

Long-term safety and feasibility of three-vessel multimodality intravascular imaging in patients with ST-elevation myocardial infarction: the IBIS-4 (integrated biomarker and imaging study) substudy

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Abstract We assessed the feasibility and the procedural and long-term safety of intracoronary (i.c) imaging for documentary purposes with optical coherence tomography (OCT) and intravascular ultrasound (IVUS) in patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary PCI in the setting of IBIS-4 study. IBIS4 (NCT00962416) is a prospective cohort study conducted at five European centers including 103 STEMI patients who underwent serial three-vessel coronary imaging during primary PCI and at 13 months. The feasibility parameter was successful imaging, defined as the number of pullbacks suitable for analysis. Safety parameters included the frequency of peri-procedural complications, and major

adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction (MI) and any clinically-indicated revascularization at 2 years. Clinical outcomes were compared with the results from a cohort of 485 STEMI patients undergoing primary PCI without additional imaging. Imaging of the infarct-related artery at baseline (and follow-up) was successful in 92.2 % (96.6 %) of patients using OCT and in 93.2 % (95.5 %) using IVUS. Imaging of the non-infarct-related vessels was successful in 88.7 % (95.6 %) using OCT and in 90.5 % (93.3 %) using IVUS. Periprocedural complications occurred <2.0 % of OCT and none during IVUS. There were no differences throughout 2 years between the imaging and control group in terms of MACE (16.7 vs. 13.3 %, adjusted HR1.40, 95 % CI 0.77–2.52, $p = 0.27$). Multi-modality three-vessel i.c. imaging in STEMI patients undergoing primary PCI is consistent a high degree of success and can be performed safely without impact on cardiovascular events at long-term follow-up.

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Keywords Optical coherence tomography · Intravascular ultrasound · ST-segment elevation myocardial infarction · Long-term safety

Abbreviations and acronyms

ARC	Academic research consortium
CI	Confidence interval
DES	Drug-eluting stent
MACE	Major adverse cardiac event
MI	Myocardial infarction
ST	Stent thrombosis
TLF	Target lesion failure
TLR	Target lesion revascularization
IVUS	Intravascular ultrasound
IVUS-VH	IVUS virtual histology
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction

Introduction

Multimodality intracoronary (i.c.) imaging using optical coherence tomography (OCT), grayscale intravascular ultrasound (IVUS), and IVUS-virtual histology (IVUS-VH) provides means to characterize coronary atherosclerosis and optimize stent implantation in a comprehensive manner. Based on near-infrared light, OCT visualizes in great detail the vascular luminal integrity, thrombus, and characteristics of plaque vulnerability and facilitates the detection of geographical miss, stent strut malapposition and edge dissections following stent implantation [1]. Although the resolution of IVUS is an order of magnitude lower than OCT, the technology provides a greater penetration depth and therefore the ability to assess plaque volume [2]. IVUS-VH is based on radiofrequency analysis and has been proposed as a method to assist the evaluation of plaque composition, particularly necrotic core [3]. The combined use of these sound- and light-based modalities theoretically increases the accuracy to detect “vulnerable” plaques [4, 5], and may thus provide a complete platform to exploit future treatment targets. Additionally, these technologies have the potential to improve cardiovascular outcomes by optimizing percutaneous coronary intervention (PCI), particularly in STEMI patients [6].

Nevertheless, the use of intracoronary imaging catheters may be accompanied by procedural complications including injury of the endothelium, which may increase the risk of short- and long-term events. Despite an increasing use of intracoronary imaging in daily practice, there is insufficient data on the feasibility and safety of multimodality imaging.

We therefore aimed to analyse the feasibility and short- and long-term safety of patients enrolled in the IBIS-4 imaging study, a prospective, observational multicenter study with the objective to assess the arterial healing after biolimus-eluting stent implantation versus bare metal stent implantation and to investigate the changes in atherosclerosis on the background of a high intensity statin therapy in the two non-infarct related arteries. [7].

Methods

Study population

IBIS 4 (NCT00962416) is a prospective cohort study nested into the COMFORTABLE-AMI, a trial comparing the safety and efficacy of a biolimus-eluting stent with a bare metal stent in 1161 STEMI patients undergoing primary PCI at 11 international centers [8]. A total of 103 patients were enrolled in this imaging study using OCT, IVUS and IVUS-VH to assess the arterial healing response following stent implantation and to quantify changes in atherosclerotic plaque characteristics in non-infarct related arteries in the presence of high dose statin therapy (rosuvastatin 40 mg daily).

Patients enrolled in the COMFORTABLE-AMI trial were eligible for participating in the IBIS 4 study when the following criteria were met: age <90 years, haemodynamic stability allowing the administration of nitroglycerine, preserved renal function (GFR >30 ml/min), \geq TIMI II flow of the infarct-related artery at the end of the intervention, and a coronary anatomy considered suitable for intracoronary imaging (e.g. absence of vessel tortuosity).

Following PCI, multimodality imaging with OCT followed by IVUS/IVUS-VH was performed, first addressing the treated culprit lesion, and then the two non-infarct related arteries. Care was taken to maintain an activated clotting time >250 s, and prior to each pullback, i.c. nitroglycerine (200 μ g) was administered to achieve maximal vasodilatation. After complete acquisition, imaging pullbacks were analyzed offline by an independent CoreLab (Cardialysis B.V., Rotterdam). The study protocol defined the intracoronary imaging as documentary. Although intervening physicians were not blinded to the acquired pullbacks, they were recommended not to perform any corrective measures based on the imaging findings.

All patients were scheduled for repeat angiography and the same three vessel multimodality imaging protocol at 13 months. In total, they were followed up to 2 years, and events were recorded at 30 days, 1 year, and 2 years. Per protocol, all patients received rosuvastatin 40 mg once daily throughout the 13 month follow-up period.

The control group of the present study consisted of 485 patients who were simultaneously enrolled in the

COMFORTABLE-AMI study at the five imaging centers, but who did not undergo imaging although they formally fulfilled the inclusion criteria for the imaging sub-study. All patients provided written informed consent for the participation in both the COMFORTABLE-AMI study and IBIS 4.

OCT

OCT images were acquired using the frequency domain (FD) C7 console system (Lightlab, St. Jude, Westford, MA, USA) and the Dragonfly catheter at a pullback speed of 20 mm/sec. Blood clearance was achieved using the non-obstructive technique with a power injector applying flushing rates of 3–6 ml/sec depending on vessel size. The regions of interest included in the culprit vessel: at least 5 mm of the proximal and distal reference vessel segments; and as much as possible of the proximal non-infarct-related arteries, though a minimum of 40 mm as measured from the respective ostia.

IVUS

IVUS-images were acquired with the Volcano s5 system (Volcano Corp., Rancho Cordova, CA) and the 2.9 French Eagle Eye catheter, which uses a 20 MHz transducer, at a continuous motorized pullback rate of 0.5 mm/sec (*R-100 pullback device; Volcano Therapeutics*). The regions of interest were the same as for OCT, as were the storage of pullbacks and transfer to CoreLab for further offline analysis.

Antithrombotic therapy regimen

All patients were loaded with aspirin (≥ 250 mg) prior to the procedure. In centers where prasugrel was available, an initial dose of 60 mg (including patients preloaded with clopidogrel) was given followed by a daily maintenance dose of 10 mg. If prasugrel was not available or contraindicated, clopidogrel was administered at a loading dose of 600 mg, followed by 75 mg twice daily for 7 days, followed by a maintenance dose of 75 mg daily. Dual antiplatelet therapy was prescribed for the duration of 13 months.

Feasibility parameters

Feasibility was defined as the acquisition of a pullback with sufficient image quality for independent CoreLab analysis, e.g. allowing the acquisition of ≥ 70 % of the region of interest and satisfactory blood clearing with visibility of ≥ 3 quadrants in ≥ 70 % of the pullback length.

Safety parameters

The following procedural complications (directly related to the imaging or within 24 h of the procedure) were prospectively collected: coronary artery dissection (angiographic) or vessel perforation, ventricular fibrillation, symptomatic brady- or tachyarrhythmia, thrombus formation, spasm and air embolism.

The primary clinical safety endpoint was a composite of cardiac death, myocardial infarction and any clinically indicated revascularization. Secondary safety endpoints included death, cardiac death, myocardial infarction, Academic research consortium (ARC)-defined definite- and definite or probable stent thrombosis and major bleeding events according to the Bleeding-ARC (BARC) definition. All definitions of endpoints used in this study have been previously reported [9]. Any revascularization refers to all revascularizations [target-lesion revascularization (TLR), target-vessel revascularization (TVR), and non-TVR]. Acute renal failure was defined as an absolute increase in serum creatinine of >1.5 fold from baseline or a glomerular filtration rate decrease of >25 % within 72 h.

Data management

Independent study monitors verified source data according to a prespecified monitoring plan. Data were stored in a central online database. Follow-up appointments were scheduled at 30 days, 1 and 2 years, and patients were questioned about the occurrence of angina, any adverse events. All events were independently adjudicated by a clinical event committee.

Statistical analysis

Categorical variables are presented as counts with percentages and compared using Chi square or Fisher's tests, and continuous variables as means with standard deviations or medians and interquartile ranges, and compared using the Student *t* test and Mann–Whitney U-test, respectively. Lesion-level data were analyzed using general or generalized linear mixed models, nesting lesions within patient identifiers, wherever applicable. Time-to-first event or composite events were analyzed using Cox's regression analysis comparing the Imaging group and the control group (at 30 days, 1 and 2 years of follow-up), both crude (presented with Kaplan–Meier graphs), and adjusted (using inverse-probability of treatment weighting (IPTW), where the treatment is the imaging performed). IPTW was calculated using the following baseline variables: age, gender, body mass index, diabetes, hypertension, hypercholesterolemia, current smoker, renal insufficiency, anemia, pain onset within 6 h, Killip II, resuscitation, left ventricular

ejection fraction, treatment of a bifurcation lesion, small vessel ≤ 2.5 mm diameter, long lesion ≥ 20 mm length, SYNTAX score, TIMI flow pre-procedure, after 20 times multiple imputation of missing data using chained equations (IPTW Adjusted Cox's Regressions weight the patients by their IPTW and are based on 20 imputed datasets). Sensitivity crude and IPTW adjusted Cox's regression analyses were conducted on the primary outcome, stratifying patients according to whether they received clopidogrel loading or prasugrel/double loading during the index procedure. Similarly, event rates at discharge were analyzed using Crude or IPTW Adjusted Poisson Regressions with robust error variances and reported as Risk Ratios RR with 95 % confidence intervals (95 % CI). *p* values from Fisher's tests are reported in case of zero events. All statistical analyses were performed with Stata 12.1 (StataCorp, Texas, USA) and differences were considered significant at $\alpha = 0.05$.

Results

A total of 103 STEMI patients undergoing primary PCI were included at five European centers into the IBIS 4 imaging study between September 2009 and January 2011.

Feasibility of multimodality intracoronary imaging

The feasibility of OCT, grayscale IVUS, and IVUS-VH at baseline and follow-up imaging is shown in Table 1. Imaging of the infarct-related artery at baseline (and follow-up) was successful in 92.2 % (96.6 %) patients using OCT, 93.2 % (95.5 %) patients using grayscale IVUS and 88.3 % (94.3 %) patients using IVUS-VH. Imaging of the non-infarct related artery at baseline (and follow-up) was successful in 88.7 % (95.6 %) patients using OCT, 90.5 % (93.3 %) patients using grayscale IVUS and 83.1 % (92.6 %) patients using IVUS-VH, respectively. In case an OCT pullback was successfully acquired, the frequency of OCT frames not analyzable both at baseline and follow-up was 0.3 %. Failure of OCT imaging was mainly related to insufficient image quality due to incomplete vessel flushing but also due to difficulties to advance the OCT catheter in the non-infarct related artery. IVUS-VH imaging failure was mainly caused by technical problems with the ECG transmission for gating of the acquisition, and by the use of manual- instead of automatic pullback.

Procedural complications

In the setting of primary PCI, in two out of 103 patients (1.9 %), the OCT pullback acquisition resulted in a complication at baseline, and in one out of 91 patients (1.1 %)

at follow-up. Specifically, a dissection at the proximal stent edge was caused by the tip of the OCT imaging catheter in one of the cases at baseline; whereas the other two complications (one at baseline, one at follow-up) consisted of ventricular fibrillation induced by vessel flushing with contrast. Complications were managed by additional stent implantation in the former case, and successful defibrillation in the other cases, without further sequelae. IVUS imaging was performed without complications; and there were no cases of i.c. related thrombus formation, perforation, air embolism, or mechanical device failure or spasm (Table 2).

Safety analysis

A total of 103 imaging patients were compared to a cohort of 485 control patients.

Baseline clinical characteristics of the two groups are shown in Table 3. Imaging patients were younger, more frequently male, had a higher BMI and were less likely to have hypercholesterolemia compared to patients not undergoing i.c. imaging. Imaging patients were more often resuscitated prior to hospital admission. Prognostically important characteristics like diabetes, Killip classification and left ventricular function were similar. Procedural characteristics are shown in Table 4. Other than a lower maximal balloon pressure and a higher amount of contrast used, there was no significant difference between groups. Antithrombotic medication prior or during the procedure and at hospital discharge is shown in Table 5. Imaging patients more frequently (58.3 vs. 32.7 %, $p < 0.001$) received a concomitant loading dose of prasugrel in addition to clopidogrel and were more frequently discharged with prasugrel as compared with control patients (77.5 vs. 52.1 %, $p < 0.001$), the proportion of patients on double antiplatelet therapy at discharge, however, was similar.

Short and long term outcomes of patients undergoing intracoronary imaging

Table 6 presents clinical outcomes at 30 days, 1 and 2 years. The primary endpoint MACE was similar for patients undergoing i.c. imaging and controls at 2 years (16.7 vs. 13.3 %, adjusted HR 1.4, 95 % CI 0.77–2.52, $p = 0.27$) (Fig. 1). Similarly, no differences in the individual endpoints including death, myocardial infarction and any revascularization were observed at 2 years (Fig. 2). Two recurrent myocardial infarctions were noted in the imaging group within 30 days. One event was related to an early stent thrombosis 4 days after stent implantation in a calcified ostial RCA lesion due to stent underexpansion. The second event occurred in a patient who was readmitted with cardiogenic shock due to ischemic mitral regurgitation

Table 1 Feasibility of OCT, IVUS, and IVUS-VH at baseline and 13 months follow-up. Bold numbers indicate the overall success of i.c. imaging

	Infarct-related vessel			Non-infarct-related vessel		
	OCT	IVUS	IVUS-VH	OCT	IVUS	IVUS-VH
Baseline						
Number of patients	103			103		
Number of vessels available for imaging	103	103	103	204	201	201
Successful imaging	95 (92.2)	96 (93.2)	91 (88.3)	181 (88.7)	181 (90.5)	172 (83.1)
Unsuccessful imaging	8 (7.8)	7 (6.8)	12 (11.7)	23 (11.3)	20 (9.5)	29 (14.4)
Failure to cross lesion	1 (1.0)	3 (2.9)	3 (2.9)	11 (5.4)	9 (4.5)	9 (4.5)
Technical problem ^c	0	1 (1.0)	6 (5.8)	0	3 (1.5)	12 (6.0)
Insufficient quality for analysis	6 (5.8)	2 (1.9)	2 (1.9)	10 (4.9)	6 (3.0)	6 (3.0)
Patient compliance ^d	1 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)
Follow-up						
Number of patients	91			91		
Total number of vessels available for imaging	91	91	91	185	183	183
Not obtained as at baseline ^a	2	2	2	25	20	20
Successful imaging^b	86 (96.6)	85 (95.5)	84 (94.3)	153 (95.6)	152 (93.3)	150 (92.6)
Unsuccessful imaging	3 (3.4)	4 (3.4)	5 (5.6)	7 (4.4)	9 (5.5)	11 (7.3)
Failure to cross lesion	2 (2.2)	2 (2.2)	2 (2.2)	0	1 (0.6)	1 (0.6)
Technical problem ^c	0	2 (1.1)	3 (3.4)	1 (0.6)	5 (3.1)	7 (4.3)
Insufficient quality for analysis	1 (1.1)	0	0	3 (1.9)	1 (0.6)	1 (0.6)
Patient compliance ^d	0	0	0	3 (1.9)	2 (1.2)	2 (1.2)

Values are number (%) or mean \pm SD

OCT optical coherence tomography, IVUS intravascular ultrasound, VH virtual histology

^a Not investigated at follow-up as no baseline was available

^b The success rate at follow-up = successful imaging/(total number of vessel available – number of not obtained as at baseline)

^c Technical problem is defined as manual pullback or DVD defect or ECG trigger missing

^d Patient compliance is defined as preterm termination of the imaging procedure due to patient discomfort in view of the prolonged catheterization time

Table 2 Complications related to imaging procedure (per patient)

	Baseline		Follow-up	
	OCT N = 103	IVUS N = 103	OCT N = 91	IVUS N = 91
Dissection	1 (1.0)	0	0	0
Ventricular fibrillation	1 (1.0)	0	1 (1.1)	0
Symptomatic brady- or tachyarrhythmia	0	0	0	0
Thrombus formation	0	0	0	0
Perforation	0	0	0	0
Air embolism	0	0	0	0
Total	2 (1.9)	0	1 (1.1)	0

Values are number (%)

OCT optical coherence tomography, IVUS intravascular ultrasonography

with documentation of stent thrombosis. There was no significant difference in the rate of acute renal failure at 30 days between 2 groups (1 vs. 1.9 %, adjusted HR 0.68,

95 % CI 0.09–5.37, $p = 0.72$). Revascularization of non-infarct related arteries (clinically indicated non-TVR) is an important surrogate for lesion progression potentially

Table 3 Baseline clinical characteristics

	Imaging group (n = 103)	Control group (n = 485)	p value
Age (yrs)	58.2 ± 10.5	61.5 ± 12.2	0.012
Male (gender)	93 (90.3)	385 (79.4)	0.008
BMI (kg/m ²)	27.8 ± 4.2	26.8 ± 4.0	0.019
Cardiovascular risk factors			
Diabetes	13 (12.6)	65 (13.4)	1.00
Hypertension	48 (46.6)	212 (43.7)	0.66
Hypercholesterolemia	42 (40.8)	259 (53.7)	0.022
Current smoker	48 (46.6)	242 (50.4)	0.52
Family history of CAD	31 (31.0)	130 (27.3)	0.46
Renal failure	1 (1.0)	13 (2.7)	0.48
Previous MI	2 (1.9)	26 (5.4)	0.20
Previous CABG	0 (0.0)	13 (2.7)	0.14
Peak CK	1847 (1045–3494)	1652 (800–2814)	0.20
Peak CK-MB	187 (107–319)	160 (72–300)	0.20
Clinical presentation			
Time from symptom onset to balloon inflation (min)	258 (170–472)	244 (164–422)	0.72
Time from arrival at hospital to balloon inflation (min)	40 (30–56)	42 (30–63)	0.18
Killip class II, III, or IV	8 (7.8)	34 (7.0)	0.83
Resuscitation before hospital arrival	5 (4.9)	7 (1.4)	0.042
LVEF (%)	47.8 ± 9.4	48.6 ± 10.1	0.52

Values are expressed as mean ± SD or number (%)

BMI body mass index, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *CK* creatine kinase, *LVEF* left ventricular ejection fraction

related to i.c. imaging. Non-TVR occurred at a similar frequency in the imaging (9.0 %) and control group (4.8 %, HR 1.70, 95 % CI 0.76–3.81, $p = 0.20$). Similarly, there was no difference in the frequency of any clinically indicated revascularization (Table 6).

To investigate whether the observed differences in the use of P2Y12 inhibitors were responsible similar MACE rates, we performed a sensitivity analysis for the primary endpoint MACE. We found hazards to be consistent for both groups at any time point of follow-up when separately comparing patients receiving a clopidogrel loading dose (imaging vs. control group, adjusted 2 year HR 1.18, 95 % CI 0.39–3.61, $p = 0.77$) and those receiving either prasugrel or a double loading dose separately (adjusted 2 year HR 1.67 95 % CI 0.81–3.43, $p = 0.16$) (Appendix Table S1).

Discussion

This is the first report on the feasibility and safety of multimodality three-vessel intracoronary imaging in the setting of a prospective observational study in STEMI patients undergoing primary PCI. Less extensive intracoronary imaging may be used in daily clinical routine, a situation for which our findings are also applicable.

The following major findings apply to this study:

1. Multimodality three-vessel i.c. imaging was consistent with high degree of success, confirming the feasibility even in the acute setting of primary PCI at centers with various level of expertise in i.c. imaging.
2. Periprocedural complications were rare (1.9 % per patient at baseline, 1.1 % at follow-up), solely related to the imaging with OCT, and resolved without sequelae in all cases.
3. Rates of death and myocardial infarction at 30 days were similar between patients undergoing i.c. imaging and controls attesting to the procedural safety of three-vessel multimodality imaging.
4. Rates of MACE up to 2 years were low and similar for both groups indicating that diagnostic serial multimodality i.c. imaging is not associated with harm.

Feasibility

The present study demonstrates an overall high feasibility of both OCT and IVUS for imaging the infarct vessel, which did not differ between the baseline acute setting and the planned follow-up investigation at 13 months, suggesting that the acute presentation does not limit the success rate of i.c. imaging except in cases of hemodynamic

Table 4 Baseline procedural characteristics

	Imaging group (n = 103)	Control group (n = 485)	p value
No of lesions treated in infarct vessel	121	542	
Infarct vessel location			0.24*
Left main coronary artery	1 (1.0)	1 (0.2)	
Left anterior descending artery	46 (44.7)	184 (38.0)	
Left circumflex artery	18 (17.5)	68 (14.0)	
Right coronary artery	38 (36.9)	229 (47.3)	
Baseline TIMI flow			0.51*
0 or 1	73 (60.8)	351 (65.0)	
2	17 (14.2)	67 (12.4)	
3	30 (25.0)	122 (22.6)	
Lesion complexity			
Bifurcation lesion,no.	14 (13.6)	44 (9.1)	0.20*
Small vessel	14 (13.6)	67 (13.9)	1.00*
Long lesion	31 (30.1)	149 (31.0)	0.91*
SYNTAX MI Score	14.7 ± 6.7	14.5 ± 8.3	0.82*
Primary PCI procedure			
No. of stents per lesion	1.22 ± 0.51	1.30 ± 0.67	0.28*
Type of stent			
Biolimus-eluting stent	64 (52.9)	268 (49.8)	0.60*
Bare metal stent	57 (47.1)	274 (50.9)	0.57*
Stent length per lesion (mm)	22.1 ± 10.5	24.1 ± 13.2	0.16*
Stent diameter (mm)	3.25 ± 0.49	3.2 ± 0.7	0.36*
Direct stenting	24 (19.8)	127 (23.6)	0.31*
Maximal balloon pressure (atm)	13.7 ± 2.9	14.9 ± 3.4	<0.001*
Thrombus aspiration performed	70 (68.0)	288 (59.5)	0.12
Intravenous vasopressors	2 (1.9)	14 (2.9)	1.00
TIMI flow post-procedure			0.76
0 or 1	0 (0.0)	3 (0.6)	
2	2 (1.7)	22 (4.1)	
3	119 (98.3)	516 (95.4)	
Total amount of contrast used during primary PCI (ml)			
BL	268.3 ± 109.8	197.9 ± 88.8	<0.001
Total amount of contrast used for imaging (ml)			
BL	174 ± 72	n.a.	
FUP	169 ± 83	n.a.	
Total time for primary PCI intervention (min)	34.3 ± 18.5	36.2 ± 20.1	0.39
Total time used for imaging (min)	44 ± 22	n.a.	

Data are expressed as number (%) unless otherwise specified

IQR interquartile range, *SD* standard deviation, *PCI* percutaneous coronary intervention, *QCA* quantitative coronary angiography, *TIMI* thrombolysis in myocardial infarction, *BL* baseline, *FUP* follow-up, *MI* myocardial infarction, *n.a.* not applicable

* Mixed model *p* value accounting for lesions nested within patient

instability or poor PCI result. As opposed to the infarct-related vessels, the success rates for evaluating non-infarct related arteries were lower. The principal reason for this was the caliber of some of the arteries, vessel tortuosity, and an untreated stenosis. This is however, not surprising since these features typically make part of the exclusion criteria in OCT studies. Nevertheless, as we aimed at a

three-vessel evaluation in an already diseased patient population, with as few exclusion criteria as possible to minimize selection bias, these vessels were included yet still contribute to an overall high success rate. Studies investigating the feasibility of multimodality three-vessel i.e. imaging in STEMI patients undergoing primary PCI are lacking. Up until now, few studies performed three vessel

Table 5 Medication during the procedure and at discharge

	Imaging group (n = 103)	Control group (n = 485)	<i>p</i> value
Periprocedural medication			
Unfractionated heparin	101 (98.1)	478 (98.6)	0.66
Bivalirudin	6 (5.8)	29 (6.0)	1.00
Glycoprotein IIb/IIIa antagonists	54 (52.4)	241 (49.7)	0.67
Loading dose of clopidogrel and prasugrel			
Clopidogrel only (600 mg)	26 (25.2)	251 (52.0)	<0.001
Prasugrel only (60 mg)	17 (16.5)	68 (14.1)	0.54
Both	60 (58.3)	158 (32.7)	<0.001
No loading dose clopidogrel and prasugrel	0 (0.0)	6 (1.2)	0.60
Medication at discharge			
Aspirin	102 (100.0)	481 (99.8)	1.00
Clopidogrel	23 (22.5)	230 (47.7)	<0.001
Prasugrel	79 (77.5)	251 (52.1)	<0.001
Any dual antiplatelet therapy	102 (100.0)	480 (99.6)	1.00

Values are n (%)

(single modality) imaging with either OCT [10] or IVUS [11], however, these reports did not disclose the number of excluded patients related to imaging failures, thus only reported the number of pullbacks excluded due to insufficient imaging quality and safety data is not available.

Periprocedural complications

Peri-procedural complications were rare and solely related to the use of OCT. In two out of 103 OCT pullbacks (1.9 %), ventricular fibrillation occurred due to prolonged flushing with contrast media. Given the overall low frequency of ventricular fibrillation in this patient group presenting for primary PCI, and in view of the prompt restoration of sinus rhythm following defibrillation, OCT can be considered as a safe diagnostic tool. Nonetheless, physicians using this technology need to be aware about the potential of inducing ventricular fibrillation. The single dissection recorded at a proximal stent edge was related to the short monorail of the previous version of the dragonfly OCT catheter, which was difficult to advance in a vessel curvature.

The largest study with time-domain (TD-) OCT where peri-procedural complications were reported included 468 mainly stable coronary artery disease patients, and observed ventricular fibrillation in 1.1 % of patients, air embolism in 0.6 % and vessel dissection in 0.2 % of patients. Only few data is available on the safety of FD-OCT [12, 13], which acquires images at frame rates at least 10 times faster than TD-OCT and results in an improved

imaging quality. The marked simplification of the acquisition procedures and reduction in the required contrast volume has decreased the imaging procedure time and increased the imaging quality [11]. The absence of complications with the use of IVUS confirms the already known high degree of safety of this technique, and may be the result of device adaptations since the introduction of the technique in the early 1990s and the high degree of experience with its use. Conversely, OCT has been introduced only 15 years later. In our study, two participating study centers initiated the use of OCT only with the occasion of this study, which increases the applicability of the study results to a broader spectrum of centers performing i.c. imaging.

Short and long-term safety

We did not limit our analysis to peri-procedural complications and compared clinical outcome measures of safety between imaging patients and a control group. At 30 days, the composite endpoint cardiac death or MI occurred at a similar rate in imaging and non-imaging patients, further supporting the procedural and long-term safety of multi-modality imaging for documentary purpose. Similarly, no difference in cardiac death or MI was noted at 1 and 2 years of follow-up.

Safety concerns related to imaging procedures in native coronary arteries are not limited to peri-procedural complications occurring during the first 30 days after imaging but also apply to a hypothetical acceleration of

Table 6 Clinical outcomes at discharge, 30 days, 1, and 2 years

	Imaging group (n = 103)	Control group (n = 485)	Crude		IPTW adjusted	
			Hazard ratio (95 % CI)	p value	Hazard ratio (95 % CI)	p value
Clinical events at 30 days ^a						
Death	1 (1.0)	8 (1.7)	0.59 (0.07–4.69)	0.62	1.20 (0.15–9.47)	0.86
Cardiac death	1 (1.0)	8 (1.7)	0.59 (0.07–4.69)	0.62	1.20 (0.15–9.47)	0.86
MI	2 (2.0)	5 (1.0)	1.89 (0.37–9.73)	0.45	2.66 (0.51–13.85)	0.25
Death or MI	3 (2.9)	13 (2.7)	1.09 (0.31–3.83)	0.89	1.79 (0.50–6.34)	0.37
Cardiac death or MI	3 (2.9)	13 (2.7)	1.09 (0.31–3.83)	0.89	1.79 (0.50–6.34)	0.37
Clinically indicated revascularization (any)	2 (2.0)	7 (1.5)	1.35 (0.28–6.50)	0.71	1.82 (0.37–8.85)	0.46
Clinically indicated non-TVR	0 (0.0)	1 (0.2)	2.34 (0.21–25.57)	1.00	.	.
Clinically indicated TVR	2 (2.0)	7 (1.5)	1.35 (0.28–6.50)	0.71	1.82 (0.37–8.85)	0.46
Clinically indicated TLR	2 (2.0)	7 (1.5)	1.35 (0.28–6.50)	0.71	1.82 (0.37–8.85)	0.46
MACE ^a	3 (2.9)	16 (3.3)	0.88 (0.26–3.03)	0.84	1.43 (0.41–4.98)	0.57
Definite ST	2 (2.0)	6 (1.2)	1.58 (0.32–7.82)	0.58	2.10 (0.42–10.50)	0.37
Definite or probable ST	2 (2.0)	11 (2.3)	0.86 (0.19–3.88)	0.84	1.22 (0.27–5.61)	0.79
Any major bleeding (BARC 3,4,5)	4 (3.9)	15 (3.1)	1.25 (0.42–3.78)	0.69	2.14 (0.57–7.69)	0.26
Acute renal failure	1 (1.0)	9 (1.9)	0.52 (0.07–4.12)	0.54	0.68 (0.09–5.37)	0.72
Clinical events at 1 year ^a						
Death	2 (2.0)	12 (2.5)	0.78 (0.17–3.48)	0.74	1.08 (0.21–5.45)	0.92
Cardiac death	2 (2.0)	10 (2.1)	0.93 (0.20–4.27)	0.93	1.29 (0.25–6.60)	0.76
MI	5 (4.9)	13 (2.8)	1.81 (0.65–5.08)	0.26	1.74 (0.57–5.29)	0.33
Death or MI	6 (5.9)	24 (5.0)	1.18 (0.48–2.88)	0.72	1.34 (0.50–3.56)	0.56
Cardiac death or MI	6 (5.9)	22 (4.6)	1.29 (0.52–3.17)	0.58	1.45 (0.54–3.89)	0.46
Clinically indicated revascularization (any)	6 (5.9)	29 (6.2)	0.96 (0.40–2.32)	0.93	0.89 (0.34–2.33)	0.82
Clinically indicated non-TVR	4 (4.0)	11 (2.4)	1.70 (0.54–5.34)	0.36	1.29 (0.39–4.25)	0.68
Clinically indicated TVR	3 (3.0)	22 (4.7)	0.63 (0.19–2.11)	0.45	0.77 (0.22–2.75)	0.69
Clinically indicated TLR	3 (3.0)	22 (4.7)	0.63 (0.19–2.11)	0.45	0.77 (0.22–2.75)	0.69
MACE ^b	7 (6.8)	39 (8.2)	0.83 (0.37–1.87)	0.66	0.90 (0.37–2.20)	0.83
Definite ST	3 (3.0)	8 (1.7)	1.77 (0.47–6.66)	0.40	2.01 (0.51–7.92)	0.32
Definite or probable ST	3 (3.0)	15 (3.1)	0.94 (0.27–3.25)	0.92	1.15 (0.31–4.17)	0.84
Any major bleeding (BARC 3,4,5)	5 (4.9)	23 (4.8)	1.02 (0.39–2.68)	0.97	1.60 (0.50–5.10)	0.43
Clinical events at 2 years ^a						
Death	2 (2.0)	19 (4.0)	0.49 (0.11–2.09)	0.33	0.68 (0.14–3.35)	0.64
Cardiac death	2 (2.0)	13 (2.7)	0.72 (0.16–3.17)	0.66	1.00 (0.20–5.02)	1.00
MI	5 (4.9)	21 (4.5)	1.11 (0.42–2.95)	0.83	1.07 (0.37–3.11)	0.90
Death or MI	6 (5.9)	39 (8.2)	0.72 (0.30–1.70)	0.45	0.82 (0.32–2.14)	0.69
Cardiac death or MI	6 (5.9)	33 (7.0)	0.85 (0.36–2.03)	0.72	0.97 (0.37–2.53)	0.95
Clinically indicated revascularization (any)	16 (15.9)	49 (10.6)	1.54 (0.87–2.70)	0.14	1.60 (0.86–2.96)	0.14
Clinically indicated non-TVR	9 (9.0)	22 (4.8)	1.93 (0.89–4.20)	0.096	1.70 (0.76–3.81)	0.20
Clinically indicated TVR	10 (10.0)	36 (7.8)	1.28 (0.64–2.58)	0.49	1.52 (0.71–3.26)	0.28
Clinically indicated TLR	9 (9.0)	34 (7.3)	1.22 (0.59–2.54)	0.60	1.46 (0.65–3.26)	0.36
MACE ^a	17 (16.7)	63 (13.3)	1.27 (0.74–2.16)	0.39	1.40 (0.77–2.52)	0.27
Definite ST	3 (3.0)	11 (2.3)	1.28 (0.36–4.58)	0.71	1.46 (0.38–5.51)	0.58
Definite or probable ST	3 (3.0)	20 (4.2)	0.70 (0.21–2.36)	0.56	0.85 (0.24–3.02)	0.80

Table 6 continued

	Imaging group (n = 103)	Control group (n = 485)	Crude		IPTW adjusted	
			Hazard ratio (95 % CI)	<i>p</i> value	Hazard ratio (95 % CI)	<i>p</i> value
Any major bleeding (BARC 3,4,5)	5 (4.9)	24 (5.0)	0.97 (0.37-2.55)	0.96	1.52 (0.48-4.83)	0.48

Data are number of first events (%) and rate ratios RR (95 % CI) with *p* values from Poisson Regressions Crude, or IPTW Adjusted, using robust error variances

CI confidence interval

^a Data are number of first events (% from Kaplan–Meier life-tables) and hazard ratios HR (95 % CI) with *p*-values from Cox’s Regressions Crude, or IPTW Adjusted

^b MACE composite of all cardiac death, myocardial infarction and any clinically indicated revascularization

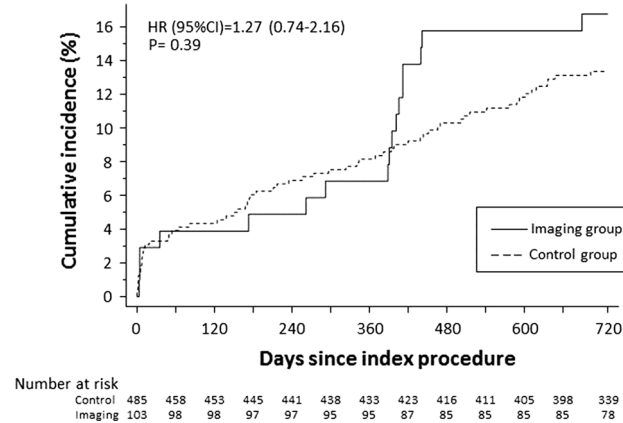


Fig. 1 Cumulative incidence curve for MACE (cardiac death, MI and any clinically indicated revascularization) throughout 2 years. Continuous line indicates imaging group, dotted line indicates control group not undergoing imaging

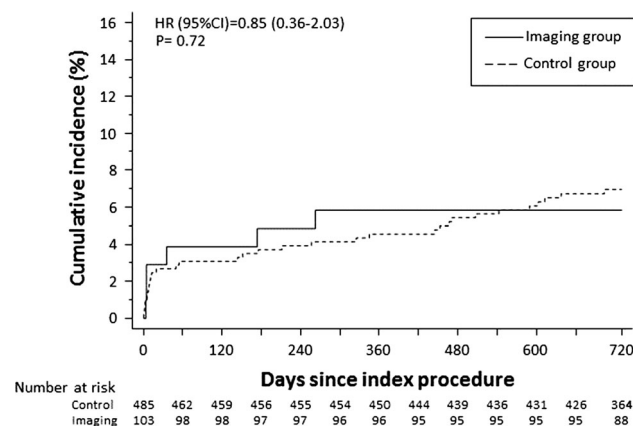


Fig. 2 Cumulative incidence curve for the composite of cardiac death or MI throughout 2 years

atherosclerosis during long-term follow-up [14–16] Hypothetically, the introduction of imaging catheters solely for diagnostic purposes (IVUS: 2.9 French, OCT: 2.7 French) may induce clinically silent endothelial injury as previously demonstrated in an experimental model [17].

The iatrogenic damage may trigger atherosclerotic disease progression by initiating clinically silent plaque ruptures with subsequent progression [18]. As non-infarct related arteries of STEMI patients are known to accommodate vulnerable plaques, and as they are potentially more sensitive to catheter-induced rupture than other lesions, we extended our evaluation to a long-term monitoring with a particular focus on repeat revascularization events in untreated segments [10, 11]. Indicators of a disease progression in untreated vessel segments are the frequency of target vessel revascularizations (TVR) and the revascularizations occurring in the untreated vessels (non-target lesion revascularization, non-TVR). Throughout 2 years, TVR and non-TVR occurred in a similar frequency when comparing the imaging with the control group. As shown in Fig. 2, the cumulative incidence curve for MACE diverges at the timepoint of the angiographic follow-up, which is solely driven by a non-significant increase in repeat revascularization procedures not directly associated with intracoronary imaging but rather related to the well-documented occluso-stenotic reflex [19]. Similar to our findings, the “Avasimibe and progression of coronary lesions assessed by IVUS” (A-PLUS trial) investigating i.c. imaging related atherosclerosis progression, found no evidence by quantitative coronary analysis of disease progression 24 months following IVUS investigation, as compared to control arteries of the same patients [15].

OCT and IVUS require the placement of an i.c. guide-wire and therefore, radiation exposure and contrast agents are important safety considerations. While we did not record the incremental radiation dosage required for three-vessel i.c. imaging, we did assess the amount of contrast agents used. OCT requires complete blood removal achieved by a proper contrast injection. In our study, the contrast use per pullback ranged between 15 and 30 ml per pullback and we used injection rates between 3.5 and 6 ml/sec. A total of 174 ml of contrast media was injected at baseline and 164 ml at follow-up. This relatively high number has to be interpreted in light of our IBIS-4 study

protocol, which required the placement of a guidewire in two non-intervened vessels, the placement and documentation of the image wire for matching purpose, the acquisition of OCT pullbacks in three vessels and a documentary final angiography after both IVUS and OCT to confirm the absence of harm. Despite the higher contrast use in imaging patients, the risk of developing renal failure after primary PCI was low and similar for patients in the imaging and control group (1.0 vs. 1.9 %, $p = 0.72$). In addition, no difference was observed in the creatinine increase from admission to peak during the index hospitalization (7.2 ± 9.2 vs. 8.8 ± 15.2 $\mu\text{mol/L}$, $p = 0.16$).

Limitation

This study has some limitations. First of all, there is to date no clinical indication for the performance of multi-modality three vessel imaging during primary PCI. However, the results observed in the setting of a maximal i.c. imaging approach can be translated to less extensive imaging procedures in daily clinical routine, attesting to their feasibility and safety.

Despite the attempt to select a comparable control group, the decision to perform i.c. imaging was not random introducing some selection bias and probably including a lower risk population in the imaging study. Repeated manipulation with the infarct related artery could potentially lead to an increasing risk for micro-embolization. Whilst myocardial blush grade was not recorded, no difference in final TIMI flow between the two groups was recorded. Although the presence of a myocardial infarction at baseline hypothetically masks the occurrence of an imaging induced peri-procedural myocardial infarction, we did not observe an increased risk at follow-up under stable conditions. In addition, the follow-up angiography and imaging procedures might increase the event rates in imaging group, however, no difference in clinical outcomes at 2 years has been observed between two groups.

In addition, we did not assess the radiation dose in both groups. Nevertheless, the total radiation time inevitably increases as positioning of the coronary wire and imaging catheter has to be documented with both OCT and IVUS. The total number of patients investigated is limited considering the presence of a complex imaging protocol.

Conclusions

Multi-modality three-vessel i.c. imaging in the acute setting of STEMI and performed for documentary purposes is consistent with a high degree of success and can be performed safely without impact on cardiovascular events at long-term follow-up. This data provides reassurance on the

feasibility and safety of intravascular imaging in daily routine, where a less extensive approach may be used.

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