Received: 17 March 2023 | Accepted: 13 May 2023
DOI: 10.1002/ccd.30699

ORIGINAL ARTICLE - CLINICAL SCIENCE

WILEY

Culprit lesion plaque characterization and thrombus grading by high-definition intravascular ultrasound in patients with ST-segment elevation myocardial infarction

Frederik T. W. Groenland MD | Annemieke C. Ziedses des Plantes BSc | Tara Neleman BSc | Alessandra Scoccia MD | Jurgen M. R. Ligthart RT | Karen T. Witberg RN | Karim D. Mahmoud MD, PhD | Rutger-Jan Nuis MD, PhD | Wijnand K. den Dekker MD, PhD | Jeroen M. Wilschut MD | Roberto Diletti MD, PhD | Felix Zijlstra MD, PhD | Nicolas M. Van Mieghem MD, PhD | Joost Daemen MD, PhD

Department of (Interventional) Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence
Joost Daemen, MD, PhD, Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Dr. Molewaterplein 40, Room Rg-628, 3015 GD, Rotterdam, The Netherlands.
Email: j.daemen@erasmusmc.nl

Funding information
MicroPort; ACIST Medical Systems

Abstract

Background: Dedicated prospective studies investigating high-definition intravascular ultrasound (HD-IVUS)-guided primary percutaneous coronary intervention (PCI) are lacking. The aim of this study was to qualify and quantify culprit lesion plaque characteristics and thrombus using HD-IVUS in patients presenting with ST-segment elevation myocardial infarction (STEMI).

Methods: The SPECTRUM study is a prospective, single-center, observational cohort study investigating the impact of HD-IVUS-guided primary PCI in 200 STEMI patients (NCT05007535). The first 100 study patients with a de novo culprit lesion and a per-protocol mandated preintervention pullback directly after vessel wiring were subject to a predefined imaging analysis. Culprit lesion plaque characteristics and different thrombus types were assessed. An IVUS-derived thrombus score, including a 1-point adjudication for a long total thrombus length, long occlusive thrombus length, and large maximum thrombus angle, was developed to differentiate between low (0–1 points) and high (2–3 points) thrombus burden. Optimal cut-off values were obtained using receiver operating characteristic curves.

Results: The mean age was 63.5 (±12.1) years and 69 (69.0%) patients were male. The median culprit lesion length was 33.5 (22.8–38.9) mm. Plaque rupture and convex calcium were appreciated in 48 (48.0%) and 10 (10.0%) patients, respectively. Thrombus was observed in 91 (91.0%) patients (acute thrombus 3.3%; subacute thrombus 100.0%; organized thrombus 22.0%). High IVUS-derived thrombus burden was present in 37/91 (40.7%) patients and was associated with higher rates of impaired final thrombolysis in myocardial infarction flow (grade 0–2) (27.0% vs. 1.9%, $p < 0.001$).

Conclusions: HD-IVUS in patients presenting with STEMI allows detailed culprit lesion plaque characterization and thrombus grading that may guide tailored PCI.

KEYWORDS

intravascular ultrasound, ST-segment elevation myocardial infarction, thrombus

1 | INTRODUCTION

In patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), intravascular ultrasound (IVUS) guidance allows tailored lesion preparation, accurate stent sizing, and optimization of suboptimal PCI results.[1–4] IVUS-guided PCI proved to be associated with lower rates of major adverse cardiovascular events and target vessel failure as compared to angiography-guided PCI in patients with stable and unstable coronary artery disease.[5–8] More recently, a large registry and a meta-analysis of mainly observational studies suggested that the superiority of IVUS guidance could be extended to patients presenting with acute myocardial infarction, including ST-segment elevation (STEMI).[9,10]

Preintervention IVUS assessment of culprit lesions in STEMI patients allows plaque characterization and thrombus evaluation. It thereby unravels underlying mechanisms causing luminal thrombosis, such as plaque rupture and convex calcium, and visualizes different types of thrombus.[11–15]

As of to date, a dedicated prospective study investigating culprit lesion plaque morphology and thrombus directly after vessel wiring (so before any lesion preparation, such as aspiration thrombectomy or predilatation), is lacking. Therefore, the aim of this study was to qualify and quantify preintervention culprit lesion plaque characteristics and thrombus using high-definition IVUS (HD-IVUS) in patients presenting with STEMI.

2 | METHODS

2.1 | Study design and patient population

The "tissue characterization and primary PCI guidance using intravascular ultrasound" (SPECTRUM) study is a prospective, investigator-initiated, single-center, observational cohort study that included 200 STEMI patients undergoing IVUS-guided primary PCI between November 10, 2020, and February 8, 2022, at the Erasmus University Medical Center, Rotterdam, The Netherlands (NCT05007535). The study was designed to assess the safety and efficacy of IVUS-guided primary PCI in a STEMI population, and to investigate culprit lesion plaque characteristics and thrombus with HD-IVUS. A detailed description of the rationale and design of the study has been published before.[16]

The study was approved by the local ethics committee on October 7, 2020, and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. All patients provided written informed consent. Institutional research support was provided by ACIST Medical Systems, Eden Prairie, Minnesota, USA, and Microport, Shanghai, China. The funding parties were not involved in any of the study-related activities.

Consecutive patients undergoing primary PCI of a culprit lesion in a native coronary artery with a vessel reference diameter of ≥2.25 mm were eligible. Exclusion criteria were limited to presentation with cardiogenic shock and presentation ≥12 h after symptom onset. The use of aspiration thrombectomy was at the discretion of the operator.

The first 100 study patients with full availability of HD-IVUS pullbacks (including a preintervention, postintervention, and post-optimization pullback (if applicable)) of a de novo coronary lesion, and regions of interest that could be matched appropriately, were subject to the extensive predefined imaging analysis presented in this manuscript.[16]

2.2 | Study procedure

In all 100 patients, a protocolized preintervention IVUS pullback was performed directly after vessel wiring (so before any lesion preparation, such as aspiration thrombectomy or predilatation) using the CE marked multifrequency high-definition (40–60 MHz broadband) KODAMA® IVUS system (ACIST Medical Systems). All HD-IVUS pullbacks were performed with an automated pullback speed of 2.5 mm/s, resulting in 24 frames per mm (based on 60 frames per second).

2.3 | IVUS analysis and IVUS definitions

Systematic analysis of the culprit lesion on the preintervention HD-IVUS pullback was performed offline for every 0.5 mm by the Erasmus University Medical Center academic core lab, using dedicated software (QCU-CMS, Leiden University Medical Center, LKEB, Division of Imaging Processing, V.4.69). The culprit lesion was matched (based on side branches) to the stented or treated (e.g., balloon dilatation only) segment on the postintervention HD-IVUS pullback.[16]

A detailed explanation of the IVUS definitions has been described previously.[16] In brief, quantitative IVUS parameters included the culprit length, vessel cross-sectional area (CSA), lumen CSA and plaque CSA, as well as the minimal lumen area (MLA), plaque burden (PB), and remodeling index. If the vessel CSA could not be determined at the MLA site (<180° of the external elastic membrane visible due to attenuation by thrombus, calcium, or soft attenuated plaque), the average vessel CSA of two adjacent frames was used to determine the plaque CSA, PB, and remodeling index. Qualitative IVUS parameters included different plaque types, as well as the presence of a plaque rupture and/or convex calcium. Three different IVUS-defined types of thrombus were distinguished: acute, subacute, and organized thrombus.[15] Furthermore, the total thrombus length, the occlusive thrombus length, and the maximum thrombus angle were determined. Occlusive thrombus was defined as thrombus occluding the lumen (lumen CSA < 1.75 mm^2) with no or minimal blood speckling around the IVUS catheter.

Finally, spasm was defined as a narrowed vessel with a thickened bright intima. In patients with spasm or bridging the remodeling index was not determined.

2.4 | IVUS-derived thrombus score

An IVUS-derived thrombus score was developed to quantify thrombus burden. The following IVUS parameters were incorporated in the thrombus score: (1) long total thrombus length (on the full preintervention IVUS pullback), (2) long occlusive thrombus length, (3) large maximum thrombus angle (Supporting Information: Figure S1). In patients with a thrombotic culprit lesion as visualized by HD-IVUS, one point was adjudicated if the optimal cut-off value (defined by receiver operating characteristic [ROC] curves) was reached. High thrombus burden was defined as a thrombus score of 2–3 points, while low thrombus burden was defined as a thrombus score of 0–1 points.

Subsequently, the association between IVUS-derived thrombus burden, angiographic, and electrocardiographic characteristics was assessed. Angiographic parameters at baseline included the initial thrombolysis in myocardial infarction (TIMI) flow (grade 0–3) and TIMI thrombus grade (grade 0–6).[17,18] Final angiographic parameters included TIMI flow (grade 0–3) and myocardial blush (grade 0–3).[17,19,20] ST-segment resolution was determined according to the single-lead ST-segment resolution technique.[21] The first available electrocardiograms before and after primary PCI were used for this analysis. ST-segment resolution was defined as complete (>70%), partial (30%–70%), or minimal (<30%).[22] Angiographic (FG, FZ) and electrocardiographic (FG) characteristics were assessed offline.

2.5 | Statistical analysis

The Shapiro–Wilk test was used to assess if continuous variables followed a normal distribution. Normally distributed continuous variables were presented as mean ± standard deviation (SD). Non-normally distributed continuous variables were presented as median with 25th–75th percentiles. Categorical variables were presented as counts with percentages. For the categorical IVUS findings, also the Clopper–Pearson 95% confidence interval for a binomial proportion was calculated.

ROC curves were used to determine optimal cut-off values of the IVUS-derived thrombus score components for predicting final TIMI flow grade 0–2. Optimal cut-off values were derived via the Youden index. The association between IVUS-derived thrombus burden and patient, angiographic, and electrocardiographic characteristics was assessed with Pearson's X^2 test or Fisher's exact test (as appropriate) for categorical variables and with the Mann–Whitney *U* test for nonnormally distributed continuous variables. Statistical analysis was performed with SPSS version 28. A two-sided $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics and pharmacotherapy

Mean (±SD) age was 63.5 (±12.1) years and 69 (69.0%) patients were male (Table 1). Diabetes was present in 16 (16.0%) patients and 44 (44.0%) patients were active smokers. Prior PCI was performed in five (5.0%) patients. The median (25th–75th percentiles) time from symptom onset to the start of the procedure was 124.0 (87.0–226.0) min. Patients were preloaded with aspirin (100%) and a P2Y12 inhibitor (clopidogrel 2.0%; prasugrel 77.0%; ticagrelor 21.0%). Periprocedural glycoprotein IIb/IIIa inhibitors were used in 22 (22.0%) patients.

3.2 | Angiographic and electrocardiographic characteristics

The angiographic culprit lesion findings are presented in Table 2. The culprit lesion was located in the right coronary artery in 43.0%, the left anterior descending in 46.0% and the left circumflex in 11.0%.

In three patients (3.0%), no cineangiographic characteristics of thrombus could be appreciated (TIMI thrombus grade 0) and in eight (8.0%) patients possible thrombus was visible (TIMI thrombus grade 1). A thrombotic occlusion (TIMI thrombus grade 5) with a corresponding baseline TIMI flow grade 0 was present in 43 (43.0%) patients.

Final TIMI flow grade 3 was observed in 87 (87.0%) patients (Supporting Information: Table S1). Myocardial blush grade 3 was present in 30/95 (31.6%) patients, while myocardial blush was poor (grade 0–1) in 17/95 (17.9%) patients. ST-segment resolution was complete (>70%) in 46/90 (51.1%) patients.

TABLE 1 Patient characteristics and pharmacotherapy.

Variable	*n* = 100
Mean age (years)	63.5 ± 12.1
Male gender	69.0 (69.0)
Hypertension	40 (40.0)
Dyslipidemia	24 (24.0)
Diabetes	16 (16.0)
Family history	24 (24.0)
Active smoker	44 (44.0)
Prior CABG	0 (0.0)
Prior PCI	5 (5.0)
Prior MI	3 (3.0)
Prior CVA/TIA	2 (2.0)
Prior PAD	3 (3.0)
Prior atrial fibrillation	2 (2.0)
Median time from symptom onset to start procedure (min)	124.0 (87.0–226.0)
Preloading pharmacotherapy	
Aspirin	100.0 (100.0)
Clopidogrel	2 (2.0)
Prasugrel	77 (77.0)
Ticagrelor	21 (21.0)
Vitamin K antagonist	1 (1.0)
Direct oral anticoagulant	1 (1.0)
Glycoprotein IIb/IIIa inhibitors	
Upstream	0 (0.0)
Periprocedural	22 (22.0)

Note: Continuous variables are presented as mean ± standard deviation or median (25th–75th percentiles), as appropriate. Categorical variables are presented as counts with percentages.

Abbreviations: CABG, coronary artery bypass graft surgery; CVA, cerebrovascular accident; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

TABLE 2 Baseline angiographic culprit lesion characteristics.

Variable	*n* = 100
Culprit vessel	
RCA	43 (43.0)
LM	0 (0.0)
LAD	46 (46.0)
LCx	11 (11.0)
ACC/AHA lesion classification	
Class A	0 (0.0)
Class B1	7 (7.0)
Class B2	27 (27.0)
Class C	66 (66.0)
Ostial lesion	1 (1.0)
Bifurcation lesion	2 (2.0)
TIMI thrombus grade	
Grade 0	3 (3.0)
Grade 1	8 (8.0)
Grade 2	7 (7.0)
Grade 3	18 (18.0)
Grade 4	21 (21.0)
Grade 5	43 (43.0)
Grade 6	0 (0.0)
TIMI flow	
Grade 0	43 (43.0)
Grade 1	3 (3.0)
Grade 2	30 (30.0)
Grade 3	24 (24.0)

Note: Categorical variables are presented as counts with percentages.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; LAD, left anterior descending; LCx, left circumflex; LM, left main; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

3.3 | Culprit lesion plaque characterization by HD-IVUS

IVUS culprit lesion characteristics are presented in Table 3. The median culprit lesion length was 33.5 (22.8–38.9) mm. The median lumen CSA at the proximal and distal reference frame was 8.2 (6.3–10.6) mm^2 and 4.9 (3.6–6.8) mm^2 respectively, while the mean PB (including thrombus if applicable) was 49.1% (±11.2) proximally and 47.7% (±14.1) distally. The median MLA was 1.6 (1.5–1.8) mm^2.

A plaque rupture was visible in 48 (48.0%) patients and convex calcium was seen in 10 (10.0%) patients (Figure 1).

A total of 85 (85.0%) patients had any type of calcification within their culprit lesion and 44 patients (44.0%) had soft attenuated plaque. In patients without spasm or bridging, positive remodeling was found in 46/87 (52.9%) patients.

3.4 | Thrombus grading by HD-IVUS

IVUS-defined thrombus was observed in 91 (91.0%) patients (Table 4). Subacute thrombus was appreciated in all 91 patients (100.0%), while acute and organized thrombus were visible in 3/91 (3.3%) and 20/91 (22.0%) patients, respectively (Figure 2). Occlusive thrombus was observed in 65/91 (71.4%) patients and

TABLE 3 Culprit lesion plaque characteristics as visualized by HD-IVUS.

Variable	*n* = 100
Median culprit lesion length (mm)	33.5 (22.8–38.9)
Proximal reference frame	–
Median vessel CSA (mm^2)	16.5 (13.5–19.9)
Median lumen CSA (mm^2)	8.2 (6.3–10.6)
Median plaque CSA[a] (mm^2)	8.0 (6.1–10.3)
Mean plaque burden[a] (%)	49.1 ± 11.2
Distal reference frame	–
Median vessel CSA (mm^2)	9.6 (6.8–13.7)
Median lumen CSA (mm^2)	4.9 (3.6–6.8)
Median plaque CSA[a] (mm^2)	4.8 (2.6–7.6)
Mean plaque burden[a] (%)	47.7 ± 14.1
MLA frame	–
Median vessel CSA (mm^2)	13.9 (10.0–16.9)
Median lumen CSA (mm^2)	1.6 (1.5–1.8)
Median plaque CSA[a] (mm^2)	11.6 (8.4–14.1)
Median plaque burden[a] (%)	83.9 (78.6–88.6)
Plaque rupture	48 (48.0, 37.9–58.2)
Convex calcium	10 (10.0, 4.9–17.6)
Adjacent to nonconvex calcium	9/10 (90.0, 55.5–99.7)
Solitary	1/10 (10.0, 0.3–44.5)
Plaque type	–
Soft	44 (44.0, 34.1–54.3)
Fibrofatty	99 (99.0, 94.6–100.0)
Calcified	85 (85.0, 76.5–91.4)
Superficial	81/85 (95.3, 88.4–98.7)
Deep	15/85 (17.6, 10.2–27.4)
Circumferential (360°)	8/85 (9.4, 4.2–17.7)
Plaque model	–
Eccentric	92 (92.0, 84.8–96.5)
Concentric	65 (65.0, 54.8–74.3)
Mean remodeling index	1.0 ± 0.2
Positive remodeling	46/87 (52.9, 41.9–63.7)
Spasm	10 (10.0, 4.9–17.6)

Note: Continuous variables are presented as mean ± standard deviation or median (25th–75th percentiles), as appropriate. Categorical variables are presented as counts with percentages, including the 95% confidence interval for the proportion.

Abbreviations: CSA, cross-sectional area; HD-IVUS, high-definition intravascular ultrasound.

[a]Including thrombus (if applicable).

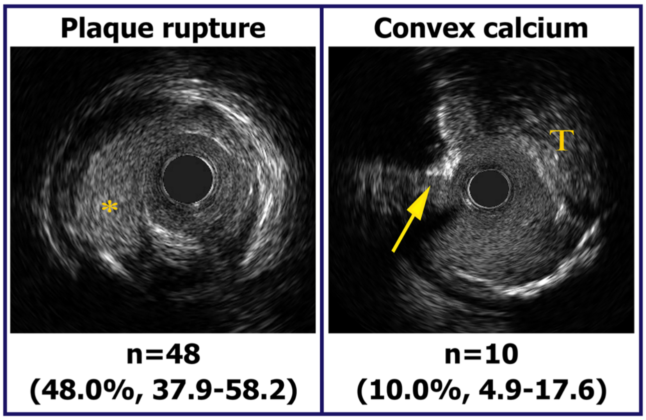

FIGURE 1 Specific culprit lesion plaque characteristics as visualized by HD-IVUS in patients presenting with STEMI. Values are counts with percentages, including the 95% confidence interval for the proportion. Asterisk indicates a plaque rupture with a cavity, while the arrow indicates convex calcium. Subacute thrombus is indicated by the letter "T." HD-IVUS, high-definition intravascular ultrasound; STEMI, ST-segment elevation myocardial infarction. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Thrombus characteristics as visualized by HD-IVUS.

Variable	*n* = 91
Thrombus	91 (91.0, 83.6–95.8)
Type	–
Acute	3 (3.3, 0.7–9.3)
Subacute	91 (100.0, 96.0–100.0)
Organized	20 (22.0, 14.0–31.9)
Median maximum angle (°)	250.0 (209.0–284.0)
Circumferential (360°)	18 (19.8, 12.2–29.4)
Occlusive	65 (71.4, 61.0–80.4)
Median occlusive length culprit (mm)	1.5 (0.5–3.0)
Median total length culprit (mm)	11.0 (7.0–17.0)
Median total length full pullback (mm)	12.0 (7.5–20.0)
Thrombus score	
0 Points	25 (27.5, 18.6–37.8)
1 Point	29 (31.9, 22.5–42.5)
2 Points	20 (22.0, 14.0–31.9)
3 Points	17 (18.7, 11.3–28.2)
High thrombus burden (2–3 points)	37 (40.7, 30.5–51.5)
Low thrombus burden (0–1 points)	54 (59.3, 48.5–69.5)

Note: Continuous variables are presented as median (25th–75th percentiles). Categorical variables are presented as counts with percentages, including the 95% confidence interval for the proportion.

Abbreviation: HD-IVUS, high-definition intravascular ultrasound.

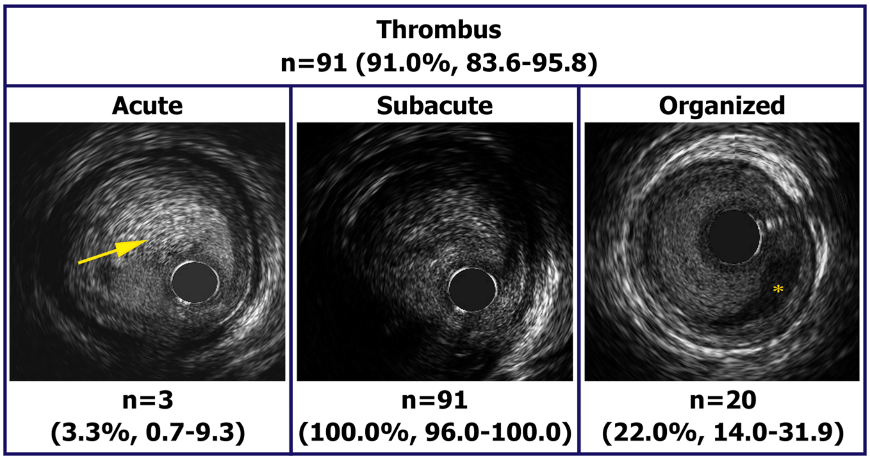

FIGURE 2 Thrombus as visualized by HD-IVUS in patients presenting with STEMI. Values are counts with percentages, including the 95% confidence interval for the proportion. The arrow indicates acute thrombus, while the asterisk indicates organized thrombus. HD-IVUS, high-definition intravascular ultrasound; STEMI, ST-segment elevation myocardial infarction. [Color figure can be viewed at wileyonlinelibrary.com]

circumferential thrombus (360°) was seen in 18/91 (19.8%) patients. The median thrombus length in the culprit lesion was 11.0 (7.0–17.0) mm.

Optimal cut-off values of the thrombus score components for predicting final TIMI flow grade 0–2 were a total thrombus length ≥14.5 mm (area under the curve [AUC]: 0.63), an occlusive thrombus length ≥1.5 mm (AUC: 0.75), and a maximum thrombus angle ≥260° (AUC: 0.76) (Supporting Information: Figure S1). Based on the IVUS-derived thrombus score, 37/91 (40.7%) patients had high thrombus burden (thrombus score 2–3 points), while 54/91 (59.3%) patients had low thrombus burden (thrombus score 0–1 points) (Table 4).

3.5 | Association between IVUS-derived thrombus burden and patient, angiographic, and electrocardiographic characteristics

The median time from symptom onset to the start of the procedure was comparable for patients with high and low IVUS-derived thrombus burden (132.0 vs. 121.0 min, $p = 0.78$). Patients with high IVUS-derived thrombus burden presented more often with baseline TIMI flow grade 0 and baseline TIMI thrombus grade 4–5 (59.5% vs. 33.3%, $p = 0.014$ and 78.4% vs. 57.4%, $p = 0.038$, respectively) (Supporting Information: Figure S2).

The discriminative ability of the thrombus score to predict final angiographic and electrocardiographic characteristics was good (0.85) for impaired final TIMI flow (grade 0–2), poor (0.58) for bad myocardial blush (grade 0–1), and moderate (0.74) for incomplete ST-segment resolution (≤70%).

Poor myocardial blush was numerically more frequent in patients with high IVUS-derived thrombus burden (22.2% vs. 11.5%, $p = 0.18$), while impaired final TIMI flow was significantly more often observed in patients with high IVUS-derived thrombus burden (27.0% vs. 1.9%, $p < 0.001$) (Supporting Information: Figure S3). Incomplete ST-segment resolution occurred significantly more frequently in patients with high IVUS-derived thrombus burden (69.4% vs. 32.6%, $p < 0.001$).

4 | DISCUSSION

To the best of our knowledge, this is the first prospective study providing dedicated HD-IVUS results of culprit lesion plaque characteristics and thrombus in patients presenting with STEMI. According to a predefined protocol, IVUS was performed directly after vessel wiring, precluding potential bias in the assessment of culprit lesion plaque morphology and thrombus grading caused by predilatation or aspiration thrombectomy. Different types of thrombus were identified and a novel IVUS-derived thrombus score was developed to quantify thrombus burden. Our main findings can be summarized as follows: (1) plaque rupture was visualized in 48 (48.0%) patients and convex calcium in 10 (10.0%) patients, (2) IVUS-defined thrombus was visible in 91 (91.0%) patients (acute thrombus 3.3%; subacute thrombus 100.0%; organized thrombus 22.0%), (3) in patients with a thrombotic culprit lesion on IVUS, high IVUS-derived thrombus burden was present in 37/91 (40.7%) patients and was associated with higher rates of impaired final TIMI flow (grade 0–2) as compared to patients with low thrombus burden (27.0% vs. 1.9%, $p < 0.001$).

4.1 | Culprit lesion plaque characterization by HD-IVUS

According to histopathological studies, three different underlying mechanisms are considered to cause luminal thrombosis leading to sudden coronary ischemia and coronary death.[11,12] A plaque rupture (ruptured thin cap fibroatheroma) is the most common cause and responsible for 55%–60% of cases, followed by plaque erosion (intact fibrous cap) in 30%–35% and a calcified nodule in up to 7%.[12] Although based on post-mortem findings, these histopathological findings correspond well with the presented IVUS results in STEMI patients. Preintervention IVUS assessment revealed a ruptured plaque in 48.0% and convex calcium, which has been closely related to calcified nodules both in vivo and ex vivo, in 10.0%.[14,23] The lower rate of IVUS-identified plaque ruptures as compared to histopathological findings (48% vs. 55%–60%, respectively) is likely explained by the presence of thrombus masking the ruptured site due to ultrasound attenuation.[15] Conversely, the identification of convex calcium is less affected by this phenomenon due to its bright and protruding appearance. Identifying plaque erosion as culprit lesion mechanism was beyond the scope of this study since this appeared only feasible with optical coherence tomography.[24]

The main benefit of preintervention IVUS assessment in patients presenting with STEMI is that successful in vivo identification of culprit lesion plaque characteristics may guide a tailored primary PCI approach. IVUS allows precise measurement of lesion length, based on PB and presence of thrombus, as well as diameters, by accounting for spasm or conversely, positive remodeling, which appeared to be present in up to 52.9% in this study. Furthermore, the presence of convex calcium or extensive calcification could require a more aggressive lesion preparation strategy, including predilatation, or more aggressive forms with scoring, cutting, or lithotripsy balloons. Of interest, 85.0% of STEMI patients had IVUS-defined calcification within their culprit lesion, supporting previous findings that IVUS detects calcium in >70% of coronary lesions.[25]

4.2 | Thrombus grading by HD-IVUS

Following recent work showing the improved ability of HD-IVUS to distinguish different types of intracoronary thrombus, the present study now quantified IVUS-defined acute, subacute and organized thrombus in a STEMI population.[15] Thrombus was visualized by HD-IVUS in 91.0% of patients and included acute thrombus (3.3%), subacute thrombus (100.0%), and organized thrombus (22.0%). The presence of multiple thrombus types within a patient seems reasonable from a perspective that thrombus formation is an ongoing process with multiple stages.[26] Moreover, a prospective histopathological study demonstrated that in at least 50% of STEMI patients, aspirated coronary thrombi contained thrombus types that were already days or weeks old, suggesting a longer period of plaque instability before the actual clinical event.[27] This finding supports the identification of organized thrombus by HD-IVUS in the present study.

Since ultrasound attenuation in thrombotic regions prevented accurate distinction between thrombus, intima, and plaque, we developed an IVUS-derived thrombus score allowing in vivo thrombus burden quantification in STEMI patients. Based on this three-component thrombus score, including optimal cut-off values representing larger amounts of thrombus, high thrombus burden (thrombus score 2–3 points) was present in 40.7% of patients. As expected, high IVUS-derived thrombus burden appeared to be associated with higher rates of baseline TIMI flow grade 0 and TIMI thrombus grade 4–5. Conversely, 57.4% of patients with a TIMI thrombus score 4–5 had a low IVUS-derived thrombus burden. This finding illustrates the superiority of IVUS over angiography to quantify thrombus burden. Furthermore, this study demonstrated that patients with a high thrombus score had increased rates of impaired final TIMI flow and worse ST-segment resolution, illustrating that high IVUS-derived thrombus burden could predict final angiographic and electrocardiographic characteristics.

4.3 | Potential treatment implications following IVUS-derived thrombus grading

Although identification of (different types of) thrombus and high thrombus burden with IVUS requires a certain degree of training and expertise, it has the potential to allow tailored use of dedicated tools and drugs. First, aspiration thrombectomy might be less beneficial in patients with IVUS-defined organized thrombus, which has a more solid structure (granulation) and is more firmly attached to the luminal border. Second, patients with high IVUS-derived thrombus burden might have a greater benefit from aspiration thrombectomy. Third, histopathological examination of thrombus revealed that the amount of platelets reduced by 50% for every ischemic hour, while fibrin increased by a factor 2 due to elevating levels of thrombin, suggesting that administration of periprocedural antiplatelet therapy (e.g., glycoprotein IIb/IIIa inhibitors) could be more efficient in patients with earlier stages of IVUS-defined thrombus, such as the IVUS-defined acute and subacute type.[28,29] Nevertheless, the latter assumptions should be considered as hypothesis generating and need further investigation.

4.4 | Limitations

The main limitation of the present study is that culprit lesion plaque characteristics and thrombus as observed with HD-IVUS were not compared to findings based on other intravascular imaging modalities (e.g., optical coherence tomography and near-infrared spectroscopy IVUS) or histopathology. This would have provided more insight into the ability of HD-IVUS to visualize culprit lesion plaque morphology and thrombus. Second, although IVUS was performed before aspiration thrombectomy and predilatation, modification of culprit lesion plaque morphology and thrombus caused by vessel wiring or advancement of the IVUS catheter cannot be ruled out. Third, interobserver variability data was not available for the present study. Fourth, in all patients with IVUS-defined thrombus, subacute thrombus was observed. This creates a sense that the IVUS definition for this subtype might be too broad in its present form. To increase the value of different IVUS-defined thrombus types with a potential impact on treatment strategy, future studies should focus on a further expansion of these definitions and investigate the potential mechanisms explaining ultrasound attenuation caused by thrombus formation. As of to date, this phenomenon has not been well clarified. Fifth, the developed thrombus score needs to be validated in an external cohort of STEMI patients undergoing preintervention HD-IVUS. Finally, the low number of patients with impaired final TIMI flow did not allow for multivariable logistic regression to investigate if thrombus burden was also independently associated with angiographic and electrocardiographic results. However, direct comparison revealed a large numerical difference with an unadjusted $p < 0.001$ for both impaired final TIMI flow and incomplete ST-segment resolution.

5 | CONCLUSIONS

HD-IVUS in patients presenting with STEMI allows detailed culprit lesion plaque characterization and thrombus grading that may guide tailored PCI.

ACKNOWLEDGMENTS

The authors would like to thank Jouke Dijkstra for providing dedicated invasive imaging software (QCU-CMS, Leiden University Medical Centre, LKEB, Division of Image Processing, version 4.69) to perform intravascular ultrasound analysis. Institutional research support was provided by ACIST Medical Systems, Eden Prairie, Minnesota, USA, and Microport, Shanghai, China. The funding parties were not involved in any of the study-related activities.

CONFLICT OF INTEREST STATEMENT

Nicolas Van Mieghem received institutional research grant support from Abbott Vascular, Abiomed, Boston Scientific, Daiichi-Sankyo, Edward Lifesciences, Medtronic, and PulseCath. Joost Daemen received institutional grant/research support from Abbott Vascular, ACIST Medical, Astra Zeneca, Boston Scientific, Medtronic, Microport, Pie Medical, and ReCor Medical, and consultancy and speaker fees from Abbott Vascular, Abiomed, ACIST Medical, Boston Scientific, CardiacBooster, Cardialysis BV, Kaminari Medical, Pie Medical, PulseCath, ReCor Medical, Sanofi, Siemens Health Care, and Medtronic. The remaining authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Frederik T. W. Groenland http://orcid.org/0000-0002-2520-2042
Jurgen M. R. Ligthart http://orcid.org/0000-0002-2544-5255
Roberto Diletti http://orcid.org/0000-0002-2344-6705
Nicolas M. Van Mieghem http://orcid.org/0000-0002-2732-1205
Joost Daemen http://orcid.org/0000-0001-9081-5518

REFERENCES

1. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology Clinical Expert Consensus Document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2001;37:1478-1492.
2. Mintz GS. Clinical utility of intravascular imaging and physiology in coronary artery disease. *J Am Coll Cardiol*. 2014;64:207-222.
3. Shlofmitz E, Ali ZA, Maehara A, Mintz GS, Shlofmitz R, Jeremias A. Intravascular imaging-guided percutaneous coronary intervention: a universal approach for optimization of stent implantation. *Circ Cardiovasc Interv*. 2020;13:e008686.
4. van Zandvoort LJC, Ali Z, Kern M, van Mieghem NM, Mintz GS, Daemen J. Improving PCI outcomes using postprocedural physiology and intravascular imaging. *JACC Cardiovasc Interv*. 2021;14:2415-2430.
5. Buccheri S, Franchina G, Romano S, et al. Clinical outcomes following intravascular imaging-guided versus coronary angiography–guided percutaneous coronary intervention with stent implantation. *JACC Cardiovasc Interv*. 2017;10:2488-2498.
6. Darmoch F, Alraies MC, Al-Khadra Y, Moussa Pacha H, Pinto DS, Osborn EA. Intravascular ultrasound imaging-guided versus coronary angiography-guided percutaneous coronary intervention: a systematic review and meta-analysis. *J Am Heart Assoc*. 2020;9:e013678.
7. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *J Am Coll Cardiol*. 2018;72:3126-3137.
8. Gao XF, Ge Z, Kong XQ, et al. 3-Year outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *JACC Cardiovasc Interv*. 2021;14:247-257.
9. Choi IJ, Lim S, Choo EH, et al. Impact of intravascular ultrasound on long-term clinical outcomes in patients with acute myocardial infarction. *JACC Cardiovasc Interv*. 2021;14:2431-2443.
10. Groenland FTW, Neleman T, Kakar H, et al. Intravascular ultrasound-guided versus coronary angiography-guided percutaneous coronary intervention in patients with acute myocardial infarction: a systematic review and meta-analysis. *Int J Cardiol*. 2022;353:35-42.
11. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262-1275.
12. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47:C13-C18.
13. Endo M, Hibi K, Shimizu T, et al. Impact of ultrasound attenuation and plaque rupture as detected by intravascular ultrasound on the incidence of no-reflow phenomenon after percutaneous coronary intervention in ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2010;3:540-549.
14. Lee JB, Mintz GS, Lisauskas JB, et al. Histopathologic validation of the intravascular ultrasound diagnosis of calcified coronary artery nodules. *Am J Cardiol*. 2011;108:1547-1551.
15. Groenland FG, Ligthart JL, Witberg KW, Daemen J. Patterns of intracoronary thrombus by high-definition intravascular ultrasound. *EuroIntervention*. 2022;18:e158-e159.
16. Groenland FTW, Mahmoud KD, Neleman T, et al. Tissue characterisation and primary percutaneous coronary intervention guidance using intravascular ultrasound: rationale and design of the SPECTRUM study. *Open Heart*. 2022;9:e001955.
17. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. clinical findings through hospital discharge. *Circulation*. 1987;76:142-154.
18. Gibson CM, de Lemos JA, Murphy SA, et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation*. 2001;103:2550-2554.
19. van't Hof AWJ, Liem A, Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. *Circulation*. 1998;97:2302-2306.

20. Kampinga MA, Nijsten MWN, Gu YL, et al. Is the myocardial blush grade scored by the operator during primary percutaneous coronary intervention of prognostic value in patients with ST-elevation myocardial infarction in routine clinical practice? *Circulation*. 2010;3: 216-223.
21. Schröder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. *Circulation*. 2004;110: e506-e510.
22. Vlachojannis GJ, Wilschut JM, Vogel RF, et al. Effect of prehospital crushed prasugrel tablets in patients with ST-segment-elevation myocardial infarction planned for primary percutaneous coronary intervention: the randomized COMPARE CRUSH Trial. *Circulation*. 2020;142:2316-2328.
23. Terada K, Kubo T, Kameyama T, et al. NIRS-IVUS for differentiating coronary plaque rupture, erosion, and calcified nodule in acute myocardial infarction. *JACC Cardiovasc Imag*. 2021;14:1440-1450.
24. Higuma T, Soeda T, Abe N, et al. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial infarction: incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2015;8:1166-1176.
25. Mintz GS, Popma JJ, Pichard AD, et al. Patterns of calcification in coronary artery disease. A statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. *Circulation*. 1995;91:1959-1965.
26. Weisel JW, Litvinov RI. Visualizing thrombosis to improve thrombus resolution. *Res Pract Thromb Haemost*. 2021;5:38-50.
27. Rittersma SZH, van der Wal AC, Koch KT, et al. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. *Circulation*. 2005;111:1160-1165.
28. Silvain J, Collet JP, Nagaswami C, et al. Composition of coronary thrombus in acute myocardial infarction. *J Am Coll Cardiol*. 2011;57: 1359-1367.
29. Kim OV, Nevzorova TA, Mordakhanova ER, et al. Fatal dysfunction and disintegration of thrombin-stimulated platelets. *Haematologica*. 2019;104:1866-1878.

SUPPORTING INFORMATION

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

How to cite this article: Groenland FTW, Ziedses des Plantes AC, Neleman T, et al. Culprit lesion plaque characterization and thrombus grading by high-definition intravascular ultrasound in patients with ST-segment elevation myocardial infarction. *Catheter Cardiovasc Interv*. 2023;1-9. doi:10.1002/ccd.30699