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FASTTRACK CLINICAL RESEARCH

Culprit lesion thrombus burden after manual thrombectomy or percutaneous coronary intervention-alone in ST-segment elevation myocardial infarction: the optical coherence tomography sub-study of the TOTAL (ThrOmbecTomy versus PCI ALone) trial

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Aims Manual thrombectomy has been proposed as a strategy to reduce thrombus burden during primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI). However, the effectiveness of manual thrombectomy in reducing thrombus burden is uncertain. In this substudy of the TOTAL (ThrOmbecTomy versus PCI ALone) trial, we compared the thrombus burden at the culprit lesion using optical coherence tomography (OCT) in patients treated with thrombectomy vs. PCI-alone.

Methods and results The TOTAL trial ($N = 10\,732$) was an international, multicentre, randomized trial of thrombectomy (using the Export catheter, Medtronic Cardiovascular, Santa Rosa, CA, USA) in STEMI patients treated with primary PCI. The OCT substudy prospectively enrolled 214 patients from 13 sites in 5 countries. Optical coherence tomography was performed immediately after thrombectomy or PCI-alone and then repeated after stent deployment. Thrombus quantification was performed by an independent core laboratory blinded to treatment assignment. The primary outcome of pre-stent thrombus burden as a percentage of segment analysed was 2.36% (95% CI: 1.73–3.22) in the thrombectomy group and 2.88% (95% CI: 2.12–3.90) in the PCI-alone group ($P = 0.373$). Absolute pre-stent thrombus volume was not different (2.99 vs. 3.74 mm^3, $P = 0.329$). Other secondary outcomes of pre-stent quadrants of thrombus, post–stent atherothrombotic burden, and post-stent atherothrombotic volume were not different between groups.

Conclusion Manual thrombectomy did not reduce pre-stent thrombus burden at the culprit lesion compared with PCI-alone. Both strategies were associated with low thrombus burden at the lesion site after the initial intervention to restore flow.

Keywords Myocardial infarction • STEMI • Optical coherence tomography • Thrombectomy • Thrombus

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Background

Manual thrombectomy has been proposed as a strategy to reduce thrombus burden and distal embolization during primary percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) patients.[1,2] However, the recently reported ThrOmbecTomy versus PCI Alone (TOTAL) trial demonstrated that routine thrombectomy compared with PCI-alone did not reduce the primary composite endpoint of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association class IV heart failure within 180 days and was associated with an increase in stroke within 30 days.[3] Potential explanations for the absence of benefit from thrombectomy may include ineffective removal of thrombus by thrombectomy, resulting in substantial residual thrombus burden at the culprit lesion, or conversely, an average culprit lesion thrombus burden that is insufficiently large to merit a routine aspiration strategy.

We conducted an optical coherence tomography (OCT) substudy in the TOTAL trial to provide insights into the mechanism of action of thrombectomy. Optical coherence tomography provides high-resolution imaging of the coronary arteries and is the most accurate method of thrombus quantification available.[4] Although a lack of effect of thrombectomy on OCT-measured thrombus burden was previously observed after stent implantation,[5] stent placement disrupts the thrombus and may lead to the development of plaque prolapse that confounds thrombus measurement. Therefore, assessment of thrombus burden prior to stent implantation may be a more reliable marker for the efficacy of thrombus removal. We have previously shown that pre-stent thrombus burden quantification with OCT in STEMI is feasible and reliable.[6]

In this prospective sub-study of the TOTAL trial, we sought to compare culprit lesion thrombus burden immediately after re-establishment of Thrombolysis in Myocardial Infarction (TIMI) 2–3 coronary flow and after stent implantation during primary PCI in patients randomized to thrombectomy or PCI-alone.

Methods

The TOTAL trial was an international, multicentre, randomized trial of routine thrombectomy (using the Export catheter, Medtronic Cardiovascular, Santa Rosa, CA, USA) compared with PCI-alone in STEMI patients treated with primary PCI ($n = 10\,732$).[3] We enrolled patients presenting with symptoms of myocardial ischaemia lasting for $\geq$30 min and definite electrocardiographic changes indicating STEMI who were referred for primary PCI and randomized within 12 h of symptom onset as previously described.[7] Participation in the OCT sub-study required restoration of TIMI 2–3 flow after the first device (pre-stent imaging) and/or following stent implantation (post-stent imaging). In patients randomized to PCI-alone, pre-stent imaging could also be performed immediately after wire placement if direct stenting was planned and TIMI 2–3 flow was present. In addition to the exclusion criteria of the TOTAL trial, patients were excluded from the OCT sub-study if they were in cardiogenic shock or had known renal failure. All patients enrolled in the OCT sub-study provided informed consent specific to the sub-study.

Optical coherence tomography imaging

Optical coherence tomography imaging was performed using the Ilumien™ OCT system and C7 Dragonfly™ catheter (St Jude Medical, Minnesota, MN, USA). The radio-opaque distal marker of the OCT system was positioned 1–2 cm distal to the target lesion or stent. Contrast was injected either manually or automatically by injector, depending on local practice. The images obtained were reviewed by the operator to ensure adequate image quality. A second and/or third image was obtained if the image quality was sub-optimal. A maximum of three images were be attempted. Acquired OCT images were exported in digital format for offline analysis.

Angiogram analysis

Angiograms of patients enrolled in the OCT sub-study were assessed in a dedicated angiographic core laboratory (Hamilton Health Sciences, Canada) blinded to treatment assignment. Pre-stent angiographic TIMI thrombus burden was assessed at the first injection of the infarct related artery.[7] Quantitative coronary angiographic (QCA) measurements were performed on the culprit lesion before intervention and after stenting (QAngioXA, Medis, Leiden, the Netherlands). Measurements included reference vessel diameter, minimum lumen diameter, lesion length, and diameter stenosis.

Optical coherence tomography analysis

Optical coherence tomography image analysis was performed by an independent OCT core laboratory (Heart Hospital, Tampere University Hospital, Finland) blinded to the treatment assignment. Analyses were performed using customized software (OCT Miner, Heart Hospital, Tampere University Hospital, Finland) and a proprietary offline research workstation (St Jude Medical) as previously described.[6] The primary outcome was pre-stent thrombus burden (%) defined as the average of the thrombus area divided by the lumen area over the length of the analysed segment. The secondary outcomes were: pre-stent thrombus volume (in mm^3); pre-stent quadrants of thrombus (absolute number); pre-stent quadrants of thrombus (mean numbers/mm); pre-stent maximal thrombus area (mm^2); post-stent atherothrombotic burden (%); post-stent atherothrombotic volume (in mm^3); and post-stent maximal atherothrombotic area (mm^2). Sample measurements are shown in *Figure 1*.

Statistics

Based on data from the first 20 patients enrolled in the TOTAL OCT substudy, we estimated a control pre-stent thrombus burden of 12% (arithmetic mean) and standard deviation of 11.6% and determined that a sample size of 163 patients would have 84% power to detect a 30% reduction in thrombus burden. Assuming that 80% of patients would have analysable pre-stent imaging, we selected a sample size of 200 patients.

Baseline variables were summarized as mean $\pm$ standard deviation for continuous variables, median (25th percentile, 75th percentile) for time variables, and *n* (%) for categorical variables. Baseline variables were compared between thrombectomy and PCI-alone groups with the Pearson χ^2 test for categorical variables and Wilcoxon two-sample test for continuous variables. No *P* values were determined when there were fewer than four observations in either group.

All pre- and post-stent values were not normally distributed. These outcomes were transformed to improve normality before statistical analysis. The final estimates were presented on the back-transformed scale. Due to non-normal distributions, geometric means were used to describe central tendency. The geometric means and 95% confidence intervals were presented. The *t*-test was used for significance testing of the transformed data for all primary and secondary outcomes. Two-sided type I error level was set at 5%. A modified intent-to-treat analysis was performed including all patients with analysable OCT images in their randomized group. Pre-specified subgroup analyses were performed for

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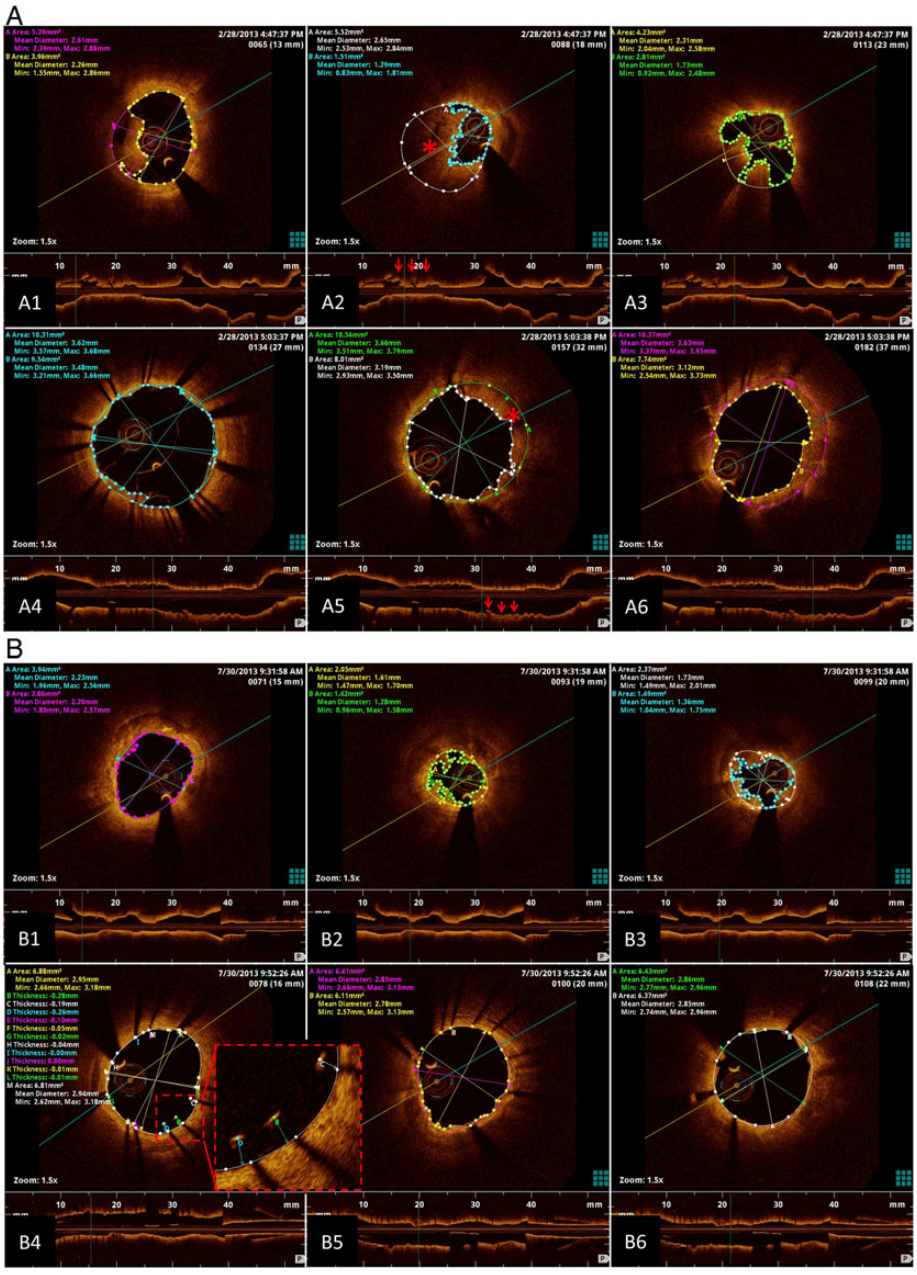

Figure 1 Measurement of thrombus burden by OCT in two STEMI patients in TOTAL OCT study. Representative cross-sectional OCT images of a patient with high (22.1%) pre-stent TB (*A*1–6) and another patient with low (3.4%) pre-stent TB (*B*1–6). Anatomically matched cross-sections of the culprit artery show the original pre-stent lumen area (Area A) and flow area (Area B) tracings in *A*1–3 and *B*1–3 and post-stent modified stent area (Area A) and flow area (Area B) tracings in *A*4–6 and *B*4–6. Intraluminal thrombus can be observed in cross sections (denoted by asterisks in *A*2 and *A*5) and in the longitudinal view (arrows in *A*2 and *A*5). An example of post-stent measurements in case of malapposition is shown in *B*4. Post-stent atherothrombotic burden was 10.2 and 2.7%, respectively, for patients A and B. OCT, optical coherence tomography, STEMI, ST-elevation myocardial infarction.

TIMI thrombus grade ≥4 vs. <4 and TIMI thrombus grade ≥3 vs. <3. Interactions between the treatment effect and subgroups were tested using linear regression models with factors for treatment, subgroup, and interaction. The Wald test was used to test for statistical interaction. The non-parametric Spearman rank correlation coefficient was used to assess the correlation between pre- and post-stent outcomes.

Results

Of the 214 patients in the OCT sub-study, 104 were randomized to thrombectomy and 110 to PCI-alone (*Figure 2*). One patient in the thrombectomy group crossed over to PCI-alone and five patients in the PCI-alone group had bailout thrombectomy after a failure of

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the initial PCI-alone strategy. Interpretable pre-stent images were obtained in 85 of 104 in the thrombectomy arm and 88 of 110 patients in the PCI-alone arm. Interpretable post-stent images were obtained in 84 of 104 patients in the thrombectomy arm and 89 of 110 patients in the PCI-alone arm. Reasons for not performing OCT imaging or for lack of interpretability of the acquired images are shown in *Figure 2*.

Baseline characteristics of the patients were well balanced (*Table 1*). The PCI procedure details and angiographic results are shown in *Table 2*. TIMI thrombus burden 5 was present in 54.5% of thrombectomy patients and 61.1% of PCI-alone patients. Direct stenting was performed more frequently in the thrombectomy group (36.5 vs. 10.9%, $P < 0.0001$). Glycoprotein IIb/IIIa inhibitor use was not different between the groups. Post PCI, TIMI 2 or 3 flow was obtained in all but one patient in each group. Rates of angiographic no reflow and distal embolization were low and not different between the groups.

The primary outcome of pre-stent thrombus burden as a percentage of the analysed segment was 2.36% (95% CI 1.73–3.22) in the thrombectomy group and 2.88% (95% CI 2.12–3.90) in the PCI-alone group ($P = 0.373$) (*Table 3*). Scatter plots of pre-stent thrombus burden by the treatment group are shown in *Figure 3*. There was no difference in percent pre-stent thrombus burden in subgroups of TIMI thrombus grade <4 vs. ≥4 or TIMI thrombus grade <3 vs. ≥3 (*Table 4*). Absolute pre-stent thrombus volume was not different (2.99 vs. 3.74 mm^3, $P = 0.329$) between thrombectomy and PCI-alone. Scatter plots of absolute pre-stent thrombus volume by treatment group are shown in *Figure 4*. Additional absolute (quadrants of thrombus, maximal thrombus area) and relative (quadrants of thrombus/mm) measures of pre-stent thrombus showed no difference between groups (*Table 3*). *Post hoc* subgroup analysis comparing baseline TIMI flow 0 or 1 vs. 2 or 3 did not show any difference in pre-stent thrombus burden (see Supplementary material online, *Table S1*). The semi-quantitative measure pre-stent quadrants of thrombus was highly correlated with our primary outcome pre-stent thrombus burden ($r = 0.91$) (see Supplementary material online, *Figure S1*).

Post-stent atherothrombotic burden was 6.23% (95% CI 5.74–6.76) in the thrombectomy group and 5.71% (95% CI 5.27–6.18) in the PCI-alone group ($P = 0.136$). There was no difference in post-stent atherothrombotic burden in subgroups of TIMI thrombus grade <4 vs. ≥4 or TIMI thrombus grade <3 vs. ≥3 (*Table 4*). Absolute measures of post-stent thrombus burden (atherothrombotic volume and maximal atherothrombotic area) also did not show any difference between the groups (*Table 3*). *Post hoc* sub-group analysis comparing baseline TIMI flow 0 or 1 vs. 2 or 3 did not show any difference in post-stent atherothrombotic burden (see Supplementary material online, *Table S1*). There was low correlation between post-stent atherothrombotic burden and pre-stent

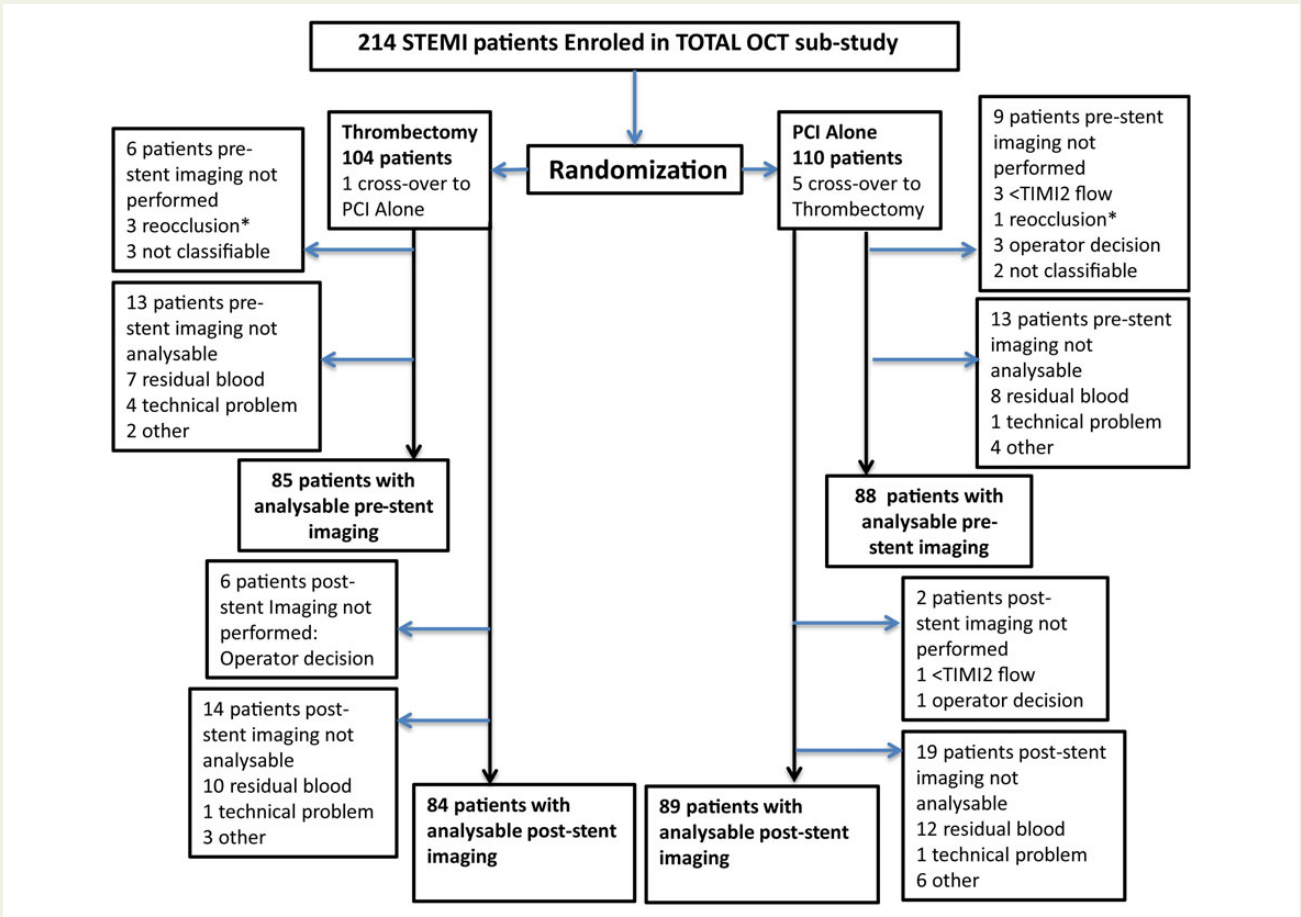

Figure 2 Patient flow diagram. Asterisk indicates TIMI 2/3 flow achieved, but vessel reoccluded by imaging catheter.

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Table 1 Baseline characteristics of randomized patients

	Thrombectomy ($n = 104$)	PCI-alone ($n = 110$)	*P*-value[a]
Age (years)	60.2 ± 11.1	61.6 ± 11.9	0.41
Male sex	77 (74.0)	90 (81.8)	0.17
Risk factor profile			
Hypertension	55 (52.9)	64 (58.2)	0.49
Diabetes	15 (14.4)	23 (20.9)	0.21
Current smoking	42 (40.4)	51 (46.4)	0.38
Prior MI	9 (8.7)	15 (13.6)	0.25
Prior PCI	8 (7.7)	15 (13.6)	0.16
MI location			0.53
Anterior	39 (37.5)	44 (40.0)	
Inferior	63 (60.6)	61 (55.4)	
Lateral or other	2 (1.9)	5 (4.5)	
Killip Class[b]			0.28
Class I	99 (95.2)	106 (96.4)	
Class II	4 (3.9)	1 (0.9)	
Class III	0 (0.0)	2 (1.8)	
Class IV	1 (1.0)	1 (0.9)	
Creatinine (μmol/L)[b]	83.3 ± 20.2	89.7 ± 24.3	0.09

Values are mean ± standard deviation for continuous variables, and *n* (%) for categorical variables.
[a]Pearson χ^2 test for categorical variables and Wilcoxon two-sample test for continuous variables.
[b]One patient has data missing in the PCI-alone group.

thrombus burden ($r = 0.34$) overall and by the treatment group (thrombectomy $r = 0.29$, PCI-alone 0.38) (*Figure 5*).

Discussion

In our OCT sub-study of STEMI patients undergoing primary PCI in the TOTAL trial, we observed no impact of thrombectomy vs. PCI-alone on pre-stent thrombus burden. Both interventions were associated with a low level of culprit lesion thrombus in the majority of patients. Post-stent atherothrombotic burden was also similar between the thrombectomy and PCI-alone groups, although this outcome measure had low correlation with pre-stent thrombus burden.

Manual thrombectomy prior to stent implantation in STEMI patients has the potential to reduce residual thrombus at the culprit lesion. In the present study, we observed a low mean level of thrombus at the culprit lesion after treatment with thrombectomy. Our findings suggest that the lack of a reduction in clinical events with thrombectomy[2,3] is not due to inadequate removal of thrombus. In fact, the low thrombus burden in most patients after thrombectomy indicates that more aggressive measures to reduce thrombus in STEMI may not improve outcomes when employed as a routine strategy. Bailout use of thrombectomy may still be appropriate in patients with high thrombus burden where an initial PCI-alone strategy fails. This occurred in 7% of patients treated initially with PCI-alone in the overall TOTAL trial.[3]

Optical coherence tomography imaging was not performed prior to the first intervention and so initial thrombus burden could not be assessed. The low thrombus burden in the PCI-alone group may be due to the effectiveness of angioplasty at breaking up thrombus in the occluded artery or a lower than expected pre-intervention thrombus burden at the lesion site. Short ischaemic times, potent antiplatelet and antithrombotic therapies may have contributed to the low culprit lesion thrombus burden.

The TROFI study previously demonstrated no impact of thrombectomy on post-stent minimum flow area.[5] In our study, we also assessed absolute and relative post-stent atherothrombotic burden and observed no difference between thrombectomy and PCI-alone. The ability to image through a stented artery and to visualize stent struts in the resulting OCT cross-sections facilitates the quantification of post-stent thrombus. However, stent placement also results in substantial changes to plaque and thrombus architecture including the development of intra-stent plaque prolapse that cannot be differentiated from thrombus by OCT. Given the high frequency of lipid-rich plaque in STEMI,[8] the propensity for plaque prolapse may be increased in comparison with other lesion subsets. This could account for the lack of correlation we observed between pre- and post-stent measures of thrombus. Prior OCT studies have assessed pre-stent thrombus using quadrants of thrombus, a measure that can be readily made by visual assessment of the OCT images.[4] Our primary outcome, in contrast, required full quantification of thrombus and vessel areas on multiple OCT cross sections throughout

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Table 2 Percutaneous coronary intervention procedure details and angiographic results

	Thrombectomy (n = 104)	PCI-alone (n = 110)	P-value[a]
Symptom onset to hospital arrival (min)	82 (51, 159)	91 (62, 128)	0.25
Hospital door to procedure (min)	68 (37, 103)	72 (35, 97)	0.97
PCI procedure time (min)	61 (49, 72)	54 (45, 71)	0.10
Pre-procedure angiographic findings[b]			
TIMI flow			0.91
0	55 (54.5)	66 (61.1)	
1	10 (9.9)	7 (6.5)	
2	11 (10.9)	10 (9.3)	
3	25 (24.8)	25 (23.2)	
TIMI thrombus grade			0.17
0	16 (15.8)	20 (18.5)	
1	9 (8.9)	10 (9.3)	
2	1 (1.0)	1 (0.9)	
3	9 (8.9)	1 (0.9)	
4	11 (10.9)	10 (9.3)	
5	55 (54.5)	66 (61.1)	
Lesion length (mm)	14.5 ± 5.6	13.5 ± 6.5	0.08
Reference vessel diameter (mm)	2.91 ± 0.73	2.82 ± 0.62	0.43
Minimum lumen diameter (mm)	0.24 ± 0.33	0.28 ± 0.45	0.76
% Stenosis	91.8 ± 10.8	90.2 ± 14.9	0.93
Procedure details			
Direct stenting	38 (36.5)	12 (10.9)	<0.0001
Medication use			
Unfractionated heparin	87 (83.7)	92 (83.6)	0.99
Bivalirudin	17 (16.3)	16 (14.5)	0.72
Enoxaparin	6 (5.8)	9 (8.2)	0.49
Glycoprotein IIb/IIIa inhibitor			
Upfront	36 (34.6)	39 (35.5)	0.90
Bailout	23 (22.1)	35 (31.8)	0.11
Post-procedure results[c]			
TIMI flow			0.60
0	0 (0.0)	0 (0.0)	
1	1 (1.0)	1 (0.9)	
2	8 (8.2)	5 (4.7)	
3	89 (90.8)	100 (94.3)	
Reference vessel diameter (mm)	3.20 ± 0.50	3.21 ± 0.49	0.87
Minimum lumen diameter (mm)	2.99 ± 0.50	3.00 ± 0.51	0.77
% Stenosis	9.0 ± 10.1	7.8 ± 4.6	0.47
Angiographic no reflow[c]	1 (1.0)	0 (0.0)	~
Distal embolization[c]	4 (4.1)	6 (5.7)	0.60
IRA closure/side branch occlusion[c]	2 (2.0)	3 (2.8)	~
Coronary dissection/perforation[c]	1 (1.0)	0 (0.0)	~

Shown are mean ± standard deviation for continuous variables, and n (%) for categorical variables.
'~' indicates no P value was determined due to less than four observations in either group.
[a]Pearson χ^2 test for categorical variables and Wilcoxon two-sample test for continuous variables.
[b]Three and two patients have data missing in the thrombectomy followed by PCI and the PCI-alone groups, respectively.
[c]Six and four patients have data missing in the thrombectomy followed by PCI and the PCI-alone groups, respectively.

the lesion. Nonetheless, we observed excellent correlation between these pre-stent measures suggesting that either outcome may be a reasonable surrogate for pre-stent thrombus in future OCT studies.

Limitations

Our study has a number of important limitations. First, the observed mean pre-stent thrombus burden was lower than

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Table 3 Quantitative optical coherence tomography analysis results in randomized treatment groups

	Thrombectomy, mean (95% CI)	PCI-alone, mean (95% CI)	*P*-value[a]
Pre-stent	*N* = 85	*N* = 88	
Thrombus burden (%)	2.36 (1.73–3.22)	2.88 (2.12–3.90)	0.373
Absolute Thrombus volume (mm^3)	2.99 (2.18–4.12)	3.74 (2.73–5.10)	0.329
Quadrants of thrombus (number)	26.88 (21.94–32.92)	29.69 (24.38–36.15)	0.488
Quadrants of thrombus/mm	0.44 (0.36–0.55)	0.47 (0.38–0.58)	0.711
Maximal thrombus area (mm^2)	1.17 (0.94–1.45)	1.34 (1.08–1.66)	0.373
Post-stent	*N* = 84	*N* = 89	
Atherothrombotic burden (%)	6.23 (5.74–6.76)	5.71 (5.27–6.18)	0.136
Absolute Atherothrombotic volume (mm^3)	14.88 (12.98–17.06)	13.27 (11.63–15.16)	0.238
Maximal atherothrombotic area (mm^2)	1.52 (1.37–1.69)	1.40 (1.27–1.56)	0.272

OCT, optical coherence tomography; CI, confidence interval.
[a]Log-transformed data.

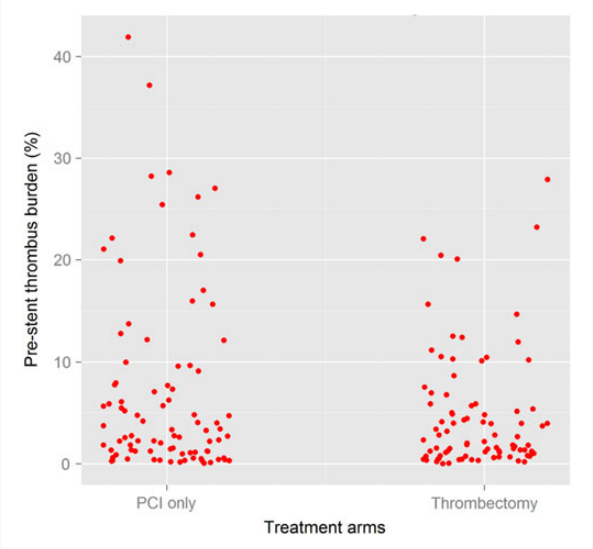

Figure 3 Scatter plot of pre-stent thrombus burden by treatment group.

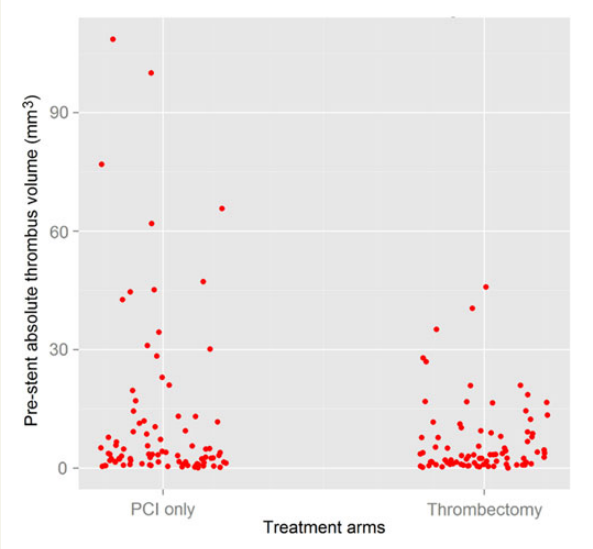

Figure 4 Scatter plot of pre-stent thrombus volume by treatment group.

anticipated in our sample size calculation. Therefore, the study may have been underpowered to detect a difference between groups. Second, our ability to image patients may have been influenced by the extent of residual thrombus burden after the first device. The presence of residual thrombus leading to vessel re-occlusion around the OCT catheter and/or the inability to clear blood prevented imaging in a small number of patients. As a consequence, we may have underestimated the prevalence of high thrombus burden patients. Third, passage of the thrombectomy, PTCA, or OCT catheters may have resulted in some displacement of thrombus from the culprit lesion prior to imaging being performed, potentially contributing in part to the low pre-stent thrombus burden observed. Finally, as enrolment in the OCT sub-study was at the operator's discretion, it is possible that some patients with more extreme thrombus burden may have been excluded. We observed that the baseline rate of TIMI 0 or 1 flow was 64% in our sub-study compared with 74% in the overall TOTAL trial. While this may be due to the play of chance, one possible explanation is that less severe patients were chosen for inclusion in the OCT sub-study. The potential exclusion of some patients with high angiographic thrombus or poor flow following initial intervention may have resulted in an inappropriately low estimation of thrombus burden by OCT.

Conclusion

In the TOTAL OCT sub-study of patients undergoing primary PCI for STEMI, manual thrombectomy did not reduce pre-stent thrombus

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Table 4 Pre-stent thrombus burden and post-stent atherothrombotic burden stratified by thrombolysis in myocardial infarction thrombus grade

	N	Thrombectomy, mean (95% CI)	*N*	PCI-alone, mean (95% CI)	*P*-value[a]	Interaction *P*-value[a]
Pre-stent thrombus burden (%)						
TIMI thrombus grade <3	22	1.65 (0.93–1.65)	24	1.65 (0.95–2.85)	0.999	0.626
TIMI thrombus grade ≥3	61	2.72 (1.88–3.93)	63	3.45 (2.41–4.95)	0.362	
TIMI thrombus grade <4	29	1.92 (1.19–3.10)	25	1.71 (1.02–2.86)	0.744	0.435
TIMI thrombus grade ≥4	54	2.68 (1.79–4.00)	62	3.44 (2.37–4.99)	0.364	
Post-stent atherothrombotic Burden (%)						
TIMI thrombus grade <3	21	6.53 (5.65–7.55)	26	5.69 (4.99–6.49)	0.163	0.691
TIMI thrombus grade ≥3	61	6.15 (5.56–6.80)	62	5.64 (5.11–6.23)	0.232	
TIMI thrombus grade <4	27	6.38 (5.62–7.25)	27	5.60 (4.93–6.36)	0.152	0.709
TIMI thrombus grade ≥4	55	6.18 (5.55–6.88)	61	5.68 (5.13–6.29)	0.263	

OCT, optical coherence tomography; CI, confidence interval; *N*, number of patients.
[a]Log-transformed data.

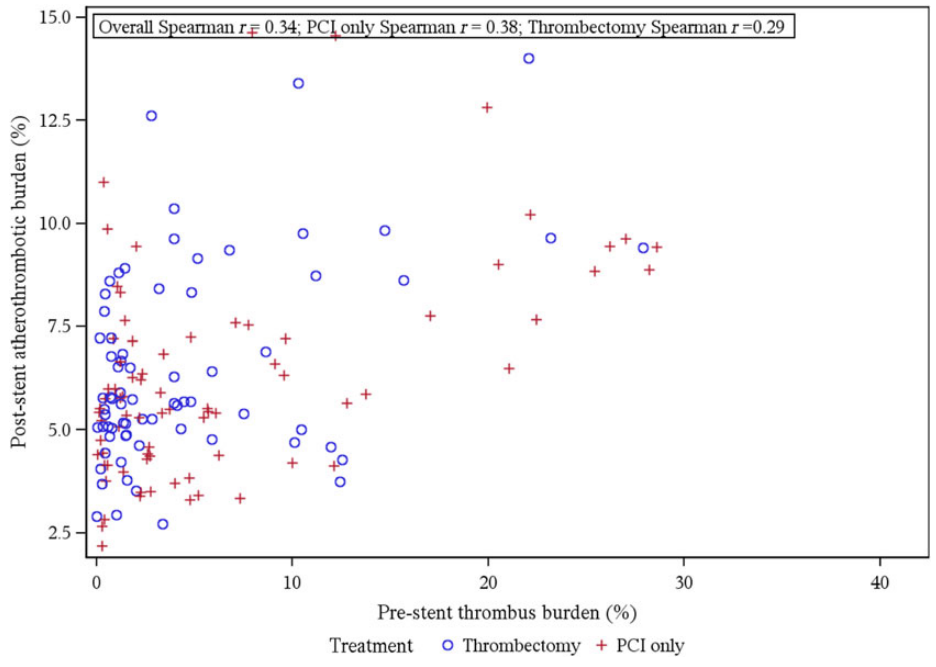

Figure 5 Correlation between pre-stent thrombus burden and post-stent atherothrombotic burden.

burden at the culprit lesion compared with PCI-alone. Both strategies were associated with low thrombus burden at the culprit lesion after the initial intervention to restore flow.

Supplementary material

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

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Conflict of interest: T.S. reports grants and personal fees from St Jude Medical, during the conduct of the study; W.J.C. reports personal fees

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from AstraZeneca, Roche Canada, and Daiichi Sankyo, outside the submitted work; A.F. reports personal fees from Proctor for St Jude Medical, outside the submitted work; S.S.J. reports grants from Medtronic and St Jude, during the conduct of the study; V.K. reports grants, personal fees, and non-financial support from Medtronic, personal fees and non-financial support from Abbott Vascular, non-financial support from B. Braun, outside the submitted work.

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