Anatomic Characteristics and Clinical Implications of Angiographic Coronary Thrombus

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

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

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

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

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

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

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

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WHAT IS KNOWN

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

WHAT THE STUDY ADDS

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

Methods

Patient Population

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

Table 1. Segment Weighing Factor

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

Table 2. Baseline Clinical Characteristics

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

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

Clinical Outcomes

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

Table 3. Baseline Angiographic Characteristics

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

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

Angiographic Assessment

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

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

Data Analysis

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

Results

Baseline Characteristics

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

Table 4. Kaplan–Meier Events Rate Comparison Between Groups

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

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

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

Angiographic Characteristics

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

Clinical Outcomes

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

Subgroup Analysis

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

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

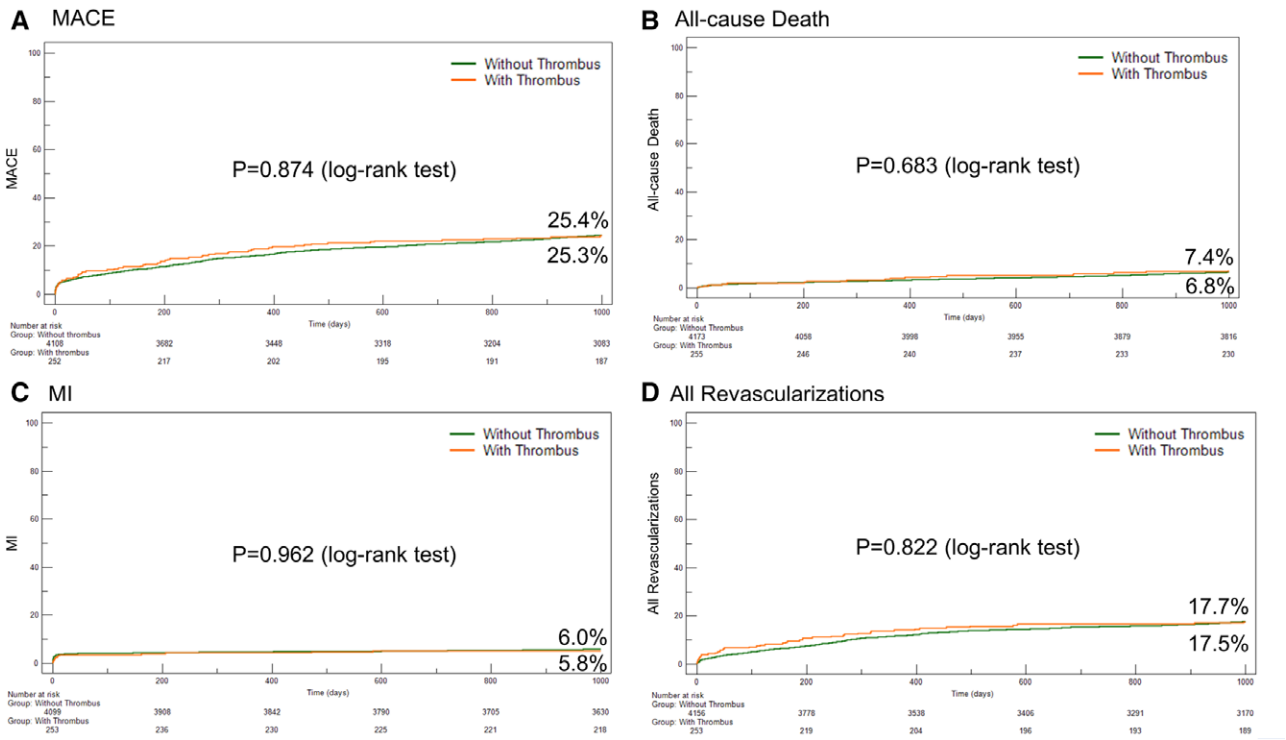


Figure 1. Kaplan–Meier cumulative curves for MACE (**A**; composite of all-cause death, myocardial infarction, and all revascularizations), all-cause death (**B**), myocardial infarction (MI; **C**), and all revascularizations (**D**). MACE indicates major adverse cardiac events; and MI, myocardial infarction.

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

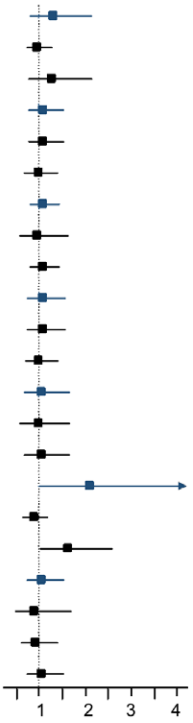


Figure 2. Stratified analysis for MACE (composite of all-cause death, all myocardial infarction, and all revascularizations according to the presence or absence of thrombus containing lesions. ACS indicates acute coronary syndromes; CAD, coronary artery disease; CI, confidence interval; CrCl, creatinine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

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

Anatomic Characteristics of Thrombus Containing Lesions

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

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

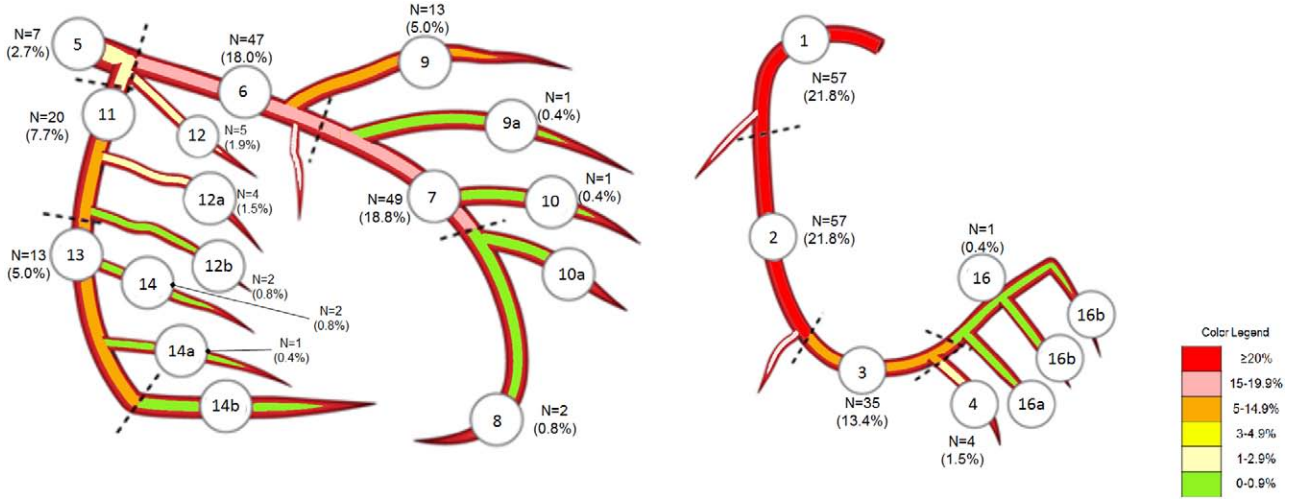
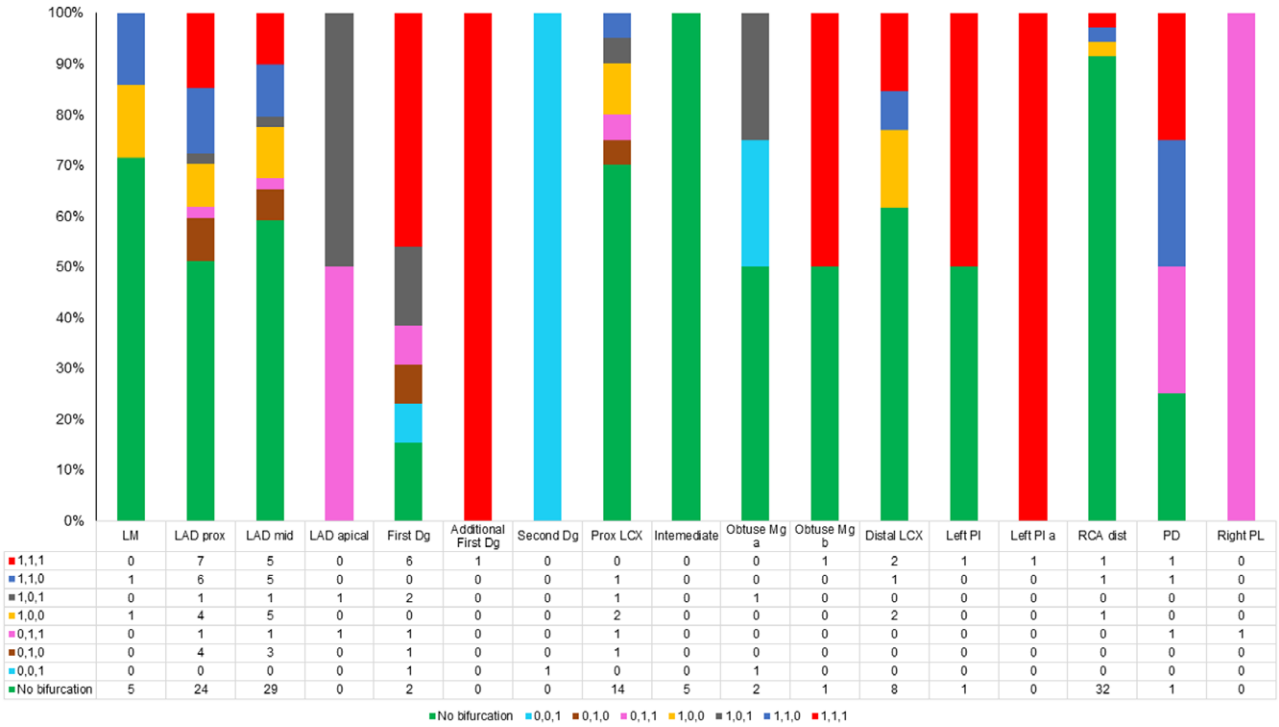


Figure 3. Distribution of angiographic thrombus containing lesions.



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

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

Clinical Outcomes According to Myocardium at Risk

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

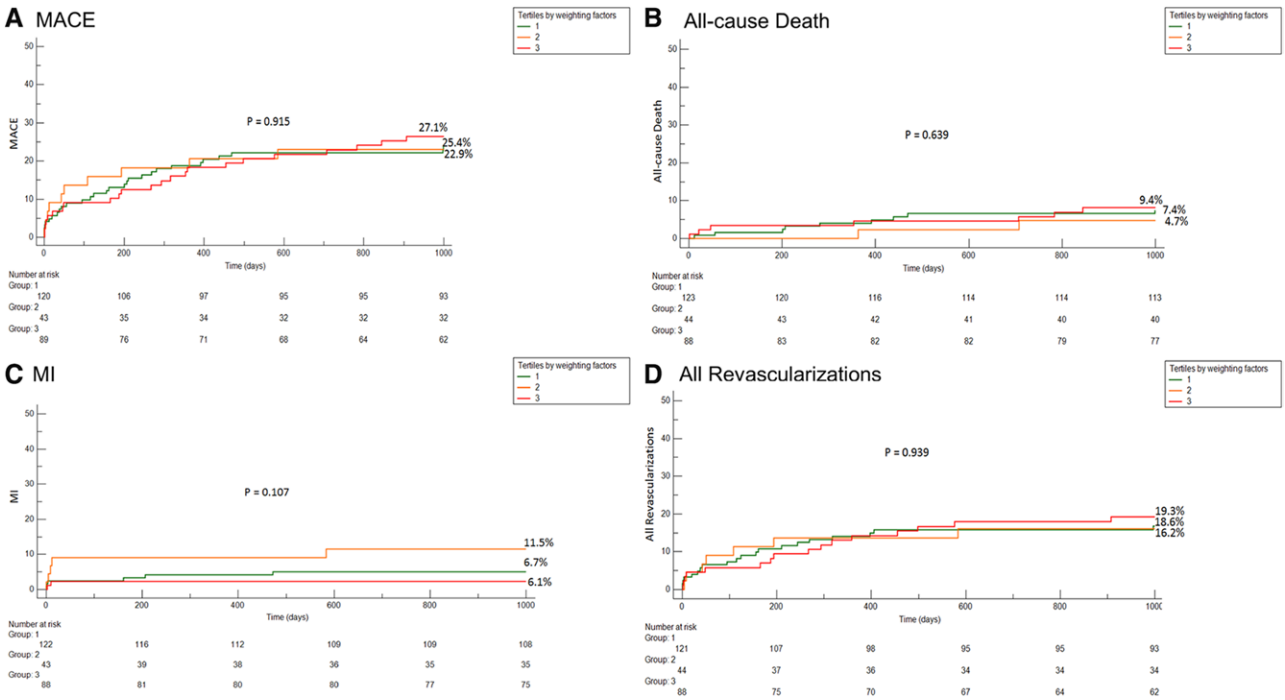


Figure 5. Kaplan–Meier cumulative curves for MACE (**A**; composite of all-cause death, myocardial infarction and all revascularizations), all-cause death (**B**), myocardial infarction (MI; **C**), and all revascularizations (**D**) according to tertiles of the sum of segment weighing factors in patients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

Table 5. Distribution of Complex Coronary Lesions

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

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

Discussion

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

Anatomy of Angiographic Coronary Thrombus

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

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

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

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

Thrombus and Clinical Events

In the present study, the presence of thrombus did not have any effect on clinical events, even when it was adjusted for the amount of myocardial at risk. Corroborating our findings, Singh et al have shown that the introduction of the coronary stents and the use of more contemporary antiplatelet therapy made the presence of thrombus irrelevant for long-term death and MI.[8] On the other hand, Sianos et al have demonstrated that large thrombus burden is an independent predictor of

major adverse events (defined as death, repeat MI infarct-related artery infarct-related artery) in patients treated with drug-eluting stents for STEMI.[9] Additionally, large thrombus burden has been related to larger myocardial damage as detected by contrast-enhanced cardiac magnetic resonance.[26] The aforementioned findings suggest that, for clinical prognostic discrimination, the angiographic thrombus assessment should be no longer classified as a binary variable but as a more detailed thrombotic burden quantification.

Limitations

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

Conclusions

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

Disclosures

None.

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Supplemental Material

Supplemental Material

Anatomic Characteristics and Clinical Implications of Angiographic Coronary Thrombus: insights from a patient-level pooled analysis of SYNTAX, RESOLUTE and LEADERS trials

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Supplemental Material

Supplemental Methods:

Discrete data were summarized as percent (frequencies) and were compared using the chi-squared test. Continuous data were expressed as mean±SD and were compared using Student's t-test or Wilcoxon rank-sum test based on their distributions. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by the log-rank test. Comparison of events rates between groups were adjusted for confounding factors in a Cox-regression model. All variables were stratified according to presence of at least one TCL using a Cox-regression model. The differences were regarded significant when $p<0.05$ (two-tailed). The Breslow-Day chi-squared test was calculated to test the statistical evidence of heterogeneity across the studies ($p<0.1$). The chi-squared test and I^2 statistic was calculated to test the statistical evidence of heterogeneity across the studies [1] (Supplementary Table 2, supplementary Figures 1-5). SPSS version 21.0 (SPSS Inc., Chicago, Illinois) was used for all other statistical analyses.

Supplemental Material

Supplemental Tables

Table 1. Summary of the trials included in the present analysis

		LEADERS[2]	RESOLUTE[3]	SYNTAX[4]
Enrolment Period		11/2006-05/2007	04/2008-10/2008	03/2005-04/2007
Study Design		RCT	RCT	RCT
Number of Patients		1707	2292	1101
Number of Patients with SYNTAX score Total (acute†)		1352 (535)	2026 (736)	1072 (0)
Stents Used		SES , BES	EES, ZES	PES
Inclusion criteria		Patients aged ≥18 years old **AND** Presentation: Stable angina, ACS, STEMI **AND** ≥1 lesion ≥50% DS in vessel with RVD 2.25-4.00mm* No restriction on total number of treated lesions, treated vessels, lesion length or number of stents implanted.		Presentation: stable angina, unstable angina or silent ischaemia, **AND** >50% DS in three major epicardial coronary arteries and/or LMS No restriction on the total implanted stent length.
Exclusion criteria		Inability to take dual anti-platelet therapy Allergy to study medicines Terminal illness <6 months life expectancy Pregnancy Participation in another trial		Previous PCI or CABG Acute MI Need for concomitant cardiac surgery
Study Procedure		Stenting procedure at operator's discretion; Direct stenting was allowed Aim for complete revascularisation		
DAPT	**Aspirin†**	100mg	≥75mg	≥70mg
	Clopidogrel (duration)	75mg (12 months)	75 mg (12 months)	75 mg (≥ 6 months)

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	LEADERS[2]	RESOLUTE[3]	SYNTAX[4]
	Giulio G Stefanini, Bindu Kalesan, Patrick W Serruys, Dik Heg, Pawel Buszman, Axel Linke, Thomas Ischinger, Volker Klauss, Franz Eberli, William Wijns, Marie-Claude Morice, Carlo Di Mario, Roberto Corti, Diethmar Antoni, Hae Y Sohn, Pedro Eerdmans, Gerrit-Anne van Es, Bernhard Meier, Stephan Windecker	Patrick W. Serruys, Sigmund Silber, Scot Garg, Robert Jan van Geuns, Gert Richardt, Pawel E. Buszman, Henning Kelbæk, Adrianus Johannes van Boven, Sjoerd H. Hofma, Axel Linke, Volker Klauss, William Wijns, Carlos Macaya, Philippe Garot, Carlo DiMario, Ganesh Manoharan, Ran Kornowski, Thomas Ischinger, Antonio Bartorelli, Jacintha Ronden, Marco Bressers, Pierre Gobbens. Manuela Negoita, Frank van Leeuwen and Stephan Windecker	Patrick W. Serruys, Marie-Claude Morice, A. Pieter Kappetein, Antonio Colombo, David R. Holmes, Michael J. Mack, Elisabeth Ståhle, Ted E. Feldman, Marcel van den Brand, Eric J. Bass, Nic Van Dyck, Katrin Leadley, Keith D. Dawkins and Friedrich W. Mohr

*2.25-3.50mm in LEADERS

†Acute- ST-elevation and Non-ST elevation myocardial infarction

Supplemental Material

Table 2. Assessment of heterogeneity among the trials:

Endpoint	Chi-square P value	I^2
All-cause death	0.13	51%
All revascularizations	0.20	38%
Myocardial Infarction	0.69	0%
MACE (composite by death, myocardial infarction and all revascularizations)	0.02	74%

There was a significant heterogeneity for MACE (Supplemental Figure 1) but interestingly was not caused by the SYNTAX trial (Supplemental Figures 2-4). The Supplemental Figure 5 shows the combined OR using Bayesian random effects in which thrombus containing lesion (TCL) did not have impact on long-term occurrence of MACE.

Supplemental Material

Table 3. Baseline clinical and angiographic characteristics according the presence/absence of thrombus in patients with stable coronary artery disease

	Without thrombus N=2131	**With thrombus N=50**	**P**
Age	63.6±11.2	61.8±11.9	0.031
Male,%	1610 (75.6)	39 (78.0)	0.868
Diabetes Mellitus,%	595 (27.9)	18 (36.0)	0.206
Body mass index, kg/m^2	27.7±4.5	27.5±4.6	0.527
Hypertension,%	1613 (75.7)	40 (80.0)	0.616
Hyperlipidemia,%	1578 (74.0)	35 (70.0)	0.517
Current smoker,%	524 (24.6)	13 (26.0)	0.794
Peripheral vascular disease,%	190 (8.9)	4 (8.0)	0.767
Family history of premature CAD,%	1394 (65.4)	34 (68.0)	0.756
History of Stroke/TIA,%	128 (6.0)	5 (10.0)	0.209
Creatinine>200 micromol/L	32 (1.5)	0 (0.0)	1.000
Creatinine clearance; ml/min	93.2±41.4	100.1±34.6	0.012
Previous myocardial infarction,%	637 (29.9)	13 (26.0)	0.639
Previous PCI, %	583 (27.4)	10 (20.0)	0.334
LVEF,%	54.8±11.6	52.0±10.9	0.01
Anatomical Characteristics			
Baseline SYNTAX score ±SD	17.1±11.3	18.0±10.2	0.276
Number of total occlusions/patient±SD	0.33±0.51	0.41±0.56	0.04
Number of aorto-ostial lesions/patient±SD	0.05±0.23	0.06±0.56	0.566
Number of lesions with severe tortuosity/patient±SD	0.74±1.07	0.68±1.02	0.425
Number of lesions with length>20mm/patient±SD	0.51±0.71	0.53±0.62	0.750
Number of lesions with heavy calcification/patient±SD	0.33±0.77	0.25±0.68	0.158
Number segments with diffuse disease/patient±SD	0.04±0.20	0.03±0.17	0.531
Lesions in left main/patient	0.08±0.29	0.06±0.26	0.246
Lesions in LAD proximal/patient	0.31±0.48	0.33±0.51	0.491
Lesions in LAD mid/patient	0.56±0.58	0.54±0.60	0.579
Lesions in LAD apical/patient	0.16±0.39	0.11±0.34	0.08
Lesions in 1st diagonal/patient	0.24±0.45	0.26±0.46	0.549
Lesions in 2nd diagonal/patient	0.01±0.12	0.01±0.12	0.875
Lesions in proximal circumflex/patient	0.18±0.40	0.16±0.37	0.587
Lesions in distal circumflex/patient	0.32±0.50	0.27±0.47	0.178
Lesions in intermediate/patient	0.10±0.31	0.07±0.26	0.155
Lesions in first obtuse marginal/patient	0.13±0.34	0.10±0.32	0.319
Lesions in second obtuse marginal/patient	0.11±0.33	0.10±0.31	0.559
Lesions in RCA proximal/patient	0.25±0.44	0.32±0.48	0.026
Lesions in RCA mid/patient	0.33±0.48	0.32±0.47	0.734
Lesions in RCA distal/patient	0.23±0.45	0.26±0.46	0.333
Lesions in Posterolateral/patient	0.03±0.18	0.02±0.14	0.787
Lesions in Posterior descending /patient	0.11±0.32	0.12±0.33	0.351

Supplemental Material

Supplemental Figures

Figure 1. Combined OR using the 3 trials using fixed effects for patients with thrombus containing lesions (TCL):

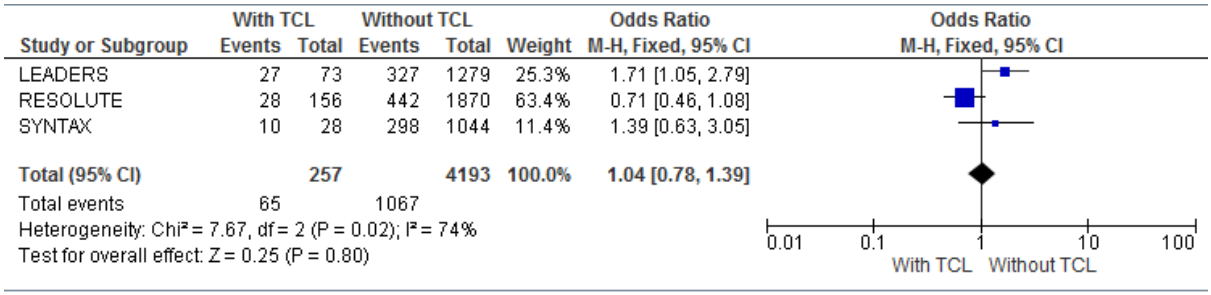


Figure 2. When the LEADERS Trial was removed from the pooled analysis there was no longer heterogeneity:

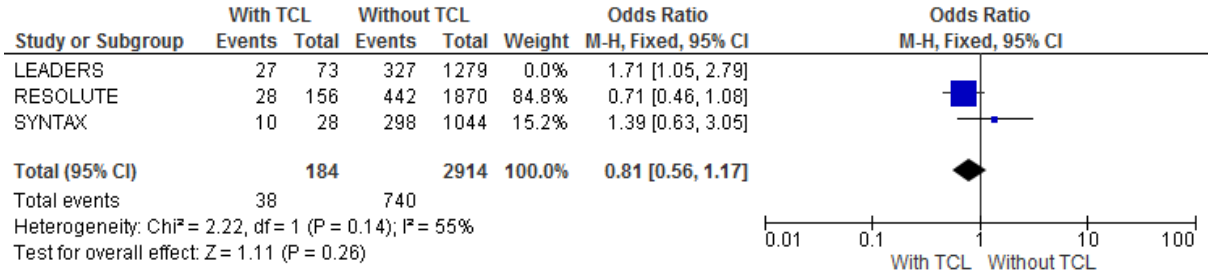


Figure 3. Also when the RESOLUTE trial was removed from the pooling there was no significant heterogeneity:

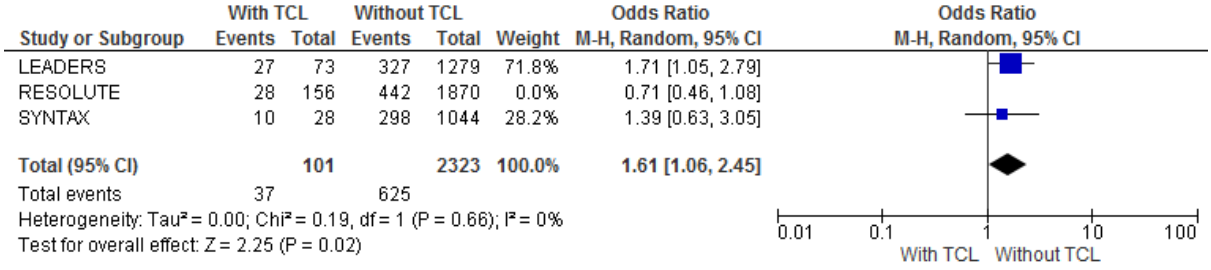
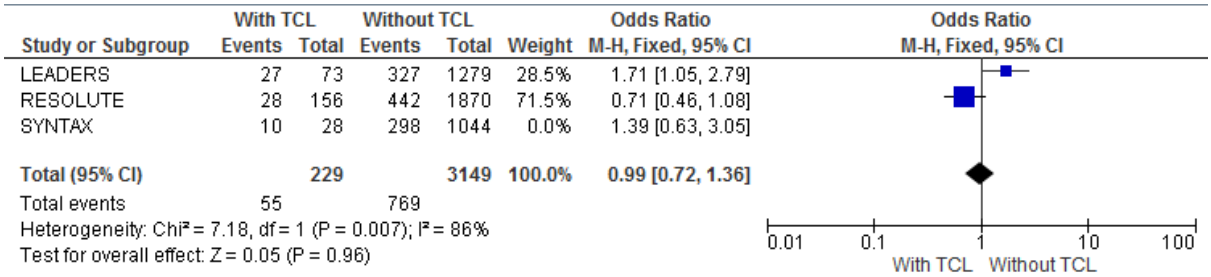
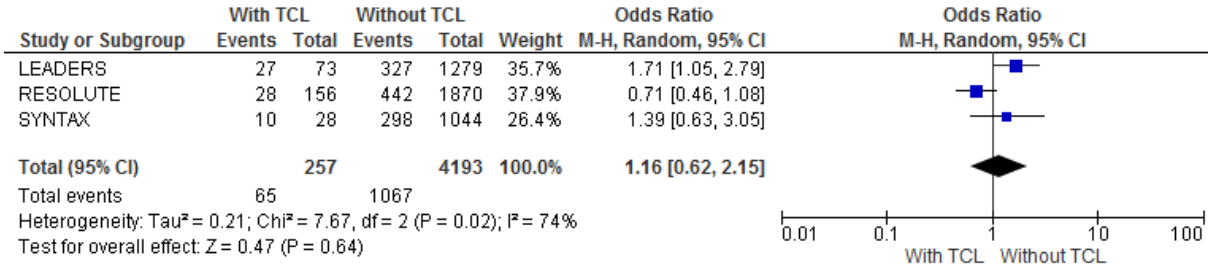


Figure 4. However, when we pool RESOLUTE and LEADERS and remove from the analysis the SYNTAX trial, the heterogeneity became even more evident:



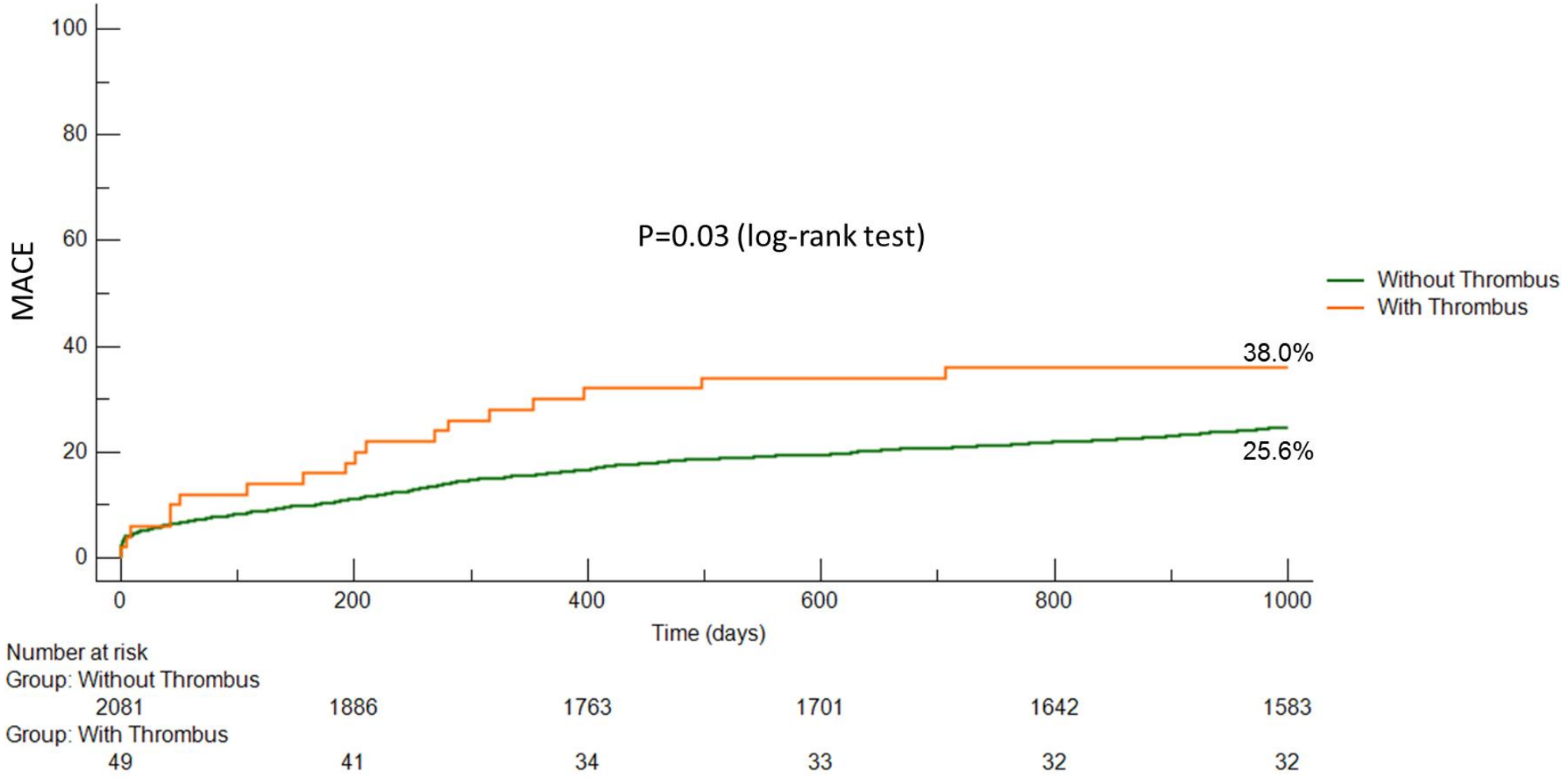
Supplemental Material

Figure 5. Pooled trial results using Bayesian random effects in which TCL did not have impact on long-term occurrence of MACE:



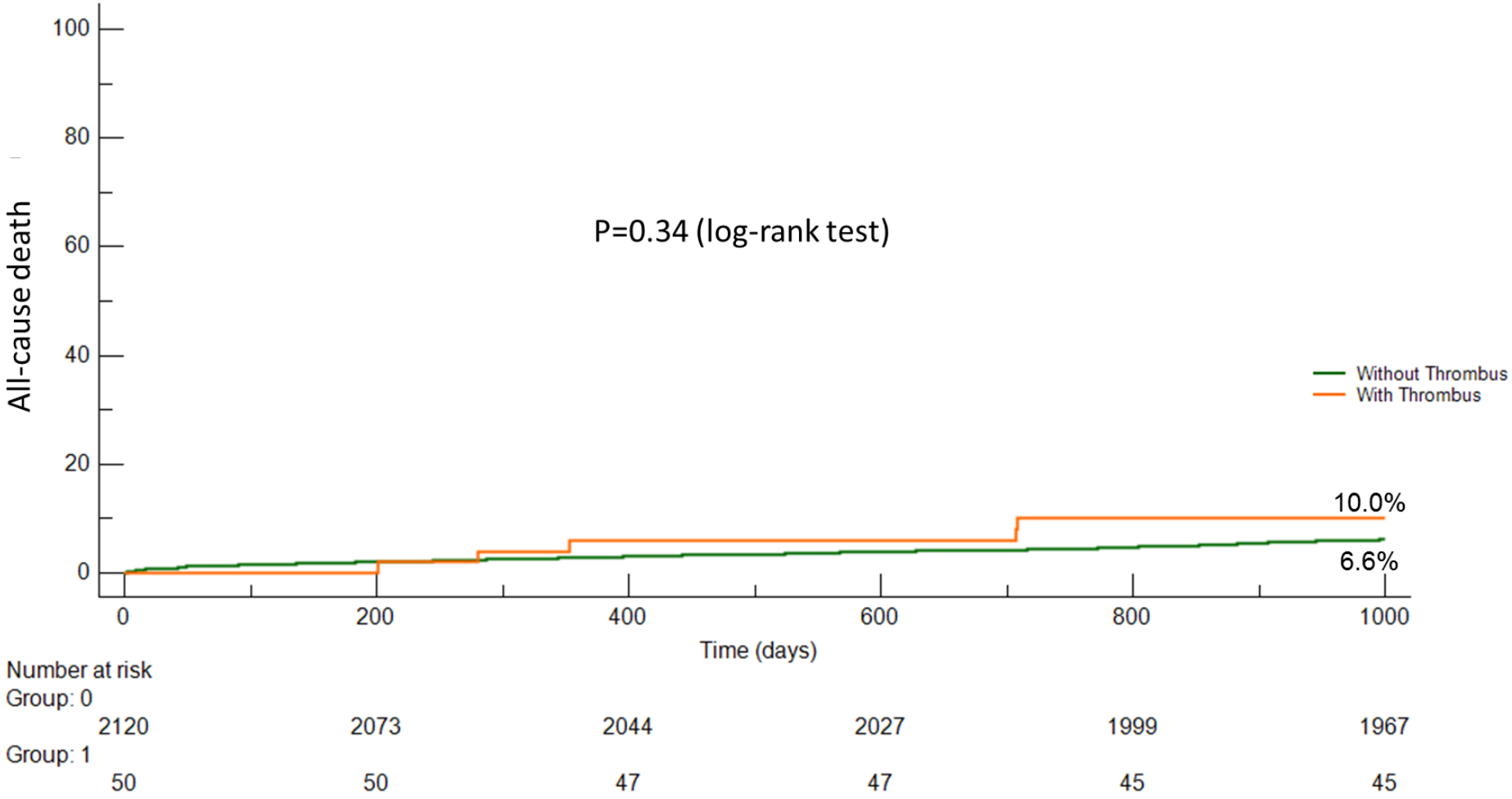
Supplemental Material

Figure 6A. Kaplan-Meier curve comparison for MACE (composite of all-cause death, all myocardial infarctions and all revascularizations) according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



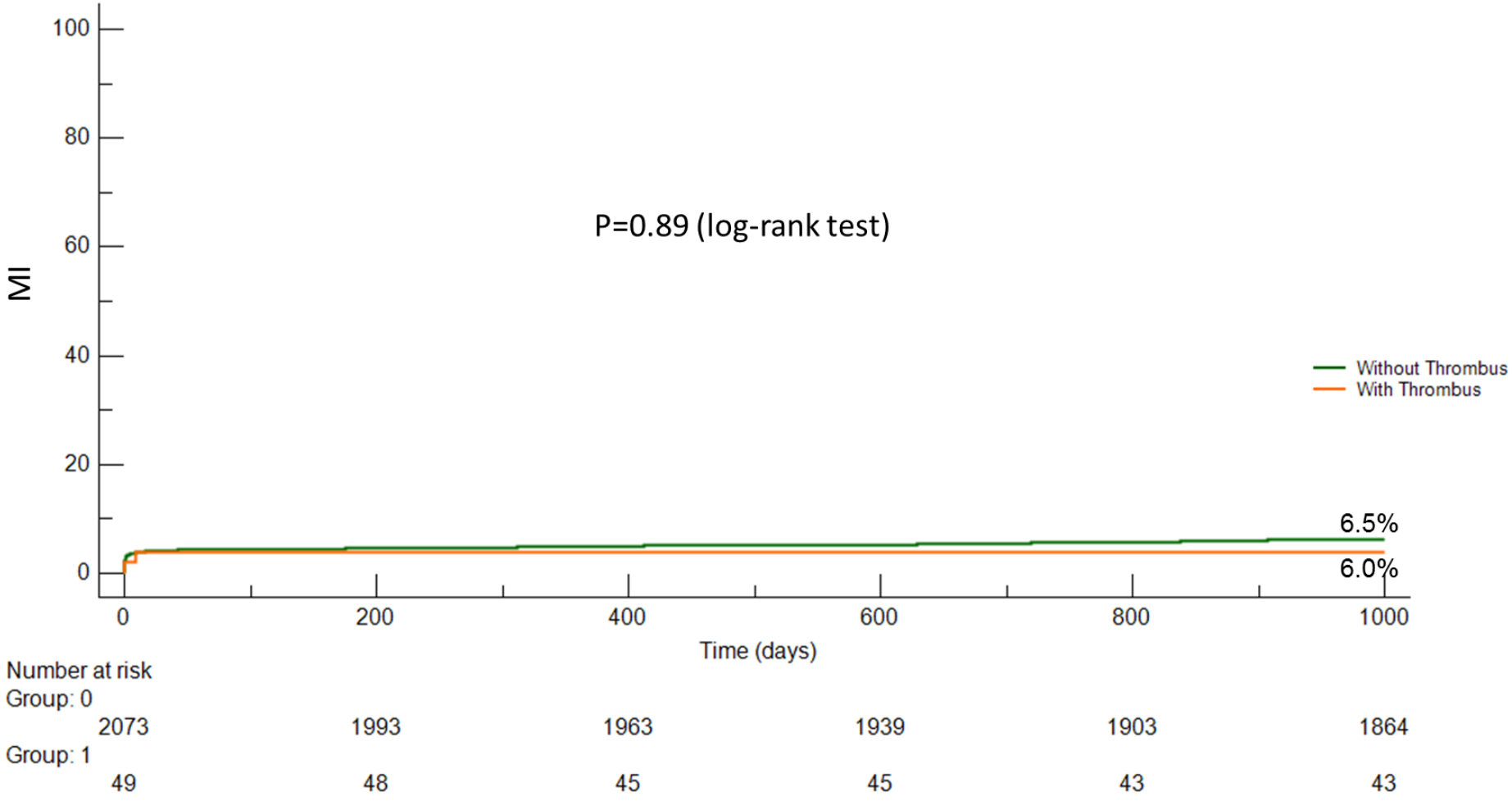
Supplemental Material

Figure 6B. Kaplan-Meier curve comparison for all-cause death according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



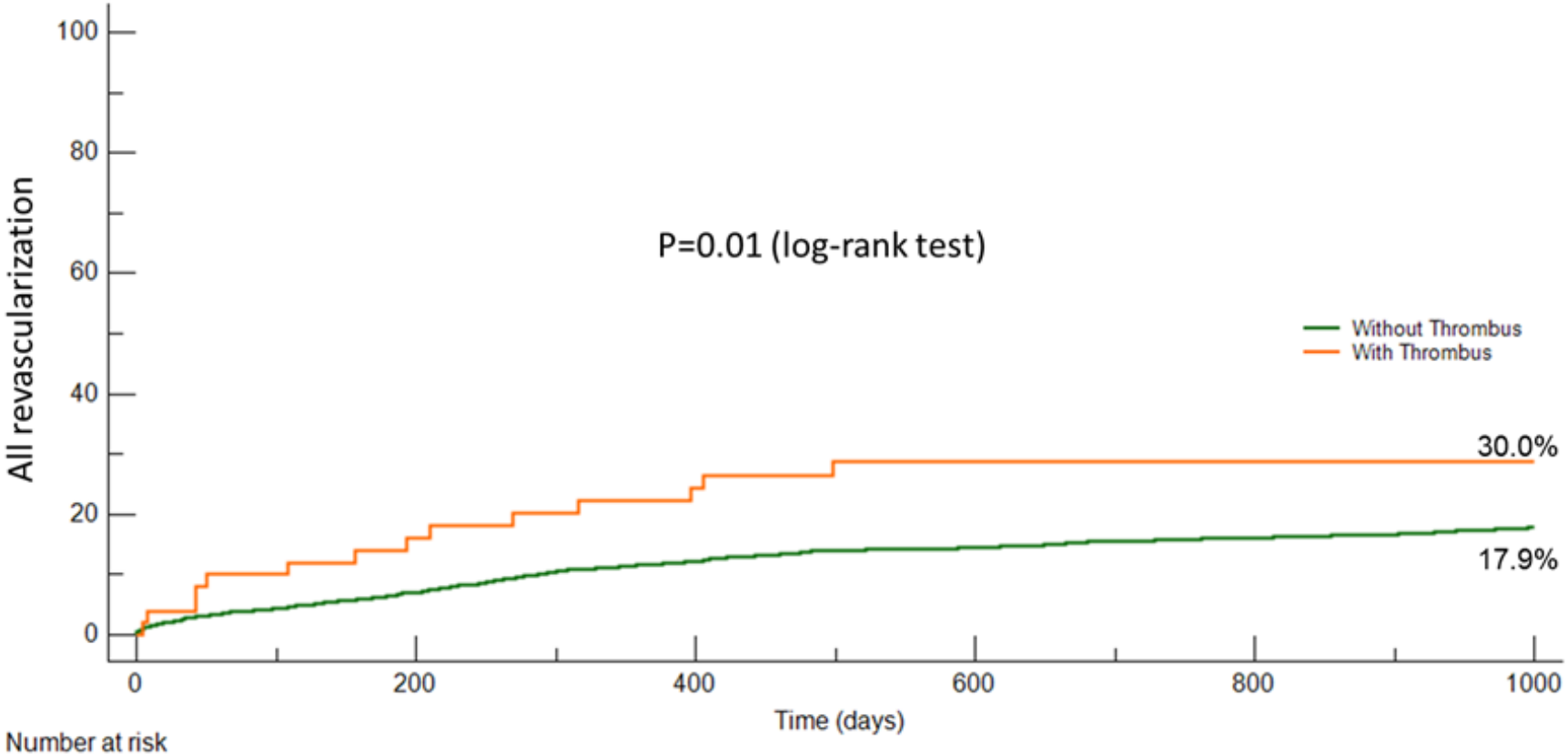
Supplemental Material

Figure 6C. Kaplan-Meier curve comparison for myocardial infarction according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



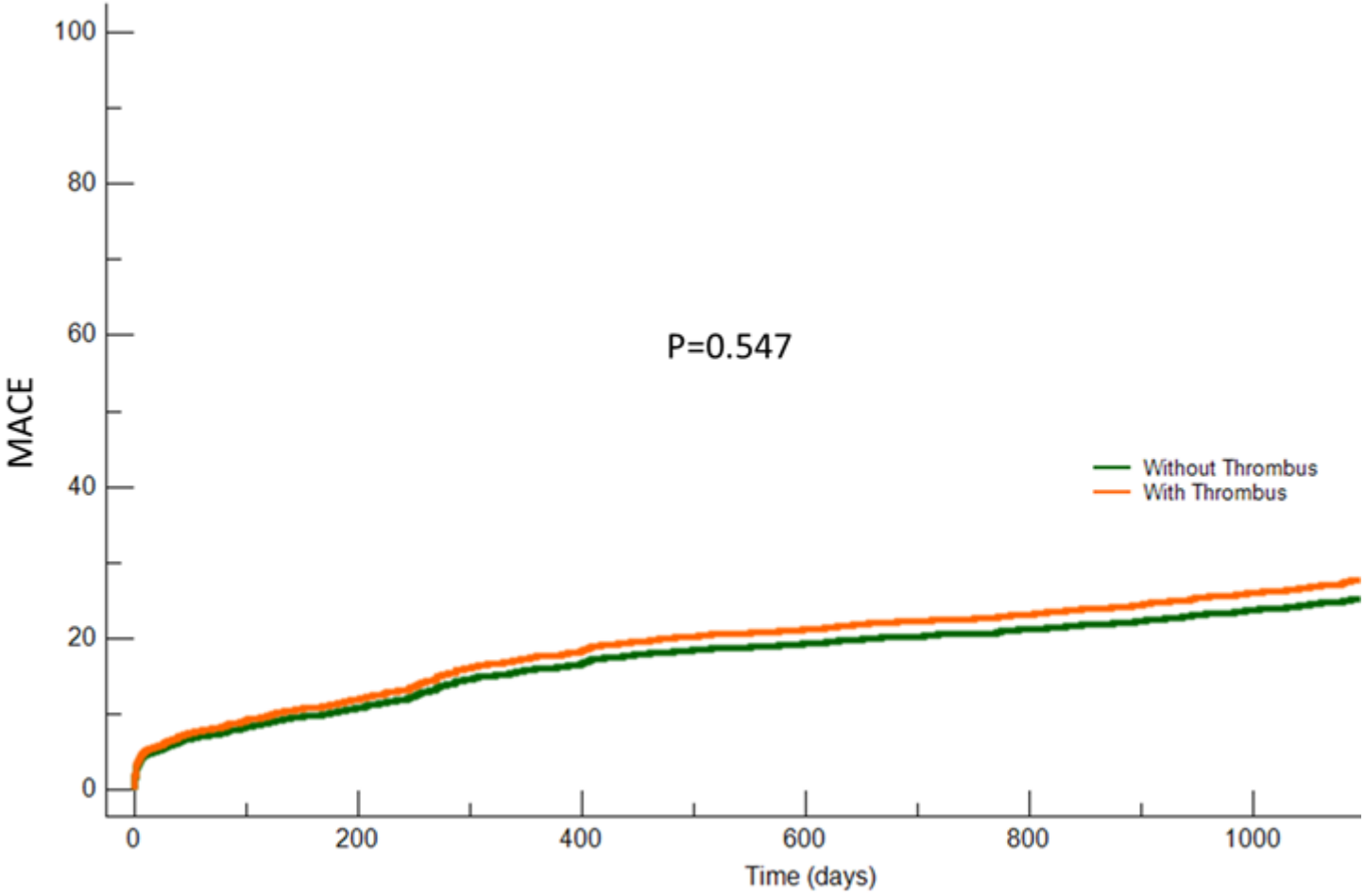
Supplemental Material

Figure 6D. Kaplan-Meier curve comparison for all revascularizations according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



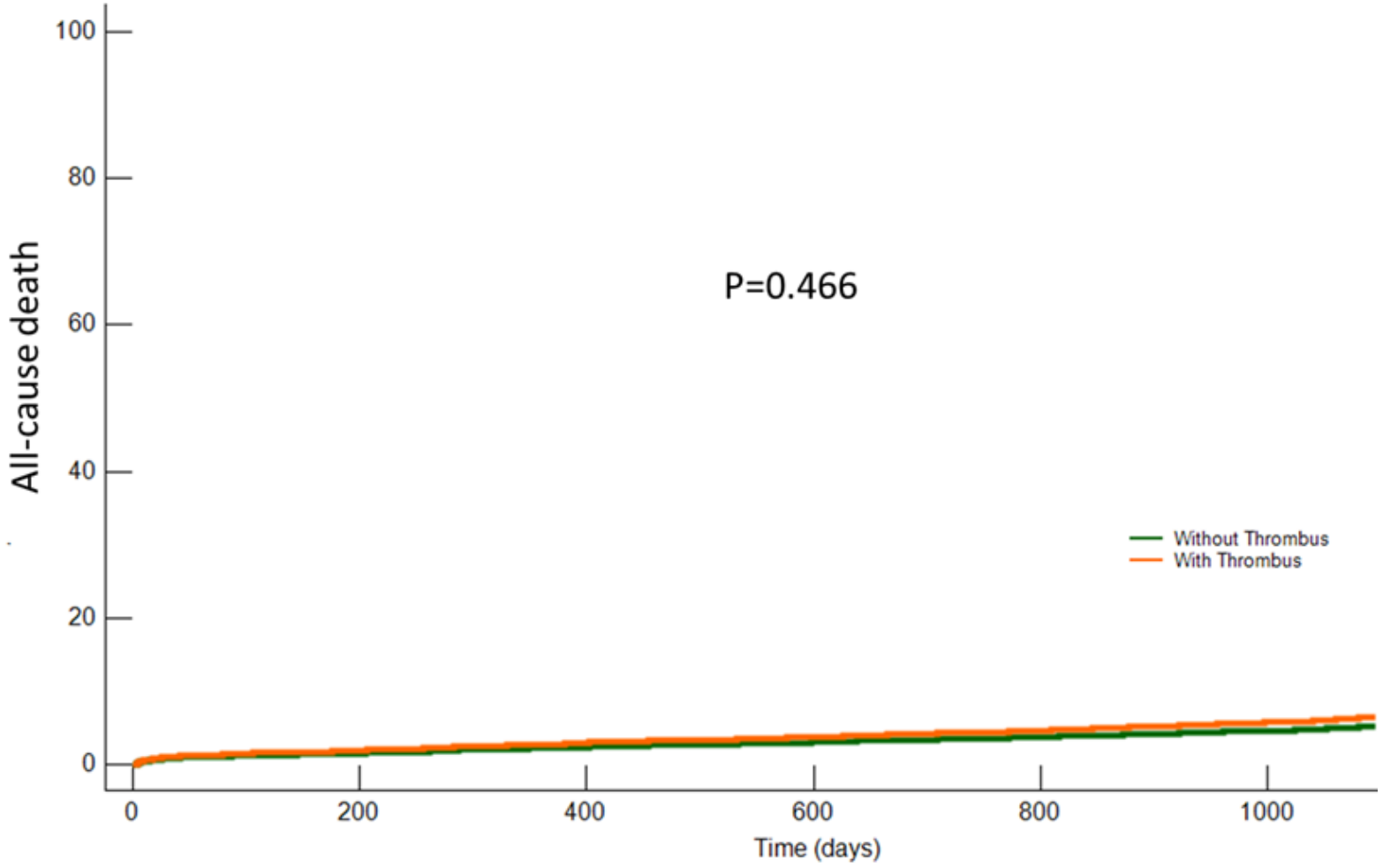
Supplemental Material

Figure 7A. Adjusted MACE (composite of all-cause death, all myocardial infarctions and all revascularizations) rate comparison according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



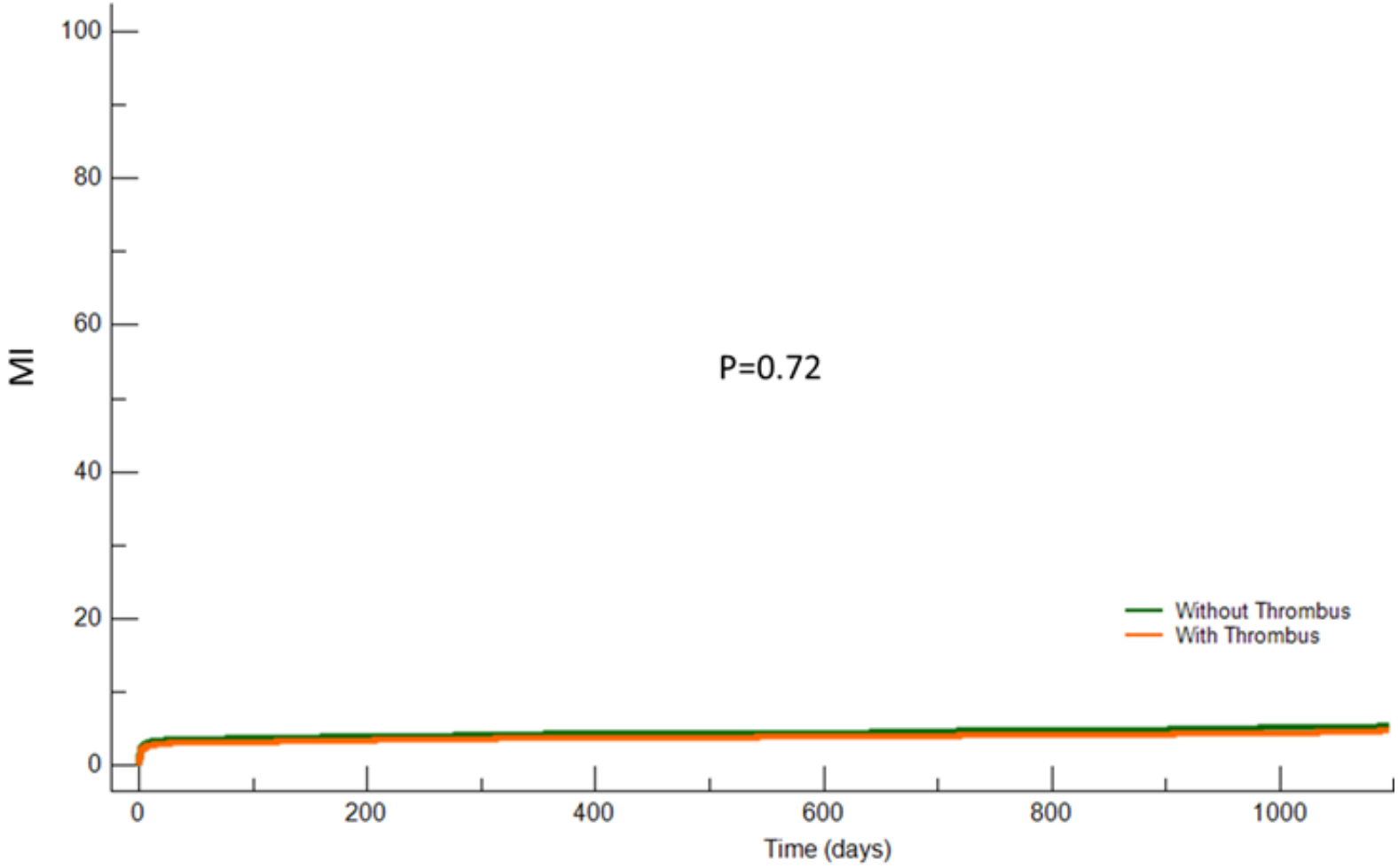
Supplemental Material

Figure 7B. Adjusted all-cause death rate comparison according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



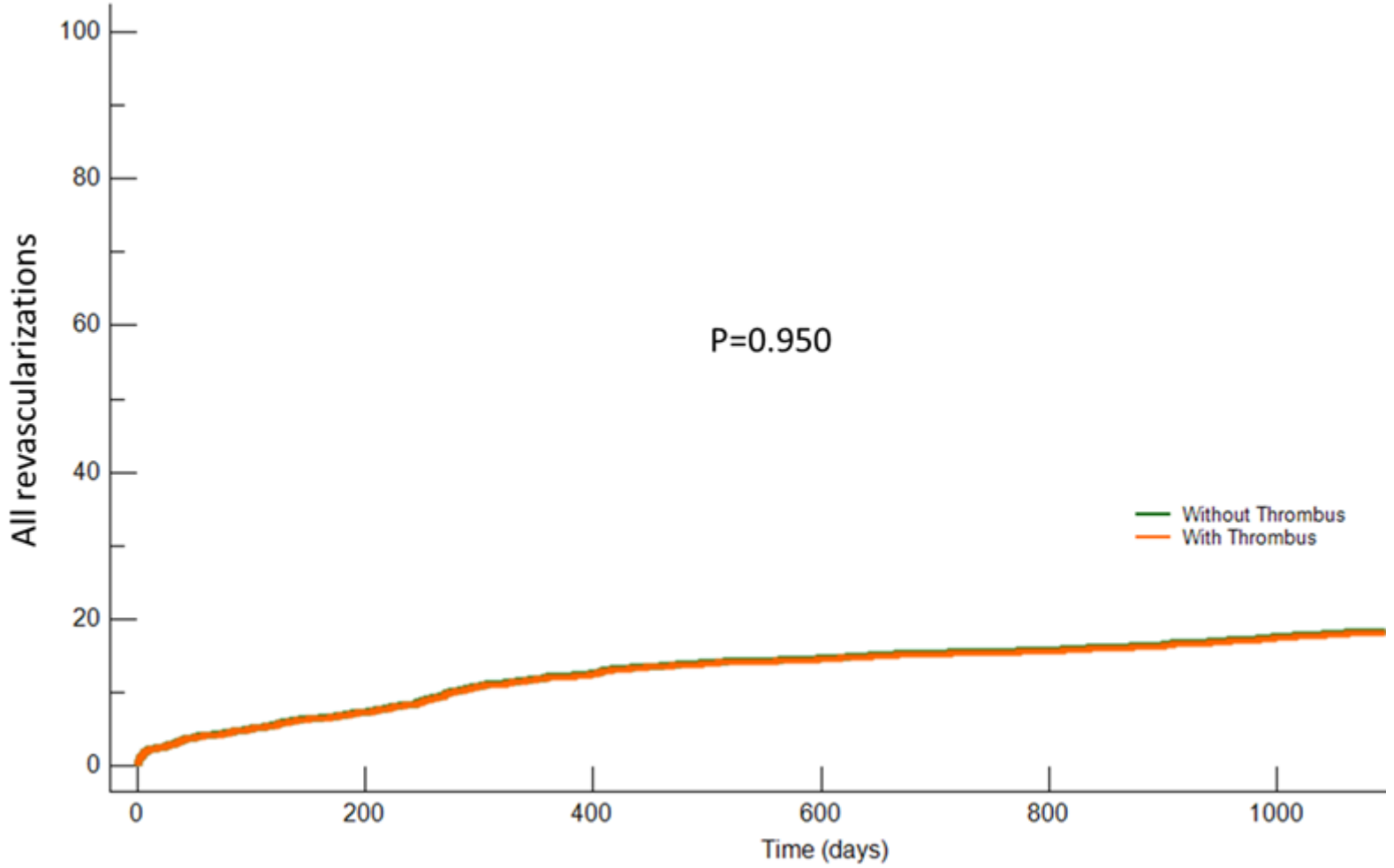
Supplemental Material

Figure 7C. Adjusted all myocardial infarctions rate comparison according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



Supplemental Material

Figure 7D. Adjusted all revascularizations rate comparison according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



Supplemental Material

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

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