified effect-modifiers: disease type (three-vessel disease or left main coronary artery disease) and anatomical SYNTAX score. We used an analogous approach to develop a model to predict the 5-year risk of major adverse cardiovascular events by use of data from the SYNTAX trial.

The predictive performance of the SYNTAX score II 2020 was internally validated in the development cohort of the SYNTAXES trial by use of a 10-fold cross-validation approach, fitting regression models to 90% of the patients, and calculating predictions for the remaining 10% of patients. The SYNTAX score II 2020 was then externally validated in the combined FREEDOM, BEST, and PRECOMBAT trial cohorts. In addition, we compared the external predictive performance of the SYNTAX score II 2020 with the original SYNTAX score II, calibrated to 5-year deaths, in the FREEDOM, BEST, and PRECOMBAT trial cohort. This calibrated original SYNTAX score II was derived by fitting calibration slopes for patients in the CABG and PCI groups of the SYNTAXES study separately, to update the association between the SYNTAX score II and 5-year deaths.

For each of these validation analyses, the discriminative ability of the SYNTAX score II 2020 for outcome risk was assessed in the separate treatment groups by use of Harrell's C statistic.[38] Calibration for outcome risk in separate treatment groups was also assessed visually by use of calibration plots (ie, agreement between observed vs predicted risk). We added a smooth calibration curve to each calibration plot on the basis of a Cox model that fitted outcomes to a restricted cubic spline of the predictions. Calibration is optimal when the smooth calibration curve is close to the

identity line (ie, diagonal), also reflected by a calibration intercept close to 0 and a calibration slope close to 1.

For models intended to predict treatment benefit, it is important to validate predicted benefits, not just predicted outcomes.[18,19] Thus, we assessed the agreement between predicted and observed benefit of treatment with CABG over PCI by use of a benefit calibration plot, which displays observed versus predicted treatment benefit in quarters of predicted treatment benefit.[39] We estimated the observed benefit of treatment with CABG over PCI by calculating the difference in Kaplan-Meier estimates between the CABG group and the PCI group.[39] We added a smooth calibration curve to each benefit calibration plot on the basis of local polynomial regression between observed and predicted treatment benefit in small groups of 40 patients with increasing predicted benefit.

Continuous variables were reported as the mean (SD), compared by use of Student's *t* tests, or median (IQR), compared by use of Mann-Whitney U tests. Categorical variables were reported as percentages and numbers, and were compared by use of χ^2 or Fisher's exact test, as appropriate. Clinical outcomes are analysed by use of the Kaplan-Meier estimates and compared with the log-rank test. HRs with 95% CIs were estimated by use of a Cox proportional hazards model.

All tests were two-sided, and a p value of less than 0.05 was considered to indicate a significant difference. The analyses were done in accordance with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement.[40] All statistical analyses were done in R, version 3.5.3.

Role of the funding source

All randomised trials included in our study were investigator-initiated, and the funders of each trial and of this report had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author (PWS), first author (KT), and last author (DvK) had full access to the data and had final responsibility for the decision to submit for publication.

RESULTS

In the SYNTAX trial,[5] 1800 patients at 85 European and US hospitals were enrolled between March, 2005, and April, 2007, and randomly assigned to either the CABG group (n=897) or the PCI group (n=903), in which they received paclitaxel-eluting

stents. At 10 years' follow-up, 460 deaths had occurred among all 1800 patients. 212 (24%) patients in the CABG group had died compared with 248 (28%) patients in the PCI group, with no significant difference in deaths observed between the two groups (HR 1.19 [95% CI 0.99–1.43], log-rank p value=0.066). By contrast, at 5 years follow-up (IQR 4.7–5.0), 185 (21%) of 903 patients in the PCI group had had a major adverse cardiovascular event compared with 140 (17%) of 897 patients in the CABG group, with a significant difference observed between the two groups (HR 1.27 [95% CI 1.02–1.59], log-rank p value=0.030).[5]

Baseline characteristics of patients grouped by 10-year all-cause deaths and 5-year incidence of major adverse cardiovascular events are summarised (table 1). Compared with those who were still alive at 10 years' follow-up, patients who had died were older (ie, those who were still alive had a mean age of 63.5 years compared with 69.9 years in those who had died), and were more likely to be female, to have comorbidities (ie, medically treated diabetes, dyslipidaemia, COPD, peripheral vascular disease, lower left ventricular ejection fraction, lower creatinine clearance, and receiving insulin), and more complex coronary artery disease, as indicated by the anatomical SYNTAX score (30.7 [SD 11.7] in those who had died vs 28.1 [11.2] in those who had not, p<0.0001). Compared with patients who had not had a major adverse cardiovascular event at 5 years' follow-up, those who had were older and were more likely to have comorbidities (ie, COPD, peripheral vascular disease, a previous myocardial infarction, lower left ventricular ejection fraction, lower creatinine clearance, and receiving insulin), and a higher anatomical SYNTAX score (30.9 [11.7] in those who had a major adverse cardiovascular event *vs* 28.3 [11.3] in those who had not, p<0.0001; table 1).

For predicting the risk of 10-year all-cause death, the prognostic index consisted of eight clinical predictors of death (age, creatinine clearance, left ventricular ejection fraction, smoking status, and whether they have medically treated diabetes, are receiving insulin, have COPD, and have peripheral vascular disease; table 2). The predictive model for this outcome included the prognostic index, initial revascularisation strategy, and two treatment interactions (three-vessel disease or left main coronary artery disease and anatomical SYNTAX score). CABG was, on average, found to be beneficial in patients with three-vessel disease (HR 0.67 [95% CI 0.53–0.86]), but not in patients with left main coronary artery disease (1.02 [0.77–1.36], $p_{interaction}$=0.028), and anatomical SYNTAX score was only associated with increased risk of death in patients who received PCI (HR per 10 points 1.17 [1.06–1.30]), but not CABG (1.00 [0.89–1.12], $p_{interaction}$=0.039). The SYNTAX score II 2020 showed helpful discriminative ability for both treatment groups for predicting 10-year all-cause

Table 1: Baseline characteristics of patients grouped by all-cause death at 10 years and major adverse cardiovascular events at 5 years

	10-year all-cause death (n=1800)			5-year incidence of a major adverse cardiovascular event (n=1800)*		
	Yes (n=460)	No (n=1340)	P value	Yes (n=328)	No (n=1472)	P value
Study group	..	..	0.063	..	..	0.012
PCI	258 (53.9%)	655 (48.9%)	..	185 (56.4%)	718 (48.8%)	..
CABG	212 (46.1%)	685 (51.1%)	..	143 (43.6%)	754 (51.2%)	..
Age (years)	69.9 (8.8)	63.5 (9.5)	<0.0001	68.8 (9.1)	64.3 (9.7)	<0.0001
Sex	..	..	0.004	..	..	0.400
Male	335 (72.8%)	1063 (79.3%)	..	249 (75.9%)	1149 (78.1%)	..
Female	125 (27.2%)	277 (20.7%)	..	79 (24.1%)	323 (21.9%)	..
Body-mass index (kg/m²)	27.8 (5.0)	28.1 (4.6)	0.280	27.6 (4.7)	28.1 (4.7)	0.074
Medically treated diabetes	152 (33.0%)	300 (22.4%)	<0.0001	96 (29.3%)	356 (24.2%)	0.055
Receiving insulin	75 (16.3%)	107 (8.0%)	<0.0001	47 (14.3%)	135 (9.2%)	0.0051
Hypertension	310 (67.4%)	886 (66.1%)	0.618	226 (68.9%)	970 (65.9%)	0.297
Dyslipidaemia	332 (73.0%)	1059 (79.6%)	0.0031	243 (74.5%)	1148 (78.7%)	0.103
Creatinine clearance (mL/min per 1.73 m²)	72.9 (20.7)	81.3 (17.4)	<0.0001	74.8 (21.1)	80.1 (17.9)	<0.0001
Left ventricular ejection fraction	55.3% (14.2)	59.4% (12.4)	<0.0001	55.1% (14.4)	59.1% (12.6)	<0.0001
Chronic obstructive pulmonary disease	64 (13.9%)	90 (6.7%)	<0.0001	44 (13.4%)	110 (7.5%)	0.0050
Peripheral vascular disease	89 (19.3%)	88 (6.6%)	<0.0001	58 (17.7%)	119 (8.1%)	<0.0001
Current smoker	105 (22.8%)	259 (19.3%)	0.107	74 (22.6%)	290 (19.7%)	0.244
Previous myocardial infarction	164 (36.2%)	421 (31.7%)	0.080	124 (38.2%)	461 (31.7%)	0.025
Previous stroke	27 (5.9%)	51 (3.8%)	0.057	17 (5.3%)	61 (4.2%)	0.380
Clinical presentation	..	..	0.003	..	..	0.061
Silent ischaemia	83 (18.0%)	177 (13.2%)	..	53 (16.2%)	207 (14.1%)	..
Stable angina	233 (50.7%)	794 (59.3%)	..	168 (51.2%)	859 (58.4%)	..

Table 1: Baseline characteristics of patients grouped by all-cause death at 10 years and major adverse cardiovascular events at 5 years (continued)

	10-year all-cause death (n=1800)			5-year incidence of a major adverse cardiovascular event (n=1800)*		
Unstable angina	144 (31.3%)	369 (27.5%)	..	107 (32.6%)	406 (27.6%)	..
Disease type	..	..	0.012	..	..	0.017
Left main coronary artery disease only	12 (2.6%)	79 (5.9%)	..	6 (1.8%)	85 (5.8%)	..
Left main coronary artery disease plus one-vessel disease	45 (9.8%)	93 (6.9%)	..	26 (7.9%)	112 (7.6%)	..
Left main coronary artery disease plus two-vessel disease	62 (13.5%)	156 (11.6%)	..	48 (14.6%)	170 (11.6%)	..
Left main coronary artery disease plus three-vessel disease	74 (16.1%)	184 (13.7%)	..	57 (17.4%)	201 (13.7%)	..
Three-vessel disease only	267 (58.0%)	828 (61.8%)	..	191 (58.2%)	904 (61.4%)	..
SYNTAX score	30.7 (11.7)	28.1 (11.2)	<0.0001	30.9 (11.7)	28.3 (11.3)	0.0002
SYNTAX score tertile	..	..	0.0006	..	..	0.028
Low (0–22)	119 (25.9%)	455 (34.0%)	..	86 (26.2%)	488 (33.2%)	..
Intermediate (23–32)	155 (33.7%)	460 (34.3%)	..	114 (34.8%)	501 (34.0%)	..
High (≥33)	186 (40.4%)	425 (31.7%)	..	128 (39.0%)	483 (32.8%)	..

Data are presented as n (%) or mean (SD). PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. *Defined as a composite of all-cause death, non-fatal stroke, or non-fatal myocardial infarction.

mortality (concordance [C]-index=0.73 [95% CI 0.69–0.76] for PCI and 0.73 [0.69–0.76] for CABG), with excellent calibration between deaths predicted by the SYNTAX score II 2020 and the observed 10-year deaths in the SYNTAXES trial (figure 1A, B). The predicted treatment benefit of CABG over PCI was also well calibrated in cross-validation of the model in the SYNTAXES study (figure 1C).

The SYNTAX score II 2020, developed for predicting 10-year all-cause death, showed similar cross-validated performance in predicting 5-year all-cause death for both PCI and CABG groups in the SYNTAX trial (C-index 0.74 [95% CI 0.69–0.78] for the PCI group and 0.72 [0.67–0.77] for the CABG group), and good agreement between observed and predicted 5-year deaths (appendix p 2). Calibration of the observed versus predicted 5-year treatment benefit of CABG over PCI was excellent (appendix p 2).

Table 2: Model for predicting risk of all-cause death at 10 years

	Coefficient	HR (95% CI)	P value
Prognostic index			
Age, per 10 years	0.72	2.05 (1.81–2.33)	<0.0001
Creatinine clearance, per 10 mL/min per 1.73 m²*	–0.07	0.93 (0.88–0.99)	0.0279
Left ventricular ejection fraction, per 10%†	–0.31	0.73 (0.63–0.84)	<0.0001
Chronic obstructive pulmonary disease	0.48	1.62 (1.24–2.12)	0.0004
Peripheral vascular disease	0.73	2.08 (1.63–2.62)	<0.0001
Medically treated diabetes	0.20	1.22 (0.95–1.57)	0.1251
Receiving insulin	0.46	1.58 (1.14–2.19)	0.0055
Current smoker	0.66	1.93 (1.52–2.45)	<0.0001
Predictive model			
Prognostic index	0.99	2.69 (2.42–3.01)	<0.0001
CABG × three-vessel disease	–0.40	0.67 (0.53–0.86)	0.0014
CABG × left main coronary artery disease	–0.08	0.92 (0.72–1.19)	0.5466
PCI × left main coronary artery disease	–0.10	0.90 (0.70–1.17)	0.4418
PCI × (SYNTAX score - 29)/10	0.16	1.17 (1.06–1.30)	0.0024

Table shows the estimated Cox regression coefficients for the prognostic index with seven variables, and for the predictive model with the predictive index and two predefined treatment interactions (three-vessel disease or left main coronary artery disease and anatomical SYNTAX score) entered into the SYNTAX II 2020 for predicting 10-year all-cause death. The formula used to predict this outcome is as follows: predicted probability of all-cause death at 10 years=1 – exp(–0.243 × exp[0.99 × {0.72 × age - 0.07 × creatinine clearance - 0.31 × left ejection fraction + 0.48 × chronic obstructive pulmonary disease + 0.73 × peripheral vascular disease + 0.20 × medically treated diabetes + 0.46 × on insulin + 0.66 × current smoker} - 0.40 × CABG × three-vessel disease - 0.08 × CABG × left main coronary artery disease - 0.10 × PCI × left main coronary artery disease + 0.16 × PCI × {SYNTAX score - 29}/10 - 2.80]), where age is expressed in years per 10 years, the creatinine clearance is expressed per 10 mL/min per 1.73 m² (capped at 90 per 10 mL/min per 1.73 m²), and the left ventricular ejection fraction is expressed per 10% (capped at 50 per 10%). CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. *Capped at 90 per 10 mL/min per 1.73 m². -Capped at 50 per 10%. HR=hazard ratio.

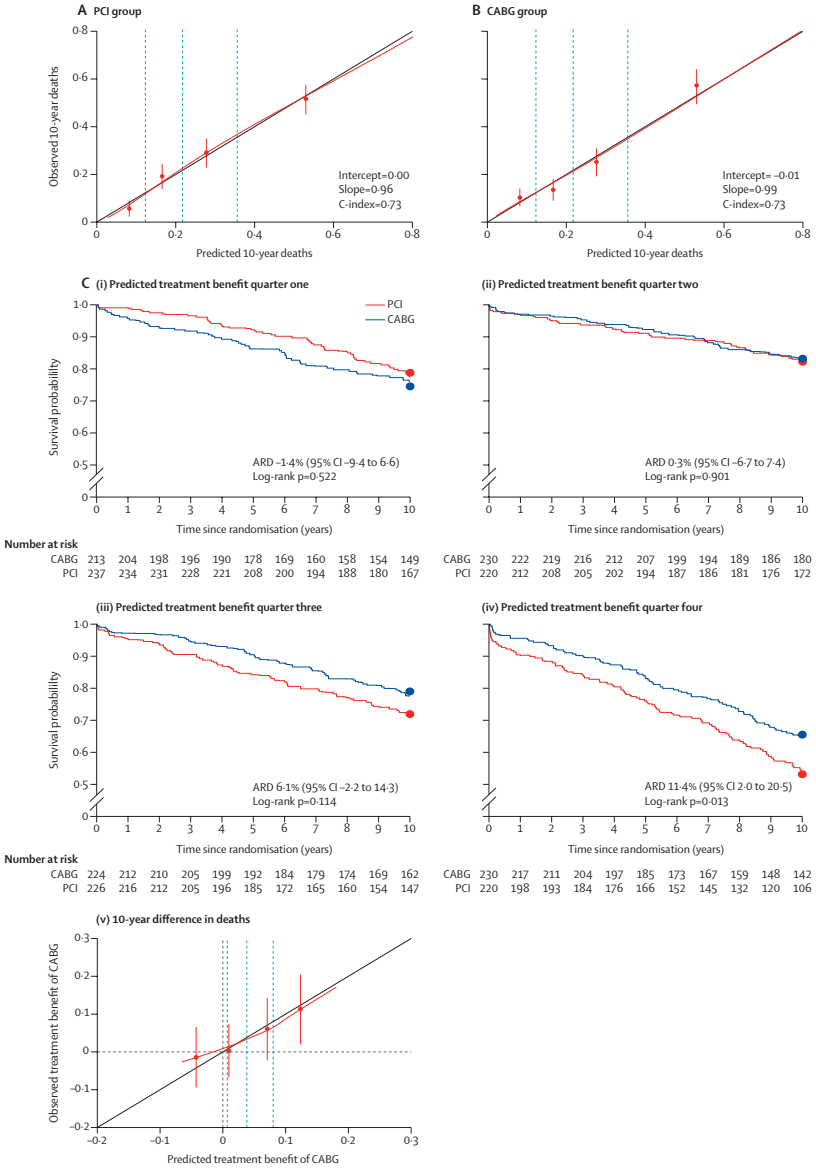

Figure 1: Cross-validation of the SYNTAX score II 2020 for predicting 10-year death in patients with three-vessel disease or left main coronary artery disease in the SYNTAX trial (n=1800)

Calibration plots showing the observed versus predicted 10-year death according to the SYNTAX score II 2020 in the PCI group (A) and in the CABG group (B). (C) Kaplan-Meier plots showing the observed versus predicted treatment benefit of CABG over PCI according to the SYNTAX score II 2020 in predicted benefit quarters (i-iv), and a calibration plot showing the observed versus predicted treatment benefit of CABG over PCI, in terms of 10-year death (v). A positive ARD represents an increase in treatment benefit of CABG over PCI. Vertical dashed lines in the calibration plots represent the quartiles of 10-year death. In the Kaplan-Meier plots, blue circles represent predicted risk of death at 10 years for CABG and red circles represent the predicted risk of death at 10 years for PCI. PCI=percutaneous coronary intervention. C-index=concordance index. CABG=coronary artery bypass grafting. ARD=absolute risk difference.

By use of data from the FREEDOM, BEST, and PRECOMBAT trials, external validation of the SYNTAX score II 2020 model showed helpful discriminative ability for 5-year all-cause death in the PCI and CABG groups (C-index=0.70 [95% CI 0.67–0.74] in the PCI group and 0.70 [0.66–0.74] in the CABG group), with excellent calibration (figure 2A, B). The SYNTAX score II 2020 model also showed good calibration for the predicted treatment benefit of CABG over PCI in this population, in terms of 5-year all-cause death (figure 2C).

The SYNTAX score II 2020 model for predicting the 5-year risk of major adverse cardiovascular events included the same prognostic index and the same two treatment effect-modifiers (ie, disease type [three-vessel disease or left main coronary artery disease] and anatomical SYNTAX score) as the 10-year death model (table 3). Cross-validation of this model with the SYNTAX trial provided a C-index of 0.65 (95% CI 0.61–0.69) in the PCI group and 0.71 (0.67–0.75) in the CABG group, with good agreement between the observed and predicted 5-year risk of major adverse cardiovascular events (appendix p 3). The model also showed excellent calibration for treatment benefit of CABG over PCI (appendix p 3). In the pooled patient cohort from the FREEDOM, BEST, and PRECOMBAT trials, the SYNTAX score II 2020 model for predicting 5-year risk of major adverse cardiovascular events showed helpful discrimination in both treatment groups (C-index=0.67 [95% CI 0.63–0.70] for PCI and 0.62 [0.58–0.66] for CABG) and good calibration (figure 3A, B). The model also showed good calibration for the observed versus predicted treatment benefit of CABG over PCI in the FREEDOM, BEST, and PRECOMBAT trials (figure 3C).

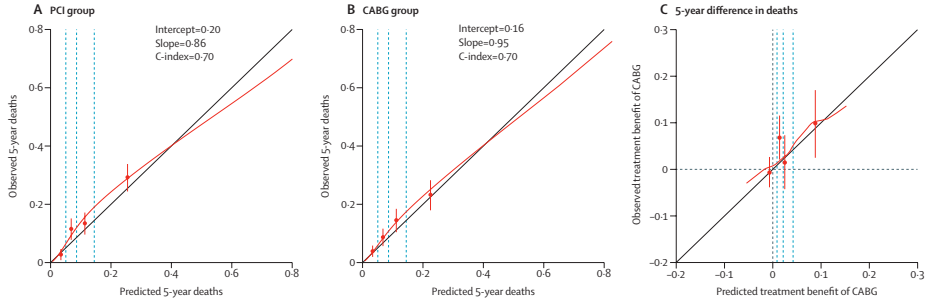

Figure 2: External validation of the 10-year death model of the SYNTAX score II 2020 for predicting 5-year all-cause death in patients with multivessel disease or left main coronary artery disease in the FREEDOM, BEST, and PRECOMBAT trials (n=3380)

Calibration plots showing the observed versus predicted 5-year deaths according to the SYNTAX score II 2020 in the PCI group (A) and CABG group (B). Vertical dashed lines represent quartiles of predicted 5-year deaths. (C) Calibration plot showing the observed versus predicted treatment benefit of CABG, according to the SYNTAX score II 2020. Vertical dashed lines represent quartiles of predicted treatment benefit of CABG. PCI=percutaneous coronary intervention. C-index=concordance index. CABG=coronary artery bypass grafting.

Table 3: Model for predicting the risk of a major adverse cardiovascular event at 5 years

	Coefficient	HR (95% CI)	P value
Prognostic index	0.74	2.10 (1.84–2.39)	<0.0001
CABG × three-vessel disease	–0.48	0.62 (0.46–0.83)	0.0012
CABG × left main coronary artery disease	–0.10	0.91 (0.67–1.22)	0.5117
PCI × left main coronary artery disease	–0.23	0.80 (0.59–1.08)	0.1397
PCI × (SYNTAX score - 29)/10	0.19	1.21 (1.07–1.37)	0.0021

Table shows the coefficients for the prognostic index, with the same seven variables as used for the 10-year all-cause death model, and two predefined treatment interactions (three-vessel disease or left main coronary artery disease and anatomical SYNTAX score), derived from a Cox multivariable model for predicting the risk of a major adverse cardiovascular event at 5 years. The predicted risk of this outcome can be calculated by use of the following formula: predicted probability of major adverse cardiovascular event at 5 years=1 – exp(–0.175 × exp[0.74 × {0.72 × age - 0.07 × creatinine clearance - 0.31 × left ejection fraction + 0.48 × chronic obstructive pulmonary disease + 0.73 × peripheral vascular disease + 0.20 × medically treated diabetes + 0.46 × on insulin + 0.66 × current smoker} - 0.48 × CABG × three-vessel disease - 0.10 × CABG × left main coronary artery disease - 0.23 × PCI × left main coronary artery disease + 0.19 × PCI × {SYNTAX score - 29} / 10 - 2.00]), where age is expressed in years per 10 years, the creatinine clearance is expressed per 10 mL/min per 1.73 m² (capped at 90 per 10 mL/min per 1.73 m²), and the left ventricular ejection fraction is expressed per 10% (capped at 50 per 10%). HR=hazard ratio. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention.

The SYNTAX score II 2020 was better able to discriminate 5-year all-cause deaths than the calibrated original SYNTAX score II in patients randomly assigned to CABG and PCI groups in the external validation cohort of the FREEDOM, BEST, and PRECOMBAT trials (figure 2, appendix p 4). Of note, the SYNTAX score II 2020 was superior to the calibrated original SYNTAX score II for predicting treatment benefit of CABG over PCI in terms of 5-year all-cause death (figure 2, appendix p 4).

DISCUSSION

In this study, we used data from the original SYNTAX trial[5] and the SYNTAXES trial[23] to develop two risk models; one to predict all-cause death at 10 years and the second to predict the risk of major adverse cardiovascular events at 5 years. The SYNTAX score II 2020 contains eight prognostic factors and two prespecified effect-modifiers (disease type and anatomical SYNTAX score). A significant treatment interaction with disease type was observed, and the anatomical SYNTAX score was only associated with death in patients who received PCI, but not in those who received CABG. We found that being female was not an independent predictor of all-cause death over the 10-year follow-up period of the SYNTAXES study. The SYNTAX score II 2020 was internally validated for its ability to predict 10-year death. In addition, we found that the SYNTAX score II 2020 was able to predict 5-year all-cause death and benefit of CABG over PCI in both internal and external validation cohorts. Using the same variables as the 10-year all-cause death model, we developed a model to predict the

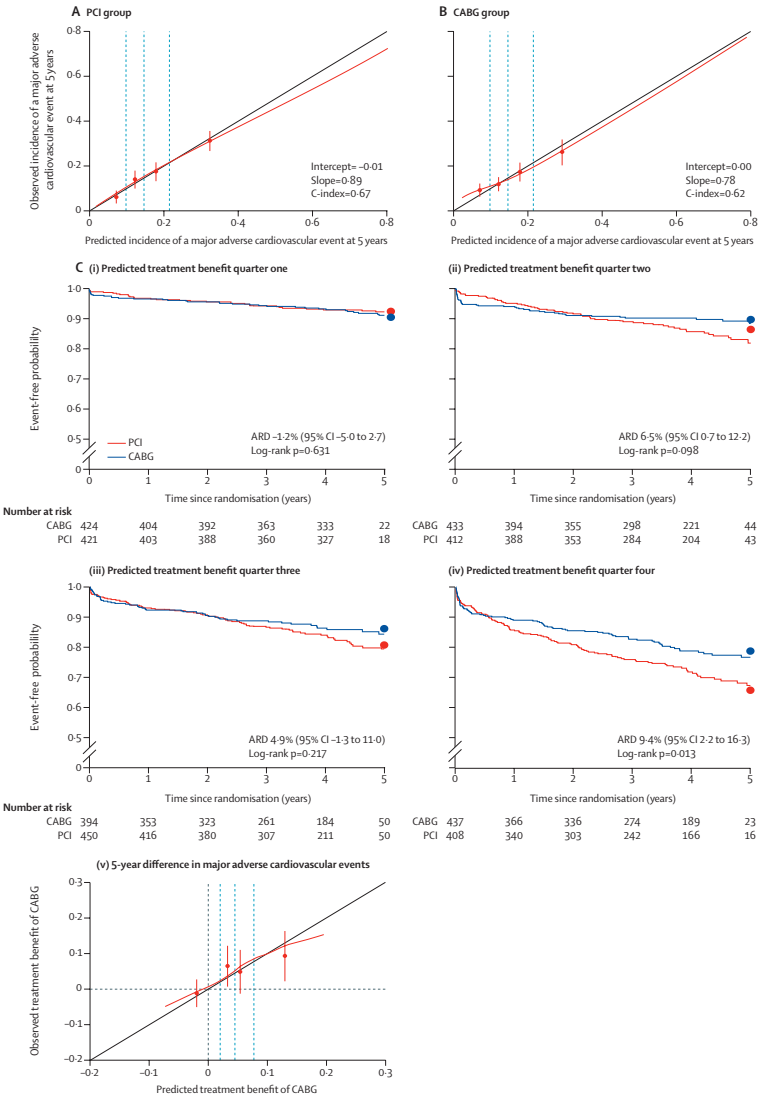

Figure 3: External validation of the SYNTAX score II 2020 for predicting major adverse cardiovascular events at 5 years in patients with multivessel or left main coronary artery disease in the FREEDOM, BEST, and PRECOMBAT trials (n=3380)

Calibration plots showing the observed versus predicted 5-year incidence of major adverse cardiovascular events in the PCI group (A), and the CABG group (B). (C) Kaplan-Meier plots showing the observed versus predicted treatment benefit of CABG over PCI according to the SYNTAX score II 2020 in quarters of predicted treatment benefit (i-iv), and a calibration plot showing the observed versus predicted treatment benefit of CABG over PCI, in terms of the incidence of major cardiovascular adverse events at 5 years (v). A positive ARD represents treatment benefit of CABG over PCI. In the calibration plots, vertical dashed lines represent quartiles of predicted major adverse cardiovascular events at 5 years. In the Kaplan-Meier plots, blue circles represent predicted 5-year major adverse cardiovascular events for CABG, and red circles represent predicted 5-year major cardiovascular events for PCI. PCI=percutaneous coronary intervention. C-index=concordance index. CABG=coronary artery bypass grafting. ARD=absolute risk difference.

	Case 1	Case 2	Case 3
Age, years	74	59	69
Diabetes	No	Yes	Yes
Receiving insulin	No	No	Yes
Creatinine clearance, mL/min per 1·73 m²	38·6	67·6	72·5
Left ventricular ejection fraction	40%	67%	55%
Chronic obstructive pulmonary disease	No	No	No
Peripheral vascular disease	No	No	No
Current smoker	Yes	No	No
Three-vessel disease or left main coronary artery disease	Left main coronary artery disease	Three-vessel disease	Three-vessel disease
Anatomical SYNTAX score	11	10	50

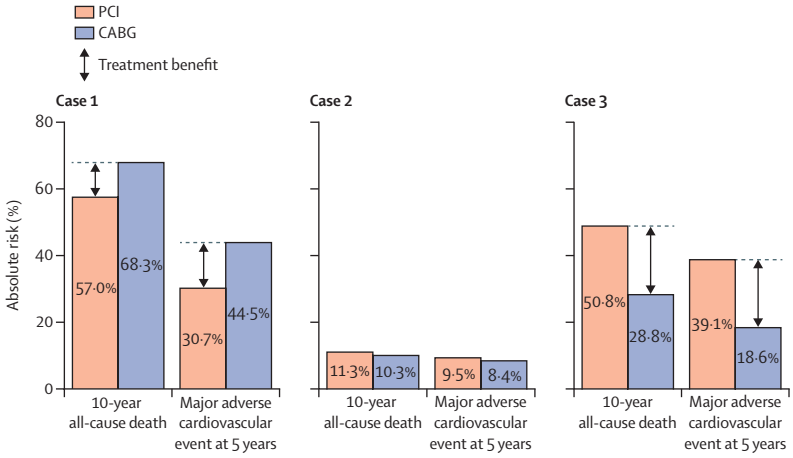

Figure 4: Use of the SYNTAX score II 2020 for individualised decision making
The bar graphs show three representative case scenarios in which the SYNTAX score II 2020 model, for predicting 10-year death and the risk of a major cardiovascular event at 5 years, can provide individualised predictions for these outcomes in different patients depending on the treatment given (PCI or CABG). In the first scenario, a male aged 74 years with left main coronary artery disease, a low left ventricular ejection fraction, and a low creatinine clearance, the model predicts a 10-year all-cause death risk of 68.3% with CABG versus 57.0% with PCI, and 5-year risk of having a major adverse cardiovascular event of 44.5% with CABG versus 30.7% with PCI. As a result, the predicted absolute treatment benefit of PCI over CABG is 11.3% for 10-year death and 13.8% for the 5-year risk of a major adverse cardiovascular event. The second scenario involves a women aged 59 years with three-vessel disease and who had medically treated diabetes, but had a low anatomical SYNTAX score. For this patient, the model predicts a 10-year all-cause death risk of 10.3% with CABG versus 11.3% with PCI, and a 5-year risk of having a major adverse cardiovascular event of 8.4% with CABG versus 9.5% with PCI. The predicted absolute treatment benefit of CABG over PCI is 1.0% for 10-year death and 1.1% for the 5-year risk of a major adverse cardiovascular event. The third scenario involves a male aged 69 years with three-vessel disease, who was given insulin and had a high anatomical SYNTAX score. For this patient, the model predicts a 10-year all-cause death risk of 28.8% with CABG versus 50.8% with PCI, and a 5-year risk of having a major adverse cardiovascular event of 18.6% with CABG versus 39.1% with PCI. The predicted absolute treatment benefit of CABG over PCI is 22.0% for 10-year death and 20.5% for the 5-year risk of having a major adverse cardiovascular event. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention.

5-year risk of major adverse cardiovascular events. This model was also internally and externally validated for its ability to predict major adverse cardiovascular events at 5 years, and showed a good calibration for treatment benefit of CABG over PCI. Finally, the SYNTAX score II 2020 showed better discrimination and calibration for outcome risk and treatment benefit of CABG over PCI compared with the original SYNTAX score II (even with recalibration).

In medicine, randomised controlled trials have been considered the gold standard for comparing the efficacy and safety of alternative therapies. When interpreting and applying the trial results to individual patients, it has generally been assumed that the average treatment effect shown by the trial applies equally to all patients involved in the trial, and among similar future patients who meet the inclusion and exclusion criteria of the trials. However, several reports have suggested that these average treatment effects might obscure considerable variation in individual treatment effects, and individual patients enrolled in clinical trials are heterogeneous with respect to baseline characteristics and consequently to the absolute risk of an outcome of interest. Thus, the application of an average relative risk to individual patients is challenging.[13–19]

To provide individual patients with the best treatment, and to make effective use of limited medical resources, there has been an increasing interest in so-called personalised medicine. To achieve a more personalised approach in patients with complex coronary artery disease, we used data from landmark clinical trials5,23 to develop a predictive model that explicitly considers baseline outcome risk, such that we can distinguish between patients who benefit from CABG and those who could benefit from PCI.[13,21] Indeed, the SYNTAXES study showed no significant difference in 10-year all-cause death between patients in the PCI group compared with those in the CABG group.[23] By contrast, our predictive model provides a more nuanced interpretation of the results of this pivotal study, as it identifies patients who derive substantial survival benefit from CABG over PCI, and those in whom there is little expected difference between the two strategies in terms of 10-year death.

During the development of the original SYNTAX score II, diabetes was not identified as an independent predictor of 4-year all-cause death in the SYNTAX trial, nor an important effect-modifier for 4-year death.[11] Conversely, multivariable analyses done in our study showed that medically treated diabetes, especially among patients taking insulin, was an independent predictor of 10-year all-cause death in both CABG and PCI groups. One possible explanation for these contradictory results could be related to the modest size of the population of patients with diabetes enrolled in

the SYNTAX trial (n=452), which provided only modest statistical power to examine this association. Indeed, a recent large-scale, nationwide, population-based study[41] involving 39 235 participants showed that Kaplan-Meier curves for all-cause death in patients with type II diabetes versus those without undergoing CABG only started to diverge a few years after the surgical procedure and that this divergence increased over time.

Regarding the female sex as a variable of the SYNTAX score II, the results of the SYNTAX trial[5] suggested that women who underwent PCI had a higher adjusted risk of all-cause death at 4 years compared with men (HR 1.70 [95% CI 1.11–2.60]), whereas the risk in those who underwent CABG was similar between the two sexes (0.59 [0.32–1.10], $p_{interaction}$=0.0059). This favourable treatment benefit from CABG over PCI in women led to the inclusion of female sex as a variable in the original SYNTAX score II.[11] However, similar findings with respect to the sex–treatment interaction for all-cause death were not observed in other randomised trials.[42] The absence of a sex–treatment interaction in a diverse spectrum of patients with multivessel disease or with left main coronary artery disease again underscores a difficulty in applying the results of an underpowered subgroup analysis (ie, male *vs* female), and underlines the need for a more sophisticated statistical approach in the choice of revascularisation strategies in patients with complex coronary artery disease.[13–21]

More recently, investigators in the FREEDOM trial developed a model for predicting the 5-year risk of major adverse cardiovascular events and the 1-year angina status to support individualised treatment decisions between CABG and PCI in patients with diabetes and multivessel disease.[43] The investigators showed that the discriminative ability of the 5-year risk of major adverse cardiovascular events model and the 1-year angina status model was the same (*C*-statistic 0.67) in both PCI and CABG groups in the derivation cohort.[43] To interpret the performance of a newly developed multivariable predictive model, Alba and colleagues[44] rightly classified a C-index range of 0.60–0.75 as possibly helpful, because a C-index in this range is only helpful when the model is able to separate substantial groups of patients across meaningful risk thresholds and when the model is calibrated. As our SYNTAX score II 2020 model is adequately calibrated over the range of predictions encompassed by the study population, and is helpful for discriminating between patients with high and low treatment benefit, we considered our model to be helpful.

Nevertheless, one might be concerned about the applicability of our new model to daily clinical practice, given that the SYNTAX trial was done using an outdated technology and strategy for treatment with PCI or CABG. The paclitaxel-eluting

stent used to treat patients in the PCI group (TAXUS Express) is no longer commercially available, and the SYNTAX II trial showed that contemporary, best practice PCI, including the use of current-generation drug-eluting stents, physiology-guided treatment, and intravascular ultrasound-mediated optimisation of stent deployment, definitely improved clinical outcomes.[45,46] Similarly, contemporary CABG, as executed in the EXCEL trial, offered superior outcomes when compared with CABG in the SYNTAX trial in a propensity-matched analysis.[47] However, contemporary randomised data are not currently available for the construction of a multivariable predictive model. In addition, physiology-guided PCI and intracoronary imaging devices are not routinely used in our daily clinical practice. When the SYNTAX score II 2020 was externally validated to compare CABG with PCI (with the everolimus-eluting durable polymer stent [Xience]) in patients with multivessel disease from the BEST trial, the predicted treatment benefit of CABG over PCI was well calibrated (appendix p 5). Therefore, we consider that our new model is worthy of testing in clinical practice.

In our study, the treatment benefit of CABG over PCI was defined as the absolute risk difference between CABG and PCI. One might conclude that patients in the fourth quarter had a significant treatment benefit of CABG over PCI in terms of 10-year all-cause death. Similar grouped outcomes can be visually illustrated by Kaplan-Meier curves. However, we consider that one treatment (CABG) is not globally superior, inferior, or equal to another treatment (PCI), but that a specific treatment is superior, inferior, or equal for a specific patient. For this individualised decision making, the SYNTAX score II 2020 generates a prediction of treatment benefit for individual patients based on their own angiographic and clinical variables. To visualise the ability of our model to predict a treatment benefit, it is crucial to use calibration plots. Lastly, the benefit threshold of 7.9% between the third and fourth quarter is highly dependent on how the cohort is grouped to display the calibration plot (ie, by tertiles, quartiles, or quintiles), and physicians rarely agree on a specific threshold at which one treatment over the other should be initiated[48] because thresholds are influenced by many factors, such as the potential risks and benefits of a particular treatment, physician or patient preferences, and economic considerations.[17]

Physician preference has traditionally played a major role in selecting a revascularisation strategy for individual patients.[49] Surgeons and interventional cardiologists provide their patients with vastly different information on myocardial revascularisation treatment options, with a bias toward a specific strategy,[50] which is exemplified by varying ratios of PCI versus CABG, not only across various European countries with a similar economic status, but also among the same geographical regions within

a country.[51,52] Many physicians in these regions might guide revascularisation strategies on the basis of subjective assessments according to their experience, specialty, or background, which do not always represent guideline recommendations,[53,54] and could potentially result in an inaccurate risk assessment[55,56] and the patient receiving inappropriate treatments with suboptimal outcomes.[56] To avoid this physician-related bias, the multidisciplinary heart team should use the SYNTAX score II 2020 in the decision making process to choose the best revascularisation strategy for each patient, thus enabling more individualised and patient-centred care in those with complex coronary artery disease. Figure 4 shows three example case scenarios in which the SYNTAX score II 2020 was applied. Using the evidence-based predicted treatment benefits of CABG over PCI that this model provides, in terms of 10-year all-cause death and 5-year risk of major adverse cardiovascular events, patients and their families can make a final decision based on their preference,[49,57] since most patients prefer PCI over CABG,[58] even if the subsequent risk of ischaemic events after PCI is much greater when compared with CABG.[59,60]

This study has several limitations. First, the SYNTAX trial5 collected baseline information on death, and the present analysis accounted for such baseline information in Cox multivariable models; however, relevant but unmeasured variables (eg, B-type natriuretic peptide) could not be included in the model. Second, the SYNTAXES study[23] evaluated vital status up to 10 years and did not assess other outcomes; thus a predictive model for estimating the risk of major adverse cardiovascular events beyond 5 years could not be constructed. Given that mean age of patients in the SYNTAX trial was 65 years at the time of randomisation, and the overall life expectancy of patients has been increasing worldwide, a predictive model for the 10-year risk of major adverse cardiovascular events could be informative to further guide the optimal revascularisation strategy in patients with complex coronary artery disease.

Using data from the SYNTAX trial[5] and the extended follow-up SYNTAXES study,[23] we have updated, and externally validated the SYNTAX score II 2020, a personalised predictive model based on eight prognostic factors and two prespecified effect-modifiers, to predict 10-year all-cause death and the 5-year risk of major adverse cardiovascular events for patients treated with either PCI or CABG. By providing the expected probabilities of 5-year and 10-year outcomes, this model could improve the ability of the heart team to inform patients and their families about the risks and benefits of these treatments for complex coronary artery disease and support a more transparent and shared decision making process. Further adequately powered, randomised trials of PCI versus CABG, with 5–10 years' follow-up, which employ

contemporary revascularisation techniques, devices, and adjunctive medical therapy, should be done to prospectively validate the SYNTAX score II 2020 model.

Contributors

PWS and KT conceived, designed, and interpreted data, drafted the manuscript, and revised and approved the final version of the manuscript for submission. DvK analysed and interpreted data, and revised and approved the final version of the manuscript for submission. VF, MEF, JAS, DJC, S-JP, D-WP, J-MA, APK, SJH, DJFMT, YO, DMK, and EWS interpreted data, and revised and approved the final version of the manuscript for submission.

Declaration of interests

PWS reports personal consultancy fees from Biosensors, Medtronic, Micell, Sino Medical Sciences Technology, Philips Volcano, Xeltis, and Heartflow, outside the submitted work. MEF reports research grants from Amgen, Novartis, and Novo Nordisk, outside the submitted work. JAS reports an equity interest in Health Outcomes Sciences; ownership of the Seattle Angina Questionnaire; consulting services to United Healthcare, Amgen, Bayer, Novartis, Janssen, Myokardia, and Janssen; a research grant from Abbott Vascular; and serving on the Board of Directors of Blue Cross Blue Shield of Kansas City, all outside the submitted work. DJC reports institutional research grants and personal fees from Medtronic, Boston Scientific, and Abbott Vascular, outside the submitted work. APK and SJH are employees of Medtronic, outside the submitted work. All other authors declare no competing interests.

Data sharing

All data, including study participant data, the data dictionary, the statistical analysis plan, and informed consent, will not be shared.

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REFERENCES

1 Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2018; 40: 87–165.

2 Ong AT, Serruys PW, Mohr FW, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006; 151: 1194–204.

3 Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009; 360: 961–72.

4 Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011; 32: 2125–34.

5 Mohr FW, Morice M-C, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013; 381: 629–38.

6 Serruys PW, Chichareon P, Modolo R, et al. The SYNTAX score on its way out or... towards artificial intelligence: part I. EuroIntervention 2019; 16: 44–59.

7 Serruys PW, Chichareon P, Modolo R, et al. The SYNTAX score on its way out or... towards artificial intelligence: part II. EuroIntervention 2019; 16: 60–75.

8 Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery, European Association for Percutaneous Cardiovascular Interventions, Wijns W, et al. Guidelines on myocardial revascularization. Eur Heart J 2010; 31: 2501–55.

9 Rothwell PM. Can overall results of clinical trials be applied to all patients? Lancet 1995; 345: 1616–19.

10 Serruys PW, Farooq V, Vranckx P, et al. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX trial at 3 years. JACC Cardiovasc Interv 2012; 5: 606–17.

11 Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013; 381: 639–50.

12 Yeh RW, Kramer DB. Decision tools to improve personalized care in cardiovascular disease: moving the art of medicine toward science. Circulation 2017; 135: 1097–100.

13 Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. Treating individuals 3: from subgroups to individuals: general principles and the example of carotid endarterectomy. Lancet 2005; 365: 256–65.

14 Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. JAMA 2007; 298: 1209–12.

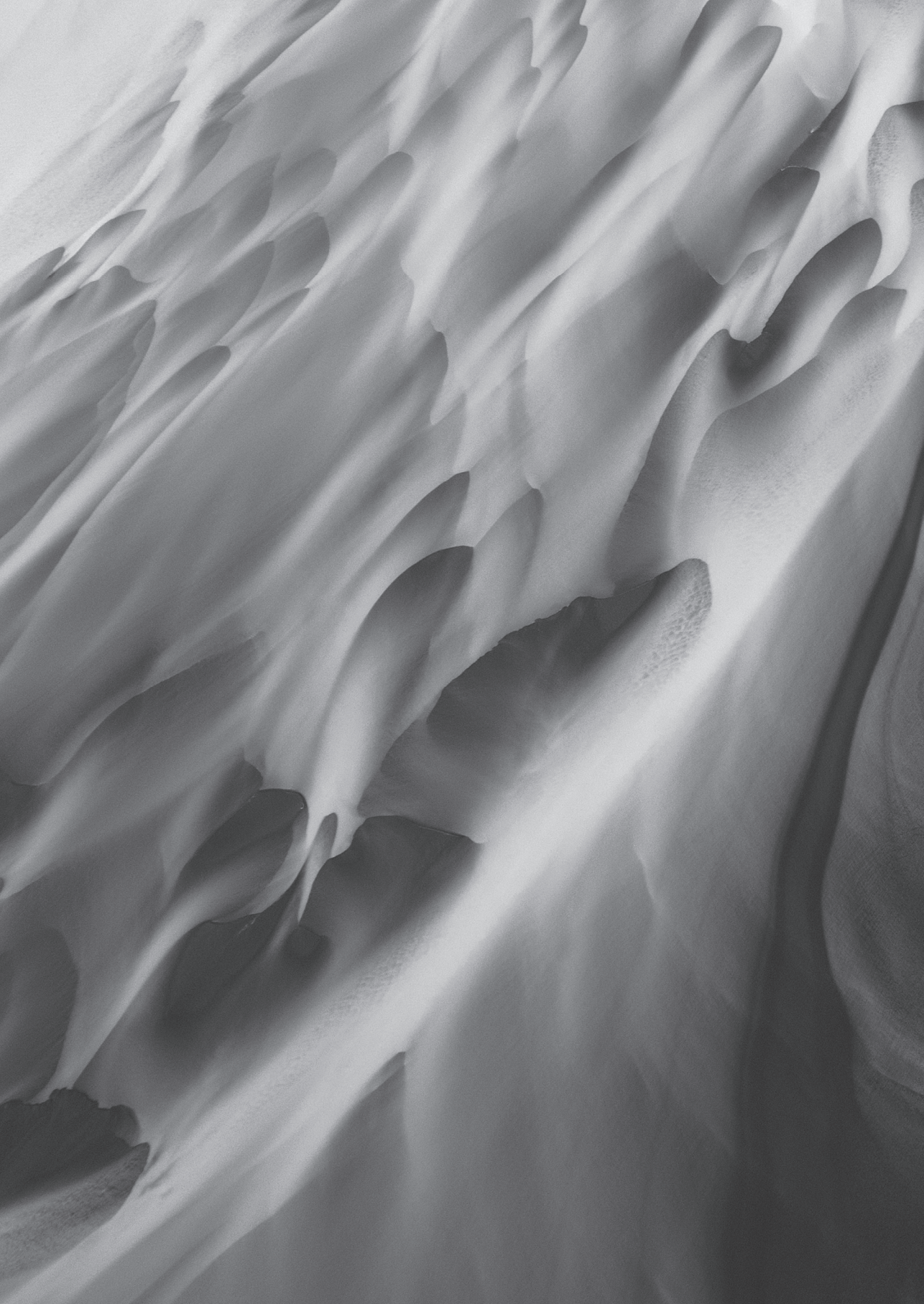
15 Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010; 11: 85.

16 Kent DM, Steyerberg E, van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. BMJ 2018; 363: k4245.

17 Dahabreh IJ, Hayward R, Kent DM. Using group data to treat individuals: understanding heterogeneous treatment effects in the age of precision medicine and patient-centred evidence. Int J Epidemiol 2016; 45: 2184–93.
18 Kent DM, Paulus JK, van Klaveren D, et al. The predictive approaches to treatment effect heterogeneity (PATH) statement. Ann Intern Med 2019; 172: 35–45.
19 Kent DM, van Klaveren D, Paulus JK, et al. The predictive approaches to treatment effect heterogeneity (PATH) statement: explanation and elaboration. Ann Intern Med 2019; 172: W1–25.
20 Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol 2004; 57: 229–36.
21 Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005; 365: 176–86.
22 van Klaveren D, Balan TA, Steyerberg EW, Kent DM. Models with interactions overestimated heterogeneity of treatment effects and were prone to treatment mistargeting. J Clin Epidemiol 2019; 114: 72–83.
23 Thuijs D, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet 2019; 394: 1325–34.
24 Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012; 367: 2375–84.
25 Farkouh ME, Domanski M, Dangas GD, et al. Long-term survival following multivessel revascularisation in patients with diabetes: the FREEDOM follow-on study. J Am Coll Cardiol 2019; 73: 629–38.
26 Park SJ, Ahn JM, Kim YH, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. N Engl J Med 2015; 372: 1204–12.
27 Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med 2011; 364: 1718–27.
28 Ahn JM, Roh JH, Kim YH, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT study. J Am Coll Cardiol 2015; 65: 2198–206.
29 Park DW, Ahn JM, Park H, et al. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: extended follow-up of the PRECOMBAT trial. Circulation 2020; 141: 1437–46.
30 Stolker JM, Spertus JA, Cohen DJ, et al. Rethinking composite end points in clinical trials: insights from patients and trialists. Circulation 2014; 130: 1254–61.
31 Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function-measured and estimated glomerular filtration rate. N Engl J Med 2006; 354: 2473–83.
32 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–12.
33 Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis 2010; 55: 622–27.
34 Parsh J, Seth M, Aronow H, et al. Choice of estimated glomerular filtration rate equation impacts drug-dosing recommendations and risk stratification in patients with chronic

kidney disease undergoing percutaneous coronary interventions. J Am Coll Cardiol 2015; 65: 2714–23.
35 Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014; 35: 1925–31.
36 van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. J Stat Softw 2011; 45: 67.
37 Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. New York, NY: Springer-Verlag, 2008.
38 Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008; 27: 157–72.
39 van Klaveren D, Steyerberg EW, Serruys PW, Kent DM. The proposed 'concordance-statistic for benefit' provided a useful metric when modeling heterogeneous treatment effects. J Clin Epidemiol 2018; 94: 59–68.
40 Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2015; 162: 55–63.
41 Holzmann MJ, Rathsman B, Eliasson B, et al. Long-term prognosis in patients with type 1 and 2 diabetes mellitus after coronary artery bypass grafting. J Am Coll Cardiol 2015; 65: 1644–52.
42 Newby LK. Sex, region, and outcomes after revascularization. Circ Cardiovasc Interv 2017; 10: e005322.
43 Qintar M, Humphries KH, Park JE, et al. Individualizing revascularization strategy for diabetic patients with multivessel coronary disease. J Am Coll Cardiol 2019; 74: 2074–84.
44 Alba AC, Agoritsas T, Walsh M, et al. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. JAMA 2017; 318: 1377–84.
45 Serruys PW, Kogame N, Katagiri Y, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study. EuroIntervention 2019; 15: e244–52.
46 Glineur D, Wijns W. The 2010-2014-2018 trilogy of ESC-EACTS guidelines on myocardial revascularisation: we cannot jump three steps this way and then return to where we began. EuroIntervention 2019; 14: 1429–33.
47 Modolo R, Chichareon P, Kogame N, et al. Contemporary outcomes following coronary artery bypass graft surgery for left main disease. J Am Coll Cardiol 2019; 73: 1877–86.
48 Kent DM, Shah ND. Risk models and patient-centered evidence: should physicians expect one right answer? JAMA 2012; 307: 1585–86.
49 Head SJ, Kaul S, Mack MJ, et al. The rationale for heart team decision-making for patients with stable, complex coronary artery disease. Eur Heart J 2013; 34: 2510–18.
50 Head SJ, Bogers AJ, Serruys PW, Takkenberg JJ, Kappetein AP. A crucial factor in shared decision making: the team approach. Lancet 2011; 377: 1836.
51 Tu JV, Ko DT, Guo H, et al. Determinants of variations in coronary revascularisation practices. CMAJ 2012; 184: 179–86.
52 Baig SS, Altman DG, Taggart DP. Major geographical variations in elective coronary revascularization by stents or surgery in England. Eur J Cardiothorac Surg 2015; 47: 855–59.

53 Rothberg MB, Sivalingam SK, Ashraf J, et al. Patients' and cardiologists' perceptions of the benefits of percutaneous coronary intervention for stable coronary disease. Ann Intern Med 2010; 153: 307–13.
54 Decker C, Garavalia L, Garavalia B, et al. Understanding physician-level barriers to the use of individualized risk estimates in percutaneous coronary intervention. Am Heart J 2016; 178: 190–97.
55 Grover SA, Lowensteyn I, Esrey KL, Steinert Y, Joseph L, Abrahamowicz M. Do doctors accurately assess coronary risk in their patients? Preliminary results of the coronary health assessment study. BMJ 1995; 310: 975–78.
56 Pereira AC, Lopes NH, Soares PR, et al. Clinical judgment and treatment options in stable multivessel coronary artery disease: results from the one-year follow-up of the MASS II (Medicine, Angioplasty, or Surgery Study II). J Am Coll Cardiol 2006; 48: 948–53.
57 Holmes DR Jr, Taggart DP. Revascularization in stable coronary artery disease: a combined perspective from an interventional cardiologist and a cardiac surgeon. Eur Heart J 2016; 37: 1873–82.
58 Doll JA, Jones WS, Lokhnygina Y, et al. PREPARED Study: a study of shared decision-making for coronary artery disease. Circ Cardiovasc Qual Outcomes 2019; 12: e005244.
59 Kipp R, Lehman J, Israel J, Edwards N, Becker T, Raval AN. Patient preferences for coronary artery bypass graft surgery or percutaneous intervention in multivessel coronary artery disease. Catheter Cardiovasc Interv 2013; 82: 212–18.
60 Ohlow MA, Farah A, Kuntze T, Lauer B. Patients' preferences for coronary bypass grafting or staged percutaneous coronary intervention in multi-vessel coronary artery disease. Int J Clin Pract 2018; 72: e13056.



Chapter 11

Improving coronary artery bypass grafting: a systematic review and meta-analysis on the impact of adopting transit-time flow measurement

Daniel J.F.M. Thuijs, Margreet W.A. Bekker, David P. Taggart, A. Pieter Kappetein, Teresa M. Kieser, Daniel Wendt, Gabriele Di Giammarco, Gregory D. Trachiotis, John D. Puskas, Stuart J. Head

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ABSTRACT

Despite there being numerous studies of intraoperative graft flow assessment by transit-time flow measurement (TTFM) on outcomes after coronary artery bypass grafting (CABG), the adoption of contemporary TTFM is low. Therefore, on 31 January 2018, a systematic literature search was performed to identify articles that reported (i) the amount of grafts classified as abnormal or which were revised or (ii) an association between TTFM and outcomes during follow-up. Random-effects models were used to create pooled estimates with 95% confidence intervals (CI) of (i) the rate of graft revision per patient, (ii) the rate of graft revision per graft and (iii) the rate of graft revision among grafts deemed abnormal based on TTFM parameters. The search yielded 242 articles, and 66 original articles were included in the systematic review. Of those articles, 35 studies reported on abnormal grafts or graft revisions (8943 patients, 15 673 grafts) and were included in the meta-analysis. In 4.3% of patients (95% CI 3.3-5.7%, I^2 = 73.9) a revision was required and 2.0% of grafts (95% CI 1.5-2.5%; I^2 = 66.0) were revised. The pooled rate of graft revisions among abnormal grafts was 25.1% (95% CI 15.5-37.9%; I^2 = 80.2). Studies reported sensitivity ranging from 0.250 to 0.457 and the specificity from 0.939 to 0.984. Reported negative predictive values ranged from 0.719 to 0.980 and reported positive predictive values ranged from 0.100 to 0.840. This systematic review and meta-analysis showed that TTFM could improve CABG procedures. However, due to heterogeneous data, drawing uniform conclusions appeared challenging. Future studies should focus on determining the optimal use of TTFM and assessing its diagnostic accuracy.

Key Words

Coronary artery bypass, Intraoperative quality control, Transit time, Transit-time flow measurement, Intraoperative graft flow assessment, Coronary artery bypass grafting

INTRODUCTION

Outcomes of coronary artery bypass grafting (CABG) have significantly improved over the first 50years since the introduction of the modern CABG procedure.[1] Despite increasing use of percutaneous coronary intervention (PCI), CABG remains the treatment of choice for patients with complex multivessel disease.[2] While outcomes of PCI are continuously improving with new advancements, many new techniques to optimize short- and long-term outcomes of CABG have not been adopted widely.[3]

One of such techniques to improve CABG outcomes and graft patency is intraoperative graft flow assessment. Early graft failure can occur due to limited outflow, graft kinking upon chest closure, thrombosis, yet also due to anastomotic problems. A metaanalysis reported a graft failure rate of ~5% and 25% at 3 and 12 months, respectively.[4] Fabricius et al. [5] reported that 23 of 2052 patients (1.1%) who underwent CABG had severely compromised haemodynamics due to postoperative myocardial infarction (MI). In 21.7% of patients, the cause of this adverse event was found to be an incorrect anastomosis. Intraoperative graft assessment has therefore been introduced to identify anastomotic problems and limited outflow before chest closure.

Multiple techniques for intraoperative graft assessment have been proposed: coronary angiography (CAG), transit-time flow measurement (TTFM), high-resolution-epicardial ultrasonography (HR-ECUS) and intraoperative fluorescence imaging (IFI).[6] Although angiography is thought to be the best and most reliable method for assessing flow, the infrastructure required for CAG is rarely available in standard operating theatres. Therefore, the most adopted strategy to assess graft functioning is TTFM. Several studies reported associations between TTFM parameters and the necessity for graft revisions as well as with short- and medium-term outcomes after CABG; however, results vary considerably.[7, 8] A summary of the evidence could provide more incentive to adopt TTFM, especially as TTFM has been criticized.[9]

We performed a systematic review and meta-analysis to evaluate the value of TTFM during CABG by determining (i) the rate of abnormal grafts and graft revisions required when using TTFM and (ii) the impact of TTFM parameters on angiographic and clinical outcomes.

METHODS

Search strategy

On 31 January 2018, a systematic literature search in the PubMed database was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline (**Supplementary Materials**) to identify full-length, English-language articles with the following search term: '(transit time OR transit-time) AND coronary artery bypass'. Studies with the following criteria were included: (i) graft assessment was performed using TTFM; (ii) subjects were adult patients undergoing CABG; and (iii) it was reported how many grafts had abnormal TTFM parameters or were revised, or an association between TTFM parameters and outcomes during follow-up was investigated.

Titles and abstracts were then screened for inclusion. When eligible, full-text articles were reviewed (D.J.F.M.T. and S.J.H.). Only original articles, articles in English, studying humans and studying TTFM in CABG procedures were considered for inclusion. If multiple articles described the same patient population, only the article with the largest number of patients or the most relevant information was included.

Data extraction

The following study characteristics were extracted: prospective versus retrospective study, the year of publication, the authors and the number of patients. Furthermore, the following data on surgical characteristics and TTFM parameters were obtained from each study: surgical procedure (on-pump or off-pump), which grafts were used (e.g. internal thoracic artery, great saphenous vein, radial artery and gastroepiploic artery), the number of grafts assessed with TTFM, the number of grafts deemed abnormal based on intraoperative TTFM parameters, the number of grafts that were revised based on intraoperative TTFM parameters, the reasons why grafts were deemed 'abnormal' or 'required revision' based on intraoperative TTFM parameters [mean graft flow (MGF), pulsatility index (PI), diastolic filling % (DF%) and percentage of backflow (%BF) (e.g. insufficiency percentage)] and fast Fourier transformation (FFT). Sensitivity, specificity, negative predictive values (NPV) and positive predictive values (PPV) were extracted to assess the diagnostic accuracy of TTFM. Postoperative short-term outcomes (e.g. till 30days) and outcomes during follow-up (e.g. beyond 30days) that were extracted consisted of major adverse cardiac and cerebrovascular events (MACCE), mortality, MI, postoperative cardiac enzyme release, stroke, requirement for intraaortic balloon pump placement, angina and graft failure.

Statistical analyses

The quality of the included studies used in the meta-analysis was assessed according to the Newcastle-Ottawa-Scale (NOS).[10] Random-effects models were generated to estimate pooled study outcomes with 95% confidence intervals (95% CI) of (i) the proportion of revised grafts compared to the total number of patients studied by TTFM, (ii) the proportion of revised grafts compared to the total number of grafts on which TTFM was applied and (iii) the proportion of revised grafts compared to the total number of abnormal grafts found by TTFM. For studies that reported zero events (e.g. no abnormal or revised grafts), 0.1 events were used to calculate an estimated event rate with 95% CI. The I^2 statistic was used to describe the proportion of variation across studies based on heterogeneity, where low values relate to homogeneity (range 0-100). Statistical analyses were executed with Comprehensive Meta-Analysis software Version 3.3 (Biostat, Englewood, NJ, USA).

RESULTS

Study selection

This systematic review included 66 studies (Fig. 1). In total, 35 unique studies reported on abnormal grafts or graft revisions with 8943 CABG patients and 15 673 grafts (Table 1) and were included in the meta-analysis. An overview of the NOS quality assessment is presented in the **Supplementary Material,** Table S1. Eight studies reported on the diagnostic accuracy of TTFM (**Supplementary Material,** Table S2). Forty-two studies reported graft patency and clinical outcomes related to TTFM assessments (**Supplementary Material,** Tables S3 **and** S4).

Meta-analysis: abnormal grafts and graft revisions

Individual studies classified grafts as abnormal based either on low MGF (arterial grafts: <15ml/min and venous grafts: <20 ml/ min), an increased PI ≥ 5 for both venous and arterial grafts, or decreased diastolic filling % (<50%). Overall reasons to revise abnormal grafts were due to kinking or twisting of a graft, graft or coronary dissection or anastomotic stenosis/thrombosis.

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM

Study	Year	Design	Number of grafts/patients	Procedure specifics[a]	Graft outcome	Reasons for abnormal or revised grafts	Results
Hashim *et al.* [**11**]	2017	Prospective	86/60	TTFM on ITA	Abnormal	PI >1.0 with an MGF <20ml/min in an arrested heart	Not specified 3.5% (*n* = 3 grafts)
					Revision	Not specified	
Hiraoka *et al.* [**12**]	2017	Prospective	104/63	TTFM on ITA, RA and SVG	Abnormal	PI >5.0 and an MGF <20 ml/min in ITA-graft or <40 ml/min in SVG	8.7% (*n* = 9 grafts)
Leon *et al.* [**13**]	2017	Retrospective	543/177	TTFM on ITA and SVG	Revision	PI ≥ 5.0	0.9% (*n* = 5 grafts)
Handa *et al.* [**14**]	2016	Retrospective	196/68	OPCAB with TTFM on ITA and SVG	Abnormal	Abnormal TTFM parameters: MGF <15 ml/min, DF <50% and PI >5.0	40% (*n* = 46 grafts) of which 54% appeared patent on postoperative CAG
					Revision	MGF <5 ml/min or DF <50% or PI >5.0	3.0% (*n* = 6 grafts)
Oshima *et al.* [**15**]	2016	Retrospective	214/196	TTFM on ITA and SVG	Abnormal	Lower mean flow (21.3 ± 16.2 ml/min) and higher PI (5.5 ± 4.7)	7.0% (*n* = 15 grafts)
Honda *et al.* [**16**]	2015	Retrospective	72/72	TTFM on *in situ* ITA	Abnormal	MGF <20 ml/min and PI = 2.0	1.4% (*n* = 1 graft)
Di Giammarco *et al.* [**17**]	2014	Prospective	717/333	TTFM on ITA and SVG	Abnormal	Grafts with MGF ≤ 15 ml/min and PI ≥ 3.0 were defined as failing	5.4% (*n* = 39 grafts)
					Revision	Failing grafts based on TTFM and surgical inspection	0.3% (*n* = 2 grafts)
Quin *et al.* [**18**]	2014	Retrospective	2738/1067	TTFM on ITA, SVG and RA	Abnormal	MGF <20 ml/min	20.7% (*n* = 568 grafts)
					Revision	MGF <20 ml/min and abnormal PI <3.0 (0.7%), 3.0-5.0 (2.9%) and >5.0 (5.8%)	2.0% (*n* = 54 grafts)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (*continued*)

Study	Year	Design	Number of grafts/patients	Procedure specifics[a]	Graft outcome	Reasons for abnormal or revised grafts	Results
Harahsheh [**19**]	2012	Prospective	1394/436	Not specified[b]	Abnormal	MGF <20 ml/min, PI >5.0 and DF <50%	7.2% (*n* = 100 grafts)
					Revision	Not specified	1.0% (*n* = 14 grafts)
							1.1% (*n* = 5 patients)
Kuroyanagi *et al.* [**20**]	2012	Retrospective	435/159	OPCAB with TTFM on ITA and SVG	Revision	Cut-off values not specified	2.0% (*n* = 9 grafts)
Kieser *et al.* [**8**]	2010	Prospective	1015/336	TTFM on ITA, SVG and RA	Abnormal	PI >5.0	7% (*n* = 74 grafts)
							18% (*n* = 59 patients)
					Revision	PI >5, MGF <15 ml/min and DF <25 with surgical signs of graft malfunctioning	2.0% (*n* = 20 grafts)
							4.2% (*n* = 14 patients)
Handa *et al.* [**21**]	2009	Retrospective	116/39	OPCAB with TTFM on ITA and SVG	Abnormal	MGF <10ml/min, PI >5.0 or DF <50%	2.6% (*n* = 3 grafts)
					Revision	MGF = 0 ml/min	1.7% (*n* = 2 grafts)
Nordgaard *et al.* [**22**]	2009	Retrospective	1390/581	TTFM on ITA and SVG	Revision	Low MGF and high PI	0.4% (*n* = 5 grafts)
Santarpino *et al.* [**23**]	2009	Prospective	238/238	TTFM on LITA + RA versus LITA + SVG	Revision	TTFM systolic waveform and PI >4.0 based on thrombosis (*n* = 2) and torsion of the graft (n = 1)	1.3% (*n* = 3 grafts)
							1.3% (*n* = 3 patients)
Waseda *et al.* [**24**]	2009	Retrospective	289/116	TTFM on ITA, SVG, RA and GEA	Abnormal	MGF <5 ml/min and PI >5	7.3%(*n* = 21 grafts)
					Revision	Failing grafts on IFI, yet acceptable TTFM (MGF >5 ml/min and PI <5) results	2.1% (*n* = 6 grafts)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (*continued*)

Study	Year	Design	Number of grafts/patients	Procedure specifics[a]	Graft outcome	Reasons for abnormal or revised grafts	Results
Herman *et al.* [**25**]	2008	Prospective	…/985	TTFM on ITA and SVG	Abnormal	PI >5	18.7% (*n* = 184 patients)
					Revision	Anastomotic (*n* = 9), conduit (*n* = 8), subclavian stenosis (*n* = 1) and unidentified (*n* = 2)	2.0% (*n* = 20 patients)
Onorati *et al.* [**26**]	2008	Retrospective	…/433	TTFM on ITA and RA	Abnormal	PI >5 and low MGF (not specified)	0.2% (n = 1 patients)
					Revision	MGF <3 ml/min and PI >5	0.7% (n = 3 patients)
Becit *et al.* [**27**]	2007	Retrospective	303/200	TTFM versus without TTFM on ITA, SVG or RA	Revision	Unsatisfactory TTFM parameters due to kinked/ twisted grafts (*n* = 4) or stenosis in proximal LITA (*n* = 2) or poor native coronary vessel (*n* = 3)	3.0% (*n* = 9 grafts)
							9.0% (*n* = 9 patients)
Mujanovic *et al.* [**28**]	2007	Prospective	2872/1000	Not specified[b]	Revision	Cut-off values not specified	2.2%(*n* = 64 grafts)
							6.3% (*n* = 63 patients)
Onorati *et al.* [**29**]	2007	RCT	90/90	TTFM on single-SVG versus sequential-SVG	Abnormal	PI >5 and low MGF (not specified)	5.6% (*n* = 5 grafts)
							5.6% (*n* = 5 patients)
					Revision	'Systolic' pattern of the curve with low MGF (4 ml/min) and high PI (7.8)"	1.1% (*n* = 1 graft)
							1.1% (*n* = 1 patient)
Desai *et al.* [30]	2006	RCT	139/106	TTFM and IFI on ITA, SVG and RA	Abnormal	DF<50%, PI >5.0 and MGF <10 ml/min	2.6% (*n* = 3 grafts)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (*continued*)

Study	Year	Design	Number of grafts/patients	Procedure specifics[a]	Graft outcome	Reasons for abnormal or revised grafts	Results
					Revision	MGF = 0 ml/min	1.4% (*n* = 2 grafts)
Poston *et al.* [**31**]	2006	Prospective	410/410	TTFM on SVG	Revision	MGF <10 ml/min	0.5% (*n* = 2 grafts)
Balacumaraswami *et al.*[**32**]	2005	Prospective	266/100	TTFM on ITA and RA	Abnormal	Not specified	9.4% (*n* = 25 grafts)
							25.0%(*n* = 25 patients)
					Revision	Persistent poor MGF with TTFM and IFI under adequate MAP (>80mmHg)	3.0% (*n* = 8 grafts)
							8.0% (*n* = 8 patients)
Kim *et al.* [**33**]	2005	Retrospective	117/58	OPCAB with TTFM on ITA, RA and GEA	Abnormal	Low MGF <3 ml/min or high PI (>20.0)	12.0% (*n* = 14 grafts)
Leong *et al.* [**34**]	2005	Prospective	322/116	TTFM on ITA and SVG	Revision	Low MGF, high PI and unsatisfactory flow curve (values not specified) due to occluded, stretched, kinked/ twisted grafts or anastomotic stenosis	2.2% (*n* = 7 grafts)
							5.2% (*n* = 6 patients)
Onorati *et al.* [**35**]	2005	Prospective	…/297	TTFM on ITA and RA	Abnormal	Low MGF and high PI, without systolic peak pattern on the flow curves	2.4% (*n* = 7 patients)
					Revision	Systolic wave-pattern, low MGF (9 ml/min) and high PI	0.3% (*n* = 1 patient)
Bergsland *et al.* [**36**]	2004	Prospective	113/46	OPCAB with TTFM on ITA and SVG	Revision	Abnormal MGF in 5 grafts due to distal anastomosis problems (*n* = 3), long grafts (*n* = 1) and vein graft stenosis (*n*=1)	4.4% (*n* = 5 grafts)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (*continued*)

Study	Year	Design	Number of grafts/patients	Procedure specifics[a]	Graft outcome	Reasons for abnormal or revised grafts	Results
Gwozdziewicz [**37**]	2004	Prospective	…/50	OPCAB with TTFM on ITA and SVG	Revision	Grafts with low MGF and high PI (>5)	0.0% (*n* = 0 grafts)
							0.0% (*n* = 0 patients)
Guden *et al.* [**38**]	2003	RCT	…/300	TTFM on ITA	Revision	MGF close to 0 ml/min and PI >5.0, due to intimal flaps and localized dissections at anastomosis site	1.3% (*n* = 4 grafts)
Sanisoglu *et al.* [**39**]	2003	Prospective	49/20	OPCAB with TTFM on ITA and SVG	Revision	Graft failure based on low MGF (5.2 ml/min) and high PI (11-9)	5.0% (*n* = 1 grafts)
							2.0% (*n* = 1 patients)
Groom *et al.* [**40**]	2001	Prospective	298/125	TTFM in ITA and SVG	Revision	Low MGF and/or high PI (not specified)	3.0% (n = 9 grafts)
							7.2% (*n* = 9 patients)
D'Ancona *etal.* [**41**]	2000	Prospective	1145/409	OPCAB with TTFM on ITA and SVG	Revision	Abnormal systolic flow patterns, PI >5.0 and low MGF due to (i) kinking, (ii) coronary dissection or (iii) thrombosis/ sten- osis at the anastomosis site	3.5% (*n* = 41 grafts)
							7.9% (*n* = 33 patients)
Jakobsen and Kjaergard [**42**]	1999	Prospective	…/280	TTFM on ITA and SVG	Abnormal	MGF <10 ml/min due to kinking, rotation or occlusion	1.8% (*n* = 5 grafts)
Walpoth *et al.* [**43**]	1998	Prospective	46/46	TTFM on ITA	Abnormal	Low-flow through ITA-graft (<0.5 ± 0.7 ml/min), high PI (147 + 96) and elevated vascular resistance	6.5% (*n* = 3 grafts)
							6.5% (*n* = 3 patients)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (*continued*)

Study	Year	Design	Number of grafts/patients	Procedure specifics[a]	Graft outcome	Reasons for abnormal or revised grafts	Results
					Revision	1 distal ITA dissection, 1 ITA intramural haematoma and 1 abnormal ECG and poor LV-anterior wall contractility	6.5% (*n* = 3 grafts)
							6.5% (*n* = 3 patients)
Canver and Dame [**44**]	1994	Prospective	…/63	TTFM on ITA	Abnormal	Absence of ITA flow due to twisting at the anastomosis site	3.2% (*n* = *2* patients)

Results are presented as percentages with the number of grafts and (if available) by the number of patients.

[a] On-pump unless specified.

[b] No specification on which grafts were assessed by TTFM.

GAG: coronary angiography; DF: diastolic filling; ECG: electrocardiogram; GEA: gastroepiploic artery; HR-ECUS: high-resolution-epicardial ultrasonography; IFI: intraoperative fluorescence imaging; ITA: internal thoracic artery; LITA: left internal thoracic artery; LV: left ventricular; MAP: mean arterial pressure; MGF: mean graft flow; OPCAB: off-pump coronary artery bypass; PI: pulsatility index; RA: radial artery; RCT: randomized controlled trial; SVG: saphenous vein graft; TTFM: transit-time flow measurement.

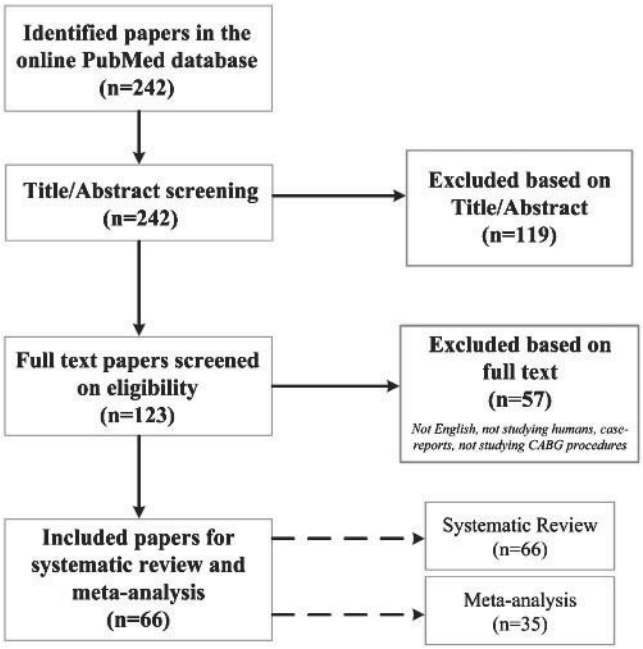

Figure 1. Flow chart of the systematic review process. Studies not written in English, not studying humans, reporting on the same patient population, reporting on transit-time flow measurement in other procedures besides CABG and case reports or reviews were excluded. In total, 66 studies were included, of which 35 studies were incorporated in the meta-analysis. CABG: coronary artery bypass grafting.

In 25 studies (n = 6488), the pooled rate of graft revisions was 4.3% when estimated per patient (95% CI 3.3-5.7%; I^2=73.9), and 2.0% (95% CI 1.5-2.5%; I^2=66.0) in 23 studies with 12 662 grafts when estimated per graft (Fig. 2). The pooled rate of graft revision among abnormal classified grafts was 25.1% (95% CI 15.5-37.9%; I^2=80.2) among 10 studies that reported both the number of abnormal grafts and graft revisions. Main reasons for not revising abnormal classified grafts were (i) no suspicion on graft failure after careful surgical inspection or (ii) no better alternative due to bad quality of the native coronary arteries.

Diagnostic accuracy

Sensitivity rates, describing the accuracy of TTFM, ranged from 0.250 to 0.457 (**Supplementary Material,** Table S2). Specificity varied between 0.941 and 0.984.[14, 17, 30] The probability of having adequate TTFM values with an open graft (e.g. NPV) ranged from 0.719 to 0.980. The probability of having abnormal TTFM values with failing graft (e.g. PPV) varied from 0.100 to 0.840.[14, 17, 30] These NPV and PPV values were based on the outcomes of angiography performed intraoperatively or on the 4th postoperative day.

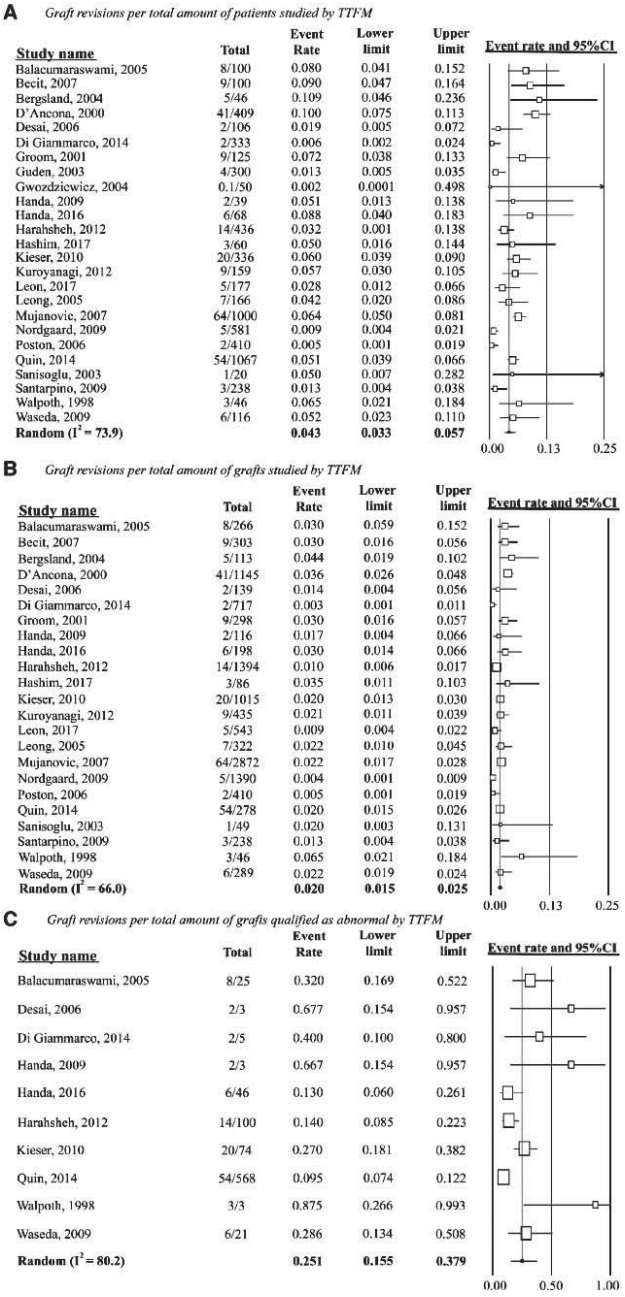

Figure 2. Random-effects models on pooled TTFM study outcomes. (**A**) Graft revision per total amount of patients studied by TTFM, (**B**) graft revisions per total amount of grafts studied by TTFM and (**C**) graft revisions per total amount of grafts qualified as abnormal by TTFM. I^2 indicates heterogeneity (range 0-100; 0 being entirely homogenous). CI: confidence intervals; TTFM: transit-time flow measurement.

Graft patency outcomes

Thirty-two studies evaluated graft patency according to TTFM values, summarized in **Supplementary Material,** Table S3.[7, 12, 14-17, 30, 38, 44-68] Currently, only one small, randomized clinical trial assigned patients to undergo isolated CABG with or without TTFM and/or IFI.[69] The Graft Imaging to Improve Patency (GRIIP) study randomized 156 patients and performed a follow-up CAG at 1 year. No differences were found in the rate of graft occlusion on CAG (30.9% vs 28.9%, imaging vs control, respectively, P = 0.82).[69] Several observational studies reported that abnormal TTFM parameters predicted graft failure at 6months to 1 year [**7**, **54**, 70]. One study reported no predictive correlation between TTFM parameters and angiographic graft stenosis at 3 and 12months [**65**].

Studies reporting on TTFM cut-off values which predict graft patency found that predictors of early graft failure were a PI >5.85 and MGF <20 ml/min for venous grafts, and an MGF of <11.5 ml/min for arterial grafts [**15**, **46**]. Lehnert et al. [**45**] found internal thoracic artery graft patency at 1 year to be significantly worse when MGF <20 ml/min and worsening with 4% failure with every 1 ml/min decrease in MGF [odds ratio (OR) 0.96, 95% CI 0.93-0.99; P= 0.005]. Une et al. [**71**] reported that a higher MGF was an independent predictor of great saphenous vein failure at 1-year follow-up (OR 0.95, 95% CI 0.91-0.99), with an optimal cut-off value of 31 ml/min. The NPV on intermediate-term graft patency (156 days) in relation to abnormal TTFM values was 0.890 (**Supplementary Material,** Table S2) [**59**]. Follow-up on venous graft patency at 3 years showed that MGF was significantly higher among patent grafts versus failing grafts (41.3 ± 22.9ml/ min vs 29.6 ± 18.7 ml/min, respectively; P = 0.01) [**55**].

Short-term clinical outcomes

Twelve studies evaluated short-term outcomes in relation with TTFM parameters (**Supplementary Material,** Table S4) [**8**, **13**, **25**, **27**, **54**, **62**, **69**, **71-75**]. Bauer et al. [**75**] compared CABG with TTFM versus without TTFM and found an increased rate of intraoperative redo-anastomoses, which coincided with significantly lower incidences of ventricular fibrillation, perioperative MI and postoperative mortality when TTFM was performed. Furthermore, another study found that CABG with TTFM resulted in lower rates of postoperative mortality (0% vs 4%), MI (0% vs 5%), intra-aortic balloon pump placement (1% vs 7%) and overall morbidity (6% vs 16%, all $P < 0.05$) [**27**]. Jokinen et al. [**54**] did not confirm the predictive capability of TTFM for these outcomes.

Studies that assessed TTFM cut-off values demonstrated that a PI >5, in arterial and venous grafts, was an independent predictor of early (30 days) major adverse cardiac events with an OR ranging from 1.8 (95% CI 1.1-2.7, *P* = 0.0097) [**25**] to 4.23 (95% CI 1.69-10.59, *P* = 0.002) [**8**]. Yet, these abnormal TTFM values did not predict mid-term mortality or hospital readmission [**25**].

A study which evaluated off-pump versus on-pump CABG found lower overall TTFM values to be associated with an increased incidence of low cardiac output syndrome (*P* = 0.049). Off-pump surgery was not associated with higher PI or lower diastolic filling %, and no differences were found in 30-day mortality and MI between patients who underwent off-pump versus on- pump CABG [**72**]. One study reported higher MGF and lower PI in off-pump procedures [**62**], while another study showed no differences in TTFM parameters between on-pump and off-pump [**52**].

Clinical outcomes during follow-up

The GRIPP trial found no differences in the composite of death, MI and repeat revascularisation at 1 year in patients who underwent CABG with intraoperative graft flow assessment versus those without intraoperative graft flow assessment (7.7% vs 7.7%, respectively) [**69**]. However, observational studies showed the positive predictive capability of TTFM on intermediate-term clinical outcomes, such as major adverse cardiac events, mortality, intra-aortic balloon pump placement or cardiac enzyme release [**8**, **75**]. Other studies reported data that showed no correlation between TTFM parameters and mid-term hospital readmission (during 1.8-year follow-up) [**25**], survival after 3.8years [**74**] or even long-term survival (7.8±0.2 years, **Supplementary Material,** Table S4) [**13**].

DISCUSSION

This systematic review and meta-analysis provides an overview of the literature on intraoperative graft flow assessment by TTFM. We found that 4.3% of patients undergoing CABG required graft revisions based on TTFM parameters. However, of all grafts that were classified as abnormal, only 25% of grafts were revised. The surgeons' clinical interpretation of the graft and the quality of the anastomosis in respect to the quality of the native coronary system was the main reason for not revising all these grafts. Indeed, the reported sensitivity of TTFM was fairly low, ranging from 0.250 to 0.457 with TTFM reported specificity varying from 0.941 to 0.984. Nevertheless, abnormal TTFM parameters were associated with postoperative

mortality and MI, and showed to be of particular importance in predicting graft patency during follow-up.

Intraoperative graft flow assessment is currently most frequently performed by TTFM, as it performs well compared to other methods of intraoperative graft quality assessment, such as thermal CAG, IFI or CAG. Although IFI is associated with higher sensitivity and specificity compared to TTFM [**30**], major limitations of IFI consist of not being able to visualize the entire graft at once and the need to reposition the heart for the laser camera to capture the immunofluorescent flow, possibly compromising natural blood flow. While intraoperative CAG would be ideal to assess graft patency and anastomotic quality, this strategy requires a 'hybrid' operating theatre that is not common in all institutions.

In this meta-analysis, we found that graft revisions were required in 2.0% of grafts and in 4.3% of patients undergoing CABG. Compared to other intraoperative complication rates, such as stroke at 1.1%, this provides the ability to significantly improve short-term outcomes, considering that TTFM usage led to graft revision and may have prevented a perioperative MI or increased cardiac enzyme release which is associated with impaired long-term outcomes [**76**].

So far, no randomized controlled trial focusing exclusively on CABG with TTFM versus without TTFM has been published. Only one small randomized controlled trial primarily studied IFI in combination with TTFM (n = 78) versus without intraoperative graft assessment (n = 78) [**69**]. No differences existed in intraoperative graft revisions, perioperative adverse events, 1-year graft patency or clinical outcomes. However, only 1.7% of the grafts were studied with TTFM exclusively, and thus, the study provides limited information on the actual impact of TTFM. Larger trials evaluating the benefit of routinely performing TTFM on early and late clinical outcomes are warranted.

Observational study data on the impact of TTFM are essential before randomized data will be available. So far, numerous studies reported improved outcomes in patients undergoing CABG with TTFM and only a few reporting no association between TTFM and postoperative outcomes. However, a great diversity in different TTFM cut-off values and methods exists. Studies used in our meta-analysis applied different methods of performing TTFM, including varying surgical and clinical scenarios, such as on-pump or off-pump procedures, varying haemodynamics, venous versus arterial grafts, different locations and number of coronary stenosis or using single versus sequential anastomoses. All of these factors have a major influence on

coronary flow and thereby on TTFM parameters. Furthermore, reasons for surgeons not to revise a graft despite abnormal TTFM parameters were that after inspecting the anastomosis, no suspicion of an anastomotic problem or graft failure was raised, or that there was no better surgical alternative due to poor native coronary arteries. Lacking standardized methods of performing and interpreting TTFM parameters, in combination with non-existent standardized TTFM cut-off values, still introduces a subjective aspect to TTFM and whether a graft should be revised. The heterogeneity of study methods and study outcomes could have contributed to the varying results on the diagnostic accuracy of TTFM (**Supplementary Material,** Table S2). This may also have contributed to the statistical heterogeneity (I^2>_66).

The strength of TTFM is that it is able to detect truly failing and truly patent grafts (true positives and true negatives, respectively). False positives (e.g. patent graft with high PI) rarely occur; however, difficulties exist in detecting poor grafts with a low PI or high MGF (false negatives), which could lead to unnecessary graft revisions [**14**]. Therefore, it remains challenging to interpret TTFM results and translate it into decision-making during each CABG procedure. Di Giammarco et al. [**77**] showed that the diagnostic accuracy of TTFM increased to 100% NPV and 100% PPV when it was combined with HR-ECUS. Adding HR-ECUS to TTFM thereby overcomes the relatively modest diagnostic accuracy of TTFM alone. By including HR-ECUS to the surgeon's appraisal of graft and anastomotic quality, in relation to native coronary targets and run-off, the best surgical and clinical outcomes for patients undergoing CABG could be ensured. Besides, HR-ECUS with TTFM could provide beneficial insights for young surgeons to further improve their surgical techniques.

Standardization on how to perform TTFM, what TTFM values to expect for specific grafts and anastomoses and which cut-offs to use for graft revision are essential to increase the use of TTFM amongst surgeons. Moreover, the studies included in current meta-analysis are of moderate quality, according to the NOS criteria. Surgeons may not be therefore convinced to use TTFM. The prospective, multicentre REQUEST registry collected information on standardized TTFM and ultrasound assessments in patients undergoing CABG (n = 1046, ClincalTrials.gov: NCT02385344). This registry could provide crucial information on how to incorporate TTFM in daily clinical practice by providing insights into whether TTFM is effective and improves outcomes in patients undergoing CABG. Furthermore, it could quantify potential benefits of combining HR-ECUS with TTFM on graft and anastomosis quality assessment.

Finally, a clinical issue that remains is that long-term graft failure may still occur as a result of other mechanisms than those controlled by TTFM. This could be one of

the reasons why surgeons doubt its clinical impact and consequently why routine use of TTFM has been limited. Other factors that potentially influence the adoption rate of intraoperative quality assessment are (i) adequately interpreting and acting upon TTFM determinants come with a learning curve, (ii) the time of the procedure might increase (e.g. depending on the need to revise a graft) and (iii) concerns might remain of needlessly revising a patent graft (e.g. due to limited diagnostic accuracy of TTFM alone) [**17**, **78**]. Furthermore, no high-quality data on the impact of TTFM on surgical and clinical outcomes after CABG exist that could influence the adoption rate of TTFM by individual surgeons. Nevertheless, this systematic review does show that TTFM provides valuable intraoperative data on graft and anastomotic quality, which could contribute to improved surgical and clinical outcomes. Despite potential shortcomings, the 2018 ESC/EACTS Guidelines on myocardial revascularisation gave TTFM for intraoperative graft assessment a class-IIa recommendation [**79**].

LIMITATIONS

As with any meta-analysis of observational studies, limitations related to the observational nature of studies cannot be overcome. One important challenge is that, currently, no consensus exists on uniform TTFM cut-off values to classify grafts as 'abnormal' or requiring revision. This could have caused the relatively increased heterogeneity of the results. To allow a conservative estimate, we have analysed the data using random-effects models, as recommended for meta-analyses on observational studies [**80**]. However, considering the heterogeneity of study definitions and end points in papers reporting the association between TTFM and graft patency and clinical outcomes, no metaanalysis was performed on these outcomes, as it was considered to be inappropriate to pool heterogeneous results.

CONCLUSION

TTFM has potential to further improve the quality of CABG procedures and could improve clinical outcomes for patients. In 4.3% of patients undergoing CABG, there was a need to revise grafts after TTFM assessment. However, only 25% of grafts, classified as abnormal based on TTFM values, were revised, suggesting that the use of TTFM can be further optimized. Indeed, reaching consensus on TTFM remains difficult due to the substantial heterogeneity in published TTFM data, which could be related to varying haemodynamics during assessment, the location of the TTFM probe (e.g. proximal or distal on the graft), varying cut-off values for revision and

the use of different graft types (e.g. internal thoracic artery, saphenous vein or radial artery) on unique coronary arteries with varying degrees of stenosis. Future studies should focus on determining the optimal use of TTFM and thereby further guiding surgeons to improve outcomes after CABG. A multicentre study with standardized TTFM use and definitions on graft revision may provide more insights into the optimal use of this technique.

Conflict of interest: Daniel J.F.M. Thuijs, Margreet W.A. Bekker, David P. Taggart, A. Pieter Kappetein, Teresa M. Kieser, Daniel Wendt, Gabriele Di Giammarco, John D. Puskas and Stuart J. Head received travelling support and/or speaking fees from Medistim ASA, Oslo, Norway. A. Pieter Kappetein and Stuart J. Head report to work as employees of Medtronic, outside the submitted work. Gregory D. Trachiotis declares no conflict of interest.

REFERENCES

1. Head SJ, Kieser TM, Falk V, Huysmans HA, Kappetein AP. Coronary artery bypass grafting: part 1—the evolution over the first 50 years. Eur Heart J 2013;34:2862-72.
2. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391:939-48.
3. Head SJ, Borgermann J, Osnabrugge RL, Kieser TM, Falk V, Taggart DP et al. Coronary artery bypass grafting: part 2–optimizing outcomes and future prospects. Eur Heart J 2013;34:2873-86.
4. Balacumaraswami L, Taggart DP. Intraoperative imaging techniques to assess coronary artery bypass graft patency. Ann Thorac Surg 2007;83:2251-7.
5. Fabricius AM, Gerber W, Hanke M, Garbade J, Autschbach R, Mohr FW. Early angiographic control of perioperative ischemia after coronary artery bypass grafting. Eur J Cardiothorac Surg 2001;19:853-8.
6. Mack MJ. Intraoperative coronary graft assessment. Curr Opin Cardiol 2008;23:568-72.
7. Kitamura H, Okabayashi H, Hanyu M, Soga Y, Nomoto T, Johno H et al. Early and midterm patency of the proximal anastomoses of saphenous vein grafts made with a symmetry aortic connector system. J Thorac Cardiovasc Surg 2005;130:1028-31.
8. Kieser TM, Rose S, Kowalewski R, Belenkie I. Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. Eur J Cardiothorac Surg 2010;38:155-62.
9. Niclauss L. Techniques and standards in intraoperative graft verification by transit time flow measurement after coronary artery bypass graft surgery: a critical review. Eur J Cardiothorac Surg 2017;51:26-33.
10. Wells GSB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (16 January 2019, date last accessed).
11. Hashim SA, Amin MA, Nair A, Raja Mokhtar RA, Krishnasamy S, Cheng K. A flowmeter technique to exclude internal mammary artery anastomosis error in an arrested heart. Heart Lung Circ 2018;27:e59–63.
12. Hiraoka A, Fukushima S, Miyagawa S, Yoshikawa Y, Saito S, Domae K et al. Quantity and quality of graft flow in coronary artery bypass grafting is associated with cardiac computed tomography study-based anatomical and functional parameters. Eur J Cardiothorac Surg 2017;52:909-16.
13. Leon M, Stanham R, Soca G, Dayan V. Do flow and pulsatility index within the accepted ranges predict long-term outcomes after coronary artery bypass grafting? Thorac Cardiovasc Surg 2017; doi: 10.1055/s-0037-1600116 [Epub ahead of print].
14. Handa T, Orihashi K, Nishimori H, Yamamoto M. Maximal blood flow acceleration analysis in the early diastolic phase for aortocoronary artery bypass grafts: a new transit-time flow measurement predictor of graft failure following coronary artery bypass grafting. Surg Today 2016;46:1325-33.

15. Oshima H, Tokuda Y, Araki Y, Ishii H, Murohara T, Ozaki Y et al. Predictors of early graft failure after coronary artery bypass grafting for chronic total occlusion. Interact CardioVasc Thorac Surg 2016;23:142-9.
16. Honda K, Okamura Y, Nishimura Y, Uchita S, Yuzaki M, Kaneko M et al. Graft flow assessment using a transit time flow meter in fractional flow reserve-guided coronary artery bypass surgery. J Thorac Cardiovasc Surg 2015;149:1622-8.
17. Di Giammarco G, Canosa C, Foschi M, Rabozzi R, Marinelli D, Masuyama S et al. Intraoperative graft verification in coronary surgery: increased diagnostic accuracy adding high-resolution epicardial ultrasonography to transit-time flow measurement. Eur J Cardiothorac Surg 2014;45:e41–5.
18. Quin J, Lucke J, Hattler B, Gupta S, Baltz J, Bishawi M et al. Surgeon judgment and utility of transit time flow probes in coronary artery bypass grafting surgery. JAMA Surg 2014;149:1182-7.
19. Harahsheh B. Transit time flowmetry in coronary artery bypass graftingexperience at Queen Alia Heart Institute, Jordan. Oman Med J 2012;27: 475-7.
20. Kuroyanagi S, Asai T, Suzuki T. Intraoperative fluorescence imaging after transit-time flow measurement during coronary artery bypass grafting. Innovations 2012;7:435-40.
21. Handa T, Katare RG, Sasaguri S, Sato T. Preliminary experience for the evaluation of the intraoperative graft patency with real color charge- coupled device camera system: an advanced device for simultaneous capturing of color and near-infrared images during coronary artery bypass graft. Interact CardioVasc Thorac Surg 2009;9:150-4.
22. Nordgaard H, Vitale N, Haaverstad R. Transit-time blood flow measurements in sequential saphenous coronary artery bypass grafts. Ann Thorac Surg 2009;87:1409-15.
23. Santarpino G, Onorati F, Scalas C, De Gori M, Cristodoro L, Zofrea S et al. Radial artery achieves better flowmetric results than saphenous vein in the elderly. Heart Vessels 2009;24:108-15.
24. Waseda K, Ako J, Hasegawa T, Shimada Y, Ikeno F, Ishikawa T et al. Intraoperative fluorescence imaging system for on-site assessment of off-pump coronary artery bypass graft. JACC Cardiovasc Imaging 2009;2: 604-12.
25. Herman C, Sullivan JA, Buth K, Legare JF. Intraoperative graft flow measurements during coronary artery bypass surgery predict in-hospital outcomes. Interact CardioVasc Thorac Surg 2008;7:582-5.
26. Onorati F, Santarpino G, Lerose MA, Impiombato B, Mastroroberto P, Renzulli A. Intraoperative behavior of arterial grafts in the elderly and the young: a flowmetric systematic analysis. Heart Vessels 2008;23:316-24.
27. Becit N, Erkut B, Ceviz M, Unlu Y, Colak A, Kocak H. The impact of intraoperative transit time flow measurement on the results of on-pump coronary surgery. Eur J Cardiothorac Surg 2007;32:313-18.
28. Mujanovic E, Kabil E, Bergsland J. Transit time flowmetry in coronary surgery–an important tool in graft verification. Bosn J Basic Med Sci 2007;7:275-8.
29. Onorati F, Pezzo F, Esposito A, Impiombato B, Comi MC, Polistina M et al . Single versus sequential saphenous vein grafting of the circumflex system: a flowmetric study. Scand Cardiovasc J 2007;41:265-71.
30. Desai ND, Miwa S, Kodama D, Koyama T, Cohen G, Pelletier MP et al. A randomized comparison of intraoperative indocyanine green angiography and transit-time flow

measurement to detect technical errors in coronary bypass grafts. J Thorac Cardiovasc Surg 2006;132:585-94.
31. Poston RS, Gu J, Brown JM, Gammie JS, White C, Nie L et al. Endothelial injury and acquired aspirin resistance as promoters of regional thrombin formation and early vein graft failure after coronary artery bypass grafting. J Thorac Cardiovasc Surg 2006;131:122-30.
32. Balacumaraswami L, Abu-Omar Y, Choudhary B, Pigott D, Taggart DP. A comparison of transit-time flowmetry and intraoperative fluorescence imaging for assessing coronary artery bypass graft patency. J Thorac Cardiovasc Surg 2005;130:315-20.
33. Kim KB, Kang CH, Lim C. Prediction of graft flow impairment by intraoperative transit time flow measurement in off-pump coronary artery bypass using arterial grafts. Ann Thorac Surg 2005;80:594-8.
34. Leong DK, Ashok V, Nishkantha A, Shan YH, Sim EK. Transit-time flow measurement is essential in coronary artery bypass grafting. Ann Thorac Surg 2005;79:854.
35. Onorati F, Olivito S, Mastroroberto P, di Virgilio A, Esposito A, Perrotti A et al. Perioperative patency of coronary artery bypass grafting is not influenced by off-pump technique. Ann Thorac Surg 2005;80:2132-40.
36. Bergsland J, Hol PK, Lingas PS, Lundblad R, Rein KA, Andersen R et al. Intraoperative and intermediate-term angiographic results of coronary artery bypass surgery with symmetry proximal anastomotic device. J Thorac Cardiovasc Surg 2004;128:718-23.
37. Gwozdziewicz M. Cardiomed coronary flow meter for prevention of early occlusion in aortocoronary bypass grafting. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2004;148:59-61.
38. Guden M, Sanisoglu I, Sagbas E, Ergenoglu MU, Ozbek U, Akpinar B. Hemodilution during off-pump coronary artery bypass grafting: can we improve flow and reduce hypercoagulability? Heart Surg Forum 2003;6: 399-402.
39. Sanisoglu I, Guden M, Balci C, Sagbas E, Duran C, Akpinar B. Comparison of intraoperative transit-time flow measurement with early postoperative magnetic resonance flow mapping in off-pump coronary artery surgery. Tex Heart Inst J 2003;30:31-7.
40. Groom R, Tryzelaar J, Forest R, Niimi K, Cecere G, Donegan D et al. Intra-operative quality assessment of coronary artery bypass grafts. Perfusion 2001;16:511-18.
41. D'Ancona G, Karamanoukian HL, Ricci M, Schmid S, Bergsland J, Salerno TA. Graft revision after transit time flow measurement in off-pump coronary artery bypass grafting. Eur J Cardiothorac Surg 2000;17:287-93.
42. Jakobsen HL, Kjaergard HK. Severe impairment of graft flow without electrocardiographic changes during coronary artery bypass grafting. Scand Cardiovasc J 1999;33:157-9.
43. Walpoth BH, Bosshard A, Genyk I, Kipfer B, Berdat PA, Hess OM et al. Transit-time flow measurement for detection of early graft failure during myocardial revascularization. Ann Thorac Surg 1998;66:1097-100.
44. Canver CC, Dame NA. Ultrasonic assessment of internal thoracic artery graft flow in the revascularized heart. Ann Thorac Surg 1994;58:135-8.
45. Lehnert P, Moller CH, Damgaard S, Gerds TA, Steinbruchel DA. Transittime flow measurement as a predictor of coronary bypass graft failure at one year angiographic follow-up. J Card Surg 2015;30:47-52.

46. Takazawa A, Nakajima H, Iguchi A, Tabata M, Morita K, Koike H et al. Impacts of intraoperative flow on graft patency of sequential and individual saphenous vein grafts. Innovations (Phila) 2015;10:85-9.
47. Uehara M, Muraki S, Takagi N, Yanase Y, Tabuchi M, Tachibana K et al. Evaluation of gastroepiploic arterial grafts to right coronary artery using transit-time flow measurement. Eur J Cardiothorac Surg 2015;47: 459-63.
48. Jelenc M, Jelenc B, Klokocovnik T, Lakic N, Gersak B, Knezevic I. Understanding coronary artery bypass transit time flow curves: role of bypass graft compliance. Interact CardioVasc Thorac Surg 2014;18: 164-8.
49. Milani R, Moraes D, Sanches A, Jardim R, Lumikoski T, Miotto G et al. Analysis of transit time flow of the right internal thoracic artery anastomosed to the left anterior descending artery compared to the left internal thoracic artery. Rev Bras Cir Cardiovasc 2014;29:148-55.
50. Genoni M, Odavic D, Loblein H, Dzemali O. Use of the eSVS Mesh: external vein support does not negatively impact early graft patency. Innovations (Phila) 2013;8:211-14.
51. Walker PF, Daniel WT, Moss E, Thourani VH, Kilgo P, Liberman HA et al. The accuracy of transit time flow measurement in predicting graft patency after coronary artery bypass grafting. Innovations (Phila) 2013;8: 416-19.
52. Cerqueira Neto FM, Guedes MA, Soares LE, Almeida GS, Guimaraes AR, Barreto MA et al. Flowmetry of left internal thoracic artery graft to left anterior descending artery: comparison between on-pump and off- pump surgery. Rev Bras Cir Cardiovasc 2012;27:283-9.
53. Balkhy HH, Wann LS, Krienbring D, Arnsdorf SE. Integrating coronary anastomotic connectors and robotics toward a totally endoscopic beating heart approach: review of 120 cases. Ann Thorac Surg 2011;92: 821-7.
54. Jokinen JJ, Werkkala K, Vainikka T, Perakyla T, Simpanen J, Ihlberg L. Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study. Eur J Cardiothorac Surg 2011;39:918-23.
55. Kim HJ, Lee TY, Kim JB, Cho WC, Jung SH, Chung CH et al. The impact of sequential versus single anastomoses on flow characteristics and midterm patency of saphenous vein grafts in coronary bypass grafting. J Thorac Cardiovasc Surg 2011;141:750-4.
56. Takami Y, Tajima K, Terazawa S, Okada N, Fujii K, Sakai Y. Transit-time flow characteristics of in situ right gastroepiploic arterial grafts in coronary artery bypass grafting. J Thorac Cardiovasc Surg 2009;138:669-73.
57. Tokuda Y, Song MH, Oshima H, Usui A, Ueda Y. Predicting midterm coronary artery bypass graft failure by intraoperative transit time flow measurement. Ann Thorac Surg 2008;86:532-6.
58. Hatada A, Yoshimasu T, Kaneko M, Kawago M, Yuzaki M, Honda K et al. Relation of waveform of transit-time flow measurement and graft patency in coronary artery bypass grafting. J Thorac Cardiovasc Surg 2007; 134:789-91.
59. Hol PK, Andersen K, Skulstad H, Halvorsen PS, Lingaas PS, Andersen R et al. Epicardial ultrasonography: a potential method for intraoperative quality assessment of coronary bypass anastomoses? Ann Thorac Surg 2007;84:801-7.
60. Tokuda Y, Song MH, Ueda Y, Usui A, Akita T. Predicting early coronary artery bypass graft failure by intraoperative transit time flow measurement. Ann Thorac Surg 2007;84:1928-33.

61. Di Giammarco G, Pano M, Cirmeni S, Pelini P, Vitolla G, Di Mauro M. Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery. J Thorac Cardiovasc Sur 2006;132:468-74.
62. Hassanein W, Albert AA, Arnrich B, Walter J, Ennker IC, Rosendahl U et al. Intraoperative transit time flow measurement: off-pump versus on- pump coronary artery bypass. Ann Thorac Surg 2005;80:2155-61.
63. Manchio JV, Gu J, Romar L, Brown J, Gammie J, Pierson RN 3rd et al. Disruption of graft endothelium correlates with early failure after off- pump coronary artery bypass surgery. Ann Thorac Surg 2005;79:1991-8.
64. Hirotani T, Kameda T, Shirota S, Nakao Y. An evaluation of the intraoperative transit time measurements of coronary bypass flow. Eur J Cardiothorac Surg 2001;19:848-52.
65. Hol PK, Fosse E, Mork BE, Lundblad R, Rein KA, Lingaas PS et al. Graft control by transit time flow measurement and intraoperative angiography in coronary artery bypass surgery. Heart Surg Forum 2001;4: 254-7; discussion 57-8.
66. Takami Y, Ina H. Relation of intraoperative flow measurement with postoperative quantitative angiographic assessment of coronary artery bypass grafting. Ann Thorac Surg 2001;72:1270-4.
67. Takami Y, Ina H. A simple method to determine anastomotic quality of coronary artery bypass grafting in the operating room. Cardiovasc Surg 2001;9:499-503.
68. Handa T, Orihashi K, Nishimori H, Fukutomi T, Yamamoto M, Kondo N et al. Maximal blood flow acceleration analysis in the early diastolic phase for in situ internal thoracic artery bypass grafts: a new transit-time flow measurement predictor of graft failure following coronary artery bypass grafting. Interact CardioVasc Thorac Surg 2015;20:449-57.
69. Singh SK, Desai ND, Chikazawa G, Tsuneyoshi H, Vincent J, Zagorski BM *et al.* The Graft Imaging to Improve Patency (GRIIP) clinical trial results. J Thorac Cardiovasc Surg 2010;139:294-301.e1.
70. Di Giammarco G, Pano M, Cirmeni S, Pelini P, Vitolla G, Di Mauro M. Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery. J Thorac Cardiovasc Surg 2006;132:468-74.
71. Une D, Deb S, Chikazawa G, Kommaraju K, Tsuneyoshi H, Karkhanis R et al . Cut-off values for transit time flowmetry: are the revision criteria appropriate? J Card Surg 2013;28:3-7.
72. Forcillo J, Noiseux N, Dubois MJ, Mansour S, Prieto I, Basile F et al. Intraoperative graft blood flow measurements for composite and sequential coronary artery bypass grafting. Int J Artif Organs 2014;37:382-91.
73. Song MH. Reappraisal of importance of the left internal mammary artery to the left anterior descending artery in improving mid-term outcome in patients with severe left ventricular dysfunction. Nagoya J Med Sci 2013; 75:113-19.
74. Beran E, Kapitan M, Machler H, Salaymeh L, Anelli-Monti M, Oberwalder P et al . Accurate preoperative echocardiography has more impact on prediction of long-term mortality than intra-operatively measured flow in coronary bypass grafts. Eur J Cardiothorac Surg 2011;40:245-8.
75. Bauer SF, Bauer K, Ennker IC, Rosendahl U, Ennker J. Intraoperative bypass flow measurement reduces the incidence of postoperative ventricular fibrillation and myocardial markers after coronary revascularisation. Thorac Cardiovasc Surg 2005;53:217-22.

76. Domanski MJ, Mahaffey K, Hasselblad V, Brener SJ, Smith PK, Hillis G et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. JAMA 2011;305:585-91.
77. Di Giammarco G, Canosa C, Foschi M, Rabozzi R, Marinelli D, Masuyama S et al . Intraoperative graft verification in coronary surgery: increased diagnostic accuracy adding high-resolution epicardial ultrasonography to transit-time flow measurement. Eur J Cardiothorac Surg 2013;45:e41–5.
78. Kieser TM, Taggart DP. The use of intraoperative graft assessment in guiding graft revision. Ann Cardiothorac Surg 2018;7:652-62.
79. Sousa-Uva M, Neumann F-J, Ahlsson A, Alfonso F, Banning AP, Benedetto U et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2019;55:4-90.
80. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

SUPPLEMENTARY MATERIAL

Supplementary material is also available at EJCTS online.

NEWCASTLE-OTTAWA-SCALE (NOS)

TABLE S1. Newcastle-Ottawa-Scale (NOS) on studies included in the meta-analysis.

	Study	Year	Selection (max=4 stars)	Comparability (max=2 stars)	Exposure/ Outcome (max=3 stars)	Total score (amount of stars)
1.	Hashim [1]	2017	*	-	***	4
2.	Hiraoka [2]	2017	***	-	***	6
3.	Leon [3]	2017	***	**	***	8
4.	Handa [4]	2016	***	-	***	6
5.	Oshima [5]	2016	***	**	***	8
6.	Honda[6]	2015	***	-	***	6
7.	Di Giammarco [7]	2014	***	-	***	6
8.	Quin [8]	2014	***	-	***	6
9.	Harahsheh [9]	2012	***	-	***	6
10.	Kuroyanagi [10]	2012	***	-	***	6
11.	Kieser [11]	2010	***	**	***	8
12.	Handa [12]	2009	***	-	***	6
13.	Nordgaard [13]	2009	***	**	***	8
14.	Santarpino [14]	2009	***	-	***	6
15.	Waseda [15]	2009	***	-	***	6
16.	Herman [16]	2008	***	**	***	8
17.	Onorati [17]	2008	***	-	***	6
18.	Becit [18]	2007	***	-	***	6
19.	Mujanovic [19]	2007	***	-	***	6
20.	Onorati [20]	2007	***	*	***	7
21.	Desai [21]	2006	***	-	***	6
22.	Poston [22]	2006	**	-	***	5
23.	Balacumaraswami [23]	2005	**	-	***	5
24.	Kim [24]	2005	**	-	***	5
25.	Leong [25]	2005	***	-	***	6
26.	Onorati [26]	2005	***	-	***	6
27.	Bergsland [27]	2004	***	-	***	6
28.	Gwozdziewicz [28]	2004	**	-	***	5
29.	Güden [29]	2003	**	-	**	4
30.	Sanisoglu [30]	2003	**	-	***	5
31.	Groom [31]	2001	**	-	***	5

TABLE S1. Newcastle-Ottawa-Scale (NOS) on studies included in the meta-analysis. (continued)

Study	Year	Selection (max=4 stars)	Comparability (max=2 stars)	Exposure/ Outcome (max=3 stars)	Total score (amount of stars)
32. D'Ancona [32]	2000	***	-	***	6
33. Jakobsen [33]	1999	**	-	***	5
34. Walpoth [34]	1998	***	-	***	6
35. Canver [35]	1994	**	-	***	5

TABLE S1. Herewith an overview of the quality of all included studies used in the meta-analysis, according to the Newcastle-Ottawa-Scale (NOS), is presented. [36] *Good quality:* a total of 7-9 stars, *Fair quality:* a total of 4-6 stars, *Poor quality:* a total of 0-3 stars.

TABLE S2. TTFM accuracy

Study	Year	Sensitivity	Specificity	NPV	PPV
Desai [21]	2006				
Detection of abnormal grafts by angiography on 4th post-operative day†		0.250	0.984	0.932	0.600
Di Giammarco [7]	2014				
Detection of abnormal grafts intraoperatively †		0.270	0.950	0.980	0.100
Handa [4]	2016				
Detection of abnormal grafts by post-operative angiography#†		0.457	0.941	0.719	0.840
Hol [37]	2007				
Detection of abnormal grafts by intraoperative angiography †		-	-	0.770	-
Intermediate-term graft patency		-	-	0.890	-
Kim [24]	2005				
Detection of abnormal grafts by angiography on 1st post-operative day		0.962	0.769	-	-
Kim [38]	2011				
Optimal cut-off values for 3-year venous graft patency:					
MGF 24.5mL/min		0.517	0.754	-	-
PI < 2.15		0.862	0.376	-	-
Tokuda [39]	2007				
LCA grafts					
MGF (<15mL/min)		0.500	0.897	0.419	0.924
PI >5.1		0.462	0.926	0.480	0.920

TABLE S2. TTFM accuracy (continued)

Study	Year	Sensitivity	Specificity	NPV	PPV
%BF >4.1		0.423	0.863	0.314	0.910
RCA grafts					
MGF (<20mL/min)		0.800	0.860	0.533	0.956
PI >4.7		0.800	0.960	0.800	0.960
%BF >4.6		0.700	0.960	0.778	0.941
Une [40]	2013				
Saphenous vein grafts					
MGF (<31mL/min)		0.636	0.674	-	-
PI > 4.8		0.227	0.907	-	-
DF (%)< 59		0.556	0.615	-	-

Table S2. An overview of all studies which reported accuracy rates of TTFM detecting abnormal grafts, the ability to assess graft patency and distinct TTFM cut-off values.

†No specification on which grafts were assessed by TTFM, #post-operative angiography date not specified. Abbreviations used: NPV; negative predictive value, PPV; positive predictive value, LCA; left coronary artery, MGF; mean graft flow, PI; pulsatility index, %BF; percentage of backflow, DF %; percentage of diastolic filling, RCA: right coronary artery.

TABLE S3. TTFM and graft patency outcomes.

Study	Year	Design	No. of grafts/patients	Procedure specifics[#]	Outcome	Result
Hiraoka [2]	2017	Prospective	104/63	TTFM on ITA, RA and SVG grafts.	Predicting factors influencing abnormal graft flow	The coronary diameter at the distal anastomosis was smaller in abnormal grafts compared to normal grafts (*P*=0.0065). "The calcium score of the target coronary artery was significantly higher in the abnormal grafts [364 (128–710)] than that in the normal grafts [177 (81–321), *P*=0.0061."
Handa [4]	2016	Retrospective	196/68	OPCAB with TTFM on ITA and SVG grafts.	Examine the association between TTFM in the early diastolic phase and postoperative assessments by CAG.	The overall sensitivity and specificity of TTFM was 0.457 for sensitivity and 0.941 for specificity (McNemar test).The PPV was 0.840 and the NPV was 0.719
Oshima [5]	2016	Retrospective	…/196	TTFM on ITA and SVG grafts.	Establish TTFM cut-off values for detecting graft failure in CTO coronary stenosis.	Multivariable analysis revealed that the PI value was a significant predictors of overall early graft failure (OR 1.23, CI 95% [1.02-1.49] P<0.028). Mean flow <11.5mL/min is a significant predictor of arterial graft failure (P=0.004). A PI > 5.85 (P=0.009) is a good predictor of venous graft failure.
Honda [6]	2015	Retrospective	…/72	TTFM on ITA grafts.	Assessing the efficacy of FFR evaluation in LITA-LAD CABG vs. the evaluation of FFR with TTFM	"As coronary stenosis severity increases, graft flow increases, PI decreases and systolic reverse flow increases." "The pulsatility index is an indicator of graft quality that decreases with the severity of the coronary stenosis."

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics#	Outcome	Result
Lehnert [41]	2015	Retrospective from two RCTs	640/345	TTFM on ITA, RA and SVG grafts.	Graft failure at 1 year	MGF in ITA grafts is recommended to be > 20mL/min (4% decrease in graft failure odds for every 1mL/min MGF increase (OR = 0.96, CI 95% [0.93-0.99], p = 0.005). For single vein grafts TTFM MGF should range >40mL/min to ensure 1 year patency.
Takazawa [42]	2015	Retrospective	480/439	TTFM on ITA and SVG grafts and early postoperative angiogram/CTa	Predictors of early graft failure (mean 3.4 months (± 9.4)	"Univariate and multivariate logistic regression analyses for 230 SVGs demonstrated insufficient flow (≤20mL/min) (*P*=0.002; OR 6.63) and the number of distal anastomoses in a sequential fashion (P=0.004; OR 2.51) were significantly correlated with failure."
Uehara [43]	2015	Prospective	83/83	TTFM on GEA grafts.	Analyse the relationship between TTFM and post-operative CAG	"There was no correlation between the early quality of the GEA graft anastomoses and the intraoperative TTFM parameter values."
Di Giammarco [7]	2014	Prospective	717/333	TTFM and HR-ECUS on ITA and SVG grafts.	Evaluate the added value of intraoperative HR-ECUS for improved graft patency verification.	TTFM sensitivity (27%), specificity (95%), PPV (10%) and NPV (98%) all without HR-ECUS. With HR-ECUS these results were respectively: 33%, 100%, 100% and 99%.
Jelenc [44]	2014	Retrospective	25/17	TTFM on ITA and SVG grafts.	Graft compliance in relation to TTFM parameters	"Graft compliance significantly influences TTFM; therefore PI cannot be used as a measure of graft patency. Only MGF should be used to judge the function of the bypass graft."
Milani [45]	2014	Retrospective	…/50	OPCAB with TTFM on ITA grafts.	Evaluating performance of internal thoracic arteries as LAD-grafts	There was no significant difference MGF in both groups. There was a significant difference between PI, LITA = 2.0 ± 0.7 versus RITA = 2.8 ± 0.9 (p = 0.003).

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics[#]	Outcome	Result
Genoni [46]	2013	Prospective	34/20	TTFM on ITA and SVG grafts.	Assess early patency rates of grafts	TTFM LITA (mean flow: 36 ± 16.5 mL/min, PI 3.0 ± 2.4) and RITA (mean flow: 34 ± 20.2 mL/min, PI 2.3 ± 0.7). All LITA and RITA grafts appeared to be patent on CT angiography at 5th post-operative day.
Walker [47]	2013	Retrospective	160/160	Robotic-assisted CABG with TTFM on LITA grafts and peri/post-operative angiography	Compare TTFM to diagnostic angiography intra- and early post-operatively	"TTFM revealed significant differences in mean flow between patent (n=152) and non-patent (n=8) grafts (34.3±16.8 mL/min vs. 23.9±12.5 mL/min, *P*=0.03), but not in PI (1.98±0.76 vs. 1.65±0.48, *P*=0.16) or DF (73.5% ± 8.45% vs. 70.9% ± 6.15%, *P*=0.13).
Cerqueria Neto [48]	2012	Retrospective	80/35	Off-pump vs on-pump CABG with TTFM on ITA grafts.	Compare TTFM parameters in off-pump vs on-pump CABG	There were no statistical differences in mean flow, PI and DF between the off-pump and on-pump groups. There was no need for graft revision.
Balkhy [49]	2011	Retrospective	85/68	Totally endoscopic OPCAB with TTFM on ITA grafts.	Graft patency at 4 months	MGF in all the internal mammary artery grafts was 76 ± 43 mL/min, and PI of 1.5 ± 0.5 Eighty grafts (n = 80, 94.1%) were patent at a mean of 4 months, assessed by angiography.
Jokinen [50]	2011	Prospective	204/75	TTFM on ITA, RA and SVG grafts.	Graft failure at 6 month	"TTFM predicts graft failure within the 6 months after CABG." TTFM parameters were neither associated with postoperative CK-MB release, nor with myocardial infarction, stroke or death.

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics#	Outcome	Result
Kim [38]	2011	Retrospective	328/309	TTFM on SVG grafts.	3-year graft patency	"The greatest accuracy for predicting graft patency was obtained at the cut-off value of 24.5 mL/min for mean flow (51.7% sensitivity and 75.4% specificity) and 2.15 for PI (86.2% sensitivity and 37.6% specificity)." Higher mean flows were associated with patent grafts versus failing grafts (41.3 ± 22.9 mL/min in patent grafts and 29.6 ± 18.7 mL/min in failing grafts; *P*=0.01)
Takami [51]	2009	Prospective	289/111	TTFM on GEA grafts and post-op CAG.	Non-functional GEA grafts on CAG	Non-functional GEA grafts (n=10; 2 occluded, 5 reverse flow and 3 grafts with competitive flow) had higher PI (> 3.7) and lower mean flow (<17 ± 18mL/min) compared to patent GEA-grafts.
Tokuda [52]	2008	Retrospective	104/51	TTFM on ITA, RA, SVG and GEA grafts.	Graft failure at 1-4 years	Multivariate analysis showed that adequate mean graft flow was an independent predictor: OR 0.95 (95% CI [0.92-0.98] *P*=0.004) for midterm graft failure.
Hatada [53]	2007	Retrospective	29/29	TTFM on SVG grafts.	Graft occlusion at 3- or 6-month angiography	Fast Fourier transformation analysis of TTFM waveforms predicts graft patency.
Hol [37]	2007	Prospective	39/39	OPCAB with TTFM on ITA and SVG grafts.	CAG at 156 days (SD 50)	The NPV of TTFM for intraoperative findings was 0.77 (30 of 39).The NPV value of TTFM for long-term patency was 0.89 (32 of 36).

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics#	Outcome	Result
Tokuda [39]	2007	Retrospective	261/123	TTFM on ITA, RA, SVG and GEA grafts and post-op CAG (day 16.2 ± 12.6).	Early graft failure	Using specific TTFM cut-off values for specific certain graft territories (LCA: Mean flow:15mL/min, PI >5.1, %BF: 4.1%) or RCA: Mean flow:20mL/min, PI >4.7, %BF: 4.6%) NPV-range 0.91-0.96 whereas PPV-range 0.31-0.80. Sensitivity and Specificity ranged from 0.423 – 0.800 and 0.897 – 0.960 resp.
Desai [21]	2006	Prospective	139/106	TTFM and IFI on ITA, RA and SVG grafts.	Compare diagnostic accuracy of TTFM and IFI at post-operative day 4 with CAG.	"The sensitivity and specificity of TTFM to detect ≥50% graft stenosis was 25% and 98.4%. The sensitivity and specificity of ICG angiography to detect ≥50% graft stenosis was 83% and 100%."
Di Giammarco [54]	2006	Retrospective	304/157	TTFM on ITA, RA, SVG and GEA grafts.	Graft failure at 1 year	Mean flow (≤15mL/min), pulsatility index (≥3.0) and percentage of backward flow (3.0%) on TTFM are independently associated with graft failure within first post-operative year.
Hassanein [55]	2005	Prospective	…/445	OPCAB with TTFM on ITA, RA and SVG grafts vs. CABG without TTFM	Compare anastomosis quality between off-pump and on-pump CABG in relation to clinical outcomes.	Average PI and mean flow were higher in off-pump compared to on-pump (2.09 ± 1.03 vs. 1.9 ± 0.98 and 39±22.63 vs. 44.19±23.58 mL/min, *P*=0.005). Patients with post-operative angina pain had lower mean flow values compared to patients without angina (37.17 ± 21.1 mL/min vs. 42.81 ± 26 mL/min, *P*= 0.015.
Kitamura [56]	2005	Prospective	…/31	OPCAB with SVG-ACS system and TTFM on SVG grafts.	1-year graft patency	Low graft flow (14.5mL/min) and poor left ventricular function (42%) were significant risk factors for graft occlusion at 1-year (*P*=0.02 and *P*=0.04 resp.).

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics[#]	Outcome	Result
Manchio [57]	2005	Prospective	217/106	OPCAB with TTFM on SVG grafts.	SVG thrombosis at 5 days assessed by CTA	Graft flow was not significantly different between patients with versus without thrombosis.
Güden [29]	2003	RCT	…/300	OPCAB with hemodilution protocol versus CABG with TTFM on ITA grafts.	Compare graft flow in on-pump and off-pump and to evaluate the effects of hemodilution OPCAB grafts.	No difference in PI values between groups. The mean flow in LAD in OPCAB patients with hemodilitution protocol was significantly higher compared to the other 2 groups. Overall graft patency, assessed by angiography post-operatively day 6, was comparable between all groups.
Hirotani [58]	2001	Retrospective	481/171	TTFM on ITA and SVG grafts.	Pre-discharge angiographic findings	No differences in flow measurements between stenotic and open ITA grafts. For SVGs, intraoperative mean flow of occluded grafts was significantly less (P<0.0001), and could thereby possibly identify early graft occlusion.
Hol [59]	2001	Prospective	124/72	TTFM on ITA and SVG grafts.	Peri-operative angiographic findings and at 3-and 12 months	There were no differences in flow and pulsatility index between grafts with <50% stenosis vs >50% stenosis.
Takami [60]	2001	Prospective	82/35	TTFM on ITA, RA, SVG and GEA grafts.	Early postoperative (14 ± 5 days) angiographic findings	Intraoperative flow parameters; mean flow, insufficiency percentage (% Insuf.), Fast Fourier transformation (FFT) and PI were significantly different in patent and non-patent grafts.
Takami [61]	2001	Prospective	70/32	TTFM on ITA, RA, SVG and GEA grafts and post-operative angiography at day 14 ± 5	Stenotic grafts on CAG	Stenotic grafts (12.9%, n=9 grafts) had lower mean flow (7.6±10.3), higher PI (30.1±26.8), higher % Insuf (40.4±34.1) and lower FFT ratio (0.68±0.27) compared to patent grafts.

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics[#]	Outcome	Result
Canver [35]	1994	Prospective	…/63	TTFM on ITA and SVG grafts.	Objectify the applicability of TTFM to quantitate ITA graft flow	"Compared with in-situ ITA flow, ITA flow after grafting to the coronary artery was increased significantly during CPB and just before sternal closure ($p < 0.001$)". Two patients had twisting of the ITA at the anastomosis site which was detected by absence of flow.

Table S3. An overview of the available literature on TTFM in relation to graft patency outcomes. *defined as postoperative myocardial infarction (MI), prolonged ventilation (>24 h), low cardiac output syndrome (low cardiac output requiring at least two inotropes and/or intra-aortic balloon pump), postoperative percutaneous coronary intervention, re-operation for graft occlusion, and in-hospital mortality. [#]not specified which grafts were assessed with TTFM. [#]On-pump unless specified.
Abbreviations: ACS system: The Symmetry Aortic Connector System (St. Jude Medical Inc., St Paul, Minnesota, USA), CAG: coronary angiogram, CI: confidence interval, CK: Creatinine-Kinase, CK-MB: Creatine-Kinase MB (heart enzyme), CPB: Cardiopulmonary bypass, CTO: Chronic Total Occlusion, DF: Diastolic Filling, EF: Ejection Fraction, FFR: Fractional Flow Reserve, FFT: Fast Fourier Transformation, HR-ECUS: High-Resolution Epicardial Ultrasonography, IABP: Intra-Aortic Balloon Pump, ICG: IndoCyanine green, IFI: intraoperative fluorescence imaging, ITA: Internal Thoracic Artery, LAD: Left Anterior Descending artery, LCA: Left Coronary Artery, LITA: Left Internal Thoracic Artery, MACE: Major Adverse Cardiac Events, MGF: Mean Graft Flow, NPV: Negative Predictive Value, OPCAB: Off-pump Coronary Artery Bypass, OR: Odds Ratio, PI: Pulsatility Index, PPV: Positive Predictive Value, RCA: Right Coronary Artery, RITA: Right Internal Thoracic Artery, RCT: Randomized Controlled Trial, SLVD: Severe Left Ventricular dysfunction (LVEF<35%), SVGs: Saphenous Vein Grafts, SD; Standard Deviation, TTFM: Transit Time Flow Measurements.

SUPPLEMENTARY MATERIAL REFERENCES

*Please note that the order of the references in the supplementary materials might differ from the original published manuscript.

[1] Hashim SA, Amin MA, Nair A, Raja Mokhtar RA, Krishnasamy S, Cheng K. *A Flowmeter Technique to Exclude Internal Mammary Artery Anastomosis Error in an Arrested Heart*. Heart Lung Circ 2017.

[2] Hiraoka A, Fukushima S, Miyagawa S, Yoshikawa Y, Saito S, Domae K *et al. Quantity and quality of graft flow in coronary artery bypass grafting is associated with cardiac computed tomography study-based anatomical and functional parameters*. Eur J Cardiothorac Surg 2017;**52**:909-16.

[3] Leon M, Stanham R, Soca G, Dayan V. *Do Flow and Pulsatility Index within the Accepted Ranges Predict Long-Term Outcomes after Coronary Artery Bypass Grafting?* Thorac Cardiovasc Surg 2017.

[4] Handa T, Orihashi K, Nishimori H, Yamamoto M. *Maximal blood flow acceleration analysis in the early diastolic phase for aortocoronary artery bypass grafts: a new transit-time flow measurement predictor of graft failure following coronary artery bypass grafting*. Surg Today 2016;**46**:1325-33.

[5] Oshima H, Tokuda Y, Araki Y, Ishii H, Murohara T, Ozaki Y *et al. Predictors of early graft failure after coronary artery bypass grafting for chronic total occlusion*. Interact Cardiovasc Thorac Surg 2016;**23**:142-9.

[6] Honda K, Okamura Y, Nishimura Y, Uchita S, Yuzaki M, Kaneko M *et al. Graft flow assessment using a transit time flow meter in fractional flow reserve-guided coronary artery bypass surgery*. J Thorac Cardiovasc Surg 2015;**149**:1622-8.

[7] Di Giammarco G, Canosa C, Foschi M, Rabozzi R, Marinelli D, Masuyama S *et al. Intraoperative graft verification in coronary surgery: increased diagnostic accuracy adding high-resolution epicardial ultrasonography to transit-time flow measurement*. Eur J Cardiothorac Surg 2014;**45**:e41-5.

[8] Quin J, Lucke J, Hattler B, Gupta S, Baltz J, Bishawi M *et al. Surgeon judgment and utility of transit time flow probes in coronary artery bypass grafting surgery*. JAMA Surg 2014;**149**:1182-7.

[9] Harahsheh B. *Transit Time Flowmetry in Coronary Artery Bypass Grafting-experience at Queen Alia Heart Institute, Jordan*. Oman Med J 2012;**27**:475-7.

[10] Kuroyanagi S, Asai T, Suzuki T. *Intraoperative fluorescence imaging after transit-time flow measurement during coronary artery bypass grafting*. Innovations (Phila) 2012;**7**:435-40.

[11] Kieser TM, Rose S, Kowalewski R, Belenkie I. *Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts*. Eur J Cardiothorac Surg 2010;**38**:155-62.

[12] Handa T, Katare RG, Sasaguri S, Sato T. *Preliminary experience for the evaluation of the intraoperative graft patency with real color charge-coupled device camera system: an advanced device for simultaneous capturing of color and near-infrared images during coronary artery bypass graft*. Interact Cardiovasc Thorac Surg 2009;**9**:150-4.

[13] Nordgaard H, Vitale N, Haaverstad R. *Transit-time blood flow measurements in sequential saphenous coronary artery bypass grafts*. Ann Thorac Surg 2009;**87**:1409-15.

[14] Santarpino G, Onorati F, Scalas C, De Gori M, Cristodoro L, Zofrea S *et al. Radial artery achieves better flowmetric results than saphenous vein in the elderly*. Heart Vessels 2009;**24**:108-15.

[15] Waseda K, Ako J, Hasegawa T, Shimada Y, Ikeno F, Ishikawa T *et al. Intraoperative Fluorescence Imaging System for On-Site Assessment of Off-Pump Coronary Artery Bypass Graft*. Jacc-Cardiovasc Imag 2009;**2**:604-12.

[16] Herman C, Sullivan JA, Buth K, Legare JF. *Intraoperative graft flow measurements during coronary artery bypass surgery predict in-hospital outcomes*. Interact Cardiovasc Thorac Surg 2008;**7**:582-5.

[17] Onorati F, Santarpino G, Lerose MA, Impiombato B, Mastroroberto P, Renzulli A. *Intraoperative behavior of arterial grafts in the elderly and the young: a flowmetric systematic analysis*. Heart Vessels 2008;**23**:316-24.

[18] Becit N, Erkut B, Ceviz M, Unlu Y, Colak A, Kocak H. *The impact of intraoperative transit time flow measurement on the results of on-pump coronary surgery*. Eur J Cardiothorac Surg 2007;**32**:313-8.

[19] Mujanovic E, Kabil E, Bergsland J. *Transit time flowmetry in coronary surgery--an important tool in graft verification*. Bosn J Basic Med Sci 2007;**7**:275-8.

[20] Onorati F, Pezzo F, Esposito A, Impiombato B, Comi MC, Polistina M *et al. Single versus sequential saphenous vein grafting of the circumflex system: a flowmetric study*. Scand Cardiovasc J 2007;**41**:265-71.

[21] Desai ND, Miwa S, Kodama D, Koyama T, Cohen G, Pelletier MP *et al. A randomized comparison of intraoperative indocyanine green angiography and transit-time flow measurement to detect technical errors in coronary bypass grafts*. J Thorac Cardiovasc Surg 2006;**132**:585-94.

[22] Poston RS, Gu J, Brown JM, Gammie JS, White C, Nie L *et al. Endothelial injury and acquired aspirin resistance as promoters of regional thrombin formation and early vein graft failure after coronary artery bypass grafting*. J Thorac Cardiovasc Surg 2006;**131**:122-30.

[23] Balacumaraswami L, Abu-Omar Y, Choudhary B, Pigott D, Taggart DP. *A comparison of transit-time flowmetry and intraoperative fluorescence imaging for assessing coronary artery bypass graft patency*. J Thorac Cardiovasc Surg 2005;**130**:315-20.

[24] Kim KB, Kang CH, Lim C. *Prediction of graft flow impairment by intraoperative transit time flow measurement in off-pump coronary artery bypass using arterial grafts*. Ann Thorac Surg 2005;**80**:594-8.

[25] Leong DK, Ashok V, Nishkantha A, Shan YH, Sim EK. *Transit-time flow measurement is essential in coronary artery bypass grafting*. Ann Thorac Surg 2005;**79**:854-7; discussion 57-8.

[26] Onorati F, Olivito S, Mastroroberto P, di Virgilio A, Esposito A, Perrotti A *et al. Perioperative patency of coronary artery bypass grafting is not influenced by off-pump technique*. Ann Thorac Surg 2005;**80**:2132-40.

[27] Bergsland J, Hol PK, Lingas PS, Lundblad R, Rein KA, Andersen R *et al. Intraoperative and intermediate-term angiographic results of coronary artery bypass surgery with Symmetry proximal anastomotic device*. J Thorac Cardiovasc Surg 2004;**128**:718-23.

[28] Gwozdziewicz M. *Cardiomed coronary flow meter for prevention of early occlusion in aortocoronary bypass grafting*. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2004;**148**:59-61.

[29] Guden M, Sanisoglu I, Sagbas E, Ergenoglu MU, Ozbek U, Akpinar B. *Hemodilution during off-pump coronary artery bypass grafting: can we improve flow and reduce hypercoagulability?* Heart Surg Forum 2003;**6**:399-402.

[30] Sanisoglu I, Guden M, Balci C, Sagbas E, Duran C, Akpinar B. *Comparison of intraoperative transit-time flow measurement with early postoperative magnetic resonance flow mapping in off-pump coronary artery surgery*. Tex Heart Inst J 2003;**30**:31-7.

[31] Groom R, Tryzelaar J, Forest R, Niimi K, Cecere G, Donegan D *et al. Intra-operative quality assessment of coronary artery bypass grafts*. Perfusion 2001;**16**:511-8.

[32] D'Ancona G, Karamanoukian HL, Ricci M, Schmid S, Bergsland J, Salerno TA. *Graft revision after transit time flow measurement in off-pump coronary artery bypass grafting*. Eur J Cardiothorac Surg 2000;**17**:287-93.

[33] Jakobsen HL, Kjaergard HK. *Severe impairment of graft flow without electrocardiographic changes during coronary artery bypass grafting*. Scand Cardiovasc J 1999;**33**:157-9.

[34] Walpoth BH, Bosshard A, Genyk I, Kipfer B, Berdat PA, Hess OM *et al. Transit-time flow measurement for detection of early graft failure during myocardial revascularization*. Ann Thorac Surg 1998;**66**:1097-100.

[35] Canver CC, Dame NA. *Ultrasonic assessment of internal thoracic artery graft flow in the revascularized heart*. Ann Thorac Surg 1994;**58**:135-8.

[36] Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* http://wwwohrica/programs/clinical_epidemiology/oxfordasp 2013.

[37] Hol PK, Andersen K, Skulstad H, Halvorsen PS, Lingaas PS, Andersen R *et al. Epicardial ultrasonography: a potential method for intraoperative quality assessment of coronary bypass anastomoses?* Ann Thorac Surg 2007;**84**:801-7.

[38] Kim HJ, Lee TY, Kim JB, Cho WC, Jung SH, Chung CH *et al. The impact of sequential versus single anastomoses on flow characteristics and mid-term patency of saphenous vein grafts in coronary bypass grafting*. J Thorac Cardiovasc Surg 2011;**141**:750-4.

[39] Tokuda Y, Song MH, Ueda Y, Usui A, Akita T. *Predicting early coronary artery bypass graft failure by intraoperative transit time flow measurement*. Ann Thorac Surg 2007;**84**:1928-34.

[40] Une D, Deb S, Chikazawa G, Kommaraju K, Tsuneyoshi H, Karkhanis R *et al. Cut-off values for transit time flowmetry: are the revision criteria appropriate?* J Card Surg 2013;**28**:3-7.

[41] Lehnert P, Moller CH, Damgaard S, Gerds TA, Steinbruchel DA. *Transit-time flow measurement as a predictor of coronary bypass graft failure at one year angiographic follow-up*. J Card Surg 2015;**30**:47-52.

[42] Takazawa A, Nakajima H, Iguchi A, Tabata M, Morita K, Koike H *et al. Impacts of intraoperative flow on graft patency of sequential and individual saphenous vein grafts*. Innovations (Phila) 2015;**10**:85-9.

[43] Uehara M, Muraki S, Takagi N, Yanase Y, Tabuchi M, Tachibana K *et al. Evaluation of gastroepiploic arterial grafts to right coronary artery using transit-time flow measurement*. Eur J Cardiothorac Surg 2015;**47**:459-63.

[44] Jelenc M, Jelenc B, Klokocovnik T, Lakic N, Gersak B, Knezevic I. *Understanding coronary artery bypass transit time flow curves: role of bypass graft compliance*. Interact Cardiovasc Thorac Surg 2014;**18**:164-8.

[45] Milani R, Moraes D, Sanches A, Jardim R, Lumikoski T, Miotto G *et al. Analysis of transit time flow of the right internal thoracic artery anastomosed to the left anterior descending artery compared to the left internal thoracic artery*. Rev Bras Cir Cardiovasc 2014;**29**:148-55.

[46] Genoni M, Odavic D, Loblein H, Dzemali O. *Use of the eSVS Mesh: external vein support does not negatively impact early graft patency*. Innovations (Phila) 2013;**8**:211-4.

[47] Walker PF, Daniel WT, Moss E, Thourani VH, Kilgo P, Liberman HA *et al. The accuracy of transit time flow measurement in predicting graft patency after coronary artery bypass grafting*. Innovations (Phila) 2013;**8**:416-9.

[48] Cerqueira Neto FM, Guedes MA, Soares LE, Almeida GS, Guimaraes AR, Barreto MA *et al. Flowmetry of left internal thoracic artery graft to left anterior descending artery: comparison between on-pump and off-pump surgery*. Rev Bras Cir Cardiovasc 2012;**27**:283-9.

[49] Balkhy HH, Wann LS, Krienbring D, Arnsdorf SE. *Integrating coronary anastomotic connectors and robotics toward a totally endoscopic beating heart approach: review of 120 cases*. Ann Thorac Surg 2011;**92**:821-7.

[50] Jokinen JJ, Werkkala K, Vainikka T, Perakyla T, Simpanen J, Ihlberg L. *Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study*. European Journal of Cardio-Thoracic Surgery 2011;**39**:918-23.

[51] Takami Y, Tajima K, Terazawa S, Okada N, Fujii K, Sakai Y. *Transit-time flow characteristics of in situ right gastroepiploic arterial grafts in coronary artery bypass grafting*. J Thorac Cardiovasc Surg 2009;**138**:669-73.

[52] Tokuda Y, Song MH, Oshima H, Usui A, Ueda Y. *Predicting midterm coronary artery bypass graft failure by intraoperative transit time flow measurement*. Ann Thorac Surg 2008;**86**:532-6.

[53] Hatada A, Yoshimasu T, Kaneko M, Kawago M, Yuzaki M, Honda K *et al. Relation of waveform of transit-time flow measurement and graft patency in coronary artery bypass grafting*. J Thorac Cardiovasc Surg 2007;**134**:789-91.

[54] Di Giammarco G, Pano M, Cirmeni S, Pelini P, Vitolla G, Di Mauro M. *Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery*. J Thorac Cardiov Sur 2006;**132**:468-74.

[55] Hassanein W, Albert AA, Arnrich B, Walter J, Ennker IC, Rosendahl U *et al. Intraoperative transit time flow measurement: off-pump versus on-pump coronary artery bypass*. Ann Thorac Surg 2005;**80**:2155-61.

[56] Kitamura H, Okabayashi H, Hanyu M, Soga Y, Nomoto T, Johno H *et al. Early and midterm patency of the proximal anastomoses of saphenous vein grafts made with a Symmetry Aortic Connector System*. J Thorac Cardiovasc Surg 2005;**130**:1028-31.

[57] Manchio JV, Gu J, Romar L, Brown J, Gammie J, Pierson RN, 3rd *et al. Disruption of graft endothelium correlates with early failure after off-pump coronary artery bypass surgery*. Ann Thorac Surg 2005;**79**:1991-8.

[58] Hirotani T, Kameda T, Shirota S, Nakao Y. *An evaluation of the intraoperative transit time measurements of coronary bypass flow*. Eur J Cardiothorac Surg 2001;**19**:848-52.

[59] Hol PK, Fosse E, Mork BE, Lundblad R, Rein KA, Lingaas PS *et al. Graft control by transit time flow measurement and intraoperative angiography in coronary artery bypass surgery*. Heart Surg Forum 2001;**4**:254-7; discussion 57-8.

[60] Takami Y, Ina H. *Relation of intraoperative flow measurement with postoperative quantitative angiographic assessment of coronary artery bypass grafting*. Ann Thorac Surg 2001;**72**:1270-4.

[61] Takami Y, Ina H. *A simple method to determine anastomotic quality of coronary artery bypass grafting in the operating room*. Cardiovasc Surg 2001;**9**:499-503.

[62] Forcillo J, Noiseux N, Dubois MJ, Mansour S, Prieto I, Basile F *et al. Intra-operative graft blood flow measurements for composite and sequential coronary artery bypass grafting*. Int J Artif Organs 2014;**37**:382-91.

[63] Song MH. *Reappraisal of importance of the left internal mammary artery to the left anterior descending artery in improving mid-term outcome in patients with severe left ventricular dysfunction*. Nagoya J Med Sci 2013;**75**:113-9.

[64] Beran E, Kapitan M, Machler H, Salaymeh L, Anelli-Monti M, Oberwalder P *et al. Accurate preoperative echocardiography has more impact on prediction of long-term mortality than intraoperatively measured flow in coronary bypass grafts*. Eur J Cardiothorac Surg 2011;**40**:245-8.

[65] Singh SK, Desai ND, Chikazawa G, Tsuneyoshi H, Vincent J, Zagorski BM *et al. The Graft Imaging to Improve Patency (GRIIP) clinical trial results*. J Thorac Cardiovasc Surg 2010;**139**:294-301, 01 e1.

[66] Bauer SF, Bauer K, Ennker IC, Rosendahl U, Ennker J. *Intraoperative bypass flow measurement reduces the incidence of postoperative ventricular fibrillation and myocardial markers after coronary revascularisation*. Thorac Cardiovasc Surg 2005;**53**:217-22.

Chapter 12

Intraoperative transit-time flow measurement and high-frequency ultrasound assessment in coronary artery bypass grafting

David P. Taggart, Daniel J. F. M. Thuijs, Gabriele Di Giammarco, John D. Puskas, Daniel Wendt, Gregory D. Trachiotis, Teresa M. Kieser, A. Pieter Kappetein, Stuart J. Head

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ABSTRACT

Objectives

We evaluated the influence of transit-time flow measurement with epicardial and epiaortic high-frequency ultrasound in patients undergoing coronary artery bypass grafting procedure.

Methods

The Registry for Quality Assessment with Ultrasound Imaging and Transit-time Flow Measurement in Cardiac Bypass Surgery study is a multicenter, prospective study among 7 international centers performing coronary artery bypass grafting procedures. The primary end point was any change in the planned surgical procedure. Major secondary end points consisted of the rate and reason for surgical changes related to the aorta, in situ conduits, coronary targets, and completed grafts, and the rate of in-hospital mortality and major morbidity.

Results

Between April 2015 and December 2017, 1046 patients were enrolled. Of those, 1016 were included in the final analyses. Mean age was 65.9 years, 14.0% were women, and diabetes was present in 39.6%. Off-pump procedures were performed in 39.6% and bilateral internal thoracic arteries in 30.5%. The primary end point occurred in 25.2% of patients (n = 256) and in 77% (197 out of 256) this was based on transit-time flow measurement and/or high-frequency ultrasound. Surgical changes were related to the aorta in 9.9%, to in situ conduits in 2.7%, and the coronary targets in 22.4%. Graft revision occurred in 7.8%, including revisions of the proximal and/or distal anastomosis in 6.6%. In-hospital adverse event rates were 0.6% for mortality, 1.0% for cerebrovascular events, and 0.3% for myocardial infarction.

Conclusions

Surgical changes related to the aorta, conduits, coronary targets, and anastomosis were made in 25% of patients. This was associated with low operative mortality and low major morbidity. Transit-time flow measurement and high-frequency ultrasound may improve the quality, safety, and efficacy of coronary artery bypass grafting procedures and should be considered as a routine procedural aspect.

Key Words

coronary artery bypass grafting, transit time, high frequency ultrasound, intraoperative quality control, REQUEST

INTRODUCTION

Since the introduction of coronary artery bypass grafting (CABG) more than 5 decades ago, surgeons have consistently focused on reducing perioperative adverse events and improving graft patency. Additionally, measures to improve long-term outcomes through superior conduit selection (more arterial grafts), implementation of less-invasive techniques and secondary preventive measures are constantly advocated.[1],[2] Although overall outcomes have significantly improved over time, the end points of mortality, stroke, and graft patency remain key targets for further optimization.[3]–[5]

Various intraoperative techniques continue to be recommended for contemporary state-of-the-art CABG.[6],[7] In terms of intraoperative quality assessment, efforts to improve surgical results have focused both on graft assessment by transit-time flow measurement (TTFM) and identification of disease-free areas of the aorta, using epiaortic high-frequency ultrasound (HFUS), to allow safe manipulation, and thereby reduce the risk of stroke. TTFM itself assesses graft flow and, by inference, the quality of the anastomosis and/or conduit and allows immediate graft revision in situations where the surgical result is not optimal.

A systematic review and meta-analysis of 6488 patients undergoing CABG reported that 4.3% of patients had graft revisions and that TTFM measurements correlated with graft patency during short- to midterm follow-up.[8] In addition, HFUS is used for epiaortic scanning to identify diseased areas before any aortic manipulation, epicardial coronary artery scanning to identify potential target-vessel anastomosis sites that are free of plaque (especially on the posterior wall), ultrasound of the conduits when dissection is suspected, and postanastomosis scanning to identify potential anastomotic characteristics that limit graft flow.

The combination of these techniques, to avoid diseased areas of aorta and to identify and correct adverse technical issues affecting bypass grafts, could, intuitively, provide an important reduction in perioperative adverse events and improvement in graft patency. Indeed, Di Giammarco and colleagues[9] reported that the diagnostic accuracy of combining TTFM with HFUS on detecting truly patent or failing grafts increased significantly, reducing the proportion of unnecessary graft revisions.

The 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularisation provide a IIa recommendation, Evidence Level B, for intraoperative graft flow assessment and Evidence Level C for

epiaortic scanning during CABG.[10] Nonetheless, published data on these techniques are limited to single-center studies and therefore its wider applicability to a broader cohort of patients in several centers is not immediately apparent. Consequently, the Registry for Quality Assessment with Ultrasound Imaging and Transit-Time Flow Measurement in Cardiac Bypass Surgery (REQUEST) study aims to determine the number and type of surgical procedure changes that are made based on intraoperative guidance information using the combination of TTFM and HFUS.

METHODS

Study Design

The REQUEST study is an international, multicenter, prospective registry that enrolled 1046 patients in 7 centers routinely performing CABG in Europe (n = 4) and North America (n = 3) between April 2015 and December 2017. This registry was designed to capture information on any changes in the proposed surgical procedure based on TTFM and HFUS parameters performed with the MiraQ or VeriQ C devices (Medistim ASA, Oslo, Norway).

All patients enrolled in the REQUEST study signed written informed consent before the surgical procedure. Each participating site received approval from their institutional review board or ethics committee before screening or enrollment of eligible patients.

The REQUEST study was funded by Medistim ASA (Oslo, Norway). The principal investigators and authors had complete scientific freedom.

The study is registered at ClinicalTrials.gov (**NCT02385344**).

Study Protocol

Participating surgeons and study coordinators at each site were trained to use and to interpret intraoperative TTFM and HFUS results according to a structured REQUEST study protocol. This protocol ensured that participating surgeons (n = 36) and personnel were trained in in the use of intraoperative TTFM and HFUS and possessed Good Clinical Practice certification. All participating surgeons had previous experience with using TTFM and HFUS and it was strongly recommended that surgeons had performed more than 20 cases with TTFM and HFUS before “participating in” the REQUEST study.

The recommended surgical steps for quality assessment included HFUS assessment of the ascending aorta to the presence or absence of any plaques (soft and hard) or vessel wall abnormalities (eg, atheromatous ulcers and dissection) to establish the safest sites for cannulation, crossclamping, and side-biting for the proximal anastomosis; HFUS assessment of in situ conduits; HFUS assessment of target coronary vessels; and checking the conduit flow with TTFM and the anatomy of the constructed anastomosis with HFUS.

During intraoperative quality assessment, a steady mean arterial pressure of 80 mm Hg was recommended and the HFUS probe frequency was set at 15 MHz. Furthermore, the REQUEST protocol advised, to standardize and optimize TTFM assessment, that the acoustic coupling index should be green or yellow (indicating the accuracy of ultrasound conductivity); the mean flow, indicated by the red line, should be steady and horizontal; the pulsatility index should be <5; the diastolic filling percent should be >70% for left-sided and >50% for right-sided coronary vessels.

It was at the discretion of the operating surgeon if and when a graft should be revised. If a graft was revised, it was recommended to reassess the conduit flow with TTFM and the anatomy of the reconstructed anastomosis with HFUS.

Although adherence to the study protocol was highly recommended it was not mandatory.

Patient Population

Patients diagnosed with multivessel coronary artery disease and scheduled for isolated CABG were eligible to be included. Patients were excluded from enrolment when undergoing emergency surgery, when concomitant surgical procedures were planned (eg, valve repair or replacement or rhythm surgery), when the medical history included the presence of a muscle disorder (eg, myopathy, myalgia, or myasthenia), or when the patient was known to be experiencing any psychological, developmental, or emotional disorder.

End Points

The primary end point was the overall frequency of any change in the planned surgical procedure as a consequence of TTFM, HFUS, and/or manual/visual assessment. Major secondary end points consisted of the rate and reason for any surgical change (eg, changes related to HFUS findings in the aorta, coronary targets, or in-situ conduits; and changes to completed grafts and/or anastomotic revision as a result of TTFM, HFUS, and/or manual/visual assessment). Additional end points consisted

of the in-hospital rate of major adverse cardiac and cerebrovascular events (MACCE) defined as the composite of all-cause death, stroke or transient ischemic attack (TIA), myocardial infarction (MI), or repeat revascularisation as well as the rates of the individual MACCE components and new hemodialysis and surgical exploration due to bleeding.

Definitions

A surgical change was defined by any change that was made intraoperatively by the operating surgeon based on TTFM, HFUS, and/or manual/visual assessment. Surgical changes related to the aorta due to the presence of calcification, plaques (soft or hard), and/or vessel wall abnormalities (ie, dissection) were divided into 3 groups: change in the proposed location of the cannulation site, the crossclamp site, and the site(s) for the proximal anastomosis (in a few cases this actually led to conversion of a planned on-pump procedure to an off-pump procedure with or without a no-touch aortic technique). Surgical changes associated with a coronary target were defined as changing the initially proposed location of the anastomosis due to severe calcification or plaque not identified by palpation (ie, usually on the posterior wall) or the detection of an intramural coronary artery that could not otherwise be found by visual assessment or manual palpation. Detailed definitions of surgical changes related to grafts and/or constructed anastomoses are shown in Table 1, along with relevant examples. In brief, surgical changes were categorized as a primary anastomotic revision, a secondary anastomotic revision, primary conduit revision, or an additional graft was used. Adding an extra suture for visual anastomotic bleeding was not classified as a surgical change. Any individual patient could have ≥1 surgical change(s).

Stroke was defined as a sudden onset of focal neurological deficit of central origin that persisted for more than 24 hours with or without verification of the event on neuroimaging. TIA was defined as transient focal neurological signs or symptoms that lasted fewer than 24 hours.[11] The diagnosis of perioperative MI was made based on clinical symptoms and additional cardiac biomarkers with or without abnormal electrocardiogram. New hemodialysis was defined as initiating renal replacement therapy in a patient with no prior history of renal replacement therapy, irrespective of the presence or absence of renal insufficiency at baseline. All clinical events were adjudicated by an otherwise blinded independent adjudicator. If consensus could not be reached, a second blinded adjudicator was consulted.

Statistical Analyses

Results are reported according to descriptive statistical methods. Categorical data are presented as proportions. Continuous data are reported as mean ± standard

deviation unless otherwise noted. Normality assumptions of the estimated proportions are based on a binomial distribution, funded on the central limit theorem

Table 1. Detailed definitions of surgical changes related to grafts with examples of surgical scenarios

Surgical changes	Definition	Surgical examples
Primary anastomotic revision	Revision of the proximal or distal anastomosis due to a primary technical problem with the anastomosis itself and not due to a problem with the conduit	i. Twisted anastomosis ii. Removal of a stitch iii. Redo of an anastomosis due to leaking, plaque, tapering, bulging, a flap or narrowing iv. Change from proximal anastomosis on the aorta to a Y- or T-graft configuration v. No other reason than poor flow
Secondary anastomotic revision	Revision of the proximal or distal anastomosis as a consequence of needing to redo graft, but not due to a problem with the anastomosis	i. Kinked graft ii. Inadequate length of the graft after the anastomosis was completed (graft is shortened, ITA is used as free graft, graft extended with additional graft) iii. Dissected graft after the anastomosis was completed iv. Change in graft configuration v. Poor distal coronary bed
Primary conduit revision	Revision of the conduit without requiring revision of the proximal or distal anastomosis	i. Obstruction removed before completion of the anastomosis (fibrin sealant removed) ii. Inadequate conduit length before the anastomosis was made iii. Conduit extension based on visual assessment before completion of the anastomosis iv. Surgical clip is removed
Additional graft(s)	Need for an additional graft due to a problem with the original anastomosis/conduit	Persistent inadequate surgical results, despite primary anastomotic revision, a secondary anastomotic revision, or primary graft revision

Detailed definitions of surgical changes used in the Registry for Quality Assessment study to classify surgical changes related to either the grafts or completed anastomoses. Illustrative surgical examples are provided to ensure better understanding of a situation during a coronary artery bypass procedure where a surgeon would use high frequency ultrasound or transit-time flow measurement to optimize patient and surgical outcomes. *ITA*, Internal thoracic artery.

and tested with the Kolmogorov-Smirnov test. Analyses were performed using SPSS software, version 24 (IBM-SPSS Inc, Armonk, NY).

RESULTS

Baseline Characteristics

The REQUEST study enrolled 1046 patients between April 2015 and December 2017. Of those, 30 patients were excluded due to screening failure (n = 8), members of the surgical team were not trained according to the REQUEST study protocol (n = 11), or

Table 2. Baseline characteristics of participants in the Registry for Quality Assessment with Ultrasound Imaging and Transit-Time Flow Measurement in Cardiac Bypass Surgery study

Characteristic	Result
Age (y)	65.9 ± 9.5 y
≥70	37.3 (379/1016)
Female sex	14.0 (143/1016)
Body mass index, median (range)	28.1 (19-45) (1011/1015)
Diabetes mellitus	39.6 (402/1016)
Insulin treated	17.4 (177/1016)
History of stroke	6.1 (62/1016)
History of myocardial infarction	32.6 (331/1016)
History of revascularisation	23.4 (238/1016)
CABG	0.3 (3/1016)
PCI	23.1 (235/1016)
History of intervention for peripheral vascular disease	4.5 (46/1016)
Carotid	2.6 (26/1016)
Peripheral	1.7 (17/1016)
LVEF (%), median (range)	51 (17-82) (978/1016)
<30	2.5 (24/978)
NYHA class	
I	37.3 (349/935)
II	42.4 (396/935)
III	17.0 (159/935)
IV	3.3 (31/935)
CCS angina classification	
I-II	46.2 (449/972)
III-IV	41.5 (403/972)
Unstable angina	30.7 (312/1016)
Left main involvement	54.8 (437/797)

Values are presented as mean ± standard deviation, median (range), or % (n/N). *CABG* , Coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *CCS*, Canadian Cardiovascular Society.

TTFM or HFUS images were unavailable for analysis (n = 11). The final analysis was performed on 1016 patients.

The mean age was 65.9 years and 14.0% (143 out of 1016) were women (Table 2). Diabetes mellitus was present in 39.6% of patients (402 out of 1016). A history of previous MI was recorded in 32.6% of patients (331 out of 1016) and 6.1% of patients (62 out of 1016) had a history of previous stroke. Multivessel disease was present in 981 patients (96.6%) and 35 patients (3.4%) had single vessel disease, which was a

Table 3. Surgical characteristics of participants in the Registry for Quality Assessment with Ultrasound Imaging and Transit-Time Flow Measurement in Cardiac Bypass Surgery study

Surgical characteristic	Result
Procedure time* (min)	257 ± 87
Off-pump surgery	39.6 (402/1016)
LITA use	97.5 (991/1016)
BITA use	30.5 (310/1016)
Radial artery use	22.6 (230/1016)
Multiarterial	43.2 (439/1016)
Complete arterial	26.1 (265/1016)
Yor T configuration–per graft	14.9 (398/2675)
Sequential grafts–per graft	8.2 (219/2675)
No. of conduits	
All	2675 (1015)
Per patient	2.6 ± 0.8 (1015)
Arterial-per conduit	58.3 (1559/2675)
Venous-per conduit	41.3 (1105/2675)
Arteriovenous †–per conduit	0.4 (11/2675)
No. of distal anastomoses	
All	2959 (1015)
Per patient	2.9 ± 1.0 (1015)
Arterial–per patient	1.7 ± 1.9 (1015)
Venous–per patient	1.2 ± 1.0 (1015)

Values are presented as mean ± standard deviation, median (range), or % (n/N). *LITA*, Left internal thoracic artery; *BITA*, bilateral internal thoracic arteries. *First incision to gloves off. †In cases where the arterial graft was too short to reach the coronary target, a venous graft was added.

protocol violation.

Surgical Characteristics

The mean procedure time was 257 minutes (Table 3). Off-pump surgery was performed in 39.6% of cases (402 out of 1016). The mean number of conduits used per

patient was 2.6 with a mean of 2.9 distal anastomoses per patient. Bilateral internal thoracic arteries were used in 30.5% (310 out of 1016), and 14.9% of grafts (398 out of 2675) were used in a Y or T configuration. Multiple arterial grafts were used in 43.2% of patients (439 out of 1016), with complete arterial revascularisation being performed in 26.1% of cases (265 out of 1016).

Intraoperative quality assessment was performed in all 1016 patients. HFUS was used to assess the ascending aorta in 79.3% (806 out of 1016), the in situ conduits in 65.1% (661 out of 1016), the coronary targets in 47.5% (483 out of 1016) and completed grafts in 59.3% (602 out of 1016). Moreover, patients who underwent off-pump surgery more frequently underwent HFUS of the ascending aorta (88.3%; 355 out of 402) compared with patients who underwent on-pump surgery (73.5%;451 out of 614). TTFM on grafts, with completed anastomoses, was performed in 99.2% (1008 out of 1016).

Primary and Secondary End Points: Surgical Changes

The primary end point of any surgical change was met in 25.2% of patients (256 out of 1016) (Table 4). In 77.0% (197 out of 256) this was the result of abnormal TTFM and/or HFUS findings, where on initial visual inspection there had been no suspicion of a diseased aorta, in situ conduit, coronary target, and/or completed graft. In 12.5% (32 out of 256) this was due to visual and/or manual assessment; for example, due to an obviously diseased aorta or a completed graft appeared unsatisfactory to the surgeon (eg, kinked or twisted graft). In 10.5% of patients (27 out of 256) it was undefined.

Surgical changes related to the aorta were made in 9.9% of patients (80 out of 806), and in 74 patients (92.5%) this was based on abnormal HFUS findings. This included changes related to the proposed locations of the cannulation site (2.9%; 23 out of 806), the crossclamp site (2.2%;18 out of 806), and the site for the proximal anastomosis (6.8%; 55 out of 806). HFUS detected the presence of soft plaques in the aorta in 9.1% of patients (73 out of 806) and calcification in 1.1% of patients (9 out of 806). The surgical strategy was changed from an on-pump to off-pump procedure in 0.2% of patients (2 out of 1016) due to plaques at the proposed cannulation or crossclamp site, and in 0.5% (5 out of 1016) proximal aortic anastomoses were avoided and patients received bilateral internal thoracic artery grafts or left internal thoracic artery-radial T-graft. On the contrary, the proposed procedure was changed from off-pump to on-pump in 0.7% (7 out of 1016) due to the extent of coronary artery disease and the concern that manipulation of the beating heart would cause

Table 4. Surgical changes in participants in the Registry for Quality Assessment with Ultrasound Imaging and Transit-Time Flow Measurement in Cardiac Bypass Surgery study

Surgical change	Result
Any surgical change	
All changes in overall cohort	25.2 (256/1016)
No. changes per patient (range)	1 (0-6)
Change as a result of TTFM and/or HFUS	77.0 (197/256)
Change as a result of visual/manual assessment	12.5 (32/256)
Undefined	10.5 (27/256)
Changes related to the aorta	
All changes	9.9 (80/806)
As a result of HFUS	92.5 (74/80)
As a result of visual/manual assessment	5.0 (4/80)
Undefined	2.5 (2/80)
Cannulation site	2.9 (23/806)
Crossclamp site	2.2 (18/806)
Proximal anastomosis site	6.8 (55/806)
Changes related to in situ conduits	
All changes	2.7 (18/661)
As a result of TTFM and/or HFUS	55.6 (10/18)
As a result of visual/manual assessment	33.3 (6/18)
Undefined	11.1 (2/18)
Dissection	0.6 (4/661)
Insufficient caliber	0.8 (5/661)
Changes related to coronary target	
All changes	22.4 (108/483)
As a result of HFUS	67.6 (73/108)
As a result of visual/manual assessment	9.3 (10/108)
Undefined	25.0 (27/108)
Diseased/calcified	10.6 (51/483)
Detection of intramural vessel	3.7 (18/483)
Insufficient caliber	3.1 (15/483)
Endarterectomies	1.2 (6/483)
Changes related to grafts	
All changes	7.8 (79/1016)
As a result of TTFM and/or HFUS	64.5 (51/79)
As a result of visual/manual assessment	34.2 (27/79)
Undefined	7.6 (6/79)
Primary anastomotic revisions	4.1 (42/1016)
Secondary anastomotic revisions	2.8 (28/1016)
Primary and secondary anastomotic revisions combined	6.6 (67/1016)
Primary graft revision	1.5 (15/1016)
Additional graft(s)	0.5 (5/1016)

One individual patient could have ≥ 1 surgical change or could have a surgical change as a result of both TTFM and HFUS with manual/visual assessment. Values are shown as mean ± standard deviation, median (range), or % (n/N). *TTFM,* Transit-time flow measurement; HFUS, high frequency ultrasound.

hemodynamic instability. Among 80 patients with a surgical change related to the aorta, 59 underwent off-pump surgery (73.8%).

Surgical changes related to in situ conduits occurred in 2.7% of patients (18 out of 661), and in 10 patients (55.6%) this was based on abnormal HFUS and/or TTFM findings. In 0.6% (4 out of 661) this was due to dissection of the conduit and 0.8% (5 out of 661) of patients had conduits of insufficient caliber. In 1.4% (9 out of 661) the reason was unspecified.

In 22.4% (108 out of 483), a surgical change was made related to the proposed coronary target, and in 73 patients (67.6%) this was the result of abnormal HFUS findings. This was due to a heavily diseased (ie, calcified) target in 10.6% of patients (51 out of 483), an intramural located coronary vessel in 3.7% (18 out of 483) and an insufficient caliber of the coronary target in 3.1% of patients (15 out of 483). Endarterectomies were performed in 1.2% of patients (6 out of 483). In 5.2% (25 out of 483) the reason for a surgical change related to the coronary target was unspecified.

Surgical changes related to grafts were performed in 7.8% of patients (79 out of 1016), including revisions to the proximal and/or distal anastomosis in 6.6% (67 out of 1016). In 4.1% of patients (42 out of 1016) this was based on a primary anastomotic revision. Surgical changes related to secondary anastomotic revisions occurred in 2.8% (28 out of 1016). In 64.5% of patients (51 out of 79) a surgical change related to a completed graft was the result of solely abnormal TTFM and/or HFUS findings (without visual and/or manual assessment), and of those 98.0% (50 out of 51) underwent repeat TTFM measurement after graft revision. In 90.0% (45 out of 50) the graft flow improved after graft revision.

Primary conduit revisions occurred in 1.5% (15 out of 1016) and in 0.5% of patients (5 out of 1016) an additional graft was needed. This resulted in any surgical revision for 3.4% of the anastomoses (100 out of 2959) Table E1.

In-Hospital Clinical Outcomes

The rate of in-hospital MACCE was 2.0% (20 out of 1016) (Figure 1). In-hospital mortality was 0.6% (6 out of 1016). A stroke or TIA occurred in 1.0% (10 out of 1016) and the rate of perioperative MI was 0.3% (3 out of 1016). One patient (0.1%) underwent repeat revascularisation by percutaneous coronary intervention. New hemodialysis occurred in 0.3% (3 out of 1016) and 0.2% (2 out of 1016) underwent surgical reexploration due to bleeding.

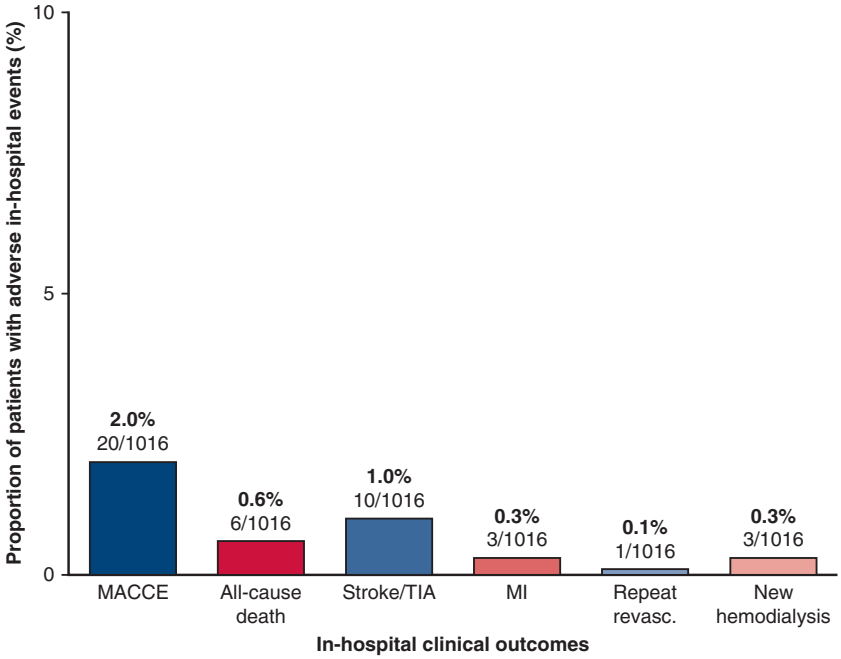


Figure 1. In-hospital clinical outcomes in the Registry for Quality Assessment with Ultrasound Imaging and Transit-Time Flow Measurement in Cardiac Bypass Surgery study. Proportion (%) of-patients with in-hospital major adverse events (clinical events/number of observations). *MACCE*, Major adverse cardiac and cerebrovascular event; *TIA*, transient ischemic attack; *MI*, myocardial infarction.

DISCUSSION

The REQUEST study is the first prospective, multicenter study that assessed the effects of routine use of TTFM with HFUS according to a prespecified protocol in patients with multivessel coronary artery disease undergoing CABG. As evidenced by the high proportion of off-pump operations and high use of multiple arterial grafts these procedures were performed by experienced CABG surgeons from 7 well-established institutions in Europe and North America. Overall, any surgical change to the initially proposed surgical strategy was made in 25.2% of patients, and in 77.0% this was solely based on otherwise unsuspected abnormal TTFM and/or HFUS findings. The present study showed that surgical changes related to the proposed site of aortic manipulation were made in 9.9% of patients and revisions to a completed graft in 7.8% of patients. Low rates of major adverse in-hospital events, and in particular mortality (0.6%), indicate that intraoperative quality assessment of the aorta, the conduits, the coronary targets and completed grafts was safe (Figure 2).

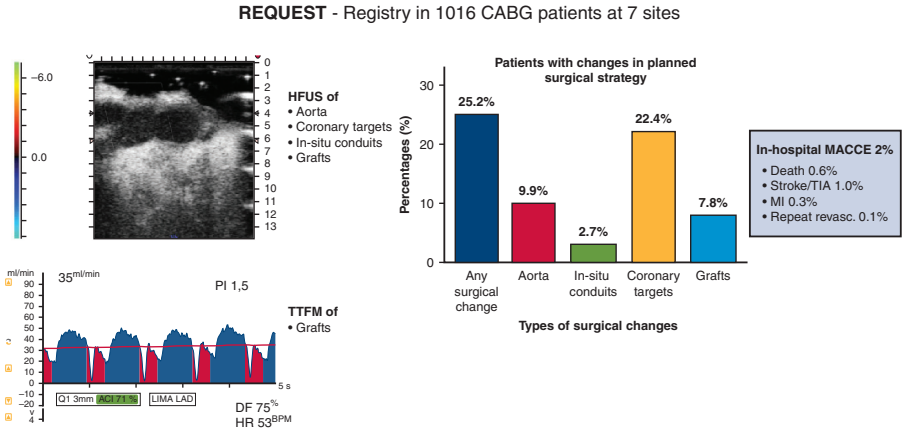


Figure 2. Changes to the planned surgical strategy were made in 25.2% of cases with few complications. *CABG*, Coronary artery by pass grafting; *HFUS*, High-frequency ultrasound; *TTFM*, transit-time flow measurement; *MACCE*, major adverse cardiac and cerebrovascular event; *TIA*, transient ischemic attack; *MI*, myocardial infarction.

Although intraoperative quality assessment of the aorta and grafts are both recommended by the 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularisation[10] potential limitations of the TTFM technique, including uncertainty over its diagnostic accuracy, have been discussed.[12] Furthermore, in the absence of clinical follow-up data, no clear consensus on the routine applicability of TTFM alone has been reached. Indeed, numerous single-center retrospective studies reported on the impact of adopting intraoperative quality assessment with TTFM, but this resulted in a substantial heterogeneity in definitions and outcomes. The overall proportion of revised grafts in relation to the number of patients studied ranged from 3.3% to 5.7% when TTFM alone was used.[8] In the REQUEST study, surgical changes related to grafts occurred in 7.8% of patients. An important initiative in the REQUEST study was the routine use of HFUS in combination with TTFM during CABG. Di Giammarco and colleagues**[9]** reported that the diagnostic accuracy of the combined use of TTFM and HFUS, reflected by the ability to detect a truly patent versus a truly failing graft (ie, positive predictive value vs negative predictive value), rose to 100% with this approach. The combination of TTFM with HFUS is therefore a potentially precise diagnostic tool for intraoperative quality assessment.

An additional important aspect of REQUEST is its contrast to previous retrospective studies reporting outcomes of intraoperative quality assessment that did not take into account the extent of surgeons' experience in using, interpreting and acting upon TTFM and HFUS findings. To address this specific issue, the REQUEST study

was conducted in centers where the participating surgical team was trained according to the structured REQUEST protocol thereby minimizing bias in interoperator experience and interpretation of TTFM and HFUS findings.

To further enhance patient outcomes and optimize graft patency, intraoperative quality assessment of the surgical conduits and coronary targets was also performed in the REQUEST study. Changes made related to the conduits themselves were uncommon (2.7%). Detection of an otherwise unrecognized dissected internal thoracic artery in some cases is likely to have prevented potential perioperative complications. In 10.6% of patients, a surgical change related to a heavily diseased and/or calcified coronary target was made. This may result in avoiding unnecessarily difficult anastomoses and/or endarterectomy. In only 1.2% of cases, an endarterectomy was performed, compared with the 4% endarterectomy rate in the Drug-Eluting Stent versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries study,[13] and this could possibly be attributed to the use of epicardial HFUS to detect and avoid unsuitable targets for an anastomoses (typically a heavily diseased posterior wall). However, in patients with extensive coronary artery disease endarterectomy has shown to be an acceptable strategy to maximize completeness of revascularisation during CABG.[14], [15]

Because stroke is among the most devastating complications of CABG, avoiding any aortic manipulation is an important technique to reduce the rate of stroke.[16]-[18] Previous studies report that during application and removal of the aortic crossclamp, particulate emboli are frequently detected.[19]-[21] Aortic manipulation is often required for on-pump or off-pump surgery where a proximal anastomosis is made, although more than half of patients undergoing CABG have atherosclerosis in the ascending aorta with its inherent risk of embolism to the cerebral arteries.[22] In the REQUEST study, off-pump CABG procedures were performed in 39.6%. Despite the high rate of off-pump surgery, surgical changes related to the aorta were made in 9.9% of all patients to choose a safe place to cannulate, crossclamp, and/or construct the proximal anastomosis.
In the REQUEST study, although there was a very high use of TTFM (99%) the use of HFUS was lower than expected. Although surgeons were advised to follow the REQUEST study protocol it was not deemed mandatory. The discrepancy in actual HFUS use most likely reflects real-world clinical decision making during coronary bypass surgery based on surgeon experience, preference, and discretion. For example, some situations in which some surgeons may decide that HFUS is not necessary might include:

- A proposed anastomotic site that looks and feels (eg, soft spot) completely normal,
- A conduit that looks completely normal after harvest, and
- A graft with excellent flow (eg, >50 mL/min with low pulsatility index) as indicated by TTFM.

Moreover, HFUS of the ascending was more frequently performed during off-pump surgery (88%; 355 out of 402) compared with on-pump surgery (73%; 451 out of 614). Additionally, patients with a surgical change related to the aorta (n = 80) were more often patients who underwent off-pump surgery (74%; n = 59) compared with on-pump surgery (26%; n = 21). The surgical changes to the aorta in the off-pump cohort were mainly related to determining the optimal (ie, disease free) location for the proximal anastomosis to diminish the detrimental effects of aortic manipulation in patients with an increased atherosclerotic burden.

Finally, while HFUS is relatively easy to use for grafts to the anterior wall, it is technically more challenging to use and to interpret for grafts on the lateral and inferior wall, especially in off-pump procedures. Therefore, the actual result of HFUS on surgical decision making and clinical outcomes might have been even greater if it had been used in all patients. However, compared with other contemporary studies there was no significant reduction in cerebrovascular events (eg, 1.0% stroke/TIA in the current study), which could have been the result of the high rate of patients with severe atherosclerotic disease (eg, diabetes was present in almost 40%) and the fact that epiaortic scanning was performed in 79% of patients.

LIMITATIONS

Although REQUEST is currently the largest prospective study to evaluate the influence of routine intraoperative quality assessment in contemporary CABG, its most obvious limitation is that it was not a randomized trial and therefore did not compare CABG with versus without use of TTFM and HFUS. The reality is that the design of such a randomized controlled trial would need an extraordinarily large patient sample size (eg, to demonstrate a reduction in operative mortality from 1%-0.5%) and extensive long-term follow-up to assess the influence of improved long-term graft patency. Furthermore, interpretation of such a trial would be complicated by a myriad of other factors that influence short- and long-term outcomes of CABG.

The focus of the REQUEST study was to prospectively evaluate the impact of TTFM with HFUS on patients who underwent CABG procedure, when performed routinely by experienced CABG surgeons. Although, as explained above, conducting an randomized controlled trial would be extremely challenging for several reasons. A further limitation is that no conclusions can be drawn on the influence of intraoperative quality assessment on long-term outcomes because clinical results were limited to in-hospital outcomes. Similarly, in the absence of long-term angiographic follow-up, no inference can be drawn on whether routine graft assessment actually improves long-term graft patency. Finally, use of TTFM and HFUS technology requires dedicated training to use the technology appropriately and to both correctly interpret data and avoid the pitfalls of misinterpretation.

CONCLUSIONS

The REQUEST study is a multicenter, prospective study designed to evaluate the effect of implementing intraoperative quality assessment by TTFM and HFUS in 1016 patients undergoing CABG. In 25.2% of patients, any change in the planned surgical strategy was made. Furthermore, rates of in-hospital mortality and major morbidity were low, showing the feasibility and safety of performing intraoperative quality assessment. To conclude, intraoperative quality assessment with TTFM and HFUS may improve the quality, safety, and efficacy of CABG procedures and should therefore be considered as a routine procedural aspect during CABG.

CONFLICT OF INTEREST STATEMENT

Dr Taggart has received research funding, speaking, and traveling honoraria from Medistim. Drs Thuijs, Trachiotis, Puskas, Wendt, Kieser, Kappetein, and Head received traveling support and/or speaking fees from Medistim. Drs Kappetein and Head are full-time employees of Medtronic outside the submitted work. All other authors have nothing to disclose with regard to commercial support.

The authors thank the study coordinators at the 7 participating study sites. Finally, the authors thank Professor Vipin Zamvar and Yasir Abu-Omar for independently adjudicating the serious adverse events in the REQUEST study.

Abbreviations and Acronyms

CABG =	coronary artery bypass grafting
HFUS =	high frequency ultrasound
MACCE =	major adverse cardiac and cerebrovascular event
MI =	myocardial infarction
REQUEST =	Registry for Quality Assessment with Ultrasound Imaging and Transit-Time Flow Measurement in Cardiac Bypass Surgery
TIA =	transient ischemic attack
TTFM =	transit-time flow measurements

REFERENCES

1. Head SJ, Kieser TM, Falk V, Huysmans HA, Kappetein AP. Coronary artery bypass grafting: part 1—the evolution over the first 50 years. Eur Heart J. 2013;34:2862-72.
2. Head SJ, Borgermann J, Osnabrugge RL, Kieser TM, Falk V, Taggart DP, et al. Coronary artery bypass grafting: part 2—optimizing outcomes and future prospects. Eur Heart J. 2013;34:2873-86.
3. Gaudino M, Antoniades C, Benedetto U, Deb S, Di Franco A, Di Giammarco G, et al. Mechanisms, consequences, and prevention of coronary graft failure. Circulation. 2017;136:1749-64.
4. Thielmann M, Massoudy P, JaegerBR, Neuhäuser M, Marggraf G, Sack S, etal. Emergency re-revascularization with percutaneous coronary intervention, reoperation, or conservative treatment in patients with acute perioperative graft failure following coronary artery bypass surgery. Eur J Cardiothorac Surg. 2006;30:117-25.
5. Dacey LJ, Likosky DS, Leavitt BJ, Lahey SJ, Quinn RD, Hernandez F Jr, et al. Perioperative stroke and long-term survival after coronary bypass graft surgery. Ann Thorac Surg. 2005;79:532-6.
6. Kowalewski M, Pawliszak W, Malvindi PG, Bokszanski MP, Perlinski D, Raffa GM, et al. Off-pump coronary artery bypass grafting improves short-term outcomes in high-risk patients compared with on-pump coronary artery bypass grafting: meta-analysis. J Thorac Cardiovasc Surg. 2016;151: 60-77.
7. Gaudino M, Bakaeen F, Davierwala P, Di Franco A, Fremes SE, Patel N, et al. New strategies for surgical myocardial revascularization. Circulation. 2018; 138:2160-8.
8. Thuijs DJFM, Bekker MWA, Taggart DP, Kappetein AP, Kieser TM, Wendt D, et al. Improving coronary artery bypass grafting: a systematic review and meta-analysis on the impact of adopting transit-time flow measurement. Eur J Cardiothorac Surg. 2019;56:654-63.
9. Di Giammarco G, Canosa C, Foschi M, Rabozzi R, Marinelli D, Masuyama S, et al. Intraoperative graft verification in coronary surgery: increased diagnostic accuracy adding high-resolution epicardial ultrasonography to transit-time flow measurement. Eur J Cardiothorac Surg. 2014;45:e41–5.
10. Sousa-Uva M, Neumann F-J, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur J Cardiothorac Surg. 2019;55:4-90.
11. Lansky AJ, Messe SR, Brickman AM, Dwyer M, Bart van der Worp H, Lazar RM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an Academic Research Consortium initiative. J Am Coll Cardiol. 2017;69:679-91.
12. Niclauss L. Techniques and standards in intraoperative graft verification by transit time flow measurement after coronary artery bypass graft surgery: a critical review. Eur J Cardiothorac Surg. 2017;51:26-33.
13. Head SJ, Parasca CA, Mack MJ, Mohr FW, Morice MC, Holmes DR Jr, et al. Differences in baseline characteristics, practice patterns and clinical outcomes in contemporary coronary artery bypass grafting in the United States and Europe: insights from the SYNTAX randomized trial and registry. Eur J Cardiothorac Surg. 2015;47:685-95.
14. LaPar DJ, Anvari F, Irvine JN Jr, Kern JA, Swenson BR, Kron IL, Ailawadi G. The impact of coronary artery endarterectomy on outcomes during coronary artery bypass grafting. J Card Surg. 2011;26:247-53.

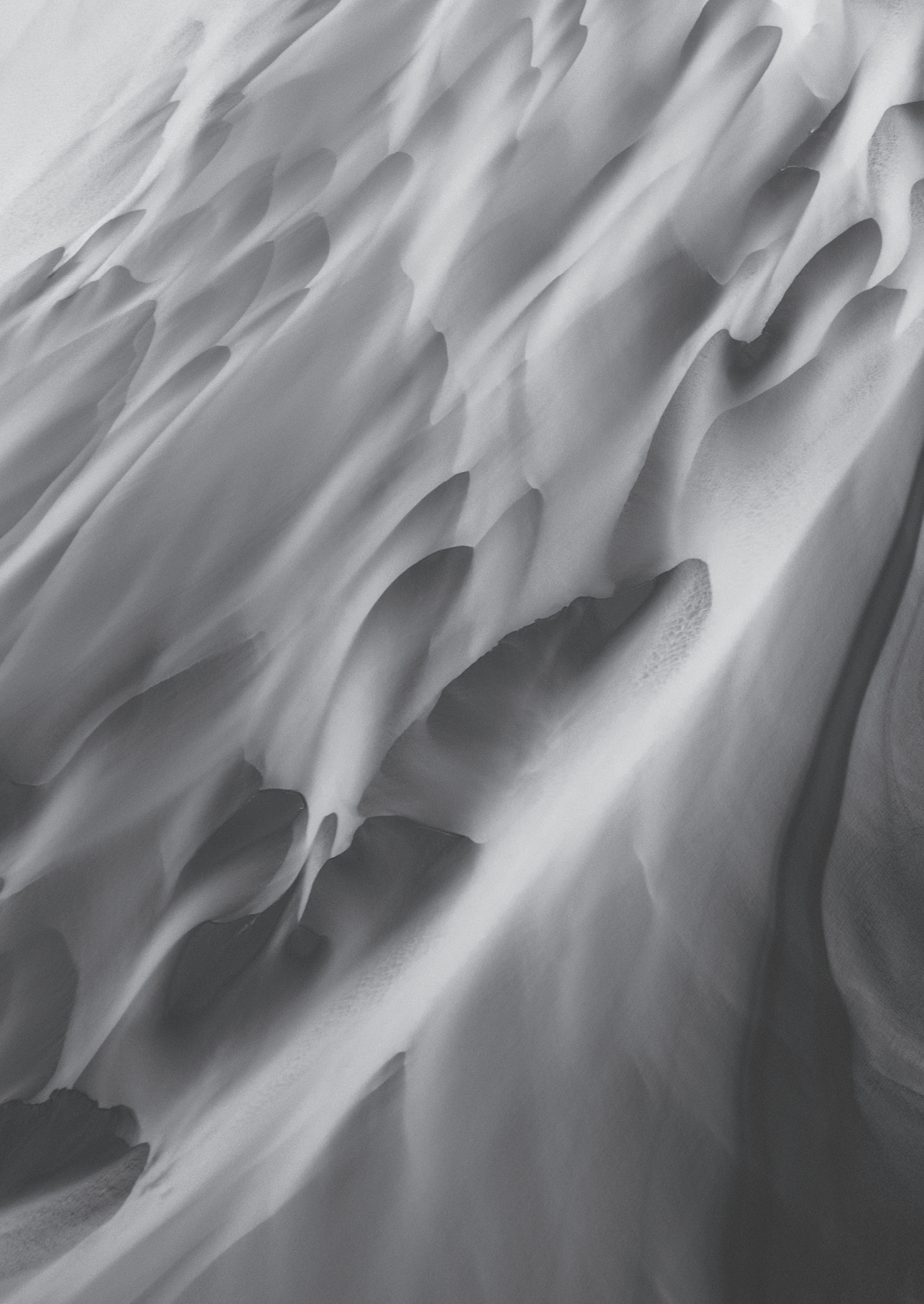
15. Garcia S, Sandoval Y, Roukoz H, Adabag S, Canoniero M, Yannopoulos D, et al. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. J Am Coll Cardiol. 2013; 62:1421-31.
16. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, et al. Stroke rates following surgical versus percutaneous coronary revascularization. J Am Coll Cardiol. 2018;72:386-98.
17. Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T, et al. Economic burden of stroke: a systematic review on post-stroke care. Eur J Health Econ. 2019;20:107-34.
18. Zhao DF, Edelman JJ, Seco M, Bannon PG, Wilson MK, Byrom MJ, et al. Coronary artery bypass grafting with and without manipulation of the ascending aorta: a network meta-analysis. J Am Coll Cardiol. 2017;69: 924-36.
19. Banbury MK, Kouchoukos NT, Allen KB, Slaughter MS, Weissman NJ, Berry GJ, et al. Emboli capture using the Embol-X intraaortic filter in cardiac surgery: a multicentered randomized trial of 1,289 patients. Ann Thorac Surg. 2003;76:508-15.
20. Christenson JT, Vala DL, Licker M, Sierra J, Kalangos A. Intra-aortic filtration: capturing particulate emboli during aortic cross-clamping. Tex Heart Inst J. 2005;32:515-21.
21. Gerriets T, Schwarz N, SammerG, BaehrJ, StolzE, Kaps M, etal. Protecting the brain from gaseous and solid micro-emboli during coronary artery bypass grafting: a randomized controlled trial. Eur Heart J. 2010;31:360-8.
22. Suvarna S, Smith A, Stygall J, Kolvecar S, Walesby R, Harrison M, et al. An intraoperative assessment of the ascending aorta: a comparison of digital palpation, transesophageal echocardiography, and epiaortic ultrasonography. J Cardiothorac Vasc Anesth. 2007;21:805-9.

SUPPLEMENTARY MATERIAL

TABLE E1. Proportion of surgical changes related to grafts, per distal anastomosis, as a result of abnormal transit-time flow measurement (TTFM) and/or high-frequency ultrasound (HFUS) findings in the Registry for Quality Assessment with Ultrasound Imaging and Transit-Time Flow Measurement in Cardiac Bypass Surgery study

Surgical change	Result
Changes related to grafts	
All changes	3.4 (100/2959)
Primary anastomotic revisions	1.6 (48/2959)
Secondary anastomotic revisions	1.0 (31/2959)
Primary graft revision	0.5 (16/2959)
Additional graft(s)	0.2 (5/2959)

Values are presented as % (n/N).



Chapter 13

Thesis summary - English
Thesis samenvatting - Nederlands

Chapter 1 is a general introduction to the subject of matter of this thesis. It described the history of surgical and percutaneous myocardial revascularisation strategies and elaborated on the advancements made in medical, surgical and stenting treatment strategies. Chapter 1 furthermore defined the aims and outline of current thesis.

Chapter 2 focused on the short-term outcomes (30-day follow-up) after CABG or PCI with second-generation everolimus-eluting stents in patients with left main coronary artery disease (LMCAD) from the randomized EXCEL trial. The study described the predictive performance of Society of Thoracic Surgeons (STS) risk models for perioperative mortality, stroke and renal failure for their discriminative ability (according to the C statistic) and calibration (Hosmer-Lemeshow goodness of fit test) among patients with LMCAD that underwent PCI with drug-eluting stents or CABG. Among the selected patients with LMCAD, the STS risk models showed to possess good discrimination for 30-day predicted risk of mortality (PROM) and renal failure for CABG, however lacked accurate predictive ability for PCI. The predictive ability for stroke was reasonably well for both PCI and CABG.

The mid-term outcomes (1 – 3 year) after myocardial revascularisation by PCI or CABG, in patients LMCAD were evaluated in **chapter 3** and **4**. **Chapter 3** investigated the impact of left ventricular ejection fraction (LVEF) on clinical outcomes in patients with LMCAD that underwent CABG or PCI in the EXCEL trial. LVEF was classified according to the definitions of the European Society of Cardiology (LVEF<40%; Heart Failure with reduced Ejection Fraction (HFrEF), LVEF 40-49%; Heart Failure with mid-range Ejection Fraction (HFmrEF) and LVEF>50%; preserved ejection fraction). Overall, patients with HFrEF compared to those with HFmrEF or preserved LVEF experienced an increased risk of all-cause death, stroke or MI, driven by an increased rate of all-cause death at 3-year follow-up. No significant differences in outcomes were identified after PCI and CABG among patients with HFrEF, HFmrEF and preserved LVEF. In **chapter 4** the influence of CABG using single versus bilateral internal thoracic arteries (SITA versus BITA) in patients from the EXCEL trial with LMCAD was determined. No significant differences in short-term (30 day) adverse event rates were identified, including an absence of difference in sternal wound complications between the SITA cohort (2.2%) and BITA cohort (1.8%). At 3 year follow-up, no clinical differences related to death, stroke or myocardial infarction were identified between CABG using SITA versus BITA in patients with LMCAD from the EXCEL trial.

The study in **Chapter 5** set out to review the plethora of published meta-analyses reporting on clinical outcomes after left main revascularisation with PCI versus

CABG. Over the recent decade, fifty-one meta-analyses reporting on the optimal revascularisation strategy in left main disease have been published. Of those, 33 were published in the recent period after the EXCEL and NOBLE publications. Outcomes varied among meta-analyses, related to a (i) randomized versus observational design, or a combination of both, (ii) the methodology and effect-measures used to report treatment-differences, (iii) a variation of sample sizes used, and (iv) the year in which the meta-analysis was published. The study concluded that the number of meta-analyses on PCI versus CABG in patients with LMCAD is disproportionate and urges the need for "quality over quantity". In order to ensure future high-quality publications, multi-disciplinary collaborations are warranted and individual patient data pooled analyses may determine true treatment-differences with more statistical certainty.

Chapter 6 to **chapter 10** described the long-term outcomes, up to 10 years and beyond, after PCI with first-generation paclitaxel-eluting stents versus CABG in patients with *de novo* three-vessel (3VD) and/or LMCAD that were originally randomized in the SYNTAX trial. In **chapter 6** 10-year survival data of the randomized cohort (N=1800; PCI n=903 and CABG n=897) was reported. The rate of completeness of follow-up was over 94%, which was equally distributed among the PCI and CABG cohorts. In the overall cohort (N=1800), no statically significant difference in all-cause death was found between PCI versus CABG at 10-year follow-up. Nonetheless, CABG provided a significant survival benefit over PCI in patients with 3VD and those with more complex CAD, defined by SYNTAX scores ≥33. While in patients with LMCAD, no difference in all-cause death at 10-year follow-up existed between PCI and CABG. **Chapter 7** aimed to determine the overall survival in patients that deemed unsuitable to be randomized for PCI or CABG in the SYNTAX trail and were followed-up in a PCI nested-registry (CABG-ineligible patients) and a CABG nested-registry (PCI-ineligible patients). Patients included in the CABG-registry were considered non-treatable by PCI due to extensive coronary complexity, the patients included in the PCI registry were considered as non-operable due to increased operative risk. Patients in the SYNTAX CABG-registry showed excellent 10-year survival (all-cause death 25.9%); comparable to all-cause death rates in the randomized CABG cohort. However, patients in the PCI-registry showed poor 10-year survival with an all-cause death rate of approximately 51.6%; almost twice as high as the all-cause death rates in the randomized PCI cohort. **Chapter 8**, estimated the impact of performing CABG using multiple arterials grafs (MAG) versus a single arterial graft (SAG) in patients that underwent CABG SYNTAX trial. MAG resulted in significantly lower all-cause death rates at 12.6-year follow-up (both unadjusted and adjusted rates), compared to a SAG CABG strategy. This striking long-term survival benefit of MAG over SAG

in the SYNTAX trial encourages a more extensive use of multiple arterial grafting in current daily practice. In **chapter 9**, the influence of complete versus incomplete revascularisation and the association with any residual coronary lesions (residual SYNTAX score; rSS), on all-cause death at 10-year follow-up was assessed. The study showed that incomplete revascularisation is common after PCI and the extent of incompleteness, defined by rSS, has a significant impact on 10-year all-cause death. Patients with a rSS ≤8 after PCI had a comparable risk of 10-year all-cause death compared with those after CABG, whereas patients with a rSS>8 after PCI experienced a substantially increased risk of 10-year all-cause death. Additionally, the predictive performance of the SYNTAX score II in accurately predicting the risk of all-cause death at 10-years was ascertained in **chapter 10**. The SYNTAX score II incorporates the presence or absence of LMCAD with the anatomical SYNTAX score and important baseline characteristics, such as: age, sex, creatinine clearance, LVEF, chronic obstructive pulmonary disease and peripheral vascular disease, in order to predict the risk of 4-year all-cause death. The study showed that the SYNTAX score II could discriminate for outcome risk beyond 4 years, although all-cause death was similar between PCI and CABG beyond 4-year follow-up.

Finally, in **chapter 11** and **chapter 12** the impact of performing intraoperative quality assessment by using transit-time flow measurement (TTFM) and/or high frequency ultrasound during coronary bypass surgery was appraised. The systematic review and meta-analysis in **chapter 11** evaluated the value of TTFM during CABG by determining (i) the rate of abnormal grafts and graft revisions required when using TTFM and (ii) the impact of TTFM parameters on angiographic and clinical outcomes. In 4.3% of patients undergoing CABG, there was a need to revise grafts after TTFM assessment; however, only 25% of grafts, classified as abnormal based on TTFM values, were revised, suggesting that the use and interpretation of TTFM can be further optimized. The outcomes of the international, multicentre prospective REQUEST study that aimed to determine the number and type of coronary surgical procedure changes that are made based on intraoperative guidance information using the combination of TTFM and HFUS were reported in **chapter 12**. In seven participating REQUEST centers that routinely perform bypass surgery, 25.2% of patients (256/1016) required a surgical change, which was accompanied by low in-hospital mortality and morbidity. Based on the results from the REQUEST study, TTFM and HFUS may improve the quality, safety and efficacy of coronary artery bypass grafting, and could therefore be considered as a routine intraoperative quality control measures during CABG.

Hoofdstuk 1 bevat de algemene introductie van het onderwerp van deze thesis. Het beschrijft de historie en ontstaansgeschiedenis van de coronaire bypass chirurgie (CABG) en de percutane coronaire interventies (PCI) ten behoeve van het revasculariseren van het myocard, waarbij aandacht voor besteed aan de medische, chirurgische en percutane mijlpalen en technologische vooruitgang die geboekt is over de recente decennia. Het doel en de onderzoeksvragen van de huidige thesis worden tevens benoemd in hoofdstuk 1.

Hoofdstuk 2 richt zich op de korte-termijn uitkomsten (30 dagen follow-up) na CABG of PCI met 2^{e} generatie "drug-eluting stents" in patiënten met een linker coronair hoofdstam stenose (HSS) welke gerandomiseerd zijn in de EXCEL studie. Het manuscript in hoofdstuk 2 beschrijft het voorspellende vermogen van de "Society of Thoracic Surgeons (STS)" risico modellen met betrekking tot perioperatieve 30-dagen mortaliteit, cerebrovasculair accident (CVA) en nierfalen, middels het toepassen van de "C statistic" (discriminerend vermogen) en de "Hosmer-Lemeshow goodness of fit" test (kalibrerend vermogen). De STS risico modellen werden toegepast bij geselecteerde patiënten met HSS welke gerandomiseerd waren voor PCI versus CABG in de EXCEL studie. Binnen de patiënten die CABG onderging bleken de STS risico modellen een goed discriminerend vermogen te bezitten om 30-dagen mortaliteit en nierfalen accuraat in te schatten, desalniettemin was dit discriminerend vermogen voor de patiënten die PCI onderging niet accuraat te zijn met betrekking tot 30-dagen mortaliteit en nierfalen. De accuraatheid om een CVA te voorspellen bleek redelijk te zijn binnen zowel de PCI als de CABG populatie.

De midden-termijn (1 – 3 jaar) na myocard revascularisatie middels PCI or CABG in geselecteerde patiënten met HSS worden gerapporteerd in **hoofdstuk 3** en **4**. **Hoofdstuk 3** onderzocht de impact van linker ventrikel ejectie fractie (LVEF) op de klinische uitkomsten in patiënten met HSS die PCI of CABG ondergingen in de EXCEL studie. LVEF werd geclassificeerd volgens de definities van de Europese Vereniging voor Cardiologie (LVEF<40% Hart Falen met gereduceerde Ejectie Fractie (HFrEF), LVEF 40-49%; Hart Falen met mid-range Ejectie Fractie (HFmrEF) en LVEF>50%; behouden ejectie fractie). Patiënten met HFrEF vergeleken met die met HFmrEF of behouden LVEF ervaarde een verhoogd risico op het samengesteld eindpunt van overlijden, CVA en/of myocard infarct (MI), gedreven door een verhoogd risico op het individueel eindpunt van 3-jaars mortaliteit. Er werden geen verschillen in klinische uitkomsten gevonden tussen patiënten die PCI of CABG onderging in relatie tot HFrEF, HFmrEF en behouden LVEF. In **hoofdstuk 4** is de invloed van CABG, gebruik makend van één ("SITA/SIMA") versus bilateraal interna mammaria arteriën ("BITA/BIMA"), in de chirurgische studie populatie met HSS in de EXCEL studie geanalyseerd.

Er werden geen significante verschillen geïdentificeerd in korte-termijn (30-dagen) complicaties waarbij er geen verschil was in sternumwond problematiek tussen het SITA (prevalentie 2.2%) en BITA cohort (prevalentie 1.8%). Na 3 jaar follow-up was er geen verschil in het samengestelde eindpunt van mortaliteit, CVA en/of MI tussen patiënten met HSS die SITA versus BITA coronaire bypass chirurgie ondergingen.

De studie in **hoofdstuk 5** had als doel om de enorme hoeveelheid aan gepubliceerde meta-analyses welke allen over het zelfde onderwerp rapporteren: klinische uitkomsten na PCI versus CABG in patiënten met HSS. Over de afgelopen decennia zijn er 51 meta-analyses gepubliceerd over dit onderwerp. Van deze studies zijn er 33 gepubliceerd in de recente periode na de publicatie van de EXCEL en NOBLE wetenschappelijke studies. Opvallend was dat de uitkomsten die gerapporteerd werden door de 51 meta-analyses verschillen van elkaar, gedreven door (i) een gerandomiseerd versus observationeel studie design, (ii) de methodologie en de effect-maten welke gebruikt werden om behandeling verschillen te objectiveren, (iii) verschillen in steekproefomvang, en (iv) het jaar waarin een meta-analyse werd gepubliceerd. Deze studie concludeerde dat het aantal meta-analyses met een en het zelfde onderwerp, klinische uitkomsten na PCI versus CABG bij patiënten met HSS, disproportioneel is en dat dit vraagt om “kwaliteit over kwantiteit”. Om toekomstige hoge kwaliteit publicaties te kunnen waarborgen kunnen gestructureerde multidisciplinaire samenwerkingen soelaas bieden. Daarnaast kunnen individueel gepoolde patiënt data analyses mogelijk een statistisch nauwkeuriger verschil tussen PCI versus CABG aantonen.

Hoofdstuk 6 tot en met **hoofdstuk 10** beschrijven de lange-termijn uitkomsten (≥ 10 jaar), na PCI met eerste generatie paclitaxel “drug-eluting stents” versus CABG in patiënt met 3-vast coronair lijden (3VD) en/of HSS welke zijn geïncludeerd en gerandomiseerd in de SYNTAX studie. **Hoofdstuk 6** rapporteert 10-jaar mortaliteit in het gerandomiseerde SYNTAX cohort (N=1800, PCI n=903 en CABG n=897). De volledigheid van follow-up was ruim 94%, welke gelijk verdeeld was over het PCI en CABG cohort. Er bleek geen verschil in overleving op 10 jaar te bestaan tussen PCI en CABG in het cohort van alle 1800 patiënten. Echter, CABG verzorgde een significant overlevingsvoordeel na 10 jaar follow-up in patiënten met 3VD en diegene met een meer complex coronair lijden, gedefinieerd door SYNTAX scores ≥33. Daarentegen werd er geen verschil in overleving op 10 jaar geïdentificeerd in patiënten met HSS die gerandomiseerd waren voor PCI of CABG. **Hoofdstuk 7** streeft naar het bepalen van de overlevingscijfers van patiënten die ongeschikt bleken te zijn om gerandomiseerd te worden voor PCI of CABG in de SYNTAX studie. Deze patiënten werden geïncludeerd in een “PCI nested-registry”; waarin patiënten werden opgenomen

waarbij het operatief risico van het ondergaan van een CABG disproportioneel hoog werden geacht, en een "CABG-nested registry"; voor patiënten waarbij de complexiteit en uitgebreidheid van het coronair lijden te groot was om adequaat middels PCI te behandelen. Patiënten in het CABG-registry toonde een uitstekende 10-jaars overleving (mortaliteit van 25.9%), te vergelijken met het gerandomiseerde CABG cohort. De 10-jaars mortaliteit van de patiënten in het PCI-registry daarentegen was hoog, waarbij de helft van dit cohort was overleden na 10 jaar follow-up (mortaliteit vaan 51.6%); bijna twee keer zo hoog in het gerandomiseerde PCI cohort. In **hoofdstuk 8** werd onderzocht wat de impact was van CABG gebruikmakend van meerdere arteriele bypass grafts (MAG) versus het gebruik van een enkele arterie (SAG), in patiënten die CABG ondergingen in de SYNTAX studie. MAG resulteerde in een significant lager mortaliteit cijfer na ruim 12 jaar follow-up (zowel de statisch ongecorrigeerde als gecorrigeerde cijfers), vergeleken met de SAG CABG strategie (gecorrigeerd hazard ratio (HR) 0.58, 95% betrouwbaarheidsinterval (BI) [0.46-0.72], *P*=0.001). Deze opvallende overlevingswinst van MAG versus SAG op lange termijn stimuleert operateurs om vaker en meer gebruik te maken van meerdere arteriele bypass grafts. **Hoofdstuk 9** rapporteert de invloed van complete versus incomplete revascularisatie en beschrijft de associatie van post procedurele aanwezigheid van onbehandelde stenoses ("residual SYNTAX score - rSS") op 10-mortaliteit. Deze studie toont aan dat incomplete revascularisatie vaker voorkomt na PCI en dat de uitgebreidheid van incomplete revascularisatie een significant negatief invloed heeft op 10-jaars mortaliteit. Patiënten met een rSS ≤8 na PCI vertoonde een vergelijkbaar risico op 10-jaars mortaliteit vergeleken met patiënten die CABG ondergingen. Daarentegen, patiënten met een rSS>8 na PCI hadden een substantieel verhoogd risico om te overlijden na 10-jaar follow-up vergeleken met het CABG cohort. Vervolgens is in **hoofdstuk 10** de voorspellende nauwkeurigheid van de SYNTAX score II bepaalt met betrekking tot het accuraat berekenen van het risico op overlijden na 10-jaar follow-up. De SYNTAX score II is een samenstelling van de aan- of afwezigheid van HSS samen met de anatomische SYNTAX score en belangrijke patiënt kenmerken zoals: leeftijd, sex, creatinine klaring, linker ventrikel ejectie fractie (LVEF), chronisch obstructief pulmonaal lijden (COPD) en perifeer vaatlijden, ten behoeve van het bepalen van het risico op 4-jaars mortaliteit. Dit onderzoek toont aan dat de SYNTAX score II kan discrimineren in mortaliteit na 4-jaar follow-up, ondanks dat er geen verschil in overleving was tussen PCI en CABG in de SYNTAX studie na deze 4-jaar follow-up.

Ten slotte, in **hoofdstuk 11** en **hoofdstuk 12** is gekeken naar de impact die intra-operatieve diagnostiek, naar de kwaliteit van de gemaakte bypass grafts, middels "transit-time flow measurement (TTFM)" en/of "high frequency ultrasound (HFUS)"

heeft op de klinische uitkomsten na chirurgische bypass chirurgie. Het systematische review onderzoek in **hoofdstuk 11** evalueerde de waarde van TTFM tijdens CABG door verschillende eindpunten te definiëren; (i) het percentage insufficiënte grafts en de mate van revisie van deze grafts wanneer TTFM werd gebruikt tijdens CABG, en (ii) de impact die TTFM heeft op angiografische en klinische uitkomsten na CABG. Bij 4.3% van de patiënten die CABG ondergingen was er een noodzaak tot revisie van de gemaakte grafts op basis van afwijkende TTFM waarden, echter slechts bij een kwart van al deze insufficiënte grafts werd er een chirurgische revisie verricht. Dit suggereert dan het gebruik en de interpretatie, met daarbij de klinische consequenties, van TTFM nog verder geoptimaliseerd zou kunnen worden. De uitkomsten van de internationale, multicenter prospectieve REQUEST studie, welke als doel had om de frequentie en type van operatieve veranderingen gebaseerd op afwijkende TTFM en/of HFUS uitkomsten vast te stellen, worden beschreven in **hoofdstuk 12**. Bij 256 van de 1016 patiënten (25.2%) die CABG ondergingen in zeven participerende REQUEST ziekenhuizen, welke allen dagelijks chirurgische bypass chirurgie verrichten, was het noodzakelijk om een chirurgische verandering door te voeren op basis van afwijkende TTFM/HFUS uitkomsten. Dit ging gepaard met een lage incidentie van 30-dagen morbiditeit en mortaliteit. Op basis van de uitkomsten van de REQUEST studie kan worden gesuggereerd dat TTFM en HFUS de kwaliteit, veiligheid en effectiviteit van chirurgische bypass chirurgie verbeterd, en daarom zouden deze technieken overwogen moeten worden om gestructureerd te gebruiken tijdens CABG.

Chapter 14

General discussion

The current thesis aimed to determine procedural and clinical outcomes after contemporaneous revascularisation treatment strategies for patients with coronary artery disease, and sought to distinguish treatment benefits and risk-predictors in patients that underwent percutaneous (PCI) versus surgical myocardial revascularisation (CABG) at short-(≤1 year), mid-(1-3 year) and long-term follow-up (≥ 10 year).

Since the introduction of surgical and percutaneous coronary interventions over four decades ago, the field of coronary artery revascularisation has progressed significantly.[1-4] Continuous developments in surgical and percutaneous techniques together with optimization of guideline directed medical treatment ensured the possibility of treating more complex patients with CAD. Numerous randomized and observational studies have reported outcomes after PCI versus CABG and herewith contributed to the continuous developments and improvements of both revascularisation strategies.[5-8] The great majority of these studies, however, only reported outcomes at short to mid-term follow-up (e.g. 30 days - 5 years). Since the overall life-expectancy of patients with coronary artery disease is steadily increasing worldwide, the presence of various cardiovascular comorbidities in these patients will affect perioperative, short-, mid- and long-term outcomes. Understanding how, and to which extent, these patients characteristics will influence clinical outcomes will offer a major advantage in determining the optimal myocardial revascularisation strategy in an individual patient with coronary artery disease requiring revascularisation PCI versus CABG.

Short-term outcomes

Risk-stratification tools showed to be useful instruments to accurately assess perioperative risks and clinical outcomes in patients undergoing CABG or PCI. To date, various risk models have been published and are used during multi-disciplinary heart team meetings to determine the optimal revascularisation strategy in patients with CAD.[9-11] Now that PCI has become a suitable treatment, as an alternative to CABG, for selected patients with coronary artery disease, accurate risk assessment is crucial to accurately determine the preferred treatment in these specific patients.[12-19]

In **chapter 2** the predictive performance of Society of Thoracic Surgeons (STS)[10] risk models for perioperative mortality, stroke and renal failure in patients undergoing CABG (n=923) for LMCAD from the randomized EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was analysed.[20] Furthermore, the efficacy of these risk models in PCI-treated subjects from the EXCEL trial (n=935) was examined.

In brief, the EXCEL trial was an international, multicenter randomized trial that compared PCI with everolimus-eluting stents with CABG in patients with LMCAD and a low to intermediate SYNTAX score (≤32). The study was designed to determine whether PCI was non-inferior to CABG regarding the primary composite endpoint of major adverse cardiac and cerebrovascular events (MACCE) defined by all-cause death, stroke or MI at 3 years. The study showed that at 3-years MACCE occurred in 15.4% of the PCI cohort and in 14.7% of the CABG cohort (hazard ratio (HR) 1.00, 95% confidence interval (CI) [0.79-1.26], *P*=0.98 for superiority and *P*=0.02 for inferiority).

The STS risk scores showed good discrimination for 30-day predicted risk of mortality (PROM) and stroke in CABG patients, with average calibration. For patients treated by PCI, the STS risk scores had no discrimination for mortality, comparable to "flipping a coin", yet average discrimination for stroke with good calibration. The predictive performance of STS renal failure risk scores was excellent in the CABG cohort, yet poor in those treated with PCI. Overall, an updated risk score model is warranted in order to accurately assess perioperative clinical outcomes and to determine which treatment strategy appears optimal for a specific patients with LMCAD, bearing in mind that between-treatment differences might emerge beyond the perioperative (30 days) timeframe.

In daily clinical practice, patients with stable coronary artery disease should be discussed in a multidisciplinary heart team.[21] During this discussion several risk prediction models can be used to better inform the heart team about the perioperative risk. Besides the STS risk models, there are multiple other risk prediction models that could be used, such as the SYNTAX score (predicts the risk of major adverse cardiovascular and cerebral events at 12 months follow-up)[5], the SYNTAX score II (predicts the risk of 4-year mortality)[22], and the EuroSCORE II (predicts in-hospital mortality)[9]. Each of these risk scores have their own advantages, shortcomings, and degrees of accuracy (calibration and discrimination). In addition to a physician's clinical judgement, these risk scores help optimize clinical outcomes and strive for optimal "personalised medicine", instead of "one-size-fits-all".

Mid-term outcomes

The overall treatment goals of myocardial revascularisation by CABG or PCI in patients with coronary artery disease is i) providing relief of angina and ii) reducing the risk of "premature" mortality together with other major adverse cardiac and cerebrovascular events. In order to determine the most appropriate revascularisation strategy in an individual patient, a structured heart team discussion weighs the benefits and shortcomings of both treatment strategy against perioperative risk

and benefit, and takes into account a patients personal preference and the existence of comorbidities (diabetes mellitus, renal insufficiency, pulmonary disease and left ventricular function). Besides, perioperative risk assessment, the expected mid- and long-term outcomes are of utmost importance to determine the best treatment strategy.[21,23]

Myocardial revascularisation guidelines recommend CABG in patients with complex multivessel CAD and severely impaired LVEF (≤35%).[17,18] Nonetheless, what the preferred treatment strategy is in patients with LMCAD and impaired LVEF (<50%) remains unclear. To date, randomized data on the impact of LVEF on clinical outcomes in patients with coronary artery disease is restricted to CABG versus medical therapy since contemporaneous randomized trials exclude patients with severely reduced LVEF (≤35%). Therefore, the impact of left ventricular ejection fraction (LVEF) on clinical outcomes at 3-years in patients with LMCAD from the EXCEL trial was evaluated in **chapter 3**.[24] Patients with preserved (≥50%) and impaired LVEF (<50%) undergoing CABG or PCI were analysed in this study. Although no treatment interaction of CABG or PCI according to baseline LVEF was found, patients with impaired LVEF showed to possess a significantly higher risk of 3-year all-cause mortality compared to patients with preserved LVEF. To date, randomized data that directly compares the impact of CABG and PCI in patients with impaired LVEF, especially patients with LMCAD, is lacking. Although our current study was not a randomized controlled trial (RCT), it provides valuable insights on treatment outcomes in patients with LMCAD and impaired LVEF that require revascularisation.

The Surgical Treatment for Ischemic Heart Failure (STICH) evaluated whether CABG with intensive medical therapy versus medical therapy alone would decrease mortality in patients with severely impaired LVEF (≤35%).[25] The intention-to-treat analysis showed no difference in mortality at a median follow-up of 56 months (HR with CABG, 0.86; 95% CI [0.72-1.04], P=0.12). In the per-treatment analysis, however, a significant survival benefit of CABG with optimal medical treatment versus medical treatment alone was found (HR 0.70, 95% CI [0.58-0.84], P<0.001). No comparisons between PCI or CABG were made in the STICH trial. The systematic review by Wolff *et al.* compared revascularisation with medical therapy. They reported an overall survival benefit of CABG over PCI in 8782 patients with LVEF ≤40% (HR 0.82; 95% [0.75-0.90]).[26] However, results are restricted by important limitations, such as a great spread in follow-up (range 12-180 months) and a heterogeneous patient population (I^2=47%).

In **chapter 4** the safety and effectiveness of performing CABG using a single internal thoracic artery (SITA) with additional venous grafts versus bilateral internal thoracic artery (BITA) was determined in patients with LMCAD and low to intermediate SYNTAX scores (≤32) from the randomized EXCEL trial.[8,27] Clinical outcomes such as all-cause death, stroke, MI and sternal wound dehiscence were assessed at 30-days and 3-year follow-up. Whether CABG should be performed by complete arterial revascularisation using BITA grafts, remains a matter of debate[28-31] Besides, some surgeons may discourage BITA-use in patients with LMCAD, especially in those where a pin-point (bi/tri-furcation) lesion is present, since the entire myocardium will be supplied of oxygen rich blood by a "new main stem"'; being a composite LITA-RITA-Y graft (e.g. LIMA-RIMA-Y graft). Our study in **chapter 4** showed low rates of sternal wound dehiscence at 30-days in both the SITA as the BITA cohort, without any statistical difference. Furthermore, at 3-years, no differences existed in the multivariable adjusted primary composite endpoint of all-cause death, stroke or MI, or the individual endpoints of ischemia-driven revascularisation and major bleeding complications. Although the rate of unplanned hospitalization was higher in SITA compared to BITA, this difference was not seen after multivariable adjustment.

Previous studies have shown that patients receiving BITA, especially those that have diabetes and/or chronic obstructive pulmonary disease (COPD), have an increased risk of developing sternal wound complications at short-term follow-up (e.g. 30-days).[32-34] Although, by meticulously selecting suitable patients, this risk can be reduced, possibly even more when ITA grafts are being harvested skeletonized.[27]

Potential clinical benefits at long-term, especially regarding survival, might only appear after long-term follow-up (≥ 10 years). This is most likely due to superior arterial graft patency compared with venous graft patency.[35-37] Various observational studies showed a significant long-term survival benefit of BITA over SITA[38-41], yet randomized data were not able to confirm this finding.[27,42] The results of the Arterial revascularisation Trial (ART), investigating differences between SITA and BITA revascularisation were therefore highly awaited.[43] Nonetheless, results at 10-year follow-up appeared disappointing for those that advocate the use of BITA during CABG procedures; as no mortality difference was found between BITA (20.3%) and SITA (21.2%, HR 0.96, 95% CI [0.82-1.12]) in the intention-to-treat analysis. The shortcomings that most likely influenced the outcomes in the ART trial were i) a high cross-over rate in the BITA (13.9%) cohort and ii) the use of a radial artery in the SITA cohort (21.8%). The as-treated analysis, comparing multiple (2 or more) arterial grafts with a single arterial graft, however, did show a survival benefit in patients

receiving multiple arterial grafts (18.6%) versus a single arterial graft (23.1%) (HR 0.81, 95% CI [0.68-0.95]).

To conclude, although arterial grafts most likely outperform venous grafts from a physiological standpoint [44], mainly circumstantial evidence is currently available that supports the use of BITA, or multi-arterial grafts, in selected patients with coronary artery disease requiring CABG. The Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts (ROMA) trial aims to determine the impact of using 2 or more arterial grafts on long-term survival and results are expected in 2025.[45] Until then, complete arterial revascularisation with the use of BITA could be seen more of "an ART than a science", as Prof. Mario Gaudino quoted.[46,47]

Over the recent decade, myocardial revascularisation for patients with LMCAD progressed significantly. Where CABG historically was the golden standard for revascularisation in patients with a left main stenosis, PCI appeared to be a suitable alternative in selected patients.[14-16] The basis for these advancements came from various randomized and observational studies. The publication of these individual studies, however, was followed up by the publication of an abundant number of meta-analyses evaluating PCI versus CABG in LMCAD. **Chapter 5**, reports a critical appraisal by systematically reviewing all published meta-analyses that focused on PCI versus CABG in LMCAD revascularisation over the past decade.[48] The search resulted in 51 meta-analyses that all published data the same topic. Of those, interestingly, 33 meta-analyses were published after the EXCEL and NOBLE publications. This resulted in overlapping and redundant outcomes, which could be attributed to study differences, such as (i) randomized versus observational studies, or a combination of both, (ii) differences in methodology, (iii) differences in sample sizes, and (iv) the timing of publication of specific meta-analyses (2009 versus 2018). Hence, caution is advised when interpreting results from these meta-analyses. Encouraging physicians and scientists to collaborate in conducting, reviewing and publishing scientific content possibly minimizes redundant, overlapping and inefficient work. By performing an individual patient-data meta-analysis, by combining patient-level outcomes from multiple randomized trials, statistical power increases and possible treatment differences between revascularisation procedures can be determined with more statistical certainty.[49]

Long-term outcomes

In the SYNTAX trial, patients that were randomized to undergo CABG or PCI with paclitaxel-eluting stents (DES) experienced a non-significant survival difference in favour of CABG at 1-year follow-up (CABG 3.5% vs PCI 4.4%, *P*=0.37).[5] This numerical

survival difference continued to increase until trail completion at 5-year follow-up. However, no statistical difference between CABG and PCI was found (CABG 11.4% vs PCI 13.9%, *P*=0.10).[50] Furthermore, the post-hoc landmark analysis from the EXCEL trial reported differences in risk of death after PCI and CABG depending on the duration of follow-up.[8] Longer-term follow-up data was warranted to adequately identify risk predictors and differences in clinical outcomes, which can subsequently aid the multidisciplinary-decision making process, in order to determine the optimal evidence-based revascularisation strategy for individual patients with coronary artery disease.

The SYNTAX Extended Survival study was presented in **Chapter 6**, which reported the long-term survival outcomes of patients with *de novo* three-vessel and left main coronary artery disease randomized to PCI with paclitaxel-eluting stents or CABG in the SYNTAX trial.[51] At 10-year, 94% of vital status information was complete for the overall cohort of 1800 included patients in the SYNTAX trial (n=1800). In the overall cohort, no significant difference existed between PCI versus CABG (28% versus 24%, p=0.066). However, CABG provided a significant survival benefit (30% risk reduction of all-cause death) in those patients with 3VD and those with high SYNTAX Scores (≥33), yet not in patients with LMCAD. Furthermore, among patients with medically treated diabetes or without diabetes no survival differences were noticed. The SYNTAXES study was the first study to report 10-year outcomes of patients with *de novo* 3VD and LMCAD randomized to PCI with DES or CABG. It provides important insight in long-term survival outcomes after CABG and PCI with DES, and will aid in determining the optimal revascularisation strategy in patients with coronary artery disease.

To date, long-term outcome of contemporaneous randomized trials comparing PCI with CABG with DES is scarce and limited to the publication of only 2 other studies. First, the LE MANS trial randomized 105 patients with unprotected LMCAD with low to intermediate complexity of coexisting coronary artery disease to CABG or PCI with bare metal stents and DES.[52] At 10-year follow-up no difference in mortality between PCI (21.6%) and CABG (30.2%) was found (*P*=0.41). These results of the LE MANS trials are like the results found in the SYNTAX Extended Survival study, being that PCI provides a numerically, yet not statistically significant, survival benefit over CABG in patients with LMCAD. Nonetheless, due to the low sample size the LE MANS study lacks statistical power and findings should be interpreted with caution. Moreover, BMS were used in 65% of patients and therefore survival outcomes of those specific patients might not be relevant to contemporary revascularisation practice.

Second, the FREEDOM trial randomized 1900 patients with diabetes mellitus and multivessel coronary artery disease (MVD) to PCI with sirolimus-eluting stents or CABG. Both treatments were performed under optimal guideline-directed medical therapy.[53] Recently, long-term follow-up data up to 8-years of 943 patients (49.6% of the original cohort) was published. In this limited cohort, all-cause mortality occurred in 23.7% of patients that underwent PCI (99 deaths) and in 18.7% of patients that underwent CABG (72 deaths) (HR 1.32, 95% CI[0.97;1.78], *P*=0.076). The SYNTAX Extended Survival study included 452 patients with diabetes mellitus that were medically treated (oral medication and/or insulin therapy). All-cause death occurred in 38.7% of patients that underwent PCI and in 36.5% of patients that underwent CABG (*P*=0.50). The relatively modest sample size could have resulted in less statistical power, besides the substantial difference in duration of follow-up between the FREEDOM trial (median 7.5 years) and the SYNTAXES study (median 11.2 years).

Besides analysing the outcomes in the randomised cohorts from the SYNTAX trial, we also investigated 10-year survival outcomes of patients enrolled in the SYNTAX trial that were entered into nested registries. The registry patients were ineligible for randomization i) due to significant comorbidities which increased the surgical perioperative risk of morbidity and mortality, and/or ii) due to extensive and complex coronary artery disease unsuitable for PCI. Such registries overcome the major limitation of randomized trials that only include a highly selected patient cohort because patients entered in such registries are a more accurate representation of patients that are discussed in daily multidisciplinary hear teams. **Chapter 7** provided insights in the risk profiles and 10-year all-cause death rates of patients that were found ineligible by a multidisciplinary heart team to be randomized to undergo PCI or CABG. When clinical equipoise with either PCI or CABG could not be reached due to coronary anatomy, comorbidities, perioperative risk, or a combination of all afore mentioned factors patients were entered into nested registries; CABG-ineligible PCI registry (198 patients) or PCI-ineligible CABG registry (1077 patients).[5,54] Of those, all 198 PCI-registry patients were selected to be followed-up for 5- and 10-years. In the CABG registry, 649 randomly selected patients were followed-up for 5- and 10 years. Patients that were entered in the CABG-registry showed excellent 10-year survival (all-cause death rate of 25.9%); comparable to outcomes in the randomized CABG cohort of the SYNTAX trial. Patients that were enrolled in the PCI-registry showed relatively poor 10-year survival with an all-cause death rate of approximately 51.6%, almost twice as high as in the randomized SYNTAX PCI cohort (28%). This study provided unique long-term survival insights in patients representing “real-word” patients with coronary artery disease included in the SYNTAX trial.

Randomized controlled trials have been considered as the gold standard to report the overall treatment effect of comparing two treatment strategies and provide a relative risk (odds ratio or hazard ratio) for the overall cohort of patients. However, not each individual patient might experience these mean relative risks derived from the calculation of the entire cohort [55,56]. Therefore, one could assume that only providing such an average risk is not meaningful for an individual patient that requires myocardial revascularisation.

The present thesis set out to establish treatment-benefits and risk-predictors for individual patients with coronary artery disease that require myocardial revascularisation. In **chapter 8** we assessed the impact of bypass surgery using multiple arterial grafts (MAG) versus a single arterial graft (SAG) on vital status at very-long term follow-up in patients enrolled in the SYNTAX trial. To date, it remains fiercely debated which graft configuration used during coronary bypass surgery provides optimal results at long-term follow-up. Studies have shown that venous graft patency, compared to arterial graft patency, is significantly worse at long-term follow-up (venous patency: 61% vs. arterial patency: 85%).[44] Various observational studies reported long-term advantages of multiple arterial grafting, compared to the use of a single arterial graft. Therefore, the long-term results of the Arterial Revascularization Trial (ART) were highly anticipated.[33,43,57] The unadjusted intention-to-treat analysis, at 10-year follow-up, appeared however disappointing for those "BITA-believers". No difference in survival was found between single versus bilateral internal thoracic grafts (21.2% vs 20.3% all-cause death, respectively). Nonetheless, the as-treated analysis showed a significant survival benefit with multiple arterial grafting compared with the use of a single arterial graft (18.6% vs 23.1% all-cause death; HR 0.81, 95% CI [0.68-0.95]).

In our prespecified post-hoc analysis (**chapter 8**), MAG resulted in a significantly lower incidence of all-cause death at 12.6 years follow-up. The survival benefit of using MAG over SAG remained significant after adjusting for differences in preselected clinically and statistically relevant patient characteristics, such as age, sex, body mass index, diabetes mellitus and vascular disease. These markedly 12.6-year survival benefits derived from using MAG revascularisation over SAG, in the SYNTAX trial encourages a more extensive use of multiple arterial grafting in contemporaneous coronary bypass surgery. Although our results are "hypothesis-generating" due to the non-randomized nature of the study, it provides very reassuring and important long-term insights in the benefits of multiple arterial grafting. We recommend that a patient's baseline and angiographic characteristics should always be adequately assessed during multidisciplinary heart team meetings when deciding

on the optimal strategy of surgical revascularisation striving for ideal short-and-long-term outcomes.

The ongoing ROMA trial randomizes coronary artery disease patients to either CABG with MAG versus SAG. The trial aims to answer two hypotheses; (i) MAG is associated with a reduction in the composite outcome of all-cause death, any stroke, post-discharge myocardial infarction and/or repeat revascularisation and (ii) MAG is associated with improved survival.[45] The ROMA trial is expected to be completed around 2030, therefore the first long-term randomized data on MAG versus SAG will not be available soon. Until then, high quality observational data, such as the insights provided by the SYNTAXES study, should inform cardiothoracic surgeons on the optimal graft configuration during CABG.

Besides the potential benefits of multiple arterial grafting during bypass surgery, completeness of revascularisation plays an important role in optimizing procedural and patient outcomes. The impact of complete versus incomplete revascularisation has been assessed by multiple studies.[58-63] A recent meta-analysis of 83,695 patients reported a significant survival benefit at 4.7 years follow-up with complete versus incomplete revascularisation (relative risk 0.76, 95% CI [0.63-0.90]).[64] Long-term outcomes after complete versus incomplete are scarcely available. Only the MASS II trial evaluated outcomes beyond 5 years, however the impact of these findings are limited due to the use of bare metal stents during PCI and the limited number of patients included in the study (PCI 205 patients, CABG 203 patients, medical therapy 203 patients). Besides evaluating the impact of (in)complete revascularisation the residual SYNTAX score (rSS) was introduced as a more accurate risk-predictor specifically for those patients that underwent PCI.[63] The rSS quantifies the remaining burden of coronary atherosclerosis after incomplete revascularisation and is divided in four subgroups; rSS of 0, rSS >0-4, rSS >4-8 and rSS 8, where a high rSS was associated with increased risks of all-cause death, stroke, myocardial infarction and repeat revascularisation. In **Chapter 9** the effect of incomplete revascularisation on 10-year survival in patients randomized to PCI versus CABG in the SYNTAX trial was evaluated. Incomplete revascularisation was more common after PCI compared with CABG. Especially those patients with three-vessel coronary artery disease were at increased risk of receiving incomplete revascularisation irrespective of the revascularisation strategy. The risk of 10-year all-cause death was similar in patients that underwent PCI with complete revascularisation compared to those that underwent CABG with complete revascularisation. On the contrary, PCI with incomplete revascularisation was associated with a significantly increased risk of all-cause death at 10-year follow-up. A rSS >8 was furthermore associated with a 3.5-fold increased risk

of 10-year all-cause death, while a rSS across 0 to 8 showed a similar risk of all-cause death. Each heart team discussion should consider the potential risk of incomplete revascularisation with either percutaneous or surgical myocardial revascularisation- Interventional cardiologists should furthermore aim to reduce the residual SYNTAX score as far as possible below the cut-off value of 8, otherwise patients will be at increased risk of MACCE during the first 5 years and at increased risk of all-cause death at 10-year. The rSS remains a purely angiographic and anatomical index which does not evaluate the hemodynamic relevance of any remaining coronary artery stenoses. It is furthermore challenging to use as a prediction-tool prior to the intervention, especially since incomplete revascularisation is influenced by multiple factors such as diffuse, small vessel coronary artery disease, heavy calcifications, extreme tortuosity, and/or chronic total occlusions. Future methods of assessing functional flow reserve, by CT FFR for example, could provide a non-invasive insight on the impact of residual coronary stenosis after both PCI as CABG.

In **Chapter 10** the predictive performance of the SYNTAX score II on 10-year all-cause death was estimated in 1800 patients with *de novo* three-vessel and left main disease followed-up by the SYNTAXES study. Although randomized trails provide the highest level of evidence and are often used to establish recommendation in clinical guidelines for most patients with coronary artery disease, it provides information for a large cohort of patients. It is however crucial to be able to recommend the best treatment-strategy for an individual patient requiring myocardial revascularisation. As mentioned before, risk stratification models are useful to steer a multidisciplinary heart team treatment recommendation by balancing be perioperative, as well as long-term risks and benefit of each treatment. Where the original SYNTAX score predicts the risk of 12-month MACCE, the SYNTAX score II was designed to predict the risk of 4-year all-cause death for an individual patient. The SYNTAX score II risk model is an instrument that combines clinically important and prognostic patient characteristics (age, renal function, left ventricular ejection fraction, left main coronary artery disease gender, chronic obstructive pulmonary disease and peripheral vascular disease) with the anatomical SYNTAX score.[22] Now, the SYNTAX Score II 2020 (SSII-2020) has been introduced, showing good calibration and discrimination to adequately assess the risk of 10-year all-cause death, using 7 clinical predictors (age, diabetes, renal function, LVEF, COPD, PVD and current smoking) in combination with type of coronary artery disease (3VD or LMCAD) and the anatomical SYNTAX score. Due to the absence of other available randomized long-term follow-up data (≥10 years), the updated SSII-2020 could not yet be externally validated. This furthermore stresses the necessity of extending follow-up of contemporaneous randomized trials, such as the EXCEL and NOBLE trials, up to 10-year follow-up

and beyond. Eventually, when more long-term data becomes available, one could pool individual patient data from various randomized trials a therewith estimate a potential treatment-benefit, of either PCI or CABG, with more statistical certainty.

Left main coronary artery revascularisation

Recently, three of the major randomized clinical trials comparing outcomes after PCI with drug-eluting stents versus CABG have published data on longer-term follow-up in patients with left main coronary artery disease, being the SYNTAX trial (10-year data), the EXCEL trial and the NOBLE trial (both reported 5-year data).[51,65,66]

In 2016, the EXCEL trial reported its 3-year outcomes, suggesting that PCI with 2nd generation everolimus-eluting stents was non-inferior to CABG in unprotected left main revascularisation regarding the primary endpoint of MACCE (major adverse cardiac or cerebrovascular events), a composite of death, stroke or myocardial infarction.[8] At 3-year follow-up, no difference in all-cause death between PCI and CABG was present. In September 2019, the EXCEL trial presented their 5-year outcomes at the Transcatheter Cardiovascular Therapeutics meeting (TCT), and simultaneously published these outcomes in the *New England Journal of Medicine*.[65] At 5-year follow-up, PCI showed to be non-inferior to CABG regarding the composite primary endpoint (difference of 2.8 percentage points; 95% CI[−0.9-6.5]; P=0.13). Death from any cause was more common after PCI compared with CABG (13.0% vs. 9.9%; 95% CI [0.2-6.1]).

The publication of the 5-year EXCEL trial outcomes substantially shook up the cardiovascular society, leading to fierce (inter)national discussions at scientific meetings, television program (BBC) and social media platforms related to the definition of myocardial infarction used in the trial (a biochemical periprocedural Myocardial Infarction definition[18] versus the Universal Definition of Myocardial Infarction[67,68]) and the increased rate of all-cause death after PCI compared with CABG at 5-year follow-up, amongst many other arguments. Eventually the European Association of CardioThoracic Surgery (EACTS) withdrew its support from the 2018 Guideline on Myocardial Revascularisation that stated that PCI is an appropriate alternative to CABG in selected patients with left main coronary artery disease, while the European Society of Cardiology (ESC) continued to support the Myocardial Revascularisation guideline.[17] The raw EXCEL 5-year data is currently being analyzed by an independent research group and results are, of course, highly anticipated.

In December 2019, the NOBLE trial published its 5-year results in *The Lancet* showing PCI with 2nd generation stents resulted in inferior clinical outcomes compared with CABG in patients with unprotected left main coronary artery disease.[66] Also NOBLE

reported on the primary endpoint of MACCE, a composite of all-cause death, non-procedural myocardial infarction, repeat revascularisation and stroke. At a median of 4.9 years of follow-up, 28% of patients that underwent PCI experienced MACCE versus 19% of patients that underwent CABG (HR 1.58, 95% CI [1.24-2.01]). There was no difference in all-cause death between PCI and CABG (NOBLE: 9% vs 9%, HR 1·08 [95% CI 0.74–1.59] compared to EXCEL: 13% vs 10% OR 1.38 [95%CI 1.-030–1.85]). Of note, the individual endpoints of MACCE used in the NOBLE trial differ substantially from the MACCE primary composite endpoints used in the EXCEL trial, making it impossible to compare these MACCE outcomes directly head-to-head. Nonetheless, the undisputed endpoint of all-cause death in the NOBLE trial did not differ between PCI and CABG.

In October 2019, the SYNTAX Extended Survival study published data on vital status up to 10-year of follow-up in patients with *de novo* three-vessel and/or left main coronary artery disease randomized to PCI with 1st generation drug-eluting stents versus CABG.[51] At 10-year follow-up, no difference in all-cause death existed in patients with left main coronary artery disease that underwent PCI or CABG (27% vs 28%, respectively).

To date, there appears not to be one correct and all-inclusive answer that eludes which revascularisation strategy, PCI versus CABG, provides optimal results in patients with left main disease due to the variety of clinical endpoints and definitions used in each individual randomized trial. It is therefore strongly recommended that the entire body of available evidence published by trails such as SYNTAX, PRECOMOBAT, NOBLE and EXCEL is adequately appraised and used to base evidence-based treatment recommendations on, accounting for all MACCE associated benefits and shortcomings of each treatment.[5,7,8,51,65,66,69,70] Multidisciplinary heart teams remain of utmost importance to ensure a well-informed, unbiased and collaborative treatment recommendation in each individual patients with coronary artery disease requiring myocardial revascularisation An undisputed collaboration between interventional cardiologists, clinical cardiologists and cardiothoracic surgeons forms the solid foundation of such successful heart team meetings.

Technological advencements in coronary artery bypass surgery

In the 2018 EACTS/ESC Guidelines on myocardial revascularisation intraoperative graft flow assessment and epiaortic ultrasound scanning were classified with a Class IIa recommendation.[17] Nonetheless, the adoption-rate of intraoperative quality assessment during CABG varies substantially between institutions and surgeons. Moreover, contemporaneous published data is mostly restricted to non-randomized

single-centre studies that report heterogeneous outcomes which furthermore complicate drawing uniform conclusions.

In **chapter 11** the results of a comprehensive systematic search and meta-analysis on the impact of using transit-time flow measurements (TTFM) during CABG to improve surgical and clinical outcomes were reported.[71] Of the 66 included studies, 35 reported on abnormal grafts or graft revisions in 8943 patients (n=15673 grafts). Of those patients, 4.3% (95% CI 3.3-5.7%) required a graft revision based on abnormal TTFM findings. This corresponded with a graft revision rate of 2.0% of grafts (95% CI 1.5-2.5%). Of the grafts classified as abnormal, the pooled rate of graft revisions was 25.1% (95% CI 15.5-37.9%). Although this was a relatively modest amount, and the diagnostic accuracy of TTFM alone was limited, TTFM has the potential to be of great importance during CABG procedures. Especially, when used in combination with high frequency ultrasound (HFUS) the diagnostic accuracy increased substantially.[72] Besides informing a well-experienced surgeon on intraoperative graft patency, TTFM could also be used to train cardiothoracic residents by providing real-time flow-data that aids surgical and tactical knowledge and optimizes surgical skills. An important limitation of the present study was that the included studies were of moderate overall quality and showed great heterogeneity regarding inclusion- and exclusion criteria, variations in endpoints and methods of reporting clinical outcomes (as indicated by high I^2 statistics).[73] This made drawing uniform conclusions challenging and underlined the need for well-structured multicenter studies.

The multicenter international REQUEST study evaluated the impact of performing intraoperative TTFM in combination with HFUS in 1016 patients that underwent CABG.[74] The REQUEST study aimed to prospectively document any changes to the initially proposed surgical strategy based on TTFM and/or HFUS findings. These surgical changes were classified as changes related to the aorta, in-situ conduits, coronary targets, completed grafts and anastomoses. Outcomes of the REQUEST study were reported in **chapter 12**. In 25.2% of patients (256/1016) a surgical change was made after TTFM and/or HFUS assessment. In 7.8% a graft revision was performed. This corresponded with any surgical revision rate in 3.4% of anastomosis (100/2959). Together with low rates of in-hospital adverse events (all-cause death in 0.6, stroke or TIA in 1.0% and myocardial infarction of 0.3%), the REQUEST study showed that intraoperative quality assessment is feasible and safe. Moreover, TTFM with HFUS may improve the quality, safety and efficacy of CABG procedures. Although the REQUEST study was the first large-scale, multicenter prospective study that assessed the impact of using TTFM and HFUS for intraoperative quality assessment based

on a structured protocol, randomized data is warranted to contribute to guideline directed CABG.

CONCLUSION AND FUTURE PROSPECTS

The present thesis set out to determine procedural and clinical outcomes in patient with coronary artery disease that underwent PCI or CABG and aimed to define treatment-specific benefits and risk-predictors for patients who require myocardial revascularisation The short- and midterm outcomes (0-5 years) of patients with left main coronary artery disease randomized to PCI with 2nd generation drug-eluting stents or CABG in the randomized EXCEL trial, together with evaluating (very) long-term (≥10 year) survival outcomes in patients with *de novo* three-vessel and/or left main coronary artery disease who underwent PCI with 1st generation drug-eluting stents versus CABG in the SYNTAX trial, were analysed. Finally, the impact of using technological advancements during bypass surgery, such as transit-time flow measurement and high frequency ultrasound, in order to improve graft patency and patient outcomes were evaluated.

Determining the most appropriate treatment strategy for an individual patient with coronary artery disease requiring myocardial revascularisation should be put forward by a multidisciplinary heart team that adequately appraises myocardial revascularisation guidelines. The heart team should take into account i) a patients revascularisation risk profile, such as the left ventricular ejection fraction, the presence or absence of diabetes and any additional comorbidities, ii) the anatomical coronary complexity, defined by the SYNTAX score, iii) combined with a patient's own treatment-preference. Procedural risks and benefits should be appropriately weighed by using various risk prediction models, such as the STS risk score, the SYNTAX score, and the SYNTAX score II 2020, to predict the risk of morbidity and mortality associated with each revascularisation strategy. In addition, an unbiased and evidence-based treatment recommendation should be formed by taking into account all PCI-and CABG-specific characteristics that influence the risk of myocardial infarction, repeat revascularisation stroke and all-cause death during short- mid and (very) long-term follow-up. This heart-team treatment recommendation should be incorporated with the preferences of an individual patient, striving to come to an individualized evidence-based shared decision regarding the optimal revascularisation strategy.

Future studies should continue to focus on optimizing treatment outcomes after PCI and CABG by aiming to analyse the most important clinical outcomes (such as all-cause death, myocardial infarction, stroke and repeat revascularisation) and treatment goals (such as quality of life, event free survival, cost-effectiveness) that will benefit both the cardiovascular patients as well as their treating physicians. Studies will most likely enrol more complex patients since the overall life-expectancy of patients with coronary artery disease will increase, which will be accompanied by a more complex cardiovascular risk profile. Continuation of the progress that has been made over the past four decades in the field of myocardial revascularisation could be achieved by i) focussing on less invasive techniques to quantify the burden and hemodynamical consequences of coronary artery disease by for example CT FFR, ii) further diminishing post-operative adverse events by careful patient-selection, iii) improving stent design to prolong patency and iv) extent the use of multiple arterial grafting during bypass surgery in selected patients. Future studies should extent follow-up beyond the perioperative period and focus on treatment effects beyond 3 and 5 years, as was done by the SYNTAX Extended Survival study. Pooling individual patient data, of each PCI versus CABG randomized trial, may overcome any differences in definitions used by individual studies and substantially increases statistical power to accurately assess potential treatment risks-and benefits for patients with coronary artery disease who are randomized to undergo PCI or CABG.

REFERENCES

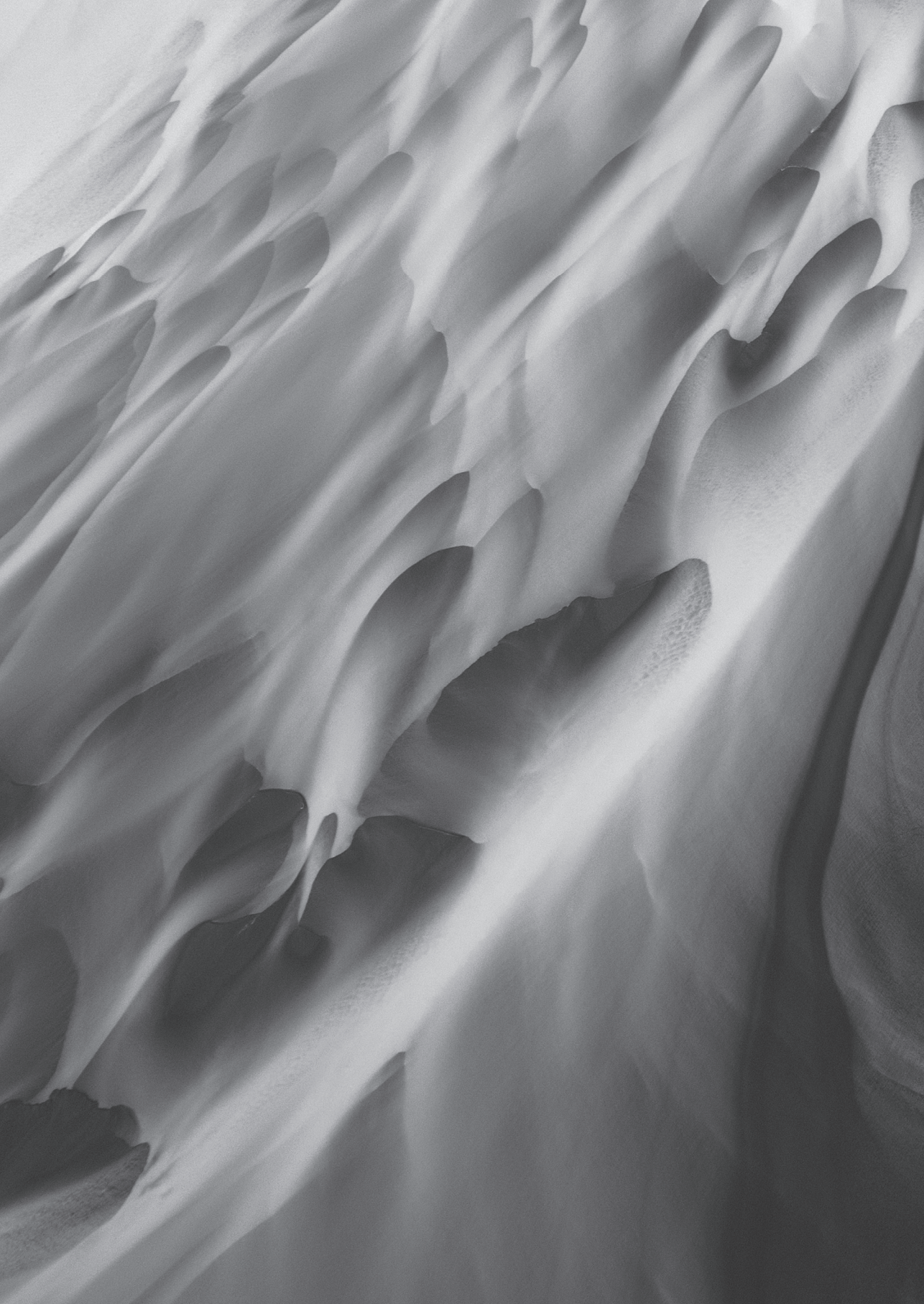
1. Olearchyk AS. Vasilii I. Kolesov. A pioneer of coronary revascularization by internal mammary-coronary artery grafting. J Thorac Cardiovasc Surg 1988;96:13-8.
2. Favaloro RG, Effler DB, Groves LK, Fergusson DJ, Lozada JS. Double internal mammary artery-myocardial implantation. Clinical evaluation of results in 150 patients. Circulation 1968;37:549-55.
3. Grüntzig A. TRANSLUMINAL DILATATION OF CORONARY-ARTERY STENOSIS. The Lancet 1978;311:263.
4. Tan C, Schatz RA. The History of Coronary Stenting. Interv Cardiol Clin 2016;5:271-80.
5. Serruys P, Morice M, Kappetein A, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
6. Park S-J, Ahn J-M, Kim Y-H, et al. Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease. New England Journal of Medicine 2015;372:1204-12.
7. Makikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. Lancet 2016;388:2743-52.
8. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. N Engl J Med 2016;375:2223-35.
9. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg 2012;41:734-44; discussion 44-5.
10. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1–coronary artery bypass grafting surgery. Ann Thorac Surg 2009;88:S2-22.
11. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation 2009;119:3053-61.
12. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190-7.
13. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146-54.
14. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol 2011;58:1426-32.
15. Morice MC, Serruys PW, Kappetein AP, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. Circulation 2014;129:2388-94.
16. Cavalcante R, Sotomi Y, Lee CW, et al. Outcomes After Percutaneous Coronary Intervention or Bypass Surgery in Patients With Unprotected Left Main Disease. J Am Coll Cardiol 2016;68:999-1009.

17. Sousa-Uva M, Neumann F-J, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Journal of Cardio-Thoracic Surgery 2018:ezy289-ezy.
18. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014;64:1929-49.
19. Palmerini T, Serruys P, Kappetein AP, et al. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: A meta-analysis of 6 randomized trials and 4,686 patients. Am Heart J 2017;190:54-63.
20. Thuijs D, Habib RH, Head SJ, et al. Society of Thoracic Surgeons Risk Scores Performance in Patients with Left Main Coronary Artery Disease Undergoing Revascularization in the EXCEL trial. EuroIntervention 2019.
21. Head SJ, Kaul S, Mack MJ, et al. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. Eur Heart J 2013;34:2510-8.
22. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639-50.
23. Domingues CT, Milojevic M, Thuijs D, et al. Heart Team decision making and long-term outcomes for 1000 consecutive cases of coronary artery disease. Interact Cardiovasc Thorac Surg 2019;28:206-13.
24. Thuijs D, Milojevic M, Stone GW, et al. Impact of left ventricular ejection fraction on clinical outcomes after left main coronary artery revascularization: results from the randomized EXCEL trial. Eur J Heart Fail 2020.
25. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364:1607-16.
26. Wolff G, Dimitroulis D, Andreotti F, et al. Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis. Circ Heart Fail 2017;10.
27. Thuijs D, Head SJ, Stone GW, et al. Outcomes following surgical revascularization with single versus bilateral internal thoracic arterial grafts in patients with left main coronary artery disease undergoing coronary artery bypass grafting: insights from the EXCEL trial. Eur J Cardiothorac Surg 2018.
28. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet 2001;358:870-5.
29. Lytle BW, Blackstone EH, Loop FD, et al. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117:855-72.
30. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1-6.

31. Aldea GS, Bakaeen FG, Pal J, et al. The Society of Thoracic Surgeons Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting. Ann Thorac Surg 2016;101:801-9.
32. Toumpoulis IK, Theakos N, Dunning J. Does bilateral internal thoracic artery harvest increase the risk of mediastinitis? Interact Cardiovasc Thorac Surg 2007;6:787-91.
33. Taggart DP, Altman DG, Gray AM, et al. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). Eur Heart J 2010;31:2470-81.
34. Dai C, Lu Z, Zhu H, Xue S, Lian F. Bilateral internal mammary artery grafting and risk of sternal wound infection: evidence from observational studies. Ann Thorac Surg 2013;95:1938-45.
35. Gaudino M, Antoniades C, Benedetto U, et al. Mechanisms, Consequences, and Prevention of Coronary Graft Failure. Circulation 2017;136:1749-64.
36. Lopes RD, Mehta RH, Hafley GE, et al. Relationship between vein graft failure and subsequent clinical outcomes after coronary artery bypass surgery. Circulation 2012;125:749-56.
37. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: is it underutilized? Curr Opin Cardiol 2011;26:528-35.
38. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. The Lancet 2001;358:870-5.
39. Grau JB, Ferrari G, Mak AW, et al. Propensity matched analysis of bilateral internal mammary artery versus single left internal mammary artery grafting at 17-year follow-up: validation of a contemporary surgical experience. Eur J Cardiothorac Surg 2012;41:770-5; discussion 6.
40. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. Ann Thorac Surg 2010;90:101-8.
41. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. Ann Thorac Surg 2004;78:2005-12; discussion 12-4.
42. Gaudino M, Di Franco A, Rahouma M, et al. Unmeasured Confounders in Observational Studies Comparing Bilateral Versus Single Internal Thoracic Artery for Coronary Artery Bypass Grafting: A Meta-Analysis. J Am Heart Assoc 2018;7.
43. Taggart DP, Benedetto U, Gerry S, et al. Bilateral versus Single Internal-Thoracic-Artery Grafts at 10 Years. N Engl J Med 2019;380:437-46.
44. Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. J Am Coll Cardiol 2004;44:2149-56.
45. Gaudino M, Alexander JH, Bakaeen FG, et al. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. Eur J Cardiothorac Surg 2017.
46. Gaudino M, Fremes S, Kolh P. The jury is still out on the use of bilateral internal thoracic arteries in coronary surgery. Eur J Cardiothorac Surg 2018.
47. Head SJ, Kappetein AP. Coronary Bypass Surgery - An ART for Dedicated Surgeons. N Engl J Med 2019;380:489-91.

48. Antonides CFJ TD, Mahtab EAF, Lenzen MJ, Kappetein AP, Bogers AJJC, Head SJ. A Critical Appraisal of a Decade of Left-Main Revascularization Meta-Analyses. J Cardiology Research and Reports 2020.
49. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391:939-48.
50. Mohr FW, Morice M-C, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. The Lancet 2013;381:629-38.
51. Thuijs D, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet 2019.
52. Buszman PE, Buszman PP, Banasiewicz-Szkrobka I, et al. Left Main Stenting in Comparison With Surgical Revascularization: 10-Year Outcomes of the (Left Main Coronary Artery Stenting) LE MANS Trial. JACC Cardiovasc Interv 2016;9:318-27.
53. Farkouh ME, Domanski M, Dangas GD, et al. Long-Term Survival Following Multivessel Revascularization in Patients With Diabetes: The FREEDOM Follow-On Study. J Am Coll Cardiol 2019;73:629-38.
54. Head SJ, Holmes DR, Jr., Mack MJ, et al. Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries. JACC Cardiovasc Interv 2012;5:618-25.
55. Rothwell PM. Can overall results of clinical trials be applied to all patients? Lancet 1995;345:1616-9.
56. Yeh RW, Kramer DB. Decision Tools to Improve Personalized Care in Cardiovascular Disease: Moving the Art of Medicine Toward Science. Circulation 2017;135:1097-100.
57. Taggart DP, Altman DG, Gray AM, et al. Randomized Trial of Bilateral versus Single Internal-Thoracic-Artery Grafts. N Engl J Med 2016;375:2540-9.
58. Bourassa MG, Kip KE, Jacobs AK, et al. Is a strategy of intended incomplete percutaneous transluminal coronary angioplasty revascularization acceptable in nondiabetic patients who are candidates for coronary artery bypass graft surgery? The Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol 1999;33:1627-36.
59. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117-24.
60. Sarno G, Garg S, Onuma Y, et al. Impact of completeness of revascularization on the five-year outcome in percutaneous coronary intervention and coronary artery bypass graft patients (from the ARTS-II study). Am J Cardiol 2010;106:1369-75.
61. Kim YH, Park DW, Lee JY, et al. Impact of angiographic complete revascularization after drug-eluting stent implantation or coronary artery bypass graft surgery for multivessel coronary artery disease. Circulation 2011;123:2373-81.
62. Head SJ, Mack MJ, Holmes DR, Jr., et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. Eur J Cardiothorac Surg 2012;41:535-41.

63. Farooq V, Serruys PW, Bourantas CV, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. Circulation 2013;128:141-51.
64. Zimarino M, Ricci F, Romanello M, Di Nicola M, Corazzini A, De Caterina R. Complete myocardial revascularization confers a larger clinical benefit when performed with state-of-the-art techniques in high-risk patients with multivessel coronary artery disease: A meta-analysis of randomized and observational studies. Catheter Cardiovasc Interv 2016;87:3-12.
65. Stone GW, Kappetein AP, Sabik JF, et al. Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease. N Engl J Med 2019;381:1820-30.
66. Holm NR, Mäkikallio T, Lindsay MM, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. Lancet 2020;395:191-9.
67. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
68. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237-69.
69. Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med 2011;364:1718-27.
70. Park DW, Ahn JM, Yun SC, et al. 10-Year Outcomes of Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease. J Am Coll Cardiol 2018;72:2813-22.
71. Thuijs D, Bekker MWA, Taggart DP, et al. Improving coronary artery bypass grafting: a systematic review and meta-analysis on the impact of adopting transit-time flow measurement. Eur J Cardiothorac Surg 2019.
72. Di Giammarco G, Canosa C, Foschi M, et al. Intraoperative graft verification in coronary surgery: increased diagnostic accuracy adding high-resolution epicardial ultrasonography to transit-time flow measurement. Eur J Cardiothorac Surg 2013.
73. Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://wwwohrica/programs/clinical_epidemiology/oxfordasp 2013.
74. Taggart DP, Thuijs D, Di Giammarco G, et al. Intraoperative transit-time flow measurement and high-frequency ultrasound assessment in coronary artery bypass grafting. J Thorac Cardiovasc Surg 2019.



Chapter 15

List of publications

1. **Thuijs DJFM**, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet 2019.

2. **Thuijs DJFM**, Milojevic M, Stone GW, et al. Impact of left ventricular ejection fraction on clinical outcomes after left main coronary artery revascularization: results from the randomized EXCEL trial. Eur J Heart Fail 2020.

3. **Thuijs DJFM**, Habib RH, Head SJ, et al. Society of Thoracic Surgeons Risk Scores Performance in Patients with Left Main Coronary Artery Disease Undergoing Revascularization in the EXCEL trial. EuroIntervention 2019.

4. **Thuijs DJFM**, Head SJ, Stone GW, et al. Outcomes following surgical revascularization with single versus bilateral internal thoracic arterial grafts in patients with left main coronary artery disease undergoing coronary artery bypass grafting: insights from the EXCEL trial. Eur J Cardiothorac Surg 2018.

5. **Thuijs DJFM**, Milojevic M, Head SJ. Doubling up on antiplatelet therapy after CABG: changing practice ASAP after DACAB? J Thorac Dis 2018.

6. **Thuijs DJFM**, Bekker MWA, Taggart DP, et al. Improving coronary artery bypass grafting: a systematic review and meta-analysis on the impact of adopting transit-time flow measurement. Eur J Cardiothorac Surg 2019.

7. **Thuijs DJFM**, Durko A, Mahtab E, et al. Composite LITA-RITA-Y graft configuration for coronary artery bypass grafting. Multimed Man Cardiothorac Surg 2018.

8. Takahashi K, Serruys PW, Fuster V, Farkouh ME, Spertus JA, Cohen DJ, Park SJ, Park DW, Ahn JM, Kappetein AP, Head SJ, **Thuijs DJFM**, Onuma Y, Kent DM, Steyerberg EW, Klaveren D, on behalf of the SYNTAXES, FREEDOM, BEST, and PRECOMBAT trial investigators. Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAX trial with external cohort validation. Lancet 2020.

9. Taggart DP, **Thuijs DJFM**, Di Giammarco G, et al. Intraoperative transit-time flow measurement and high-frequency ultrasound assessment in coronary artery bypass grafting. J Thorac Cardiovasc Surg 2019.

10. Knol W, **Thuijs DJFM**, Odink AE, et al. Preoperative chest computed tomography screening for coronavirus disease 2019 in asymptomatic patients undergoing cardiac surgery. Seminars in Thoracic and Cardiovascular Surgery 2020.

11. Hara H, Serruys PW, Takahashi K, Kawashima H, Ono M, Gao C, Wang R, Mohr FW, Holmes DR, Davierwala PR, Head SJ, **Thuijs DJFM**, Milojevic M, Kappetein AP, Garg S, Onuma Y, Mack MJ and for the SYNTAX Extended Survival Investigators. Impact of Peri-Procedural Myocardial Infarction on Outcomes After Revascularization. J Am Coll Cardiol 2020.

12. **Thuijs DJFM**, Hickey GL, Osnabrugge RLJ. Statistical primer: basics of survival analysis for the cardiothoracic surgeon. Interact Cardiovasc Thorac Surg 2018;27:1-4.

13. Domingues CT, Milojevic M, **Thuijs DJFM**, et al. Heart Team decision making and long-term outcomes for 1000 consecutive cases of coronary artery disease. Interact Cardiovasc Thorac Surg 2018.

14. Durko A, **Thuijs DJFM**, Mahtab E, et al. Conventional open harvesting of the great saphenous vein as a conduit for coronary artery bypass grafting. Multimed Man Cardiothorac Surg 2018;2018.

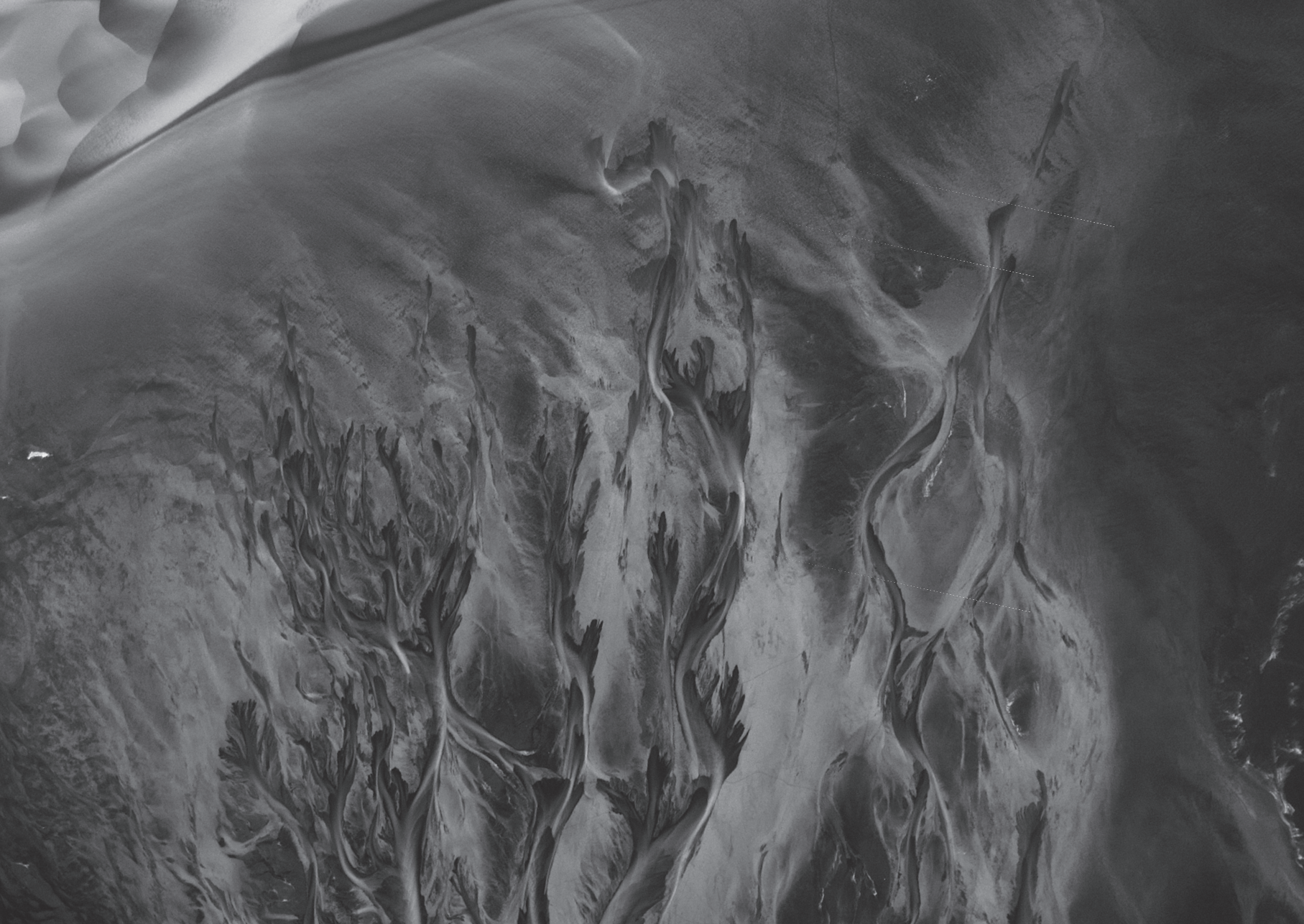
15. Milojevic M, **Thuijs DJFM**, Head SJ, et al. Life-long clinical outcome after the first myocardial revascularization procedures: 40-year follow-up after coronary artery bypass grafting and percutaneous coronary intervention in Rotterdam. Interact Cardiovasc Thorac Surg 2019.

16. Durko A, **Thuijs DJFM**, Mahtab E, et al. How to construct and use a low-fidelity coronary anastomosis simulator. Multimed Man Cardiothorac Surg 2019;2019.

17. Maat A, Durko A, **Thuijs DJFM**, et al. Extended pleurectomy decortication for the treatment of malignant pleural mesothelioma. Multimed Man Cardiothorac Surg 2019.

18. Takahashi K, **Thuijs DJFM**, Hara H, et al. Impact of the CABG SYNTAX Score on 10-year All-cause Death: Insights from the SYNTAX Extended Survival Study. EuroIntervention 2020.

19. Hara H, Takahashi K, van Klaveren D, **Thuijs DJFM** et al. Sex Differences in All-Cause Mortality in the Decade Following Complex Coronary Revascularization. J Am Coll Cardiol 2020.



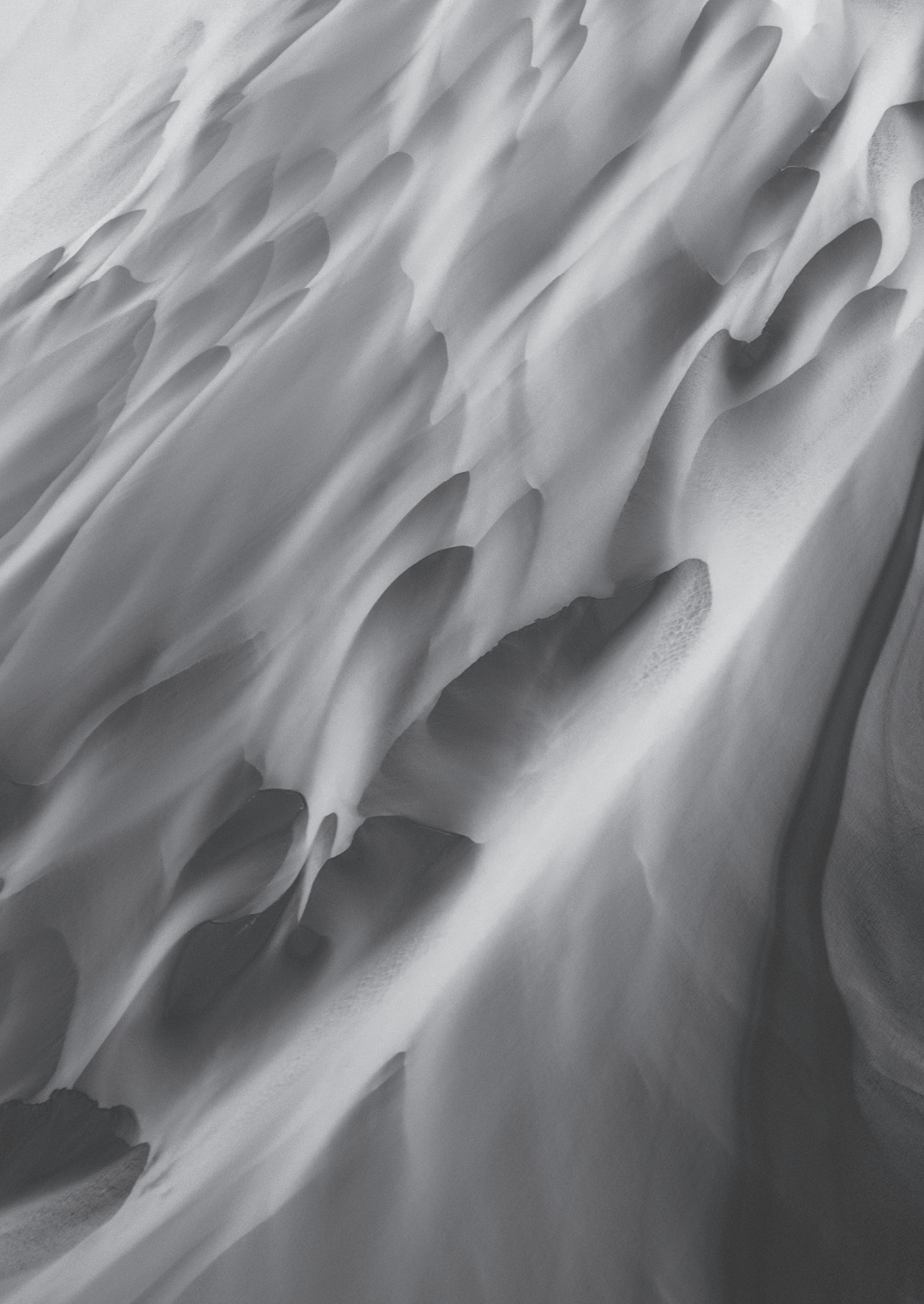
Chapter 16

PhD portfolio

Name:	Daniël Johannes Franciscus Maria Thuijs
Erasmus MC department:	Cardiothoracic Surgery
Research school:	Cardiovascular Research School (COEUR)
Ph.D. period:	June 2017 – October 2020
Promotor:	Prof. dr. A.P. Kappetein
Co-promotor:	dr. S.J. Head

Conferences (9.20)	Year	ECTS
Dutch Association for Cardiothoracic Surgery, Utrecht, The Netherlands	2017-2019	1.20
EACTS annual meeting, Lisbon, Portugal	2019	1.20
EACTS annual meeting, Milano, Italy	2018	1.20
Transcatheter Cardiovascular Therapeutics, San Diego, USA	2018	1.20
Dutch Association for Cardiothoracic Surgery/Dutch Association for Cardiology, Papendal, The Netherlands	2018	0.40
Dutch Association for Cardiothoracic Surgery/Belgium Association for Cardiothoracic Surgery, Antwerp, Belgium	2017	0.40
EACTS annual meeting, Vienna, Austria	2017	1.20
Presentations (4.80)		
EACTS annual meeting, Lisbon, Portugal	2019	0.60
European Society of Cardiology, Paris, France	2019	0.60
Transcatheter Cardiovascular Therapeutics, San Diego, USA	2018	0.60
EACTS annual meeting, Milano, Italy	2018	0.60
Dutch Association for Cardiothoracic Surgery, Utrecht, The Netherlands	2017	0.60
Dutch Association for Cardiothoracic Surgery/Belgium Association for Cardiothoracic Surgery, Antwerp, Belgium	2017	0.60
EACTS annual meeting, Vienna, Austria	2017	0.60
Transcatheter Cardiovascular Therapeutics, Denver, USA	2017	0.60
General courses (3.00)		
NIHES Biostatistical Methods – Part A	2018	1.20
NIHES Logistic Regression	2018	0.60
Research Integrity	2017	0.30
Basic course for clinical investigators (BROK)	2017	0.30
Systematic Literature Retrieval in PubMed	2017	0.30
Basic introduction course on SPSS	2017	0.30

COEUR courses (2.90)		
COEUR Ph.D. day	2017 - 2019	0.90
COEUR courses	2018 - 2019	2.00
Sex & Gender in Cardiovascular research		
Aneurysmal disease		
Endothelial erosion of plaques		
Imaging for Ischemic Heart and Brain Disease		
Solving the Mysteries of Atrial Fibrillation		
In-depth courses and educational skills (10.00)		
Local scientific Cardiothoracic Surgery meetings, Rotterdam	2018 - 2019	3.00
TV-studio host EACTS annual meeting – Vienna, Milano, Lisbon	2017-2019	3.00
Cardiac ultrasound– Left Ventricular Hypertrophy, Dordrecht	2018	0.20
Regional Oncologic Thoracic Surgery meetings, Rotterdam	2017 - 2018	0.40
Symposium – The A(orta)-Team Hart Long Centrum, Leiden	2018	0.40
Professional Leadership – EACTS, Windsor	2018	1.00
Transplantation course and symposium – Erasmus MC, Rotterdam	2018	2.00
Teaching (2.20)		
PCI vs. CABG lecture, Critical Care Unit, Erasmus MC, Rotterdam	2019-2020	0.20
Coaching medical students during bachelor, Erasmus MC, Rotterdam	2019-2021	1.50
SAVR vs. TAVR lecture, Cardiology, Sint-Franciscus Gasthuis, Rotterdam	2017-2019	0.30
Minor Cardiovascular disease – supervising students, Erasmus MC, Rotterdam	2018	0.10
Medical carrier information for students, Carrier-event, Erasmus MC, Rotterdam	2018	0.10



Chapter 17

About the author

Daniël Johannes Franciscus Maria Thuijs, son of Alphons and Inge was born August 22nd, 1988 in 's-Hertogenbosch, The Netherlands. He graduated from high school the "Sint-Jans Lyceum" in August 2007, after which he started "Sportmarketing and Management" at the "Hogeschool van Amsterdam", where he obtained his propaedeutic certificate of applied sciences in January 2009.

From January to August 2009 he worked as an account-manager in their family-run business "Ties International". During that period he gained valuable knowledge regarding management, sales and how to set your own goals and continue to pursue them. Then he also realized that he wanted to pursue his ambition of becoming a medical doctor.

In August 2009 he studied Biology, Physics and Chemistry at the "James Boswell Institute" in Utrecht, The Netherlands. After successfully passing all courses in July 2010, he started studying Medicine at the Erasmus University Rotterdam in August 2010. Throughout his study, he worked as a medical student at the department of Cardiothoracic Surgery, gathering valuable clinical knowledge, as well as learning the pre- and postoperative trajectory from a patients perpestice after cardiac or thoracic surgery. This laid the foundation for his carrier in Cardiothoracic Surgery. For his master thesis he studied the influence of reactive oxygen species (ROS) on the endothelium of coronary arteries at the department and laboratory of Experimental Cardiology, in close collaboration with the Cardiothoracic Surgery the Intensive Care and the Pharmacology department of the Erasmus University Medical Centre.

In December 2016 he obtained his medical degree and started working as a resident-not-in-training at the Cardiothoracic Surgery department in the Erasmus University Medical Centre. After 5 months at the Cardiothoracic Surgery department, he was offered an opportunity to start his scientific carrier by working on this Ph.D. thesis. This opportunity was followed by the priceless possibility to start as a resident in training in Cardiothoracic Surgery in October 2019. To date, Daniel works as a Cardiothoracic surgeon in training in Rotterdam.

Besides spending time and energy in obtaining his Ph.D. degree and becoming a skilful cardiothoracic surgeon, he loves to spend time on the beach to go surfing, on the snowy slopes to go snowboarding, on a motorbike and with his girlfriend, family and friends. For Daniel, surfing, snowboarding and riding motorbikes are

the ultimate ways of regaining energy, staying focussed and clearing his mind. This helps him to aim for a healthy work-life balance and striving to excel on a daily basis.

Chapter 18

Acknowledgements

First, I would like to start off with a statement in which I truly believe: "You can become anything you want in life, only if you put your mind to it". Over the past years, I have put my mind into becoming a cardiothoracic surgeon in training; aiming to eventually develop myself as a skilful and successful Cardiothoracic Surgeon. This journey also enabled me to contribute scientifically and work on my Ph.D. thesis. Therefore, having completed my Ph.D. thesis in the field of myocardial revascularisation makes me extremely proud and grateful. Herewith, I would like to thank all of you that encouraged and supported, contributed to my scientific and clinical cardiothoracic surgery journey and provided me with important life-lessons along the way.

I would gratefully like to thank my promotor**, Professor dr. A. Pieter Kappetein**, for introducing me to the (inter)national playfield of scientific research in cardiothoracic interventions. Thereby, I would like to thank you for the opportunity to work on my Ph.D. thesis over the past few years and collaborate with many international "giants in the field" of cardiology and cardiothoracic surgery. You have opened a lot of doors for me. Moreover, I would also like to thank you for sharing your knowledge on locating the best coffee roasters in town when we were on conferences in various cities around the world. My Google Maps account has been enriched with dozens of new handbrewn, V60 and French Press coffee locations. Thank you for believing in me.

Then I would like to express my sincere gratitude to **dr. Stuart Head** that helped me develop my scientific knowledge. Stuart motivated me to be (even more) disciplined, to work (even) harder, and to keep pursuing my goals and dreams. For me it felt more as working together with Stuart, as a colleague, than working under the supervision of Stuart as him being my co-promotor. I believe that this way of working enabled me to fully commit to obtaining the long-awaited 10-year survival data for the SYNTAXES study. Thereby, drinking fresh Californian beers at a rooftop- bar after an afternoon of surf in San Diego are moments that I will never forget. Not to mention the drinks and dances in Vienna and Milan! Thank you for all your support and encouragement, sharing you knowledge and steering me in the right direction!

Professor dr. Ad Bogers, thank you very much for providing numerous opportunities to develop myself as a medical doctor and as a researcher. During my Bachelors and Masters study in Medicine, I worked as a medical student-assistant at the cardiothoracic surgery department where I had the possibility to gain valuable knowledge on perioperative care for patients requiring surgery. I spent my final clinical rotation as "oudste co-assistent" at the department, where I learned the tips and tricks

of working as a medical doctor in cardiothoracic surgery. During this rotation I applied for a position as resident not in training. I prepared myself well by dressing up in a suit and tie, brought some letters of recommendation, printed out my CV and thought of all the hard questions that you could ask me. However, during a brief and informal conversation you ensured me that by being "well-prepared and dressed in a suit and tie" you had to hire me! Exciting months as resident not in training in the operating theater and at the department followed, after which I started my Ph.D. trajectory. During this trajectory you supervised my Ph.D. process, reviewed some of my manuscripts and fulfilled a crucial role in the regulatory process of the SYNTAXES study. Thank you very much for your guidance, advice and assistance during my medical career.

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During my Ph.D. I had the privilege to have my desk located at various locations inside the Erasmus MC building. Starting in the BD-hallway of the "historical" Thoraxcentre, moving to the "basement" in the Z-flat and ending in the new, incredibly "practical", office in the RG building (a.k.a. de "kantoortuin"). Besides seeing lots of new faces passing by every day in the "kantoortuin", it was there that I also realized that I cannot imagine a well-functioning department without a proper working back-office that coordinates and manages a lot of the "behind the scenes" cardio-

thoracic hassle. Therefore, I would also like to thank the CTC back-office colleagues from the "kantoortuin"; **Wilma**, **Jos**, **Maureen**, **Caroline, Solita, Titia** and **Maaike**.

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A special thanks also goes out to explorer, adventurist and photographer **Chris Burkard** and his team. I am honored that you have allowed me to use of one of your amazing photographs, shot from an airplane in Iceland. This image now enriches the cover of my thesis. For me it resembles freedom, adventure, curiosity and the glacial rivers also look a bit like (coronary) blood vessels I believe. Keep up your great work!

I am blessed to have so many friends surrounding me. Close friends with whom I can celebrate special, and also not so special, occasions with; friends that support me in my decisions and ambitions; friends that can also be critical and allow me to reconsider my thoughts and actions; friends with whom I can share emotional moments with; with whom I can laugh and cry, and friends with whom I can go on our traditional yearly surf-trip! Thanks to all my **buddies** for being there, and I am looking forward to all the great and exciting parties, drinks, diners, surf trips and personal victories yet to come! My special thanks go out to **Jens** and **Yaar**, my "promovendi partners-in-crime". I am proud to have you both at my side during my PhD defense as paranymphs We know each other since the beginning of our medical career and luckily we have spent much time together both inside as outside the hospital. Our trip to Costa Rica was definitely the highlight! I hope we stay friends, colleagues and doctors for life!

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An important cornerstone in my life is my **family.** I have great admiration and respect for how my parents, **Alphons** and **Inge**, live their lives and how they have raised me. My parents are very ambitious, highly supportive, extremely positive and most of all great humans! I want to thank them for all the opportunities that they warranted and created for me, for allowing me to transfer from an economical study to a career in Medicine, for letting me chase my goals and dreams and most of all for guiding me to grow up to the person that I am today! I am truly blessed with you.

Although times might have been challenging the last couple of years, you remain positive, keep looking for opportunities and never stop developing and believing in yourself. I am exceptionally proud of you and I love you!

Moreover, I am very lucky to have an awesome brother and sister! It is great to realize that I can learn a lot from you both! **Annique**, the way you blast through life, fully committed to everything you do, and you do a lot, a whole lot! Working hard, yet enjoying life even harder. Exploring all continents, riding your motorbike, meeting new people, planning to learn kite-surfing, it seems that there are no limitations to your capabilities Although choosing what to do first seems challenging sometimes, you inspire me with your enthusiasm and living life to the fullest. I love you! **Wieger**, my "younger" brother, I look up to you my friend! I am very proud to call you my brother, and I believe that you should be very proud of who you are today and all that you have accomplished over the years. Since a couple of years, I can no longer see you as my "little" brother, since you are a full-grown man that now runs his own business. You have shown to be a thoughtful, ambitious, loyal, caring and one hell of a good friend to me! Keep up your head, walk with your chest

forward and chin up, “grab life by the balls” and be incredibly proud of yourself, each and every day. You deserve that! I love you!

My grandmother, **Hanna**, played an important role in developing my curiosity and interest in the medical field. As a kid we watched all the Emergency Rooms TV shows and called each other when a (live) operation was being aired on television. Thank you for your enthusiasm, (life)-lessons and being a proud grandmother.

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Ps. I truly believe that you will be the best mother in the world for our **baby boy**! Exciting times are up ahead and I cannot wait to see what the future has to bring for as a family! Simone, ik heb je lief!