

**IMPACT OF THROMBUS MODIFICATION WITH STENT RETRIEVER THROMBECTOMY
COMPARED TO MANUAL THROMBUS ASPIRATION AND STENTING ALONE ON
INTRACORONARY THROMBUS BURDEN AND CORONARY FLOW IN ST SEGMENT ELEVATION
MYOCARDIAL INFARCTION**

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Vittorio Zuccarelli, Stefano Andreaggi, **Jason Leo Walsh**, Rafail Kotronias, Miao Chu, Johnathan Vibhishanan, Adrian Banning and Giovanni Luigi De Maria. Treatment and Care of Patients with ST-Segment Elevation Myocardial Infarction: What Challenges Remain after Three Decades of Primary Percutaneous Coronary Intervention? Journal of Clinical Medicine. May 2024. PMID: 38792463

Abstract

ST-segment elevation myocardial infarction (STEMI) is typically caused by thrombotic coronary occlusion, resulting in myocardial hypoperfusion and necrosis.

Despite re-opening the occluded artery with percutaneous coronary intervention (PCI), downstream myocardial perfusion often remains impeded, in part, due to embolization of thrombotic material. This results in prognostically relevant myocardial injury, particularly in STEMI with a large thrombus burden (LTB).

Manual aspiration (MA), when used, is the prevailing technique for removing coronary thrombus prior to stenting. However, routine MA use has failed to demonstrate reductions in major adverse cardiovascular events in STEMI, perhaps due to limitations of this thrombus aspiration technology and/or a lack of patient selection in trials.

Stent-retriever thrombectomy (SRT) (using a “stent-retriever” device to extract thrombus), is a highly effective treatment for ischemic stroke. This thesis is the first to evaluate its efficacy and safety for extracting coronary thrombi in STEMI.

STEMI patients with LTB were prospectively randomized 1:1:1 to either PCI alone, MA-assisted PCI or SRT-assisted PCI. Key outcome measures were: 1) change in coronary thrombus volume/burden pre- to post-thrombus modification; 2) microcirculatory resistance; 3) safety and 4) surrogates of myocardial perfusion and infarct size.

Both MA and SRT significantly reduced coronary thrombus volume and improved clinical surrogates compared to stenting alone. Coronary thrombus volume reduction increased proportionally with increasing baseline thrombus volume for both techniques. Notably, angiographic thrombus score was shown to be an unreliable indicator of true coronary thrombus burden, verified by intracoronary ocular coherence tomography (OCT). This thesis demonstrates the safety and feasibility of SRT in STEMI and underscores the potential value of thrombus modification in selected STEMI patients with a true LTB, especially when thrombus burden is accurately assessed using OCT.

Abbreviations

Abbreviation	Definition
ACS	Acute coronary syndrome
ADE	Adverse device effect
AE	Adverse event
AF	Atrial fibrillation
AiMI	Rheolytic Thrombectomy with Percutaneous Coronary Intervention for Infarct Size Reduction in Acute Myocardial Infarction
AMI-HOT II	Acute Myocardial Infarction with Hyperoxemic Therapy II
ANOVA	Analysis of variance
ASPECTS	Alberta Stroke Program Early CT Score
AUC	Area under the curve
CABG	Coronary artery bypass grafting
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CAT Rx	Indigo CAT RX Aspiration System
caFFR	Coronary angiography-derived fractional flow reserve
caIMR	Coronary angiography-derived index of microvascular resistance
CHEETAH	A Prospective, Multi-centre Study to Evaluate the Safety and Performance of the CAT Rx Aspiration Catheter in Patients with a High Thrombus Burden Acute Coronary Vessel Occlusion

Abbreviation	Definition
CI	Confidence interval
CMR	Cardiac magnetic resonance imaging
CPR	Cardiopulmonary resuscitation
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
CFR	Coronary flow reserve
DAWN	Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct
DANAMI 3-DEFER	Third Danish Study of Optimal Acute Treatment of Patients With STEMI: Deferred Stent Implantation
DEFUSE 3	Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 3
DISTAL	Endovascular Treatment for Stroke Due to Occlusion of Medium or Distal Vessels
DTU	Door-to-unloading
ECG	Electrocardiogram
EF	Ejection fraction
ESC	European Society of Cardiology

Abbreviation	Definition
ESCAPE	Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke
ESCAPE-MeVO	Endovascular Treatment of Stroke Due to Medium-Vessel Occlusion
EXTEND-IA	Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection
FDA	Food and Drug Administration
FFR	Fractional flow reserve
FFR _{angio}	Angiography-derived fractional flow reserve
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICD	Implantable cardioverter-defibrillator
IC-HOT	Intracoronary Hyperoxemic Oxygen Therapy
iFR	Instantaneous wave-free ratio
IMR	Index of microcirculatory resistance
IMR _{angio}	Angiography-derived index of microcirculatory resistance
IRB	Independent Review Board
IVUS	Intravascular ultrasound
LAD	Left anterior descending coronary artery

Abbreviation	Definition
LCx	Left circumflex coronary artery
LTB	Large thrombus burden
LVEF	Left ventricular ejection fraction
MA	Manual aspiration
MACE	Major adverse cardiac events
MACCE	Major adverse cardiac and cerebrovascular events
MAP	Mean arterial pressure
MBG	Myocardial blush grade
MeVO	Medium-vessel occlusion
MHRA	Medicines and Healthcare products Regulatory Agency
MINAP	Myocardial Infarction National Audit Project
MIMI	Minimizing Infarct Size with Deferred Stenting in STEMI
ML	Machine learning
MR CLEAN	Multicentre Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MR CLEAN-LATE	Endovascular Treatment versus No Endovascular Treatment after 6-24 Hours in Patients with Ischaemic Stroke and Collateral Flow on CT Angiography
MVO	Microvascular obstruction

Abbreviation	Definition
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
NSTEMI	Non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
OCT	Optical coherence tomography
OFDI	Optical frequency domain imaging
PCI	Percutaneous coronary intervention
pPCI	Primary percutaneous coronary intervention
PICSO	Pressure-controlled Intermittent Coronary Sinus Occlusion
PIL	Participant/Patient Information Leaflet
QFR	Quantitative flow ratio
R&D	NHS Trust Research and Development Department
RCA	Right coronary artery
RCT	Randomised controlled trial
REC	Research Ethics Committee
RES	Research Ethics Service

Abbreviation	Definition
RFR	Resting full-cycle ratio
ROSC	Return of spontaneous circulation
SADE	Serious adverse device effect
SAE	Serious adverse event
SAVE	Stent-retriever Assisted Vacuum-locked Extraction
SD	Standard deviation
SELECT2	Trial of Endovascular Thrombectomy for Large Ischemic Strokes
SEM	Scanning electron microscopy
SOP	Standard Operating Procedure
SRT	Stent-retriever thrombectomy
SSO ₂	Super-saturated oxygen
STEMI	ST-segment elevation myocardial infarction
SWIFT PRIME	Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment
SYNTAX	Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score
TA	Thrombus area
TAPAS	Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study

Abbreviation	Definition
TASTE	Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia
TIMI	Thrombolysis in Myocardial Infarction
TOTAL	Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI
TSG	Oxford University Hospitals NHS Foundation Trust Trials Safety Group
TV	Thrombus volume
USADE	Unanticipated serious adverse device effect
VF	Ventricular fibrillation
vFFR	Vessel fractional flow reserve

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Images in developed in collaboration with Sam Thomas of the VPmed group, reproduced here with their permission.

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Figure 40. *In the future, several thrombus modification techniques aimed at reducing downstream embolization and infarct size may become available for clinical use, provided they demonstrate a meaningful impact on clinical outcomes. I anticipate that a range of these techniques could be employed (either alone or in combination), guided by intravascular imaging assessment.*

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Table 10. *Post-thrombus modification optical coherence tomography measurements. (*

**1 patient in the MA arm had unanalysable post-thrombus modification OCT imaging, 1 patient in the MA arm died prior to post modification OCT, **1 patient in the SRT arm crossed over to stenting-only and so did not have a post-thrombus modification OCT run).*

Table 11. *Post-stenting optical coherence tomography measurements. (*1 patient in the MA arm died prior to stenting, **2 patients in the SRT arm had unanalysable post-stent OCT runs and 1 was crossed over to stenting-only.*

Chapter 3:

Table 12. *Hemodynamic and microcirculatory parameters by treatment arm. Data include pre- and post-stenting mean arterial pressure (MAP), quantitative flow ratio (QFR), derived IMR_{angio} measurements, and proportion of patients with $IMR_{angio} \geq 40\%$ for each treatment group (stent-retriever thrombectomy, manual aspiration, and stenting-alone) and the combined cohort. Values are presented as median (interquartile range) except for post-stent $IMR \geq 40\%$, which is reported as number of cases and (percentage).*

Chapter 4:

Table 13. *Final TIMI flow by treatment arm.*

Table 14. *Final Myocardial blush grade by treatment arm.*

Table 15. *All serious adverse events reported, by treatment arm.*

Chapter 1: Introduction & background

The problem: ST-segment elevation myocardial infarction with large thrombus burden

STEMI

Ischaemic heart disease remains the leading cause of death globally, despite major advances in diagnostics and treatment.¹ In the England, Wales and Northern Ireland, the latest Myocardial Infarction National Audit Project (MINAP) report (2024) recorded ~82,000 confirmed myocardial infarctions over 1 year, of these 29,265 were ST-segment elevation myocardial infarctions (STEMI).²

STEMI usually occurs due to the rupture or erosion of an atherosclerotic plaque, which results in the formation of a thrombus that occludes the coronary artery. This occlusion arrests blood flow to the myocardium leading to infarction. The formation of a coronary thrombus starts when the exposed tissue of a ruptured plaque activates the clotting cascade, leading to platelet adhesion and aggregation. The mainstay of pharmacological treatment is to attenuate these processes with antiplatelet and anticoagulant drugs, inhibiting platelet aggregation and the clotting cascade, respectively. Gold standard interventional management of STEMI is via primary percutaneous coronary intervention (pPCI). pPCI is a strategy whereby a patient with STEMI is taken rapidly to a catheterisation laboratory where a range of equipment including coronary catheters, wires, balloons and stents are used to mechanically restore flow to the artery.

Prior to pPCI, thrombolysis was the treatment of choice for STEMI, this involves the administration of a drug that degrades fibrin (typically a tissue plasminogen activator),

promoting dissolution of the occlusive coronary thrombus and thereby restoring coronary flow. However, numerous randomised controlled trials (RCTs) have consistently demonstrated clear benefits of mechanical pPCI over thrombolysis in terms of major adverse cardiovascular and cerebrovascular events (MACCE).³ As a result of its efficacy the number of pPCI centres has expanded worldwide. In the United Kingdom and other developed nations, thrombolysis for the treatment of STEMI is now relatively uncommon, reserved for circumstances such as rural settings, where it is not possible to access a pPCI centre within 120 minutes of STEMI diagnosis.⁴

STEMI with LTB

Not all STEMIs are created equal. One factor that varies substantially from case to case is the quantity of thrombus within the lesion. Bhindi *etal* measured thrombus volume using optical coherence tomography (OCT) in 214 STEMI patients. Intracoronary thrombus volume ranged from 0 to 98mm³ (mean 3.7mm³)⁵ (Figure 1).

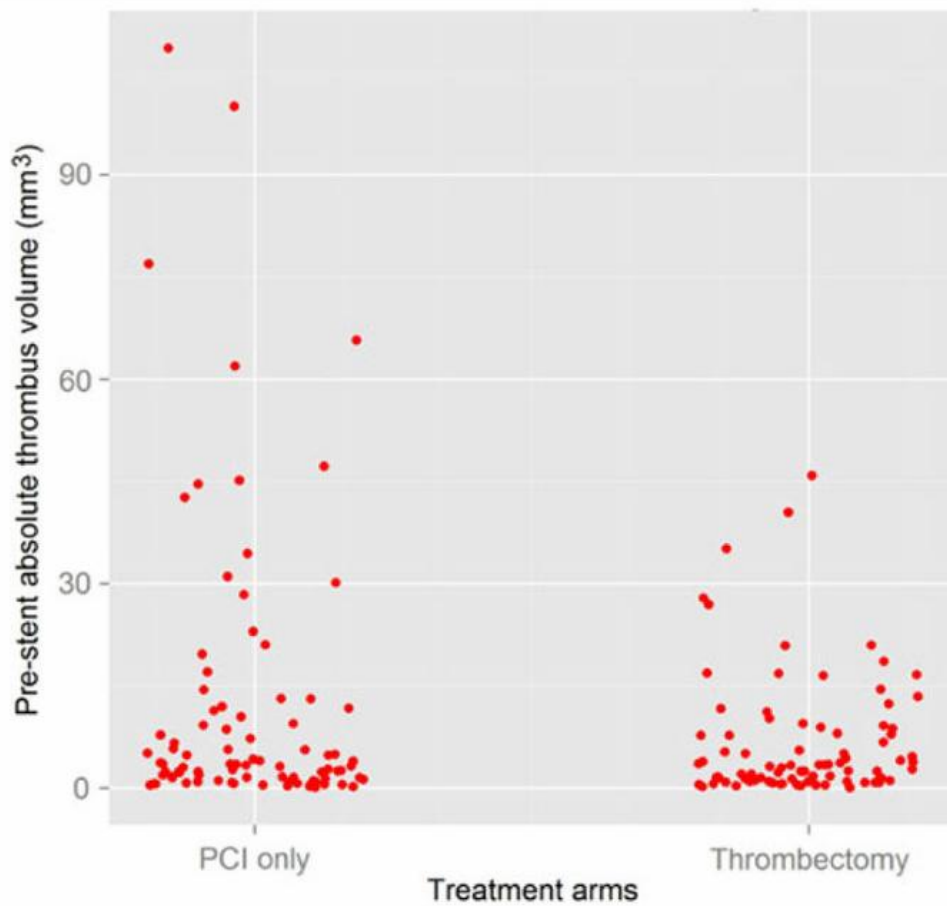


Figure 1. Scatter plot showing volume of intracoronary thrombus in patients presenting with STEMI, measured by optical coherence tomography before stenting in patients treated with stenting alone (PCI only) and those treated with manual aspiration (thrombectomy). Reproduced from Bhindi et al (permissions: Oxford University Press, Licence number: 5992620273218).

The traditional method to quantify thrombus burden in the STEMI literature has been using a semiquantitative angiographic thrombus burden score, for which filling defects created by presumed thrombus are visually assessed on the angiogram. The most widely used angiographic thrombus score is the “Thrombolysis in Myocardial Infarction (TIMI) thrombus grade”, which classifies thrombus burden as follows:

- **Grade 0:** No angiographic evidence of thrombus.
- **Grade 1:** Angiographic characteristics suggestive of thrombus, such as reduced contrast density, haziness, irregular lesion contour, or a smooth convex meniscus at the site of total occlusion, suggestive but not diagnostic of thrombus.
- **Grade 2:** Definite thrombus with the greatest dimension less than half the vessel diameter.
- **Grade 3:** Definite thrombus with the greatest dimension more than half but less than two times the vessel diameter.
- **Grade 4:** Definite thrombus with the largest dimension equal or greater than two times the vessel diameter.
- **Grade 5:** Total occlusion of the vessel after a coronary wire has been passed through the lesion.

Grades 4 and 5 are widely considered in the literature to represent LTB.^{6,7} However, this has never been validated with a quantitative measure of intracoronary thrombus.



Figure 2: *Coronary angiogram showing a large filling defect (indicated by white circle), within the left circumflex artery, indicative of a large thrombus. The length of the filling defect is more than twice the vessel diameter, therefore this lesion would be classified as Grade 4 on the Thrombolysis in Myocardial Infarction (TIMI) thrombus grade.*

With the advent of the high-resolution intravascular imaging technique optical coherence tomography (OCT), intracoronary thrombus can be more clearly visualised and accurately measured. Therefore, some recent studies investigating thrombus burden have measured the volume of intracoronary thrombus in mm³ using OCT.^{5,8} Despite now being able to quantify intracoronary thrombus with OCT, no consensus or discussion in the literature exists on what could constitute LTB according to OCT.

LTB in STEMI, as determined by angiographic thrombus score, has been shown to be an independent predictor of MACCE in several studies.^{5,8-12}

Several factors can influence the quantity and characteristics of thrombus within a lesion. Factors associated with a higher burden of thrombus in STEMI include: elevated Lipoprotein(a),¹³ larger vessels,¹⁴ hypertension,¹⁵ smoking,¹⁶ absence of pre-infarction angina,¹⁷ well developed coronary collateral circulation,¹⁸ diabetes, more complex coronary disease (higher SYNTAX score) and longer symptom to reperfusion time.¹⁹ However, in these particular studies thrombus burden was estimated using the semi-quantitative Thrombolysis in myocardial infarction (TIMI) thrombus grade. Thrombus composition can also vary between cases, Silvain et al performed histological analysis of coronary thrombus in STEMI, finding that higher time from symptom onset to reperfusion resulted in more organised thrombus with a higher red-cell content.²⁰ Red cell-rich thrombi in STEMI are associated with worse myocardial reperfusion,²¹ more distal embolisation of thrombus during PCI,²² and a worse prognosis.^{23,24} Interestingly, in ischaemic stroke intervention, red-cell rich thrombi have been shown to be more amenable to mechanical thrombectomy (stent-retriever or manual aspiration).²⁵⁻²⁹

It is unclear why red cell-rich thrombi in STEMI are associated with worse outcomes. One possibility is that dense red cell-rich thrombi directly cause more severe obstruction of microvasculature and therefore worse myocardial injury. Alternatively, or additionally, the presence of red-cell rich thrombi may be a marker of independent predictors of outcome and infarct size such as longer time to reperfusion or LTB.

A probable mechanism by which LTB contributes to a worse prognosis in STEMI despite PCI is microvascular obstruction (MVO), with thrombus embolizing distally from the lesion becoming lodged in the microcirculation, impairing myocardial perfusion and promoting infarct expansion. LTB has been demonstrated to increase the likelihood of both spontaneous and procedure-related thrombus embolization, contributing to coronary MVO, leading to the no-reflow phenomenon, where despite successful reopening of an occluded artery, blood flow remains impaired.³⁰ A larger extent of MVO is linked to increased infarct size, impaired ventricular remodelling and function, and higher rates of cardiac death, heart failure, and myocardial re-infarction.³¹⁻³³ Stone et al demonstrated that for every 5% increase in infarct size there is a 20% increased risk of mortality and/or heart failure within 1 year, whilst De Waha et al demonstrated a 1% increase in MVO extent translates to a 14% increase in mortality and 8% increase in heart failure within 1 year.^{34,35}

However, embolisation of thrombotic material is not the only contributor to MVO and infarct size in STEMI. In 1974 Kloner et al temporarily occluded blood flow to the left anterior descending arteries of dogs using a snare, for either 40 or 90 minutes. After release of the major epicardial coronary occlusion at 40 minutes, blood flow was typically restored to most of the myocardium as indicated by tracer being distributed evenly throughout the tissue. After 90 minutes of coronary occlusion was released,

significant endocardial portions of the myocardium typically remained under perfused. This demonstrated the no-reflow phenomenon for the first time; whereby myocardial blood flow remains impaired despite re-opening of major epicardial vessels. Subsequent electron microscopy of the myocardial tissue identified capillary swelling, endothelial damage, and microvascular collapse in myocardial tissue, giving the first insights into the mechanisms of MVO.³⁶

Since this landmark study, several mechanisms thought to contribute towards MVO have been described including: atherothrombotic embolism, ischaemia and reperfusion injury triggering an inflammatory response resulting in myocardial and endothelial oedema leading to capillary compression,³⁷ inflammatory infiltration causing microvascular plugging with leukocytes and platelets, loss of capillary wall integrity resulting in intramyocardial haemorrhage (IMH) and microvascular vasospasm.³⁸⁻⁴⁰ (figure 3) IMH represents a severe consequence of ischemia /reperfusion injury and is recognised as a critical determinant of adverse outcomes following STEMI. IMH occurs when ischaemic damage to the capillary endothelium results in loss of microvascular structural integrity, allowing extravasation of red blood cells into the surrounding myocardial interstitium upon reperfusion.⁴¹ IMH is proposed to exacerbate MVO through direct physical compression of already damaged capillaries, further impeding microvascular flow. Further, degradation of extravasated red blood cells deposits iron within the myocardium, perpetuating oxidative stress, inflammation, and cardiomyocyte death. This residual iron, detectable on CMR months after STEMI, is associated with ongoing adverse ventricular remodelling.^{42,43} The prognostic significance of IMH is well established, IMH is independently associated with all-cause death and heart failure hospitalisation, providing incremental prognostic value beyond infarct size and MVO alone.⁴⁴

Beyond the structural and inflammatory mechanisms described above, vasoactive substances released during ischaemia and reperfusion likely play a significant role in the pathogenesis of MVO by promoting sustained microvascular vasoconstriction. Endothelin-1 (ET-1), a potent vasoconstrictor peptide produced by endothelial cells, has been implicated in the pathogenesis of MVO. Plasma ET-1 levels are significantly elevated in patients with STEMI, and higher concentrations predict no reflow post PCI,^{45,46} and increased mortality.⁴⁷ ET-1 exerts vasoconstrictive effects via activation of ETA receptors on vascular smooth muscle cells, and shown to promote sustained vascular spasm that persists even after successful epicardial recanalization.⁴⁸

Neuropeptide Y (NPY) is another vasoactive mediator implicated in MVO. NPY is a sympathetic co-transmitter released from perivascular sympathetic nerve terminals when sympathetic drive is high. Herring et al performed a translational study combining clinical observations in STEMI patients with basic science experiments in animal models and human tissue to investigate the role of NPY in coronary microvascular dysfunction following STEMI. In STEMI patients NPY levels were three-fold higher compared to acute coronary syndrome/angina and normal coronary artery groups. STEMI patients were divided into low coronary sinus (CS) NPY and high CS NPY groups. High CS NPY was associated with: higher IMR, lower CFR, greater microvascular obstruction on CMR, greater myocardial oedema on acute CMR, lower ejection fraction at 6 months and larger ventricular volumes at 6 months. Further, CS NPY positively correlated with infarct size at 6 months.

In isolated microvascular coronary arteries NPY caused dose-dependent vasoconstriction of isolated coronary micro-arteries and vasoconstriction was prevented

by a Y1 receptor antagonist. In Langendorff perfused (rat) hearts NPY increased coronary vascular resistance, significantly increased infarct size relative to area at risk, with these effects blocked by Y1 receptor antagonism.

Immunohistochemistry of human coronary micro-arteries (samples obtained during cardiothoracic surgery) confirmed Y1 receptor expression in human vascular smooth muscle cells in the media.⁴⁹ These findings implicate NPY as a key vasoactive mediator of MVO in STEMI.

Brain natriuretic peptide (BNP), while primarily recognised as a biomarker of myocardial wall stress and heart failure, it has also been investigated in the context of MVO. Elevated BNP levels in the acute phase of STEMI have been associated with greater MVO extent and larger infarct sizes on CMR, perhaps reflecting the degree of myocardial injury and ventricular dysfunction resulting from impaired microvascular perfusion, rather than a direct mediator of MVO.⁵⁰ Other substances implicated in MVO through mediation of platelet aggregation include thromboxane A2 and serotonin.^{51,52} Given the multiple mechanisms of MVO that exist it is unclear if LTB and no-reflow are simply markers of worse MVO or if they directly contribute (and if so to what degree). It is possible that LTB and the associated distal embolization may not cause no reflow and MVO, it may be that these phenomena are caused by or coexist with a larger infarct that has already caused significant injury to the microvasculature. If this hypothesis were true then the outcomes of TASTE and TOTAL may truly be indicating the futility of thrombus modification in STEMI, as it either does not contribute to further MVO or the degree to which it contributes is insignificant.^{53,54} On review of the data up to 2021 Kleinbongard and Heusch concluded: *“the contribution of coronary embolization compared with other causes of microvascular obstruction, such as endothelial and interstitial oedema, vasoconstriction, leukocyte adherence, capillary*

destruction or haemorrhage, is impossible to quantify”⁵⁵ Furthermore, the degree to which the microvascular insult has already occurred when a patient arrives for pPCI and therefore the scope for MVO reduction (by thrombectomy and other approaches) has yet to be elucidated. As standard, contemporary STEMI studies typically perform an acute CMR 2 to 5 days post procedure, quantifying the aftermath of STEMI and pPCI.^{56,57} With the advent of rapid CT based MVO assessment,⁵⁸ it is feasible that degree of MVO could be assessed in STEMI before and after reperfusion, to help pick apart what degree of microvascular injury has already occurred and therefore determine if there is potential to mitigate MVO in STEMI. The purpose-built catheterisation laboratory equip with a photon counting CT scanner at the John Radcliffe Hospital is well placed to assess this.

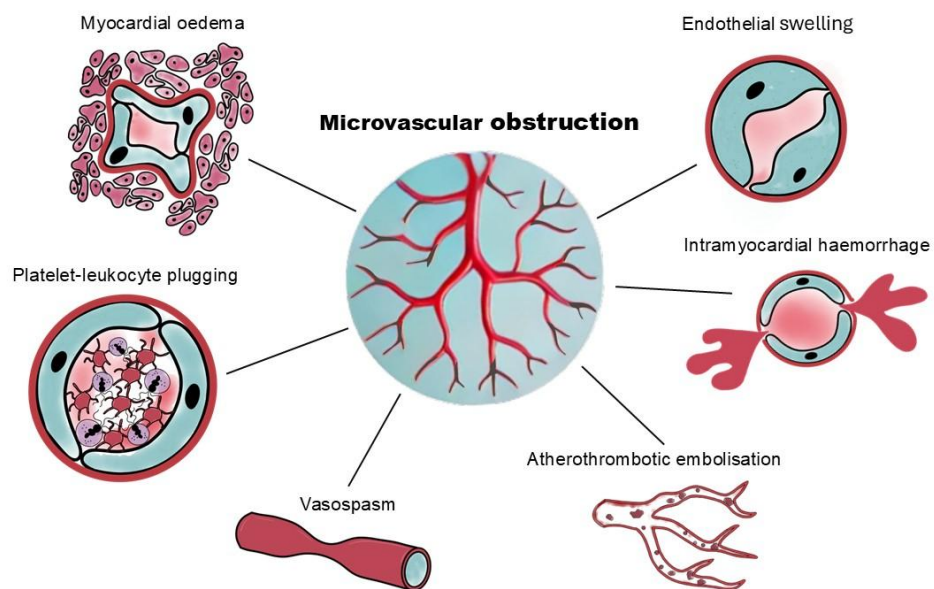


Figure 3: *Major pathophysiological mechanisms contributing to coronary microvascular obstruction.*

Susceptibility to MVO appears to vary between individuals, due to factors such as genetic polymorphisms impacting on microvascular function and ischaemic preconditioning.⁴⁰ The relative importance of each underlying mechanism of MVO remains unclear. However, it is clear that a larger thrombotic burden predicts a greater extent of MVO and infarct size and independently predicts worse outcomes in STEMI.^{12,59,60} Therefore, LTB potentially remains a prognostically relevant clinical challenge, and effectively reducing thrombus burden in STEMI, with techniques such as manual aspiration (MA) of thrombus or stent-retriever thrombectomy (SRT) may represent an unmet clinical need, to reduce MVO, infarct size and ultimately improve morbidity and mortality in STEMI (Figure 4).

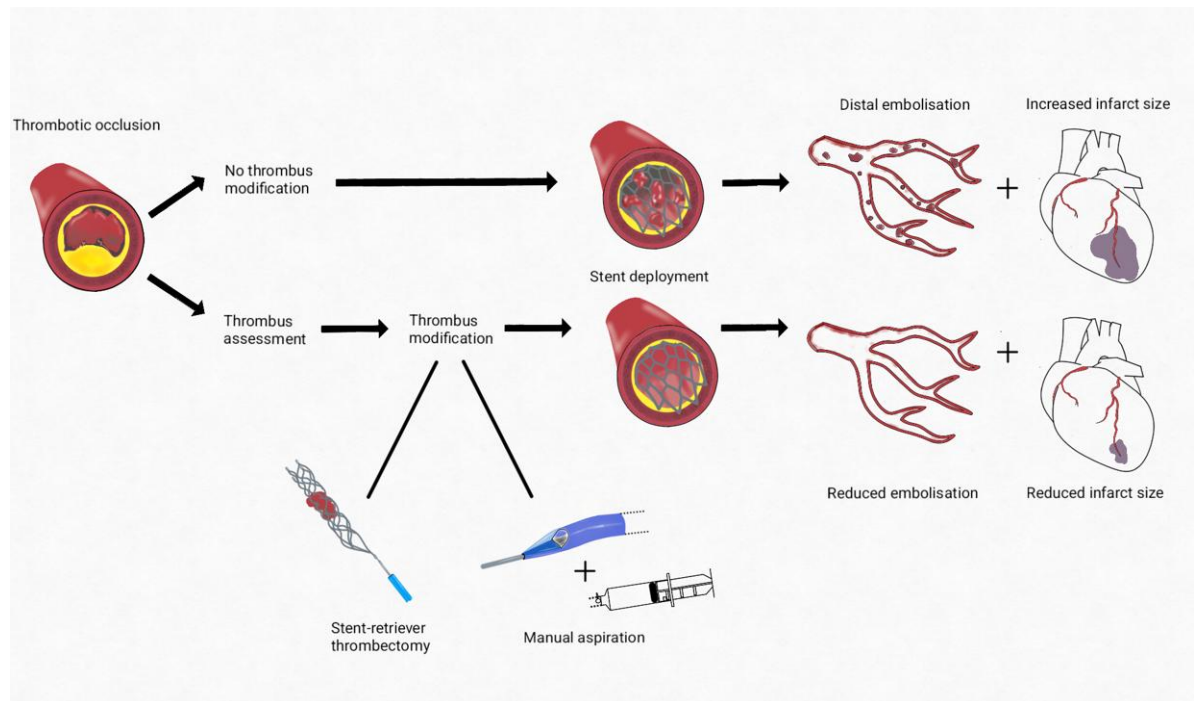


Figure 4. *The aims of thrombus modification versus stenting alone in ST elevation myocardial infarction (STEMI) with large thrombus burden (LTB). In STEMI, a thrombotic occlusion can be treated with a stent alone or thrombus burden can be assessed (angiographically or with intravascular imaging techniques) and an attempt to extract the thrombus can be made. Thrombus modification techniques include manual aspiration and stent-retriever thrombectomy. Theoretically, effective thrombus modification should result in reduced downstream embolization, microvascular obstruction and infarct size.*

Manual aspiration for the treatment of large thrombus burden in STEMI

A number of interventional thrombus modification techniques (techniques that remove or dissipate coronary thrombus) for the treatment of STEMI have been developed (Table 1).⁶¹ However, only one technique is currently widely used in clinical practice. Manual aspiration (MA) is the prevailing thrombus modification approach used during STEMI, aiming to reduce coronary thrombus burden, MVO, infarct size and ultimately improve prognosis. MA utilizes specialized coronary catheters that attach to a retracted vacuum syringe to generate suction. Commonly used devices include the Export (Medtronic Inc., Minnesota, USA), Hunter (IHT Cordynamic, Barcelona, Spain) and Pronto V4 (Vascular Solutions, Minnesota, USA) catheters. Following an aspiration run, the contents of the aspiration syringe and catheter are purged into a basket designed to capture the extracted thrombus. The syringe and catheter are then flushed with saline, ready for reuse if needed. Typically, MA is performed prior to stenting during STEMI, a single run or multiple runs of aspiration can be performed at the operator's discretion.

An important consideration as with any interventional technology, is exactly how the device is used. The prevailing approach for using MA in our centre is to place the tip of the MA catheter distal to the thrombus, turn on suction at this position and slowly withdraw. However, this is not standardised. Conversely, the TOTAL trial design and rationale manuscript advocates bringing the tip of the MA catheter proximal to the lesion, then turning on suction and advancing slowly distally.⁶² Selection of either approach appears to be based on dogma rather than evidence. Representing a genuine gap in the literature. Comparative efficacy of beginning suction proximally or distally could be initially investigated in a bench model.

Manual aspiration catheters gained popularity in 2008 following the publication of the randomized controlled trial (RCT) TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study). TAPAS randomized 1071 patients with STEMI to either manual aspiration or conventional PCI. The primary endpoint was myocardial blush grade, a semiquantitative angiographic marker of myocardial perfusion, which was significantly better in the manual aspiration group. It also reported reduced major adverse cardiac events and 30-day mortality in the manual aspiration arm, although it was not powered to assess hard clinical endpoints. The authors concluded that manual thrombus aspiration could be performed in the majority of patients with STEMI, irrespective of angiographic features (e.g. visible thrombus). The findings of this trial guided the design of subsequent larger trials of MA in STEMI.⁶³

The findings of subsequent large RCTs powered to evaluate clinical outcomes conflicted with the findings of TAPAS. The TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) trial randomized 7244 patients to MA or conventional PCI. STEMI patients over 18, pain onset within 24-hours and ability to give informed consent could be recruited. TASTE found no significant difference in the primary endpoint all-cause mortality at 30 days and no significant differences in rehospitalization, stent thrombosis, and major adverse cardiovascular events. It was concluded that routine thrombus aspiration before PCI does not reduce 30-day mortality or improve other clinical outcomes in patients with STEMI.⁵⁴

The TOTAL (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI) trial published in 2015 randomized 10,732 patients with STEMI 1:1 to routine MA or PCI alone. Patients with STEMI, over 18, able to consent, presenting within 12 hours of pain onset and without prior thrombolysis were eligible.

TOTAL found no difference in a composite endpoint of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure at 180 days. Additionally, it found that MA was associated with an increased risk of stroke at 180 days, raising the concern that MA could displace thrombus proximally causing stroke. However, peri-procedural stroke (within 48 hours of the procedure), was no different between MA and stenting alone.⁵³

The TASTE and TOTAL trials heavily influenced subsequent practice and guidelines discouraging the routine use of manual thrombus aspiration use in STEMI. The negative findings of TASTE and TOTAL could be interpreted as: 1) extracting thrombus during STEMI does not confer benefit; 2) MA is not an effective technology for extracting thrombus or 3) A lack of patient selection (e.g. recruiting all STEMI patients regardless of thrombus burden) resulted in the impact of MA being diluted.

A 2017 meta-analysis of TASTE, TOTAL and TAPAS examined a subgroup of patients with LTB (defined in this analysis as TIMI thrombus grade ≥ 3). This analysis demonstrated fewer cardiovascular deaths in patients randomly assigned to manual aspiration (2.5% versus 3.1% in the PCI alone group; $P=0.03$),¹² suggesting a potential benefit of MA in patients with LTB.

An optical coherence tomography (OCT) sub-study of TOTAL, where OCT was used pre-stent in a sample of 214 patients (104 MA pre-stent, 110 no thrombus modification pre-stent) found no difference in the average pre-stenting thrombus volume in lesions pre-treated with manual aspiration versus patients treated with PCI only,⁵ suggesting on first assessment poor efficacy of MA for significantly reducing thrombus burden. However, a closer look at the data from this study (see figure 1), shows a trend of lower thrombus volume pre-stent in patients who received MA compared to those that did not,

with the majority of participants having a very low or no thrombus burden on OCT.

Suggesting any impact of MA may be diluted by the majority of patients recruited having minimal intracoronary thrombus.

These findings suggest that future studies of thrombus modification techniques should focus on selecting patients with LTB and that there may be an unmet clinical need for more efficacious thrombus extraction techniques.

Other interventional approaches to STEMI with large thrombus burden

Beyond MA, other interventional thrombus techniques in STEMI have been developed, aiming to reduce downstream embolization, microvascular obstruction and myocardial damage (Figure 4; Table 1).

Sustained aspiration catheters

A second-generation aspiration catheter, referred to as a sustained or mechanical aspiration catheter has been developed. The primary distinction between traditional MA catheters and the sustained aspiration catheter lies in their suction mechanism.

Sustained aspiration catheters are connected to a vacuum device, enabling continuous suction with consistent negative pressure. In contrast, MA catheters rely on manually generated suction, which diminishes over time. Currently, the only available device for coronary aspiration is the Indigo CAT RX aspiration system (Penumbra Inc, Alameda, CA). Currently, one human clinical study exists assessing the CAT Rx system in STEMI. The CHEETAH study (A Prospective, Multi-centre Study to Evaluate the Safety and Performance of the CAT Rx Aspiration Catheter in Patients with a High Thrombus Burden Acute Coronary Vessel Occlusion) evaluated sustained aspiration therapy prior to PCI in 400 patients with myocardial infarction and a LTB, defined as a

thrombus grade of 4 or 5 on the TIMI thrombus grade. The results indicated a good safety profile, low rates of distal embolization, and good angiographic markers of myocardial perfusion.⁶⁴ However, as this was a single armed study with no control group, effectively a large case series, it is not possible to be clear on the comparative efficacy of the device. RCTs comparing sustained aspiration with the current standard of care (manual aspiration or no thrombus modification) are necessary to establish if the device demonstrates any efficacy and if it should be adopted in STEMI management.

Sonothrombolysis

Sonothrombolysis involves the delivery of high mechanical index ultrasound impulses to the heart during a microbubble infusion. These impulses induce microbubble cavitation, generating mechanical forces that fragment intracoronary thrombi while also promoting vasodilation. This aims to dissipate thrombus and improve myocardial flow. The technique has been extensively studied in animal models, more recently small-scale human RCTs have demonstrated that sonothrombolysis, when administered before and after STEMI, can improve vessel recanalization, left ventricular function and reduce infarct size.⁶⁵⁻⁶⁸ However, an RCT investigating post-STEMI sonothrombolysis only, showed no benefit in ST-resolution or infarct size.⁶⁶ Further, larger scale RCTs are needed to verify the efficacy and optimal delivery of sonothrombolysis, which may support its future role as a routine adjunct in STEMI management.

Rheolytic thrombectomy

Rheolytic thrombectomy employs a specialized intravascular catheter equipped to deliver high-velocity saline jets, which create localized negative pressure through the Venturi effect. This mechanism facilitates the fragmentation of thrombus material, which is then aspirated and removed through the catheter system. While rheolytic thrombectomy has demonstrated utility in the treatment of peripheral vascular

thromboses,⁶⁹ it has failed to demonstrate convincing clinical benefit in the context of STEMI.^{70,71} In fact, the AiMI Trial (Rheolytic Thrombectomy with Percutaneous Coronary Intervention for Infarct Size Reduction in Acute Myocardial Infarction) suggested harm in the context of STEMI showing larger infarct size and greater mortality with rheolytic thrombectomy compared to stenting alone. However, with 480 patients, the trial was not powered to detect a difference in MACE.⁷¹ Since no convincing benefits have been demonstrated and a signal of harm has been seen, rheolytic thrombectomy is not commonly used in the context of STEMI.

Intracoronary thrombolysis

Another interventional strategy aiming to reduce intracoronary thrombus burden in STEMI is the intracoronary administration of low-dose thrombolytic agents prior to stent implantation. This approach aimed to enhance thrombus dissolution, aiming to improve downstream microvascular perfusion and reduce MVO. The most notable trial, the T-TIME trial investigated the efficacy of intracoronary alteplase administered during PCI, before stent implantation. Patients were randomised to either 20mg of intracoronary alteplase, 10mg of intracoronary alteplase or routine PCI. After 453 patients were recruited an interim analysis revealed no significant difference in microvascular obstruction between the thrombolysis arms and the control arm, therefore the study was terminated early due to futility. These findings suggest that intracoronary thrombolysis with alteplase does not confer a meaningful advantage in preserving microvascular integrity in the acute management of STEMI.⁷² However, like in the TASTE and TOTAL trials of MA, LTB was not part of the inclusion criteria, therefore, as shown by the OCT sub study of TOTAL (figure 1),⁵ most patients included likely had a small intracoronary thrombus burden.

Deferred stenting

During pPCI, particularly in cases with a LTB, angiographic no-reflow is frequently observed following stent deployment, likely due to thrombotic embolization secondary to stent implantation. This has led to the investigation of a deferred stenting strategy, in which the culprit vessel is initially opened, and a glycoprotein IIb/IIIa inhibitor infusion is initiated, with stent implantation postponed, typically for 24–48 hours.

While some studies have suggested improvements in angiographic markers of coronary flow with this approach,⁷³ the three major RCTs in this field have uniformly yielded negative results. The MIMI trial found no significant difference in MVO on cardiac MRI or in MACE at six months between immediate and deferred stenting.⁷⁴ This finding was further reinforced by the larger DANAMI 3-DEFER trial ($n = 1,215$) and the INNOVATION study, both of which failed to demonstrate a significant reduction in infarct size or MVO with deferred stenting.^{75,76}

Given the lack of proven clinical benefit, deferred stenting is not recommended as a routine strategy in STEMI management.

Milli-spinner thrombectomy

The Milli-Spinner is a novel thrombectomy device that combines mechanical compression with aspiration to facilitate thrombus removal. It consists of a catheter with a rotating distal element featuring fins and slits, which generates both suction and compressive forces. The device's developers propose that its compressive action may offer advantages over existing thrombectomy technologies, particularly in the removal of dense, fibrin-rich thrombi that are typically resistant to other modalities.

To date, the Milli-Spinner's clot extraction efficacy has been demonstrated in benchtop cerebral and pulmonary artery models, as well as in the maxillary and renal arteries of

an in vivo swine model using injected thrombus.⁷⁷ However, clinical data on its safety and effectiveness in real pathology are still pending, and its performance in human subjects remains to be established.

Table 1. *interventional thrombus modification techniques.*

Technique	Description	Evidence summary
Manual Aspiration	An aspiration catheter attached to a retracted suction syringe to extract thrombus from the coronary artery	Two large randomised controlled trials in all-comer STEMI, failed to demonstrate an impact on outcome. Smaller studies showing positive impacts on clinical surrogates ^{5,54,78,79}
Stent-retriever Thrombectomy	Expandable mesh tube, deployed in the thrombus to ensnare and extract it	Only case reports and case series in STEMI ^{80,81} . Multiple RCTs showing a significant reduction in disability with stent-retriever use in large vessel ischaemic stroke ^{82,83}
Sustained Aspiration	A second-generation aspiration catheter attached to a mechanical vacuum allowing for continuous suction	A single armed study, effectively a case series ⁶⁴
Sonothrombolysis	Use of high mechanical index ultrasound with a microbubble infusion to enhance thrombus breakdown	Animal studies and a small RCT demonstrated an improvement of surrogate markers of clinical impact. ^{65,66} A recent RCT of post PCI sonothrombolysis failed to show benefit ⁷²
Rheolytic Thrombectomy	A catheter with high-velocity saline jets aiming to break-up and aspirate coronary thrombus	Mixed results in clinical trials in STEMI, ^{71,84} with the AiMI Trial demonstrating larger infarct size and greater mortality with rheolytic thrombectomy ⁷¹
Intracoronary Thrombolysis	Injection of a thrombolysis agent at a low dose directly into the coronary artery	The T-time trial showed no benefit of intracoronary thrombolysis ⁷²
Deferred Stenting	After opening the occluded vessel, stenting is deferred for at least 24 hours, aiming to give time for antiplatelet agents to dissipate thrombus in the interim	RCTs have all failed to show an impact on MVO, infarct size or MACE ⁷⁴⁻⁷⁶
Milli-spinner Thrombectomy	A tube containing a spinning element at the distal end which generates compressive forces and suction to extract thrombus	Limited data in pre-clinical bench and swine models demonstrating its ability to compress and extract injected thrombus ⁷⁷

Other interventional approaches aiming to reduce microvascular obstruction in STEMI

Thrombus embolization is thought to be a major contributor to MVO in STEMI, however, several other pathophysiological mechanisms exist (figure 3).⁴⁰ Here, I discuss the evidence for other interventional techniques, beyond thrombus modification, aiming to reduce MVO. These include induced hypothermia, Pressure-controlled Intermittent Coronary Sinus Occlusion (PiCSO), left ventricular unloading and supersaturated oxygen therapy (table 2).

Therapeutic hypothermia

Inducing hypothermia, aiming to reduce inflammation, metabolic demand and preserve critical tissues has been trialled in a number of contexts including stroke, post cardiac arrest, sepsis and STEMI.^{85,86} The only context in which therapeutic hypothermia has shown consistent efficacy (reductions in death and/or disability) is neonatal encephalopathy.^{87,88}

In STEMI therapeutic hypothermia aims to reduce MVO by suppressing ischemia-reperfusion induced inflammation. While animal models show significant reduction in MVO and infarct size,⁸⁹⁻⁹¹ human trials where systemic hypothermia is induced during STEMI have failed to demonstrate similar benefits.⁹²⁻⁹⁴

This discrepancy between human and animal trials has been attributed to factors such as failure to achieve target temperatures, insufficiently rapid cooling (both harder to achieve in adult humans than smaller animals and neonates), lack of selective myocardial cooling (to the affected myocardium), and underpowered studies.⁹⁵ A meta-analysis of human RCTs suggests a reduction in infarct size with systemic hypothermia but also reported an increased risk of bleeding complications.⁹⁶ To address the

limitations of systemic cooling, the selective intracoronary hypothermia technique was developed. This involves a specialized coronary catheter that occludes the vessel with an intracoronary balloon, whilst infusing cool saline distal to the occlusive balloon and coronary lesion, allowing selective and rapid cooling the myocardial area at risk. Once the area at risk is cooled sufficiently the balloon is deflated and a cold saline infusion is continued to maintain local hypothermia.^{97,98} However, the first RCT evaluating this approach, failed to demonstrate infarct size reduction compared to standard pPCI.⁹⁹ Hypothermic interventions in STEMI are still being investigated for clinical effectiveness, for example, the STEMI-COOL trial is currently ongoing investigating coronary cooling combined with haemodilution (aiming to dilute inflammatory metabolites and oxidative stress leading to MVO).¹⁰⁰ Due to limited efficacy in human trials today, myocardial cooling is not recommended for clinical use.

Pressure-controlled Intermittent Coronary Sinus Occlusion

Pressure-controlled Intermittent Coronary Sinus Occlusion (PiCSO)[®] (Miracor Medical, Brussels, Belgium), another interventional approach aiming to reduce MVO and infarct size involves a specialized balloon being inserted into the coronary sinus and inflated cyclically. The resulting intermittent increase in coronary sinus pressure aims to create back pressure, enhancing blood flow to the ischemic myocardium. Early non-randomized studies suggested that it may reduce infarct size and microvascular resistance.¹⁰¹⁻¹⁰⁵ However, the randomized controlled trial PiCSO-AMI-I, which compared standard pPCI with pPCI plus PiCSO in anterior STEMI patients, found no significant reduction in infarct size at six months and increased procedure time. Consequently, PiCSO is not recommended in clinical practice.¹⁰⁴

Left ventricular unloading

The hypothesis that reducing cardiac wall strain and myocardial oxygen demand during STEMI can minimize reperfusion injury and infarct size is supported by animal studies. Kapur et al. randomized pigs to either 120 minutes of LAD occlusion (control) or 150 minutes of LAD occlusion with mechanical circulatory support during the last 30 minutes before reperfusion (left ventricular unloading). Despite delayed reperfusion, infarct size was 49% of the ventricle in the control group and 28% in the left ventricular unloading group.¹⁰⁶

Building on this, the DTU-Pilot trial assessed left ventricular unloading using the Impella CP system in anterior STEMI patients, comparing immediate (n=25) versus delayed reperfusion (n=25), showing no difference between the groups, demonstrating the safety and feasibility of delaying reperfusion in this context.¹⁰⁷ These findings informed the ongoing multicentre STEMI-DTU trial, which is evaluating whether 30 minutes of LV unloading with Impella before PCI improves outcomes.¹⁰⁸ Since the initial submission of this thesis the results have been presented at the American College of Cardiology Conference 2026, showing that use of the Impella CP system did not reduce infarct size in anterior STEMI patients, but did increase major bleeding or vascular complications, resulting in a net harm to patients.¹⁰⁹

Super-saturated oxygen therapy

Super-saturated oxygen (SSO₂) therapy involves the delivery of oxygen-enriched blood to ischemic myocardium via a coronary catheter following pPCI. The AMI-HOT II randomized controlled trial demonstrated a significant reduction in infarct size with a 90-minute intracoronary SSO₂ infusion compared to standard pPCI in STEMI.¹¹⁰ The technique was subsequently refined in the IC-HOT single-arm study, which reduced the infusion time to 60 minutes and incorporated additional procedural adjustments.¹¹¹ At

one year, patients from the IC-HOT trial were compared to a propensity-matched cohort of patients that received standard of care pPCI, showing a reduction in mortality and new-onset heart failure or heart failure-related hospitalizations in the SSO₂ group.¹¹²

The proposed mechanism by which SSO₂ exerts its cardioprotective effects in STEMI involves enhanced oxygen delivery to ischemic and viable myocardial tissue. This is thought to reduce endothelial oedema, inflammation, and leukocyte adhesion while mitigating reactive oxygen species-mediated cytokine secretion and local coagulation.¹¹³ These effects collectively improve regional myocardial perfusion and contribute to a reduction in infarct size. SSO₂ therapy has received FDA approval for use in anterior STEMI cases presenting within six hours of symptom onset. However, its widespread adoption remains limited, likely due to several reasons including:

- 1) The logistical complexity of delivering a prolonged post-PCI intracoronary infusion, which increases cath lab time and requires additional equipment, staff familiarity, and workflow integration, which could make it unattractive to busy cardiac centres.
- 2) The absence of clear MACE reduction in repeated randomized trials, relying on one randomized trial and a subsequent propensity-matched analysis.^{110,112}
- 3) The relatively narrow approved indication (anterior STEMI within 6 hours of symptom onset).
- 4) Prohibitive cost of the equipment.

These practical and evidence base limitations are reflected by a lack of recommendations for the use of SSO₂ therapy in contemporary guidelines.

In summary, while several novel interventional strategies have been explored to mitigate MVO in STEMI beyond thrombus modification, clinical evidence supporting their efficacy remains limited. Induced hypothermia, PiCSO, and left ventricular unloading have showed promise in preclinical models but have not demonstrated consistent benefits in large-scale human trials. Super-saturated oxygen therapy is the only approach with regulatory approval, though its clinical uptake is constrained by a limited evidence base, and logistical, and cost considerations.

Except for MA, none of the interventional techniques aiming to reduce MVO (whether involving thrombus modification or not) are currently part of routine clinical use.

Table 2. *Non-thrombus modification based interventional techniques aiming to reduce microvascular obstruction.*

Technique	Description	Evidence summary
Therapeutic hypothermia	Several strategies have been explored to induce hypothermia in STEMI, including both systemic cooling methods and targeted myocardial hypothermia techniques	All human RCTs investigating induced hypothermia in STEMI have failed to demonstrate clinical efficacy ^{92,93,99}
Pressure-controlled Intermittent Coronary Sinus Occlusion	A catheter-based technique that cyclically increases coronary sinus pressure, aiming to enhance perfusion of the ischaemic myocardium	The PiCISO AMI I trial failed to show a reduction in infarct size with PiCISO compared to standard of care in STEMI ¹⁰⁴
Left ventricular unloading	The use of mechanical circulatory support, such as the Impella device, to reduce left ventricular wall stress and oxygen demand before reperfusion	The STEMI-DTU trial showed no reduction in infarct size with an increase in bleeding or vascular complications. ¹⁰⁹
Supersaturated oxygen therapy	Delivering oxygen-enriched blood to the infarct-related artery after primary PCI to enhance oxygenation of ischemic myocardium	The AMI-HOT II trial demonstrated a reduction in infarct size compared to standard of care in STEMI ¹¹⁰

Stent-retriever thrombectomy, a solution to STEMI with large thrombus burden?

Lessons from ischaemic stroke intervention.

Stent-retrievers are expandable wire mesh tubes, which when expanded in a vessel grip thrombus, allowing it to be withdrawn into a catheter and removed (figure 5).

Commonly used stent-retriever models in stroke intervention include the Solitaire X™ (Medtronic Inc., Minnesota, USA) and the NeVA™ (Vesalio, Tennessee, USA) devices.

In the current practice of stroke intervention, thrombectomy can be performed using a thrombus aspiration catheter (like in STEMI), a stent-retriever device or a combination of the two.¹¹⁴ Currently, only case reports and series exist demonstrating the feasibility of their use for thrombus extraction in STEMI (Table 3).^{80,81,115-118} It is therefore unknown if SRT could be useful in addressing the unmet clinical need of effective thrombus extraction in STEMI with a LTB.

In the wake of TASTE and TOTAL interest in and use of thrombus modification in STEMI declined. In the USA between 2009 and 2011 (following the positive TAPAS trial) 13.8% of STEMI patients undergoing pPCI had MA, in 2016 (post TOTAL) usage had more than halved to 4.7%.¹¹⁹ Concurrent with this decline was a renaissance in interventional thrombus modification in ischaemic stroke.

The use of thrombus-extraction devices (termed endovascular therapy in the stroke literature), with careful imaging-based patient selection, has been shown to be highly efficacious in large vessel acute ischaemic stroke (table 4).^{82,120-125}



Figure 5. *Expanded stent-retriever device entangled with red thrombus extracted from the left circumflex artery of a patient during a STEMI.*

The MR CLEAN trial (A randomized trial of intraarterial treatment for acute ischemic stroke) in 2015 was the first to show a clinical benefit of thrombus modification with SRT in ischaemic stroke. Inclusion criteria included being within 6 hours of stroke onset, having a large vessel occlusion (distal intracranial carotid artery, M1/M2 middle cerebral arteries, or A1/A2 anterior cerebral arteries) confirmed with CT angiogram, MR angiogram or digital subtraction angiography and a NIH Stroke Scale score of ≥ 2 .

Table 3. Case reports and case series describing coronary stent-retriever thrombectomy in myocardial infarction.

Reference	Article type	Device Used	Summary	Outcome
Walsh et al., 2025 ⁸⁰	Case report	Solitaire X (Medtronic)	69-year-old man with inferior STEMI due to left circumflex artery occlusion. Large thrombus burden visualised on optical coherence tomography.	Successful thrombectomy with optical coherence tomography visualization of thrombus extraction
Zhi et al., 2024 ⁸¹	Case series	NeVa (Vesalio)	15 patients underwent thrombectomy with the NeVa device.	Thrombectomy was successfully performed in 14/15 patients
Costabile & Brugaletta, 2023 ¹¹⁶	Case report	NeVa (Vesalio)	53-year-old man with inferior STEMI. Extensive thrombus; failure of balloon dilation and manual aspiration	Successful thrombus extraction, TIMI III flow achieved post stenting
Spirito et al., 2022 ¹¹⁵	Case series	NeVa (Vesalio)	61 patients with acute coronary syndrome and large thrombus burden. Stent-retriever thrombectomy was combined with a vacuum-assisted aspiration technique in the last 51 patients	Case were associated with high rates of vessel recanalisation and thrombus removal.
Bhoopalan et al., 2019 ¹²⁶	Case report	Solitaire AB (Medtronic)	30-year-old man with inferior STEMI and coronary artery ectasia, with large thrombus burden. Failed aspiration and intracoronary thrombolysis.	Successful thrombus extraction, TIMI II+ flow achieved; stenting performed 24 hours later with TIMI III flow
Patel et al., 2017 ¹¹⁷	Case report	Solitaire FR (Medtronic)	33-year-old man with left main coronary artery thrombus presenting as STEMI. Failed manual aspiration.	Successful thrombectomy with a 6x30mm stent-retriever
Uribe et al., 2017 ¹¹⁸	Case report	Solitaire AB (Medtronic)	40-year-old man with anterior STEMI with large thrombus in the left main stem.	Successful thrombectomy with 6x20mm stent-retriever

Patients were randomised to SRT with alteplase or alteplase alone. The primary endpoint was Modified Rankin score, a measure of severity of disability (1 = No significant disability, able to carry out all usual activities despite some symptoms; 2 = Slight disability, able to look after own affairs without assistance; 3 = Moderate disability, needs some help but can walk unassisted; 4 = Moderately severe disability, unable to attend to own bodily needs without assistance; 5 = Severe disability, bedridden, incontinent, and requiring constant care; 6 = Dead). Patients in the SRT arm had significantly less disability, with 13.5% more being functionally independent (Modified Rankin score of 1-2) at 90 days.

Since MR CLEAN multiple large RCTs demonstrating clear clinical benefits of SRT in large vessel ischaemic stroke have been published (Table 4).

The SWIFT PRIME trial (Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment) also selected ischaemic stroke patients within 6 hours of symptom onset, imaging proven large vessel occlusion and a high ASPECTS score on CT (suggesting a significant volume of salvageable cerebral tissue that would benefit from reperfusion). Patients were randomised to SRT with thrombolysis or thrombolysis alone, the study was stopped for efficacy after 198 patients were recruited, 25% more patients were functionally independent (modified Rankin scale score, 0 to 2) in the SRT arm, with no difference in safety.⁸³ Whilst the similar ESCAPE (Randomized assessment of rapid endovascular treatment of ischemic stroke) trial demonstrated a mortality improvement in addition to a reduction in disability with SRT.¹²³

The REVASCAT trial (Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke), again randomised patients to SRT with thrombolysis or thrombolysis

alone, and found the benefits of reduced disability were maintained when extending the inclusion window to 8 hours of symptom onset.¹²¹

The EXTEND-IA trial (Endovascular therapy for ischemic stroke with perfusion-imaging selection) utilised advanced CT perfusion imaging to select patients with salvageable cerebral tissue and randomised patients to SRT thrombectomy plus thrombolysis or thrombolysis alone, finding improved reperfusion, neurologic recovery, and functional outcomes.¹²⁷

The MR CLEAN-LATE (Endovascular treatment versus no endovascular treatment after 6-24 h in patients with ischaemic stroke and collateral flow on CT angiography); DAWN (Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct) and DEFUSE3 (Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging) trials combined a later presentation window post symptom onset (6 to 24, 6 to 24 and 6 to 16 hours, respectively) and advanced perfusion imaging to select patients with salvageable tissue and a small core of infarct, all finding a significant reduction in disability in the SRT arm.^{124,128,129}

The eligibility of patients with ischaemic stroke for SRT were expanded further by the SELECT2 (Trial of Endovascular Thrombectomy for Large Ischemic Strokes) and RESCUE-Japan LIMIT (Endovascular Therapy for Acute Stroke with a Large Ischemic Region) trials, which showed reduced disability with SRT in patients with larger infarct cores on imaging than in previous trials.^{130,131}

However, recent trials have extended SRT use to smaller vessel ischaemic strokes (medium and distal vessels)¹³². These trials found that SRT is not effective for strokes due to medium or distal vessel occlusion, according to the recently published ESCAPE-MeVO (Endovascular Treatment of Stroke Due to Medium-Vessel Occlusion) and

DISTAL (Endovascular Treatment for Stroke Due to Occlusion of Medium or Distal Vessels) trials. Both showed no added clinical benefit over best medical therapy, and ESCAPE-MeVO reported higher mortality in the thrombectomy group.^{133,134} These results underscore the current lack of evidence to support thrombectomy in non-large-vessel occlusion stroke.

The extensive clinical RCT evidence for the efficacy of SRT in large vessel stroke is clear. It is unclear whether benefits in stroke will translate into benefits in STEMI with LTB. Carefully examining the approach and findings of the stroke SRT trials could guide SRT trials in STEMI, being mindful of key differences and similarities between ischaemic stroke and STEMI. Key differences between stroke and STEMI include the tissues affected (neural versus myocardial), the origin of the occlusion (a significant proportion of the occlusions being embolic in stroke) and pharmaceutical thrombolysis (this remains part of standard care alongside interventional thrombus modification in stroke, but not in STEMI).

A key similarity between ischaemic large vessel stroke and STEMI is that proximal cerebral artery diameters are similar in diameter to major coronary arteries. For example, average internal carotid artery diameter is ~4.7mm, whilst the left main coronary artery diameter averages ~4.5mm. The M1 segment of the middle cerebral arteries averages 3mm, whilst the left anterior descending, left circumflex and right coronary arteries average ~3.5, 3 and 3.5mm, respectively.^{135,136} Therefore, standard stent-retriever devices should be compatible with major coronary arteries. This is supported by effective coronary thrombus extractions described in case reports (Table 3). However, there are also key differences in the anatomy and physiology of coronary and cerebral arteries. Cerebral arteries tend to have a thicker internal elastic lamina, thinner media, fewer elastic fibres in the media, lack an external elastic lamina and

thinner adventitia compared to coronary and other arteries.¹³⁷ This will likely have implications for comparative biomechanical properties such as distensibility, which could have implications for safety of and efficacy of SRT in STEMI. Another important physiological difference lies in autoregulatory mechanisms. Cerebral vessels are primarily pressure regulated, maintaining a relatively constant cerebral blood flow across a wide range of perfusion pressures via myogenic, metabolic and carbon dioxide dependent mechanisms. In contrast, coronary circulation is predominantly metabolically regulated, with blood flow closely matched to myocardial oxygen demand and strongly influenced by vasoactive metabolites such as adenosine.^{138,139} This could have implications for responsiveness and reactivity to mechanical stimuli.

Table 4. Summary of major randomized controlled trials comparing endovascular therapy for ischaemic stroke with medical therapy.

Trial	Year	Reperfusion Window	Vessel Size	Infarct Size	Summary
MR CLEAN ¹²⁴	2015	≤6 hours	Large	Small	First trial to show a significant functional improvement with endovascular therapy.
SWIFT PRIME ⁸³	2015	≤6 hours	Large	Small	Significant functional improvement with endovascular therapy.
REVASCAT ¹²¹	2015	≤8 hours	Large	Small	Showed functional benefit maintained with longer time window to reperfusion.
ESCAPE ¹²³	2015	≤12 hours	Large	Small	The first trial to show a mortality benefit with endovascular therapy.
EXTEND-IA ¹²⁷	2015	≤6 hours	Large	Small	Used perfusion imaging to select patients. Strong benefit, reduced disability with endovascular therapy.
DAWN ¹²⁸	2017	6–24 hours	Large	Small	Disability reduction with endovascular therapy in a late window in patients found to have viable ischaemic tissue with a small infarct size on perfusion/diffusion imaging.
DEFUSE 3 ¹²⁹	2018	6–16 hours	Large	Small	endovascular therapy is effective in a 6–16-hour window with mismatch criteria.
BASICS ¹⁴⁰	2021	≤6 hours	Basilar artery	Not specified	Functional outcome was not significantly different between endovascular therapy and medical therapy.
MR CLEAN-LATE ¹²⁴	2022	6–24 hours	Large	Small	Functional benefit with endovascular therapy beyond 6 hours in patients with imaging mismatch.
RESCUE-Japan LIMIT ¹³¹	2022	≤24 hours	Large	Large	Functional benefit of endovascular therapy shown even in large infarct core patients.
SELECT 2 ¹³⁰	2023	≤24 hours	Large	Large	Functional benefit of endovascular therapy shown even in large infarct core patients.
ESCAPE-MeVO ¹³³	2024	≤12 hours	Medium	Small/moderate	No added clinical benefit of endovascular therapy over best medical therapy.
DISTAL ¹³⁴	2024	≤24 hours	Medium/distal	Small	No added clinical benefit of endovascular therapy over best medical therapy.

It is notable that endovascular therapy trials in stroke utilize careful imaging-based selection of patients, identifying factors such as occlusions amenable to treatment (e.g. in large vessels) and viable ischemic tissue (e.g. with perfusion imaging). In contrast, the major trials of thrombus modification in STEMI (TASTE and TOTAL) recruited all-comers with STEMI presenting within 12 hours of symptom onset.^{53,54} Unlike the brain, the heart is a continuously moving organ, so CT coronary and myocardial perfusion imaging is a time-intensive process and therefore selection of patients using these modalities is not currently viable in the acute STEMI setting. However, the TOTAL sub-study by Bhindi *et al*, which used intravascular imaging (OCT) to measure thrombus volume before stenting clearly demonstrated that most STEMI patients had a low intracoronary thrombus volume.⁵ They concluded that thrombus volume could be an important variable to select STEMI patients suitable for thrombus modification and could be an explanation as to why TASTE and TOTAL were negative trials. Thrombus burden is a variable that can be feasibly assessed in STEMI using angiographic thrombus score or intravascular imaging.

Intravascular imaging is not routinely employed in stroke practice or research; consequently, there are no available OCT data assessing thrombus burden in relation to stroke outcomes or the efficacy of thrombus modification devices. However, studies in stroke have explored the relationship between thrombus characteristics, assessed via CT and histological analysis of retrieved thrombi and the effectiveness of thrombus modification.^{25,141}

A sub-study of the MR CLEAN trial demonstrated that CT-based radiographic measures of thrombus permeability to contrast agent independently predicted both functional outcomes and successful vessel recanalization. Higher thrombus permeability was associated with better outcomes, irrespective of treatment modality (intravenous

thrombolysis or endovascular therapy). These findings suggest that imaging markers of thrombus perviousness could help identify thrombotic lesions more likely to respond to thrombus modification strategies.¹⁴¹

Histological analyses of thrombi extracted during stroke intervention have revealed associations between thrombus composition and the success of endovascular therapy. The relative proportions of fibrin and red blood cells are key determinants of a thrombus's mechanical and biochemical properties, influencing its response to both thrombectomy and thrombolysis. Fibrin-rich thrombi tend to be denser and more rigid, making them more difficult SRT and less permeable to, and responsive to, thrombolytic agents. In contrast, red blood cell rich thrombi are typically softer and more deformable, facilitating extraction with SRT and increasing susceptibility to thrombolysis. However, these thrombi are also more prone to fragmentation, which may lead to distal embolization.²⁵

Thrombus volume and composition appear to be important factors affecting the success of SRT. These should be considered when designing and analysing future studies on thrombus modification in STEMI. For instance, patients with LTB and red cell rich thrombi are likely to respond better to SRT and could be specifically selected for inclusion in such studies

Aside from a lack of patient selection, the failure of the large MA trials (TASTE and TOTAL) could be explained by inefficacy of the MA device. It may be SRT offers enhanced efficacy. However, no trials in STEMI or stroke intervention have compared the efficacy of these devices. Stroke trials have assessed the use of a single device or a combination of thrombus modification devices, but have not compared devices head-to-head.

Several reasons for why SRT could be superior to MA in coronary thrombus extraction may be hypothesised:

1) Thrombus position: Coronary thrombus often adheres to the wall of the vessel (forming on an ulcerated or ruptured plaque). Whilst the lumen of the aspiration catheter is often in the central portion of the vessel lumen, minimising thrombus-catheter interaction.

2) Thrombus-catheter size mismatch: The lumen of an average coronary artery is between 3-3.5mm in diameter, representing a cross-sectional area of $\sim 7.0\text{-}9.6\text{mm}^2$. Aspiration catheter lumen cross-sectional area is $0.9\text{-}1\text{mm}^2$, covering only 9.5-14% of the average coronary lumen. This mismatch is even more marked in large or ectatic vessels, which have greater potential to hold more thrombus.

3) Guidewire bias: tortuosity of coronary arteries and the necessity for catheters to slide over a guidewire can bias the device away from the thrombus, which is not under operator control.

4) Transient diminishing negative pressure: MA catheters rely on a retracted air-filled syringe to generate suction; this means suction is short-lived with diminishing negative pressure as the retracted syringe fills with blood. This may limit the volume of thrombus aspirated.

Stent-retriever devices may avoid many of these limitations as they expand to fill the entire vessel interacting more closely with the thrombus and ensnare the thrombus rather than relying on suction. Therefore, we hypothesize that stent-retrievers may offer greater thrombus extraction efficacy than manual aspiration catheters.

However, it is important to consider the potential for harm when intraluminal devices are deployed in novel clinical settings. Specifically, there is a legitimate concern as to whether stent-retriever thrombectomy (SRT) may cause injury to otherwise normal vessels, thereby resulting in adverse patient outcomes. A meta-analysis of SRT trials in acute ischaemic stroke ($n = 1,287$), did not identify an excess of parenchymal haematoma or intracranial haemorrhage compared with standard medical care, suggesting no significant signal for clinically relevant device-related vascular injury.¹⁴² Conversely, a subsequent and larger meta-analysis ($n = 1,764$) did identify a signal for higher rates of haemorrhage in a subgroup of patients with large established infarct cores, raising the possibility that SRT may precipitate vascular injury under certain pathological conditions.¹⁴³ Importantly, however, both meta-analyses concluded that, in the context of large vessel occlusion stroke, the demonstrable benefits of SRT outweigh the associated risks.

Histological analyses conducted in animal models, including both rabbit and porcine vasculature, have demonstrated that stent-retriever deployment and retrieval can induce acute endothelial injury.^{144,145} Whether such injury translates into clinically significant sequelae in the setting of STEMI remains to be seen. To date, the largest published case series of SRT use in STEMI, comprising only 61 patients, did not report any device-related dissections, but reversible coronary spasm occurred in 10 patients.¹¹⁵ However, the small sample size and reliance on angiographic assessment alone limit the sensitivity of these observations. In our study, the systematic use of OCT imaging in every case will afford a substantially more sensitive assessment, enabling the detection of subclinical device-related endothelial injury.

This project is unique as it represents the first systematic evaluation of SRT in STEMI. It is also the first to directly compare SRT with manual aspiration and stenting alone, and the first trial of thrombus modification in STEMI to specifically select patients with LTB, who are more likely to respond and derive clinical benefit.

Measuring the impact of thrombus modification in STEMI

When evaluating the efficacy of a thrombus modification device such as a stent retriever or MA catheter in STEMI, it is prudent to consider the therapeutic objectives (Figure 4). Primarily, these devices are designed to remove thrombus from the coronary artery. The rationale for thrombus extraction is to minimise distal embolisation, thereby reducing microvascular obstruction and its detrimental effects on the myocardium. The ultimate goal is to limit myocardial injury to improve clinical outcomes. Importantly, any therapeutic strategy must confer a net clinical benefit. This necessitates not only the evaluation of efficacy but also the identification and documentation of potential adverse effects associated with the treatment used.

Accordingly, measuring the impact of thrombus modification in STEMI should evaluate multiple parameters including coronary thrombus, distal embolization, microvascular obstruction, myocardial injury, clinical outcomes and device safety.

Thrombus assessment

Intracoronary thrombus can be visualized using traditional angiography through the assessment of filling defects or with much greater accuracy and resolution with intravascular imaging techniques. Of the two main intravascular imaging modalities, OCT offers greater resolution than IVUS and therefore allows the greatest accuracy for

identifying and quantifying thrombus.^{146,147} Quantification of intracoronary thrombus on OCT has been demonstrated to be highly repeatable.¹⁴⁸

Angiographic assessment

The status quo for categorising an MI patient as having a LTB in current research is the “Thrombolysis in Myocardial Infarction (TIMI) thrombus grade”, a semi-quantitative angiographic thrombus score.^{6,59,64} As outlined in greater detail above, the TIMI thrombus grade is based on visual assessment of the angiogram, assigning a score from 0 to 5. A score of 0 indicates no visible filling defect, while a score of 5 denotes total occlusion of the vessel with no distal flow despite successful guidewire passage, potentially indicative of a substantial thrombus burden in the context of STEMI. An example of a TIMI thrombus grade 4 is demonstrated in Figure 2, where the length of the filling defect is at least twice the diameter of the vessel.

Angiographic thrombus assessment has several limitations. Firstly, filling defects seen on angiography do not always represent thrombus. For, example filling defects may be a result of other structures such as calcific nodules, dissection flaps or non-thrombotic embolised material. Another limitation is that the 2-dimensional angiographic filling cannot accurately quantify thrombus i.e. in mm³. Furthermore, the grades 0-5 appear to be arbitrary (not based on data).⁶ However, following the creation of the TIMI thrombus grading scale, attempts have been made to validate it. Sianos et al found that grade 4 was an independent predictor of 2-year mortality and MACE when compared to grades 0-3.⁶ Bhindi et al compared thrombus score to measured intracoronary thrombus burden (%) by OCT in a sample of patients from the TOTAL trial. Patients with a thrombus grade of ≥ 4 had a mean thrombus burden of 3.44% (n = 62, 95% confidence interval: 2.37–4.99%), whilst patients with a thrombus grade of < 4 had a mean thrombus burden of 1.71% (n = 25, 95% confidence interval: 1.02–2.86%).⁵ This supports that higher

thrombus grade may represent higher burden of thrombus. However, no well-powered studies have systematically attempted to validate angiographic thrombus grading against either OCT or extracted thrombus quantity.

The clear advantage of angiographic thrombus grading is that it can be done rapidly, allowing STEMI patients with a LTB to be identified on the catheterisation laboratory table. It is not clear what proportion of patients with a TIMI thrombus grade of ≥ 4 truly have a high burden of thrombus, but as thrombus grade of ≥ 4 predicts higher MACE and is associated with higher thrombus burden measured by OCT it is perhaps a reasonable tool for rapidly categorising STEMI patients as having LTB or small thrombus burden.

Intravascular imaging

As previously discussed, OCT is the intravascular imaging modality with the highest spatial resolution ($\sim 10\text{-}20\text{ }\mu\text{m}$), making it the most accurate technique currently available for measuring and characterising intracoronary thrombus. In a study of 30 acute coronary syndrome cases by Kubo et al, OCT identified 100% of intracoronary thrombus, whilst IVUS detected 33%.¹⁴⁷ Accordingly, this section will focus on OCT.

The optical properties of OCT enable assessment of thrombus density. Dense red thrombus, which has a high red blood cell and fibrin content, attenuates the OCT light signal, resulting in signal dropout or shadowing of the underlying vessel wall. In contrast, less dense white thrombus, which is richer in platelets and white blood cells, produces minimal signal attenuation and appears bright on OCT imaging (Figure 6).¹⁴⁹ The distinction between red and white thrombi observed on OCT has been shown to correlate well with histopathological findings in post-mortem analyses sensitivity (90%) and specificity (88%).¹⁵⁰

This ability to differentiate thrombus types using OCT may, in the future, help guide interventional strategies, however, its clinical utility in this context has yet to be established.

More recently, polarization-sensitive OCT has been developed. This technology utilises the polarisation state of light to provide additional tissue contrast and structural information. Van Zandvoort et al applied polarization-sensitive OCT to coronary thrombi in the setting of acute coronary syndrome, demonstrating that quantifiable polarimetric properties could be used to characterise thrombus composition in greater detail.¹⁵¹ Examples of polarization-sensitive OCT images can be seen in figure 1 of Van Zandvoort et al recent paper: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10782573/>.¹⁵¹

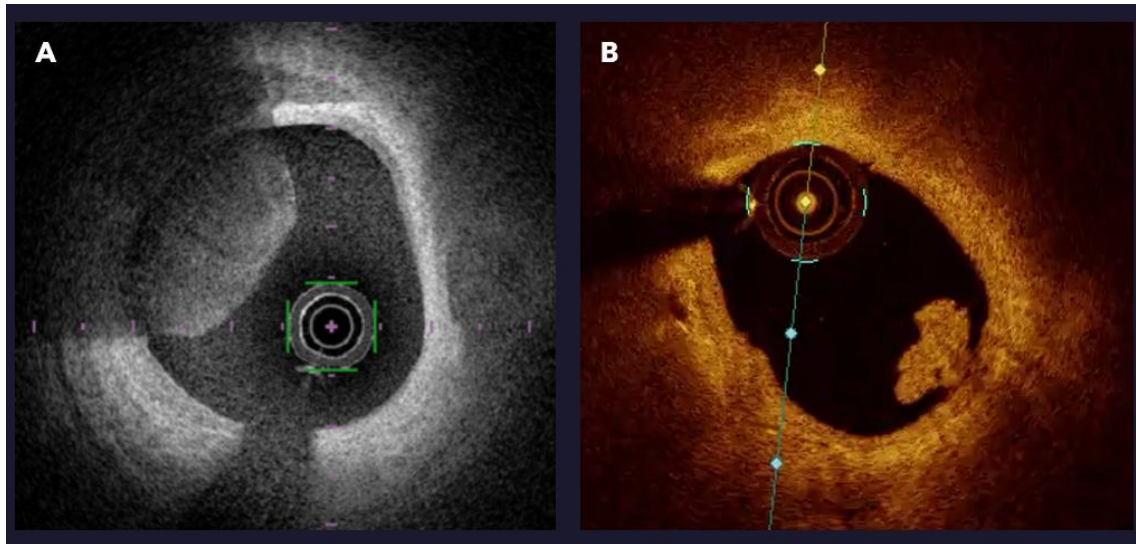


Figure 6. *A: Optical coherence tomography image of a dense “red” thrombus causing high attenuation of the light signal resulting in shadowing of the vessel wall. This likely represents a fibrin and red cell rich thrombus. This image was taken using the Optical Frequency Domain Imaging catheter (OFDI: LUNAWAVE®, Terumo Corporation, Tokyo, Japan). B: Optical coherence tomography image of a low-density “white” thrombus, with the optical characteristics of high backscatter (resulting in the thrombus appearing bright) and low-attenuation (structures behind the thrombus are visualised clearly). This likely represents a platelet-rich thrombus. This image was taken using the Abbott Dragonfly OpStar™ catheter (Abbott, Santa Clara, CA).*

Measuring the quantity of thrombus using OCT was initially performed in a semi-quantitative manner, using an OCT thrombus score (much like an angiographic thrombus score). Prati et al developed an OCT thrombus score, this method assesses thrombus burden based on the number of vessel quadrants containing thrombus in each OCT cross-section. Each cross-section is scored from 0 to 4, depending on whether thrombus occupies 0, 1, 2, 3, or all 4 quadrants. The total thrombus score is calculated by summing the scores across all cross-sections within the analysed segment.¹⁵²

More quantitative methods of measuring intracoronary thrombus on OCT have since been developed. Magro et al measured thrombus volume (mm³) and atherothrombotic burden (% of lumen) on OCT in STEMI patients post-stenting.

First, thrombus area (TA) within the stent was calculated for each OCT cross-section using the formula: $TA = SA - LA + FTA + ISA$, where SA is the stent area, LA is the lumen area, FTA is the free thrombus area, and ISA accounts for area of incomplete strut apposition. The mean TA is then multiplied by the length of the thrombus-containing stented segment to derive the thrombus volume (TV). Finally, the atherothrombotic burden is expressed as the ratio of thrombus volume to total stent volume. They found that a higher post-stenting atherothrombotic burden was associated with worse ST-segment resolution, worse myocardial blush grade, a higher incidence of no reflow and more distal vessel occlusion, suggestive of distal embolization.¹⁵³ This method of measuring thrombus volume and burden was subsequently validated pre-stenting by Kajander et al. This OCT sub-study of the TOTAL trial assessed the feasibility and reproducibility of quantifying thrombus volume and burden before stent implantation in STEMI patients. 8111 OCT cross-sections were analysed. Inter- and intra-observer analyses showed high repeatability, with narrow limits of agreement. The study concluded that OCT-based pre-stent TB measurement is feasible and reliable, and

may provide additional value in assessing thrombus burden during STEMI intervention.¹⁴⁸

As measuring intra-coronary thrombus using OCT appears to be repeatable, measuring intracoronary thrombus volume and burden pre- and post-thrombus modification to calculate a delta, would likely be a reasonable approach for estimating thrombus extraction efficacy. However, this approach has yet to be attempted or validated.

Extracted thrombus measurements

Thrombus is not a homogenous tissue. Numerous studies show it is highly heterogeneous, composed of varying ratios of various components including fibrin, leukocytes, platelets, polyhedrocytes, neutrophil extracellular traps and cholesterol crystals. The composition can be determined by several factors such as the location (i.e. cerebral artery, coronary artery, peripheral artery) and the age of the thrombus.^{20,154} Further, the composition has been shown to determine its responsiveness to treatment such as fibrinolysis and interventional treatments.^{29,155} For example, Maekawa *et al* found that in acute ischaemic stroke intervention, red-cell rich thrombus predicted shorter procedure time with fewer manoeuvres required for successful thrombectomy, conversely, fibrin-rich thrombi were more resistant to mechanical thrombectomy requiring longer procedure times.²⁹ Therefore, insight into extracted thrombus composition in STEMI has the potential to support the development of novel thrombus modification strategies.

Coronary thrombus extracted during STEMI could be characterised and quantified via several methods.

Composition of thrombus has been investigated in a number of ways including: scanning electron microscopy,^{20,156} Laser scanning confocal microscopy,¹⁵⁷ histological staining and immunofluorescence,¹⁵⁸ spectral analysis¹⁵⁹ and visual inspection.¹⁶⁰

Scanning electron microscopy offers high-resolution images of surface and microstructural features of thrombus, revealing fine ultrastructural details (e.g. fibrin network, platelets, RBC morphology) which are not visible with light microscopy. In addition it gives information on spatial relationships between thrombus components.^{154,156} However, this technique requires the possession of an electron microscope and the associated expertise. Furthermore, the thrombus needs to be dehydrated and fixated, which may alter the morphology and makes the tissue unviable for any other further analysis such as histological staining and immunofluorescence.¹⁵⁴ Laser Scanning Confocal Microscopy is a non-destructive technique that produces high-resolution, three-dimensional images of biological specimens using laser light. This technique has been used to gather detailed morphological information on thrombi and can be enhanced with immunofluorescent labelling specific components (e.g. fibrin, platelets, erythrocytes and leukocytes).^{157,161} However, this technique does not have the resolution of electron microscopy, but like electron microscopy requires highly specialised equipment and staff.

Traditional histological staining and examination of thrombi with the addition of immunofluorescent labelling is another effective approach to understanding the composition of thrombi. For example, Staessens *et al* examined 177 thrombi extracted by thrombectomy during acute ischemic stroke, describing a spectrum of RBC- and platelet-rich compositions.¹⁶² Further, they describe two distinct types of thrombus material: red-cell rich/platelet poor (which visually appear red) and platelet rich/red cell poor (which visually appear white). In other studies the presence of macroscopically

“red” thrombus are generally associated with worse clinical outcomes than macroscopically “white” thrombus.^{21-24,160} For example, Yang et al examined 137 thrombi extracted by MA during STEMI, finding that macroscopically red thrombus was associated with significantly worse MACE than white thrombus.²⁴ Therefore, even a simple visual inspection of extracted thrombus, may provide clinically relevant information, without the requirement of highly specialised equipment and staff. Figure 7 demonstrates the typical macroscopic appearance of red and white thrombi, extracted during STEMI.

Building on the knowledge that visual appearance of extracted thrombi reflects composition, Kotronias et al developed a light reflectance method to characterise thrombus composition. They performed hyperspectral imaging on 306 coronary thrombi extracted during STEMI, they found certain spectral signatures correlated with measures of microvascular resistance and microvascular obstruction.¹⁵⁹

As discussed previously, quantity of residual coronary thrombus is a strong independent predictor of outcome in STEMI.⁸⁻¹²

Quantity of extracted thrombus could be measured in a number of ways including: volumetric analysis with CT imaging,^{163,164} weighing thrombus¹⁶⁵ and measuring thrombus area.¹⁶⁶

Karagiannidis et al. conducted micro-computed tomography analysis of 113 thrombi aspirated during STEMI, quantifying thrombus volume, surface area, and density. Increased thrombus volume was independently associated with a higher incidence of distal embolization, no-reflow, residual thrombus, and reduced ST-segment resolution.¹⁶⁴ The drawback of this method of measuring is the requirement for a Micro-CT scanner and the associated expertise.

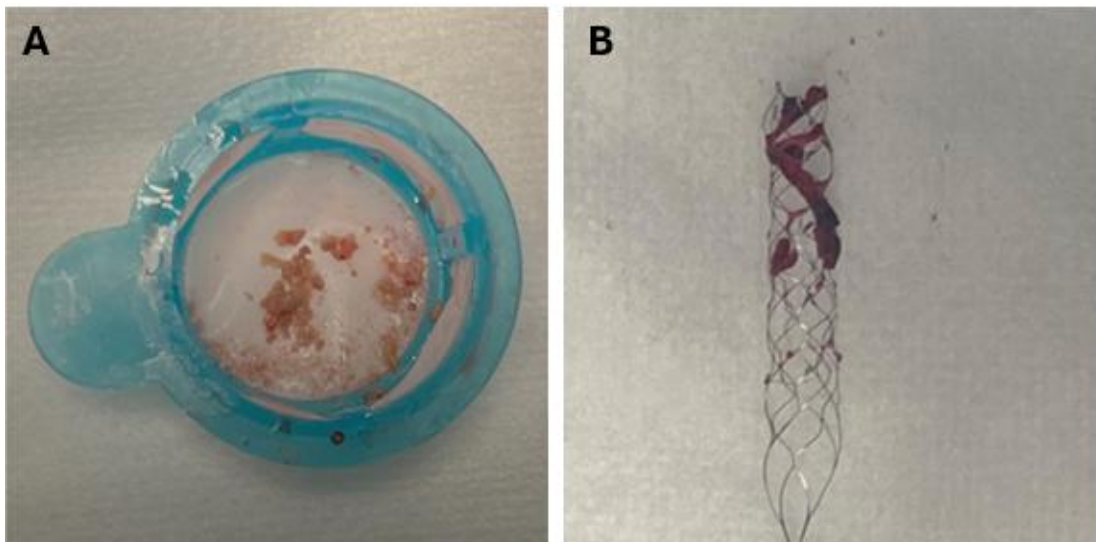


Figure 7. Macroscopic appearance of **A)** white thrombus, extracted using an export manual aspiration catheter, suggestive of a platelets-rich composition and **B)** Red thrombus, extracted using a Solitaire XTM stent-retriever, suggestive of a red cell-rich composition.

Less comprehensively, but more accessibly numerous studies have quantified thrombus by weight (mg)^{165,167,168} or measuring thrombus area (mm²).^{166,169}

For example, Pituk et al examined thrombi extracted by MA in STEMI and found that a high aspirated thrombus weight (>20 mg) was found to be an independent predictor of mortality in STEMI. Fitzgerald et al examined 550 thrombi extracted during stroke intervention and found that clots extracted from larger vessels had a larger thrombus area (mm²) and that the administration of thrombolysis was associated with a smaller extracted clot area.¹⁶⁶ Therefore, both thrombus weight and area of extracted clot appear to be associated with important clinical parameters.

In summary, both the composition and quantity of extracted thrombus provide important clinical information. However, extracted thrombus measurements do not account for thrombus material that bypasses retrieval and lodges distally, contributing to microvascular obstruction and myocardial injury.

Measurement of downstream embolization, microvascular obstruction and myocardial injury

Downstream embolization, microvascular obstruction, and myocardial injury can be evaluated using a range of modalities, including angiographic assessments, invasive and non-invasive coronary flow measurements, cardiac imaging techniques, such as cardiac magnetic resonance imaging (CMR), as well as electrocardiographic and biochemical markers.

Angiographic assessments

Angiographic parameters that can be assessed in STEMI include the visualisation of distal embolisation, the presence or absence of the no reflow phenomenon and scores such as the TIMI (Thrombolysis In Myocardial Infarction) flow grade and myocardial blush grade (MBG).

Angiographic distal embolization refers to filling defects detected in downstream branches during or after PCI, typically caused by dislodged thrombus, figure 8 (A+B) shows examples. The appearance of distal embolization is related to more extensive myocardial damage and a worse prognosis in STEMI.^{170,171} Distal embolization is closely related to the angiographic no reflow phenomenon. Figure 8C shows a case of no reflow, where despite opening the occlusion with a stent in the mid RCA, there is no flow to the distal vessel, as a result of microvascular obstruction. In a sub-analysis of the TOTAL trial, angiographic no reflow in STEMI was associated with worse MACE (a composite of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA Class IV heart failure) and thrombectomy with MA significantly reduced the likelihood of no reflow compared to stenting alone.¹⁷²

The timing and research definition of no reflow are important considerations. How trials define no reflow varies, common definitions range from a more liberal TIMI flow ≤ 2 ,¹⁷³ to a stricter TIMI flow of ≤ 1 , whilst others factor in both TIMI flow and MBG. By definition no reflow can occur any time after an occluded vessel has become recanalized. No reflow is particularly frequent post-stenting and is associated with post-dilation, leading to the common recommendation to avoid/minimise post-dilatation in STEMI.^{174,175} Therefore, studies typically assess no-reflow post PCI, however they often do not specify if and in what proportion of cases, post-dilatation had

occurred.^{173,176} Distal embolization, where thrombus from a plaque rupture or erosion travels distally from a lesion, can occur anytime, but is also associated with PCI dislodging atherothrombotic material. Some studies, such as Fokkema et al looked for embolization that occurred post-PCI,¹⁷⁷ whereas Henriques et al looked for embolization occurring in any of the angiographic images.¹⁷⁰ Both found that distal embolization is associated with a worse prognosis and markers of myocardial perfusion. The limitations of angiographic embolization and no reflow include that they are binary and not quantitative (i.e. they are seen or not seen) and interobserver agreement is poor.¹⁷² Despite these limitations, the clear relationship between angiographic no reflow and distal embolization with hard clinical outcomes make them useful surrogate endpoints in research assessing the impact of thrombus modification techniques in STEMI.

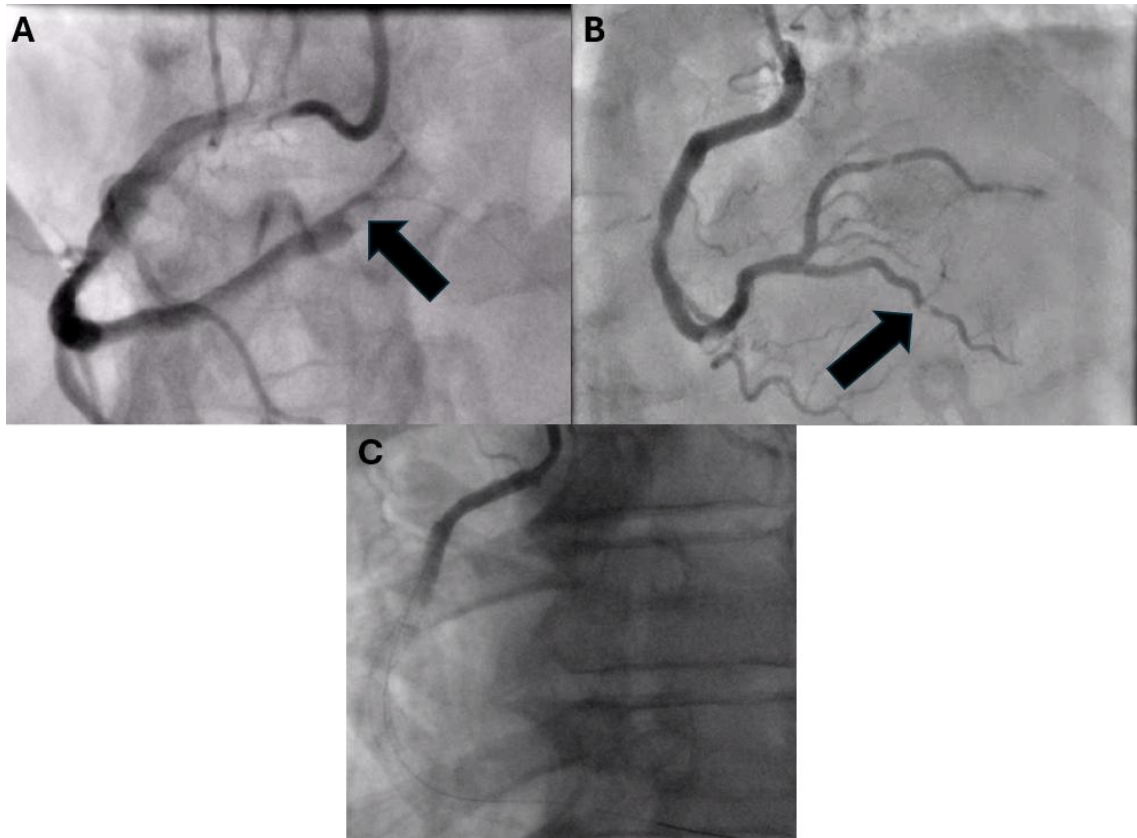


Figure 8. (A + B) angiographic appearances of distal embolization and (C) the no reflow phenomenon. Black arrows point to filling defects indicative of distally embolised thrombi.

TIMI flow grade and MBG are angiographically derived semi-quantitative scores of myocardial perfusion.

TIMI flow grade is an angiographic scale developed to assess epicardial coronary artery flow following thrombolytic therapy or PCI. It is graded visually by the operator on a 0–3 scale. The grades are defined as follows:

Grade 0 = No flow. Complete occlusion (no antegrade flow beyond the point of occlusion).

Grade 1 = Penetration without perfusion. Contrast passes beyond the obstruction but does not opacify the distal coronary bed.

Grade 2 = Partial perfusion. Contrast opacifies the distal vessel bed, but flow is delayed or incomplete compared to a normal artery.

Grade 3 = Full perfusion. Normal antegrade flow filling the distal vessel bed as rapidly as in a normal vessel.^{178,179}

MBG is an angiographic scale designed to assess microvascular perfusion of the myocardium (in contrast to TIMI flow grade, which assesses flow in the major epicardial arteries) after reperfusion therapy in STEMI (figure 9).

MBG is scored visually in the infarct-related artery territory on the angiogram, typically in the final contrast injection after PCI. The grades are defined as follows:

Grade 0 = No myocardial blush or contrast density visible, suggests no tissue-level perfusion

Grade 1 = Minimal blush present but much less than in a non-infarct territory, contrast fails to enter most of the microvascular bed.

Grade 2 = Moderate blush, but less than in an uninvolved (reference) artery, suggests partial microvascular reperfusion.

Grade 3 = Normal blush, contrast density comparable to a non-infarct area with normal clearance, reflects full microvascular perfusion.^{180,181}

Like angiographic embolization and no reflow, TIMI flow grade and MBG post STEMI are strongly associated with hard clinical endpoints. For example, in an analysis by Mehta et al of 3362 STEMI patients, a post PCI TIMI flow grade of ≤ 2 was strongly associated with higher in-hospital and 1-year events, and independently associated with 1-year mortality.¹⁷³ For MBG, Brener et al analysed 2367 STEMIs, finding that a higher MBG (grade 2/3) post PCI independently predicted lower 3-year mortality.¹⁸²

A key limitation of TIMI flow grade and MBG is high interobserver variability.

Corrected TIMI frame count was developed as a more quantitative angiographic method for measuring epicardial coronary flow and has been shown to significantly enhance reproducibility over the traditional TIMI frame count.^{183,184}

In corrected TIMI frame count, the starting point is the first angiographic frame where contrast fully enters the artery's origin and opacifies both vessel walls. The end point is the first frame in which contrast reaches a predefined distal landmark, such as the LAD bifurcation, the distal branch of the LCx, or the posterolateral branch of the RCA. The number of frames between these two points is counted, and for the LAD this value is divided by 1.7 to account for its greater length. Typical normal values are:

RCA = ~20 frames, LCx = ~22 frames and LAD = ~36 raw frames (~21 corrected).¹⁸⁴

However, several variables impact on the accuracy of corrected TIMI frame count including angiogram quality, contrast injection speed, visibility of coronary landmarks and frame rate settings.

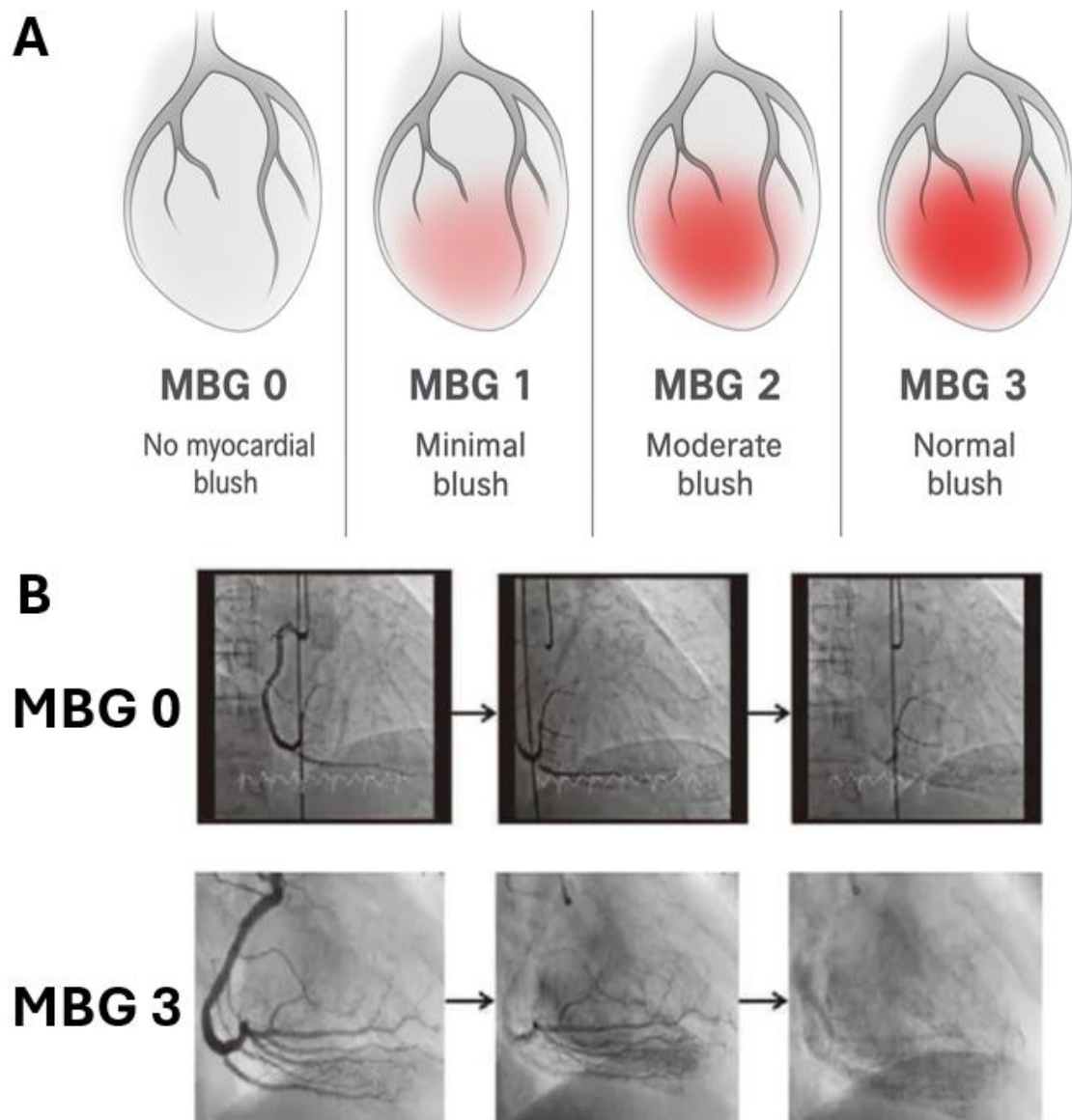


Figure 9. *A) Illustration of the myocardial blush grade (MBG) B) Angiographic examples of MBG 0, showing no blush within the myocardium and MBG 3 showing normal myocardial blush.*

More precise methods for quantifying epicardial and microvascular flow have since been developed in the form of invasive physiological techniques and computational fluid dynamic assessments.

Invasive physiology and computational fluid dynamic assessments

A variety of techniques have been developed to quantify epicardial and microvascular coronary blood flow, ranging from invasive approaches that employ specialised pressure-temperature sensor wires inserted into coronary arteries during angiography to non-invasive methods using computational fluid dynamic analyses of angiograms. A summary of each of the assessments is as follows:

Invasive assessments:

Fractional Flow Reserve (FFR): is a pressure-derived index measured during induced hyperaemia (typically using adenosine), representing the ratio of distal coronary pressure to aortic pressure. It quantifies the physiological significance of an epicardial stenosis, a ratio of <0.8 being considered significant. Techniques that do this without inducing hyperaemia are Instantaneous wave-free ratio (iFR) and Resting full-cycle ratio (RFR), however, these are typically less accurate than FFR due to an unfavourable signal to noise ratio, the cut-off considered abnormal for these tests is <0.89 . As these measurements, focus on significance of an epicardial stenosis, they are mostly used for guiding PCI decisions on a stable epicardial stenosis, for which there is extensive trial data to support this.^{185,186} FFR measures are not used during acute coronary syndrome as unstable microcirculatory changes can affect the reliability of the measurements.

Coronary Flow Reserve (CFR): is a ratio of hyperaemic to resting coronary blood flow, assessed invasively with bolus thermodilution or Doppler. This measurement reflects combined epicardial and microvascular function. An abnormal CFR is considered to be a ratio of <2.0. A CFR of <2.0 is a predictor of poor prognosis and is linked with a higher degree of microvascular obstruction. However, another measure, index of microcirculatory resistance (IMR) is a superior predictor of microvascular obstruction and prognosis in STEMI.^{187,188}

Index of Microcirculatory Resistance (IMR): Is calculated during hyperaemia (usually with adenosine) using a pressure-temperature sensor-tipped coronary wire and bolus thermodilution transit time of saline. It provides a quantitative measure of microvascular resistance, less influenced by epicardial stenosis than CFR. IMR is calculated as:

$$\text{IMR} = \text{distal coronary pressure (Pd)} \times \text{saline transit time (Tmn)}$$

A high IMR post STEMI (≥ 40) predicts worse prognosis, larger infarct size and has shown to be superior for risk stratification post STEMI than CFR, MBG, persistent ST elevation and ischaemic time.^{188,189} Therefore, IMR should be strongly considered as a tool to assess the impact of thrombus modification in STEMI.

Continuous Thermodilution: Uses continuous intracoronary saline infusion via a dedicated catheter combined with a pressure-temperature sensor tipped coronary wire to quantify measures such as absolute coronary flow (Q) and microvascular resistance (R_{μ}). Measurements using continuous thermodilution have been shown to be significantly more reproducible than with bolus thermodilution measures.¹⁹⁰⁻¹⁹² Further, hyperaemia is induced by a higher rate of infused saline, eliminating the need for adenosine administration. As a newer technique, extensive validation of its use in the

context of STEMI is lacking. Some data exist demonstrating the feasibility of the use of continuous thermodilution in the context of STEMI. It is possible that in future continuous thermodilution based measurement of microvascular resistance will emerge as the most reliable physiological technique for quantifying microvascular resistance post STEMI.¹⁹³

The drawbacks of performing invasive coronary physiological studies after STEMI to assess microvascular resistance include prolonged procedure time, the procedural risks associated with introducing a pressure wire into the coronary artery, and the adverse effects of adenosine, such as hypotension and bronchospasm. As an alternative, non-invasive approaches based on computational fluid dynamics have been developed

Non-invasive assessments

Non-invasive approaches to coronary physiology overcome the practical limitations of invasive pressure-wire based techniques during STEMI. Among these, $\text{FFR}_{\text{angio}}$ and $\text{IMR}_{\text{angio}}$ use angiographic images combined with computational fluid dynamics to estimate functional indices of epicardial and microvascular physiology, providing a wire-free, drug-free assessment during routine angiography.

Angiographically derived FFR: refers to a group of techniques that derives FFR values from combined high resolution angiographic images using computational fluid dynamic algorithms. The most commonly used non-invasive angiographic FFR indices developed are vessel FFR (vFFR) (Pie Medical Imaging, Maastricht, the Netherlands); coronary angiography-derived FFR (caFFR) (RainMed Medical Technology, Suzhou, China) and quantitative flow ratio (QFR) (Medis, Leiden, The Netherlands). All three (vFFR, caFFR and QFR) use two orthogonal high frame rate angiographic projections to create a 3D reconstruction of the coronary artery. Pressure loss across the lesion is

then estimated with computational models (Figure 10). The models differ in how they estimate flow and pressure.¹⁹⁴

These angiographically derived FFR systems all show good agreement with invasive FFR.¹⁹⁴ QFR has been the most extensively studied, via the FAVOR (Functional Assessment by Various Flow Reconstructions) series of trials. The FAVOR I trial identified the most accurate model for deriving angiographic QFR,¹⁹⁵ demonstrating both high reproducibility and strong concordance with invasive FFR.¹⁹⁶ The subsequent, larger FAVOR II trials (FAVOR II China and FAVOR II Europe-Japan) further confirmed these findings, showing consistent reproducibility and robust agreement with invasive FFR across diverse populations.^{196,197} Interestingly, a study by Hwang et al showed QFR had significantly better agreement with FFR than invasive iFR.¹⁹⁸

The FAVOR III China trial provided the first outcome data for angiographically derived FFR. The trial was a large, multi-centre, randomized study enrolling 3,825 patients with stable angina or acute coronary syndromes. Patients were randomized to undergo QFR-guided PCI versus angiography-guided PCI. QFR-guided PCI significantly reduced the risk of MACE compared with angiography-guided PCI at 1 year (5.8% vs 8.8%; hazard ratio 0.65, $p=0.004$), supporting the use of angiography-derived physiology in routine practice.¹⁹⁷ However, FAVOR III Europe (a non-inferiority trial) compared QFR guided PCI to invasive FFR guided PCI in acute and chronic coronary syndrome. 2000 patients were randomised, QFR was not found to be non-inferior to FFR. At 1 year MACE was 6.7% for QFR versus 4.2% for FFR; hazard ratio 1.63, (95% CI 1.11–2.41), the non-inferiority margin was not met.

Since the initial submission of this thesis, two large trials supporting the use of angiographic FFR have been presented at the American College of Cardiology conference.

In the ALL RISE trial (Angiography-Derived Fractional Flow Reserve to Guide PCI), 1930 patients with at least one intermediate coronary stenosis on angiography were randomly assigned to physiological assessment with angiography-derived FFR (FFRangio) or a pressure wire based approach. At 1 year, the composite outcome of death, myocardial infarction, or unplanned clinically indicated revascularization occurred in 6.9% of the FFRangio group and 7.1% of the pressure wire group ($p < 0.001$ for noninferiority), demonstrating that FFRangio was noninferior to pressure-wire assessment.¹⁹⁹

In the FAST III trial (Angiography-Based Physiology to Guide Coronary Revascularization), patients with intermediate coronary lesions were randomly assigned to angiography-derived FFR (vFFR) or pressure wire guided revascularization. At 1 year, the composite outcome of death, myocardial infarction, or revascularization occurred in 7.5% of both groups ($p = 0.004$ for noninferiority), demonstrating that vFFR-guided revascularization was noninferior to FFR-guided revascularization.²⁰⁰

These trials support the use of angiographic physiology in this trial, and in retrospect use of vFFR or FFRangio technologies may have been better than QFR.

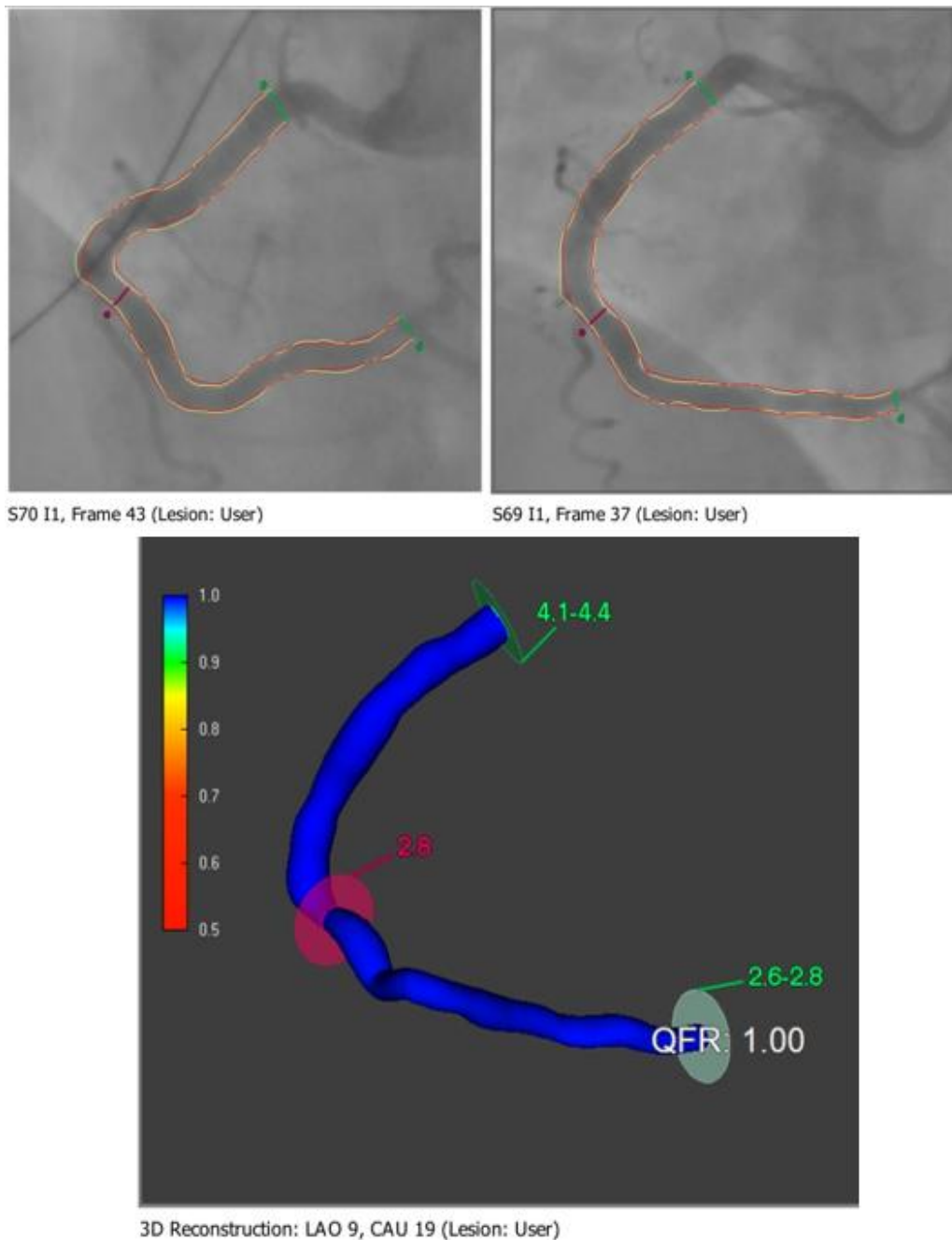


Figure 10. Two high frame rate angiograms $>25^\circ$ apart (above) to create a 3D model of the right coronary artery (below) from which angiographic FFR is derived, in this example, using the Quantitative flow reserve (QFR) software.

Like FFR, angiographic measures of FFR like QFR measure epicardial flow not microvascular resistance/obstruction, therefore may not be useful for assessing the impact of thrombus modification in STEMI. However, QFR forms the basis of a non-invasive measure of microvascular resistance: IMR_{angio} .

Angiographic index of microvascular resistance: Is a computational analogue of IMR, derived from angiography and contrast transit times combined with computational fluid dynamic models, providing a non-invasive estimate of microvascular resistance. Like angiographic FFR, vendors have developed different approaches to estimate angiographic IMR, these include: caIMR (coronary angiography-derived index of microvascular resistance), A-IMR (angio-based index of microcirculatory resistance), Angio-IMR (wire- and adenosine -free microcirculatory resistive index), IMR_{angio} (angiography-derived index of microcirculatory resistance), AccuIMR (Angiography-based index of microcirculatory resistance). Of these IMR_{angio} has been most validated in the context of STEMI.²⁰¹⁻²⁰⁴

IMR_{angio} requires: 1) two orthogonal angiographic views to be input into the QAngio® XA 3D software (Medis, Leiden, the Netherlands) to generate a QFR and 2) the mean arterial pressure at the time of the angiogram. IMR_{angio} is derived using the following formula as per De Maria et al:²⁰¹

$$IMR_{\text{angio}} = Pa \times QFR \times N \text{ frames/fps}$$

Where Pa is mean arterial pressure, N frames is the number of frames it takes contrast to travel from the tip of the guide catheter to the distal vessel and fps is frames per second.

De Maria et al first validated the use of angiography-derived IMR ($\text{IMR}_{\text{angio}}$) in a cohort of 45 STEMI patients. They demonstrated a strong correlation between $\text{IMR}_{\text{angio}}$ and wire-based IMR. They found $\text{IMR}_{\text{angio}}$ is significantly higher in infarct-related arteries compared with non-infarct arteries and in patients with microvascular obstruction (MVO) on CMR. Post-PCI $\text{IMR}_{\text{angio}}$ showed excellent diagnostic accuracy for identifying elevated IMR (AUC 0.96) and good accuracy for detecting MVO (AUC 0.81).²⁰¹ In a subsequent larger study of 568 STEMI patients, the same group found that an elevated $\text{IMR}_{\text{angio}}$ (≥ 40) was associated with a substantially higher rate of early cardiovascular complications compared with values < 40 (18.1% vs 1.4%). Further, $\text{IMR}_{\text{angio}}$ independently predicted early cardiovascular complications and provided incremental prognostic value beyond clinical, angiographic, and echocardiographic parameters. An $\text{IMR}_{\text{angio}} < 40$ demonstrated an excellent negative predictive value (98.6%) for excluding early cardiovascular complications post-STEMI.²⁰²

These studies suggest that $\text{IMR}_{\text{angio}}$ is a promising, non-invasive method for assessing microvascular function in STEMI, with potential utility for risk stratification and guiding discharge strategies.

Overall, $\text{IMR}_{\text{angio}}$ represents an appealing tool for post-STEMI assessment, as it can be performed post-hoc without prolonging procedural time or necessitating the insertion of coronary wires, thereby reducing patient risk. Its demonstrated correlation with microvascular obstruction and clinical outcomes further supports its potential utility in evaluating the impact of thrombus modification in STEMI. However, compared with invasive IMR, $\text{IMR}_{\text{angio}}$ remains less extensively validated, particularly with respect to its predictive value for clinical outcomes.

Cardiac magnetic resonance imaging (CMR) is widely regarded as the gold standard for assessing infarct size and microvascular obstruction in STEMI.^{205,206} This statement is supported by a substantial body of evidence, including validation studies against post-mortem samples²⁰⁷⁻²⁰⁹ and multiple investigations linking CMR-derived measures with clinical outcomes.^{35,210} For instance, Stone et al. conducted a meta-analysis of RCTs involving 1,889 patients in whom infarct size was quantified by CMR following pPCI. They demonstrated that infarct size within one month was strongly associated with all-cause mortality, and at one year with hospitalisation for heart failure.²¹⁰ Similarly, De Waha et al. performed a meta-analysis assessing the association between CMR-derived measurement of MVO with outcomes. They found the presence and extent of MVO within 1 year after pPCI was strongly associated with mortality and heart failure hospitalisation.³⁵ These meta-analyses suggest CMR-derived infarct size and MVO may be robust prognostic endpoints to be used in STEMI trials.

While these findings highlight the prognostic relevance of CMR, several limitations remain. CMR is resource-intensive and often not readily available. Also, as MVO and infarct size are dynamic phenomena, measurement at a consistent time point post STEMI is important. For instance, MVO post STEMI patients typically peaks early, with CMR studies showing a threefold increase in extent within the first 48 hours post-infarction with a maximum burden around day 2, thereafter, MVO decreases.²¹¹ Relevant to our department (where CMR access is limited), obtaining a CMR at a set time point post STEMI would be a major logistical challenge.

Furthermore, although associations of CMR measures with outcomes are consistent, the extent to which CMR-derived infarct size provides incremental prognostic information beyond established clinical, physiological and angiographic predictors is uncertain.

Echocardiography is a cheaper and more readily available tool for ventricular assessment post STEMI. Multiple measures can be taken during an echocardiographic study, the measurement with the most evidence linking it to outcomes is left ventricular ejection fraction (LVEF), however other more precise measurement such as global longitudinal strain have been shown to offer incremental prognostic value.²¹² However, a major drawback of echocardiography is that it cannot characterise the myocardium to determine MVO and infarct size. Further, echocardiographic measurement of ejection fraction is less reproducible and precise than CMR, to quote the electrophysiologist and podcaster John Mandrola “[echocardiographic] assessments of left ventricular ejection fraction are a bit like judges who give harsher sentences before versus after lunch”.²¹³

More recently, with the advent of ultrahigh resolution photon counting CT scanners, techniques have been developed for cardiac tissue characterisation by CT. Enabling measurement of both MVO and infarct size.^{58,214} Theoretical advantages of this approach is that CT offers higher resolution than CMR and can allow simultaneous high definition coronary imaging with coronary flow analysis (which CMR cannot). However, these CT tissue characterisation techniques are currently under development, so are not widely available in clinical practice and research.

Biomarkers

A classical measure of myocardial injury is the serum levels of cardiac biomarkers such as creatine kinase, creatine kinase MB and troponins, with troponin being more specific to myocardial injury and showing superior prognostic value and correlation with infarct size.²¹⁵⁻²¹⁸ After MI, serial troponins with area under the curve (AUC) or a single sample at 72 hours from presentation show reasonable correlations with infarct

size.^{219,220} However, troponin is not a direct measure of necrotic mass, as the rise and fall of levels are influenced by several factor including the success of reperfusion, the extent of microvascular obstruction and renal clearance. Degree of troponin elevation is a predictor of mortality and heart failure in STEMI, but not in elective PCI^{221,222}.

Overall, although cardiac biomarkers provide valuable prognostic information in STEMI, they remain an imperfect measure of myocardial injury owing to several confounders, including sample timing and renal clearance. At our centre, a further limitation is that the high-sensitivity troponin I assay in use has an upper reporting limit of >50,000 ng/L, a threshold frequently exceeded in a large STEMI shortly after revascularisation. This ceiling effect could restrict meaningful comparison between cases.

Electrocardiographic measurement

The electrocardiogram (ECG) provides a wealth of measurable data. In the context of STEMI, ST-segment resolution on 12-lead ECG is a widely used surrogate of successful myocardial reperfusion. ST-segment resolution is typically measured as the percent fall in summed ST-elevation from the pre-reperfusion tracing to a post-reperfusion ECG at ~60-90 minutes. The most common convention for categorising ST-segment resolution is: complete resolution = $\geq 70\%$ (figure 11), partial resolution = 30-70%, and no resolution = $< 30\%$. Greater ST-segment resolution is associated with greater myocardial salvage, smaller infarct size, and better outcomes.^{223,224} Additionally, ECGs are inexpensive and readily available, are essential for the diagnosis of STEMI and can easily be performed at a set time period following revascularization.

An ECG sub-study of the CADILLAC trial (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) evaluated several methods of

quantifying ST-segment resolution in approximately 700 patients with STEMI treated by primary PCI. The analysis demonstrated that incomplete resolution was an independent predictor of 30-day and one-year mortality and reinfarction across most measurement approaches. Importantly, the investigators concluded that a simple method (measuring the maximal residual percentage of ST-elevation on a single post-procedure ECG in the lead with the greatest baseline elevation) was both the most practical and as powerful a predictor of survival and reinfarction as more complex techniques.²²⁴ A further ECG sub-study of the CADILLAC trials found in an elderly subgroup, absent ST-segment resolution independently predicted early adverse events.²²⁵ In both sub-studies the prognostic value of ST-segment resolution persisted even when angiographic epicardial flow had been restored (TIMI flow iii), highlighting ST-segment resolution's role as a surrogate for microvascular reperfusion.

Residual ST-segment elevation post STEMI has been shown to predict the presence of MVO on CMR.^{226,227} However, Husser et al. found that incomplete ST-segment resolution (defined as STR <70%) was not an independent predictor of MVO on CMR, whereas the absolute sum of ST-segment elevation (sum of ST-segment elevation >3 mm at 90 minutes post-PCI) was.²²⁸ Therefore, the classic measure of incomplete ST-segment resolution is not a perfect predictor of MVO.

Advances in artificial intelligence ECG interpretation promise more accurate MVO detection.^{229,230} For example, an AI model developed by Traverse et al, utilised several ECG features to predict MVO on CMR post STEMI, it was found to have 94% specificity and 60% sensitivity for detecting MVO. The model was intentionally optimized for high specificity.²²⁹ Such models are likely to improve in future with larger training sets and advances in model architecture.

Overall, the use of ST-segment resolution is an inexpensive and likely clinically meaningful endpoint for evaluating thrombus modification strategies in STEMI, as it reflects microvascular reperfusion beyond epicardial patency. However, its lack of anatomical specificity and susceptibility to confounding by baseline ECG abnormalities highlight that, while valuable, ST-segment resolution is probably best interpreted alongside complementary imaging or angiographic measures.

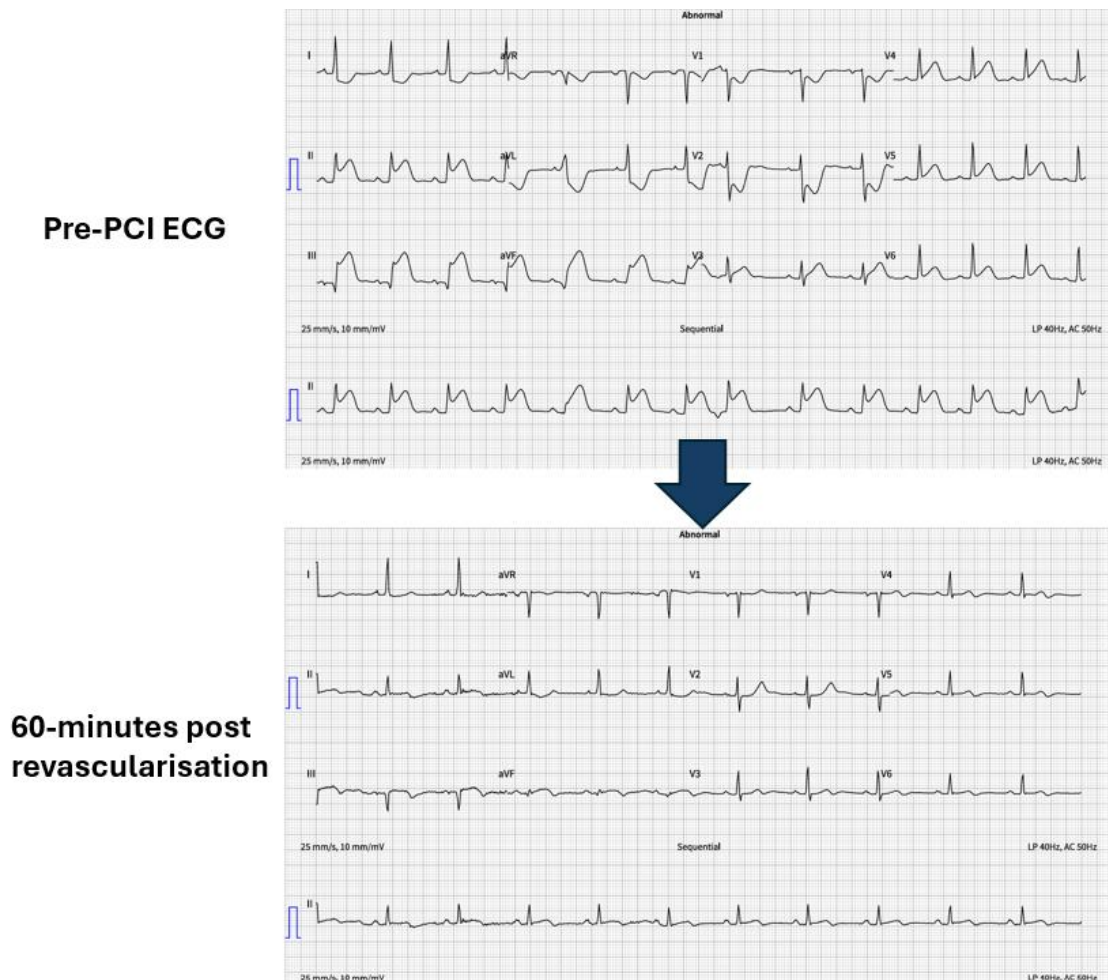


Figure 11. Example of complete ST-segment resolution ($\geq 70\%$) between presenting ECG (above) of an inferior ST-elevation myocardial infarction and 60 minutes post primary percutaneous coronary intervention (below).

Measuring safety and clinical outcomes

For any medical intervention, it is essential that the overall benefit to the patient outweighs the risks. Potential harms must be justified by a reasonable expectation of clinical benefit. Accordingly, in trials evaluating new devices or established devices in new clinical contexts (such as the use of stent-retrievers in the context of STEMI), a rigorous assessment of both risks and benefits is required. To safeguard this principle, legal frameworks and regulatory guidance mandate the reporting of adverse events during clinical trials and provide mechanisms to intervene, including trial suspension or termination, when it is suspected that an intervention is causing unacceptable harm or when its risks exceed its benefits.

Safety

The Solitaire XTM stent-retriever device (Medtronic Inc., Minnesota, USA) has a wealth of safety data in the context of endovascular thrombectomy in acute ischaemic stroke and is therefore licenced in this context. For example, the SWIFT PRIME trial randomised 196 ischaemic stroke patients to SRT with thrombolysis or thrombolysis alone, no serious adverse device related events were detected and no difference in intracranial haemorrhage between groups was observed.⁸³ However, a meta-analysis of seven randomized controlled trials of endovascular therapy (predominantly using stent-retrievers) in acute ischemic stroke found a modestly increased risk of intracranial haemorrhage among a subgroup of patients with very large baseline infarcts, but no overall difference in intracranial haemorrhage rates across the entire study population (n=1,764). Importantly, endovascular therapy was associated with a significant reduction in disability.²³¹

In STEMI, stent-retriever devices are not licenced for use, as no trials had been conducted (prior to this work) in this context. This thesis presents the first trial to assess a stent-retriever device in STEMI, therefore careful safety assessment, systematic reporting of adverse events and engagement with regulatory processes (detailed in Chapter 2 - methods) is mandatory and desirable.

In the context of STEMI a major theoretical safety concern is causing a stroke by translocating thrombus proximally using a thrombectomy device. In the TOTAL trial the rate of stroke (up to 180 days post procedure) was significantly higher in the MA group (compared to stenting alone). However, periprocedural stroke (within 48 hours of the procedure) was not significantly higher in the thrombus aspiration group compared to stenting alone.⁵³ It is unclear what the mechanism would be for aspiration to cause stroke beyond 48 hours of the procedure. Nonetheless, the potential risk of stroke is an important one, so vigilance for this specific complication is essential. In STEMI, stroke is a known but uncommon complication, being reported in 0.25% to 0.5% of cases.²³²⁻
²³⁴ If the peri-procedural stroke rate became higher than this in a STEMI trial with a new device, cessation of the trial should be considered.

Clinical Outcomes

Outcomes in cardiovascular trials typically refer to clinically meaningful events such as all-cause mortality, cardiovascular death, myocardial infarction, repeat revascularization, heart failure, and stroke. The ultimate goal of most cardiovascular interventions is to reduce the incidence of one or more of these events. Large interventional trials often assess these individually or, more commonly, as a composite endpoint, most frequently termed MACE (Major Adverse Cardiac Events) or MACCE

(Major Adverse Cardiac and Cerebrovascular Events). Using a composite of clinically important events increases statistical power, since outcomes such as death or myocardial infarction are relatively infrequent during the timeframe of a clinical trial. There is no universal definition of MACE, the specific components included vary depending on what is considered most relevant in the trial context. Similarly, the duration of follow-up differs between studies according to their design and objectives.

For example, the major MA trials TASTE and TOTAL had different outcomes measures. TASTE measured all-cause mortality at 30 days as the primary endpoint and secondary outcome measures included recurrent myocardial infarction, stent thrombosis, target-vessel revascularization, target-lesion revascularization and a composite MACE endpoint of all-cause mortality or recurrent myocardial infarction at 30 days.⁵⁴ In contrast, the primary outcome for TOTAL was a composite MACE endpoint of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure at 180 days.⁵³ The heterogeneity of these outcome measures between two RCTs examining exactly the same thing (MA versus stenting alone in all comers STEMI) highlights that which outcomes and when they are measured is down to the investigators discretion. There is ongoing debate in the literature about whether MACE outcomes should be standardized across trials or tailored individually for each study, with some authors advocating the use of statistical modelling to design bespoke composite endpoints for specific patient populations and interventions.²³⁵⁻²³⁸

In the context of this small single-centre DM project, there will not be enough power to detect a meaningful signal that differentiates key clinical outcomes such as cardiovascular death and recurrent myocardial infarction between groups. However, outcomes should be systematically recorded on follow-up to allow for an initial exploratory analysis.

Summary

STEMI remains a leading cause of morbidity and mortality worldwide, with outcomes particularly poor in the presence of a LTB. Manual aspiration, the standard thrombus modification strategy, has failed to demonstrate consistent clinical benefit in large RCTs. However, these studies enrolled unselected STEMI populations, many of whom had minimal thrombus burden, potentially diluting any treatment effect. In contrast, SRT, widely adopted in the management of acute ischemic stroke, has consistently demonstrated substantial clinical benefit across multiple RCTs. Given the comparable calibre of large cerebral and coronary arteries, SRT may represent a superior approach to thrombus removal in STEMI patients with LTB.

A rigorous evaluation of thrombus modification strategies in STEMI requires a multidimensional approach encompassing measurement of thrombus burden, distal embolization, microvascular obstruction, myocardial injury, and clinical outcomes, while assessing patient safety. Angiographic TIMI thrombus grading and intravascular optical coherence tomography (OCT) provide measures of thrombus quantity and morphology, with OCT enabling high-resolution volumetric assessment and differentiation between red and white thrombus.

The downstream consequences of thrombus modification can be assessed through a range of modalities: angiographic surrogates (TIMI flow grade, myocardial blush grade, no-reflow), invasive physiological indices (IMR and CFR), non-invasive computational methods (IMRangio and QFR), cardiac imaging (CMR, echocardiography, and emerging photon-counting CT), circulating biomarkers, and electrocardiographic indices such as ST-segment resolution.

In practice, the optimal assessment strategy must balance robustness and clinical relevance against feasibility, local expertise, study power, resource availability, and patient safety. Within this thesis, the principal outcome measures include intracoronary OCT (thrombus burden pre- and post-intervention), IMRangio, TIMI flow grade, myocardial blush grade, angiographic embolization and no reflow, ST-segment resolution, echocardiographic left ventricular ejection fraction, and systematic monitoring for adverse events (see Chapter 2 Methods for details).

This thesis presents the first systematic evaluation of SRT in STEMI. Patients with angiographically confirmed LTB are prospectively randomized in a 1:1:1 design to pPCI alone (standard of care), aspiration thrombectomy-assisted PCI (standard of care), or SRT-assisted PCI (experimental arm). This represents not only the first dedicated thrombus modification trial restricted to STEMI patients with LTB, but also the first to evaluate changes in thrombus burden pre- and post-intervention using OCT and the first to directly compare SRT, MA and stenting-alone in STEMI.

Chapter 2: Methods

Introduction

We hypothesised that SRT in STEMI with LTB would reduce coronary thrombus burden more effectively than MA and improve markers of microvascular resistance and myocardial perfusion, without increasing adverse events compared with standard care (MA-assisted PCI or PCI with stenting alone). This chapter describes the development and implementation of the methods used to test this hypothesis.

The central component of this project was a single-centre, investigator-initiated, pilot, randomised controlled trial. In this chapter the overall trial design is first outlined chronologically, followed by a description of the devices and procedural techniques, including operator training methods using a bench model. The outcome measures are then described and their selection justified, including the development and validation of novel endpoints. Finally, the statistical methods and ethical considerations are presented, including safety reporting and engagement with regulatory bodies.

Trial protocol

Patients admitted with STEMI for pPCI who met the inclusion criteria (Table 5) and none of the exclusion criteria (Table 6) were prospectively enrolled and randomly assigned in a 1:1:1 ratio to one of three treatment arms: (1) PCI with stenting alone, (2) manual aspiration (MA)-assisted PCI, or (3) stent-retriever thrombectomy (SRT)-assisted PCI. A total of 81 participants with angiographic evidence of large thrombus burden were recruited. The trial protocol is outlined in seven stages below and summarised in figure 11.

Stage 1. Recruitment and assent:

Diagnostic angiography in STEMI patients followed standard clinical practice, coronary flow was established by pre-dilation of the occlusion with a 1.5mm or 2.0mm semi-compliant balloon.

At this point eligible patients were identified (tables 5 and 6), particularly ensuring an estimated vessel size $\geq 3.0\text{mm}$ at the site of occlusion and angiographic thrombus score ≥ 4 based on Thrombolysis in Myocardial Infarction (TIMI) thrombus grade.⁶ If eligible the pPCI operator verbally sought assent for participation in a research study, informing the patient they would be randomised to either an experimental technique for removing blood clots from the arteries of the heart or one of our usual practices, which is removing blood clots with a suction tube or stenting alone. It was made clear that if they agreed to participate it could extend the procedure time by 10-15 minutes due to extra measurements and slightly more time required for the new technique. A registered medical practitioner not involved in the research witnessed the assent process acting as a patient advocate, this process was recorded with an emergency consent record (Appendix 1), which was completed by me or the other research fellow, then signed by the assenting operator and advocate at the end of the procedure.

Stage 2. Randomisation

If assent was given, participants were randomized in the catheter laboratory to one of the study arms (figure 11). Randomisation was via sealed brown envelope. A random number generator was used in R studio (randomizeR package), to put numbers 1,2 and 3 (27 of each) in a random order. This order was passed to an assistant who decided which arm 1,2 and 3 represented, then put the words “aspiration”, “retriever” or “stent alone” in sealed numbered envelopes.

Stage 3. Baseline OCT thrombus measurement:

OCT imaging of baseline thrombus burden was performed using Optical Frequency Domain Imaging (OFDI: LUNAWAVE®, Terumo Corporation, Tokyo, Japan).

Operators were not blinded to the images.

Stage 4. Thrombus modification and post-thrombus modification measurements:

Arm 2 (MA-assisted PCI), proceeded according to standard clinical practice with a thrombus aspiration device (Export Catheter, Medtronic, Minnesota, USA). Arm 3 (SRT-assisted PCI), proceeded with the Solitaire X™ stent-retriever device (Medtronic, Minnesota, USA), according to the steps outlined in the “devices, interventions and bench model for operator training” section and figure 13. Unblinded OCT imaging was performed post thrombus modification in arms 2 and 3. Two high-frame rate angiograms were also obtained to allow later angiography-derived coronary physiology measurements to be made.

Stage 5. Stenting and post-stent measurements:

Stenting proceeded as per routine clinical practice in all arms. Unblinded OCT measurements were performed following a successful angiographic PCI result. Two further high frame rate angiograms were obtained to allow later angiography-derived coronary physiology measurements.

Stage 6. Consent:

Full written informed consent was sought from the patients at least 24 hours post procedure (Appendix 2).

Stage 7. 6-month follow-up:

Patients had a scheduled follow-up to gather information, including adverse cardiac and cerebrovascular events (appendix 3).

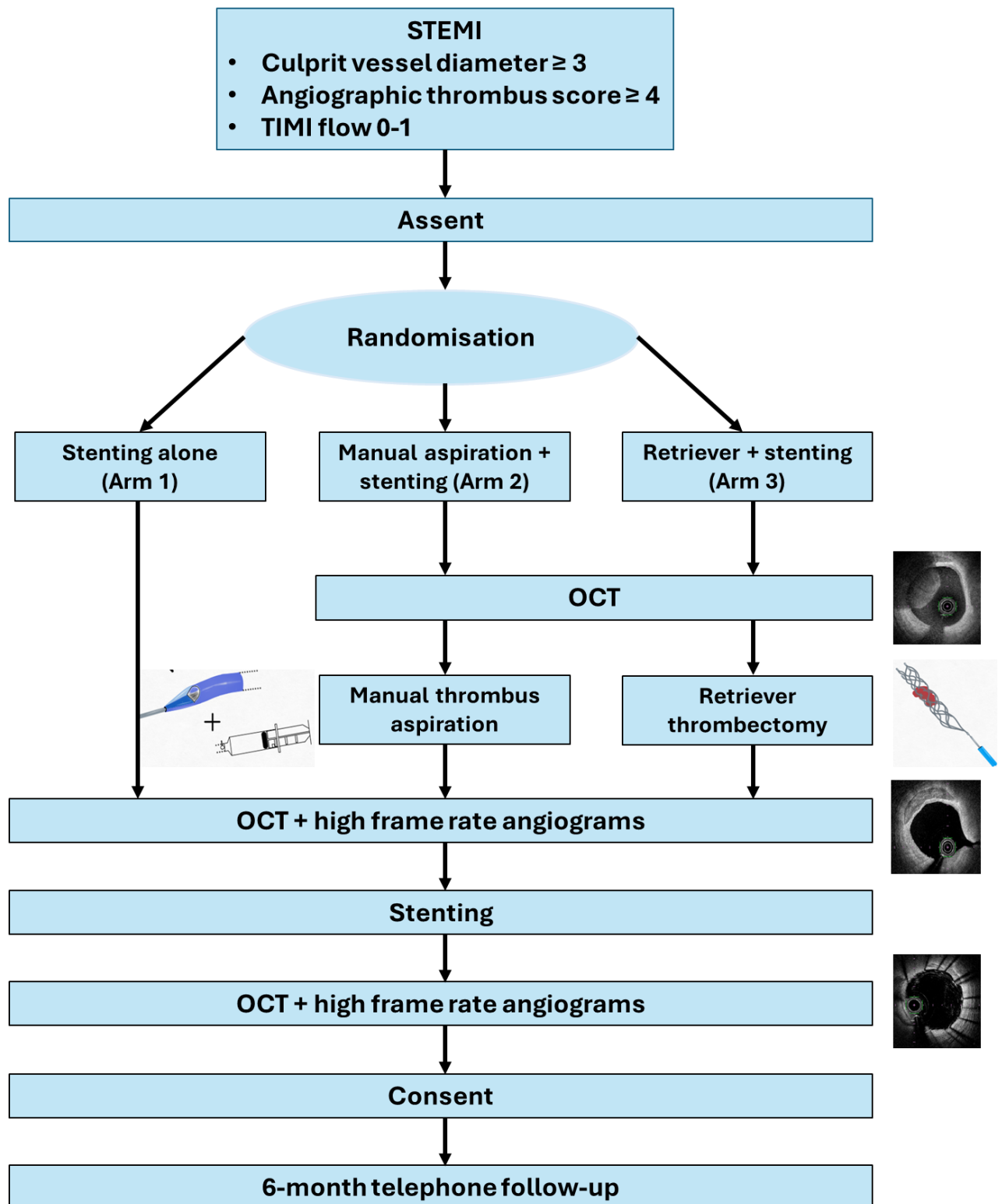


Figure 11. Trial protocol.

Study population

Adults (≥ 18 years) presenting to the catheterisation laboratory with STEMI within 12 hours of symptom onset, who had TIMI flow grade 0-1, showed angiographic evidence of a large thrombus burden after restoration of coronary flow and met inclusion and exclusion criteria (tables 5 and 6), were invited to participate.

Justification for selecting this population are as follows:

The presence of a LTB was a key inclusion criterion. As outlined in Chapter 1, large, randomized trials of MA in STEMI demonstrated no overall clinical benefit. One likely explanation is that these studies recruited unselected, all-comer STEMI populations, which included many patients with little or no thrombus. This may have diluted any potential benefit in those with LTB. Supporting this, both meta-analyses and subgroup analyses suggest a clinical advantage in patients with significant thrombus burden,^{11,12} while an OCT sub-study of the TOTAL trial confirmed that only a minority of patients had a LTB.⁵ Consequently, this project specifically targeted patients with LTB, in whom thrombus modification is most plausibly beneficial.

Patients presenting **more than 12 hours after symptom onset** were excluded in accordance with contemporary evidence and guidelines. The 2023 ESC Guidelines for the Management of Acute Coronary Syndromes define late presenters as STEMI patients presenting beyond 12 hours, noting that primary PCI within 12 hours confers clear clinical benefit.⁴

Only **larger-calibre coronary arteries (>3.0 mm in diameter)** were included, as this is where manual aspiration (MA) technology is currently considered inadequate. As discussed in Chapter 1, one proposed explanation for the limited efficacy of MA is

catheter-vessel mismatch. For example, a 3 mm diameter vessel has a lumen area of approximately 7 mm², whereas a typical MA catheter has a lumen area of only about 1 mm². This mismatch becomes more pronounced as vessel size increases, meaning that the catheter engages only a small proportion of the vessel's cross-sectional area. In contrast, stent-retrievers are designed to expand to the size of the vessel. Focusing on larger vessels therefore targets the setting in which MA may be insufficient and SRT may address an unmet need. However, according to the manufacturer the SRT device used in this project can be used in vessels ranging from 2.0-5.5 mm in diameter (appendix 4).

Patients were excluded from enrolment in conditions where extended procedure time may confer additional risk **including haemodynamic instability** (Defined as Killip class iii or iv and/or bradycardia <40 bpm), **renal failure** and **being pregnant or lactating**.

Patients were excluded in situations where there was likely a higher risk of a vascular complications such as coronary dissection or perforation or devices becoming entrapped, these were: a **heavily calcified culprit vessel** as determined by the operators impression on the angiographic images **bifurcation or left main stem lesions; in stent thrombosis or a prior stent at the site of occlusion; and prior coronary artery bypass grafts; high vessel tortuosity** as defined as ≥ 3 consecutive curvatures 90° to 180° at end diastole in a coronary artery ≥ 3 mm in diameter.²³⁹

Patients with **suspected spontaneous coronary artery dissection** were excluded as use of thrombus modification and stenting (unless there is a persistent occlusion) is generally inappropriate and instrumentation of the coronary artery in this situation is likely to extend the dissection.²⁴⁰

The Solitaire X stent-retriever is made of **Nickel-titanium**, therefore patients with a known **allergy** were excluded.

Unconscious patients or patients who lacked capacity were excluded as they could not provide assent, as per Section 32(9) of the mental capacity act.²⁴¹

Table 5. Inclusion criteria.

Inclusion Criteria
- Male or female ≥ 18 years old - ST elevation myocardial infarction for primary percutaneous coronary intervention - TIMI 0-1 flow at presentation - Angiographic TIMI thrombus grade ≥ 4 - Vessel diameter ≥ 3.0mm at site of occlusion, measure on angiography

Table 6. Exclusion criteria

Exclusion Criteria
- Pregnant or lactating - Hypersensitivity to nickel-titanium - Unconscious at presentation - Late presenter > 12 hours pain to wire time - Killip class iii or iv and/or bradycardia <40 bpm - Known renal failure - High vessel tortuosity* at or prior to the culprit lesion - Heavily calcified vessel - Bifurcation or left main stem lesion - Suspected spontaneous coronary artery dissection - Stent thrombosis - Prior stent at the occlusion site - Prior coronary artery bypass grafts - Prior ST elevation myocardial infarction or cerebrovascular event

* ≥ 3 consecutive curvatures 90° to 180° at end diastole in a coronary artery ≥ 3 mm in diameter²³⁹

Recruitment process

All patients presenting to the John Radcliffe Hospital catheterisation laboratory with an electrocardiogram confirmed STEMI were screened by myself or the other research fellow (RK), 24 hours a day 7 days per week, when pPCI operators involved in the trial were on duty (GDM, JL, AB and KC).

All inclusion and exclusion criteria (Tables 5 and 6) were displayed on laminated sheets in the catheterisation laboratory and reviewed by the research fellow while the operator proceeded with the procedure according to routine practice. Following pre-dilatation of the coronary lesion with a 1.5 mm or 2.0 mm balloon and restoration of coronary flow, the research fellow assessed the final inclusion criteria, including angiographic thrombus burden (TIMI thrombus grade) and estimated vessel diameter at the occlusion site. If the patient met these criteria, the operator or research fellow sought assent, defined here as the patient's affirmative agreement to participate in research in a context where fully informed consent is not immediately feasible (i.e whilst the patient is on the table for a pPCI procedure). Assent requires an active expression of willingness, not merely the absence of objection. Full written informed consent was required to utilise any patient data once the patient had recovered sufficiently to review written information and reflect on participation.

Section 32(9) of the mental capacity refers to a situation where a patient cannot provide informed consent to be enrolled in research or where it is not immediately practical or safe to obtain fully informed written consent for research enrolment. In this situation it advises that: a) there is agreement from a medical practitioner not involved in the research and b) there is approval from the appropriate body (in our case we obtained approval from the Research Ethics Committee).²⁴¹

Regarding a), we ensured a patient advocate not involved in the research observed the assent process. This individual was typically a catheterisation laboratory nurse, physiologist, or radiographer, who was previously trained to monitor the assent process, helping to confirm that communication was clear and that the patient actively agreed to participate without any signs of coercion. If the patient advocate was satisfied with how the assent was conducted, they signed an emergency assent record form after the procedure to document this (Appendix 1).

Our advisory script on how to seek assent was:

“You came in with a heart attack caused by a blocked blood vessel. We have opened the blockage, but you still need a stent to keep the artery open. This hospital also carries out heart attack research. We would like to invite you to take part in a study. In your artery there is a blood clot. At the moment, doctors are not sure of the best way to treat these clots, so this study is designed to help find this out. There are three ways we can treat the clot: use a new experimental device to try and pull it out, use a tube to suck it out, which is a method we use regularly or place a stent over the clot, also a method we use regularly. If you take part, you would be randomly assigned to one of these treatments. The research adds about 10-15 minutes to your procedure. After you have recovered from the procedure, we will give you more detailed written information and check again if you are happy to stay in the study. You can change your mind and withdraw at any time. Would you like to take part in the study, or would you prefer us to continue with the procedure as usual?”

Operators or the research fellow used their own words to deliver this information.

Once assent was given the research fellow opened a sealed numbered brown envelope.

Envelopes were opened sequentially. Within the envelope was a piece of paper with

either “aspiration”, “retriever” or “stent alone” printed on them, indicating which arm the patient was randomised to. The paper was shown to the operator so they knew which technique to proceed with.

After the procedure the patient was given a patient information leaflet, corresponding to the treatment they received (MA, SRT or stent alone) (appendix 5) and told someone would come to talk to them more about the study once they had recovered and have had time to read the leaflet (in at least 24 hours).

After 24 hours, if the patient was well, I approached them to request informed written consent for: 1) use of data already acquired during their pPCI and 2) continued participation in the trial. After introducing myself I confirmed they had read the study information, if not I came back later in the day once they had read the information. I summarised the information provided (purpose of the study and what it would mean for them, primarily allowing us access to their medical records and use of their medical data, including the pictures taken during their procedure for analysis). I informed them that if they agreed to participate, they would be called in 6-months for a follow-up telephone consultation for the purpose of collecting data for the study. If the patient expressed that they wanted to participate in the study they initialled, signed and dated the consent form (appendix 2). A copy of the consent form was left with the patient, a copy was filed in the medical notes and the original was kept in the research file.

It was made clear that the patient could completely or partially withdraw from the study at any time. If a patient wished to withdraw from the study, they were offered the following options:

- **Partial withdrawal:** stopping active follow-up and direct contact, while allowing the research team to continue corresponding with the patient’s general practitioner and accessing medical records for research data collection.

- **Withdrawal with use of existing data:** stopping active follow-up and preventing further access to medical records, but permitting the use of data already collected up to the point of withdrawal in the study analysis.
- **Complete withdrawal:** removing all data collected up to the point of withdrawal so that it was not used in the study analysis, with no further research follow-up or data collection.

If patients withdrew this was recorded in a withdrawal record form, indicating the type of withdrawal (Appendix 6).

Once fully informed written consent was given the participants GP was informed of their recruitment to the study via a standardised letter (appendix 7) and provided with a patient information leaflet (appendix 5).

Thrombus modification devices, interventional techniques and operator training

Three interventional approaches to managing coronary thrombus in STEMI were compared. 1) extraction of coronary thrombus using a stent-retriever followed by stenting, 2) extraction of coronary thrombus using manual aspiration followed by stenting and 3) stenting alone.

Use of MA or stenting-alone are the current status quo for managing coronary thrombus in STEMI with LTB, left to operator discretion.⁴ All the operators in this project were experts in using MA and stent-deployment each with well in excess of a decade of experience. However, prior to the design of this project, all operators were novices at SRT.

The introduction of novel medical devices and techniques such as SRT is associated with a learning curve, during which operators acquire proficiency and procedural

performance stabilises, this is particularly well described in the surgical literature.²⁴²⁻²⁴⁴

This phenomenon can have a significant impact on trial outcomes, particularly in early phases, where higher complication rates, longer procedure times, and reduced efficacy may reflect operator inexperience rather than the intrinsic limitations of the intervention itself.^{242,245} As a result, failure to account for the learning curve risks underestimating the true safety and effectiveness of an intervention. Several approaches have been proposed to mitigate this effect, including the incorporation of run in phases prior to formal trial commencement, minimum competency thresholds for participating doctors, stratification or adjustment of outcomes by operator experience, and the use of advanced statistical modelling to explicitly account for learning effects.^{243,244,246-251} It was therefore essential to consider the potential impact of operator inexperience with SRT and how this may be mitigated.

Here, I describe the two devices used for thrombus modification: MA and stent-retriever. Then describe our standardised technique for SRT and the bench model used to: 1) train operators in SRT, aiming to mitigate the impact of a learning curve and 2) take initial intravascular images post SRT and MA to allow a descriptive analysis and perhaps gain mechanistic insights into SRT and MA.

Stent-retriever (investigational device)

The Solitaire™ X used in this project is a self-expanding, retrievable stent-retriever designed for the mechanical removal of intravascular thrombus. It is CE-marked for use in the endovascular treatment of acute ischaemic stroke, where it has been shown to restore perfusion by physically engaging and extracting occlusive thrombus from large intracranial arteries.^{82,83} The device operates by expanding within the target vessel, embedding its struts into the thrombus, and subsequently removing the clot upon

retrieval, thereby re-establishing distal blood flow. Radiopaque markers along the working length improve fluoroscopic visualisation and facilitate precise deployment. A range of device diameters and lengths are available, making it adaptable to a spectrum of vessel sizes. It is licensed in ischaemic stroke for use in vessels between 2.0 and 5.5 mm in diameter at the site of occlusion (appendix 4). No stent-retriever devices, including the Solitaire™ X are currently licensed for use in STEMI. Figures 5 and 7b show expanded stent-retrievers entangled with thrombus, extracted from a coronary artery during a STEMI.

Manual aspiration catheter (comparator)

The Export™ aspiration catheter used in this project is a MA catheter designed for the removal of intravascular thrombus during PCI. It is clinically approved and CE-marked for use in patients with STEMI to facilitate reperfusion by reducing thrombus burden. The device functions by advancing a flexible catheter over a guidewire to the site of the occlusion, where negative pressure is applied using a dedicated aspiration syringe. This generates suction within the catheter lumen, enabling mechanical aspiration and removal of intraluminal thrombus. The Export™ catheter is widely used in clinical practice in selected cases, all operators in this project have extensive experience using this device.

Stent-retriever thrombectomy technique

The standardised SRT technique used in this project is illustrated in figure 13. SRT is routinely employed in stroke intervention. A well-established approach is the Stent-retriever Assisted Vacuum-locked Extraction (SAVE) technique, which involves advancing a stent-retriever through a microcatheter over a guidewire, withdrawing the

guidewire, and subsequently retrieving the stent-retriever with concurrent aspiration using a specialised neuro-aspiration catheter.²⁵²

Spirito *et al* adapted this technique for coronary intervention using standard, widely available equipment. In lieu of the neuro-aspiration catheter, a guide-extension catheter was employed, and a second ‘safety wire’ was positioned to maintain continuous coronary access. This modification ensured that access was preserved throughout the procedure and enabled prompt stent delivery following thrombectomy (a step not required in stroke intervention).¹¹⁵

Our approach closely follows the method described by Spirito et al¹¹⁵. The technique involves the following steps (Figure 13):

1. A workhorse coronary wire, such as a Sion® Blue (Asahi Intecc, Seto, Japan), is advanced through the thrombotic lesion into the coronary artery.
2. A 6 Fr guide extension catheter, typically a Guidezilla™ (Boston Scientific Corporation, Minnesota, USA), is advanced over the coronary wire into the proximal vessel.
3. A second workhorse wire is then positioned in the distal vessel.
4. A microcatheter, specifically the Phenom™ (Medtronic Inc., Minnesota, USA), is advanced over the first wire through the thrombotic lesion, with its tip placed just distal to the lesion.
5. The wire within the microcatheter is removed.
6. A stent-retriever (Solitaire™ X, Medtronic Inc., Minnesota, USA) is introduced through the microcatheter. The radiopaque tip of the stent-retriever is carefully aligned with the radiopaque tip of the microcatheter to ensure deployment within the thrombus.

7. The microcatheter is withdrawn while gentle forward pressure is applied to the stent-retriever, allowing it to expand in situ. Once fully deployed, the stent-retriever is left expanded for three minutes.
8. After three minutes, suction is applied at the proximal end of the guiding catheter using VacLok® syringes (Merit Medical Systems, Inc., Utah, USA). Under suction, the stent-retriever is withdrawn into the guide extension catheter, and the guide extension with the stent-retriever is then removed from the patient.
9. The retrieved stent-retriever is rinsed with saline and inspected for captured thrombus.

This process may be repeated up to two additional times, in accordance with the trial protocol.

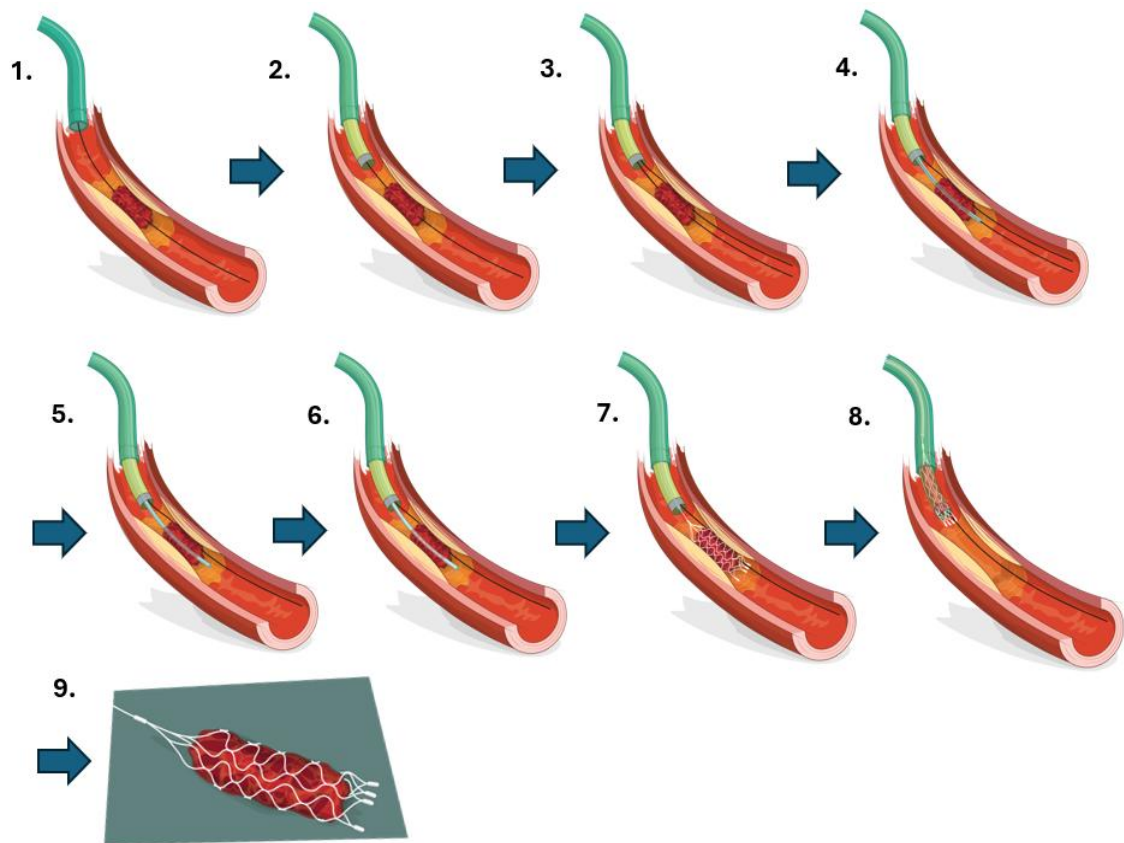


Figure 13: Standardised thrombectomy technique with a stent-retriever device used in this project, based on Spirito et al.¹¹⁵ 1. A guide catheter is engaged with the coronary artery, with a coronary wire placed through the thrombotic lesion. 2. A guide extension catheter is advanced over the wire into the proximal vessel. 3. A second safety-wire is advanced into the distal coronary. 4. A microcatheter is advanced over the first wire so it crosses the thrombotic lesion. 5. The wire inside the microcatheter is removed. 6. A stent-retriever is advanced to the tip of the microcatheter, so it is aligned with the thrombotic lesion. 7. The microcatheter is withdrawn, unsheathing the stent-retriever, allowing it to expand. 8. The stent-retriever is withdrawn into the guide extension catheter and both are removed together whilst suction is applied using aspiration syringes at the proximal end of the guide catheter. 9. The extracted thrombus is inspected.

Images in developed in collaboration with Sam Thomas of the VPmed group, reproduced here with their permission.

Operator training and the bench model

To minimise the influence of the learning curve on trial outcomes, operators were trained in SRT using a transparent silicone coronary bench model (figure 14). Initial instruction was provided by a Medtronic product specialist. Thereafter, operators had unrestricted access to the bench model and all necessary equipment for practice, including guide catheters, coronary wires, microcatheters, guide extension catheters, stent-retrievers and simulated thrombus (butter or jam). Most operators reported that the learning curve was minimal, as the SRT technique relies on skills already familiar to interventional cardiologists, such as coronary wire manipulation, microcatheter handling, and guide extension use.

A secondary use of the coronary bench model was to examine the comparative impact of SRT and MA on the simulated thrombi using OCT imaging. See a short descriptive analysis of this in chapter 3.

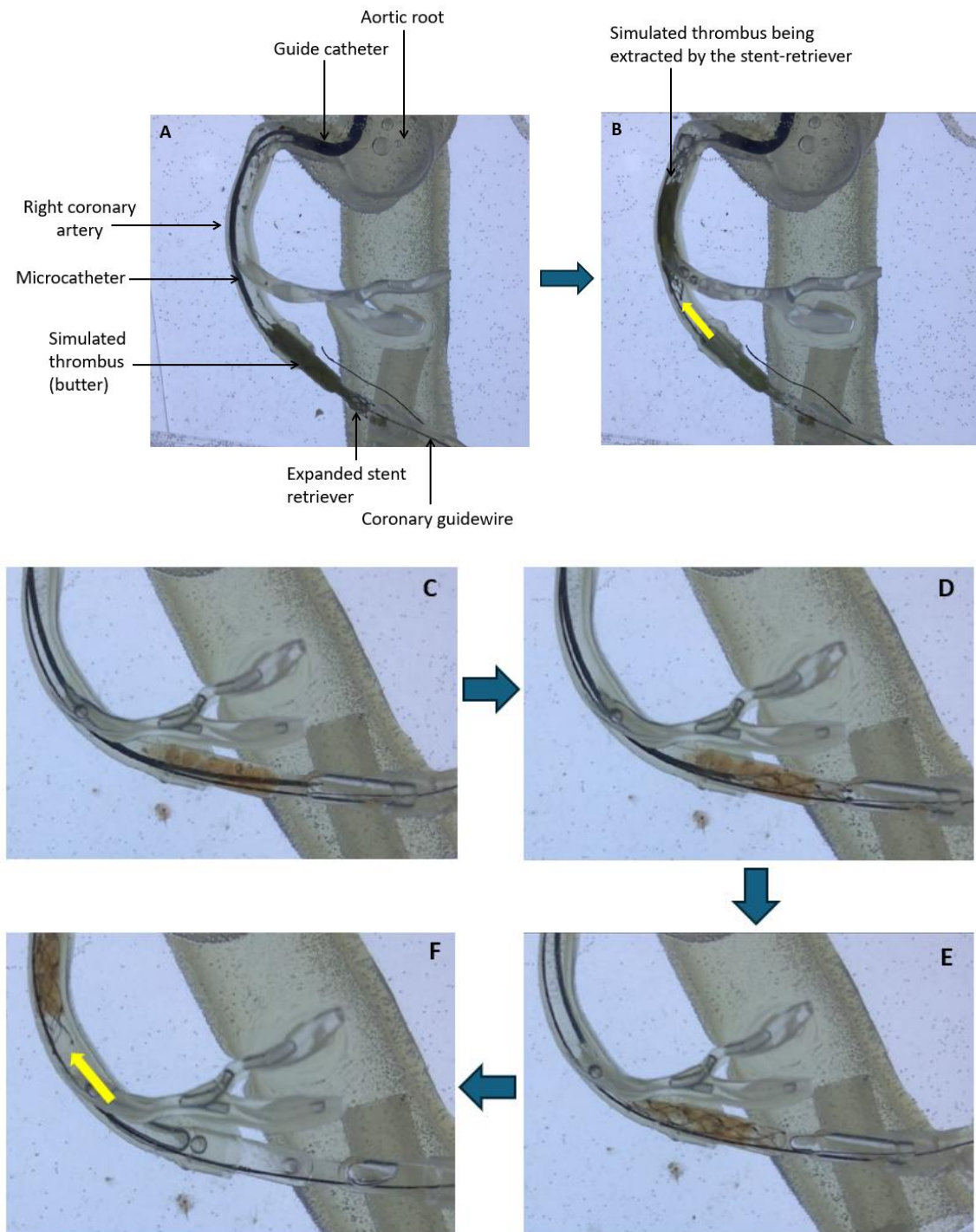


Figure 14: Photographs of the coronary bench model being used for stent-retriever thrombectomy training. **A.** Shows an expanded stent retriever (mostly obscured by the butter being used as simulated thrombus), the microcatheter retracted back on the stent retriever wire and a safety wire. **B.** Shows the simulated thrombus being retrieved from coronary model. **C.** Shows the tip of the microcatheter through the (jam) simulated thrombus, with the collapsed stent-retriever inside the microcatheter. **D.** Shows the stent-retriever expanding as the microcatheter is retracted. **E.** Shows the fully expanded stent-retriever in the simulated thrombus. **F.** Shows the simulated thrombus entangled in the stent-retriever being removed from the model artery.

Outcome measures

As outlined in Chapter 1, evaluating the efficacy of SRT and MA is multi-faceted. The objective of these techniques is thrombus extraction, with the intention of reducing distal embolization, thereby minimising MVO and ultimately limiting myocardial injury. By reducing myocardial injury, the ultimate aim is to improve long-term outcomes and decrease the risk of adverse events such as heart failure and death. Further, all interventional strategies carry inherent risk, which must remain within acceptable limits to ensure a net clinical benefit.

Accordingly, outcome measures should align as closely as possible with these therapeutic goals, encompassing thrombus removal, distal embolization, MVO, myocardial injury, clinical outcomes, and procedural safety. However, the choice of optimal outcome measures must be balanced against several factors: feasibility, patient acceptability (i.e. avoiding undue distress or discomfort), safety (i.e. avoiding measurements that may introduce significant complications), resource availability (i.e. access to advanced modalities such as cardiac MRI or electron microscopy) and statistical power. In this context (a pilot RCT conducted for a doctoral thesis), will be inherently limited in both sample size and duration of follow-up. Consequently, it will lack sufficient power to detect effects on relatively infrequent but clinically important outcomes, such as death, hospitalisation for heart failure, or recurrent myocardial infarction.

With local expertise, resources and scope of this project in mind the following measurement tools were chosen: OCT (for various metrics of thrombus quantity, stent expansion and apposition), computational fluid dynamic software (ultimately to allow calculation of angiographic index of microvascular resistance), angiographic scores (TIMI flow, myocardial blush grade) and features (visible embolization, no reflow),

Serial ECGs (ST-segment resolution), echocardiography (to derive left ventricular ejection fraction), troponin and systematic safety monitoring.

Specific outcome measures are detailed below and summarised in table 7.

Table 7. *Measurement tools, outcome measures and measurement time points.*

Measurement tool	Measurements	Timepoint of measurement
Optical coherence tomography (OCT)	1) Thrombus burden (% of lumen volume containing thrombus)	a) Baseline (after initial coronary flow obtained with balloon) b) Post-thrombus modification (in the MA and SRT arms only) c) Post stenting
	2) Thrombus volume (mm ³)	a) Baseline (after initial coronary flow obtained with balloon) b) Post-thrombus modification (in the MA and SRT arms only) c) Post stenting
	3) Change in thrombus burden (Δ burden %)	Difference between a) baseline and b) post-thrombus modification in matched coronary segments
	3) Change in thrombus volume (Δ volume mm ³)	Difference between a) baseline and b) post-thrombus modification in matched coronary segments
	4) Stent expansion	Post stenting
	5) Stent apposition	Post stenting
Computational fluid dynamic assessment of angiographic flow	1) Angiographic Index of Microvascular resistance (IMRangio)	a) Pre-stenting b) Post-stenting
	2) Change in microvascular resistance pre-to post stenting	Difference between a) pre-stent and b) post-stent
ECG	1) ST-segment resolution	Difference between pre-PCI ECG and post-PCI ECG
Visual assessment of angiograms	1) No reflow present or absent	Post-stenting (after post-dilatation)
	2) Distal embolisation present or absent	Any time throughout procedure
	3) TIMI flow grade	Post stenting (after post-dilatation)
Safety assessments	1) Target vessel complications	a) Intraprocedural + peri-procedure
	2) Adverse events	b) On discharge
		c) 6 months
Echocardiogram	1) Left ventricular ejection fraction (LVEF)	a) post procedure b) 6 months
	2) Change in LVEF from post procedure to 6 months	Difference between a) post procedure and b) 6 months
Troponin	1) peak post procedure troponin	Within 72 hours of procedure
Extracted thrombus photography	1) Visual categorisation of thrombus type	Post procedure

Thrombus volume and burden

Thrombus volume (TVol, mm³) and thrombus burden (TB, expressed as a percentage of the lumen volume) was quantified on OCT imaging in line with the methods described by Kajander et al, detailed below.¹⁴⁸ This was done at three time points: baseline, post thrombus modification (MA and SRT arms only), and post stenting. Segmenting was performed using the QIVUSTM software (Medis Medical Imaging, Leiden, Netherlands), blinded to randomized allocation (Figure 14).

Changes in thrombus volume from baseline to post thrombus modification were calculated for the MA and SRT arms.

For each OCT slice containing thrombus, the lumen area (LA) and thrombus area (TA) were segmented using QIVUSTM. The flow area (FA, mm²) was defined as the lumen area minus the thrombus area (LA – TA) (Figure 14).

For each OCT run, total thrombus volume (TVol, mm³) and lumen volume (LVol, mm³) were calculated by integrating the thrombus area (TA) and lumen area (LA) along the length of the region of interest (ROI). The length of the ROI was calculated by computing slice thickness for each run. OCT Pullback speed was standardized at 40 mm/s.

Thrombus burden (TB, %) was calculated by dividing the (Tvol, mm³) by the LVol, mm³.

Change in thrombus volume (Δ TVol, mm³) and thrombus burden (Δ TB, %) were calculated as follows:

$$\Delta\text{TVol, mm}^3 = \text{pre-modification Tvol} - \text{post modification Tvol}$$

$\Delta TB\% = (\text{pre-modification TVol} / \text{Pre-modification LVol}) - (\text{post modification TVol} / \text{post modification LVol})$.

Pre- and post-thrombus modification OCT runs were co-registered using anatomical landmarks (e.g. side branches, calcification, or vessel segments) to ensure that thrombus quantification was performed within the same region of interest (ROI) before and after modification. The ROI was defined by first identifying, across the two runs, the segment with the greatest longitudinal extent of thrombus. This segment was then used to guide matching in the corresponding run, ensuring that the same vessel segment was segmented and analysed.

Summary of pre-stenting OCT-derived measurements:

Per OCT slice:

- Thrombus area (TA, mm²)
- Lumen area (LA, mm²)
- Flow area (FA, mm²)

Per OCT run:

- Thrombus volume (TVol, mm³)
- Thrombus burden (TB, %)

For comparison of pre- and post-thrombus modification runs:

- Change in thrombus volume ($\Delta TVol$, mm³)
- Change in thrombus burden (ΔTB , %)

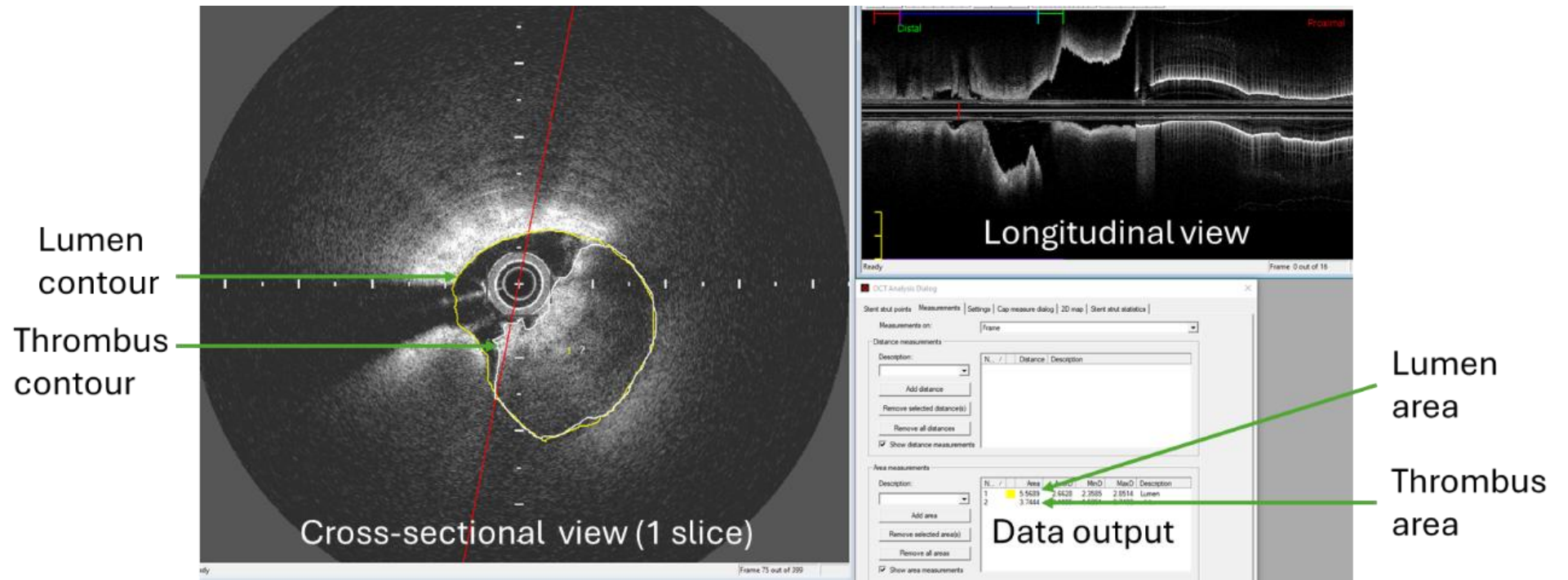
For post-stenting OCT runs, stent struts were identified, and any residual or prolapsed thrombus within the stented segment was segmented. The lumen area (LA) was defined as the area bounded by the stent struts, and residual thrombus area was measured for each cross-sectional slice (mm²). Thrombus volume (TVol) and thrombus burden (TB) were then calculated as described above.

In addition, the following stent-related parameters were assessed:

- **Minimum stent area (MSA, mm²):** defined as the frame with the smallest in-stent lumen area.²³⁹
- **Malapposition:** defined as struts not in contact with the vessel wall; significant malapposition was defined as strut separation >0.3 mm from the vessel wall extending over >3 mm in length.^{253,254}
- **Underexpansion:** defined as an MSA <80% of the reference lumen area (calculated as the mean of the proximal and distal reference segments) and/or an absolute MSA <4.5 mm².^{149,239}
- **Stent edge dissection:** defined as a disruption of the arterial lumen surface adjacent to the stent edge, visible in at least two consecutive frames.^{253,255}

To maximise the accuracy of OCT segmentation, all segmentations were reviewed by a panel of three cardiology registrars experienced in OCT interpretation (JW, RK, and SA). Frames with contentious segmentation were flagged and subsequently reviewed by a cardiology consultant with extensive OCT expertise (GDM). Consultant reviews were conducted in a conference room, with segmentations projected onto a large screen and analysed using QIVUS™ software. Any required adjustments were made live during the review.

Figure 14: Example of thrombus and lumen measurements in a single frame made on the QIVUS™ software.



Validation of the Δ thrombus volume measurement

No prior studies had examined changes in intracoronary thrombus quantity before and after thrombus modification using OCT as an indicator of thrombus extraction efficacy. As this was the first application of measuring change in thrombus volume (Δ TVol, mm^3) from pre- to post-modification, validation of this approach was warranted.

Because Δ TVol was designed as an estimate of the quantity of thrombus extracted, the chosen method of validation was to correlate Δ TVol with a direct measure of actual extracted thrombus. Extracted thrombi were systematically photographed using a standardized setup with an IMEC Snapscan Hyperspectral imaging camera (IMEC, Leuven, Belgium) (Figure 15). Thrombus area (mm^2) was selected as the metric of extracted thrombus quantity as this was the only feasible measurement using the standardised thrombus photographs.

Thrombus area measurements were performed using the open-source ImageJ software (National Institutes of Health, Bethesda, Maryland, USA). Images were calibrated using device-specific markers (Figures 16A and 17A). For stent-retriever cases, calibration was based on the known 31 mm distance between the outer edges of the proximal and distal radiopaque markers (Figure 16A). For manual aspiration cases, the central diameter of the inner rim of the thrombus collection basket was used for calibration (Figure 17A). Following calibration, visible thrombus was segmented for area measurement (Figures 16B and 17B).

Finally, measured area of the extracted thrombus (mm^2) was correlated with Δ TVol (mm^3) on OCT using Spearman's rank correlation for SRT and MA, respectively.

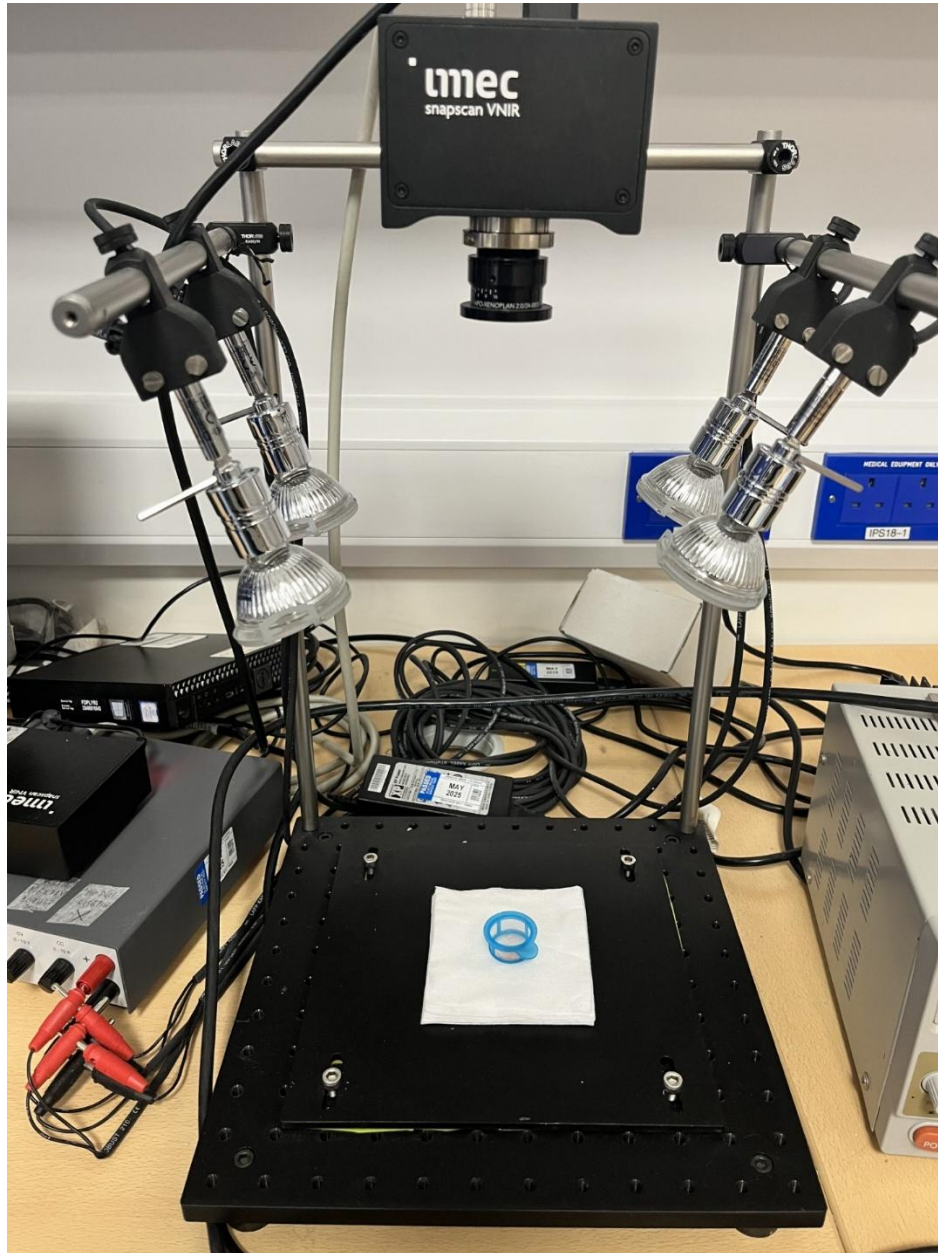


Figure 15: Camera rig for standardised photography of extracted thrombi, using an IMEC Snapscan Hyperspectral imaging camera (IMEC, Leuven, Belgium).

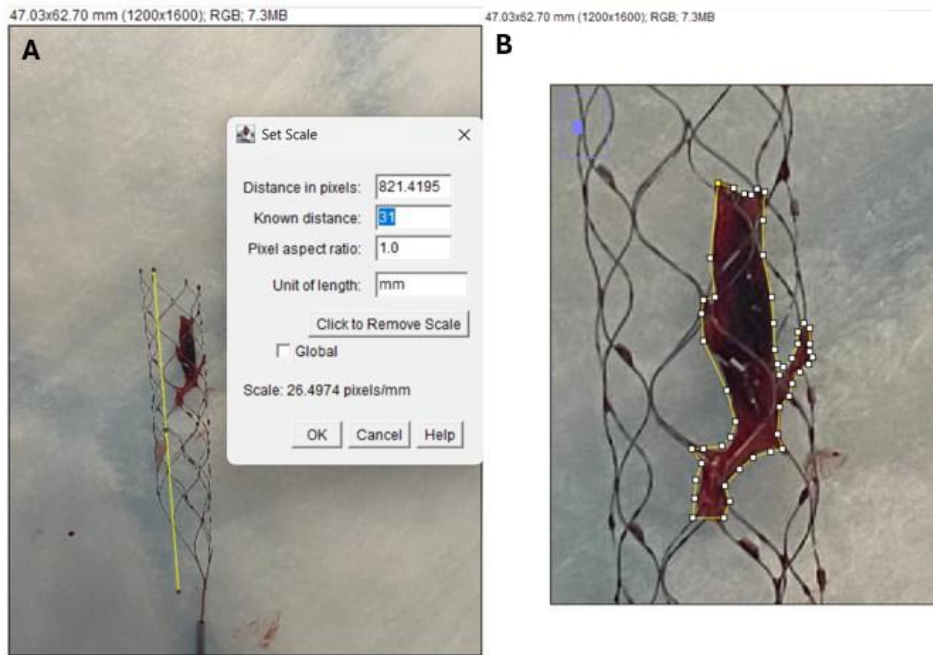


Figure 16: Thrombus area measurement on a stent-retriever using ImageJ. **A.** Image calibration was performed using the known 31 mm distance between the proximal and distal radiopaque markers on the device. **B.** The visible thrombus was segmented, and the thrombus area was quantified (mm^2).

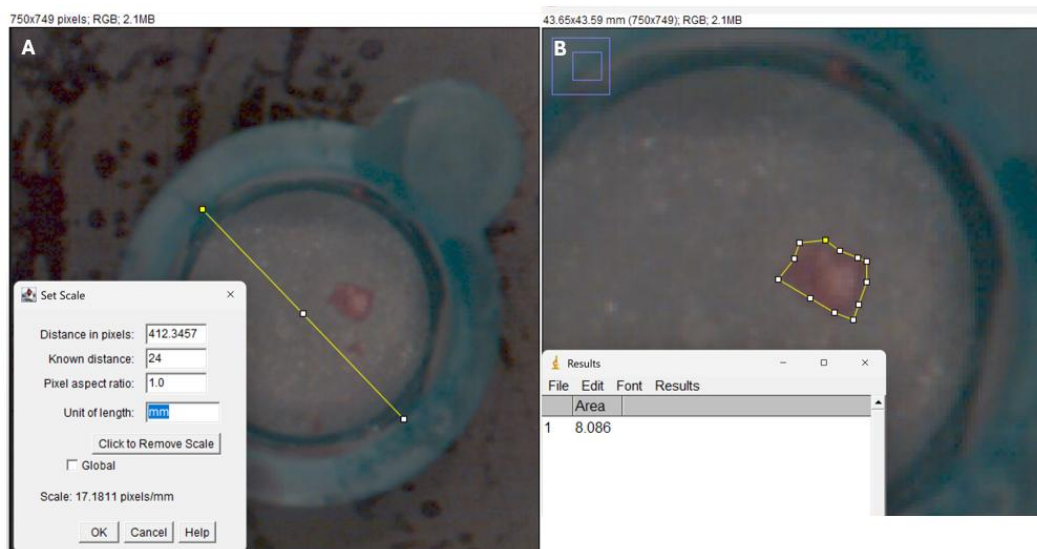


Figure 17: Thrombus area measurement of aspirated thrombus using ImageJ. **A.** Image calibration was performed using the known 24 mm diameter of the internal rim of the aspiration catheter's collection basket. **B.** The visible thrombus was segmented, and the thrombus area was quantified (mm^2).

Attempted development of a machine learning model for automated thrombus segmentation

An attempt was made to automate segmentation of coronary thrombus on OCT, ultimately this failed, and segmentations were performed manually. The rationale and approach to this is briefly explained here.

Intravascular OCT provides PCI operators an abundance of detailed information on vessel and lesion characteristics, it's use has been shown to enhance patient outcomes in several contexts.²⁵⁶ OCT generates particularly clear images of intravascular thrombus, allowing for accurate measurement of thrombus volume.¹⁴⁸

Machine learning (ML) algorithms have been developed to make automated vessel measurements on OCT. The clinically available Ultron 2.0™ software (Abbott Laboratories, Illinois, USA) primarily highlights calcified coronary plaques and makes automated vessels size measurements. More recently the Cardiovascular Innovative Instrument and Intelligent Computing (CIIC) lab at Shanghai Jiao Tong University developed models that automatically characterize, annotate and quantify various phenotypes of coronary plaque on OCT.²⁵⁷ However, no ML algorithms existed that automatically identify and quantify intracoronary thrombus.

Manual measurement of intravascular thrombus (figure 14) is an onerous task. For each OCT run up to 600 image slices are generated. In this project we recruited 81 patients with 2-3 runs per participant (2 runs in the stent only arm, 3 runs in the SRT and MA arms). This generates 216 OCT runs containing up to 129600 image slices. Therefore, we initially set out to automate thrombus segmentation process in collaboration with a computer scientist with experience in developing ML models for segmenting coronary plaque on OCT (MC). The key aims of automating this process were to:

- 1) Reduce time spent on manual thrombus measurements.
- 2) Make measurements consistent and repeatable, avoiding human error and bias.

We generated initial ML models trained on OCT data that had been collected previously for research.²⁵⁸

ML models for detecting intracoronary thrombus on OCT were developed by a computer scientist (MC).²⁵⁸ Previously collected OCT images (395 OCT pullbacks comprising a total of 5649 frames) were manually segmented by a software engineer (MC) and cardiology trainees (SA, JW) (figure 14). This data was used as the ground truth to train ML models aiming to identify and quantify intracoronary thrombus. The ML architecture used was state of the art dual-coordinate cross-attention transformer network (DCCAT), described in Chu et al.²⁵⁸ This is a specialized type of neural network architecture, often highly effective for tasks such as accurate medical image segmentation.

OCT runs from the first 35 cases recruited to our study were used as the validation cohort for the ML models. However, the models did not achieve sufficient accuracy to warrant their use in this research (see Results, Chapter 3). Consequently, all OCT segmentations analysed for this project were performed manually.

As detailed in Chapter 1, restoration of epicardial coronary flow with pPCI in STEMI often fails to achieve optimal myocardial perfusion, in part due to distal thrombus embolisation leading to microvascular obstruction (MVO).²⁰⁶ Reliable assessment of microvascular function is therefore essential when evaluating thrombus modification techniques in STEMI.

The index of microcirculatory resistance (IMR) is a validated, quantitative measure of microvascular function and a predictor of infarct size and prognosis in STEMI.¹⁸⁸

However, its traditional measurement requires pressure wire insertion into the coronary artery and pharmacological hyperaemia, which adds time and risk in the acute setting.

Computational fluid dynamic modelling now permits post-hoc calculation of IMR directly from routine angiography (IMR_{angio}), providing a practical, wire-free alternative.

Our group previously validated the use of IMR_{angio} in STEMI, demonstrating a strong correlation with invasive IMR and showing that elevated IMR_{angio} (>40) is associated with early cardiovascular complications in STEMI.^{201,202} Given its non-invasive nature, validation in STEMI, and our group's expertise, IMR_{angio} was selected as a key outcome measure for this project.

The starting point for deriving IMR_{angio} was to measure Quantitative Flow Ratio (QFR) using QAngio® XA 3D software (Medis, Leiden, The Netherlands) (Figure 18). QFR is a non-invasive, angiography-based method for estimating the physiological significance of a coronary artery stenosis. It uses coronary angiograms to reconstruct a 3D model of the vessel, then applies computational fluid dynamics to simulate blood flow. From this,

it derives the pressure gradient along an epicardial coronary vessel, closely approximating invasive FFR.^{196,197,259-262}

For maximal accuracy in constructing the coronary model, QFR was derived from two high frame rate angiograms (15 frames per second, compared with the standard 7.5 frames per second) of the same vessel acquired at least 25° apart.²⁶³ High frame rate angiograms were obtained at two time points, pre-stenting and post-stenting (Figure 11). Invasive blood pressure was recorded immediately before each angiogram was taken to permit later IMR_{angio} calculation. QFR was then computed from the 3D model generated using QAngio® XA 3D QFR, based on lumen contours and contrast flow velocity (Figure 18). QFR analysis was performed offline, with the reader (JW) blinded to randomised allocation.

For each patient at each time point IMR_{angio} was derived using the following formula:

$$IMR_{\text{angio}} = Pa \times QFR \times N \text{ frames/fps}$$

Pa is mean arterial pressure, N frames is the number of frames it takes contrast to travel from the tip of the guide catheter to the distal vessel and fps is frames per second (set to 15 frames per second).

IMR_{angio} pre-stent, post-stent and the change in IMR_{angio} pre to post stent ($\Delta IMR_{\text{angio}}$) were then compared between groups (Stent-only, MA and SRT).

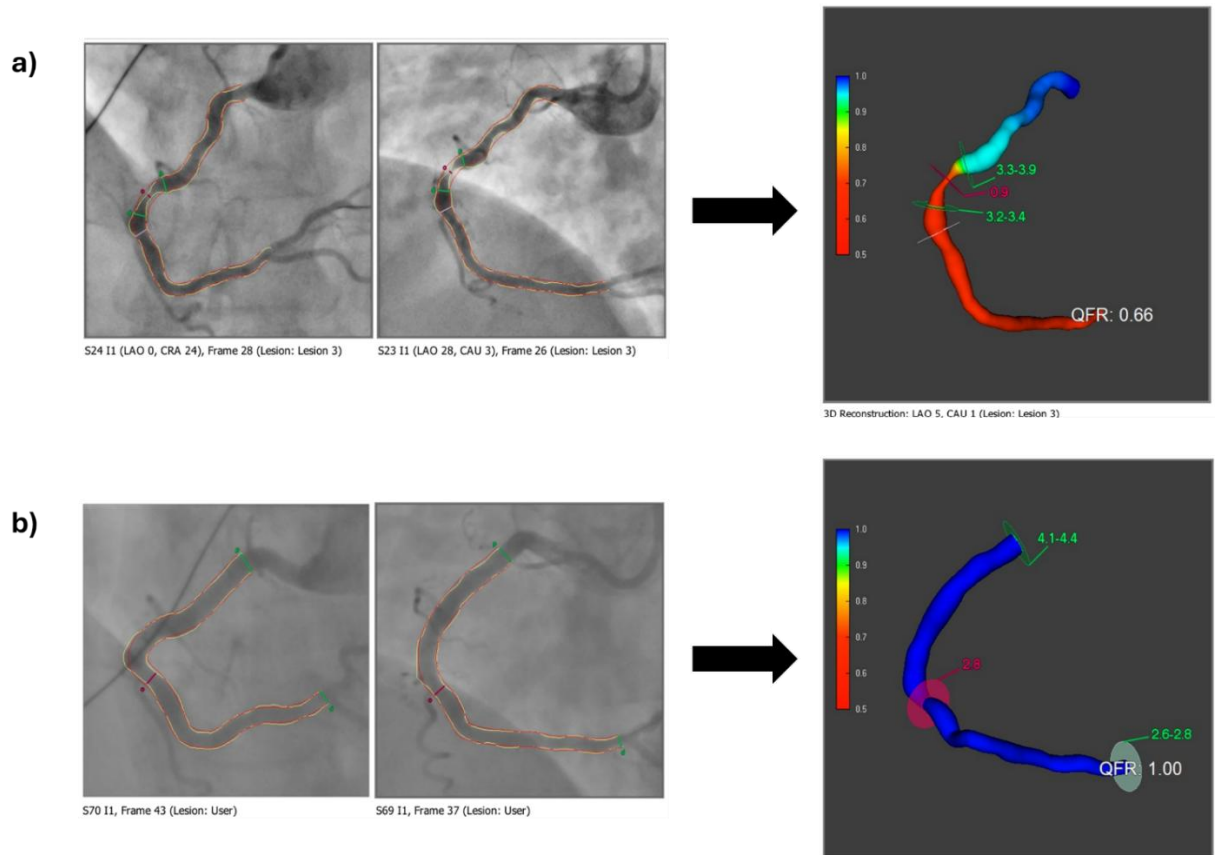


Figure 18: Quantitative flow ratio (QFR) model generation **a)** pre- stenting and **b)** post-stenting. Two high frame rate angiograms $>25^\circ$ apart are used to generate the 3D model, from which QFR is derived.

Angiographic measurements

Angiographic measurements are a mainstay in STEMI research for assessing epicardial flow, microvascular flow and myocardial perfusion. Discussed in detail in chapter 1.

Angiographic data is acquired as a matter of course during pPCI, the resulting images yield valuable measurements with established associations with cardiovascular outcomes.^{170-173,182}

In this project, the angiographic endpoints used (all associated with hard clinical endpoints) were 1) no-reflow (present/absent), 2) distal embolization (present/absent), 3) Thrombolysis in Myocardial Infarction (TIMI) flow grade, and 4) myocardial blush grade (MBG).

1) No-reflow phenomenon. No-reflow was defined as a final TIMI flow grade ≤ 2 at the end of the procedure (post-stenting, following post-dilatation), in the absence of residual epicardial obstruction such as dissection, thrombus, spasm, or high-grade stenosis. Although definitions of no-reflow vary between trials, this working definition remains the most widely adopted in contemporary STEMI studies and in large analyses demonstrating its association with adverse clinical outcomes, including a sub-study of the TOTAL trial by d'Entremont et al.^{172,264-267} The caveat of no epicardial coronary obstruction is important as no reflow has been universally defined as hypoperfusion secondary microvascular obstruction in the context of patent epicardial coronary arteries since its original description.³⁶

In this project the angiogram reader (JW) was blinded to treatment allocation. RK supplied anonymised post-PCI angiograms for each patient, which were coded and linked to an anonymised spreadsheet for which only RK held the key. The reader assessed each patient's angiographic study for presence of no-reflow using the definition described above, recording a "1" if no-reflow was present and a "0" if absent.

2) Distal embolisation. We used the angiographic definition of distal embolisation validated by Henriques et al.:

"Distal filling defect(s) with an abrupt 'cut-off' in one of the peripheral coronary branches of the infarct related artery, distal to the angioplasty site."

Henriques et al evaluated 178 angiographic studies in pPCI patients.

Finding that 15% had angiographic embolisation using the above definition. Angiographic embolisation was shown to be a strong predictor of more extensive myocardial injury and a poor prognosis.

Further, embolisation was associated with reduced ST segment elevation resolution and MBG.¹⁷⁰

Figure 8 (panels A and B) show examples of angiographic distal embolisation seen in our cohort.

In this project RK supplied anonymised full angiographic studies for each participant to the reader (JW), which were coded and linked to an anonymised spreadsheet for which only RK held the key. The reader assessed each angiographic study for the presence of distal embolisation using the definition described above, recording a "1" if embolisation was present at any point(s) in an angiographic study and a "0" if absent.

3) **Final TIMI (Thrombolysis in Myocardial Infarction) flow grade.**

TIMI flow grade is a semi-quantitative angiographic measure of epicardial coronary flow, used in PCI or thrombolysis. It classifies flow from complete absence of flow to normal flow, based on both the speed and completeness of contrast opacification in the distal coronary bed.²⁶⁸

TIMI flow grade has been used in STEMI trials since 1987, with multiple studies establishing it as a strong predictor of clinical outcomes post STEMI.^{173,269,270}

TIMI flow grade is defined as follows:

Grade 0 = No flow. Complete occlusion (no antegrade flow beyond the point of occlusion).

Grade 1 = Penetration without perfusion. Contrast passes beyond the obstruction but does not opacify the distal coronary bed.

Grade 2 = Partial perfusion. Contrast opacifies the distal vessel bed, but flow is delayed or incomplete compared to a normal artery.

Grade 3 = Full perfusion. Normal antegrade flow filling the distal vessel bed as rapidly as in a normal vessel.

In this project final TIMI flow grade was assessed as an outcome measure on the post-stenting angiograms for each patient. The angiogram reader (JW) was blinded to treatment allocation. Anonymised post-PCI angiograms were supplied by RK, coded, and linked to an anonymised spreadsheet, to which only RK held the key. The reader evaluated each angiographic study and recorded the final TIMI flow grade (0–3), according to the definitions above.

In addition to serving as an outcome measure, TIMI flow grade was also applied as an inclusion criterion for trial enrolment. Only patients with TIMI flow grades 0–1 were included, ensuring selection of true occlusive culprit lesions with absent or minimal antegrade flow (Table 5).

- 4) Final myocardial blush grade (MBG).** MBG is a semi-quantitative angiographic score of tissue-level perfusion, based on how intensely and quickly contrast opacifies and clears from the myocardium on angiography (figure 9). Like final TIMI flow grade (at the end of a PCI procedure) final MBG is a strong predictor of clinical outcomes.^{173,182}

MBG was defined as follows:

Grade 0 = No myocardial blush or contrast staining.

Grade 1 = Minimal or weak myocardial blush with minimal or absent washout.

Grade 2 = Moderate myocardial blush, with delayed washout.

Grade 3 = Normal myocardial blush, with rapid washout.

Final MBG was assessed on the post-stenting angiograms for each patient. The angiogram reader (JW) was blinded to treatment allocation.

Anonymised post-PCI angiograms were supplied by RK, coded, and linked to an anonymised spreadsheet, to which only RK held the key.

The reader evaluated each angiographic study and recorded the final MBG (0–3), according to the definitions above.

Electrocardiographic, echocardiographic and biomarker measurement

Electrocardiograms (ECGs), echocardiography, and serum biomarkers (particularly cardiac troponin) are integral to the routine management of STEMI, serving to establish the diagnosis, guide treatment decisions, and provide prognostic information. Beyond clinical care, these modalities are widely employed in STEMI research as surrogate endpoints for clinical outcomes. Commonly utilised measures include the degree of ST-segment resolution on ECG following STEMI, left ventricular ejection fraction (LVEF) on echocardiography, and the magnitude of troponin elevation.^{224,271-274}

Electrocardiographic: ST segment resolution

As per an ECG sub-study of the CADILLAC trial (discussed in chapter 1) ST-segment resolution was quantified comparing a baseline and post-procedure twelve lead ECG.²²⁴ The lead demonstrating the greatest ST-elevation at baseline was identified, and resolution was expressed as the percentage of residual ST-elevation on the post procedure ECG in the same lead relative to the baseline, calculated as:

$$\text{ST-segment resolution (\%)} = \frac{\text{Baseline ST-elevation} - \text{Post-procedure ST-elevation}}{\text{Baseline ST-elevation}} \times 100$$

ST-segment elevation resolution % was categorised as complete (>70%), partial (30-70%), or incomplete (<30%). Post-procedure twelve-lead ECGs were obtained 60-90 minutes post-procedure.

Pre-and post-procedure ECGs were paired and anonymised by RK and provided to the reader JW, who calculated ST-segment resolution for each case. In accordance with the

CADILLAC definition, ST-segment elevation was quantified 20 ms following the termination of the QRS complex (J-point), with the TP segment serving as the isoelectric reference.²²⁴ Figure 19 shows examples of complete and incomplete ST-segment resolution and where on the ECG measurements were made.

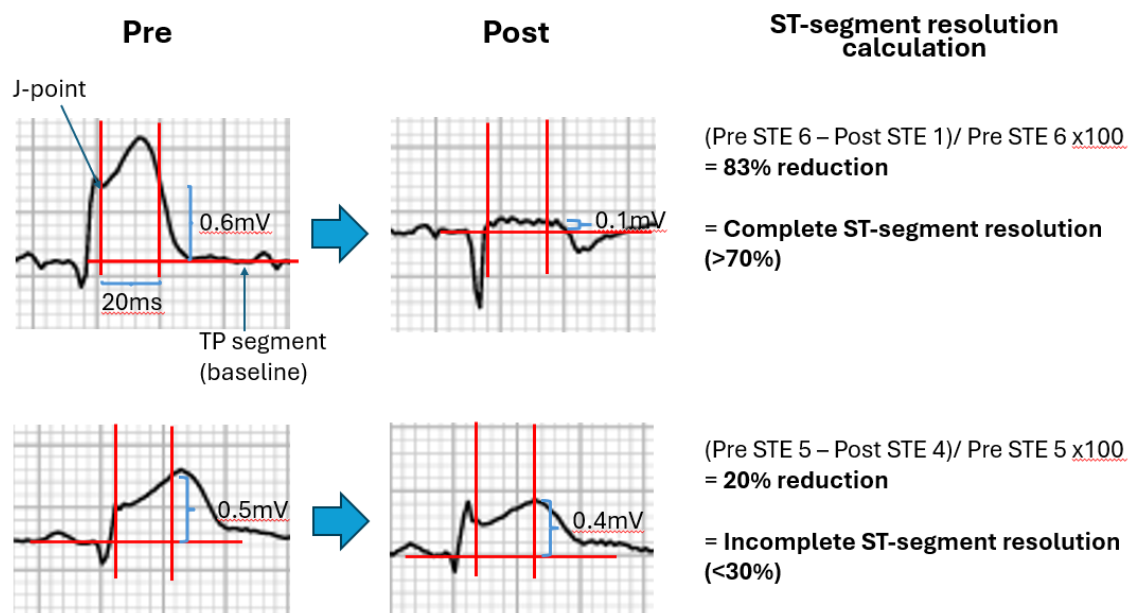


Figure 19: To quantify ST-segment resolution, ST-segment elevation was measured in the lead with the highest ST-elevation at baseline and the same lead post-PCI. The J-point was identified, and ST-segment elevation was measured 20ms after the J-point. Degree of ST-elevation was measured from the TP-segment. Examples of complete (>70%) and incomplete (<30%) ST-segment resolution are shown.

Echocardiographic: Left ventricular ejection fraction

Transthoracic echocardiography was performed as part of routine clinical care.

Contemporary guidelines, including the 2023 ESC ACS guidance give a Class I recommendation to determine left-ventricular ejection fraction (LVEF) before discharge, with echocardiography as the first-line modality. The guidelines also advise follow-up imaging when LVEF is reduced after STEMI.⁴ Post-STEMI, LVEF is a strong, independent predictor of clinical outcomes.²⁷⁵

In line with best practice, we requested an inpatient echocardiogram for all patients post STEMI and where LVEF was reduced requested a 6-month outpatient follow-up echocardiogram.

Clinical records were reviewed to obtain left ventricular ejection fraction (LVEF, %) measurements derived from echocardiography. For each patient, LVEF was recorded following primary PCI (if an echocardiogram was performed within 7 days of the procedure) and at 6 months, when available. Where paired acute and 6-month LVEF measurements were available, the change in LVEF (%) was documented.

Biomarkers: Troponin I

Like LVEF, high-sensitivity troponin I was collected as part of routine clinical practice. It is recommended that all patients with suspected ACS have high-sensitivity troponin measured for diagnosis and prognostication.⁴ Peak troponin within 72 hours of PCI is a robust predictor of cardiovascular outcomes in STEMI.²⁷⁶ Therefore, we accessed patient notes and recorded peak high-sensitivity troponin (ng/L) <72 hours of PCI. As the upper reporting limit of the local assay is 50,000 ng/L and large STEMIs typically exceed this, we took a practical approach and recorded if peak troponin for each case exceeded 50000 (recorded as “1”) or was below 50000 (recorded as “0”).

Extracted thrombus phenotyping

Several approaches (discussed in Chapter 1) can be taken to characterise extracted coronary thrombus including histological analysis, SEM imaging and visual assessment. Our analysis consisted of a visual assessment only, due to a lack of access to the required technology and expertise for more advanced evaluations such as SEM and histological assessment. However, a simple visual categorisation of extracted thrombus in STEMI, according to colour and appearance, categorising samples as “red”, “white” or “mixed” has been shown to be a good predictor of thrombus composition according to histology and SEM, with higher platelets and fibrin content in visually “white” thrombus and higher red blood cell content in “red” thrombi.²⁷⁷

When thrombectomy was successful a standardised photograph was taken of the thrombus within the device with a standardised photography set-up (figure 15).

On completion of recruitment, extracted thrombus photographs were assessed. JW categorised extracted thrombus photographs as red, white or mixed, recording the result. Categorisation was verified by a second operator RK.

Examples of extracted thrombus types are seen in figure 20.

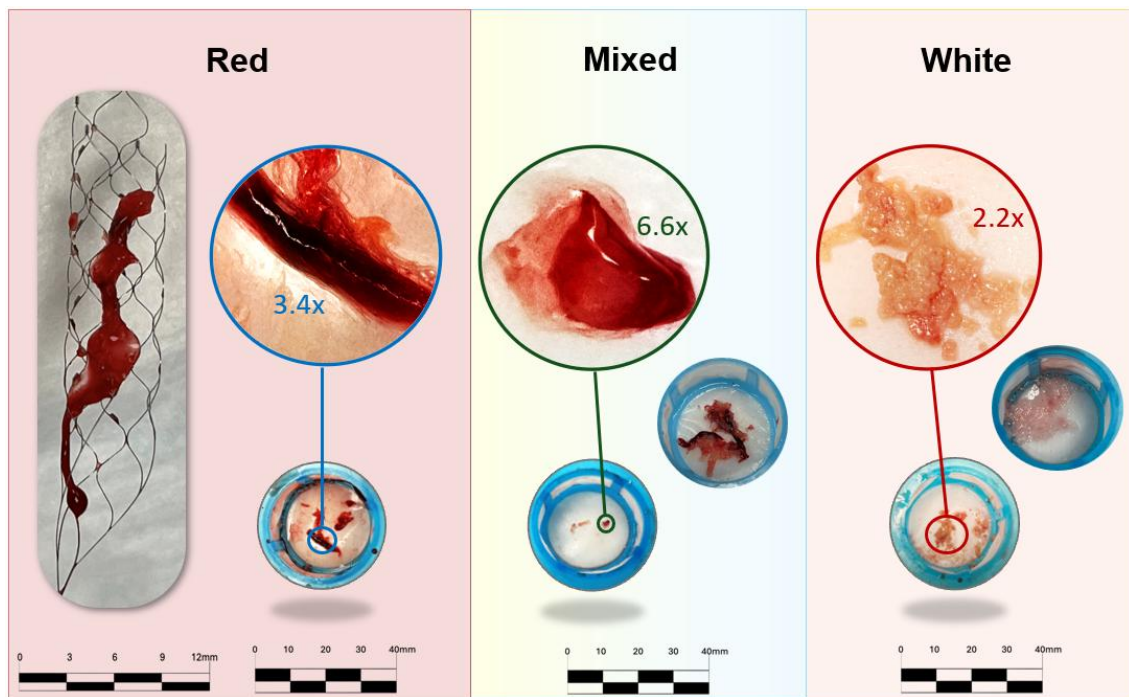


Figure 20: Examples of extracted coronary thrombi visually classified as “red”, “mixed” and “white”.

Safety

As discussed in Chapter 1, safety monitoring is paramount when evaluating medical devices in new clinical contexts. While SRT has been demonstrated to be safe in the setting of stroke intervention,⁸³ MA thrombectomy in STEMI has been associated with higher rates of stroke.⁵³ Consequently, rigorous safety monitoring, particularly active surveillance for cerebrovascular events, is essential.

Safety data were systematically collected at three time points: (1) intra- and peri-procedure, (2) on discharge and (3) at 6-month follow-up (table 7). However, any adverse events identified at any time were reported in accordance with the European Commission Guidelines on Medical Devices Serious Adverse Event Reporting (MEDDEV 2.7/3).²⁷⁸

The following were recorded on a paper case report forms (appendices 3,8 and 9) by JW or RK:

1. **During and immediately post-procedure (appendix 8):**

- Whether no-reflow occurred. (A final TIMI flow grade ≤ 2 at the end of the procedure (post-stenting), in the absence of residual epicardial obstruction).
- Whether an arterial dissection occurred. If yes, its grade (NHLBI classification, see appendix 8).²⁷⁹
- Whether a coronary perforation occurred. If yes, its grade (Ellis classification, see appendix 8).²⁸⁰
- Whether a stroke or transient ischaemic attack (TIA) occurred. If yes, whether it occurred pre-thrombus modification and PCI, post-thrombus modification, or post-stent.

2. On discharge (appendix 9):

- Length of hospital stay.
- Any complications.
- The presence or absence of the following were documented: death, cardiac death, embolic stroke, haemorrhagic stroke, TIA, re-infarction, emergency CABG, elective CABG, repeat catheterisation without PCI, re-intervention with PCI, radial artery complication, defibrillation, pulmonary oedema, cardiogenic shock, mechanical circulatory support use, non-invasive ventilation, invasive ventilation, temporary pacing, permanent pacing, blood product transfusion, renal failure, dialysis, gastrointestinal bleeding, and cardiac tamponade.

3. 6-month telephone follow-up (Appendix 3):

- Symptoms.
- Any complications.
- Any acute coronary syndromes (further STEMI or NSTEMI).
- Any further revascularisation (target vessel PCI, target lesion PCI, target vessel CABG, non-target vessel PCI, or non-target vessel CABG).
- Stent thrombosis and its timing.
- Any of the following outcomes: death, cardiac death, heart failure, cardiogenic shock, acute coronary syndrome admission, stable angina diagnosis, pacemaker implantation, ICD implantation, cardiac transplant, LV assist device use, ischaemic stroke, haemorrhagic stroke, or TIA.

The above data was transcribed from the case report forms (appendices 3,8 and 9) into a single spreadsheet to allow for data analysis.

Adverse event detection and reporting

Adverse events were defined and reported as per the European Commission Guidelines on Medical Devices Serious Adverse Event Reporting.²⁷⁸ Details of an adverse event were recorded on an adverse event reporting form (appendix 10).

Definitions

Adverse Event (AE)

“Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory findings) in participants, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or comparator, events related to the procedures involved (any procedure in the protocol). For users or other persons this is restricted to events related to the investigational medical device.”

Adverse Device Effect (ADE)

“An adverse device effect related to the use of an investigational medical device. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. This definition also includes any event resulting from user error or from intentional misuse of the investigational device.”

Serious Adverse Event (SAE)

“Any untoward medical occurrence that:

- Results in death,*
- Is life-threatening,*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,*
- Results in persistent or significant disability/incapacity, or*
- Is a congenital anomaly/birth defect.*
- Other important medical events.*

Included herein are device deficiencies that might have led to a serious adverse event if:

- a) suitable action had not been taken or*
- b) intervention had not been made or*
- c) circumstances had been less fortunate.*

These are handled under the SAE reporting system.

Planned hospitalisation for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event.

The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event.

Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above."

Serious Adverse Device Effect (SADE)

"Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above.

Unanticipated Serious Adverse Device Effects (USADE) is any serious adverse device effect which, by its nature, incidence, severity or outcome, has not been previously identified."

Device deficiency

"Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling.

*Device deficiencies that did not lead to an adverse event, but could have led to a medical occurrence if suitable action had not been taken, or intervention had not been made or if circumstances had been less fortunate."*²⁷⁸

Severity definitions

Mild: Awareness of signs or symptoms that do not interfere with the participant's usual activities, or that are transient and resolve spontaneously without treatment or lasting effects.

Moderate: Signs or symptoms that interfere with the participant's usual activities.

Severe: Incapacitating signs or symptoms that prevent the participant from working or performing usual activities.

Arterial injury severity: Coronary dissections and perforations were classified according to the NHLBI and Ellis criteria.^{280,281} A significant coronary dissection was defined as a dissection leading to coronary flow impairment or occlusion.

Causality

The relationship of each adverse event to the trial device was determined by the manufacturer and/or a medically qualified investigator according to the following definitions:

Not related: The event was clearly attributable to other factors, such as the participant's clinical condition, therapeutic intervention, or concomitant medication.

Unlikely: The event was most likely produced by other factors, such as the participant's clinical condition, therapeutic intervention, or concomitant medication, and did not follow a known response pattern associated with the device.

Possibly related: The event occurred within a reasonable temporal relationship to the placement or administration of the device and/or followed a known response pattern, but could also have been caused by other factors, such as the participant's clinical condition, therapeutic intervention, or concomitant medication.

Most probable: The event occurred within a reasonable temporal relationship to the placement or administration of the device and/or followed a known response pattern, could not reasonably have been explained by other factors, and improved following discontinuation or removal of the device.

Recording adverse events

All AEs were recorded in the reporting form (appendix 10) as soon as they were detected.

SAEs and SADEs were reported to the trial safety group or sponsor immediately or no later than 24 hours after the investigator became aware of the event. These events were also reported to the device manufacturer, the The Medicines and Healthcare products Regulatory Agency (MHRA), and the Research Ethics Committee (REC) within two calendar days of detection of the event. The AE reporting form was submitted via email to ouhsae.reports@ouh.nhs.uk.

Trial cessation rules

The following stopping rules were agreed upon with the sponsor and the research ethics committee to trigger cessation of the trial:

- More than two transient ischaemic attack or ischaemic stroke-related SADEs.
- More than two coronary perforation-related SADEs.
- More than two significant coronary dissection-related SADEs.

Statistical analysis

A flow diagram summarising the number of patients screened and recruited was prepared. Descriptive statistics, including means, medians, standard deviations, and variances, were computed at each time point for all relevant data types and study groups (e.g., baseline characteristics, OCT parameters, IMR_{angio}, and angiographic measurements).

Statistical analyses were conducted using R Studio (ggplot2) and SPSS 29 (IBM). Continuous variables were summarised as mean $\pm$ standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Categorical variables were summarised as counts and percentages. Correlations were assessed visually using scatterplots and analytically using Spearman's rank correlation coefficient due to the non-normal distributions seen.

For continuous variables, normality was assessed using the Shapiro-Wilk test ($\alpha = 0.05$). As most continuous variables were non-normally distributed, between-group differences were assessed using the Kruskal-Wallis test. Pairwise comparisons were performed using the Wilcoxon rank-sum test, with Bonferroni correction applied to adjust for multiple comparisons.

Categorical variables were compared between treatment arms using Chi-square tests (e.g., no-reflow, MBG, ST-segment resolution). All hypothesis tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Analyses were performed on an intention-to-treat basis, i.e., participants were analysed according to their original randomisation.

As thrombus and lumen segmentation (figure 14) were novel measurements central to the key outcome measures of this work, inter- and intra-observer variability were

assessed using the dice similarity index for frame level thrombus and lumen area measurements.

Sample size

This was the first study to assess SRT in coronary intervention. As a small pilot study aiming to assess the efficacy of SRT in the context of STEMI with LTB, it was not powered to detect an impact on hard clinical outcomes, and assumed unlikely to detect a significant impact on clinical surrogates. However, we did expect this pilot study would be suitably powered to detect significant changes in thrombus extraction capacity, measured by OCT.

Based on prior studies that measured thrombus burden on OCT in STEMI and our focus on patients with LTB we assumed a mean pre-stent thrombus volume (TVol) of 9.6 mm³ with SD 5.1 mm³ in the standard-of-care arms (stent only and MA).^{5,282} No prior data existed for stent-retriever use in STEMI, we hypothesised a 33% reduction in mean pre-stent TVol with SRT (absolute difference $\approx$ 3.2 mm³) to be significant.

We assumed the primary analysis would be a one-way ANOVA with two pre-specified pairwise comparisons: SRT vs PCI-only (primary) and MA vs PCI-only (secondary), two-sided $\alpha=0.05$ (family-wise), adjusted for two comparisons. Power calculations indicate that n=48 provides 80% power to detect the hypothesised difference for a single two-group contrast (n=24 per arm). Extending this to the three-arm design with both planned contrasts leading to a total sample size of n=72 (24 per arm).²⁸³

Allowing for 12.5% non-analysable OCT studies, we decided to enrol n=81 (27 per arm) to preserve $\geq 80\%$ power for the primary contrast under the stated assumptions.

Ethical considerations

Ethical approval was obtained from the South Central Oxford C Research Ethics Committee (REC; reference 21/SC/0220; IRAS ID 294665). Regulatory authorisation for use of the stent-retriever as an investigational device was granted by the UK Medicines and Healthcare products Regulatory Agency (MHRA; CI/2021/0077/GB). The study was sponsored by the host institution and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and in conformity with relevant European Commission medical-device guidance. Written informed consent was obtained from all participants prior to enrolment. The trial was prospectively registered on ClinicalTrials.gov (NCT05307965) and reported in line with CONSORT recommendations for randomised controlled trials.²⁸⁴

Summary

This chapter detailed our approach to testing the hypothesis that, in STEMI with LTB, SRT would reduce intracoronary thrombus more effectively than MA or stenting alone, improve microvascular perfusion, and do so without excess adverse events.

Adults presenting within 12 hours of symptom onset with STEMI, culprit-artery TIMI 0-1, angiographic thrombus grade ≥ 4 and an estimated vessel diameter ≥ 3.0 mm were considered for recruitment. After restoration of initial flow by small-balloon pre-dilation, willing eligible patients provided on-table assent witnessed by an independent advocate and were randomised (sealed envelopes; 1:1:1) to PCI only, MA-assisted PCI, or SRT-assisted PCI. Written informed consent was obtained ≥ 24 hours later. Operators received SRT training on a transparent silicone bench model to mitigate learning-curve effects.

Optical coherence tomography (OCT) quantified thrombus volume and burden at baseline, after thrombus modification (MA or SRT), and post-stenting. Paired runs were co-registered, and segmentations were performed, blinded to allocation and panel reviewed. Two high-frame-rate angiograms (pre- and post-stent) enabled computation of the angiography-derived index of microvascular resistance (IMR_{angio}) derived from QFR-based modelling. Angiographic outcomes included no-reflow (final TIMI ≤ 2 without epicardial obstruction), distal embolisation, final TIMI flow grade, and final myocardial blush grade; readings were blinded. ST-segment resolution was measured on 12-lead ECGs 60-90 minutes post-procedure at the J-point + 20 ms using the TP segment as the isoelectric baseline. Transthoracic echocardiography provided post-procedure LVEF measurements and 6-month LVEF measurement (when post-procedure LVEF was reduced). Peak high-sensitivity troponin within 72 hours of pPCI was recorded. When present, extracted thrombus was photographed and visually categorised (red, white or mixed). Extracted thrombus area measurements were utilised to validate our novel $\Delta TVol(mm^3)$ measurement. Statistical methods and our approach to monitoring and reporting safety are described.

These methods provided a comprehensive framework for evaluating the efficacy and safety of SRT in STEMI with large thrombus burden, the results of these analyses are presented in the following chapters.

Chapter 3: Baseline characteristics, impact of thrombus modification on optical coherence tomography parameters and validation of a novel OCT outcome measure

Introduction

As discussed in Chapter 1, the major randomized trials TASTE (n=7,244) and TOTAL (n=10,732), found no MACE benefit of routine thrombectomy versus stenting alone in STEMI.^{53,54}

Several factors could explain these negative findings: (1) the null hypothesis is true: thrombectomy does not improve clinical outcomes in STEMI; (2) MA provides limited thrombus-extraction efficacy; and (3) unselected, all-comer enrolment diluted any benefit confined to specific subgroups (e.g., patients with large thrombus burden).

The latter is supported by a meta-analysis of major thrombectomy trials restricted to patients with LTB (defined as TIMI thrombus grade ≥ 3), which showed fewer cardiovascular deaths with manual aspiration versus PCI alone (2.5% vs 3.1%; P=0.03).¹² Further, the TOTAL OCT sub-study clearly demonstrated that a large proportion of patients recruited had little to no coronary thrombus as demonstrated by OCT.⁵ It is highly plausible that thrombectomy would not confer any clinical benefit when no coronary thrombus is present.

The traditional research method for assessing coronary thrombus burden (angiographic thrombus grading) is imprecise. By contrast, OCT provides high-resolution imaging that enables more precise, quantitative measurement of thrombus. OCT is therefore well suited to evaluate the impact of thrombus-modification strategies in STEMI. However, studies using OCT to quantify thrombus burden are limited.^{5,148} This project aims to leverage the powers of OCT and is the first to measure coronary thrombus burden by

OCT both before and after thrombectomy. Demonstrating thrombus-extraction efficacy with OCT could reignite interest in thrombectomy for selected STEMI patients and justify larger, focused trials powered for clinical outcomes.

In this chapter I present:

- 1) Baseline characteristics of the participants recruited.
- 2) Results of OCT-derived outcome measures:
 - Change in thrombus volume ($\Delta\text{TVol,mm}^3$) and burden ($\Delta\text{TB,\%}$) pre- to post-thrombus modification.
 - Post-stenting thrombus volume (mm^3), burden (%) and stent parameters.
- 3) Results of the validation of ΔTVol (ΔTVol versus extracted thrombus area).
- 4) A description of the attempt to develop an automated machine learning OCT thrombus segmentation model.

To generate OCT-derived measurements 7820 OCT frames were segmented from 213 OCT runs.

Recruitment

Of 213 STEMI patients screened, 132 were excluded for not meeting inclusion criteria or meeting ≥ 1 exclusion criterion (Tables 5 and 6). The most common reasons for exclusion were low angiographic thrombus burden, pre-PCI TIMI flow >1 , haemodynamic instability (Killip class III/IV or bradycardia <40 bpm), and an estimated culprit-vessel diameter <3.0 mm. After 1:1:1 randomisation, one patient crossed over from the SRT arm to stent-only owing to device-delivery difficulty. In the MA arm, one patient died intraprocedurally (VF arrest before stenting) and another had non-diagnostic OCT images. In total, OCT datasets were analysable for 28 patients receiving a stent-only arm, 25 receiving MA arm, and 26 receiving SRT (Figure 21).

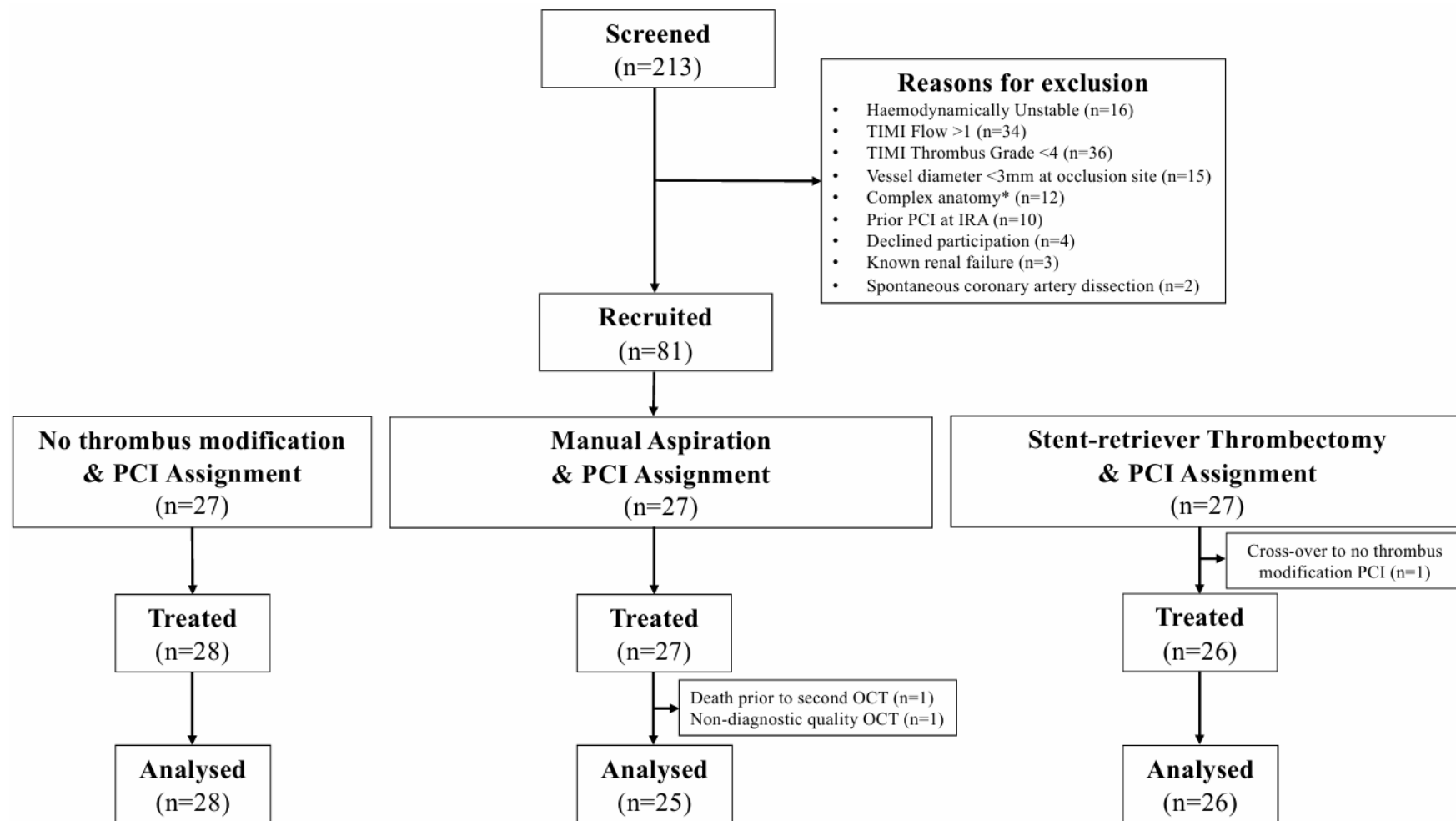


Figure 21: PRISMA diagram of participants screened, recruited, excluded, treated and data analysed with specific exclusion reasons.

Baseline characteristics

Of the 81 STEMI patients with LTB recruited 15% (12) were female, mean age was 64 ± 12 years.

Demographic variables between groups were generally well balanced between the three arms (table 8). Age did not differ between arms (67 ± 12 vs 63 ± 12 in MA and 63 ± 13 in SRT) $p = 0.34$. Median ischaemic time (symptom to wire down time) did not differ ($p = 0.18$).

Procedural variables were mostly well balanced between arms. Anti-platelet loading prior to PCI was achieved in all patients. There was a preponderance of presentations where the RCA was the culprit-artery (51% overall), particularly in the MA and SRT arms (56% each) versus the stenting-only arm (41%). LAD lesions accounted for 38% of all presentations. LAD lesions were more frequent in the stenting-only arm (52%) compared to the MA (26%) and SRT (37%) arms. LCx lesions accounted for 11% of presentations. Post-dilatation was performed in almost all cases. It was omitted in one patient in the MA group because the patient died during the procedure, and in one patient in the stenting-only group because no stent was implanted, with the lesion instead treated using a drug-eluting balloon.

However, bailout glycoprotein IIb/IIIa inhibitor use during the procedure was most frequent in the stenting-only arm (13 cases; 50.0%), followed by the SRT arm (10 cases; 40.0%) and the MA arm (4 cases; 15.4%). A statistically significant difference was detected between arms ($p = 0.02$).

At presentation, TIMI flow was 0 in 94% of cases and 1 in 6% of cases, with similar distributions across groups. TIMI thrombus grade was high as per the trial protocol: grade 5 in 58% and grade 4 in 42%, evenly distributed between arms.

With the exception of glycoprotein IIb/IIIa inhibitor use, the three groups were broadly comparable at baseline..

Table 8. Baseline demographic and procedural variables. (LAD = Left anterior descending artery, LCx = Left Circumflex artery, RCA = Right coronary artery).

	Overall (n=81)	Stenting- only (n=27)	Manual aspiration (n=27)	Stent-retriever thrombectomy (n=27)	P-value
Demographics					
Age (mean $\pm$ SD)	64 $\pm$ 12	67 $\pm$ 12	63 $\pm$ 12	63 $\pm$ 13	0.34
Female sex, n (%)	12 (15%)	3 (11%)	5 (19%)	4 (15%)	0.70
Hypertension, n (%)	35 (43%)	13 (48%)	11 (41%)	11 (41%)	0.82
Hyperlipidaemia, n (%)	22 (27%)	7 (26%)	8 (30%)	7 (26%)	0.90
Previous MI, n (%)	3 (4%)	3 (11%)	0 (0%)	0 (0%)	0.11
Current smoker, n (%)	20 (25%)	5 (19%)	8 (30%)	7 (26%)	0.25
Ischaemia time, min (median [IQR])	200 (145–338)	217 (161–383)	200 (142–293)	180 (144–252)	0.18
Procedural variables					
Antiplatelet loading, n (%)	81 (100%)	27 (100%)	27 (100%)	27 (100%)	N/A
Bailout Glycoprotein iib/iiia inhibitor use n (%)	27 (34%)	13 (50%)	4 (15.4%)	10 (40%)	0.02
Post dilatation Performed n (%)	79 (98%)	27 (100%)	26 (96%)	26 (96%)	0.34
Culprit artery, n (%)					
LAD	31 (38%)	14 (52%)	7 (26%)	10 (37%)	0.14
LCx	9 (11%)	2 (7%)	5 (18%)	2 (7%)	0.37
RCA	41 (51%)	11 (41%)	15 (56%)	15 (56%)	0.43
TIMI flow at presentation, n (%)					
0	76 (94%)	25 (93%)	26 (96%)	25 (93%)	0.87
1	5 (6%)	2 (7%)	1 (4%)	2 (7%)	0.84
TIMI thrombus grade, n (%)					
4	34 (42%)	11 (41%)	12 (44%)	11 (41%)	0.96
5	47 (58%)	16 (59%)	15 (56%)	16 (59%)	0.96

Baseline OCT characteristics

Baseline OCT measurements were obtained on the initial run (pre-thrombus modification and pre-stenting; see Figure 11) and are summarised in Table 9. Of 81 enrolled patients, 80 baseline OCT runs were analysable. At baseline median thrombus volume in the entire cohort was 10.6mm³, and was highly variable (IQR: 5.4-26.9 mm³). Thrombus volume was highest in the SRT arm (median 18.3 mm³ [IQR 6.7–54.4]). It was significantly greater than MA (7.6 mm³ [3.3–27.1]; p=0.03) but not significantly higher than stenting-only (9.8 mm³ [4.5–18.1]; p=0.32) (Figure 22).

After accounting for lumen size, thrombus burden (% lumen occupied by thrombus) did not differ significantly between SRT and MA (median 30.9% [15.1–40.8] vs 22.3% [11.7–31.0]; p=0.29). Lumen volume was larger in SRT (median 78.4 mm³ [44.3–145]) than MA (46.0 mm³ [18.6–119.3]) but did not reach statistical significance (p=0.10). Dissections were rare at baseline (stenting-only 0/27, MA 1/26, SRT 1/27).

Overall, the SRT cohort presented with significantly greater baseline thrombus volume, while proportional thrombus burden was similar between arms.

Table 9. Baseline optical coherence tomography measurements.

	No thrombus modification (Stenting-only) (n=27)	Manual aspiration (n=26)	Stent-retriever thrombectomy (n=27)	P-value
Thrombus volume, mm ³ median (IQR)	9.8 (4.5–18.1)	7.6 (3.3–27.1)	18.3 (6.7–54.4)	0.03
Lumen volume, mm ³ median (IQR)	43.9 (24.2–79.2)	46.0 (18.6–119.3)	78.4 (44.3–145)	0.10
Thrombus burden, % median (IQR)	22.8 (10.4–27.7)	22.3 (11.7–31.0)	30.9 (15.1–40.8)	0.29
Dissection, n (%)	0 (0%)	1 (3.8%)	1 (3.7%)	N/A

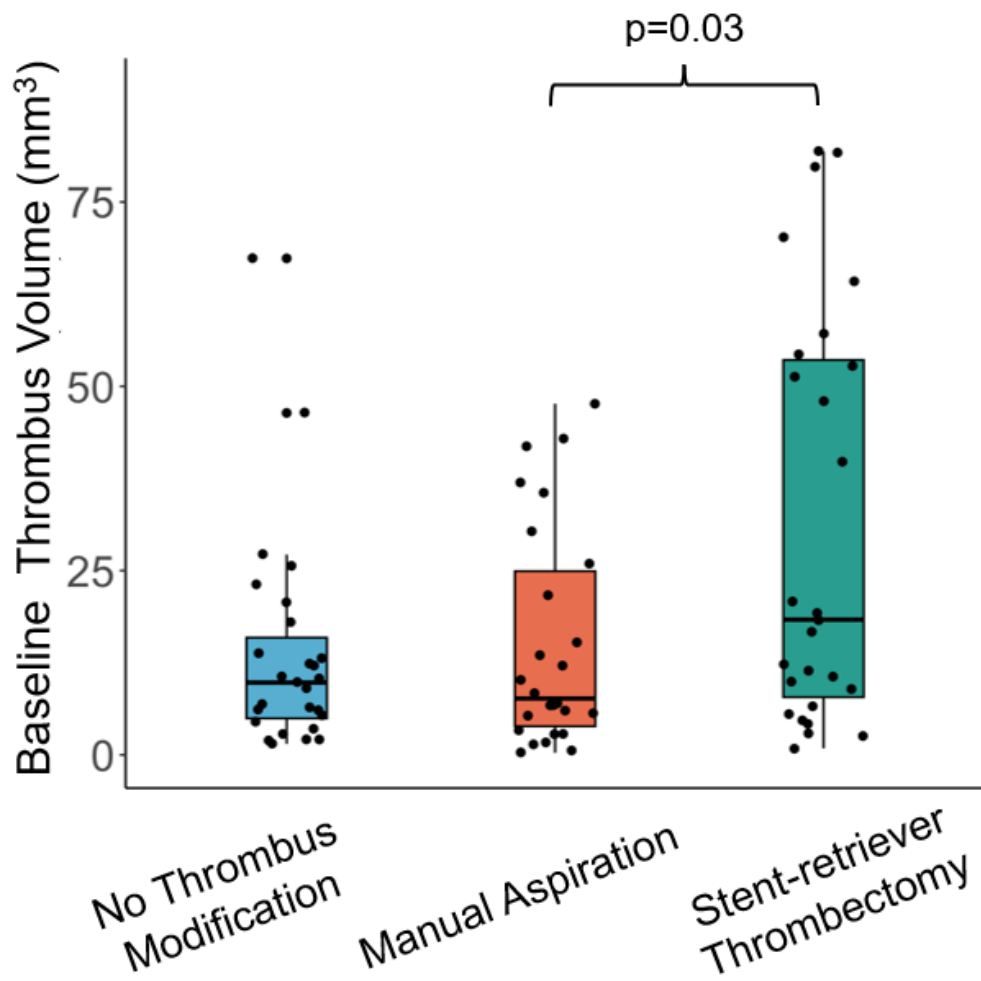


Figure 22. Baseline thrombus volume on OCT by treatment arm (no thrombus modification, manual aspiration, and stent-retriever thrombectomy). Medians are shown, the stent-retriever arm had the highest baseline thrombus volume and was significantly higher than manual aspiration ($p=0.03$).

Post thrombus modification OCT findings

Post thrombus modification OCT measurements (taken in the SRT and MA arms) are summarised in table 10.

Post-modification thrombus volume did not differ significantly between SRT than MA (median 7.7 mm³ [IQR 2.3–18.6] vs 4.8 mm³ [1.8–8.4]; p=0.08). Lumen volume did not differ significantly between SRT (70.4 mm³ [50.4–136.5]) and MA (40.9 mm³ [19.2–97.6]; 0.06), and post-modification thrombus burden was similar (SRT 12.8% [4.4–21.5] vs MA 13.0% [3.8–19.4]; 0.6). No coronary dissections were detected after modification in either arm.

Table 10. Post-thrombus modification optical coherence tomography measurements.

(*1 patient in the MA arm had unanalysable post-thrombus modification OCT imaging, 1 patient in the MA arm died prior to post modification OCT, **1 patient in the SRT arm crossed over to stenting-only and so did not have a post-thrombus modification OCT run).

	Manual aspiration (n=25)*	Stent-retriever thrombectomy (n=26)**	p-value
Thrombus volume, mm ³ median (IQR)	4.8 (1.8–8.4)	7.7 (2.3–18.6)	0.08
Lumen volume, mm ³ median (IQR)	40.9 (19.2–97.6)	70.4 (50.4–136.5)	0.06
Thrombus burden, % median (IQR)	13.0 (3.8–19.4)	12.8 (4.4–21.5)	0.60
Dissection, n (%)	0 (0%)	0 (0%)	N/A

Change in thrombus volume and burden pre- to post- thrombus modification

In both SRT and MA arms, post-modification thrombus volume (mm^3) and thrombus burden (%) were significantly reduced compared to baseline ($p < 0.001$ for each, Figure 22).

Reduction in thrombus volume (ΔTVol ; mm^3) was significantly higher in the SRT arm (8.0 [IQR 1.6–31.5]) than the MA arm (2.6 [IQR 0.0-16.1]) $p=0.03$. However, once corrected for lumen volume, thrombus burden reduction (ΔTB ; %) did not differ between the SRT (47 [IQR 28.8-78.2]) and MA (37 [IQR -1.7-68.4]) ($p = 0.41$) arms. Further, there was no difference between the proportion of increased versus decreased thrombus burden cases between the MA and SRT arms ($P 0.29$);(figure 23).

A representative case with successful thrombus volume/burden reduction is shown in figure 24.

There were very strong significant correlations between baseline thrombus volume and ΔTVol (mm^3) for both the SRT ($\rho = 0.84$; CI: 0.63-0.96; $P < 0.001$) and MA ($\rho = 0.92$; 95% CI: 0.82-0.98; $P < 0.001$) arms (Figure 25). Notably, 18% of patients recruited had a very low/negligible thrombus volume ($<3\text{mm}^3$) at baseline, despite angiographic selection for LTB. Half of these patients had a TIMI thrombus grade of 5.

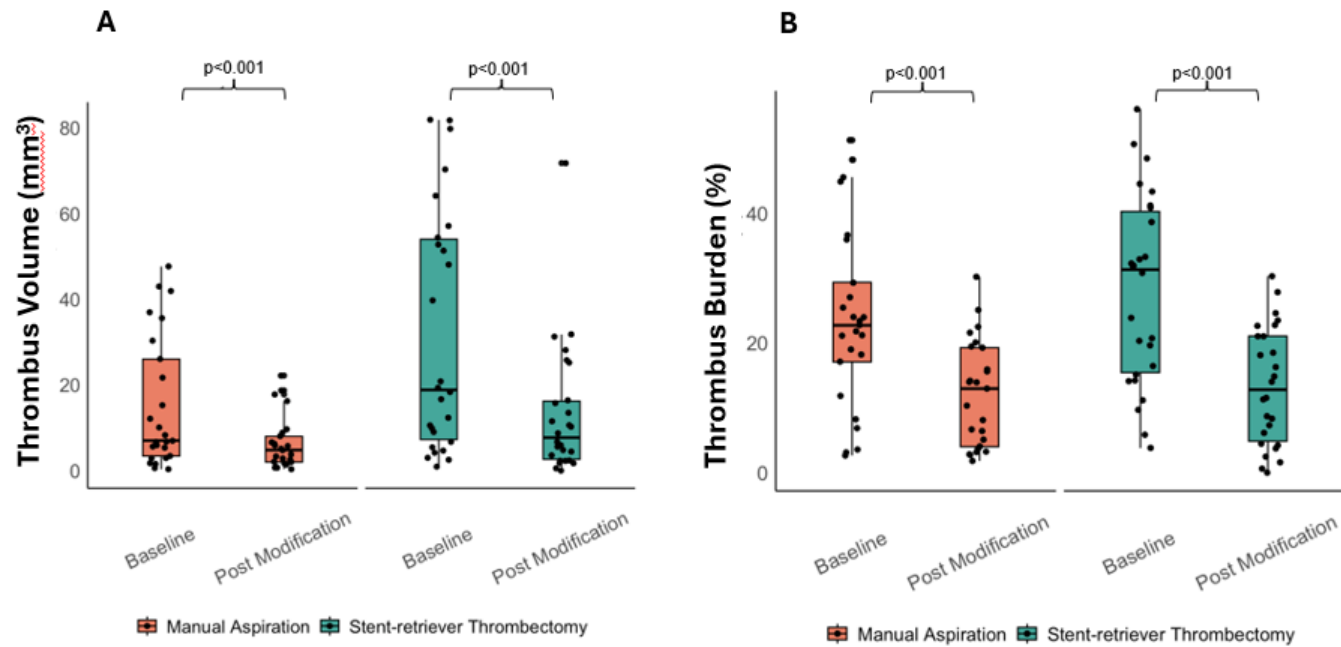


Figure 22. OCT-derived coronary thrombus at baseline and post-modification with manual aspiration versus stent-retriever. **(A)** Thrombus volume (mm³) and **(B)** thrombus burden (%) at baseline and post-modification for the manual aspiration (orange) and stent-retriever thrombectomy (teal) arms. Boxes show median and interquartile ranges (IQR), whiskers, 1.5 × IQR. P values above brackets are for within-arm baseline vs post-modification comparisons (Wilcoxon rank-sum). Both techniques demonstrated significant reductions in thrombus volume and burden pre- to post modification ($p < 0.001$ in each arm).

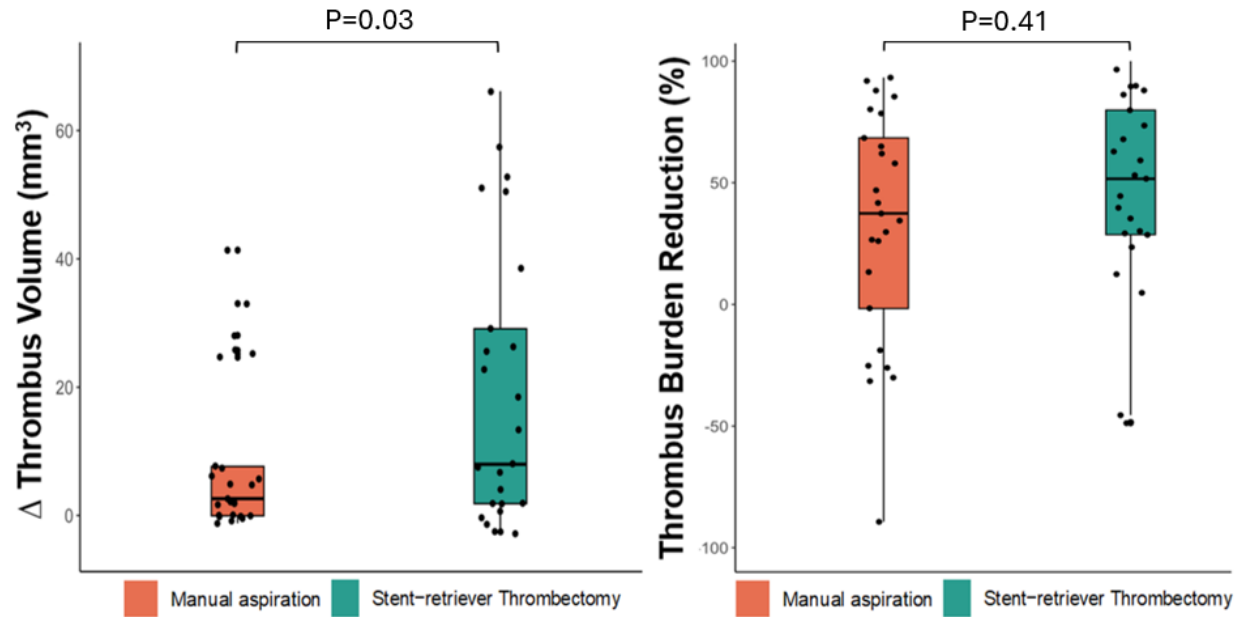


Figure 23. Reduction in coronary thrombus by technique. (A) Δ Thrombus Volume (baseline minus post-modification volume, mm³) and (B) Thrombus Burden Reduction (%), comparing manual aspiration (orange) with stent-retriever thrombectomy (SRT) (teal). Points are individual patients, boxes indicate median and interquartile ranges (IQR), whiskers, $1.5 \times \text{IQR}$. Between-group p-values are from the Wilcoxon rank-sum test. SRT achieved a larger absolute reduction in thrombus volume ($p=0.03$), while percent burden reduction did not differ significantly between arms.

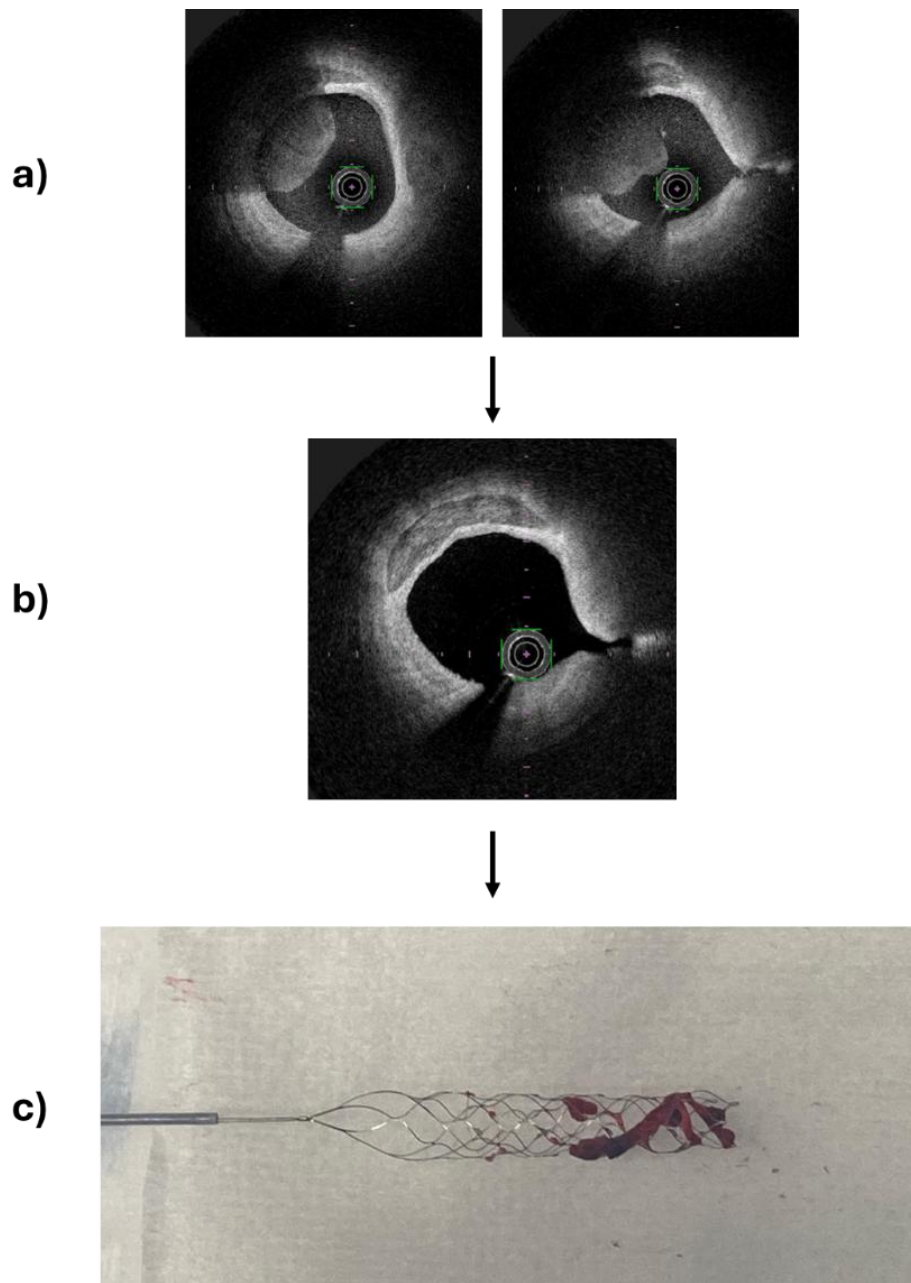


Figure 24. Example case of an effective coronary thrombus extraction during STEMI using a stent retriever. a) baseline OCT slices showing thrombus within the coronary vessel; b) post stent retriever OCT slice showing no thrombus within the same segment of vessel; c) photograph showing extracted thrombus attached to the stent-retriever device.

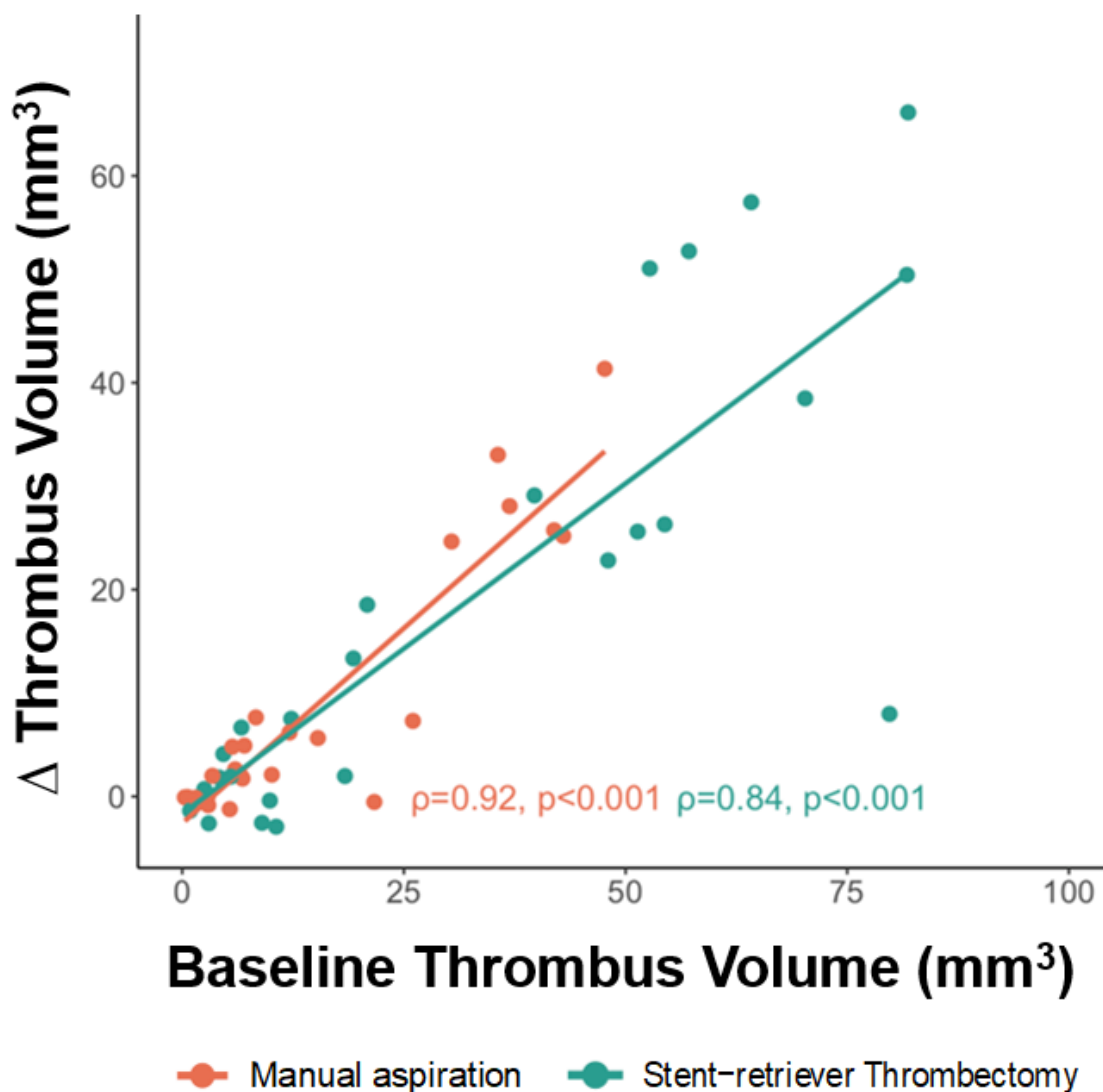


Figure 25. Baseline thrombus volume versus thrombus volume reduction.

Δ thrombus volume (mm³) - defined as baseline minus post-modification OCT thrombus volume), against baseline thrombus volume (mm³), by technique: manual aspiration (orange) and stent-retriever thrombectomy (teal). Points represent individual patients, solid lines depict linear trend lines for visualisation. Associations were assessed with Spearman's rank correlation: manual aspiration $\rho = 0.92$, $p < 0.001$; stent-retriever thrombectomy $\rho = 0.84$, $p < 0.001$.

Post-stenting OCT findings

Post-stenting OCT-derived measurements are summarised in table 11. Residual post-stenting thrombus volume was lowest in the SRT arm (median: 0.5 mm³ [IQR 0.0–2.8]), intermediate in the MA arm (1.8 mm³ [IQR 0.6–4.7]) and highest in stenting-only (3.4 mm³ [IQR 1.1–6.3]), there was a statistically significant difference between groups ($p=0.01$ (Kruskal-Wallis test), but no difference between MA and SRT arms $p=0.08$.

Minimum stent area (MSA) did not differ significantly between groups, SRT was (7.2 mm² [IQR 5.4–8.7]) versus MA (6.3 mm² [IQR 5.0–7.4]) and stenting-only (5.9 mm² [IQR 4.7–7.1]). Rates of stent-edge dissection, malapposition, and underexpansion were low.

Example OCT frames showing residual thrombus, stent-area measurements and significant and non-significant malposition are shown in figure 25 (see chapter 2 for definitions).

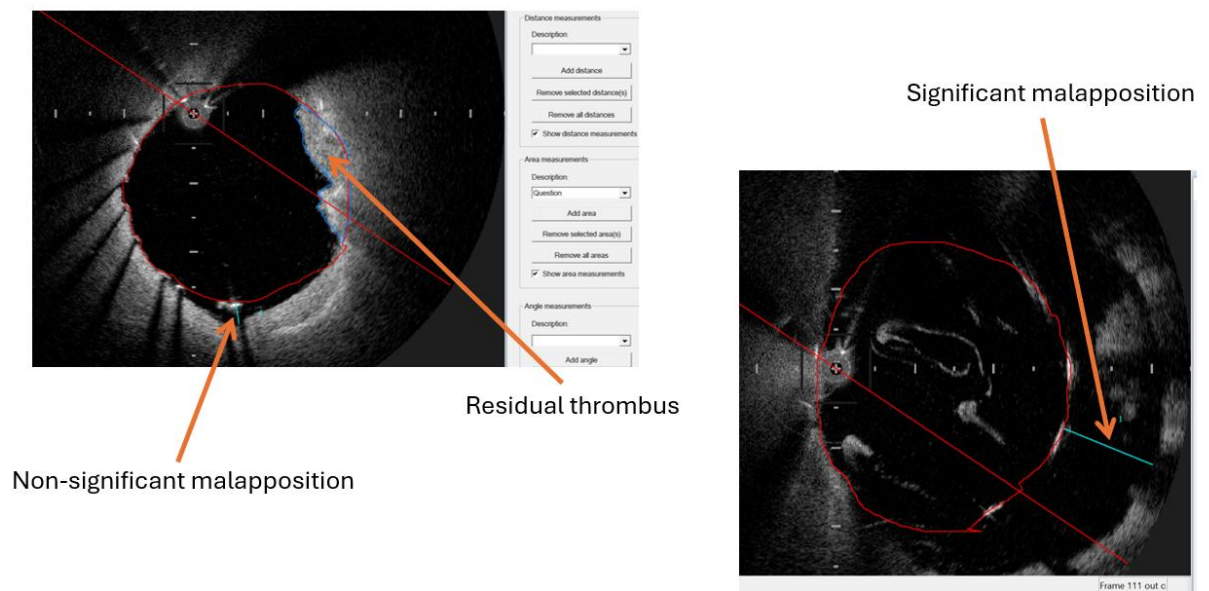
Inter and intra-observer agreement for lumen and thrombus area measurements

Inter- and intra-observer agreement for frame-level lumen measurements, assessed using the Dice similarity index, were 0.93 (95% confidence interval [CI]: 0.92–0.94; $n = 169$) and 0.94 (95% CI: 0.94–0.95; $n = 169$), respectively. For frame-level thrombus measurements, inter- and intra-observer agreement were 0.74 (95% CI: 0.69–0.77; $n = 126$) and 0.78 (95% CI: 0.75–0.80; $n = 126$), respectively.

Table 11. Post-stenting optical coherence tomography measurements. *1 patient in the MA arm died prior to stenting, **2 patients in the SRT arm had unanalysable post-stent OCT runs and 1 was crossed over to stenting-only.

	No thrombus modification (stenting-only) (n=28)	Manual aspiration (n=26)*	Stent-retriever thrombectomy (n=24)**	p-value (MA vs SRT)
Residual thrombus volume, mm ³ — median (IQR)	3.4 (1.1–6.3)	1.8 (0.6–4.7)	0.5 (0.0–2.8)	0.08
Minimum stent area, mm ² — median (IQR)	5.9 (4.7–7.1)	6.3 (5.0–7.4)	7.2 (5.4–8.7)	0.22
Stent-edge dissection, n (%)	1 (3.6%)	1 (3.8%)	0 (0%)	N/A
Malapposition, n (%)	5 (17.8%)	1 (3.8%)	2 (8.0%)	0.61
Underexpansion, n (%)	5 (17.8%)	3 (11.5%)	1 (4.0%)	0.61

Figure 25. Example post stenting OCT images showing residual thrombus (outlined in blue), stent area (red outlines) and stent malapposition (measured with teal lines) stent malapposition



Validation of ΔTVol measurement

The change in OCT measured thrombus volume pre- to post-thrombus modification (ΔTVol , mm^3) measurement, was designed for this project and therefore had not been previously used or validated. ΔTVol aims to assess the efficacy of coronary thrombus extraction, therefore a logical way to assess this was to compare the actual amount of thrombus extracted with this novel OCT measure.

For SRT a standardised photograph of the stent-retriever post thrombectomy attempt was taken for 23 cases, visible thrombus was seen in 14 cases. For MA a standardised photograph of the aspiration basket post thrombectomy was taken for 16 cases, visible thrombus was seen in 11 cases. Mean area of extracted thrombus for SRT was 7.1 mm^2 .

Mean of extracted thrombus was MA was 7.9 mm^2 .

Strong significant correlations were seen between extracted thrombus area and OCT-derived ΔTVol (mm^3), for SRT ($\rho = 0.91$; $P = <0.001$) and MA ($\rho = 0.69$; $P = <0.01$), using Spearmann's rank correlation (figure 26).

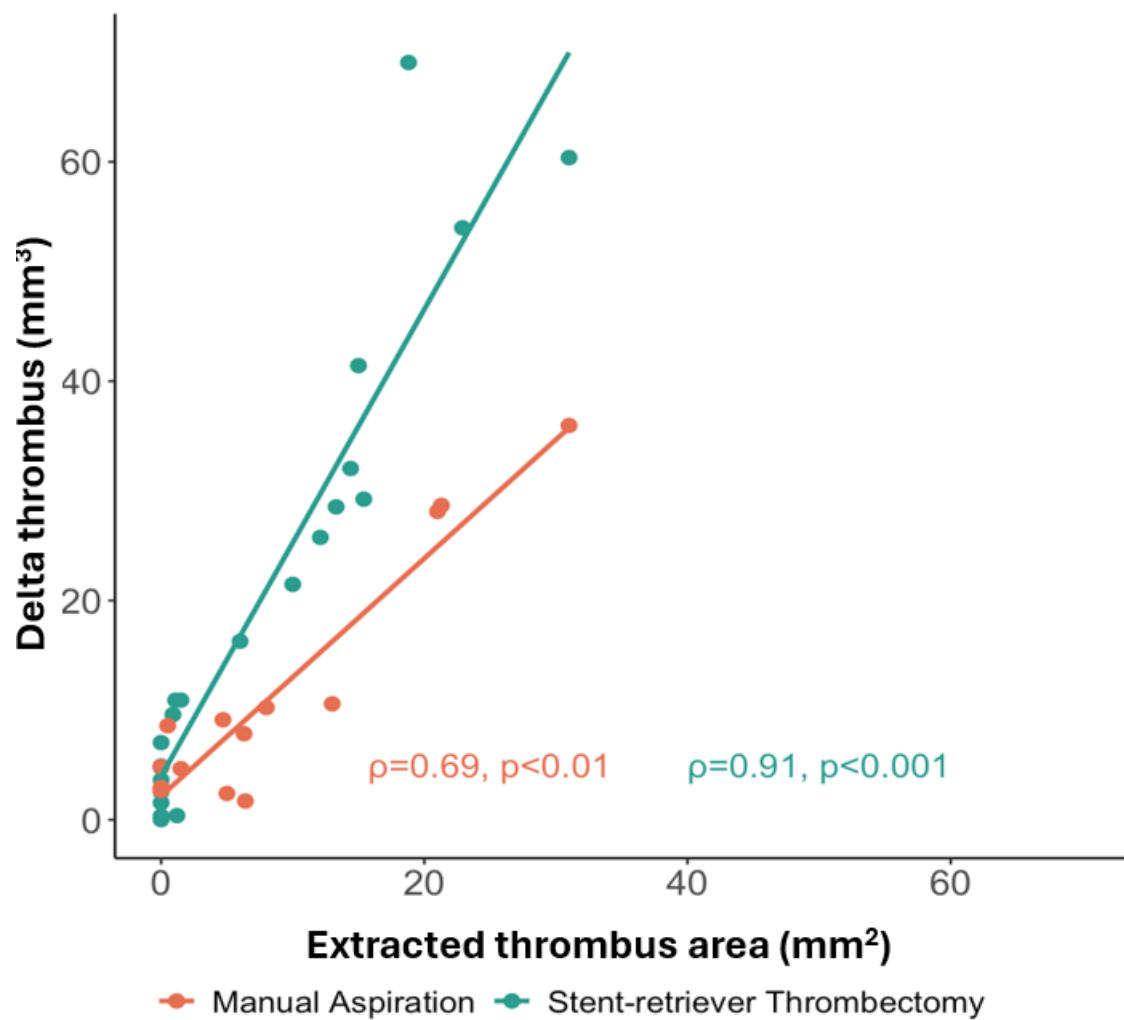


Figure 26. Scatter plot of Δ thrombus volume (mm³) versus photographed extracted thrombus area (mm²). Larger extracted thrombus area correlated with greater OCT-measured thrombus reduction, supporting Δ thrombus volume as a surrogate of coronary thrombus burden reduction for manual aspiration (orange) and stent-retriever thrombectomy (teal). Associations were tested with Spearman's rank correlation: MA $\rho=0.69, p<0.01$; SRT $\rho=0.91, p<0.001$.

Machine learning models for automated thrombus segmentation

In collaboration with a software engineer (MC) three dual-coordinate cross-attention transformer network (DCCAT) based machine learning models were trained to automatically segment thrombus on OCT (Models A,B and C) on previously collected OCT images²⁵⁸. We manually segmented 395 OCT pullbacks comprising of 5649 frames, to act as the ground truth to train the models.

The models were tested on the OCT runs of the first 35 patients in our project. The models generated automated segmentations on individual images slices. I performed a simple analysis of these automated segmentations, reviewing each image. For each image I deemed if the segmentation was correct “1” or incorrect “0”.

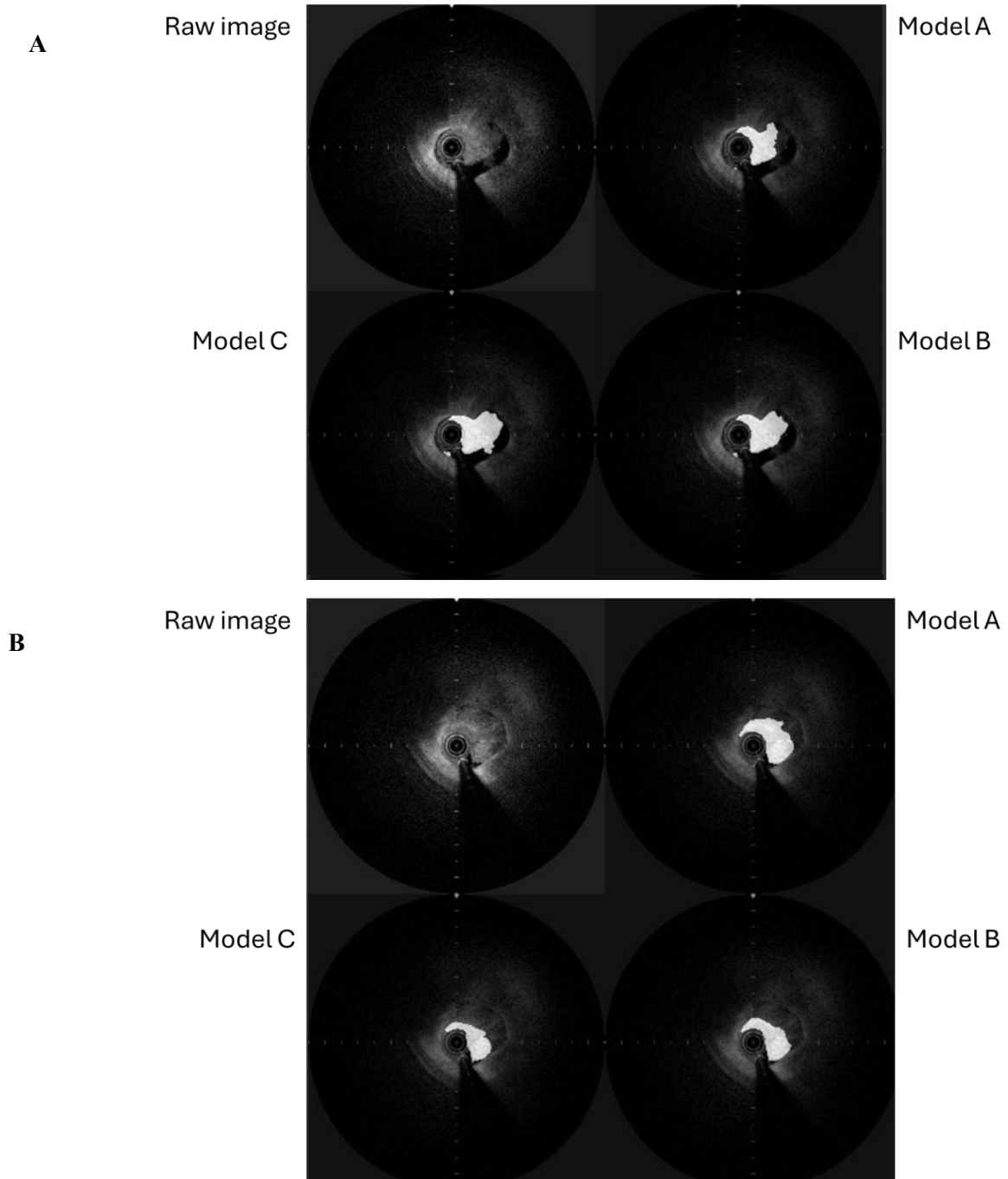
I reviewed 2999 automatically segmented thrombus containing OCT frames for each model. For model “A” 24% (n = 720) of thrombus containing frames had a correct segmentation; for model “B” 27% (n=810) of thrombus containing frames had a correct segmentation and for model “C” 35% (m=1050) of thrombus containing frames had a correct segmentation.

Figure 27 shows examples of A: correct automated thrombus segmentations (for all models) and B: incorrect automated thrombus segmentations (for all models).

Qualitatively, common mistakes made by all models were not segmenting areas of thrombus, where high density thrombus caused areas of signal dropout (as seen in 27 B) and segmenting areas of atherosclerotic plaque as thrombus. Further examples of automated thrombus segmentations are shown in appendix 11.

Due to the perceived low level of accuracy of these machine learning based thrombus segmentation models we segmented thrombus manually for this project with QIVUS™ (Medis Medical Imaging, Leiden, Netherlands) software.

Figure 27. Examples of automated machine learning (ML) thrombus segmentations on OCT (white highlighted area) for three ML models, deemed **A)** correct and **B)** incorrect.



Summary and interpretation

This chapter describes baseline characteristics, the effect of thrombus modification techniques (MA and SRT) on OCT metrics, validation of a novel OCT endpoint (reduction in coronary thrombus volume; ΔTVol) and an exploratory evaluation of machine-learning segmentation.

Across demographic and procedural variables, the three randomised arms were broadly comparable. Some OCT parameters, however, were imbalanced at baseline: the SRT arm had a higher median thrombus volume (18.3 mm^3) than MA (7.6 mm^3) and stenting-only (9.8 mm^3), and a larger lumen volume (78.4 mm^3 vs 46.0 mm^3 and 43.9 mm^3 , respectively). After accounting for lumen volume, baseline thrombus burden (percentage of lumen occupied by thrombus) was similar between groups.

Both SRT and MA produced significant reductions in thrombus volume and thrombus burden. The absolute reduction in thrombus volume was greater with SRT than with MA. This difference likely reflects, at least in part, the higher baseline thrombus volume in the SRT arm, consistent with the strong correlation observed between baseline thrombus volume and ΔTVol . When corrected for lumen size, the percentage reduction in thrombus burden did not differ between SRT and MA.

A notable finding was that 18% of participants had negligible thrombus on baseline OCT ($<3 \text{ mm}^3$) despite angiographic selection for LTB (TIMI thrombus grade ≥ 4), underscoring the limitations of angiographic thrombus grading for selecting patients with LTB. Bhindi et al. demonstrated in an OCT sub-study of the TOTAL trial that higher TIMI thrombus grade correlates with greater thrombus burden on OCT. Specifically, mean pre-stenting thrombus burden was 3.44% (2.37–4.99%) among patients with high TIMI thrombus grade (≥ 4), compared to 1.65% (0.95–2.85%) in

those with low grade (<3).⁵ However, despite TIMI thrombus grade serving as an indicator of thrombus burden, the data in this chapter indicate that it is far from precise.

These data support OCT-based selection for future studies targeting LTB. Alternatively, machine learning based techniques could be developed to automatically detect and quantify thrombus burden on angiography. The aim of this would be to outperform TIMI thrombus grade and avoid more time and equipment intensive OCT runs. AI-based angiographic analysis has already shown promise in detecting new markers that can predict outcomes in PCI, such as angiographic radial wall strain.²⁸⁵ The powers of AI are likely to be able to optimise angiography-based thrombus assessment.

The ΔTVol measure was validated by comparison with photographed extracted thrombus area, demonstrating strong correlations and supporting ΔTVol as a suitable surrogate of thrombus removal. In contrast, preliminary dual-coordinate cross-attention transformer (DCCAT) models for automated thrombus segmentation achieved modest accuracy (24–35%), and manual segmentation was therefore used, further model development may improve performance of such ML models. Inter- and intra-observer agreement for manual segmentations were excellent for frame-level lumen measurements and good for frame-level thrombus measurements.

In summary, both thrombus-modification strategies effectively reduced OCT-measured thrombus. The following chapters examine the impact of such thrombus burden reduction on measures of myocardial perfusion, assess safety of the thrombectomy techniques and examine extracted thrombus phenotype by technique.

Chapter 4: Microvascular resistance pre and post stenting by angiographic index of microvascular resistance

Introduction

The aim of this chapter is to report the results of the computational fluid-dynamic based assessment of microvascular function using IMR_{angio} . Pre-stenting and post-stenting IMR_{angio} values, as well as within arm change ($\Delta IMR_{\text{angio}}$), are presented for each treatment arm (stenting-only, MA, and SRT), alongside between-arm comparisons.

Beyond the angiographically visible major epicardial coronary arteries, STEMI causes significant injury and obstruction of the coronary microcirculation via several pathophysiological mechanisms (figure 3). Thrombus embolization into the microvasculature in STEMI is one such mechanism that has been linked with a higher incidence of cardiovascular death.^{10,12,286} It follows that microvascular flow should be rigorously assessed when evaluating the performance of thrombus extraction devices that aim to reduce downstream embolisation.

Traditional semi-quantitative measures of myocardial perfusion such as MBG and TIMI flow lack precision. However, the index of microcirculatory resistance (IMR) measurement allows for a more precise quantification of microvascular perfusion. IMR is traditionally measured using a specialised intracoronary wire incorporating pressure and temperature sensors. Microvascular resistance is derived from change in pressure and flow measured in the coronary. Flow is calculated by assessing the speed at which coronary temperature returns to normal after a bolus of saline is injected, whilst maximal hyperaemia is induced. Elevated IMR is an independent predictor of increased infarct size in STEMI.^{287,288}

However, traditional IMR measurement requires insertion of a pressure wire and administration of hyperaemic agents adding time and procedural risk in the acute setting. With the use of computational fluid dynamic techniques, physiological measurements can now be obtained from angiograms alone without the use of wires. De Maria et al validated the pressure wire-free, angiographically derived index of microcirculatory resistance (IMR_{angio}) in STEMI, used here.²⁰¹ They also found in the context of STEMI an elevated $IMR_{\text{angio}} \geq 40$ was associated with a substantially higher rate of early cardiovascular complications compared with values <40 .²⁰² Given its practicality, prior validation in STEMI, and prognostic relevance, IMR_{angio} was selected as the key endpoint for this chapter.

Constituent data of IMR_{angio}

As detailed in chapter 3, the IMR_{angio} measurement was derived from two main constituents 1) epicardial coronary flow measured by quantitative flow ratio (QFR) and 2) mean arterial pressure at the time the angiogram was taken.

The QFR measurements were generated using QAngio® XA 3D software (Medis, Leiden, the Netherlands). QFR measurements are generated by reconstructing a 3D model of the coronary artery from two angiographic views, estimating contrast flow velocity and using computational fluid dynamics to estimate hyperaemic pressure drop and derive a pressure ratio (distal/aortic) approximating FFR. In this study we took high frame rate (15 frames/second) to maximise accuracy.

Table 12 summarises the constituent data and IMR_{angio} output for each arm and the entire cohort.

Table 12. Hemodynamic and microcirculatory parameters by treatment arm. Data include pre- and post-stenting mean arterial pressure (MAP), quantitative flow ratio (QFR), derived IMR_{angio} measurements, and proportion of patients with $IMR_{angio} \geq 40\%$ for each treatment group (stent-retriever thrombectomy, manual aspiration, and stenting-alone) and the combined cohort. Values are presented as median (interquartile range) except for post-stent $IMR \geq 40\%$, which is reported as number of cases and (percentage).

	Stent-retriever	Manual Aspiration	Stenting-alone	All arms
Pre-stenting MAP, median (IQR)	84 (76-96)	69 (65-90)	83 (68-91)	82 (68-92)
Post-stenting MAP, median (IQR)	81 (76-84)	76 (69-89)	86 (71-96)	80 (71-89)
Pre-stenting QFR, median (IQR)	0.70 (0.52-0.79)	0.71 (0.52-0.79)	0.71 (0.67-0.82)	0.71 (0.63-0.81)
Post-stenting QFR, median (IQR)	0.96 (0.92-0.99)	0.97 (0.94-0.99)	0.95 (0.91-0.98)	0.97 (0.92-0.99)
Pre-stenting IMR_{angio} , median (IQR)	43 (24-60)	28 (16-42)	36 (26-58)	36 (22-51)
Post-stenting IMR_{angio} , median (IQR)	43 (35-55)	41 (32-47)	48 (38-70)	45 (34-55)
ΔIMR_{angio} pre to post stenting, median (IQR)	8.6 (-13-21)	14 (-0.3-25)	10 (-1-23)	11 (-1-24)
Post stent $IMR_{angio} \geq 40\%$, n (%)	10 (55%)	12 (55%)	17 (70%)	35 (55%)

Pre-stenting MAP did not differ significantly between arms, with a median of 82 mmHg across the cohort. Post-stenting MAP was similar across all groups, with a median of 80 mmHg, p 0.13.

Pre-stenting QFR was comparable across arms, indicating impaired epicardial flow with a median of 0.71. Post-stenting QFR showed substantial improvement across all groups, with a median of 0.97 indicating good epicardial flow.

Pre-stenting IMR_{angio} did not differ significantly between arms p 0.07. Post-stenting IMR_{angio} was similar between groups p 0.21 (Kruskal-Wallis test).

The change in IMR_{angio} ($\Delta IMR_{\text{angio}}$) from pre- to post-stenting showed no statistically significant difference between arms p 0.4 (Kruskal-Wallis test).

The proportion of patients with $IMR_{\text{angio}} \geq 40\%$ post-stenting was 70% in the stent-only group compared to 55% in both the MA and SRT groups, with no statistically significant difference detected between arms p 0.4 (chi-squared test) (figure 28).

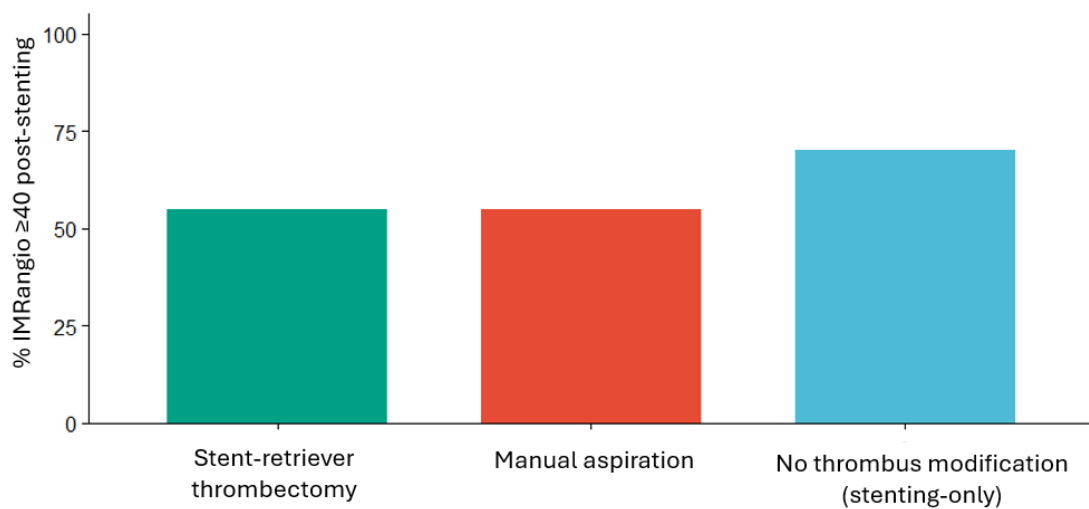
Missing data

Of the 81 participants recruited, IMR_{angio} measurements were successfully generated in 55 (68%) pre-stenting and 63 (78%) post-stenting. Paired IMR_{angio} measurements (pre- and post-stenting) were available in 54 (67%) participants.

Reasons for IMR_{angio} data not being available for the remaining cases (pre-stenting, post-stenting or both) are: additional high-frame rate angiograms for QFR intentionally omitted by operator (e.g. due to concern about contrast load) (n=10); Poor/no distal vessel opacification, so QFR analysis not possible (n=8); insufficient frame rate of angiograms (<15 frames per second) (n=2); inadequate angle separation <25° of paired

angiograms (n=2); unknown reason for missing high frame rate angiogram(s) (n=3) and death of a patient during the procedure in the MA arm (n=1).

Figure 28. Proportion of participants with a post-stenting $IMR_{angio} \geq 40$ in each arm (Stent-retriever thrombectomy, manual aspiration and no thrombus modification (stenting-only)). No statistically significant difference was detected between groups, chi-squared, P 0.4.



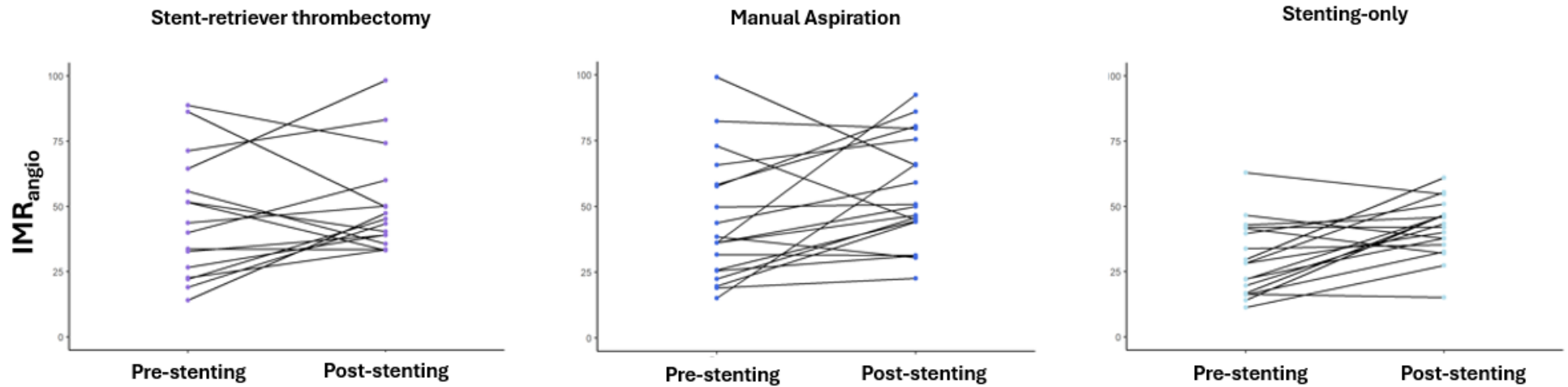
Microvascular resistance by $\text{IMR}_{\text{angio}}$ pre- to post-stenting

$\text{IMR}_{\text{angio}}$ values were elevated (>20) at both pre-stenting and post-stenting timepoints (table 12). Across the entire cohort, there was a trend towards post-stent $\text{IMR}_{\text{angio}}$ being higher than pre-stent $\text{IMR}_{\text{angio}}$, but this did not reach significance $P = 0.07$. Figure 29 presents individual participant data for each treatment arm, displayed as dot-and-line plots illustrating the changes from pre- to post-stenting.

In the MA group, post-stenting $\text{IMR}_{\text{angio}}$ was significantly higher than pre-stenting $\text{IMR}_{\text{angio}}$ ($P < 0.01$). Similarly, in the stenting-only group, $\text{IMR}_{\text{angio}}$ was significantly elevated post-stenting ($P < 0.05$). In contrast, the SRT group demonstrated no significant difference between pre-stenting and post-stenting $\text{IMR}_{\text{angio}}$ values ($P 0.44$) (Figure 30).

The change in $\text{IMR}_{\text{angio}}$ from pre- to post-stenting ($\Delta\text{IMR}_{\text{angio}}$) demonstrated an increase of similar magnitude across all treatment arms. Median values were 14 [IQR: -0.3 to 25] for MA, 8.6 [IQR: -13 to 21] for SRT, and 10 [IQR: -1 to 23] for stenting only. There was no statistically significant difference in $\Delta\text{IMR}_{\text{angio}}$ between treatment arms (Figure 31).

Figure 29: Angiographically-derived index of microvascular resistance (IMR_{angio}) pre and post stenting for individual patients in the stent-retriever thrombectomy, manual aspiration and stenting-only arms.



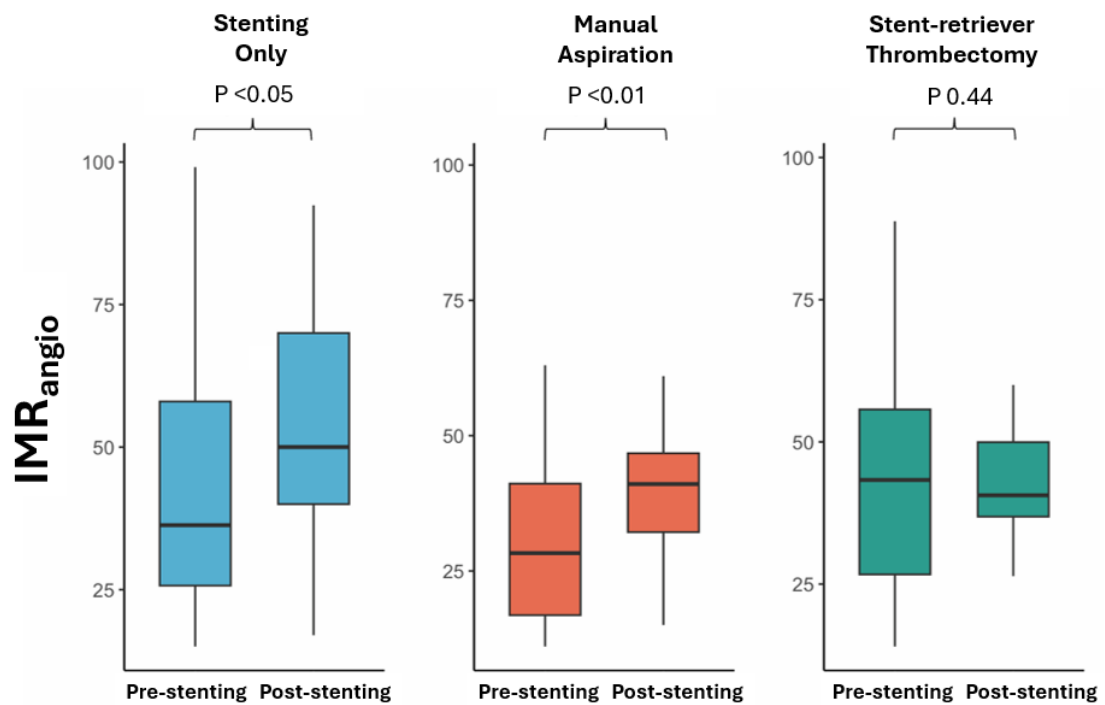
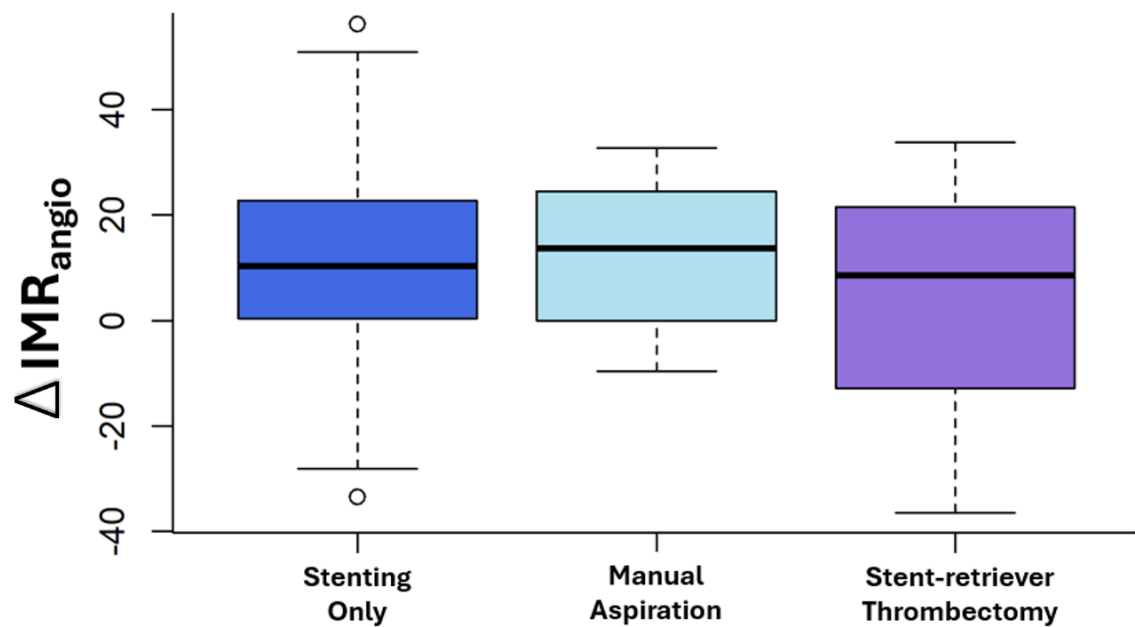


Figure 30: Angiographically-derived index of microvascular resistance (IMR_{angio}) before and after stenting, by treatment arm. Boxplots display medians and interquartile ranges (whiskers indicate range). Within-group pre- vs post-stenting comparisons are annotated above each panel: stenting only, $p < 0.05$; manual aspiration, $p < 0.01$; stent-retriever thrombectomy, $p = 0.44$.

Figure 31: Change in angiographically derived index of microvascular resistance (ΔIMR_{angio}) pre to post stent. Box-and-whisker plots show ΔIMR_{angio} for the three arms: stenting only, manual aspiration, and stent-retriever thrombectomy. Positive values indicate higher IMR_{angio} after stenting; negative values indicate a reduction. Boxes represent the interquartile range with the median as a horizontal line; whiskers extend to $1.5 \times IQR$ and open circles denote outliers.



Summary and interpretation

This chapter assessed microvascular function using angiography-derived index of microvascular resistance (IMR_{angio}) before and after stenting in STEMI patients, comparing three treatment strategies: stenting-only, MA, and SRT.

Microvascular obstruction from thrombus embolization is a major contributor to adverse outcomes in STEMI.^{170,171} IMR_{angio} offers a wire-free, computationally derived alternative to invasive IMR measurement, validated in STEMI, with $IMR_{\text{angio}} \geq 40$ associated with worse outcomes.²⁰¹⁻²⁰³ This made it an attractive endpoint for evaluating whether thrombus extraction devices could preserve or improve microvascular function.

As expected, epicardial flow improved markedly across all groups, with QFR increasing from 0.71 to 0.97 pre- to post-stenting.²⁸⁹

Interestingly, IMR_{angio} increased significantly following stenting in both the stenting-only and MA groups, but not in the SRT arm (Figure 30). This increase may be attributable to distal embolisation during stent deployment, which could exacerbate microvascular obstruction (MVO). Alternatively, it may simply reflect the natural temporal evolution of MVO, which is known to worsen during the early post-reperfusion period.²⁹⁰

The absence of a rise in IMR_{angio} from pre- to post-stenting in the SRT group may indicate that effective thrombectomy reduced thrombus embolisation and, consequently, MVO. This interpretation is supported by the observation that the SRT arm yielded the largest volume of extracted thrombus (Figure 23A). However, alternative explanations warrant consideration. The relatively shorter reperfusion time in the SRT group (Table 8) may have limited the progression of MVO. Additionally, microvascular resistance was already elevated in the SRT group prior to stenting compared with the MA and

stenting-only arms (although not significantly), suggesting that MVO may have already reached its peak in this group before stent implantation, possibly as a consequence of the higher baseline thrombus burden observed in this arm (Figure 22).

A notable trend was observed in the distribution of elevated post-stenting $\text{IMR}_{\text{angio}}$ values across treatment arms. A higher proportion of patients demonstrated an $\text{IMR}_{\text{angio}} \geq 40$ in the stenting-only arm (70%) compared with both the MA and SRT arms (55% each). However, this difference did not reach statistical significance. This lack of statistical significance may represent a Type II error (false negative), the higher proportion of participants with $\text{IMR}_{\text{angio}} \geq 40$ post stenting could reflect a reduction in microvascular obstruction following thrombus modification; however, such an interpretation remains speculative given the limited statistical power of this analysis.

The $\text{IMR}_{\text{angio}}$ analysis was likely underpowered for two principal reasons: first, the inherent constraints of a small pilot randomised controlled trial divided across three treatment arms; and second, substantial attrition of $\text{IMR}_{\text{angio}}$ data.

A key limitation of this analysis is the incomplete acquisition of $\text{IMR}_{\text{angio}}$ measurements. Of the 81 patients randomised, paired pre- and post-stenting $\text{IMR}_{\text{angio}}$ data were available for only 54 patients (67%). The most frequent causes of missing data were operator decisions to omit high-frame-rate angiograms ($n=10$) and inadequate distal vessel opacification precluding quantitative flow ratio analysis ($n=8$). This 33% data loss substantially reduced statistical power and introduces potential selection bias, as high-frame-rate angiograms may have been preferentially omitted in haemodynamically unstable patients. Notably, eight of the ten operator-omitted angiograms were attributable to a single operator. This loss of $\text{IMR}_{\text{angio}}$ data could be mitigated in future research with steps such as improved operator training and perhaps

newer computational fluid dynamic QFR algorithms requiring just a single angiographic acquisition.²⁹¹

Despite these limitations, this chapter demonstrates that $\text{IMR}_{\text{angio}}$ represents a potentially valuable non-invasive measure for use in STEMI trials. Although complete data capture was not achieved in all cases, $\text{IMR}_{\text{angio}}$ measurements were successfully obtained in the majority of patients, and acquisition rates could be improved through implementation of the methodological refinements described above. Importantly, the method detected statistically significant and physiologically plausible within-arm changes, specifically increased microvascular resistance from pre- to post-stenting, whilst avoiding the need for hyperaemic agents or intracoronary wire instrumentation.

The principal physiological findings were that microvascular resistance increased following stenting in both the MA and stenting-only arms, yet remained unchanged in the SRT arm. These findings are hypothesis-generating and suggest that SRT could minimise thrombus embolisation, although confirmation in adequately powered studies is required. An alternative explanation is that baseline imbalances, specifically higher pre-stent $\text{IMR}_{\text{angio}}$ values in the SRT arm may account for the absence of a significant increase in this group.

Notably, all treatment arms demonstrated persistently elevated microvascular resistance despite excellent epicardial recanalisation (QFR 0.97). This observation underscores that STEMI-related microvascular injury extends beyond obstruction of the epicardial vessel and may not be fully mitigated by mechanical thrombectomy strategies alone.

In summary, this chapter provides proof-of-concept evidence that $\text{IMR}_{\text{angio}}$ can quantify microvascular resistance in STEMI trials without invasive instrumentation. However, the analysis is exploratory, statistically underpowered, and affected by substantial

missing data, precluding definitive conclusions regarding comparative treatment efficacy. Despite these limitations, the findings support the use of IMRangio as a scalable physiological endpoint in future, adequately powered randomised trials evaluating microvascular protection strategies in STEMI.

Chapter 5: The impact of thrombus modification on angiographic parameters, peak troponin, echocardiographic ejection fraction and ST-segment resolution; extracted thrombus phenotyping and safety of stent-retriever thrombectomy.

Introduction

Chapters 3 and 4 examined the impact of stenting-alone, MA, and SRT on novel outcome measures: OCT-derived thrombus volume and burden (TVol [mm³] and TB [%]); and angiographically derived microvascular resistance (IMR_{angio}). The present chapter focuses on the effects of the three treatment arms on conventional measures of myocardial reperfusion commonly employed in STEMI trials. These include angiographic parameters, peak troponin levels, echocardiographic ejection fraction (EF), and ST-segment resolution on electrocardiography. Additionally, a descriptive analysis of extracted coronary thrombus following MA and SRT is presented, along with the first comparative safety data for SRT in coronary intervention.

As outlined in chapter 1, semi-quantitative angiographic measures can be used to measure the completeness of reperfusion at both the epicardial (TIMI flow grade) and microvascular/tissue level (MBG and no-reflow). Further, the absence or presence of distal embolisation of thrombus can be identified angiographically. Each of these parameters have been associated with short- and long-term clinical outcomes after STEMI.^{170,172,173,178,180-182}

Like angiographic markers of reperfusion, ST-segment resolution, peak post-PCI troponin concentration, and left ventricular ejection fraction are well-established surrogate endpoints with robust associations with both clinical outcomes and final infarct size.^{212,219-221,223,273,292,293} Specifically, in the context of thrombectomy in STEMI,

Bianchini et al. conducted a meta-analysis of randomised controlled trials comparing MA with stenting alone, demonstrating significantly improved left ventricular function in patients who underwent thrombus aspiration.⁷⁹ In my study, all angiographic, electrocardiographic, and echocardiographic measurements were performed by a single investigator (JW) who was blinded to treatment allocation by another investigator (SA).

In addition to examining surrogates of outcome this study provided a unique opportunity to examine extracted coronary thrombi obtained via both MA and SRT. As discussed in Chapter 1, thrombus composition demonstrates considerable variability and evolves over time, with potential implications for microvascular obstruction, distal embolisation, myocardial injury, and responsiveness to intervention.^{22,25} In this chapter, a straightforward visual classification system is presented, whereby extracted coronary thrombi were categorised as "red," "white," or "mixed" based on colour and gross appearance for both thrombectomy techniques. This macroscopic classification approach has been validated in previous studies, demonstrating strong correlation with histological and scanning electron microscopy findings. Specifically, thrombi classified as visually "white" have been shown to be predominantly composed of platelets and fibrin, whereas those designated as "red" exhibit a higher proportion of erythrocytes.²⁷⁷

Finally, a safety assessment of any novel medical intervention is essential to ensure a net clinical benefit. Such an evaluation is of particular importance in this context, as this thesis represents the first RCT to assess the use of SRT in coronary intervention.

Moreover, the risk of proximal thrombus embolisation during thrombectomy, potentially resulting in stroke, represents a significant concern highlighted by the findings of the TOTAL trial.⁵³ The analysis presented in this chapter constitutes the first systematic safety evaluation of SRT in comparison to current standard approaches (stenting alone or MA). This analysis examines the following outcomes across

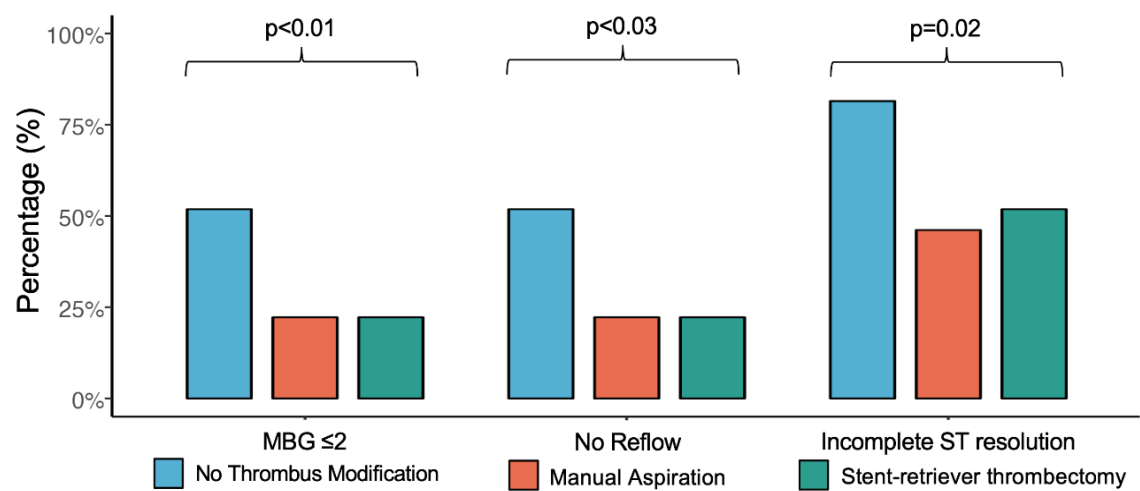
treatment arms: intraprocedural and periprocedural complications, in-hospital adverse events, and clinical outcomes at six-month follow-up.

In summary, this chapter presents the results of analyses of conventional reperfusion outcomes across the three treatment arms, complemented by a descriptive assessment of extracted thrombus characteristics and the first comparative safety evaluation of SRT in coronary intervention.

Angiographic outcomes

This section presents the results of the blinded angiographic analysis of final TIMI flow, MBG, no reflow and angiographic distal embolization. Key significant findings are summarised in figure 32.

Figure 32: Proportion of patients with impaired myocardial blush grade (MBG ≤ 2), angiographic no reflow, and incomplete ST-segment resolution following primary percutaneous coronary intervention, stratified by treatment allocation: no thrombus modification (blue), manual aspiration (orange), and stent-retriever thrombectomy (teal). Both thrombectomy techniques were associated with significantly lower rates of impaired MBG ($p < 0.01$) and no reflow ($p < 0.03$) compared to stenting alone. Incomplete ST-segment resolution was most frequent in the no thrombus modification group, with manual aspiration demonstrating the lowest incidence ($p = 0.02$) (Chi-squared).



No-reflow and distal embolization

A statistically significant difference in angiographic no-reflow incidence at the end of the procedure (post-stenting and following post-dilatation) was observed across treatment arms ($p=0.03$), with the no thrombus modification (stenting-only) group exhibiting a rate of 50.0% compared to 22.2% and 18.5% for MA- and SRT-assisted PCI, respectively (Figure 32).

The overall incidence of angiographically detected distal embolisation was low across all groups. In the stenting-only arm, distal embolisation was detected in 7 of 28 cases (5 pre-stenting, 2 post-stenting). In the MA arm, distal embolisation occurred in 2 of 27 cases, both pre-stenting. In the SRT arm, distal embolisation was observed in 7 of 26 cases (5 pre-stenting, 2 post-stenting). No statistically significant differences in the rate of distal embolisation were detected across arms.

Final TIMI flow grade

Across the three treatment arms final TIMI flow 0 occurred only once, in the MA arm due to intraprocedural death. TIMI i flow was also uncommon, observed in 2/27 (7.4%) in the MA arm and 1/27 (3.7%) in the SRT arm, with none in the no thrombus modification arm. TIMI ii flow occurred in 10/27 (37.0%) in the no thrombus modification arm, compared with 2/27 (7.4%) in the manual aspiration arm and 4/27 (14.8%) in the stent-retriever thrombectomy arm. Final TIMI flow iii occurred in 22/27 (81%) in both the MA and SRT arms, and occurred in 17/27 (63%) of the stenting only arm, table 13. No statistically significant difference was found between arms ($p=0.08$).

Table 13. *Final TIMI flow by treatment arm.*

Final TIMI flow	No Thrombus Modification n (%)	Manual Aspiration n (%)	Stent-Retriever Thrombectomy n (%)
0	0 (0%)	1 (3.7%)	0 (0%)
1	0 (0%)	2 (7.4%)	1 (3.7%)
2	10 (37%)	2 (7.4%)	4 (14.8%)
3	17 (63%)	22 (81.4%)	22 (81.4%)

Final myocardial blush grade (MBG)

Overall, higher MBG scores (indicating better myocardial perfusion) were most frequent in the MA and SRT arms, with 21 patients (77.7%) in both achieving MBG 3. In contrast, less than half of patients in the stenting-only arm reached MBG 3 (table 14).

Lower MBG scores were more common in the stenting-only arm. Specifically, MBG 1 was observed in 5 patients (18.5%) and MBG 2 in 9 patients (33.3%). The MA arm had 6 patients (22.2%) with MBG 1 and no patients with MBG 2, while the SRT arm had the lowest proportion of MBG 1 (2 patients, 7.4%) and 4 patients (14.8%) with MBG 2.

Importantly, there was a statistically significant difference between treatment arms in the proportion of individuals with an MBG ≤ 2 ($p < 0.01$, chi-squared test), indicating that myocardial perfusion outcomes differed meaningfully across the three strategies,

with thrombus modification approaches associated with more favourable MBG distributions (figure 32).

Table 14. *Final Myocardial blush grade by treatment arm.*

Myocardial Blush Grade (MBG)	No Thrombus Modification n (%)	Manual Aspiration n (%)	Stent-Retriever Thrombectomy n (%)
1	5 (18.5%)	6 (22.2%)	2 (7.4%)
2	9 (33.3%)	0 (0.0%)	4 (14.8%)
3	13 (48.1%)	21 (77.7%)	21 (77.7%)

ST-segment resolution

Incomplete or partial ST-segment resolution was highest in the stenting-only arm: 22 patients (81%), compared with 12 patients (46.2%) in the MA group and 14 (51.9%) patients in the SRT group. The difference in proportions between the three treatment arms was statistically significant ($p = 0.02$, chi-squared test), see figure 32.

The inverse of this is that complete ST-segment resolution occurred in 18.5% of the stenting-only arm, 53.8% of the MA arm and 48.1% of the SRT group.

Echocardiographic outcomes

Echocardiographic left ventricular ejection fraction (LVEF) was obtained in line with routine clinical practice. The aim was for all patients to have an early echocardiogram within 7 days of STEMI in line with best practice. If LVEF was reduced ($<55\%$) post STEMI a further echocardiogram was ordered at approximately 6-months post-discharge.

Early post-PCI LVEF

Echocardiographic assessment was performed within seven days of STEMI in 80 of the 81 recruited patients, one patient died during the index procedure and therefore did not undergo imaging. Early left ventricular ejection fraction (LVEF) was comparable across treatment groups: the stenting-only arm demonstrated a median LVEF of 48% (IQR 40–52%; $n = 28$), the MA arm 52% (IQR 44–55%; $n = 26$), and the SRT arm 48% (IQR 45–55%; $n = 26$). No statistically significant difference in early LVEF was observed between treatment arms (Kruskal-Wallis test; $p = 0.31$).

Six-month LVEF and LVEF change

Of the 81 patients recruited, 51 had a follow-up echocardiogram at approximately six months, providing paired LVEF measurements from early post-PCI to six-month follow-up. Median six-month LVEF was 52% (IQR 43.75–55; $n = 17$) in the stenting-only arm, 55% (IQR 50–57.5; $n = 17$) in the MA arm, and 56% (IQR 43–60; $n = 17$) in the SRT arm. No statistically significant difference in six-month LVEF was detected between treatment arms (Kruskal-Wallis test; $p = 0.22$; Figure 33).

The median change in LVEF from early post-PCI to six-month follow-up was 1.5% (IQR $-2.4 - 5$; $n = 17$) in the stenting-only arm, 2.5% (IQR $0 - 6.5$; $n = 17$) in the MA

arm, and 4% (IQR $-0.75 - 10$; $n = 17$) in the SRT arm. No significant difference was observed between arms (Kruskal-Wallis test; $p = 0.55$; Figure 34).

Figure 33: Six-month left ventricular ejection fraction by treatment arm.

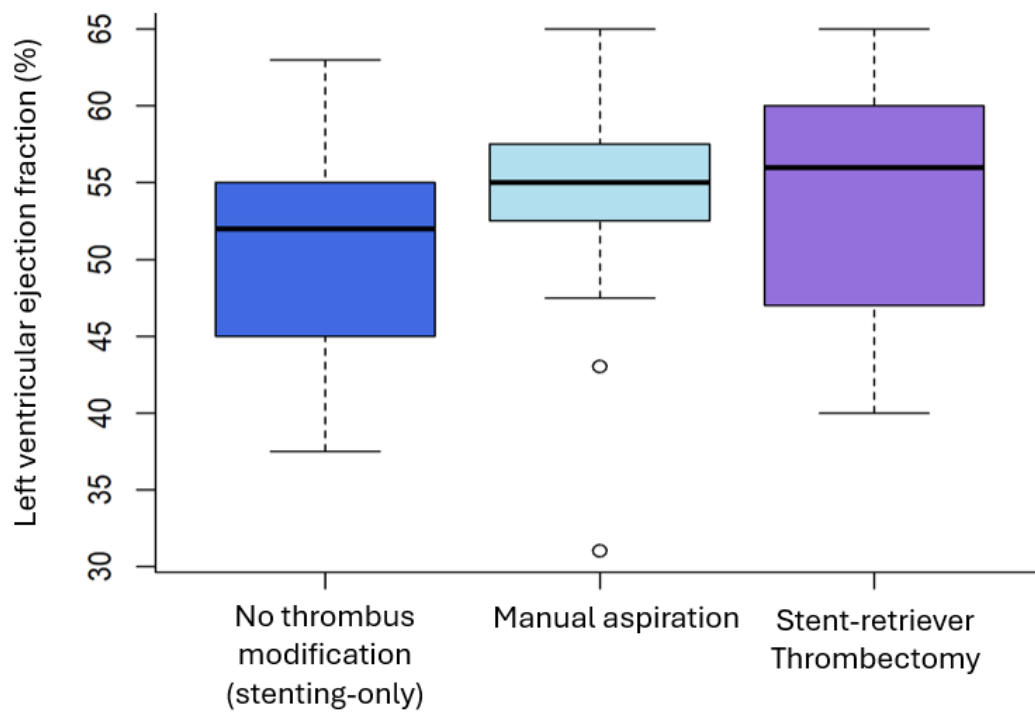
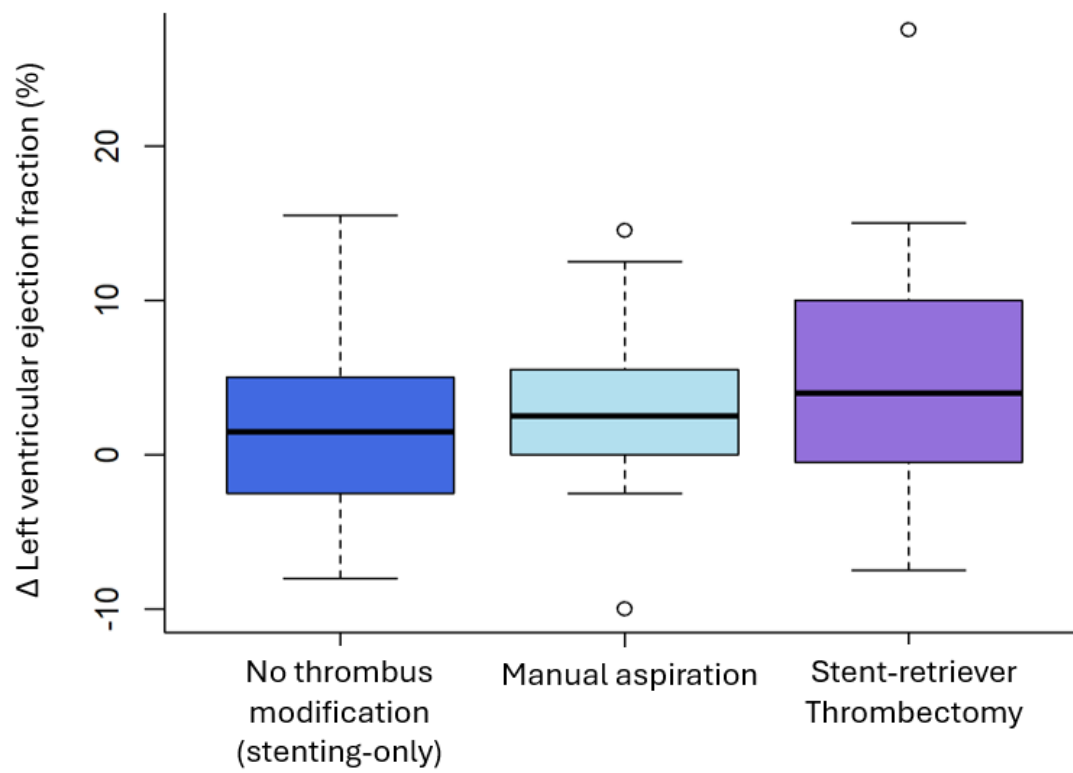


Figure 34: Change in left ventricular ejection fraction from early post-STEMI to six-months post STEMI by treatment arm.



Due to small sample size (17 patients per arm), the two thrombectomy groups MA and SRT were combined into one group (combined thrombectomy) and compared to stenting only for 6-month LVEF and change in LVEF.

At 6-months median LVEF was 52% (IQR 43.75-55; $n = 17$) in the stenting-only group and 55.5% (IQR 47.5-60) in the combined thrombectomy group. The difference between the two groups was not significant (Wilcoxon rank sum with continuity correction; $p = 0.086$; figure 35)

Change in LVEF from early post STEMI to 6-months post STEMI was a median of 1.5% (IQR -2.4-5; $n = 17$) in the stenting-only group and 2.5% (IQR 0-7.7; $n = 34$) in the combined thrombectomy group. There was no significant difference between these groups (Wilcoxon rank sum with continuity correction; $p = 0.3$; figure 36).

Figure 35: Six-month left ventricular ejection fraction in the stenting-only group and combined thrombectomy group (stent-retriever thrombectomy and manual aspiration).

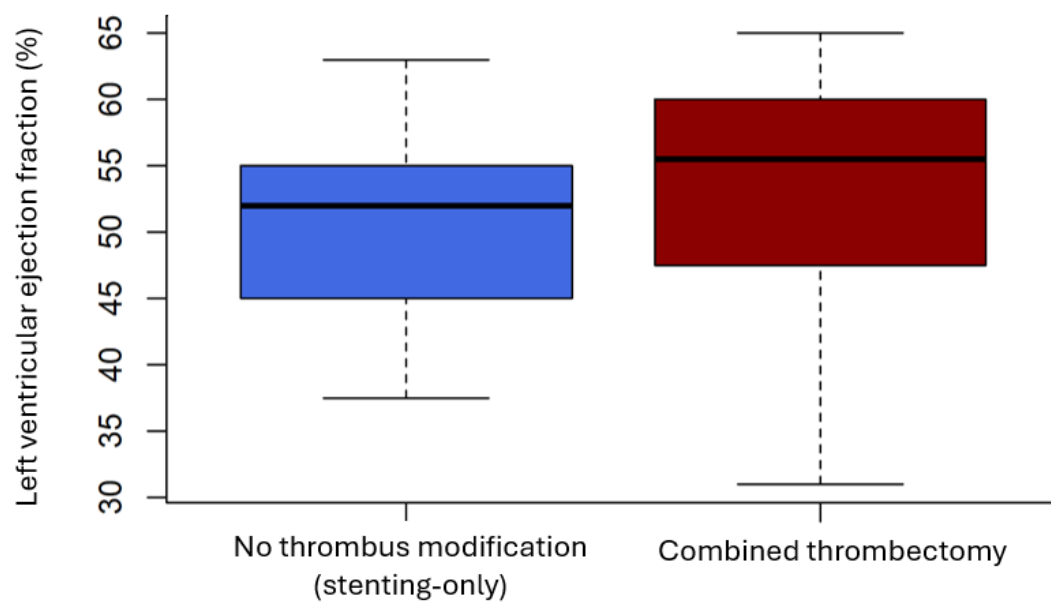
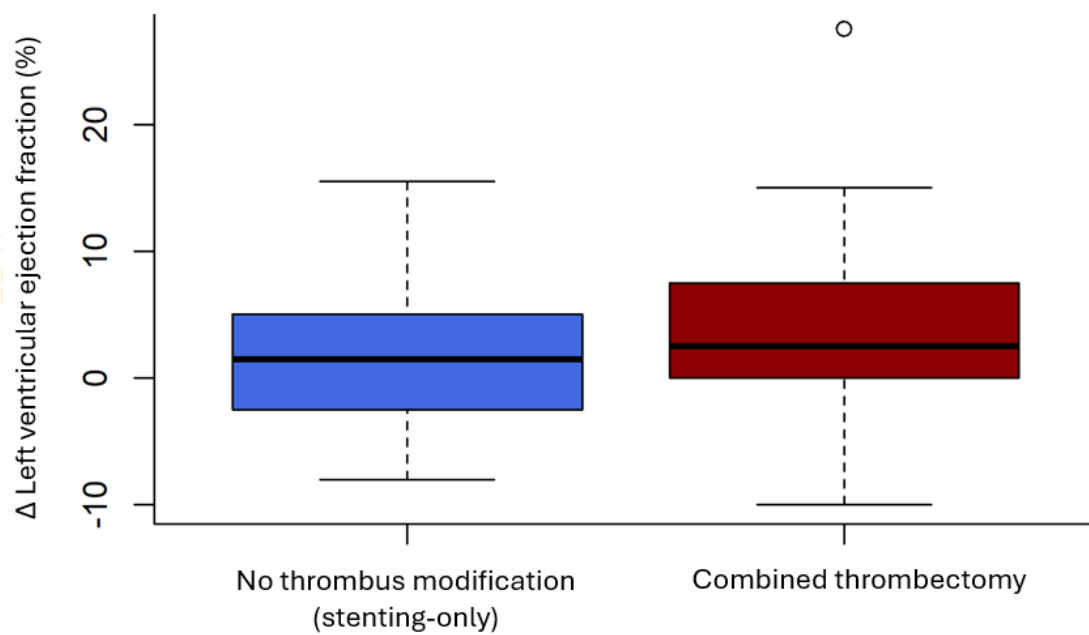


Figure 36: Change in left ventricular ejection fraction from early post-STEMI to six-months post STEMI in the stenting-only group and combined thrombectomy group (stent-retriever thrombectomy and manual aspiration).



Troponin I outcomes

Troponin I measurements were obtained in accordance with routine clinical practice.

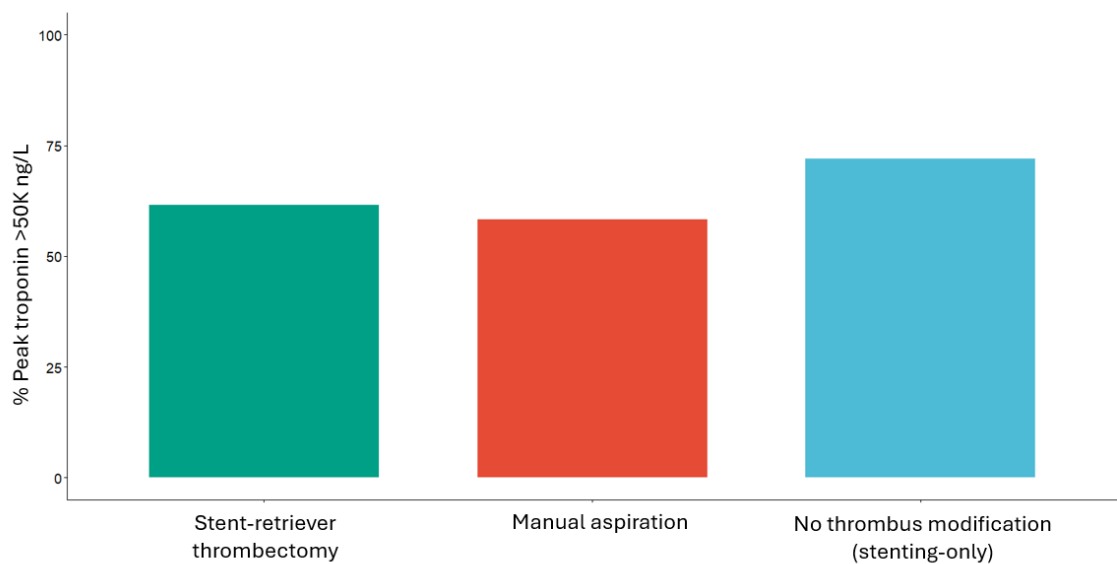
Typically, samples were collected in the catheterization laboratory during the procedure, followed by daily measurements during the post-procedural admission to the coronary care unit.

A notable limitation is that the troponin assay used at the John Radcliffe Hospital has an upper detection threshold of 50,000 ng/L, values exceeding this limit are reported as “>50,000 ng/L”. Given that large ST-elevation myocardial infarctions (STEMIs) frequently produce peak troponin I levels above this threshold, it was not possible to calculate a true area under the curve or determine actual peak troponin values for most patients in the study. Consequently, a pragmatic approach was adopted: the proportion of patients with a peak troponin >50,000 ng/L within 72 hours was assessed for each arm.

Peak high-sensitivity troponin I

In the stenting-only arm, 25 patients had peak troponin measurements available, of whom 18 (72%) had values >50,000 ng/L. In the MA arm, 24 patients had peak troponin measurements, with 14 (58%) exceeding 50,000 ng/L. In the SRT arm, 26 patients had peak troponin measurements, of whom 16 (62%) had values >50,000 ng/L. No statistically significant difference was observed between treatment arms (chi-squared test, $p = 0.46$; Figure 37).

Figure 37. Proportion of patients with peak high-sensitivity troponin I >50,000 ng/L by treatment arm, within 72 hours of primary percutaneous coronary intervention. No significant difference found between arms ($p = 0.46$).



Extracted thrombus phenotyping

Thrombi extracted via MA and SRT were photographed, examined macroscopically, and classified as predominantly red, predominantly white, or mixed in accordance with Tessarolo *et al.*²⁷⁷

Visible thrombus was successfully retrieved in 13 MA cases and 15 SRT cases. All thrombi extracted via SRT were classified as red. Among thrombi extracted via MA, 5 (38%) were classified as red, 4 (31%) were classified as white, and 4 (31%) were classified as mixed (Figure 38). Figure 39 shows further representative images with magnification of red, white and mixed thrombi, extracted by MA.

Figure 38. Proportions of macroscopic thrombus phenotypes (red, white, or mixed) extracted by stent-retriever thrombectomy (SRT) and manual aspiration (MA). Pie charts illustrate the relative distribution of thrombus phenotypes for each extraction technique. Inset photographs show representative macroscopic examples of thrombi corresponding to each phenotype.

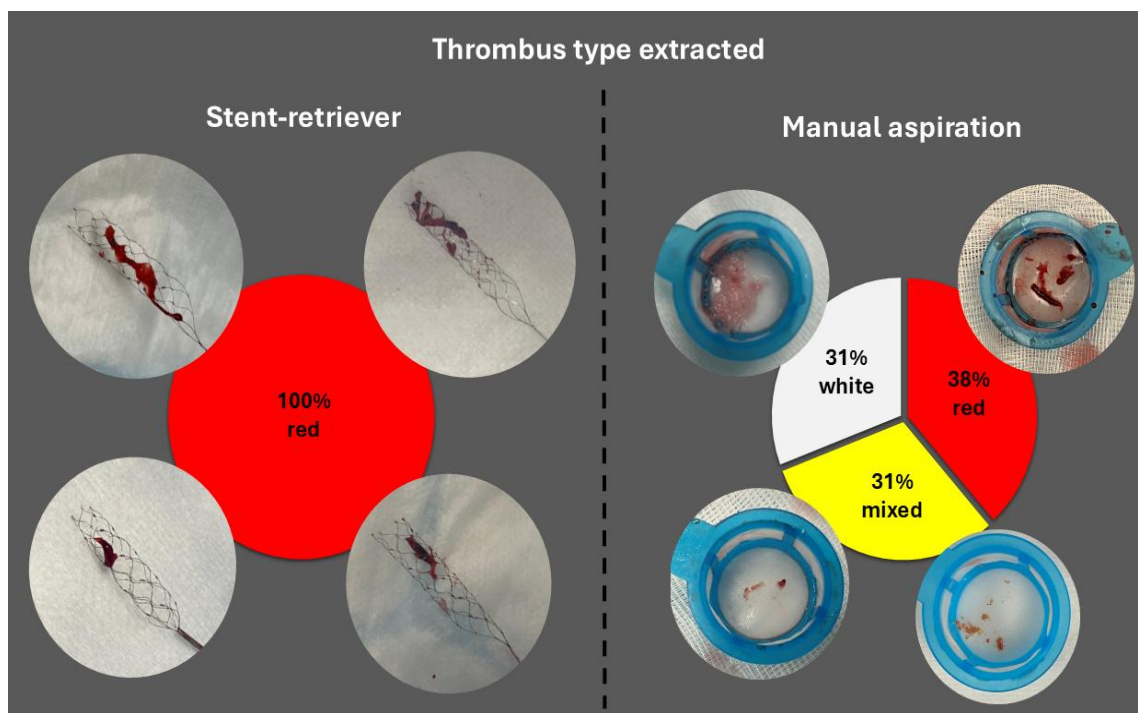
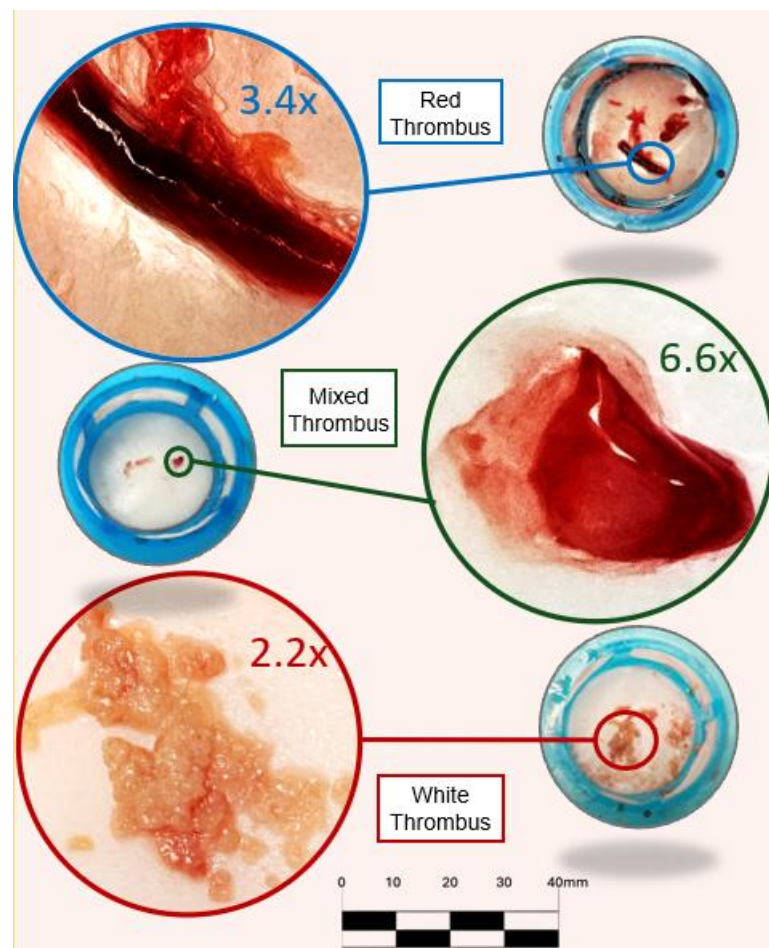


Figure 39. Representative macroscopic examples of red, white, and mixed thrombi extracted by manual aspiration (MA). Zoomed inset images highlight characteristic features of each thrombus phenotype at the indicated magnifications. Scale bar shown.



Safety outcomes

Intra and peri-procedural complications

Overall, rates of intra- and peri-procedural complications were low across all treatment arms. As detailed in the angiographic outcomes section, no-reflow demonstrated a statistically significant difference between arms ($p = 0.03$; Figure 32), with the highest incidence observed in the stenting-only arm.

No cases of coronary perforation occurred during the trial. Similarly, no intra- or peri-procedural strokes or transient ischaemic attacks were recorded.

Significant coronary dissection, defined as a dissection resulting in coronary flow impairment or occlusion, occurred once in each treatment arm, with no significant difference observed between groups.

Non-flow-limiting arterial dissections identified by OCT at baseline (post-pre-dilatation) were observed once in the MA arm and once in the SRT arm, but were not detected in the stenting-only arm. Following thrombus modification (MA or SRT), no new dissections were identified by OCT in either group. After stent deployment, coronary dissection was observed once in the stenting-only arm and once in the MA arm but did not occur in the SRT arm. Overall, no difference in OCT-detected dissection rates was observed between groups.

One intra-procedural death occurred during the trial, in the MA arm. Cardiogenic shock occurred intra- or peri-procedurally in two cases in the stenting-only arm and one case in the SRT arm but did not occur in the MA arm.

In-hospital outcomes

At the time of discharge, no further deaths had occurred. No strokes or transient ischaemic attacks were recorded. No additional emergency revascularisation procedures were required.

Pulmonary oedema was detected in two cases in the MA arm and one case in the stenting-only arm. One major bleeding event occurred in the stenting-only arm, consisting of haematemesis resulting in shock and requiring blood transfusion. One resuscitated ventricular fibrillation arrest occurred during a staged PCI in the MA arm.

Six-month clinical outcomes

At 6-month follow-up, two deaths had occurred in the stenting-only group (one cardiac, one non-cardiac). No further deaths occurred in the MA arm, and no deaths occurred in the SRT arm.

No strokes or transient ischaemic attacks were recorded across any treatment group.

Target lesion revascularisation did not occur in any arm. Non-target lesion revascularisation occurred once in the stenting-only arm and once in the MA arm.

Hospital readmission occurred once in the stenting-only group (arrhythmia), three times in the MA group (two patients with collapse, one with palpitations), and once in the SRT arm (chest pain).

Serious adverse events (SAEs), serious adverse device related events (SADEs) and device deficiencies.

Overall, 12 SAEs occurred, 6 in the stenting-only arm, 4 in the MA arm and 2 in the SRT arm (table 15). All of these have been reported to the Sponsor and the MHRA.

No SADEs occurred.

No strokes or transient ischaemic attacks occurred. None of the pre-specified stopping rules were triggered (more than two transient ischaemic attacks or ischaemic stroke-related SADEs; more than two coronary perforation-related SADE; or more than two significant coronary dissection-related SADEs).

One device deficiency event occurred in the SRT arm. The device could not be delivered into the coronary due to vessel tortuosity, resulting in the patient being crossed over into the stenting-only arm.

No signal for disproportionate harm was detected in the SRT group.

Table 15. All serious adverse events reported, by treatment arm.

	Stenting-only	Manual aspiration	Stent-retriever thrombectomy
Serious adverse event description	Death five months post-discharge.	Collapse two weeks post-discharge. Admitted and investigated as an outpatient with an ambulatory ECG.	Episode of asystole after final angiogram. ROSC after short episode of CPR and metaraminol administration.
	Cardiogenic shock peri-procedure.	Death during procedure. Cardiac arrest prior to stenting.	Admission with chest pain.
	Death two months post-discharge secondary to heart failure.	Readmission with palpitations 3 months post discharge.	
	Haematemesis and hypotension post-procedure.	Collapse 3 months post discharge, admitted and investigated as outpatient for arrhythmias.	
	Post-MI pericarditis resulting in extension of admission.		
	Readmission 3 weeks post-discharge with AF and tach-brady syndrome.		

Summary and interpretation

The results presented in this chapter evaluate whether coronary thrombus modification using MA or SRT improves conventional surrogate markers of myocardial reperfusion and injury compared with stenting alone in patients presenting with STEMI.

Additionally, it provided a descriptive assessment of extracted thrombus characteristics and represents the first randomised safety evaluation of SRT in coronary intervention.

The principal findings relate to myocardial reperfusion. Both MA and SRT were associated with significantly improved angiographic markers of microvascular perfusion compared with stenting alone. Angiographic no-reflow occurred in approximately half of patients treated with stenting alone, but in fewer than one quarter of those undergoing MA or SRT. Similarly, impaired myocardial blush (MBG ≤ 2) was significantly more common in the stenting-alone arm.

Both thrombectomy strategies were also associated with higher rates of complete ST-segment resolution. Together, these angiographic and electrocardiographic findings support the concept that thrombus modification enhances tissue-level reperfusion following STEMI. These results are consistent with prior thrombectomy trials, including the TAPAS trial, which demonstrated improved myocardial blush and ST-segment resolution with MA.⁶³ The high rates of no-reflow and incomplete ST-segment resolution in the stenting only arm was anticipated in this study, as it was enriched by selection of patients with LTB, with a higher thrombus grade cut off than most studies for LTB (>4 rather than >3). The no reflow rate of 50% is in line with other studies looking specifically at patients with LTB. For example, Luo et al. compared the impact of a delayed vs immediate stenting strategy in STEMI with LTB, finding a 55% rate of no-reflow in patients in the immediate stenting group.²⁹⁴ Further, Ahn et al. who defined

LTB more liberally than in this study (TIMI thrombus grade of >3) found that no reflow occurred in 34% of the LTB group without thrombectomy, 21% in the LTB in the group with thrombectomy and 10% in patients with low thrombus burden.³⁰ Complete ST-segment resolution defined as ST-segment resolution >70% was particularly low (20%) in our stenting only arm. A study by Jeon et al. investigated the impact of failed thrombus aspiration in patients with LTB (again defined more liberally as a TIMI thrombus grade of >3), finding complete ST-segment resolution in 35% (so incomplete in 65%).¹⁷¹ The slightly lower rate of complete (and therefore higher rate of incomplete) ST-segment resolution is likely to be related to greater enrichment for LTB and possibly error due to a small sample size.

No statistically significant differences were observed between treatment arms for biochemical or echocardiographic measures of myocardial injury or function. The proportion of patients with markedly elevated peak high-sensitivity troponin I (>50,000 ng/L) was similar across groups. Troponin interpretation was limited by the assay ceiling that precluded quantification of peak values or area-under-the-curve analysis.

Six-month LVEF and Δ LVEF were also comparable between groups, with no significant differences observed even when MA and SRT were combined. These neutral findings could reflect limited statistical power and the relative insensitivity of echocardiography to modest differences in infarct size, rather than an absence of biological effect. A larger future STEMI thrombectomy trial could restrict enrolment to LAD territory infarcts alone. The larger area of myocardium at risk could magnify the effect size (if one exists) and reduce heterogeneity. Conversely, this strategy would compromise generalisability and slow recruitment. Importantly, RCA and LCx infarcts are not benign, and can cause substantial LV impairment. I would therefore favour

recruiting all infarct territories with pre-specified, territory-stratified sub-analyses, balancing statistical efficiency with clinical applicability.

Another limitation with the ejection fraction analysis performed here is we did not take account of bystander disease. Patients with significant bystander disease are likely to have worse ventricular impairment than those with single vessel disease, therefore it is an important confounder that should be documented and accounted for in a future trial.

A novel aspect of this chapter was the macroscopic phenotyping of extracted coronary thrombus. SRT exclusively retrieved red thrombi, whereas MA extracted a broader spectrum of thrombus types. This observation aligns with experimental and clinical data from stroke intervention, which demonstrate greater efficacy of SRT in extracting red-cell-rich thrombi.²⁵ The distinct thrombus phenotypes removed by SRT versus MA likely reflect the devices' designs: SRT is a loose circular mesh that cannot not plausibly capture small particles such as platelet-rich white thrombi, whereas MA is a small-lumen tube with suction, ideal for capturing smaller particles.

Safety outcomes were favourable across all treatment arms, with low rates of intraprocedural, periprocedural, in-hospital, and six-month adverse events. Importantly, no strokes or transient ischaemic attacks occurred, addressing a key safety concern raised by prior coronary thrombectomy trials.^{11,53} No serious device-related adverse events were observed. These data represent the first randomised evidence supporting the feasibility and apparent safety of SRT in the coronary circulation.

In summary, coronary thrombus modification using either MA or SRT was associated with improved angiographic and electrocardiographic markers of myocardial reperfusion compared with stenting alone. Although these improvements did not translate into statistically significant differences in LVEF or troponin. The favourable

safety profile of SRT supports its potential role as a novel adjunctive strategy in primary PCI.

The following chapter integrates these findings with OCT-derived thrombus measurements and microvascular resistance data presented in Chapters 3 and 4. It will critically evaluate the limitations of the present study and outline priorities for future research, including adequately powered trials incorporating robust clinical endpoints to determine whether the observed improvements in microvascular reperfusion translate into meaningful clinical benefit.

Chapter 6: Discussion, limitations and future directions

Discussion and summary

This thesis addresses a persistent and clinically important challenge in interventional cardiology: how to best manage STEMI complicated by large thrombus burden (LTB). As established in Chapter 1, LTB drives distal embolisation, MVO, no-reflow, larger infarct size, and worse clinical outcomes.^{5,8-12,30,31} Despite a compelling pathophysiological rationale for thrombectomy, large-randomised trials of routine thrombectomy with MA have consistently failed to demonstrate clinical benefit.^{54,78} Consequently, contemporary guidelines have de-emphasised thrombus modification strategies.⁴

A central idea of this thesis is that these neutral findings stem not from a lack of biological efficacy, but 1) a lack of patient selection, specifically the inclusion of unselected STEMI populations rather than those with confirmed LTB and/or 2) inherent limitations of MA technology. This thesis represents the first randomised trial to systematically evaluate the use of a novel SRT device for coronary thrombectomy.

Primary outcomes: intracoronary thrombus reduction measured by OCT

The primary finding of this work is that both MA and SRT significantly reduce intracoronary thrombus, as quantified by OCT (figure 22). Two key metrics of coronary thrombus quantity reduction by OCT were used: thrombus volume (mm³) and thrombus burden (% of lumen volume occupied by thrombus). OCT measured thrombus volume reduction correlated strongly with the quantity of actual thrombus extracted, providing

the first validation of an intracoronary thrombus reduction measurement with OCT (Figure 26).

SRT reduced thrombus volume significantly more than MA, however when correcting for lumen volume, there was no difference in thrombus burden reduction between arms (figure 23). This discrepancy could be explained by the higher baseline thrombus burden and lumen size in the SRT group. As patients were randomised and the sample size in each arm was small these baseline discrepancies likely occurred through chance. Alternatively, the greater coronary thrombus volume reduction with SRT could indicate superior thrombus extraction efficacy but given the baseline imbalances described this cannot be concluded with confidence.

Interestingly, magnitude of thrombus reduction with thrombectomy increased proportionally with increasing baseline thrombus volume (figure 25). This relationship suggests thrombectomy is most effective in patients with genuinely large thrombus burden. This relationship further highlights that the greater thrombus volume reduction seen in the SRT arm could be explained by the greater baseline thrombus burden in this arm, rather than superior efficacy of the device over MA.

A potential drawback of the unblinded OCT imaging in this work is that it could have, and likely did, influence stent sizing and/or post-dilatation decisions. In future OCT-based STEMI studies, blinding operators to OCT findings could be considered, though there are arguments both for and against this approach.

For blinding OCT: In current clinical practice, intravascular imaging is not routinely used during STEMI, and therefore the results of a STEMI trial using unblinded OCT for research measurements may not be representative of common practice. Furthermore, post-dilatation has been linked to no-reflow,¹⁷⁴ and one could argue that intravascular

imaging may prompt operators to post-dilate a stent when they would not have otherwise, potentially precipitating more no-reflow.

Against blinding OCT: Intravascular imaging is being utilised with increasing frequency during PCI, driven by a growing body of evidence for its benefit, this trend is reflected in the 2024 ESC guidelines, which upgraded intravascular imaging use to a Class 1A recommendation for PCI of complex lesions.²⁹⁵ Additionally, our group advocates for the use of intravascular imaging during STEMI, meaning this trial was consistent with local practice. It is also well established that undersized stents and significant stent malapposition predict stent/target vessel failure,^{174,296} and imaging-guided optimisation may help mitigate this risk. So there is a potential ethical implication to blinding operators to imaging, as intravascular imaging may detect a serious complication not detected on angiography, which would go untreated.

Based on my experience during this study, intravascular imaging often seemed helpful in the STEMI setting and could offer benefits over angiography alone. I am therefore in favour of not blinding operators to OCT findings in future studies. That said, a randomised controlled trial comparing intravascular imaging-guided with angiography-guided pPCI would help settle this debate.

Angiographic thrombus scores: fit for purpose?

This trial employed TIMI thrombus grade (≥ 4) as an inclusion criterion to select for patients with LTB. However, OCT imaging revealed that approximately one in five enrolled patients (TIMI thrombus grade ≥ 4) had a negligible coronary thrombus volume ($< 3 \text{ mm}^3$) at baseline. This discordance represents a key contribution of this thesis, demonstrating (with OCT) the inherent imprecision of angiography-based thrombus

burden assessment. In contrast, OCT enables accurate volumetric quantification of thrombus and should therefore be the preferred modality for identifying patients with LTB and quantifying thrombus in future studies. An alternative would be development of a machine learning model that can quantify thrombus on angiography. Such a model would need to be validated against OCT-based thrombus quantification and significantly outperform TIMI thrombus grading to be of utility.

As things stand, our group proposes a fundamental reappraisal of current practice: future trials and clinical decision-making should employ OCT-based rather than angiography-based thrombus measurement, where possible, to reliably identify patients most likely to benefit from thrombus modification strategies.

Impact on myocardial perfusion and injury

Despite the failure of trials to demonstrate impact on clinical outcomes with coronary thrombectomy, several have demonstrated impact on markers of myocardial perfusion, consistent with the idea that distal thrombus embolization drives MVO, impairing myocardial perfusion.^{63,297-300} For example, the EXPIRA trial randomised patients with STEMI to either stenting alone or MA-assisted PCI, demonstrating significantly improved MBG and greater ST-segment resolution in the MA group. In addition, among a predefined subset of patients with anterior STEMI, MA was associated with a reduction in microvascular obstruction as assessed by CMR.²⁹⁸ More recently, Jeon et al. reported improved markers of myocardial perfusion in patients undergoing successful thrombectomy compared with those in whom thrombectomy was unsuccessful. Unsuccessful thrombectomy was defined by the absence of thrombus retrieval, the presence of residual thrombus prior to stent deployment on angiography, or angiographic evidence of distal embolisation.¹⁷¹

The findings presented in this thesis are consistent with this body of evidence, showing improved markers of myocardial perfusion with thrombectomy compared to stenting-alone, and is the first to demonstrate improved MBG, ST-segment resolution and no-reflow incidence with SRT compared to stenting-alone (figure 32). Additionally, the higher rate of bailout glycoprotein IIb/IIIa inhibitor use in the stenting-only arm may reflect operator recognition of impaired myocardial perfusion markers during the procedure, prompting adjunctive pharmacological therapy. Alternatively, this finding may be attributable to the absence of operator blinding to treatment allocation, operators aware that thrombectomy was not being performed may have had a lower threshold for administering antithrombotic therapy to mitigate the perceived impact of an untreated thrombus burden.

Regarding myocardial injury, this project examined two markers: troponin and echocardiographic left ventricular ejection fraction. Unlike markers of myocardial perfusion, data supporting reduced myocardial injury with the use of thrombectomy in STEMI are limited. Examples include the EXPIRA trial, described above, where infarct size was reduced in the MA group compared to stenting-alone on CMR and a meta-analysis of thrombectomy trials showing improved echocardiographic left ventricular function with MA over stenting alone.^{79,298} However, several other trials of thrombectomy in STEMI have shown no impact on infarct size or biomarkers of myocardial injury (CK-MB and troponin),^{53,63,299,301} whilst the AiMI trial comparing rheolytic thrombectomy to stenting-alone in STEMI actually showed a larger infarct size in the thrombectomy group.⁷¹

In line with the bulk of the evidence on the impact of thrombectomy on myocardial injury, the data from this project showed no significant impact on infarct size or peak troponin. Major limitations of the LVEF and troponin analysis were 1) small sample

size 2) the echo and troponin data were collected as per clinical need, not systematically and 3) the troponin assay used has a maximum threshold of >50000 so a true peak troponin could not be obtained in many patients. For these reasons the echocardiographic and troponin data presented here should be interpreted with caution. It remains biologically plausible that effective thrombectomy in selected patients with LTB could reduce infarct size in STEMI. Particularly when considering all previous STEMI thrombectomy trials enrolled unselected, all-comer populations. However, this hypothesis has yet to be robustly demonstrated in a suitably powered RCT.

Microvascular resistance

This thesis presents the first analysis to utilise IMR_{angio} , a computational fluid dynamics-derived measure of microvascular resistance, within the context of a randomised trial in STEMI. Notably, our research group was the first to validate this technique in the STEMI setting, establishing its feasibility and physiological plausibility as a non-invasive assessment of the coronary microcirculation.^{201,202}

Traditional methods for assessing myocardial perfusion in STEMI trials, such as MBG and incidence of no-reflow are inherently limited by their semi-quantitative nature and significant interobserver variability.^{302,303} In contrast, both invasive wire based IMR and IMR_{angio} offer a more objective and quantitative assessment of myocardial perfusion. IMR_{angio} forgoes the need for hyperaemic agents, invasive intracoronary instrumentation and can be performed post-hoc, making it a more attractive measurement to use in acutely unwell STEMI patients.

In the analysis presented in chapter 4, epicardial flow improved markedly across all treatment arms following stenting, with QFR increasing from 0.71 to 0.97. However,

microvascular resistance, as measured by IMR_{angio} , increased significantly from pre- to post-stenting in both the stenting-only and MA arms. No significant increase in pre- to post-stenting IMR_{angio} was seen in the SRT arm.

This differential response could reflect reduced distal thrombus embolisation and consequent attenuation of MVO in the SRT arm. However, alternative explanations warrant consideration, including the shorter reperfusion time, higher baseline IMR_{angio} values observed in the SRT group or a type II error due to small sample size.

The lack of significant improvement seen in IMR_{angio} between arms (despite excellent epicardial recanalization in all groups, QFR 0.97) could be explained by:

- 1) Microvascular injury being multifactorial. Perhaps MVO is not fully mitigated by thrombectomy as several other mechanisms are also at play that potentiate MVO during STEMI (Figure 3).³¹
- 2) An underpowered analysis. Perhaps a difference between groups would have emerged with a larger sample.

There are important limitations with the IMR_{angio} analysis presented, which preclude a firm conclusion being drawn. First, the analysis was underpowered due to the inherent constraints of a small pilot trial with participants distributed across three treatment arms. Second, substantial data attrition occurred. Missing data resulted primarily from operator omission of high-frame-rate angiograms and inadequate distal vessel opacification in some angiograms. This data loss may have introduced selection bias, as less stable patients may have been disproportionately excluded from analysis. Future studies could mitigate these issues through enhanced operator training and adoption of newer computational fluid dynamic algorithms requiring only single angiographic acquisitions.²⁹¹

Despite these limitations, the analysis provides a proof-of-concept that IMR_{angio} can provide a feasible quantitative measure of microvascular resistance in STEMI trials. The analysis also suggests these measurements are likely physiologically meaningful, as the microvascular resistance values obtained are consistent with those expected from invasive IMR measurements in STEMI.³⁰⁴⁻³⁰⁶

The IMR_{angio} findings presented here are hypothesis-generating. The lack of a significant rise in microvascular resistance from pre- to post-stenting in SRT arm could suggest an impact of thrombectomy. However, larger, appropriately powered trials are needed before definitive conclusions on the impact of thrombectomy on microvascular resistance can be drawn.

Thrombus phenotype

As discussed in detail in chapter 1, all thrombi are not created equal, thrombus composition varies widely depending on various factors including age of thrombus and location.^{19,20} Thrombus composition impacts on prognosis and treatment. In particular red-cell rich thrombi are associated with worse myocardial perfusion and prognosis than white platelet-rich thrombi.^{21 23,24} Further, the neurointerventional literature shows red-cell rich thrombi tend to be more amenable to thrombectomy (extraction is more likely to be successful and fewer maneuvers are required for successful extraction).²⁵⁻²⁹ Therefore, examining the phenotype of thrombus extracted in thrombectomy trials is relevant.

In this thesis, I compared the macroscopic appearance of thrombi retrieved by SRT and MA. Extracted thrombus phenotype differed significantly by technique: all thrombi retrieved with SRT were classified as red, whereas MA yielded a heterogeneous distribution (38% red, 31% white, and 31% mixed) (figure 38).

This variation seen, supports the concept of biologically distinct thrombus phenotypes. SRT consistently extracted red thrombi, whereas manual aspiration exported a broader spectrum of thrombus types. This aligns with experimental and clinical evidence from stroke intervention, showing that red-cell-rich thrombi respond better to SRT.²⁵ In contrast, platelet- and fibrin-rich white thrombi may be less responsive to SRT but more amenable to manual aspiration.

These observations raise the possibility that available thrombectomy strategies could be tailored to thrombus phenotype, which may be identifiable in advance using OCT.

A key limitation of this analysis is that the macroscopic thrombus classification was not corroborated by histological analysis, so conclusions regarding composition should be interpreted cautiously.

Safety of stent-retriever thrombectomy

This thesis provides the first randomised safety evaluation of SRT in the coronary circulation. Reassuringly, no severe adverse device-related coronary events occurred, specifically no stroke or transient ischaemic attacks occurred.

Twelve total SAEs were detected, 6 in the stenting-only arm, 4 in the MA arm and 2 in the SRT arm. Within these, 1 intraprocedural death occurred in the MA arm and 2 deaths were detected on 6-month follow up in the stenting-only arm (one cardiac and one non-cardiac).

Overall, no concerning safety signals were detected in the SRT arm compared with the standard of care. However, as device related events are often rare, a large suitably powered trial is needed to confidently establish safety of SRT in coronary intervention.

Limitations

Several important limitations of this work must be acknowledged.

First, this was a small, single-centre pilot study. The trial was designed primarily to detect differences in thrombus volume and burden as measured by OCT. Consequently, owing to the inherently small sample size within each arm, compounded by missing data, analyses of microvascular resistance, troponin, and echocardiographic left ventricular ejection fraction were underpowered. Therefore, it cannot be determined if the trends seen in these datasets are true signals or noise.

Second, despite randomisation, there was an imbalance in baseline thrombus volume between groups, with a significantly higher baseline thrombus volume observed in the SRT arm. A key finding of this study is that higher baseline thrombus volume correlates with a greater reduction in coronary thrombus volume with thrombectomy, irrespective of whether SRT or MA was employed. Additionally, a primary observation was that SRT achieved a greater reduction in coronary thrombus volume compared with MA. Owing to the higher baseline thrombus volume in the SRT group, it cannot be definitively concluded whether the greater reduction observed with SRT reflects superior thrombus extraction device efficacy or is attributable to the higher baseline thrombus volume. The latter interpretation is supported by the finding that the reduction in coronary thrombus was not significantly different between groups when corrected for lumen volume.

Third, infarct size and MVO were not assessed using the current gold standard, CMR imaging.^{4,205,206} This limitation precludes comparison of observed thrombus reduction

and physiological findings with robust measures of myocardial injury. The less robust surrogate measures of infarct size (troponin and echocardiographic LVEF) were used in lieu. This limitation was due to the prohibitive cost and availability of CMR locally.

Fourth, microvascular resistance was assessed using IMR_{angio} rather than invasively measured IMR with pressure-temperature sensor guidewires. While IMR_{angio} offers a practical, wire-free approach suited to the time-sensitive STEMI setting, it is less well validated than invasive IMR.^{287,306}

Fifth, despite efforts to enrol patients with LTB using TIMI thrombus grade as an inclusion criterion, one-fifth of participants were demonstrated to have low thrombus burden on OCT. Incorporating OCT-based thrombus burden assessment as part of the inclusion criteria would have ensured a purer sample of STEMI patients with a true LTB. Conversely, some patients may have not been recruited due to a low TIMI thrombus grade, but actually had a LTB.

Sixth, OCT thrombus measurements relied on manual thrombus segmentation, as early machine-learning algorithms, aiming to improve accuracy and reproducibility demonstrated suboptimal performance (work beyond the scope of this thesis is ongoing to develop accurate automated thrombus measurement). However, inter- and intra-observer reproducibility of manual measurements were good.

Seventh, OCT estimates of extracted thrombus were validated against extracted thrombus area, measured on standardised photographs of extracted thrombus, with measurements calibrated to known device dimensions (stent-retriever or aspiration collection basket).²⁷⁷ More precise extracted thrombus measurement may have been

thrombus weight, thrombus volume on CT or photographs taken from other angles to also measure thrombus depth.¹⁶⁴

Finally, extracted thrombus was classified as red, white or mixed based on a simple visual assessment,²⁷⁷ rather than more precise methods such as histological analyses and scanning electron microscopy.^{156,307} The use of these more advanced techniques were limited by local expertise and access to specialised equipment.

Future directions

The findings of this thesis prompt consideration of several promising avenues for future research and practice.

A definitive randomised-controlled trial. The data presented in this thesis provide justification for a multicentre RCT comparing thrombectomy techniques with stenting alone in patients with STEMI and LTB, adequately powered to assess hard clinical endpoints. Importantly, patient selection for LTB should be guided by OCT, as the angiographic thrombus scoring has been shown here to be unreliable. Such a trial should incorporate robust clinical endpoints, including major adverse cardiovascular and cerebrovascular events, accurate surrogate endpoints such as CMR- or CT-derived infarct size and MVO, and systematic safety monitoring (as in this thesis but on a larger scale). The data from this work could potentially be utilised to guide a power calculation for a larger future RCT. This would likely not be wise for the exploratory endpoints such as IMR_{angio} , troponin and echocardiographic ejection fraction, as this risks amplifying noise as a true effect, resulting in a misleading sample size. On the other hand, the OCT parameters such as the absolute measures and deltas of thrombus

volume and burden could potentially be used to inform future studies. This would depend on factors such as: study endpoints (e.g. difference in pre-stenting thrombus volume/burden or delta thrombus volume/burden between arms); number of study arms; and whether the study is assessing superiority or non-inferiority.

However, as there was a baseline imbalance of thrombus volume in this study likely due to a small sample size a power calculation from this data should be used cautiously.

Usefully, the amount of missing OCT data was low (only 2/81 (2.5%) of patients in the study had unanalysable OCTs), this could be factored into future sample size calculations. In summary if our group or other groups design a larger RCT, the data from this thesis may be of value.

Use of photo-counting CT for outcome measures. Our research group has ready access to high-definition photon-counting CT scanning and have validated its use against CMR for measuring infarct size and MVO measurement.^{308,309} Potential benefits of myocardial characterisation post MI with CT over CMR include: higher resolution imaging, concurrent imaging and assessment of the coronaries and shorter scanning time.³¹⁰ Even more recently another group have developed a CT based measure of microvascular resistance “IMR_{CT},” validated against IMR.³¹¹ Therefore in future STEMI thrombectomy trials, CT could become an extremely valuable tool allowing a comprehensive assessment of infarct size, MVO, epicardial coronaries and microvascular resistance.

Artificial intelligence for real-time OCT thrombus analysis. In 1997 AI defeated the reigning chess world champion Garry Kasparov, in the form of the chess computer

“Deep Blue”. Twenty-eight years later the powers of AI are beginning to be incorporated into intracoronary imaging interpretation. Like in chess, it is inevitable that advanced AI techniques will outperform the best interventional cardiologists. Currently, automated AI interpretation has been incorporated into OCT and IVUS via the Ultron 2.0™ (Abbott Laboratories, Illinois, USA) and Automated Lesion Assessment™ (Boston Scientific, Massachusetts, USA) software, respectively. These have begun to be used clinically, primarily to aid detection of calcified coronary plaques and make automated vessel measurements in real-time.³¹²

Currently, no automated, AI-based algorithms for detecting and quantifying intracoronary thrombus on OCT are available in clinical practice. In this thesis, we evaluated preliminary machine-learning models for thrombus segmentation, developed in collaboration with computer scientist colleagues.²⁵⁸ As detailed in Chapter 3, these models did not achieve sufficient accuracy for research use, so all thrombus measurements reported here were performed manually. Although further AI-based tools for thrombus detection and measurement are under development, they lie beyond the scope of this work. Manual quantification of thrombus on OCT is highly time- and labour-intensive, which limits its real-time clinical applicability. While an operator can visually estimate thrombus burden and distinguish predominantly “red” from “white” thrombus on OCT at a glance,¹⁴⁹ a robust, automated AI model that accurately detects, measures, and characterises thrombus would deliver precise, real-time data to support both research activities and clinical decision-making.

Characterisation of plaque and thrombus phenotype. In addition to information about thrombus characteristics, OCT provides detailed information on plaque characteristics and can identify the underlying cause of the STEMI, most commonly

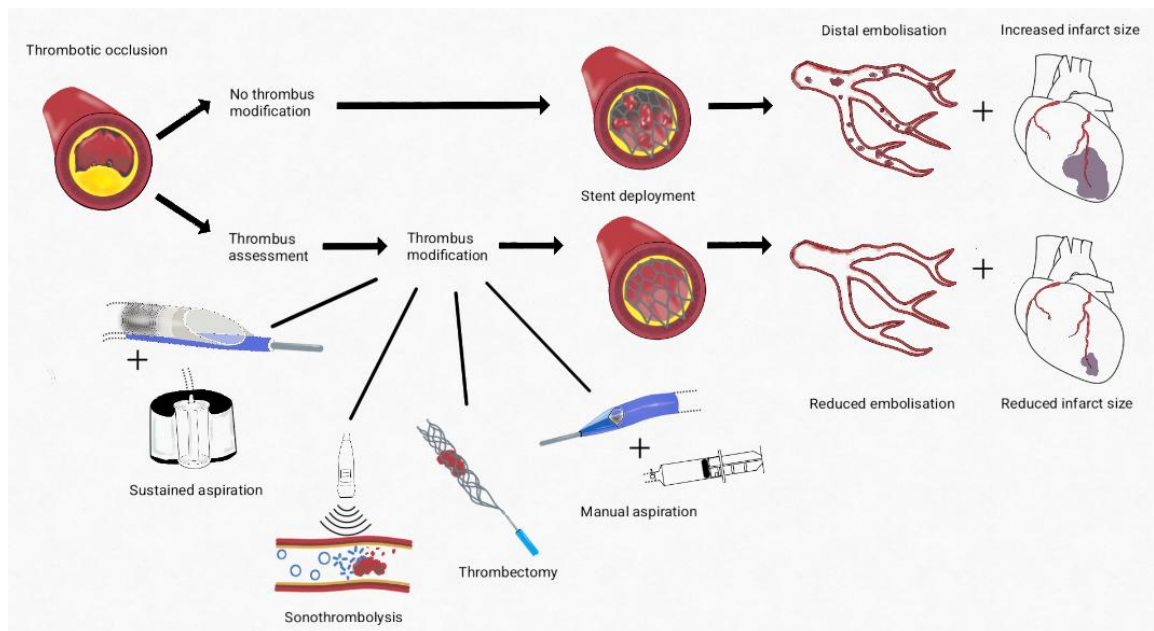
plaque rupture and less commonly, plaque erosion.³¹³ The OCT datasets collected in this study are being further interrogated to characterise underlying plaque pathology and thrombus type. With this we have built and are building predictive models to linking OCT-based lesion and thrombus characteristics to outcomes such as successful thrombectomy or degree of coronary thrombus reduction. For example, in our dataset we found that plaque erosion as the underlying cause of the STEMI is an independent predictor of thrombus burden reduction with thrombectomy.³¹⁴ Such insights emphasize the potential of OCT not only as a diagnostic tool but also as a guide for procedural interventional strategy. By linking imaging-defined plaque and thrombus characteristics with mechanical responsiveness, OCT could in future enable real-time, individualized decision-making in the catheterization laboratory.

Evaluation of emerging thrombus modification technologies. Several next-generation thrombus modification technologies are being developed, as outlined in chapter 1 (e.g. sustained aspiration catheters, sonothrombolysis and Milli-spinner thrombectomy). All have yet to be well-validated.

The methodological framework established in this thesis can be used to guide future studies evaluating the efficacy of such technologies.

If such validation occurs and efficacy is established in future, imaging-guided thrombus and lesion characterisation may inform a personalized approach to thrombus modification, enabling tailored selection of individual or combinations of techniques to optimize patient outcomes (figure 40).

Figure 40. In the future, several thrombus modification techniques aimed at reducing downstream embolization and infarct size may become available for clinical use, provided they demonstrate a meaningful impact on clinical outcomes. I anticipate that a range of these techniques could be employed (either alone or in combination), guided by intravascular imaging assessment.



Conclusions

The work presented in this thesis represents the first RCT to evaluate the use of SRT in coronary intervention, and specifically the first to assess the feasibility, preliminary efficacy, and safety of SRT in STEMI patients with LTB.

Several novel findings emerged from this work:

- 1) Coronary thrombus modification using either MA or SRT effectively reduced OCT-measured thrombus burden in STEMI with LTB. The novel OCT-based assessment of coronary thrombus reduction was validated against extracted coronary thrombus.
- 2) The magnitude of coronary thrombus burden reduction achieved with thrombectomy (both MA and SRT) increased proportionally with baseline thrombus burden.
- 3) SRT reduced coronary thrombus volume significantly more than MA, but thrombus burden reduction was similar between the two modalities. This discrepancy may be attributable to the higher baseline thrombus volume in the SRT arm.
- 4) Markers of myocardial perfusion (MBG, no-reflow incidence and ST-segment resolution) were improved in both thrombectomy arms compared with stenting-only.

- 5) Post-stenting microvascular resistance measured by IMR_{angio} , did not differ significantly between arms. However, microvascular resistance increased significantly pre-to post stenting in both the MA and stenting-only arms, but not the SRT arm. Given the limited sample size, it is unclear if this observation represents a genuine signal of preserved microvascular function with SRT or statistical noise.
- 6) Markers of infarct size (peak troponin and echocardiographic LVEF) did not differ significantly between arms. Trends favouring improved troponin levels and LVEF were observed in the thrombectomy arms, however, whether these trends would achieve statistical significance with a larger sample size remains uncertain.
- 7) Preliminary safety analysis identified no device-related or cerebrovascular events, with no difference in severe adverse events between arms.
- 8) A clear discrepancy between angiographic thrombus score and OCT-measured thrombus burden was demonstrated, with approximately 1 in 5 patients classified as having LTB by angiography, subsequently shown to have a negligible baseline coronary thrombus by OCT.

Although constrained by sample size, these findings provide a rationale for larger, adequately powered, OCT-guided trials of thrombus modification techniques in STEMI with LTB. Such studies are needed to determine whether targeted thrombus modification applied to appropriately selected patients will translate into meaningful reductions in microvascular obstruction, infarct size, and hard clinical outcomes.

Collectively, these findings tentatively challenge the shift away from thrombectomy in STEMI instigated by the large all-comer trials TASTE and TOTAL. Rather than an all-or-nothing approach, the evidence presented here suggests a possible paradigm shift towards a more nuanced, selective imaging-guided thrombus modification strategy. Such a personalised approach would align coronary intervention with the imaging-guided practice now considered standard of care in stroke intervention. Nevertheless, for this paradigm to be adopted in clinical practice, the burden of proof remains, adequately powered, prospective trials must convincingly demonstrate that selective thrombectomy confers meaningful clinical benefit. Only through such investigation can the interventional cardiology community determine whether imaging-guided thrombus modification represents a frontier in optimising outcomes for patients with STEMI.

7. Appendices

Appendix 1: emergency assent record.

RETRIEVE-AMI Emergency Assent Record

RETRIEVE-AMI Study ID			Patient initials	

Date of PCI							Time of PCI* 24 hour clock			:		
	D	D	M	M	Y	Y						

Please tick one

Conscious and able to give verbal consent/assent	
Conscious unable to give verbal consent/assent	
Unconscious	

Name of Advocate	Name of Researcher
Signature	Signature
Date	Date

Comments	

Patient randomised to (tick appropriate)

- ☐ STENT RETRIEVER ARM
- ☐ ASPIRATION (SUCTION) ARM
- ☐ DIRECT STENT PLACEMENT ARM

*Time of PCI is wire down time.

Recorded by		Date	

Appendix 2: Consent form.



Oxford University Hospitals
NHS Foundation Trust

Dr Giovanni Luigi De Maria

Oxford University Hospitals – NHS Foundation Trust

John Radcliffe Hospital

Headley Way, Headington, Oxford, OX3 9DU

Email: Giovanniluigi.Demaria@ouh.nhs.uk

Tel No: 01865 228 364

Participant identification number:

CONSENT FORM

**STENT RETRIEVER THROMBECTOMY FOR THROMBUS BURDEN REDUCTION
IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION – RETRIEVE-AMI study**

1. I confirm that I have read the information sheet date 24/01/2022 (version 1.1) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that during my treatment so far, data including imaging data have been collected and additional investigations have been performed. I am aware that I can withdraw this already collected data. I understand the information and data obtained so far will be stored in a format that prevents my identification as outlined in the information sheet. I am aware that this data may be shared with commercial parties. I give permission for this already collected data to be stored and used for this study and subsequent research publications/reports.	
4. I understand that relevant sections of my medical records and data, including imaging data, collected during the study may be looked at by individuals from the Sponsor, from regulatory authorities and from the Oxford University Hospitals NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
5. I understand who will have access to my personal data, how the data will be stored and what will happen to the data at the end of the study.	
6. I understand that if I have a complication related with the stent retriever or the optical coherence tomography imaging, this will be reported, where required, to the	

respective device manufacturers. I understand that I will not be identifiable in relevant reports. I give permission for this.		
7. I agree to my General Practitioner being informed of my participation in the study and for any study related adverse events.		
8. I agree to my General Practitioner being contacted to provide the research team with information on my progress.		
9. I agree to gift images taken for the purpose of the research study to the Oxford University Hospitals NHS Foundation Trust. If a commercial product were developed as a result of this study, I will not profit financially from such a product.		
10. I agree to continue to take part in this study.		
Optional:		
11. I agree to be contacted about ethically approved research studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	Yes	
	No	
12. I agree for my anonymised data, including imaging data to be used in future ethically approved research, here or abroad by academic or commercial collaborators.	Yes	
	No	
13. I agree to be contacted with the results of the study.	Yes	
	No	

Name of Participant *Date* *Signature*

Name of Person taking Consent *Date* *Signature*

*1copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes

Appendix 3: 6-month follow-up proforma.

RETRIEVE-AMI study ID			Patient initials	

1.	
Recorded by	
Date	

2. Functional status		
NYHA class		Tick
No dyspnoea		
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.	
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.	
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.	
IV	Severe limitations. Experiences symptoms even while at rest . Mostly bedbound patients.	
CCS grade		Tick
No angina		
Class I	Angina only during strenuous or prolonged physical activity	
Class II	Slight limitation, with angina only during vigorous physical activity	
Class III	Symptoms with everyday living activities, i.e., moderate limitation	
Class IV	Inability to perform any activity without angina or angina at rest, i.e., severe limitation	

3. Coronary Clinical Outcomes					
Acute Coronary Syndromes	Yes	No	Unknown	Date	Details
Myocardial infarction STEMI					
Myocardial infarction NSTEMI					
MI with PCI					
Target Vessel MI					
Non-Target Vessel MI					
Bypass surgery CABG					

Revascularisation	Yes	No	Unknown	Date	
Clinically Indicated Target lesion PCI					
Clinically Indicated Target vessel PCI					
Clinically Indicated Target vessel CABG					
Non-target vessel PCI					
Non-target vessel CABG					
Scaffold/Stent Thrombosis					
			Tick		
Scaffold/Stent Thrombosis timing	Acute				
	Sub-acute				
	Late				
	Very late				
Scaffold/Stent Thrombosis evidence	Definite				
	Probable				
	possible				

4. Cardiovascular Health (newly diagnosed/new admission)			
	Yes	No	Date & Comment
Death			
Cardiac Death			
Cardiac Arrest			
Heart failure			
Cardiogenic shock			
Acute Coronary Syndrome admission			
Stable Angina diagnosis			
Pacemaker			
ICD			
Transplant			
LV assist device			
CVA			
TIA			

5. General Health (newly diagnosed/new admission)			
	Yes	No	Detail
Re-admission other cause			
Period acute non- card illness			
Other surgery			
Other			

6. Progress Note				
Clinical action required?		Yes		No

7. Medication			
	Yes	No	Detail (Dose/frequency)
Aspirin			
Clopidogrel			
Ticagrelor			
Prasugrel			
Apixaban/Rivaroxaban/Edoxaban			
Warfarin			
Oral/Buccal nitrates (not PRN GTN)			
Beta Blocker			
Beta blocker – atenolol			
Beta blocker – bisoprolol			
Ace/ARB Inhibitor			
ACE inhibitor – ramipril			
ACE inhibitor - lisinopril			
Statin			
Statin– atorvastatin			
Statin– simvastatin			
Diuretic			
Ca Channel blocker			
Potassium Channel Blocker			
Aldosterone Antagonist			
Other Anti-arrhythmics			
Other Cardiac Medication			
Other Medication			
Diabetic therapy			

Appendix 4: Solitaire X stent-retriever sizing guide.

SOLITAIRE™ X REVASCULARIZATION DEVICE ORDERING INFORMATION ⁴												
Model	Recommended Vessel Diameter ^A (mm)		Minimum Microcatheter ID (inch)		Push Wire Length	Stent Diameter	Usable Length ^B	Stent Length	Length from Distal Tip to Fluoroscope Marker	Radiopaque Markers		Radiopaque Stent Markers Spacing
	(min)	(max)	(min)	(max)	(cm)	(mm)	(mm)	(mm)	(cm)	Distal	Prox.	(mm)
SFR4-4-20-05	2.0	4.0	0.021	0.027	200	4.0	20.0	31.0	<130	3	1	5
SFR4-4-20-10	2.0	4.0	0.021	0.027	200	4.0	20.0	31.0	<130	3	1	10
SFR4-4-40-10	2.0	4.0	0.021	0.027	200	4.0	40.0	50.0	<130	3	1	10
SFR4-6-20-10	2.0	5.5	0.021	0.027	200	6.0	20.0	31.0	<130	4	1	10
SFR4-6-24-06	2.0	5.5	0.021	0.027	200	6.0	24.0	37.0	<130	4	1	6
SFR4-6-40-10	2.0	5.5	0.021	0.027	200	6.0	40.0	47.0	<130	4	1	10

A. Based on the smallest vessel diameter at thrombus site.
B. Usable length that is at least as long as the length of the thrombus.

Up to 3 retrieval passes⁴

1. TR-NV16168 Rev A; 2. TR-NV12692 Rev A; 3. Compared to Solitaire™ Platinum; 4. 71042-001 Rev B; 5. Umansky, F. et al. Microsurgical anatomy of the proximal segments of the middle cerebral artery; 6. TR-NV13807 Rev A; 7. TR-NV12180 Rev A; 8. DWGSFG15XXX-YYY-Zz Rev B; 9. DWGSFG15XXX-YYY-Zz Rev B; 10. Solitaire™ FR Received CE Marking 2009; 11. TR-NV15666A Rev A; 12. Phenom 21 Catheter; 13. STRATIS, SWIFT PRIME, ESCAPE, Nasa Registry, THRACE, MR CLEAN, STAR, EXTEND IA, HERMES, SEER, REVASCAT, DEFUSE 3. Note: The Solitaire™ X Revascularization Device was not evaluated in these studies.

Appendix 5: Patient information leaflets.



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PARTICIPANT INFORMATION SHEET – ASPIRATION (SUCTION)

STENT RETRIEVER THROMBECTOMY FOR THROMBUS BURDEN REDUCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION – RETRIEVE-AMI study

We would like to invite you to continue being part in the RETRIEVE-AMI study. *Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it*

with others if you wish. Part 1 explains the purpose of this study and what will happen to you if you continue to take part. Part 2 gives you more detailed information about the way the study is carried out

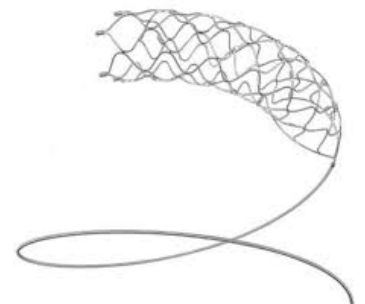
PART 1

What is the purpose of the study?

Our study is investigating how good a new device known as a stent retriever is in removing a clot that causes a heart attack from inside one of your heart vessels (coronary artery). Heart attacks are caused by the sudden formation of a clot inside a diseased coronary artery which reduces blood flow beyond the blockage site. During conventional treatment of the heart attack, the clot that has formed is disrupted and is pushed further down which can lead to damage in smaller blood vessels supplying the heart muscle. This additional damage can lead to long-term heart muscle damage influencing recovery and wellbeing. We have so far not been able to find a good solution for treating heart attack clots, with two approaches currently in clinical use. Your participation in this study will help us explore if the stent retriever can improve how we remove blood clots causing a heart attack compared to the two conventional treatments.

What is a stent-retriever?

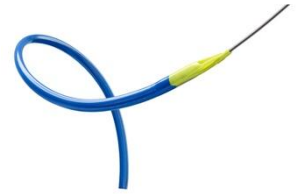
A stent retriever (see picture) is a basket-like device that can trap a clot. This device is currently being used to remove blood clots in patients having a stroke. During the coronary angioplasty/stent procedure to fix your heart attack, we insert the stent retriever in the blocked artery and then expand it in the blockage area to capture the blood clot. Once it has expanded, we gently pull back the stent retriever until it is outside your body bringing with it captured clot material. We then complete the procedure by inserting a stent; a stainless-steel tube that keeps the artery open.



What is conventional treatment?

There are currently two main approaches used to treat heart attacks with clots during a coronary angioplasty/stent procedure:

- 1) In the first one, we use a suction device (see picture) to remove as much clot as possible before we place a stent.
- 2) The second approach involves the placement of a stent without removing any clot.



Both approaches are currently being used, as the concept of clot removal is still studied. Even though it makes sense that removing a clot would help with limiting the damage from a heart attack and improve patient outcomes, studies in the past have not confirmed this. Since both approaches are currently in clinical use, we designed a study to compare both available clinical approaches with the stent retriever.

Why have I been invited to take part?

You have just had a coronary angioplasty/stent procedure at the John Radcliffe Hospital to treat your heart attack. During the procedure, we discussed with you our clinical research study and at the time you permitted us to go ahead with recruiting you. As a result, you could be allocated by chance to either: stent-retriever followed by stent placement or aspiration (suction) followed by stent placement or stent placement. You were allocated to have treatment with:

ASPIRATION (SUCTION) FOLLOWED BY STENT PLACEMENT

As part of the procedure, we took measurements from within the artery to investigate the amount of clot removed using a special imaging method known as optical coherence tomography – OCT and evaluated how well the circulation of your heart works using the pictures obtained during the procedure. We also took pictures of the clots that came out during the procedure.

With the emergency treatment over, we now wish to invite you to continue participation in this study. Please be assured that at all times your safety has been and will be the number one priority, and your heart attack treatment is in no way compromised by being included in any part of this study.

What will happen to me if I continue to take part?

You will join up to 81 patients who will be recruited in this study. We will collect clinical data and images/scans from your procedure and medical records. We also want to monitor your recovery after the heart attack by following you up in 6 months' time by telephone call. We may also follow your progress by accessing your medical records or by contacting your GP, if appropriate.

Do I have to carry on with the study?

Your continuing participation in the study is voluntary. Please be assured that you can withdraw from the study at any stage. Your withdrawal would not affect the standard of care you receive. Are there any possible disadvantages or risks from taking part?

In your participation in the study, you received conventional treatment with aspiration followed by stent placement. There are no additional risks associated with participation in the study above those already discussed with you as part of your standard care. In brief, patients having treatment for their heart attack may notice discomfort, bruising or bleeding from the access site that is related to the procedure itself and not the research you take part in. Injury to an artery due to the stenting procedure is reported in 4 patients for every 50 treated patients. Serious complications are usually identified and treated during the procedure. Please be assured that if artery injury is encountered during stenting procedures, our team is highly experienced in treating it using the same techniques that we treat your heart attack with. Moreover, there is a risk of thrombi breaking off from the devices used during your stenting and lodging themselves elsewhere. In some cases, these small thrombi may lodge in the brain leading to a stroke. Strokes are encountered as part of routine stenting practice in up to 1 every 100 treated patients and if this were to happen to you, we will treat you according to current best practice. Finally, there are other complications that you may encounter during the study that are related to having had a heart attack and not to the research study itself. Your medical team will discuss these with you.

Is there any radiation involved in this study?

Coronary angioplasty is the routine treatment for a heart attack. By participating in this study, you had a conventional coronary angioplasty procedure. This procedure uses ionising radiation to form images of your body, provide treatment and provide your doctor with other clinical information. Ionising radiation may cause cancer many years or decades after the exposure. The chances of this happening to you are the same whether you took part in this study or not.

What are the possible benefits of taking part?

We are hoping that you will directly benefit from your participation because we will be using a special imaging method known as optical coherence tomography. This imaging method, even though available in clinical practice is not routinely used, mainly due to its cost. Using this method during your stent procedure enables us to fit the stent better to your artery. We know from previous studies that fitting the stent better, reduces your chance of stent complications in the future.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

Will my taking part in the study be kept confidential?

Yes. All investigators have a duty of confidentiality to you as a research participant. We will follow ethical and legal practice and all information about you will be handled in confidence. When you first join the study you will sign an informed consent form that contains personal data (name, signature). We will also complete a contact record form linking your unique trial ID number with your personal identifiable data (name, hospital ID, personal address, emails or telephone numbers) so that we are able to call you back and check on your progress. Any other research data, including imaging data, will be identified through your unique trial ID number and will thus not contain any personal information such as name, initials or date of birth. In that way you will not be directly identifiable from this data. Your data will be kept in files located at the Oxford University Hospitals NHS Foundation Trust. Study documents containing personal data such as your name, hospital ID, home address, email address and telephone number (consent form, contact record form) will be kept in a separate folder and stored securely at the Oxford University Hospitals NHS Foundation Trust. Imaging data will be stored in a format that does not allow your direct identification in a password protected Oxford University Hospitals NHS Foundation Trust computer. Selected data controllers will have access to this folder.

Responsible members of the Oxford University Hospitals NHS Foundation Trust and authorised representatives from the regulatory authority/sponsor may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest'. We will be using the information we gain from you and your medical records including imaging data in order to undertake this study. The Oxford University Hospitals NHS Foundation Trust, as sponsor, is the data controller. This means that we, as researchers, are responsible for looking after your information and using it properly. We will use the minimum personally identifiable information possible. We will keep identifiable information about you for 1 year after the study has finished and store them securely at the Oxford University Hospital NHS Foundation Trust. We will store research data that cannot be traced back to you and any research documents with personal information, such as the consent form, securely at the Oxford University Hospitals NHS Foundation Trust for 10 years after the end of the study. Access

to your study records and personal information will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. You can find out more about how we use your data by contacting Dr Giovanni Luigi De Maria.

Data protection regulation provides you with control over your personal data and how it is used. Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at <https://www.ouh.nhs.uk/privacy/default.asp>

Will my General Practitioner/family doctor (GP) be informed of my participation?

We will inform your GP of your participation in the study by sending him a copy of this patient information sheet.

We may also follow your progress by contacting your GP, if appropriate

What if relevant new information becomes available?

Sometimes we (the study investigators) get new information about the procedures being studied. If this happens, one of us will tell you and discuss whether you should continue in the study.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time and for any reason. It will have no effect on your future care. There are three options for withdrawal:

- 1) You may withdraw from the telephone follow-up part of the study, but allow us to use of the information and data we already have about you, continue to access your medical records and write to your GP to follow your progress.
- 2) You may withdraw from the study but permit us to use data collected until the point of withdrawal for the research study. In this case we will not collect any more data and destroy any identifiable information we hold about you.
- 3) You may withdraw completely from the study and also withdraw the data collected up until the point of withdrawal.

If you would like to withdraw from the study you can let us know by contacting the Principal Investigator Dr Giovanni Luigi De Maria whose details can be found at the end of this information sheet.

Will I be reimbursed for taking part?

There are no reimbursement provisions for your participation in this study.

What if something goes wrong or I have a complaint?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated, or how your information was handled during the course of this study, you should contact Dr Giovanni Luigi De Maria [details at the end of this document] or you can contact the Patient Advisory Liaison Service (PALS); a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact: 01865 221473 or email: PALS@ouh.nhs.uk .

There are no special compensation arrangements. Oxford University Hospitals NHS Foundation Trust will provide indemnity for this study. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

How have patients and the public been involved in this study?

In designing this study, we have taken into account patient opinions on the consent process. Members of the public were involved in reviewing the Participant Information Sheets.

What happens at the end of the study?

When the research study stops your participation in the study would end. We are hoping that we can publish our research findings and/or present them in conferences. Any images/videos used in research publications will be in a format that prevents your direct identification. Copies of any publications related to the study are available on request from Dr Giovanni Luigi De Maria (contact information can be found at the end of the document).

Collaboration and Partnership with Commercial Companies & Third Parties

The Oxford University Hospitals Trust and the RETRIEVE-AMI study will receive support from commercial companies by providing the devices and imaging technology used during your heart attack treatment and the research investigations. As part of this collaboration, the study team will be providing Medtronic and Terumo Inc with progress reports and, where required, reports on complications related to the investigational device (optical coherence tomography imaging catheter). The results of the study will be shared with Medtronic and Terumo Inc up to 14 days before they are made publicly available. We will ensure that you will not be identifiable in these reports.

In the future, we may share research data, including imaging data, with the University of Oxford or other specialised centres (academic or commercial) in partnership with The Oxford University Hospitals NHS Foundation Trust and the RETRIEVE-AMI study for specialist analysis techniques that may not be available to the local research team. We will ensure that you will not be identifiable from the shared research data.

Who is organising and funding the study?

The investigators are Dr Giovanni Luigi De Maria, Prof Adrian Banning, Prof Keith Channon, Dr Jason Walsh, Dr Rafail Angelos Kotronias and Dr Jeremy Langrish. If you wish to know more about any aspect of the study, please contact Giovanni Luigi De Maria (details are provided at the end of the document).

The research is funded by Medtronic (Minnesota, US) and Terumo Corporation (Tokyo, Japan). The study is sponsored by Oxford University Hospitals NHS Foundation Trust.

Your doctors will not be paid for including you in the study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by South Central – Oxford C Research Ethics Committee and the Medicines & Healthcare products Regulatory Agency.

Participation in future research

We will ask if we can contact you about future studies. This is optional i.e. you can take part in this study but decline to be contacted for future research. If you consent, we will keep your name, address, telephone number, as well as a copy of your consent form, in a separate and securely stored folder to which only authorised individuals will have access. You can withdraw your consent for future contact at any time. Consent to be contacted for future research opportunities in no way obliges you to participate.

Further information and contact details:

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Consultant Cardiologist

Oxford University Hospitals – NHS Foundation Trust

John Radcliffe Hospital

Headley Way, Headington, Oxford OX3 9DU

Email : Giovanniluigi.Demaria@ouh.nhs.uk

Tel No: 01865 228 364

Thank you for considering taking part.



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NHS Foundation Trust

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Tel No: 01865 228 364

PARTICIPANT INFORMATION SHEET – STENT RETRIEVER

STENT RETRIEVER THROMBECTOMY FOR THROMBUS BURDEN REDUCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION – RETRIEVE-AMI study

We would like to invite you to continue being part in the RETRIEVE-AMI study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with others if you wish. Part 1 explains the purpose of this study and what will happen to you if you continue to take part. Part 2 gives you more detailed information about the way the study is carried out.

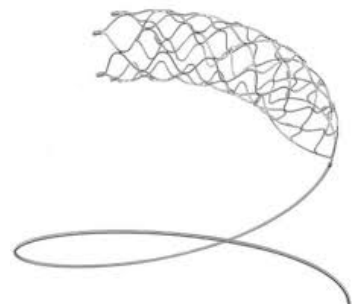
PART 1

What is the purpose of the study?

Our study is investigating how good a new device known as a stent retriever is in removing a clot that causes a heart attack from inside one of your heart vessels (coronary artery). Heart attacks are caused by the sudden formation of a clot inside a diseased coronary artery which reduces blood flow beyond the blockage site. During conventional treatment of the heart attack, the clot that has formed is disrupted and is pushed further down which can lead to damage in smaller blood vessels supplying the heart muscle. This additional damage can lead to long-term heart muscle damage influencing recovery and wellbeing. We have so far not been able to find a good solution for treating heart attack clots, with two approaches currently in clinical use. Your participation in this study will help us explore if the stent retriever can improve how we remove blood clots causing a heart attack compared to the two conventional treatments.

What is a stent-retriever?

A stent retriever (see picture) is a basket-like device that can trap a clot. This device is currently being used to remove blood clots in patients having a stroke. During the coronary angioplasty/stent procedure to fix your heart attack, we insert the stent retriever in the blocked artery and then expand it in the blockage area to capture the blood clot. Once it has expanded, we gently pull back the stent retriever until it is outside your body bringing with it captured clot material. We then complete the procedure by inserting a stent; a stainless-steel tube that keeps the artery open.

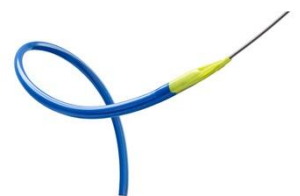


What is conventional treatment?

There are currently two main approaches used to treat heart attacks with clots during a coronary angioplasty/stent procedure:

- 3) In the first one, we use a suction device (see picture) to remove as much clot as possible before we place a stent.
- 4) The second approach involves the placement of a stent without removing any clot.

Both approaches are currently being used, as the concept of clot removal is still studied. Even though it makes sense that removing a clot would help with limiting the damage from a heart attack and improve patient outcomes, studies in the past have not confirmed this. Since both approaches are currently in clinical use, we designed a study to compare both available clinical approaches with the stent retriever.



Why have I been invited to take part?

You have just had a coronary angioplasty/stent procedure at the John Radcliffe Hospital to treat your heart attack. During the procedure, we discussed with you our clinical research study and at the time you permitted us to go ahead with recruiting you. As a result, you could be allocated by chance to either: stent-retriever followed by stent placement or aspiration (suction) followed by stent placement or stent placement. You were allocated to have treatment with:

STENT RETRIEVER FOLLOWED BY STENT PLACEMENT

As part of the procedure, we took measurements from within the artery to investigate the amount of clot removed using a special imaging method known as optical coherence tomography – OCT and evaluated how well the circulation of your heart works using the pictures obtained during the procedure. We also took pictures of the clots that came out during the procedure.

With the emergency treatment over, we now wish to invite you to continue participation in this study. Please be assured that at all times your safety has been and will be the number one priority, and your heart attack treatment is in no way compromised by being included in any part of this study.

What will happen to me if I continue to take part?

You will join up to 81 patients who will be recruited in this study. We will collect clinical data and images/scans from your procedure and medical records. We also want to monitor your recovery after the heart attack by following you up in 6 months' time by telephone call. We may also follow your progress by accessing your medical records or by contacting your GP, if appropriate.

Do I have to carry on with the study?

Your continuing participation in the study is voluntary. Please be assured that you can withdraw from the study at any stage. Your withdrawal would not affect the standard of care you receive.

Are there any possible disadvantages or risks from taking part?

There are no additional risks associated with participation in the study above those already discussed with you as part of your standard care. In brief, patients having treatment for their heart attack may notice discomfort, bruising or bleeding from the access site that is related to the procedure itself and not the research you take part in. Even though stent retrievers have not been used to treat heart attacks, we have information from their use in stroke. Device malfunction is uncommon and injury to the treated artery was observed in 1 every 50 treated patients. The reported risk of artery injury from the stent retriever (4 for every 170 treated patients) is lower than the risk of artery injury from the stenting procedure itself (4 for every 50 treated patients). Serious complications are usually identified

and treated during the procedure. Please be assured that if artery injury is encountered during stenting procedures, our team is highly experienced in treating it using the same techniques that we treat your heart attack with. Moreover, there is a risk of thrombi breaking off from the device as we are pulling it out of your body and lodging themselves elsewhere. In some cases, these small thrombi may lodge in the brain leading to a stroke. As this is the first study with this device in heart attacks, we have no information on how frequent this is. However, strokes are encountered as part of routine stenting practice in up to 1 every 100 treated patients and if this were to happen to you, we will treat you according to current best practice. Finally, there are other complications that you may encounter during the study that are related to having had a heart attack and not to the research study itself. Your medical team will discuss these with you.

Is there any radiation involved in this study?

Coronary angioplasty is the routine treatment for a heart attack. By taking part in this study, you had stent retriever thrombectomy during the coronary angioplasty procedure. This procedure uses ionising radiation to form images of your body, provide treatment and provide your doctor with other clinical information. Ionising radiation may cause cancer many years or decades after the exposure. The chances of this happening to you are the same whether you took part in this study or not.

What are the possible benefits of taking part?

We are hoping that you will directly benefit from your participation because we will be using a special imaging method known as optical coherence tomography. This imaging method, even though available in clinical practice is not routinely used, mainly due to its cost. Using this method during your stent procedure enables us to fit the stent better to your artery. We know from previous studies that fitting the stent better, reduces your chance of stent complications in the future.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

Will my taking part in the study be kept confidential?

Yes. All investigators have a duty of confidentiality to you as a research participant. We will follow ethical and legal practice and all information about you will be handled in confidence. When you first join the study you will sign an informed consent form that contains personal data (name, signature). We will also complete a contact record form linking your unique trial ID number with your personal identifiable data (name, hospital ID, personal address, emails or telephone numbers) so that we are

able to call you back and check on your progress. Any other research data, including imaging data, will be identified through your unique trial ID number and will thus not contain any personal information such as name, initials or date of birth. In that way you will not be directly identifiable from this data. Your data will be kept in files located at the Oxford University Hospitals NHS Foundation Trust. Study documents containing personal data such as your name, hospital ID, home address, email address and telephone number (consent form, contact record form) will be kept in a separate folder and stored securely at the Oxford University Hospitals NHS Foundation Trust. Imaging data will be stored in a format that does not allow your direct identification in a password protected Oxford University Hospitals NHS Foundation Trust computer. Selected data controllers will have access to this folder.

Responsible members of the Oxford University Hospitals NHS Foundation Trust and authorised representatives from the regulatory authority/sponsor may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest'. We will be using the information we gain from you and your medical records including imaging data in order to undertake this study. The Oxford University Hospitals NHS Foundation Trust, as sponsor, is the data controller. This means that we, as researchers, are responsible for looking after your information and using it properly. We will use the minimum personally identifiable information possible. We will keep identifiable information about you for 1 year after the study has finished and store them securely at the Oxford University Hospital NHS Foundation Trust. We will store research data that cannot be traced back to you and any research documents with personal information, such as the consent form, securely at the Oxford University Hospitals NHS Foundation Trust for 10 years after the end of the study. Access to your study records and personal information will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. You can find out more about how we use your data by contacting Dr Giovanni Luigi De Maria.

Data protection regulation provides you with control over your personal data and how it is used. Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at <https://www.ouh.nhs.uk/privacy/default.aspx>

Will my General Practitioner/family doctor (GP) be informed of my participation?

We will inform your GP of your participation in the study by sending him a copy of this patient information sheet.

We may also follow your progress by contacting your GP, if appropriate

What if relevant new information becomes available?

Sometimes we (the study investigators) get new information about the procedures being studied. If this happens, one of us will tell you and discuss whether you should continue in the study.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time and for any reason. It will have no effect on your future care. There are three options for withdrawal:

- 4) You may withdraw from the telephone follow-up part of the study, but allow us to use of the information and data we already have about you, continue to access your medical records and write to your GP to follow your progress.
- 5) You may withdraw from the study but permit us to use data collected until the point of withdrawal for the research study. In this case we will not collect any more data and destroy any identifiable information we hold about you.
- 6) You may withdraw completely from the study and also withdraw the data collected up until the point of withdrawal.

If you would like to withdraw from the study you can let us know by contacting the Principal Investigator Dr Giovanni Luigi De Maria whose details can be found at the end of this information sheet.

Will I be reimbursed for taking part?

There are no reimbursement provisions for your participation in this study.

What if something goes wrong or I have a complaint?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated, or how your information was handled during the course of this study, you should contact Dr Giovanni Luigi De Maria [details at the end of this document] or you can contact the Patient Advisory Liaison Service (PALS); a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS

patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact: 01865 221473 or email: PALS@ouh.nhs.uk .

There are no special compensation arrangements. Oxford University Hospitals NHS Foundation Trust will provide indemnity for this study. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

How have patients and the public been involved in this study?

In designing this study, we have taken into account patient opinions on the consent process.

Members of the public were involved in reviewing the Participant Information Sheets.

What happens at the end of the study?

When the research study stops your participation in the study would end. We are hoping that we can publish our research findings and/or present them in conferences. Any images/videos used in research publications will be in a format that prevents your direct identification. Copies of any publications related to the study are available on request from Dr Giovanni Luigi De Maria (contact information can be found at the end of the document).

Collaboration and Partnership with Commercial Companies & Third Parties

The Oxford University Hospitals Trust and the RETRIEVE-AMI study will receive support from commercial companies by providing the devices and imaging technology used during your heart attack treatment and the research investigations. As part of this collaboration, the study team will be providing Medtronic and Terumo Inc with progress reports and, where required, reports on complications related to the investigational devices (stent retriever and optical coherence tomography imaging catheter). The results of the study will be shared with Medtronic and Terumo Inc up to 14 days before they are made publicly available. We will ensure that you will not be identifiable in these reports.

In the future, we may share research data, including imaging data, with the University of Oxford or other specialised centres (academic or commercial) in partnership with The Oxford University Hospitals NHS Foundation Trust and the RETRIEVE-AMI study for specialist analysis techniques

that may not be available to the local research team. We will ensure that you will not be identifiable from the shared research data.

Who is organising and funding the study?

The investigators are Dr Giovanni Luigi De Maria, Prof Adrian Banning, Prof Keith Channon, Dr Jason Walsh, Dr Rafail Angelos Kotronias and Dr Jeremy Langrish. If you wish to know more about any aspect of the study, please contact Giovanni Luigi De Maria (details are provided at the end of the document).

The research is funded by Medtronic (Minnesota, US) and Terumo Corporation (Tokyo, Japan). The study is sponsored by Oxford University Hospitals NHS Foundation Trust.

Your doctors will not be paid for including you in the study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by South Central – Oxford C Research Ethics Committee and the Medicines & Healthcare products Regulatory Agency.

Participation in future research

We will ask if we can contact you about future studies. This is optional i.e. you can take part in this study but decline to be contacted for future research. If you consent, we will keep your name, address, telephone number, as well as a copy of your consent form, in a separate and securely stored folder to which only authorised individuals will have access. You can withdraw your consent for future contact at any time. Consent to be contacted for future research opportunities in no way obliges you to participate.

Further information and contact details:

Dr Giovanni Luigi De Maria

Consultant Cardiologist

Oxford University Hospitals – NHS Foundation Trust

John Radcliffe Hospital

Headley Way, Headington, Oxford OX3 9DU

Email : Giovanniluigi.Demaria@ouh.nhs.uk

Tel No: 01865 228 364

Thank you for considering taking part.



Oxford University Hospitals NHS Foundation Trust

Dr Giovanni Luigi De Maria
Oxford University Hospitals – NHS Foundation Trust
John Radcliffe Hospital
Headley Way, Headington, Oxford, OX3 9DU
Email: Giovanniluigi.Demaria@ouh.nhs.uk
Tel No: 01865 228 364

PARTICIPANT INFORMATION SHEET – STENT PLACEMENT

STENT RETRIEVER THROMBECTOMY FOR THROMBUS BURDEN REDUCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION – RETRIEVE-AMI study

We would like to invite you to continue being part in the RETRIEVE-AMI study. *Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with others if you wish. Part 1 explains the purpose of this study and what will happen to you if you continue to take part. Part 2 gives you more detailed information about the way the study is carried out.*

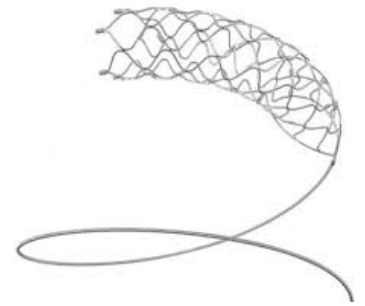
PART 1

What is the purpose of the study?

Our study is investigating how good a new device known as a stent retriever is in removing a clot that causes a heart attack from inside one of your heart vessels (coronary artery). Heart attacks are caused by the sudden formation of a clot inside a diseased coronary artery which reduces blood flow beyond the blockage site. During conventional treatment of the heart attack, the clot that has formed is disrupted and is pushed further down which can lead to damage in smaller blood vessels supplying the heart muscle. This additional damage can lead to long-term heart muscle damage influencing recovery and wellbeing. We have so far not been able to find a good solution for treating heart attack clots, with two approaches currently in clinical use. Your participation in this study will help us explore if the stent retriever can improve how we remove blood clots causing a heart attack compared to the two conventional treatments.

What is a stent-retriever?

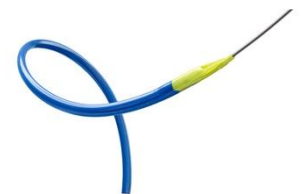
A stent retriever (see picture) is a basket-like device that can trap a clot. This device is currently being used to remove blood clots in patients having a stroke. During the coronary angioplasty/stent procedure to fix your heart attack, we insert the stent retriever in the blocked artery and then expand it in the blockage area to capture the blood clot. Once it has expanded, we gently pull back the stent retriever until it is outside your body bringing with it captured clot material. We then complete the procedure by inserting a stent; a stainless-steel tube that keeps the artery open.



What is conventional treatment?

There are currently two main approaches used to treat heart attacks with clots during a coronary angioplasty/stent procedure:

- 5) In the first one, we use a suction device (see picture) to remove as much clot as possible before we place a stent.
- 6) The second approach involves the placement of a stent without removing any clot.



Both approaches are currently being used, as the concept of clot removal is still studied. Even though it makes sense that removing a clot would help with limiting the damage from a heart attack and improve patient outcomes, studies in the past have not confirmed this. Since both approaches are currently in clinical use, we designed a study to compare both available clinical approaches with the stent retriever.

Why have I been invited to take part?

You have just had a coronary angioplasty/stent procedure at the John Radcliffe Hospital to treat your heart attack. During the procedure, we discussed with you our clinical research study and at the time you permitted us to go ahead with recruiting you. As a result, you could be allocated by chance to either: stent-retriever followed by stent placement or aspiration (suction) followed by stent placement or stent placement. You were allocated to have treatment with:

STENT PLACEMENT

As part of the procedure, we took measurements from within the artery to investigate the amount of clot in your artery using a special imaging method known as optical coherence tomography – OCT and evaluated how well the circulation of your heart works using the pictures obtained during the procedure. We also took pictures of the clots that came out during the procedure.

With the emergency treatment over, we now wish to invite you to continue participation in this study. Please be assured that at all times your safety has been and will be the number one priority, and your heart attack treatment is in no way compromised by being included in any part of this study.

What will happen to me if I continue to take part?

You will join up to 81 patients who will be recruited in this study. We will collect clinical data and images/scans from your procedure and medical records. We also want to monitor your recovery after the heart attack by following you up in 6 months' time by telephone call. We may also follow your progress by accessing your medical records or by contacting your GP, if appropriate.

Do I have to carry on with the study?

Your continuing participation in the study is voluntary. Please be assured that you can withdraw from the study at any stage. Your withdrawal would not affect the standard of care you receive.

Are there any possible disadvantages or risks from taking part?

In your participation in the study, you received conventional treatment with stent placement. There are no additional risks associated with participation in the study above those already discussed with you as part of your standard care. In brief, patients having treatment for their heart attack may notice discomfort, bruising or bleeding from the access site that is related to the procedure itself and not the research you take part in. Injury to an artery due to the stenting procedure is reported in 4 patients for every 50 treated patients. Serious complications are usually identified and treated during the procedure. Please be assured that if artery injury is encountered during stenting procedures, our team is highly experienced in treating it using the same techniques that we treat your heart attack with. Moreover, there is a risk of thrombi breaking off from the devices used during your stenting and lodging themselves elsewhere. In some cases, these small thrombi may lodge in the brain leading to a stroke. Strokes are encountered as part of routine stenting practice in up to 1 every 100 treated patients and if this were to happen to you, we will treat you according to current best practice. Finally, there are other complications that you may encounter during the study that are related to having had a heart attack and not to the research study itself. Your medical team will discuss these with you.

Is there any radiation involved in this study?

Coronary angioplasty is the routine treatment for a heart attack. By participating in this study, you had a conventional coronary angioplasty procedure. This procedure uses ionising radiation to form images of your body, provide treatment and provide your doctor with other clinical information. Ionising radiation may cause cancer many years or decades after the exposure. The chances of this happening to you are the same whether you took part in this study or not.

What are the possible benefits of taking part?

We are hoping that you will directly benefit from your participation because we will be using a special imaging method known as optical coherence tomography. This imaging method, even though available in clinical practice is not routinely used, mainly due to its cost. Using this method during your stent procedure enables us to fit the stent better to your artery. We know from previous studies that fitting the stent better, reduces your chance of stent complications in the future.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

Will my taking part in the study be kept confidential?

Yes. All investigators have a duty of confidentiality to you as a research participant. We will follow ethical and legal practice and all information about you will be handled in confidence. When you first join the study, you will sign an informed consent form that contains personal data (name, signature). We will also complete a contact record form linking your unique trial ID number with your personal identifiable data (name, hospital ID, personal address, emails or telephone numbers) so that we are able to call you back and check on your progress. Any other research data, including imaging data, will be identified through your unique trial ID number and will thus not contain any personal information such as name, initials or date of birth. In that way you will not be directly identifiable from this data. Your data will be kept in files located at the Oxford University Hospitals NHS Foundation Trust. Study documents containing personal data such as your name, hospital ID, home address, email address and telephone number (consent form, contact record form) will be kept in a separate folder and stored securely at the Oxford University Hospitals NHS Foundation Trust. Imaging data will be stored in a format that does not allow your direct identification in a password protected Oxford University Hospitals NHS Foundation Trust computer. Selected data controllers will have access to this folder.

Responsible members of the Oxford University Hospitals NHS Foundation Trust and authorised representatives from the regulatory authority/sponsor may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest'. We will be using the information we

gain from you and your medical records including imaging data in order to undertake this study. The Oxford University Hospitals NHS Foundation Trust, as sponsor, is the data controller. This means that we, as researchers, are responsible for looking after your information and using it properly. We will use the minimum personally identifiable information possible. We will keep identifiable information about you for 1 year after the study has finished and store them securely at the Oxford University Hospital NHS Foundation Trust. We will store research data that cannot be traced back to you and any research documents with personal information, such as the consent form, securely at the Oxford University Hospitals NHS Foundation Trust for 10 years after the end of the study. Access to your study records and personal information will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. You can find out more about how we use your data by contacting Dr Giovanni Luigi De Maria.

Data protection regulation provides you with control over your personal data and how it is used. Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at <https://www.ouh.nhs.uk/privacy/default.aspx>

Will my General Practitioner/family doctor (GP) be informed of my participation?

We will inform your GP of your participation in the study by sending him a copy of this patient information sheet.

We may also follow your progress by contacting your GP, if appropriate

What if relevant new information becomes available?

Sometimes we (the study investigators) get new information about the procedures being studied. If this happens, one of us will tell you and discuss whether you should continue in the study.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time and for any reason. It will have no effect on your future care. There are three options for withdrawal:

- 7) You may withdraw from the telephone follow-up part of the study, but allow us to use of the information and data we already have about you, continue to access your medical records and write to your GP to follow your progress.

- 8) You may withdraw from the study but permit us to use data collected until the point of withdrawal for the research study. In this case we will not collect any more data and destroy any identifiable information we hold about you.
- 9) You may withdraw completely from the study and also withdraw the data collected up until the point of withdrawal.

If you would like to withdraw from the study you can let us know by contacting the Principal Investigator Dr Giovanni Luigi De Maria whose details can be found at the end of this information sheet.

Will I be reimbursed for taking part?

There are no reimbursement provisions for your participation in this study.

What if something goes wrong or I have a complaint?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated, or how your information was handled during the course of this study, you should contact Dr Giovanni Luigi De Maria [details at the end of this document] or you can contact the Patient Advisory Liaison Service (PALS); a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact: 01865 221473 or email: PALS@ouh.nhs.uk.

There are no special compensation arrangements. Oxford University Hospitals NHS Foundation Trust will provide indemnity for this study. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

How have patients and the public been involved in this study?

In designing this study, we have taken into account patient opinions on the consent process. Members of the public were involved in reviewing the Participant Information Sheets.

What happens at the end of the study?

When the research study stops your participation in the study would end. We are hoping that we can publish our research findings and/or present them in conferences. Any images/videos used in research publications will be in a format that prevents your direct identification. Copies of any publications related to the study are available on request from Dr Giovanni Luigi De Maria (contact information can be found at the end of the document).

Collaboration and Partnership with Commercial Companies & Third Parties

The Oxford University Hospitals Trust and the RETRIEVE-AMI study will receive support from commercial companies by providing the devices and imaging technology used during your heart attack treatment and the research investigations. As part of this collaboration, the study team will be providing Medtronic and Terumo Inc with progress reports and, where required, reports on complications related to the investigational device (optical coherence tomography imaging catheter). The results of the study will be shared with Medtronic and Terumo Inc up to 14 days before they are made publicly available. We will ensure that you will not be identifiable in these reports.

In the future, we may share research data, including imaging data, with the University of Oxford or other specialised centres (academic or commercial) in partnership with The Oxford University Hospitals NHS Foundation Trust and the RETRIEVE-AMI study for specialist analysis techniques that may not be available to the local research team. We will ensure that you will not be identifiable from the shared research data.

Who is organising and funding the study?

The investigators are Dr Giovanni Luigi De Maria, Prof Adrian Banning, Prof Keith Channon, Dr Jason Walsh, Dr Rafail Angelos Kotronias and Dr Jeremy Langrish. If you wish to know more about any aspect of the study, please contact Giovanni Luigi De Maria (details are provided at the end of the document).

The research is funded by Medtronic (Minnesota, US) and Terumo Corporation (Tokyo, Japan). The study is sponsored by Oxford University Hospitals NHS Foundation Trust.

Your doctors will not be paid for including you in the study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable

opinion by South Central – Oxford C Research Ethics Committee and the Medicines & Healthcare products Regulatory Agency.

Participation in future research

We will ask if we can contact you about future studies. This is optional i.e. you can take part in this study but decline to be contacted for future research. If you consent, we will keep your name, address, telephone number, as well as a copy of your consent form, in a separate and securely stored folder to which only authorised individuals will have access. You can withdraw your consent for future contact at any time. Consent to be contacted for future research opportunities in no way obliges you to participate.

Further information and contact details:

Dr Giovanni Luigi De Maria

Consultant Cardiologist

Oxford University Hospitals – NHS Foundation Trust

John Radcliffe Hospital

Headley Way, Headington, Oxford OX3 9DU

Email : Giovanniluigi.Demaria@ouh.nhs.uk

Tel No: 01865 228 364

Thank you for considering taking part.

Appendix 6: Withdrawal record form.

RETRIEVE-AMI study ID			Patient initials	

8.	
Recorded by	
Date	

9. Withdrawal	
Patient does not want further communication but agreed to us keeping data and monitoring health progress via medical records/contact with GP	
Patient withdrew consent – data collected to date can be retained	
Patient withdrew consent – destroy all data	

Appendix 7. General practitioner letter



Oxford University Hospitals
NHS Foundation Trust

OXFORD HEART CENTRE
OXFORD UNIVERSITY HOSPITALS – NHS FOUNDATION TRUST

Dr. Giovanni L. De Maria
Level 0, Cardiac Investigation Annexe, John Radcliffe Hospital, Oxford OX3 9DU
Tel: +44(0)1865 226539
Email: giovanniluigi.demaria@ouh.nhs.uk

____/____/____

Dear Doctor,

Re: _____

The patient above has agreed to take part in a research study titled:

**STENT RETRIEVER THROMBECTOMY FOR THROMBUS BURDEN REDUCTION IN PATIENTS
WITH ACUTE MYOCARDIAL INFARCTION – RETRIEVE-AMI study**

RETRIEVE-AMI is an investigational device randomised controlled trial in patients presenting with ST-elevation myocardial infarction at the John Radcliffe Hospital, Oxford, UK. We are exploring the efficacy of the stent retriever device for clot removal before stent placement compared to the two conventional treatment approaches either i) stent placement or ii) aspiration (suction) thrombectomy followed by stent placement. The use of the investigational device in our study is outside its current CE marking. However, the device has been CE marked to remove clots in patients having ischaemic strokes.

As part of the study your patient had an investigation known as optical coherence tomography – OCT that enables us to check the results of our stenting procedure and where necessary intervene to optimise them. The RETRIEVE-AMI study will contact your patient via telephone at approximately 6 months following discharge to follow them up for the purposes of the study data collection. The research team may also ask you for medical information about the patient's progress.

From a clinical perspective the study will not consider any specific follow up for your patient who will be continued to be reviewed in the standard NHS pathway according to clinical indications.

Please find enclosed the RETRIEVE-AMI study patient information sheet for further details about the study.

If you have any queries, please do not hesitate to contact me.

Yours sincerely,

Dr Giovanni Luigi De Maria
Consultant Cardiologist
RETRIEVE-AMI Chief Investigator

Enclosed: Patient Information Leaflet

Appendix 8. Intra and peri-procedure case report form

RETRIEVE-AMI study ID			Patient initials	
1. Intra procedural angiographic data/complications				
No Reflow	Yes		No	
Arterial Dissection	Yes		No	
NHLBI Grading (A-F) (see diagram 1 and specify type)				
Timing (circle)	pre PCI	Post retriever/aspiration	post PCI	
Management (circle)	Conservative	percutaneous	surgical	
Stent edge Dissection				
Coronary perforation	Yes		No	
Coronary perforation Ellis Grade (see diagram 2 and circle)	Type I	Type II	Type III	Type III CS
Timing (circle)	pre PCI	Post retriever/aspiration	post PCI	
Management (circle)	Conservative	percutaneous	surgical	
CVA	Yes		No	
Timing (circle)	pre PCI	Post retriever/aspiration	post PCI	
TIA				
Timing (circle)	pre PCI	Post retriever/aspiration	post PCI	
TIMI flow (0-3) end of procedure				
Myocardial Blush Grade (1-3)				
QFR acquisitions end of procedure	Yes		No	

2. Investigational Device Information	
Solitaire X Lot No	
Solitaire X Expiry Date	
Microcatheter Lot No	
Microcatheter Expiry Date	
OFDI Catheter Lot No	
OFDI Catheter Expiry Date	

Diagram 1- NHLBI Coronary Artery Dissection Classification Scheme ¹

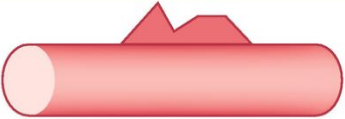
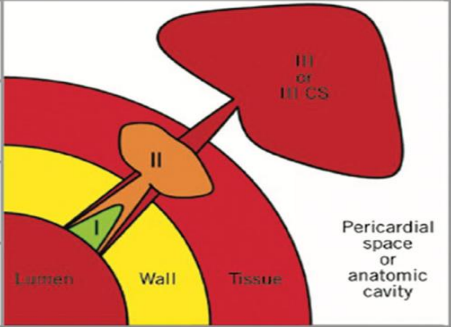
Type A: luminal haziness: minor radiolucent areas within the coronary lumen during contrast injection with no persistence of contrast after the dye has cleared	
Type B: linear dissection: parallel tracts or a double lumen, with no persistence of dye	
Type C: extra-luminal contrast staining: extra luminal "cap" of dye with persistence of contrast	
Type D: spiral dissection, usually with excessive contrast staining of the false lumen	
Type E: dissection with persistent filling defects in the coronary lumen	
Type F: dissection with total occlusion of the coronary lumen and no distal anterograde flow	

Diagram 2 – Ellis Coronary Perforation Classification Scheme²

Type I	Extraluminal crater without extravasation	
Type II	Pericardial or myocardial blush without contrast jet extravasation	
Type III	Extravasation through frank (≥ 1 mm) perforation	
*Type III cavity spilling (CS)	Perforation into an anatomic cavity, chamber, coronary sinus, etc.	

*Sometimes referred to as Type IV

¹ Malik N., Raphael C.E., Gershlick A.H. (2016) Coronary Dissection. In: Lindsay A., Chitkara K., Di Mario C. (eds) Complications of Percutaneous Coronary Intervention. Springer, London. https://doi.org/10.1007/978-1-4471-4959-0_17

² Ellis SG, Ajluni S, Arnold AZ, et al. Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. *Circulation*. 1994; 90: 2725-2730.

Appendix 9: Hospital discharge case report form

RETRIEVE-AMI study ID		Patient initials	

1. Discharge Data			
	Alive	Dead	
Status at discharge			
Discharge date (ddmmyy)			
Discharge time (24 hr clock)			
Length of Hospital stay (nights)			
PCI hospital outcome	No complications		
	Death		
	Cardiac Death		
	CVA (embolic)		
	CVA (bleed)		
	Transient ischaemic attack (TIA)		
	Re-infarction		
	Emergency CABG		
	Re-intervention PCI		
	Re-cath no PCI		
	Elective CABG		
	Radial Artery complication		
	Defibrillation		
	Pulmonary oedema		
	Cardiogenic shock		
	Intra-Aortic Balloon Pump (IABP)		
	Duration of IABP (hours)		
	Non-invasive ventilation (CPAP, BiPAP)		
	Invasive ventilation (intubation)		
	Temporary pacing wire		
	Permanent Pacemaker		
	Blood product transfusion		
	Renal failure/dialysis		
	GI bleed		
	Cardiac Tamponade		
	Unlisted		

2. Medications at Discharge			
Drug Name	Yes	No	Dose/Type (Type when relevant)
Aspirin			
Ticagrelor			
Clopidogrel			
Prasugrel			
Apixaban/Rivaroxaban/Edoxaban			
Warfarin			
Low molecular Weight Heparin			
Nitrates (buccal/oral)			
Beta blocker			
ACE/ARB inhibitor			
Statin			
Diuretic			
Ca Channel Blocker			
Potassium Channel Modulator			
Other Anti-arrhythmic			
Other Cardiac Medication			
Other Medication			

Recorded by		Date	

Appendix 10: Adverse event reporting form

SERIOUS ADVERSE EVENT REPORTING FORM	Oxford University Hospitals  NHS Foundation Trust

Study Name: RETRIEVE-AMI	
REC reference Insert details	SAE Identifier:
Site name:	Type of Report:
Principal Investigator name:	Initial ☐ or Follow up ☐ Number: __

Participant ID: (unique participant study code or reference number)	
Age:	Height (if relevant):
Male ☐ Female ☐	Weight (if relevant):

Details of SAE	
Why was the event Serious? ☐ resulted in death, ☐ is life threatening, ☐ requires inpatient hospitalisation or prolongation of existing hospitalisation, ☐ persistent or significant disability/incapacity, ☐ congenital anomaly/birth defect, ☐ <u>other</u> important medical event.	Date of SAE awareness at site: * (dd/mm/yyyy) (hh:mm 24 hour clock) *If reported late confirm reason for lateness in the additional information section below.

Main SAE diagnosis (Enter the MAIN EVENT TERM, the medical term that best summarises the event)	Grade or Severity (CTCAE or in protocol)	Date SAE started dd/mm/yyyy	SAE status See code list A	Date SAE ceased to be serious dd/mm/yyyy

Narrative (provide an account of the event including any associated symptoms. You must add further information about the nature of the sequelae if 'SAE status' is ticked 'resolved with sequelae')

Study Intervention		Refer to code list C, D, E for below		
Study Intervention (List all study interventions and for study drugs indicate their route using code list B)	Date of Procedure dd/mm/yyyy	Causal relationship to SAE	Expectedness** (For related events only)	Action taken due to SAE
Insert details				
Insert details				

Other treatments (exclude therapies given for the treatment of the SAE, include concomitant medication, radiotherapy, surgery and palliative care, and rescue medication. Continue on separate sheet if necessary)						Indicate if <u>not</u> applicable ☐	
Treatment Give generic name	Dose (Indicate if total dose, daily dose etc)	Route See code list B	Start Date dd/mm/yyyy	Ongoing Yes/No	End Date dd/mm/yyyy	Causal relationship to SAE See code list C	Action taken due to SAE See code list E

Additional information		
Do you consider this event likely to have been caused by anything other than the treatment listed previously on this form?	No ☐	Yes ☐
If yes please specify: (for example medical history, family history, findings from special investigations, disease progression, co-morbidity)		
Is there any further information you would like to add or outstanding results e.g. imaging or laboratory to forward, details of medication given for the SAE, reason for late reporting of SAE?	No ☐	Yes ☐
If yes, please specify:		

Reporter's signature:	
Date: dd/mm/yyyy	/ /
Printed name and position:	
Phone and email contact details:	
Signature of medically qualified investigator who has assigned causality:	
Date: dd/mm/yyyy	/ /
Printed name and position:	
Phone and email contact details:	

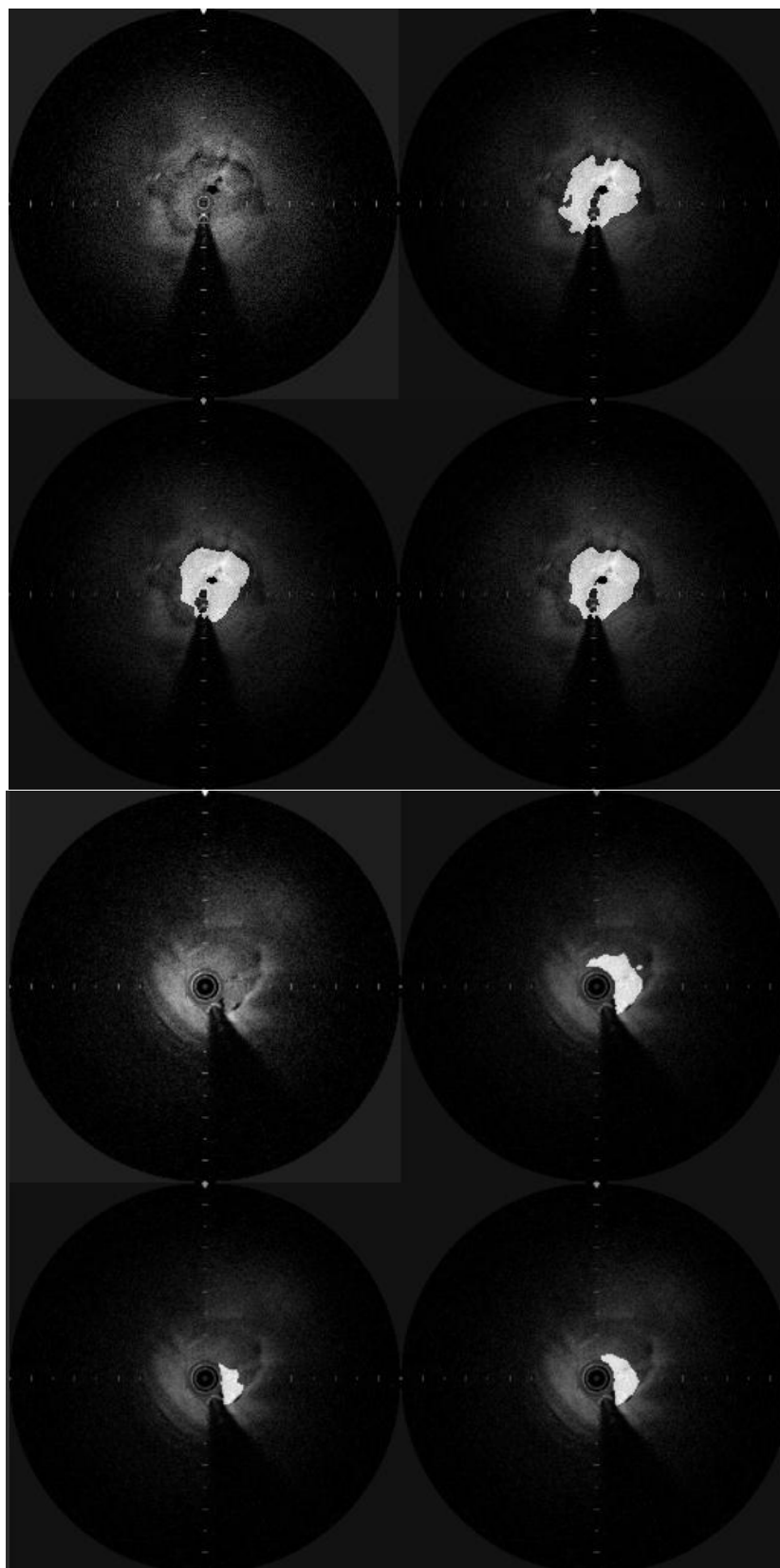
Submit the signed SAE form to ouh.sponsorship@oxnet.nhs.uk within 24 hours of site awareness. Do not delay sending the form if all information is not available.

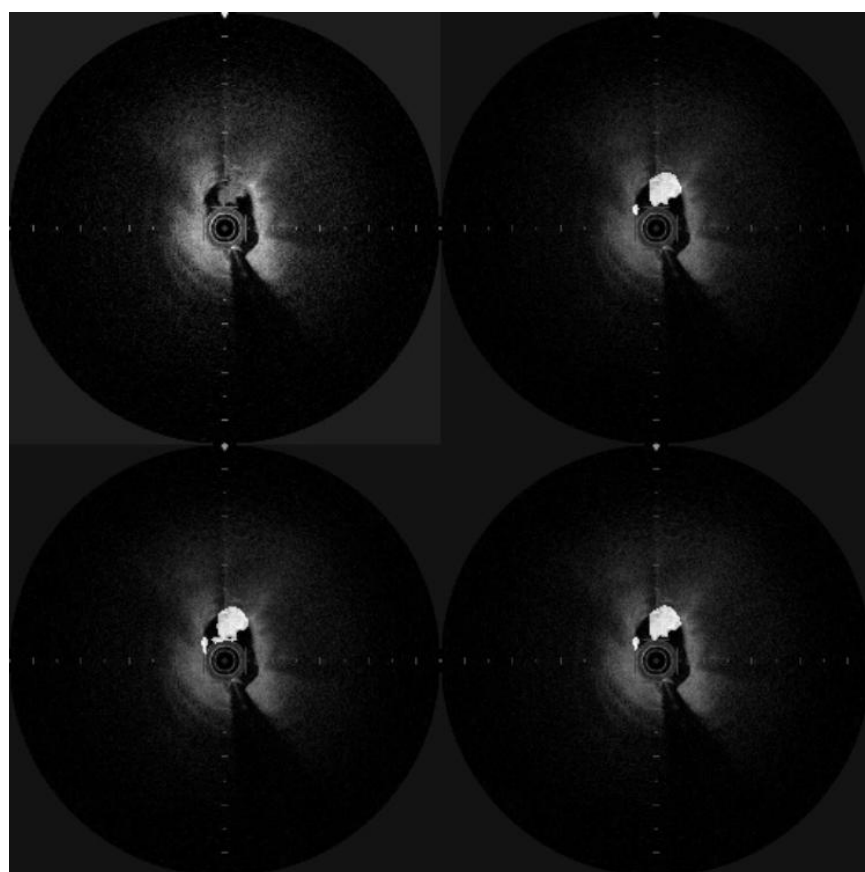
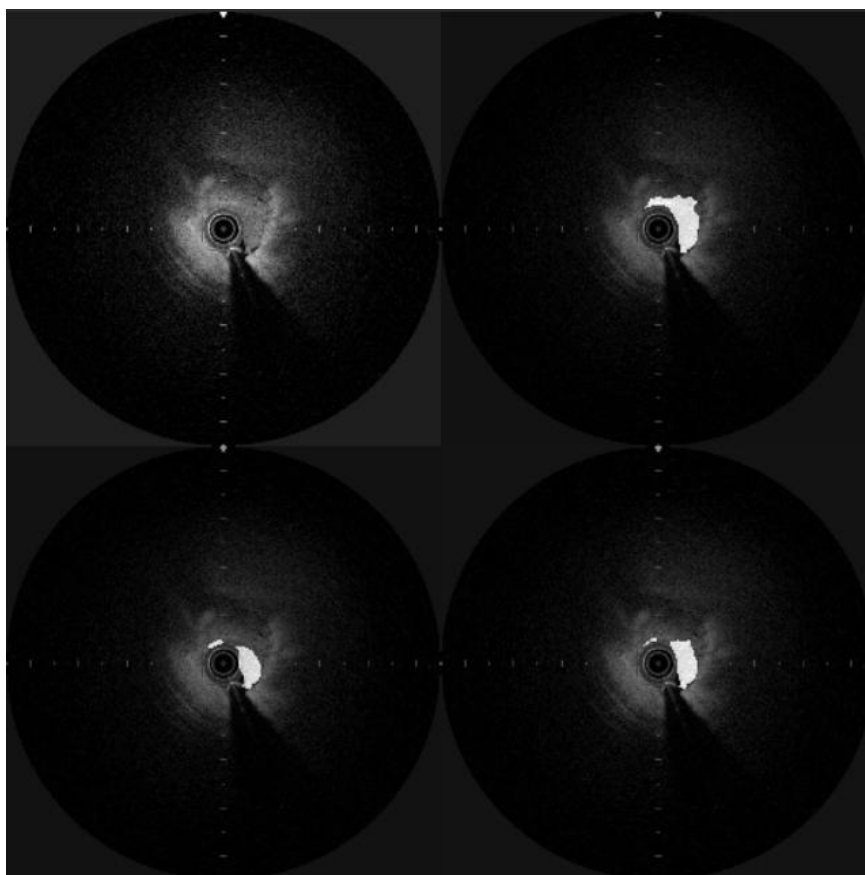
File the original in the Trial Master File or Investigator Site File, and ensure that the event is recorded in patient hospital notes and case report form where applicable.

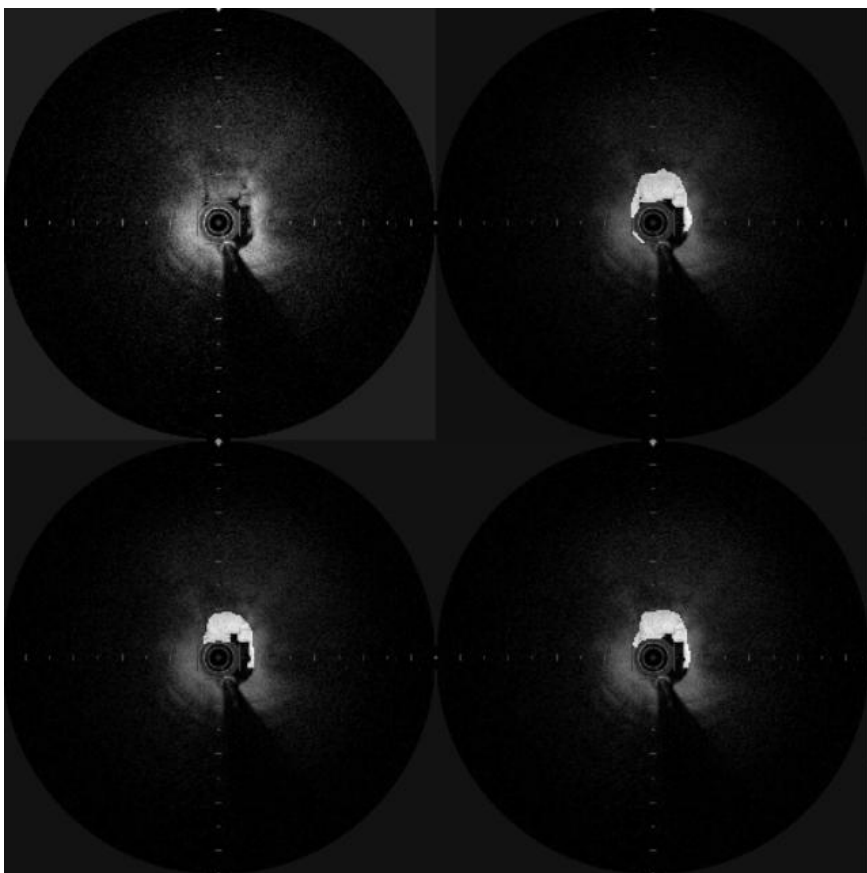
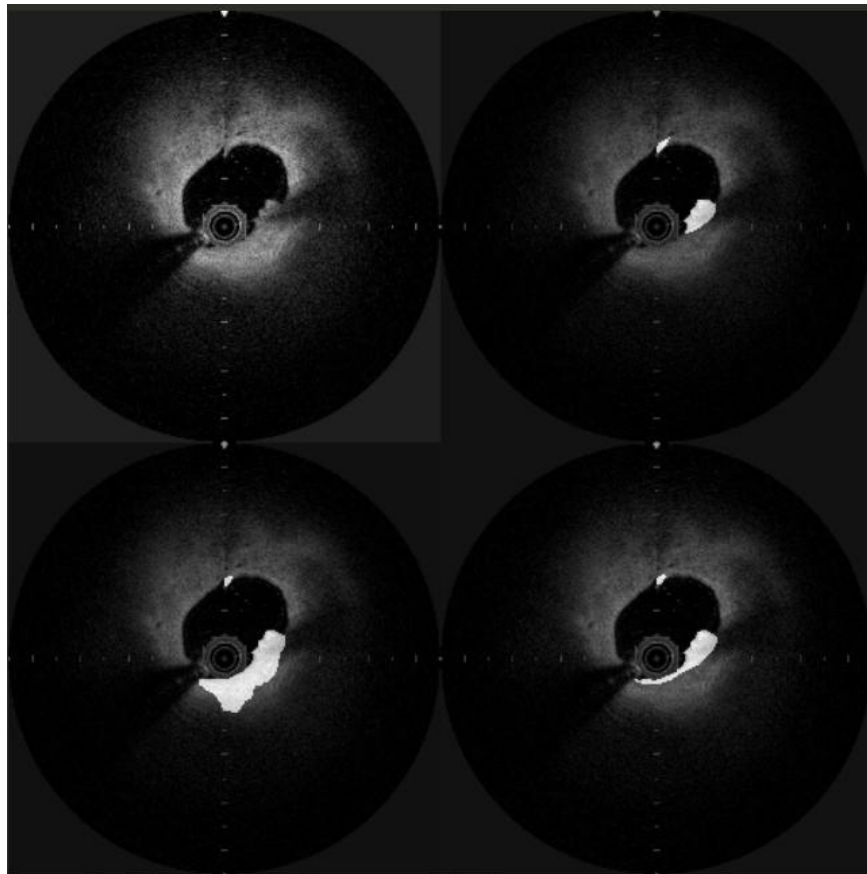
Coding					
A: SAE status	1= Resolved	2= Resolved with sequelae	3= Ongoing	4= Fatal	
B: Route	1 = Local				
C: Causality	0 = Unrelated	1 = Related	Causality must be completed by a medically qualified investigator. If protocol gives degrees of causality i.e. definitely, probably, etc., then update the coding table in this template in line with the protocol before use		
D: Expectedness	1 = Expected	2 = Unexpected	Expected events are those complications mentioned in the protocol		
E: Action	0 = none	1 = Retriever thrombectomy abandoned	2 = Conservative management	3 = PTCA management	4 = Surgical management

Unit / Coordinating Centre Office Use Only
Coordinating Centre SAE Identifier:
Report received by: (print name and trial role / designation)
Is the event a SAE requiring immediate reporting in accordance with the protocol? [yes/no]
If yes to above, confirm date SAE report forwarded to CTRG/R&D for review by TSG medical monitor: (DDMMYYYY)

Appendix 11: Further examples of automated machine learning thrombus segmentations on OCT. For each image, the top right tile shows the original OCT image, clockwise from top right shows automated thrombus segmentations (white) for models A, B and C.







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