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Comparison of intra-procedural vs. post-stenting prolonged bivalirudin infusion for residual thrombus burden in patients with ST-segment elevation myocardial infarction undergoing: the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and angioX) OCT study

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Aims To compare prolonged bivalirudin infusion vs. an intra-procedural only bivalirudin infusion administration in subjects with ST-segment elevation myocardial infarction (STEMI) regarding residual stent strut thrombosis.

Methods and results Multivessel STEMI patients undergoing primary percutaneous coronary intervention (PPCI) and scheduled for a staged percutaneous coronary intervention (PCI) before hospital discharge were selected among those allocated to either prolonged bivalirudin or intra-procedural only bivalirudin infusion in the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and angioX) Treatment-Duration study. Optical coherence tomography (OCT) of the infarct-related artery was performed at the end of PPCI and 4–5 days thereafter during staged intervention. The predefined endpoint was the percentage difference in the number of stent cross-sections with a thrombotic area >5% at the end of PPCI and at the time of staged PCI (ΔThCS). Between September 2013 and November 2015, 137 were randomized to either intra-procedural only bivalirudin infusion ($N = 64$) or prolonged bivalirudin ($N = 73$) at 16 European sites. Mean stent area, minimum lumen area, percentage of malapposed struts, and mean percent thrombotic area were comparable after index or staged PCI. The difference in the proportion of frames with percent thrombotic area >5% (ΔTh > 5%) were -7.7 (-22.1 to 5.1) in the intra-procedural

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bivalirudin infusion group and -8.8 (-23.1 to 2.6) in the prolonged infusion group ($P = 0.994$). Time from index to follow-up OCT imaging and the infarct vessel artery did not affect this OCT-based endpoint.

Conclusion A strategy of prolonged bivalirudin infusion after PPCI did not reduce residual stent strut thrombosis when compared with intra-procedural only bivalirudin infusion administration (funded by The Medicines Company and Terumo; MATRIX ClinicalTrials.gov number, NCT01433627).

Keywords coronary • ST-segment elevation myocardial infarction • bivalirudin • optical coherence tomography

Introduction

Primary percutaneous coronary intervention (PPCI) is the treatment of choice for patients presenting with acute ST-segment elevation myocardial infarction (STEMI). Anti-thrombin therapy is essential to prevent adverse ischaemic events during PPCI.[1] Bivalirudin and heparin are the two most commonly used anti-thrombin strategies during PPCI; when compared with heparin, bivalirudin decreases the risk of major bleeding at the expense of an increased risk of acute stent thrombosis (AST).[2–5] In order to overcome this relatively rare yet potentially fatal event, a prolonged infusion regimen of bivalirudin after PPCI has been tested in recent randomized controlled trials.[2,6] A meta-analysis of these studies suggests that the risk of AST may be mitigated by continuing a full dose infusion of bivalirudin for 3–4 h post-operatively.[7]

Residual thrombus burden within the infarct related artery has been consistently observed with optical coherence tomography (OCT) at the end of PPCI.[8] Residual thrombosis of stent struts was detectable in 100% of subjects undergoing PPCI and its amount has been shown to negatively affect myocardial perfusion.[9] Furthermore, residual thrombosis of stent struts may promote further thrombus growth and may represent a risk factor for AST.[10] The only trial, which aimed at mitigating post-stenting thrombus burden, as assessed by OCT, by means of manual thrombectomy in PPCI patients, failed to show an impact of this mechanical intervention on minimum flow area (MinFA).[11]

The value of prolonged administration of anti-thrombotics to minimize residual thrombus burden after PPCI has never been investigated. Yet, many practitioners advocate this empirical strategy in patients showing high residual thrombus burden at angiography at the end of intervention.

We sought to assess whether an on-label administration of post-percutaneous coronary intervention (PCI) bivalirudin, when compared with a purely intra-procedural bivalirudin regimen, reduces the residual thrombus burden at matched OCT assessments.

Methods

Study population

The Anti-thrombin MATRIX study is a multicentre, prospective, randomized, open-label, factorial trial, which assessed the comparative effectiveness and safety of unfractionated heparin with provisional glycoprotein IIb/IIIa inhibitors (GPI) vs. bivalirudinin patients affected by either non-ST-elevation acute coronary syndrome or STEMI. MATRIX Treatment-Duration was a randomized comparison, nested within the Anti-thrombin MATRIX, of prolonged bivalirudin administration during and after PCI vs. short-term bivalirudin administration during PCI only, in the 3610 patients assigned to bivalirudin. Multivessel STEMI patients were eligible for MATRIX OCT if recruited in one of the 16 participating sites, required a staged intervention before discharge at discretion of the treating physician, provided study specific consent and infarcted related artery was deemed suitable for repeated imaging (Supplementary data online, *Table S1*). Patients received either intra-procedural only bivalirudin infusion or post-PCI bivalirudin according to the MATRIX Treatment-Duration randomization scheme.

Treatments

Bivalirudin was dosed as per current label with a bolus of 0.75 mg/kg and followed by 1.75 mg/kg/h infusion until PCI completion and then stopped (intra-procedural only bivalirudin) or continued based on the randomization scheme. In the post-PCI bivalirudin group, bivalirudin was administered either at the full dose for up to 4 h or at a reduced dose of 0.25 mg/kg/h for ≥6 h, with the choice between those two regimens made at the discretion of the treating physicians. GPI use was allowed during PCI for bailout reasons only.[2] The use of manual or mechanical thrombectomy was at the discretion of the treating physician.

Imaging endpoint definitions

The primary endpoint was defined as the difference in minimal flow area (ΔMinFA) measured at the end of PPCI and at the time of staged PCI. MinFA was defined as: [stent area + incomplete stent apposition (ISA) area] - (intraluminal defect + tissue prolapse area) (*Figure 1*). The key secondary predefined endpoint was defined as percentage difference in the number of stent cross-sections with a thrombotic area >5% at the end of PPCI and at the time of staged PCI (ΔThCS). OCT of the infarct-related artery was carried out at the end of PPCI and repeated at the time of staged PCI.

Optical coherence tomography acquisition and analysis

All OCT examinations were performed using full anticoagulation with bivalirudin. The catheter was advanced into the vessel so that the proximal marker was at least 1 cm downstream from the distal edge of the stent. The coronary artery was flushed during the automated OCT pullback with X-ray contrast at 37°C and a flush rate of 3 mL/s for the right coronary artery (RCA) and 4 mL/s for the left coronary artery. The OCT pullback was carried out at a speed of 20 mm/s. At follow-up, the flush settings as applied during the baseline imaging procedure were repeated.

Analysis of OCT images was performed by Cardialysis BV (Rotterdam, The Netherlands). Analysis of contiguous cross-sections at 1 mm longitudinal intervals within the treated segment was performed using offline software QCU CMS (LKEB, Leiden, the Netherlands). The stent and lumen areas were drawn. Further, the number of stent struts was

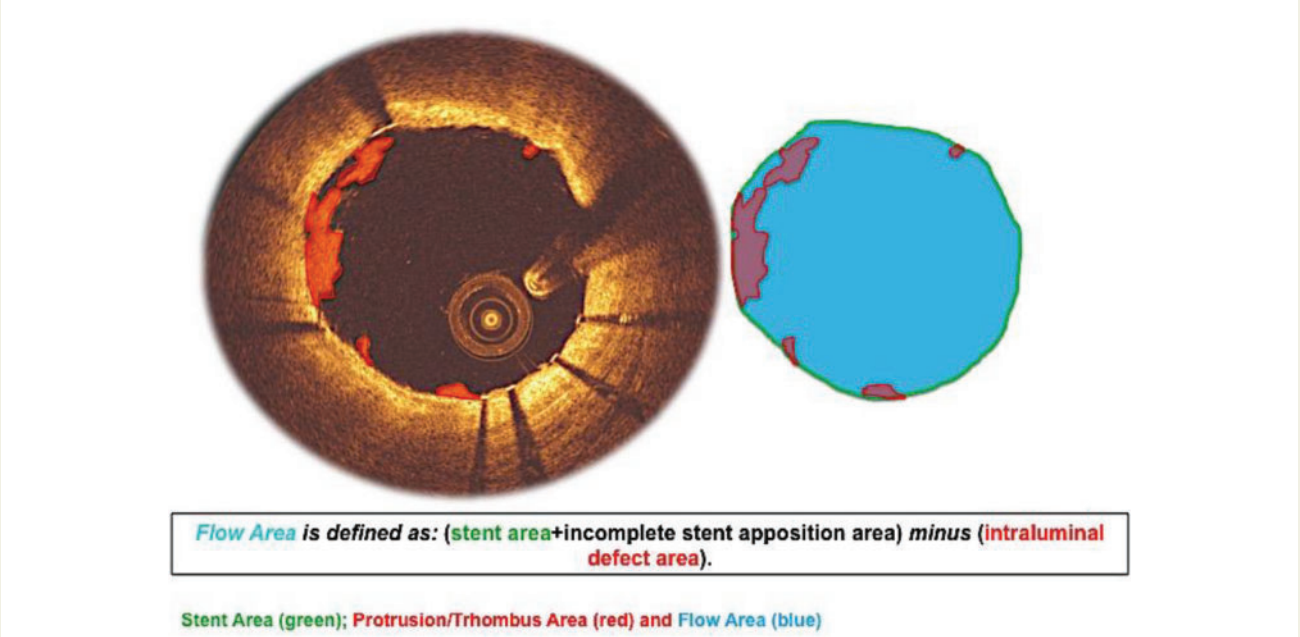

Figure 1 Methods of analysis of optical coherence tomography. The stent area is shown in green, this contour follows the position of the metallic struts. The intraluminal defect areas are drawn in red circles. They can be either non-attached or attached to the vessel wall. The flow area is the area in blue.

determined in each cross section. Struts were classified as apposed (when the strut was in contact with the vessel wall) or malapposed if protruding into the lumen at a distance greater than the strut thickness.

In addition, we analysed all individual masses within the stent area, which were defined as intraluminal defect area (IDA). IDA was categorized into IDA attached to vessel wall (i.e. thrombus or prolapse) and non-attached IDA. In this study, plaque prolapse and thrombus attached to the vessel wall were categorized as a single variable, attached IDA.

Follow-up, outcomes, and sample size considerations

Clinical follow-up was performed at 30 days. Major adverse cardiovascular events were defined as a composite of death from any cause, myocardial infarction, or stroke, up to 30 days, and net adverse clinical events were defined as a composite of major bleeding that was not related to coronary artery bypass grafting [Bleeding Academic Research Consortium (BARC) type 3 or 5]. Other endpoints were urgent target-vessel revascularization, definite stent thrombosis, and bleeding. All outcomes were prespecified and adjudicated by an independent and blinded clinical-events committee.

The sample size calculations were based on the TROFI trial,[11] where OCT analysis was performed after stenting in STEMI patients: minimal flow area was 7.08 ± 2.14 mm^2 in the thrombectomy group and 6.51 ± 1.99 mm^2 in the group without thrombus aspiration.[11] Since manual thrombectomy was left to the discretion of the treating physician, we hypothesized a MinFA of 6.8 mm^2 in the intra-procedural only bivalirudin group. Therefore, a potential treatment effect of 20% on the change in MinFA between prolonged and intra-procedural bivalirudin infusion strategy was expected to be shown at a >90% power and a two-sided α-level of 0.05. We planned to enroll at least 120 patients (2×60 patients), taking into account a drop-out rate of at least 10%.

The primary endpoint only of the MATRIX OCT trial was previously reported.[12] In this article, we report the full results of the trial including all primary and secondary endpoints results stratified by actual bivalirudin regimen employed after PCI and predefined subgroup analyses.

Statistical analysis

Categorical variables were expressed as percentages and were compared by Fisher's exact test. Continuous variables are presented as mean with standard deviation or median and interquartile range (IQR). Normally distributed variables were compared by *t*-test, whereas non-parametric Wilcoxon rank-sum test was used for variables without normal distribution. All statistical tests were two tailed, and *P*-value of 0.05 was considered as statistically significant. All analyses were performed on an intention-to-treat basis using Stata version 14.2 (Stata Corp., College Station, TX, USA) and R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between September 2013 and November 2015, 316 were screened and 137 were randomized at 16 sites in Italy, the Netherlands, and Spain to receive intra-procedural bivalirudin infusion ($N = 64$) or prolonged bivalirudin infusion group ($N = 73$). Overall, five patients were excluded because of poor quality OCT images and two patients because the OCT data were not recorded in an analysable format after PPCI (*Figure 2*). Seven patients did not undergo repeat OCT imaging at the time of staged PCI. Thus, 123 patients with matched and analysable OCT data were finally included in the study (*Figure 2*). Follow-up OCT assessment occurred at a median of 3 days (IQR 2–5) after index PCI, ranging from 1 day to 12 days. Patient baseline and

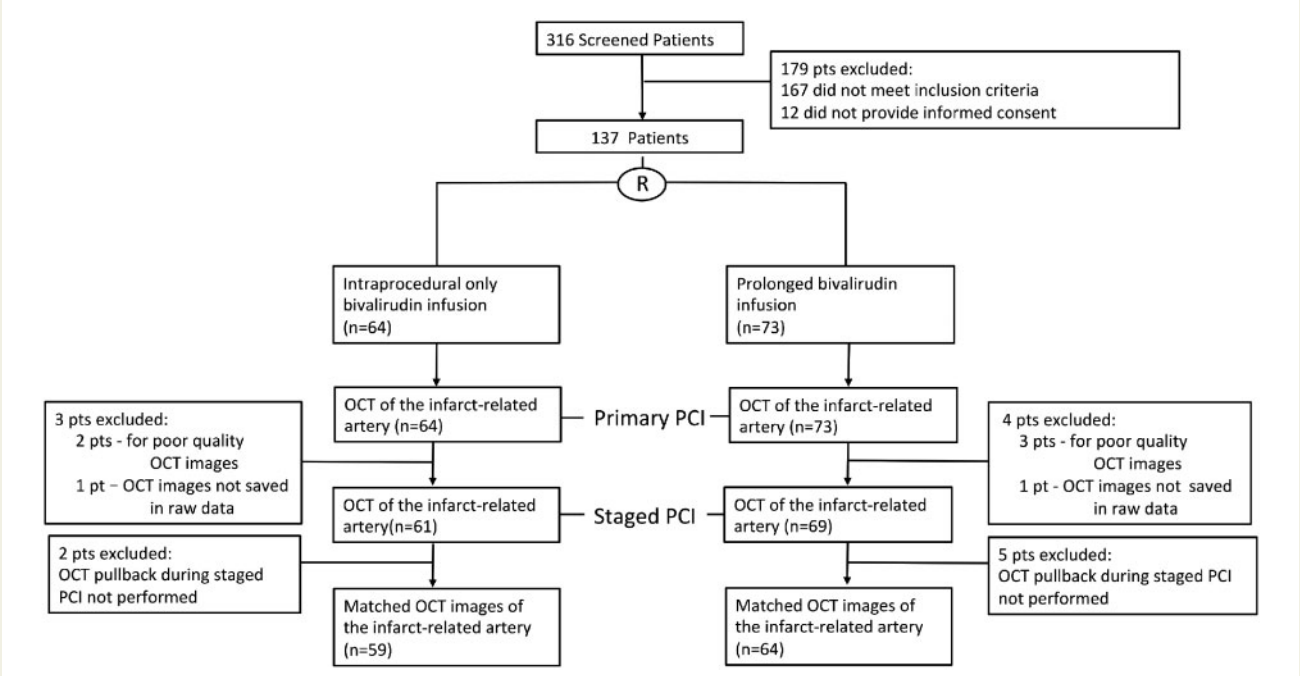

Figure 2 Patient disposition. GPI, glycoprotein IIb-IIIa inhibitors; OCT, optical coherence tomography; R, randomization; STEMI, ST-segment elevation myocardial infarction.

procedural characteristics were well matched between the two groups (*Tables 1* and *2*). Medications prior, during or after the procedure were similar between the two groups, except for the bivalirudin infusion duration (*Table 2*). The left anterior descending artery (LAD) constituted most of the treated vessels and nearly all patients received drug-eluting stents (*Table 2*).

Optical coherence tomography findings

Stent lengths, stent, lumen areas, and percentage of malapposed struts were comparable at baseline. Similarly, areas of thrombotic material, protruded tissue, ISA, and minimum flow area did not differ between the two groups, nor they were found to differ at follow-up analysis (*Table 3*).

The primary endpoint change in minimum flow area from baseline to follow-up (ΔMinFA) in the intra-procedural bivalirudin infusion group was 0.22 mm^2 vs. 0.32 mm^2 in the prolonged infusion group, resulting in a between-group difference of -0.071 (-0.280 to 0.153), $P = 0.565$ (*Figures 3* and *4*, *Table 3*).

The difference in the proportion of frames with percent thrombotic area > 5% (ΔTh > 5%) were -7.7 (-22.1 to 5.1) in the intra-procedural bivalirudin infusion group and -8.8 (-23.1 to 2.6) in the prolonged infusion group ($P = 0.994$, *Table 3*).

Stratified analysis based on post-PCI bivalirudin regimen

In the 41 patients who received post-PCI bivalirudin infusion at 1.75 mg/kg/h for a mean duration of 240.2 ± 23.8 min, ΔMinFA did not differ when compared with the 23 patients who received the 0.25 mg/kg/h regimen for a mean of 256.3 ± 83.6 min (0.3930 mm^2 vs. 0.2538 mm^2; $P = 0.89$, Supplementary data online, *Figure S1* and *Table S2*) nor did other OCT-based secondary endpoints.

Additional sensitivity analyses

Time from index to follow-up OCT imaging did not affect the primary endpoint (ΔMinFA in patients undergoing OCT in 1 or 2, 3, 4, or more than 4 days was 0.254 mm^2, IQR -0.019 to 0.921; 0.367 mm^2, IQR 0.034–0.785; 0.092 mm^2, IQR -0.137 to 0.527; 0.311 mm^2, IQR 0.064–0.682, respectively, $P = 0.477$ for trend, Supplementary data online, *Figure S2*) or other OCT-based secondary endpoints.

Similarly, ΔMinFA (mm^2) remained consistent across the imaged coronary vessels (LAD 0.219, IQR 0.048–0.685; left circumflex artery 0.271, IQR -0.018 to 0.456; RCA 0.315, IQR -0.095 to 0.879; $P = 0.82$ for trend) (Supplementary data online, *Figure S3*).

We further stratified the population based on ΔMinFA and identified 90 (73%) patients with positive values, indicating at least some degree of thrombus regression and 33 (26.8%) patients with positive values, indicating a persistent pro-thrombotic state (Supplementary data online, *Table S3*). Stent post-dilatation was almost twice as frequent in patients with negative ΔMinFA (76.5% vs. 42.4%, $P = 0.002$). None of the administered medications, before, during, or after intervention, including unfractionated heparin, bivalirudin, or type of oral P2Y12 inhibitors were associated to positive ΔMinFA values.

Clinical outcomes at 30 days

The co-primary composite endpoints of all-cause mortality, myocardial infarction (MI) or stroke or all-cause mortality, MI, stroke and bleeding did not differ between patients receiving intra-procedural or

Table 1 Baseline characteristics and medications administered before the catheterization laboratory

	Intra-procedural only bivalirudin (*N* = 59)	Prolonged bivalirudin (*N* = 64)	*P*-value
Age (years)	60.9 ± 13.8	61.8 ± 11.0	0.6802
Male sex, *n* (%)	52 (88.1)	49 (76.6)	0.1055
Weight (kg)	78.8 ± 11.8	78.1 ± 13.3	0.7695
Body mass index (kg/m^2)	26.8 ± 3.4	27.0 ± 3.9	0.7131
Diabetes mellitus, *n* (%)			
Insulin-dependent	2 (3.4)	1 (1.6)	0.6070
Non-insulin dependent	7 (11.9)	9 (14.1)	0.7926
Smoker, *n* (%)			
Current smoker	24 (40.7)	27 (42.2)	0.8652
Previous smoker	11 (18.6)	5 (7.8)	0.1068
Hypercholesterolemia, *n* (%)	18 (30.5)	29 (45.3)	0.0989
Hypertension, *n* (%)	33 (55.9)	35 (54.7)	1.0000
Previous myocardial infarction, *n* (%)	1 (1.7)	3 (4.7)	0.6201
Previous PCI, *n* (%)	3 (5.1)	6 (9.4)	0.4946
Previous CABG, *n* (%)	0 (0.0)	0 (0.0)	NA
Previous TIA or stroke, *n* (%)	1 (1.7)	3 (4.7)	0.6201
Peripheral vascular disease, *n* (%)	1 (1.7)	2 (3.1)	1.0000
Chronic obstructive pulmonary disease, *n* (%)	3 (5.1)	2 (3.1)	0.6701
Renal failure, *n* (%)	0 (0.0)	0 (0.0)	NA
Clinical presentation			
Cardiac arrest, *n* (%)	0 (0.0)	3 (4.7)	0.2451
Killip Class II (ref Class I), *n* (%)	3 (5.1)	3 (4.7)	1.0000
STEMI, *n* (%)	59 (100.0)	64 (100.0)	
Previous lytic therapy, *n* (%)	3 (5.1)	1 (1.6)	0.3493
Systolic arterial pressure (mmHg)	136.9 ± 34.0	133.9 ± 24.6	0.5854
Heart rate (min^{-1})	74.2 ± 14.7	74.3 ± 18.0	0.9649
Left ventricular ejection fraction (%)	48.3 ± 7.8	48.1 ± 7.8	0.9121
eGFR	84.5 ± 34.4	85.7 ± 26.5	0.8479
Medications administered before the catheterization laboratory, *n* (%)			
Aspirin	54 (91.5)	59 (92.2)	0.8932
Clopidogrel	7 (11.9)	11 (17.2)	0.4040
Prasugrel	12 (20.3)	14 (21.9)	0.8349
Ticagrelor	25 (42.4)	22 (34.4)	0.3618
Enoxaparin	3 (5.1)	2 (3.1)	0.6701
Fondaparinux	1 (1.7)	0 (0.0)	0.4797
ACE inhibitors	5 (8.5)	5 (7.8)	1.0000
Angiotensin II receptor antagonist	3 (5.1)	1 (1.6)	0.3493
Statins	8 (13.6)	7 (10.9)	0.6571
Beta blockers	9 (15.3)	6 (9.4)	0.3195
Warfarin	1 (1.7)	1 (1.6)	0.7313
Previous unfractionated heparin	21 (35.6)	23 (35.9)	0.9683
Glycoprotein IIb/IIIa inhibitors	0 (0.0)	0 (0.0)	

Data are presented as mean and standard deviation; %, percentages. NA, not applicable.

post-PCI bivalirudin, as was the case for the other ischaemic or bleeding endpoints (*Table 4*).

Discussion

The main findings of this prospective study nested within the MATRIX programme can be summarized as follows:

(1) Prolonged bivalirudin infusion failed to affect the change in minimum flow area from baseline to follow-up, when compared with intra-procedural only bivalirudin infusion, as previously reported;
(2) All imaging-related secondary endpoints, including the proportion of frames with percent thrombotic area >5%, were also superimposable between the two study groups;
(3) At stratified analyses, the full post-PCI bivalirudin regimen did not affect any primary or secondary imaging related endpoint and no

Table 2 Procedural medications and characteristics

	Intra-procedural only bivalirudin (*N* = 59)	Prolonged bivalirudin (*N* = 64)	*P*-value
Medications administered in and after the catheterization laboratory			
Aspirin	2 (3.4)	5 (7.8)	0.290
Clopidogrel	4 (6.8)	1 (1.6)	0.143
Prasugrel	3 (5.1)	9 (14.1)	0.130
Ticagrelor	12 (20.3)	13 (20.3)	0.997
Glycoprotein IIb/IIIa inhibitors	3 (5.1)	5 (7.8)	0.719
Planned GPI	0 (0.0)	0 (0.0)	NA
Bailout GPI	3 (5.1)	5 (7.8)	0.719
Abciximab	1 (1.7)	3 (4.7)	0.620
Bolus	1 (1.7)	3 (4.7)	0.620
Bolus and infusion	0 (0.0)	0 (0.0)	NA
Tirofiban	0 (0.0)	2 (3.1)	0.497
Bolus	0 (0.0)	2 (3.1)	0.497
Bolus and infusion	0 (0.0)	2 (3.1)	0.497
Eptifibatide	2 (3.4)	0 (0.0)	0.228
Bolus	2 (3.4)	0 (0.0)	0.228
Bolus and infusion	1 (1.7)	0 (0.0)	0.480
Unfractionated heparin	1 (1.7)	2 (3.1)	1.000
Bolus	1 (1.7)	2 (3.1)	1.000
Bolus and infusion	0 (0.0)	0 (0.0)	NA
Unfractionated heparin (units per kilo)	26.6	43.7 ± 21.4	NA
Sub-therapeutic regimen (<50 units per kg)	1 (1.7)	1 (1.6)	1.000
Therapeutic regimen (≥50 units per kg)	0 (0.0)	1 (1.6)	1.000
Bivalirudin	59 (100.0)	64 (100.0)	
Bolus and infusion	59 (100.0)	64 (100.0)	
Prolonged infusion post-PCI	0 (0.0)	64 (100.0)	<0.001
Average duration of post-PCI bivalirudin infusion		246.0 ± 53.5	
Patients receiving full bivalirudin regimen post-PCI (min)	0 (0.0)	41 (64.1)	<0.001
Average duration of full bivalirudin regimen (min)		240.2 ± 23.8	
Patients receiving low bivalirudin regimen post-PCI	0 (0.0)	23 (35.9)	<0.001
Average duration of low bivalirudin regimen (min)		256.3 ± 83.6	
Procedure characteristics			
Allocated to radial access	29 (49.2)	35 (54.7)	0.590
TIMI 3 flow in all treated lesions	58 (98.3)	62 (98.4)	1.000
Coronary stenosis <30% in all treated lesions	58 (98.3)	64 (100.0)	0.480
Procedural success in all treated lesions	57 (96.6)	62 (98.4)	0.610
Treated vessel(s) per patient			
Left anterior descending artery	28 (47.5)	25 (39.7)	0.387
Left circumflex artery	16 (27.1)	12 (19.0)	0.289
Right coronary artery	17 (28.8)	26 (41.3)	0.150
At least two vessels treated	2 (3.4)	0 (0.0)	0.232
Lesions treated per patient (interquartile range)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.681
One lesion	51 (86.4)	56 (88.9)	
Two lesions	8 (13.6)	7 (11.1)	
At least one complex lesion	35 (59.3)	44 (69.8)	0.258
Median number of stents per patient (interquartile range)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.762
Overall stent length per patient (mm)	31.7 ± 18.1	32.9 ± 16.8	0.706
Lesions			
Number of lesions with PCI	*N* = 67	*N* = 70	
Lesions stented	65 (97.0)	68 (97.1)	0.965

Continued

Table 2 *Continued*

	Intra-procedural only bivalirudin (*N* = 59)	Prolonged bivalirudin (*N* = 64)	*P*-value
At least one drug-eluting stent	63 (94.0)	65 (92.9)	0.782
At least one bare-metal stent	2 (3.0)	3 (4.3)	0.724
TIMI flow pre-procedure			
0 or 1	36 (53.7)	47 (67.1)	0.179
2	11 (16.4)	7 (10.0)	0.322
3	20 (29.9)	16 (22.9)	0.382
TIMI flow post-procedure			
0 or 1	1 (1.5)	0 (0.0)	
2	0 (0.0)	2 (2.9)	
3	66 (98.5)	68 (97.1)	0.643
Procedural success	65 (97.0)	68 (97.1)	0.705
Total stent length per lesion (mm)	28.8 ± 16.3	30.5 ± 15.5	0.531
Average stent diameter per lesion (mm)	3.1 ± 0.4	3.2 ± 0.4	0.121
At least one direct stenting	17 (26.2)	14 (20.6)	0.436
Post-dilatation	33 (50.8)	35 (51.5)	0.941

signal emerged that bivalirudin at this regimen may provide greater anti-thrombotic activity when compared with the reduced dose of 0.25 mg/kg/h;

(4) In almost three-fourth of the patients, thrombus burden did not regress at follow-up, which remained consistent across the instrumented coronary vessels and time to follow-up imaging. None of the other anti-thrombotic agents in current use for the treatment of STEMI patients, including pre-hospital UFH and type of oral P2Y12 inhibitors were associated to thrombus regression.

This is the first trial using intravascular imaging for the evaluation of the mechanistic effect of an antithrombotic drug in the context of PPCI for the treatment of STEMI. Reduction of thrombotic burden, either by thrombus aspiration and co-adjuvant antithrombotic therapy, or the combination thereof, has been regarded as key during PPCI. In the TROFI trial,[11] the use of PPCI, with or without manual thrombectomy, was compared in terms of minimum flow area. PPCI plus thrombectomy did not show an increase in minimum flow area compared with PPCI without thrombectomy. Of note, in the subsequent large TAPAS, TOTAL, and TASTE clinical trials,[13] the use of routine thrombus manual aspiration during PPCI did not reduce major clinical outcomes at follow-up.

Unlike a recent meta-analysis,[14] which suggested that prolonging bivalirudin infusion at full regimen 3–4 h post-procedure may mitigate the risk for AST, we observed that the two employed post-PCI bivalirudin regimens showed similar reduction in intravessel thrombus (thereby same increase in minimum flow area) resulting in no treatment effect between patients receiving or not receiving bivalirudin infusion after index intervention. Moreover, in the comparison of patients who received post-PCI treatment, high vs. low dose bivalirudin infusion did not affect the change in minimum flow area at follow-up.

Since the time from index to follow-up varied, it was important to explore whether there could be any association between the delay with which repeated imaging was obtained and the primary endpoint. In the sensitivity analysis, the time from index to follow-up did not impact the changes in minimum flow area. This may be due to the fact that bivalirudin has a short half-life (25 min), and therefore, it is not expected that in the following days after the index procedure there could be any treatment effect of the drug. There is, however, a vulnerable period for increase in the amount of thrombus arising from a gap between the waning of the antithrombin effect of bivalirudin and the onset of platelet inhibition from oral P2Y12 inhibitors, which it has not been seen in this report either.

Interestingly, some patients (27%) had at least some degree of thrombus progression; among those patients, stent post-dilatation (76.5% vs. 42.4%, $P = 0.002$) was more frequently performed. This mechanical squeeze of the vessel wall induced by the post-dilatation might have created an increase in the amount of tissue protruding through the struts resulting in reduction of the flow area. Alternatively, post-dilatation *per se* may further induce a prothrombotic environment, possibly due to vessel dissection outside the stented area or due to further vessel wall injury after stent deployment. Stent post-dilatation did not have an effect on flow area because it was performed in around 50% in both bivalirudin groups, which balanced out the results. On the other hand, ISA increased slightly, albeit not significant, at follow-up. This was due to the observed slight decrease in thrombotic burden, although not significantly either (*Figure 3*).

Therefore, when taken together, our current OCT findings provide a mechanistic framework to explain the null findings on clinical outcomes observed in the treatment duration programme.

Limitations

This was a relatively small-randomized controlled trial powered for an OCT endpoint, which allowed two post-PCI bivalirudin regimens.

Table 3 OCT findings

Index	Intra-procedural only bivalirudin (*N* = 59)	Prolonged bivalirudin (*N* = 64)	Difference	*P*-value
Mean lumen area (mm^2)	6.75 (6.0451–8.5120)	7.44 (5.9381–9.7246)	-0.690 (-1.481 to 0.122)	0.102
Minimum lumen area (mm^2)	5.25 (4.3249–6.8219)	5.43 (4.4784–7.3241)	-0.278 (-0.904 to 0.339)	0.403
Minimum lumen diameter (mm)	2.07 (1.8680–2.5176)	2.21 (1.9125–2.5897)	-0.075 (-0.226 to 0.082)	0.323
Mean stent area (mm^2)	7.13 (6.2450–8.9971)	7.97 (6.2719–9.9848)	-0.638 (-1.473 to 0.167)	0.116
Minimum stent area (mm^2)	5.81 (4.8963–7.3329)	6.16 (4.8939–7.9248)	-0.350 (-1.058 to 0.315)	0.305
Minimum stent diameter (mm)	2.44 (2.1522–2.7973)	2.56 (2.2996–2.7974)	-0.102 (-0.251 to 0.050)	0.202
Mean total ISA area (mm^2)	0.20 (0.0909–0.3501)	0.25 (0.1542–0.3851)	-0.041 (-0.105 to 0.025)	0.243
Maximum largest ISA area (mm^2)	0.68 (0.3336–1.8554)	0.80 (0.4138–1.8570)	-0.090 (-0.363 to 0.162)	0.496
Mean total tissue protrusion area (mm^2)	0.49 (0.3459–0.7001)	0.45 (0.3206–0.6684)	0.030 (-0.049 to 0.108)	0.438
Maximum largest tissue protrusion area (mm^2)	1.01 (0.6652–1.4546)	0.91 (0.6276–1.3487)	0.075 (-0.110 to 0.288)	0.437
Mean thrombotic area (mm^2)	0.50 (0.3426–0.7001)	0.45 (0.3267–0.6684)	0.029 (-0.050 to 0.107)	0.453
Mean percent thrombotic area (%)	6.7 (5.3–8.8)	6.1 (4.8–7.8)	0.58 (-0.29 to 1.5)	0.183
Proportion of frames with percent thrombotic area >5% (%)	56.3 (37.6–71.0)	50.0 (33.3–66.7)	4.4 (-3.8 to 12.9)	0.319
Minimum flow area (mm^2)	5.22 (4.3245–6.8194)	5.43 (4.4404–7.3233)	-0.273 (-0.896 to 0.337)	0.403
% malapposed struts	4.4 (0.99–8.4)	5.7 (1.4–10.8)	-0.84 (-3.0 to 0.58)	0.297
Follow-up	**Intra-procedural only bivalirudin**	**Prolonged bivalirudin**	**Difference**	**P-value**
Mean lumen area (mm^2)	7.34 (6.1537–8.6568)	7.82 (6.4237–9.6425)	-0.650 (-1.413 to 0.148)	0.101
Minimum lumen area (mm^2)	5.59 (4.7211–7.0916)	6.08 (4.6953–7.7003)	-0.406 (-1.077 to 0.332)	0.289
Minimum lumen diameter (mm)	2.31 (1.9798–2.6433)	2.37 (2.0728–2.6604)	-0.096 (-0.262 to 0.076)	0.271
Mean total ISA area (mm^2)	0.20 (0.1078–0.4138)	0.33 (0.1551–0.5119)	-0.070 (-0.154 to 0.009)	0.074
Maximum largest ISA area if SA is present (mm^2)	0.87 (0.3462–1.7101)	1.45 (0.6454–2.0510)	-0.344 (-0.688 to -0.007)	0.046
Mean total tissue protrusion area (mm^2)	0.43 (0.2723–0.5647)	0.38 (0.2510–0.5538)	0.015 (-0.057 to 0.090)	0.652
Maximum largest tissue protrusion area (mm^2)	0.76 (0.5171–1.2403)	0.78 (0.5037–1.0984)	-0.002 (-0.172 to 0.170)	0.974
Mean intraluminal defect area (mm^2)	0.03 (0.0180–0.0391)	0.04 (0.0213–0.0785)	-0.011 (-0.033 to 0.010)	0.311
Mean thrombotic area (mm^2)	0.43 (0.2726–0.5653)	0.38 (0.2510–0.5552)	0.012 (-0.061 to 0.088)	0.693
Mean percent thrombotic area (%)	4.84 (4.0454–6.2847)	4.84 (3.1994–6.7795)	0.281 (-0.615 to 1.116)	0.532
Proportion of frames with percent thrombotic area >5% (%)	35.5 (23.5–69.7)	36.7 (17.0–65.4)	3.5 (-6.275 to 12.186)	0.477
Minimum flow area (mm^2)	5.59 (4.7191–7.0889)	6.07 (4.6953–7.7003)	-0.404 (-1.080 to 0.332)	0.287
% malapposed struts	4.0 (1.4–8.6)	6.1 (1.4–11.0)	-0.646 (-3.066 to 0.809)	0.399
Difference: follow-up–index	**Intra-procedural only bivalirudin**	**Prolonged bivalirudin**	**Difference**	***P*-value**
Mean lumen area (mm^2)	0.2426 (-0.0254 to 0.5340)	0.2318 (-0.1063 to 0.6964)	0.013 (-0.188 to 0.223)	0.877
Minimum lumen area (mm^2)	0.2152 (-0.0361 to 0.6820)	0.3282 (-0.0117 to 0.8587)	-0.066 (-0.277 to 0.157)	0.575
Minimum lumen diameter (mm)	0.1136 (-0.0538 to 0.2347)	0.1102 (0.0137 to 0.3008)	-0.023 (-0.121 to 0.059)	0.649
Mean total ISA area (mm^2)	0.0290 (-0.0546 to 0.1210)	0.0589 (-0.0796 to 0.1940)	-0.026 (-0.096 to 0.046)	0.469
Maximum largest ISA area (mm^2)	0.0827 (-0.2160 to 0.4363)	0.2526 (-0.2296 to 0.7920)	-0.178 (-0.458 to 0.074)	0.172
Mean total tissue protrusion area (mm^2)	-0.0718 (-0.2390 to 0.0303)	-0.0648 (-0.1509 to 0.0016)	-0.005 (-0.064 to 0.049)	0.857
Maximum largest tissue protrusion area (mm^2)	-0.2572 (-0.6462 to 0.1372)	-0.0764 (-0.4032 to 0.1512)	-0.119 (-0.302 to 0.060)	0.188
Mean intraluminal defect area (mm^2)	-0.0083 (-0.0229 to 0.0094)	-0.0101 (-0.0316 to -0.0028)	0.004 (-0.068 to 0.037)	0.872
Mean thrombotic area (mm^2)	-0.0752 (-0.2389 to 0.0276)	-0.0648 (-0.1555 to 0.0016)	-0.006 (-0.066 to 0.048)	0.837
Mean percent thrombotic area (%)	-1.1 (-3.2 to 0.07)	-1.1 (-2.4 to -0.11)	-0.11 (-0.86 to 0.59)	0.726
Proportion of frames with percent thrombotic area >5% (%)	-7.7 (-22.1 to 5.1)	-8.8 (-23.1 to 2.6)	0.0 (-7.6 to 7.4)	0.994
Minimum flow area (mm^2)	0.22 (-0.0357 to 0.6818)	0.32 (-0.0091 to 0.8587)	-0.071 (-0.280 to 0.153)	0.565
% malapposed struts	0.38 (-0.93 to 2.6)	0.0 (-2.7 to 3.9)	0.372 (-1.189 to 1.865)	0.627

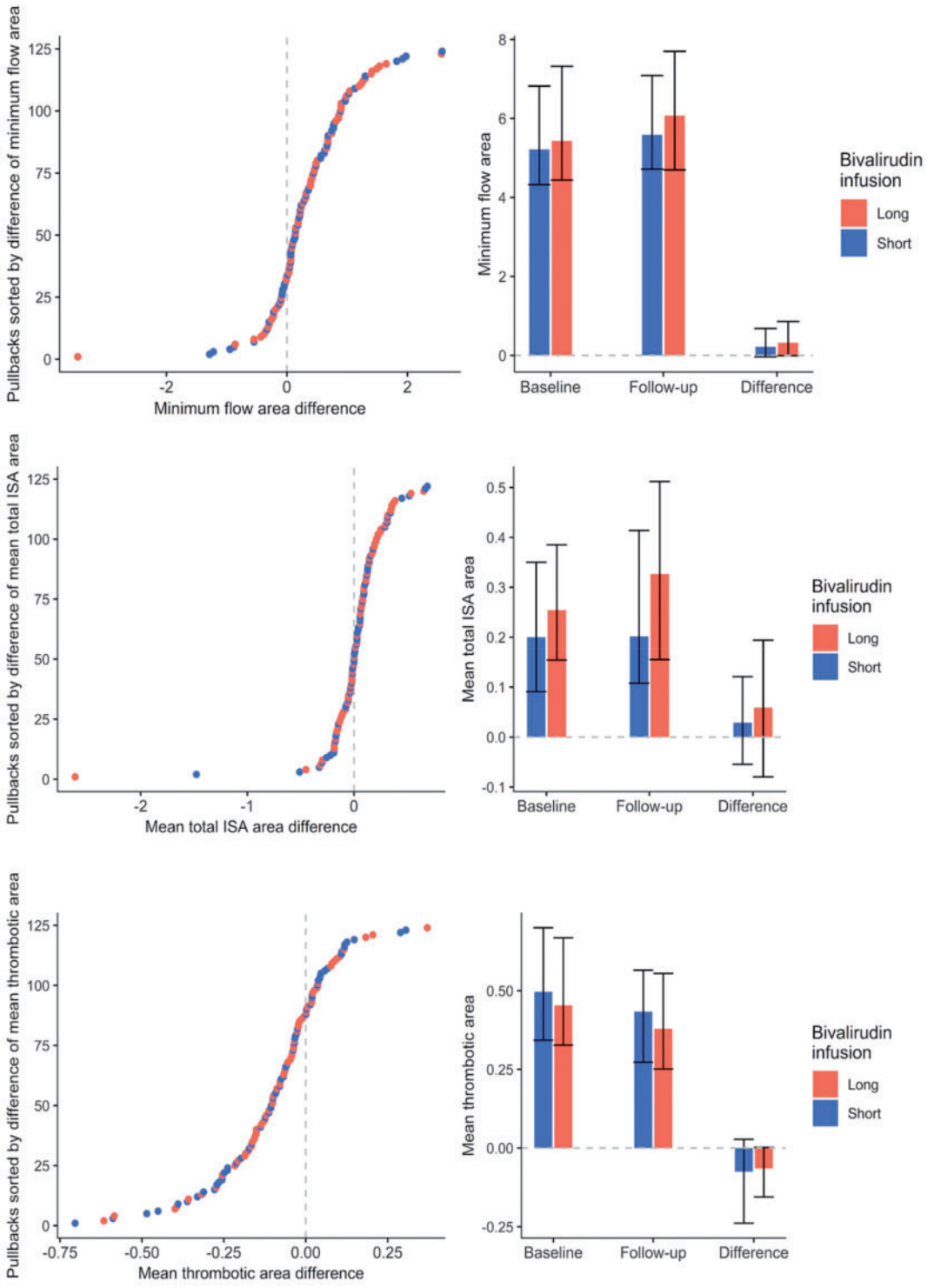

Figure 3 Temporal changes in minimum flow area, stent area, incomplete apposition and thrombus areas. The patient-level change is shown for both groups, intra-procedural only bivalirudin (short – blue) and prolonged infusion (long – red). The per-group summaries and the observed differences are also shown in the graphs adjacent to each patient-level graph. Top figure has been published in Picchi *et al.*[12]

Hence, this study is underpowered for assessing outcomes. Although there was no difference in the OCT findings between these two doses, a potential heterogeneity in the treatment response cannot be ruled out. Fourteen patients could not be included in the analysis due to various reasons; although this number is in the range of many other trials using imaging endpoints at follow up and accounted for in

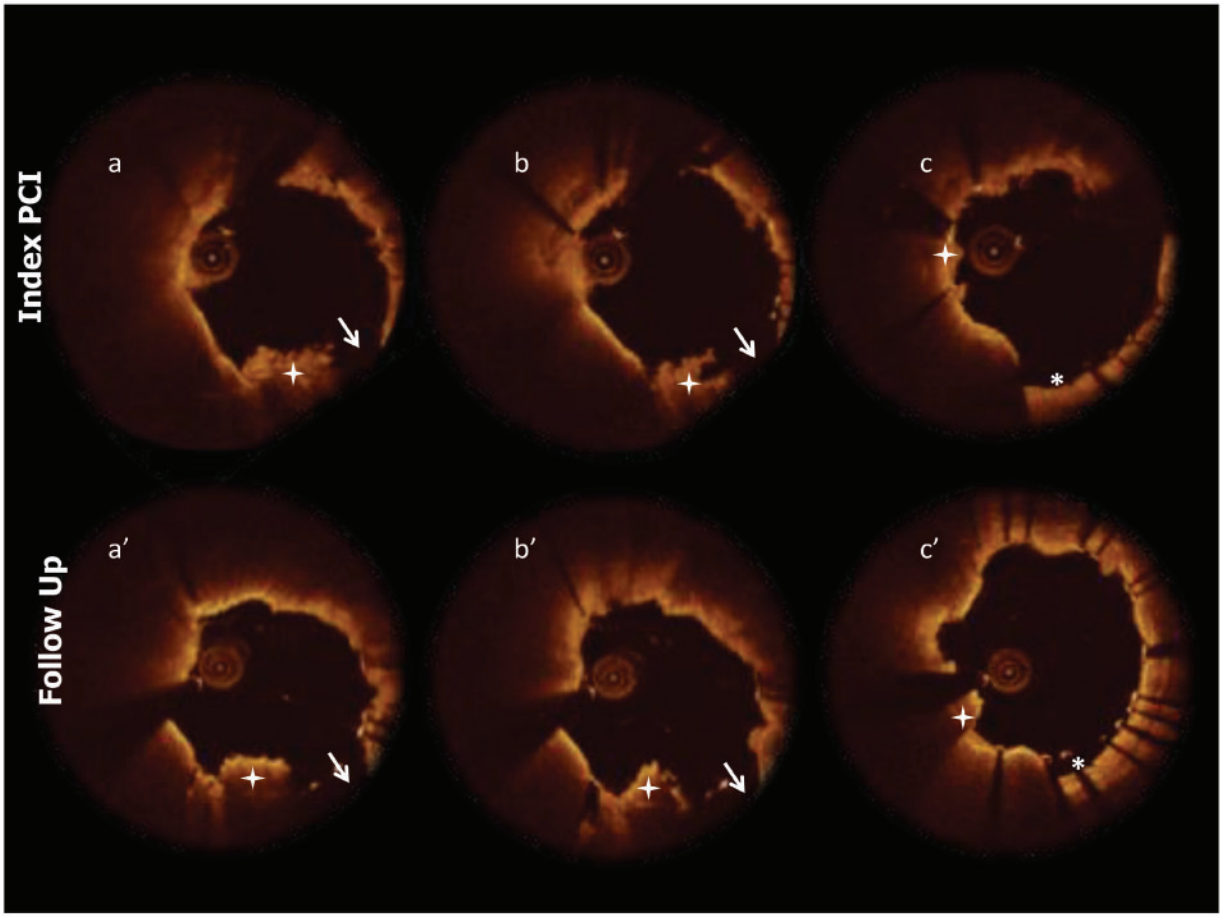

Figure 4 Representative OCT cross-sections obtained from a patient who was allocated to the prolonged bivalirudin infusion group. Index PCI optical coherence frames (top row) show protruding irregular masses (stars), possibly resulting from a combination of thrombus and protruding plaque through the stent struts. Please note a side branch (arrow) in *A* and *B*. In *C*, there is a malapposition area (*). At the bottom, the follow up corresponding frames are shown. Please note the protruding material has slightly increased over a period of 12 days.

Table 4 Clinical outcomes through 30 days

	Intra-procedural only bivalirudin (*N* = 59)	Prolonged bivalirudin (*N* = 64)	*P*-value
Co-primary composite endpoint of all-cause mortality, MI, or stroke, *n* (%)	3 (5.1)	2 (3.7)	0.6646
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5, *n* (%)	3 (5.1)	2 (3.7)	0.6646
All-cause mortality, *n* (%)	1 (1.7)	1 (1.9)	0.9591
Myocardial infarction, *n* (%)	2 (3.4)	1 (1.7)	0.5539
Stroke, *n* (%)	0 (0.0)	0 (0.0)	NA
Transient ischaemic attack, *n* (%)	0 (0.0)	0 (0.0)	NA
Definite or probable stent thrombosis, *n* (%)	0 (0.0)	1 (1.9)	1.0000
Any Bleeding, *n* (%)	4 (6.8)	4 (7.0)	0.9660
Type 1, *n* (%)	2 (3.5)	2 (3.4)	0.9985
Type 2, *n* (%)	2 (3.4)	2 (3.6)	0.9635
Type 3 or 5, *n* (%)	0 (0.0)	0 (0.0)	NA
Type 2, 3, or 5, *n* (%)	2 (3.4)	2 (3.6)	0.9635

the sample size calculation, a selection bias cannot be excluded. The absence of an anti-thrombotic effect of post-PCI bivalirudin does not *per se* contradict prior evidence, albeit inconclusive, suggesting that post-PCI *full* bivalirudin regimen may mitigate the occurrence of AST. A *full* bivalirudin regimen may prove effective in preventing further accumulation of thrombus within the stented area, and thus being effective for stent thrombosis prevention, but it may still remain an insufficient anti-thrombotic agent to achieve thrombus regression. Alternatively, the duration of infusion of bivalirudin after PCI may have been too short to allow measurable thrombus burden regression. However, a longer duration of bivalirudin infusion after PCI remains off-label and no study has so far investigated its efficacy, safety, and cost-effectiveness implications.

We acknowledge the potential for a selection bias inherent in our study design since only multivessel patients requiring a staged intervention during hospitalization, at discretion of the treating physician, were enrolled in the study. Further research on the capability of alternative anti-thrombotic strategies to mitigate thrombus burden is required.

Conclusions

The use of prolonged on-label infusion of bivalirudin showed comparable effects to intra-procedural only bivalirudin infusion administration in terms of percentage of frames with a thrombotic area >5% as assessed by OCT. At further stratified analyses the results remained consistent across defined subgroups, including the actual bivalirudin regimen employed after PCI as well as across multiple pre-defined secondary imaging endpoints. We, therefore, conclude that this imaging study does not provide mechanistic evidence supporting the use of prolonged bivalirudin infusion to reduce thrombotic burden after intervention.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: H.M.G.-G. report consultancy fees from Abbott during the conduct of this study. F.V. reports personal fees from Chiesi, personal fees from Bayer, personal fees from Astrazeneca, personal fees from Daichisankyo, personal fees from Boehringer, personal fees from Pfizer BMS, personal fees from Menarini, personal fees from Servier, personal fees from ALVIMEDICA CID, personal fees from STENTYS, personal fees from ABBOTT VASCULAR, grants from SANITEX, grants from BIOTRONIK, outside the submitted work. G.A. reports non-financial support from Terumo, during the conduct of the study; personal fees from Daiichi-Sankyo, personal fees and non-financial support from Bayer, personal fees from Pfizer-BMS, non-financial support from Boehringer-Ingelheim, personal fees from AstraZeneca, personal fees and non-financial support from Menarini, non-financial support from Abbott, non-financial support from Philips Volcano, non-financial support from Boston Scientific, outside the submitted work. M.V. reports grants from Medtronic, personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Servier, personal fees from Boehringer, personal fees from Daiichi Sankyo, outside the submitted work. All other authors declared no conflict of interest.

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