Anatomical, physiological and inflammatory characterization of nonculprit vessels in patients undergoing primary PCI for ST-elevation myocardial infarction in the presence of multivessel disease: Rationale and design of the PICNIC study

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ABSTRACT

Background Up to 50% of patients presenting with ST-elevation myocardial infarction (STEMI) have multivessel coronary artery disease (CAD). Randomized trials suggest that complete revascularization improves outcomes, but the mechanism and identification of patients who benefit remain unclear. This study aims to assess the association between blood and coronary imaging biomarkers and clinical events, to identify patient-, vessel-, and lesion-specific risk in STEMI patients with bystander disease.

Method PICNIC is a multicenter, international, prospective, observational study enrolling 320 patients with STEMI and multivessel CAD undergoing primary PCI of the culprit vessel without complete revascularization. Participants will undergo blood sampling for inflammatory markers and coronary CT angiography (CTCA) to assess: (1) plaque burden and morphology, (2) artificial intelligence-enabled fractional flow reserve derived from CTCA (FFR_{CT}) analysis of plaque and hemodynamic features, and (3) fat attenuation index (FAI) to evaluate perivascular inflammation.

The primary analysis will evaluate the association between a composite 24-month clinical endpoint (including all-cause mortality, myocardial infarction, ischemia-driven revascularization as first layer and cardiac arrest, heart failure, stroke, and ventricular tachyarrhythmia (second layer)) and: (1) serum inflammatory markers, and (2) anatomical and physiological characteristics of non–infarct-related arteries (NIRA) assessed by CTCA, FFR_{CT}, and FAI. Statistical and machine learning methods will be applied to determine which combinations of clinical, imaging, and biomarker data best predict patient-, vessel-, and lesion-specific risk.

Conclusion PICNIC will characterize the anatomical, physiological, and inflammatory features of NIRA lesions in STEMI patients treated with culprit-only PCI in order to develop an AI-based risk prediction model. If such a model is successful it could be used to inform personalized revascularization strategies. (Am Heart J 2026;292:107298.)

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Background

Primary percutaneous coronary intervention (PPCI) is the gold standard of care for patients presenting with ST-elevation myocardial infarction (STEMI).[1,2] Up to 50% of STEMI patients undergoing PPCI have multivessel coronary artery disease (CAD), defined as significant disease in coronary territories not supplied by the culprit vessel.[3] At least 9 randomized control trials (RCT) have shown that complete revascularization (CR) of bystander lesions, either at the time of PPCI or as a staged procedure, is safe and reduces the risk of subsequent MI and/or repeat revascularization[4-12] (Table 1). Based upon this body of evidence, CR in this patient cohort now has a class 1a indication in both the European Society of Cardiology and ACC/AHA/SCAI guidelines.[13,14]

Despite the wealth of data in support of CR, 4 areas of uncertainty remain when considering the application of CR in routine clinical practice. Firstly, the patient populations in the RCTs were highly selective. For example, of all the patients screened for enrolment, 19% were included in PRAMI,[6] 35% in CvLPRIT,[7] and 14% in DANAMI-3-PRIMULTI.[8] Complex anatomy (mean SYNTAX score in COMPLETE was 14) including chronic total occlusions, heavily calcified lesions, left main and other complex bifurcations, patients in cardiogenic shock (a clinical scenario in which CR has been shown to be harmful[15]), and frail or comorbid patients were excluded. Furthermore, the results are not applicable to patients presenting 12 hours beyond symptom onset as there is currently no consensus regarding optimal timing and PCI strategy in

Table 1. List of randomized-controlled trials comparing a strategy of complete revascularization (CR) vs culprit lesion (CL) only revascularization in patients presenting with ST-elevation myocardial infarction (MI) and multivessel CAD.

Study	Intervention	Control	Definition of significant stenosis	Primary endpoint	Outcome
HELP AMI	CR at index procedure ($n = 52$)	CL only PCI ($n = 17$)	Not specified	Incidence of repeat revascularization	CR 17% vs CL 35%; $P = .247$
Politi et al	NCL PCI either at index (CR; $n = 65$) or staged (SR; $n = 65$)	CL only PCI ($n = 84$)	Visual estimation: DS > 70%	Composite of cardiac death, noncardiac death, in-hospital death, reinfarction, rehospitalization with ACS and new revascularization	CR 23% vs staged 13% vs CL 50%
PRAMI	NCL PCI during the index procedure (CR; $n = 234$)	CL only PCI ($n = 231$)	Visual estimation: DS >50%	Composite of cardiac death, nonfatal MI, and refractory angina	CR 9% vs CL 23% (HR 0.35;95% CI 0.21-0.58)
CvLPRIT	NCL PCI at index procedure or index admission (CR; $n = 138$)	CL only PCI ($n = 139$)	Visual estimation: DS >70% in 1 view >50% in 2 views	Composite of all-cause death, recurrent MI, heart failure, and ischemia-driven revascularization	CR 10% vs CL 21.2% (HR 0.45; 95% CI 0.24-0.84)
DANAMI-3-PRIMULTI	NCL PCI at index admission (CR; $n = 314$)	CL only PCI ($n = 313$)	Angio-guided NCL PCI: DS > 90% FFR-guided NCL PCI: DS >50% and FFR ≤0.80	Composite of all-cause death, reinfarction, and ischemia-driven revascularization	CR 13% vs CL 22% (HR: 0.56; 96% CI 0.38-0.83)
COMPARE-ACUTE	NCL PCI at index procedure or admission (CR; $n = 295$)	CL only PCI ($n = 590$)	QCA FFR guided PCI: DS >50% and FFR≤0.80	Composite of all-cause death, nonfatal MI, any revascularization, and cerebrovascular events	CR 7.8% vs CL 20.5% (HR: 0.35; 95% 0.22-0.55)
COMPLETE	NCL PCI at index admission or staged ($n = 2,106$)	CL only PCI ($n = 2,025$)	Visual estimation: angio-guided PCI: DS >70% FFR-guided PCI: DS>50-69% and FFR≤0.80	Composite of cardiovascular death and MI; and composite of cardiovascular death, MI, and ischemia-driven revascularization	Outcome 1: CR7.8% vs CL 10.5% (HR: 0.74; 95% CI:0.60-0.91) Outcome 2: CR 8.9% vs CL 16.7% (HR: 0.51; 95% CI: 0.43-0.61)
FLOWER-MI	FFR guided NCL PCI at index procedure or admission ($n = 586$)	CL only PCI ($n = 577$)	Visual estimation: DS ≥50% and FFR ≤0.80	Composite of death from any cause, nonfatal MI, unplanned hospitalization leading to revascularization	FFR-guided group 5.5% vs angiography-guided group 4.2% (HR: 1.32; 95% CI: 0.78-2.23)
FIRE (only 35.2% were STEMI patients)	CR either at index procedure or admission utilising FFR/iFR or QFR ($n = 720$)	CL only PCI ($n = 725$)	Visual estimation: DS 50-99%	Composite of death, MI, stroke, ischemia-driven revascularization	CR 15.7% vs CL 21% (HR: 0.73; 95% CI: 0.57-0.93)

ACS, acute coronary syndrome; CI, confidence interval; DS, diameter stenosis; FFR, fractional flow reserve; HR, hazard ratio; NCL, nonculprit lesion; PCI, percutaneous coronary intervention.

such patients. Thus, the relevance of the outcomes of these highly selected groups to the wider STEMI population within routine clinical practice is uncertain.

Secondly, the definition of what constituted significant angiographic disease in noninfarct related arteries (NIRA) is inconsistent across the trials, in most cases being defined visually as either a 50% or 70% minimum diameter stenosis. Furthermore, in some trials, there was a requirement for positive invasive FFR as well as angiographic minimum stenosis of the bystander lesion(s), which resulted in lower inclusion rates for NIRA, so that 31% of patients randomized to CR did not qualify for NIRA revascularization in DANAMI-3-PRIMULTI, and 44% in COMPARE-ACUTE. We can assume that, in contrast to these trials, physiologically nonsignificant (ie, FFR negative) NIRA lesions may have been treated in the angiography-guided PRAMI and CvLPRIT studies, as well as in the COMPLETE trial, in which less than 1% actually underwent pressure wire assessment. Interestingly, the hazard ratios for recurrent MI and repeat revascularization in these trials were similar, despite differences in the criteria for revascularization. These data raise the question as to whether the benefit of CR in these trials is based upon anatomical or physiological criteria for defining bystander disease.

Thirdly, the underlying mechanism(s) that drives the benefit in CR across these trials remain(s) unresolved, if defined by which specific clinical event was reduced by the intervention. For example, neither PRAMI nor CvLPRIT reported dominant differences in specific components of their composite clinical endpoints, whereas ischemia-driven revascularization was the clear driver for benefit in both DANAMI-3-PRIMULTI and COMPARE-ACUTE, whereas lower incidence of new MI was the main driver of benefit in COMPLETE.

Finally, 2 important observations that stimulate the PICNIC hypothesis are that: (a) most patients enrolled into the above trials did not experience a clinical event during follow up, even in the culprit-only arms and (b) less than half of the clinical events were eliminated in the CR groups.

Limitations of the current trial data raise uncertainty about the concept that all bystander disease should be subject to CR in STEMI patients. We speculate that, rather than a "one size fits all" approach to CR, a tailored approach based upon personalized detection of patient-, vessel- and possibly lesion-level risk would be dominant. The PICNIC study, therefore, aims to determine the anatomical, physiological, and inflammatory features of lesions in the NIRA of patients presenting with STEMI who are treated with culprit-only PCI, and to identify potential associations with subsequent clinical events. In order to achieve this, we will employ novel imaging technology in the form of both fat attenuation index (Caristo) and FFR_{CT}-mediated adverse plaque and hemodynamic characteristics (HeartFlow) to assess vessel- and lesion-specific features of risk.

Methods

The PICNIC study is an investigator led, multicenter, prospective, observational study being performed in 3 UK and 3 South Korean sites. The UK part of the study received full ethical approval in July 2024 (Queen Square Research Ethics Committee, London [REC Reference 24/LO/0394, IRAS project ID: 341232]) and is registered at ClinicalTrials.gov (NCT06506448). Enrolment started in February 2025 and 28 patients have been recruited to date. Recruitment is expected to conclude by December 2026. The follow-up end date will be December 2029 and primary endpoint results will be reported in 2030. A study flowchart is shown in Figure.

Study hypothesis

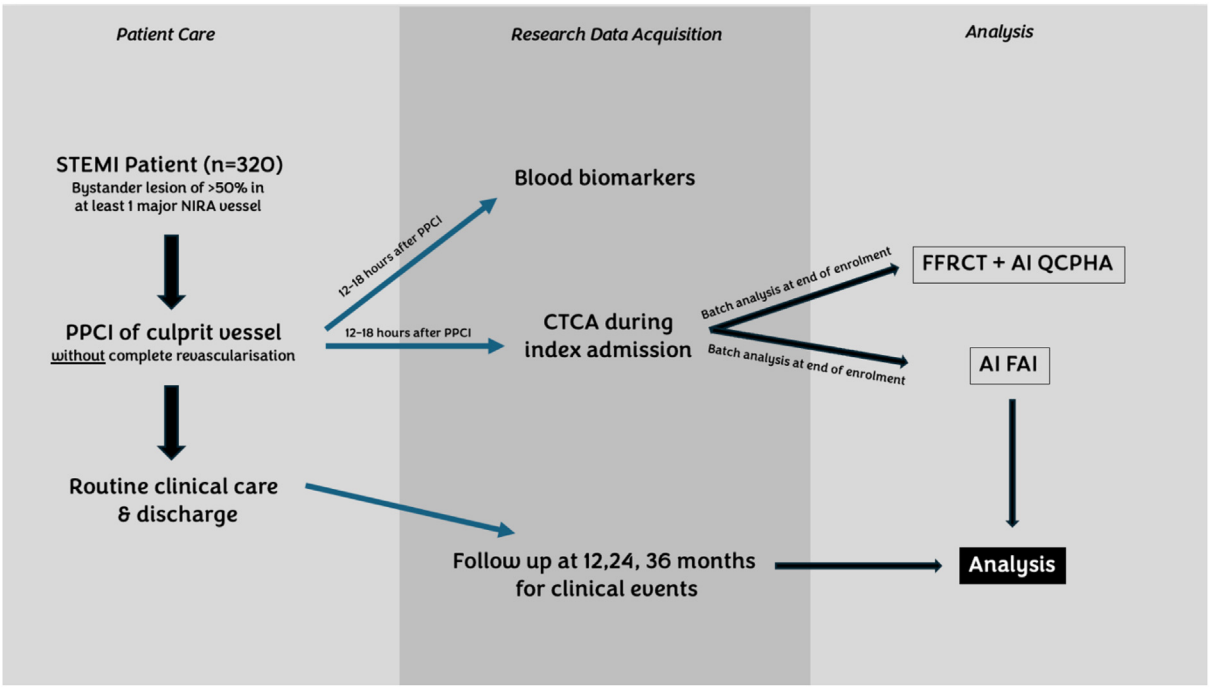
We hypothesize that the susceptibility of nonculprit disease to ischemic events after PPCI is variable between individuals, and that this may be vessel- and, perhaps, lesion-specific. Specifically, we postulate that this susceptibility may be related to multiple factors including anatomical and physiological vulnerability, and local vascular inflammatory status. To test this hypothesis, we will systematically examine the following parameters in each bystander coronary vessel in patients who present with STEMI and have undergone PPCI: (1) blood biomarkers of systemic inflammation; (2) plaque anatomy including lesion severity and markers of lesion vulnerability on CTCA; (3) assessment of individual coronary vessel inflammation using CT-derived fat attenuation index (FAI), and (4) vessel- & lesion-specific anatomical and physiological parameters derived by HeartFlow including FFR_{CT}, Δ FFR_{CT}, wall shear stress and axial plaque stress, as described below.

Using both traditional statistical assessment and an AI-driven model, incorporation of clinical, inflammatory, and imaging parameters, our aim is to develop a risk assessment tool for individuals, vessels and lesions that are at the greatest risk of being associated with subsequent clinical event(s). If we are able to construct a model that predicts vessel- and/or lesion-specific risk, it may be plausible to design a randomized trial of CR that only targets the highest risk bystander lesions, rather than the strategy of stenting all lesions of a certain diameter stenosis.

Primary analysis

The primary analysis is to define whether there is a correlation between a composite endpoint that includes all-cause mortality, myocardial infarction and unplanned revascularization at 24 months and (1) serum inflammatory markers, and (2) anatomical and physiological characteristics of coronary vessels and lesions in the NIRA as

Figure. Study flow. STEMI. AIQCPHA, artificial intelligence coronary plaque & hemodynamic analysis; FAI, fat attenuation index; FFRCT, fractional flow reserve derived from CT; PPCI, primary percutaneous coronary intervention; ROC, receiver operating characteristic; STEMI, ST elevation myocardial infarction.



assessed by CTCA/FFR_{CT}/FAI. This is with a view to the development of a risk model with a predefined discrimination/ calibration using the parameters we collect to predict clinical endpoints.

Secondary endpoints

The secondary endpoints are: (1) anatomical, physiological, and inflammatory features of lesions in the NIRA(s) at 12, 24 and 36 months; (2) association between anatomical, physiological, and inflammatory features and the risk of nonculprit lesions causing the more extensive composite of clinical events (death, myocardial infarction, unplanned revascularization, cardiac arrest, acute coronary syndrome, additional revascularization by CABG or PCI, rehospitalization for angina, heart failure, stroke, ventricular tachyarrhythmia) at 12, 24, and 36 months; (3) correlation between parameters of inflammation and CTCA based anatomical, hemodynamic, and plaque characteristics with individual components of the clinical event composite; (4) differences between patient groups with clinical events vs those without in terms of serum inflammatory markers, anatomical and physiological characteristics of coronary vessels/lesions in the NIRA; (5) the feasibility to build a multidimensional AI model that would best predict the risk of events in the NIRA vessels and NIRA lesions employing all the studied parameters (serum biomarkers, CTCA lesion severity, CTCA plaque characteristics, FFR_{CT} derived plaque characteristics and FAI).

Patient population

Patients aged ≥18 years of age presenting with STEMI within 12 hours of symptom onset who have undergone PPCI and fulfilling the eligibility criteria (Table 2) will be recruited. All patients will need to have undergone successful PCI to the culprit vessel, using stent(s), and have at least 1 coronary stenosis of ≥50% diameter stenosis by visual estimation in a NIRA with a minimum diameter of 2.5 mm. Key exclusion criteria include cardiogenic shock or ongoing hemodynamic instability, significant complication or poor outcome relating to the culprit lesion PCI, intention to perform complete revascularization. We will exclude patients who are considered likely to require surgical revascularization because (1) they are unlikely to be suitable for complete revascularization by PCI and (2) we will not be able to follow the natural history of bystander disease if they have undergone bypass graft surgery. Stent thrombosis cases are excluded because we seek to investigate *de novo* disease, and because such patients may have factors such as hyporesponsiveness to antiplatelet therapy that compounds variables.

Table 2. Inclusion and exclusion criteria.

Inclusion criteria
1. Age 18 to 85 years
2. Ability to provide written informed consent post primary PCI
3. Presentation with acute ST-elevation myocardial infarction within 12 hours of symptoms onset
4. Culprit lesion only primary PCI
5. Coronary stenosis of ≥50% diameter stenosis by visual estimation in the NIRA with a minimum diameter of 2.5 mm.
Clinical exclusion criteria
1. Cardiogenic shock
2. Decompensated heart failure requiring intubation, inotropes, or IABP
3. Refractory ventricular arrhythmia
4. Previous coronary artery bypass surgery
5. Stent thrombosis and in-stent restenosis
6. An intention before inclusion into the study to revascularize a nonculprit lesion
7. Active malignancy or inflammatory disorders such as rheumatoid arthritis or inflammatory bowel disease
8. Severe valvular heart disease requiring surgery
9. Planned surgical revascularization
10. Active participation in another clinical trial
11. Life expectancy less than 12 months
12. Contraindication to CTCA such as presence of internal defibrillator, allergy to iodinated contrast, pregnancy, contraindication to beta blocker/sublingual nitrate administration, mechanical prosthetic heart valve, and renal impairment with creatinine >200
Anatomical exclusion criteria
1. NIRA stenosis ≥50% in the left main stem or ostia of both the left anterior descending and circumflex arteries
2. <TIMI III flow in the NIRA
3. Evidence of thrombus in the NIRA

CTCA, Computed tomography coronary angiography; IABP, intra-aortic balloon pump; NIRA, Noninfarct related artery; PCI, Percutaneous coronary intervention.

Study procedure

Enrolment

Culprit lesion PPCI will be undertaken as an emergency as standard of care according to local practice and operator discretion. The transradial approach will be strongly encouraged. Per protocol, patients will not undergo CR as part of their routine clinical care. CR will be recommended only in cases with recurrent ischemic chest pain or recurrent acute coronary syndrome event during the index admission. Patients will be approached for study consent following PPCI within 12-18 hours of their return to the ward. Upon consent, 30 ml of blood will be collected for measurement of serum inflammatory markers. As part of routine clinical care, infarct size will be assessed using peak hs-Troponin levels and echocardiographic measurement of left ventricular function.

Patients will then undergo CTCA during the index admission. The CTCA will be performed according to existing local protocols which will be consistent with the requirement for HeartFlow and Caristo analysis. The CTCA dataset will be nested for later FFR_{CT} and FAI analysis, as described below.

Blood sampling for inflammatory markers

Whole blood will be collected using EDTA, centrifuged and then stored at −80°C for batch analysis. The following serum inflammatory markers will be measured using standard assays: interleukins-1ß, 6, 8; tumor necrosis factor α; adhesion molecule-1; vascular cell adhesion molecule-1; and E-selectin; C-reactive protein (hs-CRP), soluble CD40 ligand; fibrinogen; pregnancy associated plasma protein A; matrix metalloproteinase 9.

CT coronary angiography

Patients with a heart rate of greater than 60 beats per minute and systolic blood pressure >110 mmHg will receive intravenous metoprolol until the resting heart rate is ≤60 beats per minute, at the discretion of the supervising CT practitioner, in accordance with standard routine clinical practice. Patients with a contraindication to beta-blockade will be considered for oral verapamil, diltiazem, or ivabradine depending on local protocols. Patients will also receive 0.5-1mg of sublingual GTN, unless specifically contraindicated, as per standard clinical practice. Coronary angiography will be conducted during contrast enhancement using prespecified protocols as recommended by the scanner manufacturers during a single breath hold with prospective electrocardiographic gating.

Results from this protocol driven CTCA will be nested and not shared with the clinical team. It is anticipated that on occasion the CTCA will lead to the identification of incidental findings, such as lung masses or abnormal nodes. These findings will be forwarded to the clinical care team and should be dealt with in accordance with local clinical practice pathways.

FFR_{CT} (AI-QCPHA) analysis

A secure, web transfer portal will be established to allow transfer of the raw CTCA data to HeartFlow, where analysis according to their published FFR_{CT} protocol will be undertaken. Each scan will be evaluated for

the following plaque and hemodynamic parameters on all coronary vessels with a reference diameter of more than 2.0 mm.: (1) formal plaque analysis including total plaque volume, high risk features (including low attenuation plaque, spotty calcification, napkin ring sign), plaque burden (a cross-sectional plaque area/vessel area at the minimum lumen area site); noncalcified plaque volume (NCPV) (plaque composition of 30-130 HU); low-attenuation plaque volume (LAPV) (plaque composition of −30 to 30 HU); (2) the following hemodynamic characteristics: averaged wall shear stress (WSS), peak WSS, averaged axial plaque stress (APS), peak APS, change in fractional flow reserve derived from coronary CTA (FFRCT) across the lesion (ΔFFR_{CT}), peak FFRCT gradient, averaged percent/peak percent total myocardial blood flow (MBF).. An analysis of these features will be performed by an AI-enabled model, known as quantitative coronary plaque and hemodynamic analysis (AI-QCPHA), as described in the EMERALD II study.[16] Using this established AI algorithm, an assessment of lesion- and vessel-specific risk, as determined by association with clinical events (primary composite and secondary composite) will be undertaken in PICNIC.

Fat attenuation index analysis

The CTCA raw dataset for each patient will be transferred to CARISTO (a spinout company by the Academic Cardiovascular Unit, University of Oxford, Oxford, UK) for analysis as previously described.[17] All scans will be reviewed initially for quality and presence of artefact precluding a reliable qualitative and quantitative evaluation. To measure the perivascular FAI, we will trace the proximal 40mm segments of all 3 major epicardial coronary arteries (right coronary artery, left anterior descending artery, and circumflex artery) and define respective perivascular fat as the adipose tissue within a radial distance from the outer vessel wall equal to the diameter of the vessel. The FAI will be calculated by quantifying the weighted perivascular fat attenuation after adjustment for technical parameters based on the attenuation histogram of perivascular fat within the range of −190 HU to −30 HU.[17] As described in detail in the ORFAN study,[18] CaRi-Heart version 2.5 medical device will de used to compute the FAI and AI-Risk parameters. The FAI Score is derived using a proprietary algorithm that incorporates FAI inflammatory status of left anterior descending, circumflex and right coronary arteries and then adjusts for clinical, biological and anatomical factors. The highest FAI Score for the vessels can then be incorporated into the same model used in ORFAN that includes traditional clinical risk factors (diabetes, smoking, hyperlipidemia, and hypertension) and plaque burden (modified Duke CAD index, an angiographic score integrating proximal CAD, plaque extent, and left main disease). This assessment will facilitate both vessel-specific and patient-specific analysis of the association with events in PICNIC.

Planned analysis

We will assess the association between the primary and secondary layers of clinical events and (1) the AI QCPHA model and (2) FAI AI models separately. These analyses will follow the methodology laid out in previous cited publications using these models, that incorporate clinical factors, in order to derive a prediction tool for events at patient-, vessel- and lesion-level.

We will also combine the outputs for both AI QCPHA and FAI into a single multivariable model.

Sample size calculation

PICNIC is a proof-of-concept pilot study. After formal review with an expert medical statistician (EK) it is apparent that a standard power calculation is not appropriate for this project given the lack of comparative groups and the unknown elements of our primary aim, which is exploratory. The project is further limited by the practicalities of affordability within our budget constraints. We therefore aim to accrue enough events to provide the best possible assessment for the proof of our proposed concept within our current budget. We have used composite event rates from PRAMI, CvLPRIT, DANAMI-3-PRIMULTI, COMPARE-ACUTE, COMPLETE, to estimate that a sample size of 320 patients will accrue a rate of composite events of at least 25% at 24 months, or 80 events. Our proposed composite events are taken from previous trials, in which the chosen events are heterogeneous, as described above, and have included a range of events that we anticipate may reflect either directly or indirectly the consequence of new or ongoing coronary artery pathology. The output from PICNIC will undoubtedly inform accurate power calculations for future projects.

Discussion

PICNIC is a prospective observational pilot study of patients who have had PPCI for STEMI and have bystander disease that will use blood and CTCA-derived imaging biomarkers to build an AI-model to test the hypothesis that it is possible to describe patient-, vessel- and lesion specific-risk of future adverse clinical events. Proof of this hypothesis will stimulate & facilitate the design of randomized trials that compare CR vs culprit only intervention in high risk bystander vessels and/or lesions rather than in all such lesions, as recommended by current international clinical guidelines.

There are now 9 randomized trials that indicate significant clinical outcome advantage for a strategy of complete revascularization vs culprit only primary PCI in patients presenting with ST-elevation MI. This evidence has resulted in a class 1A recommendation for CR in international clinical practice guidelines, presumably based upon the concept that prophylactic stenting of all previously unheralded and unselected bystander lesions

prevents them from precipitating further acute ischemic events. Despite this, there are a number of important concerns about applying routine and universal stenting to bystander disease in STEMI patients, so that many front-line interventionists apply this recommendation only selectively in their patients.

Objections to the notion that it is justifiable to perform PCI on all bystander lesions as a strategy of complete revascularization can be summarized as follows. Firstly, across the published RCTs that demonstrate outcome benefit for CR, the criteria used to define significant bystander disease are highly variable both in terms of qualifying degree of diameter stenosis and whether they are physiologically significant or not. Secondly, the composite endpoints across the trials vary extensively, as do the apparent drivers of the significant difference between the groups. For example, in some RCTs, there is a substantial and significant reduction in recurrent MI, an endpoint that might plausibly be expected to be prevented by prophylactic stenting, but not in others. It is notable, however, that in none of the trials is there any mortality advantage to complete revascularization. Thirdly, although all the trials demonstrate outcome advantage to complete revascularization when compared to a culprit only strategy, in most cases the degree to which event rate is reduced in the complete revascularization arms is less than 50% of the total events seen in the culprit only group. This observation indicates that stenting all bystander disease using the highly variable criteria in these trials does not prevent the majority of subsequent events. These observations taken together raise several important research questions. Firstly, for example, is the strategy of stenting bystander lesions beneficial for some lesions but not others? Secondly, is the strategy of stenting bystander lesions beneficial for some patients and not others? Finally, is the combination of lesion and patient factors valuable?

In PICNIC, our aim is to use imaging biomarkers that have previously been shown to identify features of coronary artery lesions that indicate risk of being the substrate for a future clinical event and apply them in bystander vessels in STEMI patients who have undergone culprit-only PCI. CTCA studies have repeatedly described plaque features associated with the development of acute coronary events including positive remodeling (PR), low attenuation plaque (LAP), spotty calcification, and napkin-ring sign.[19,20] Furthermore, the flow limitation model described by FFR_{CT} analysis in itself offers prognostically important information, given that in all the studies to date using FFR_{CT} the clinical ischemic event rates (MI, IDR) in patients with atheroma on CTCA, but in whom the FFR_{CT} is negative for ischemia, is low.[21,22] Further, in several studies including ADVANCE,[23] FORECAST[24] & FISH & CHIPS[25] there is a dose response relationship between the degree of FFR_{CT} abnormality present and the risk of subsequent events.

Other novel models have further refined the ability of CTCA imaging to yield an assessment of risk of acute coronary events. The EMERALD study evaluated the potential utility of a detailed assessment of plaque and hemodynamic characteristics in the identification of high-risk plaques that caused subsequent ACS identified 72 patients with ACS who had undergone CTCA at 1 month to 2 years before their event.[26] Specifically, the scans were evaluated for: (1) diameter stenosis, (2) adverse plaque characteristics (APC) defined as lesions showing LAP, PR, napkin-ring-sign, and spotty calcification, (3) adverse hemodynamic characteristics (AHC) defined by FFR_{CT}, ΔFFR_{CT}, wall shear stress (WSS), and axial plaque stress. The incremental discriminant and reclassification abilities for ACS prediction were compared among 3 models: (1) model 1: percentage diameter stenosis (%DS) and lesion length, (2) model 2: model 1 plus APC, and (3) model 3: model 2 plus AHC. Culprit lesions for the ACS event were shown to have higher %DS ($55.5 \pm 15.4\%$ vs $43.1 \pm 15\%$; $P < .001$) and higher prevalence of APC (80.3% vs 42%; $P < .001$) than nonculprit lesions. Regarding hemodynamic parameters, culprit lesions showed lower FFR_{CT} and higher ΔFFR_{CT}, WSS, and axial plaque stress than nonculprit lesions. Among the 3 models, model 3 showed the highest concordance statistic and better discrimination (c-index 0.789 vs 0.747; $P = .014$) and reclassification abilities (category-free net reclassification index 0.287; $P = .047$) than model 2. Lesions with both APC and AHC showed significantly higher risk of being the culprit for subsequent ACS than those with no APC/AHC (HR: 11.75%; $P = .001$) and with either APC or AHC (HR: 3.22; $P < .001$). This study thus suggests that a combination of anatomical and hemodynamic parameters may be utilized in identifying lesions that are at risk of being the site for subsequent ACS. Subsequently, the EMERALD II study extended this concept using an artificial intelligence (AI)-enabled analysis for the quantitative assessment of coronary plaque and hemodynamic analysis (AI-QCPHA) derived from CTCA and showed that this improved the prediction of ACS over standardized assessment of stenosis severity as well as the presence of high-risk plaque characteristics.[16] The AI-QCPHA features utilized hemodynamic data including WSS, axial plaque stress, FFR, and myocardial blood flow as well as anatomical data including plaque burden, total plaque volume, low-attenuation and plaque volume in a cohort of 351 ACS patients who had undergone CTCA from 1 month to 3 years. The median interval from CTCA to an ACS event was 375 days and 63.5% presented with an MI. The probability of ACS culprit lesions increased with higher CAD-Reporting and Data System (RADS) and the presence of high risk plaque which is routinely available on CTCA. The best AI-QCPH features that provided additive values ACS culprit lesions over CAD-RADS and HRP were ΔFFR_{CT}, plaque burden, total plaque volume, low attenuation plaque volume, and

averaged total myocardial blood flow. Finally, ΔFFR_{CT} was found to be the most impactful feature in the risk prediction model. These data suggest that this AI-QCPHA model may have promise in identifying bystander lesions in STEMI patients carrying the greatest, and lowest, risk of being the site for a future acute ischemic event, which is why it is used as an investigational component in the PICNIC trial.

The other main CTCA-based imaging tool that will be used in PICNIC is Fat Attenuation Index (FAI). This is founded on the concept that inflammation-induced metabolic changes in coronary perivascular fat represent a surrogate for vessel vulnerability for a future acute event.[17] Specifically, the FAI, which is also modelled from a routine CTCA dataset, has been shown to inversely correlate with the expression of adipose genes and average adipocyte size, which is driven by intracellular lipid accumulation. A *post hoc* analysis of 2 prospectively obtained clinical cohorts involving 3912 patients undergoing elective CTCA for investigation of stable chest pain, has shown that FAI is independently associated with all-cause mortality (HR: 1.49; 95% CI: 1.20-1.85; $P < .001$ in the derivation cohort; 1.84; 1.45-2.33, $P < .001$ in the validation cohort) and cardiac mortality (HR: 2.15; 95% CI 1.33-3.48; $P = .0017$ in the derivation cohort; 2.06, 1.50-2.83, $P < .0001$ in the validation cohort).[27] The recent ORFAN study has also examined the association of FAI as part of an AI-risk prognostic algorithm to predict future cardiovascular events.[18] The study included 40,091 consecutive patients undergoing clinically indicated CTCA across 8 UK hospitals (cohort A) and who were followed up for MACE (MI, new-onset heart failure, or cardiac death) over a median of 2.7 years. Coronary inflammation was measured using the FAI score and its prognostic score was evaluated in the presence and absence of obstructive CAD in 3,393 consecutive patients (cohort B) from the 2 hospitals with the longest follow-up (7.7 years). An AI-enhanced cardiac risk prediction algorithm (integrating the FAI score, coronary plaque metrics, and clinical risk scores) was then applied to cohort B to assess its ability to change clinical management. Over a 2.7 year median follow up, patients without obstructive CAD (81.1% of the total study population) accounted for 66.3% of the total MACE and 63.7% of the total cardiac death in cohort A. Increased FAI score in all the 3 coronary arteries had an additive impact on the risk for cardiac mortality (HR 29.8; 95% CI: 13.9-63.9; $P < .001$) or MACE (HR 12.6; 95% CI: 8.5-18.6; $P < .001$) comparing 3 vessels with an FAI score in the highest vs lowest quartile for each artery. FAI score in any coronary artery predicted cardiac mortality and MACE independently from CV risk factors and the presence or extent of CAD. The AI-Risk classification was positively associated with cardiac mortality (HR 6.75; 95% CI: 5.17-8.82; $P < .001$ for very high risk vs low or medium risk) and MACE (HR 4.68; 95% CI: 3.93-5.57; $P < .001$ for very high risk vs low or medium risk). We postulate, based upon these data, that an analysis of FAI in bystander vessels of STEMI patients might provide an assessment of patient- and vessel-specific risk of future events.

The PICNIC study represents an opportunity to investigate, as proof of concept, whether future events in STEMI patients treated by culprit only intervention are associated with vascular inflammation, and/or AI-QCPHA or the AI FAI model focused upon bystander disease. The hypothesis is that, using these parameters in an AI-enabled hierarchical risk model, it is possible to detect high risk and low risk bystander vessels and/or lesions. If such an association can be demonstrated in PICNIC, and we accept that the concept of complete revascularization is to prevent acute events in these bystander lesions, then we can then logically suggest a research strategy to test whether only selective patients/vessel/lesions require bystander PCI in a larger, formalized study, whose size and design can be informed by these findings. By contrast, such a result would imply that, in some patients/vessels/lesions, bystander PCI would be futile. If this notion is correct then it is likely that future trials that focus on a personalized PCI strategy for bystander disease in STEMI patients will yield much greater differences between culprit only and complete revascularization strategies, even though the total number of bystander interventions would be far less than is recommended in the current guidelines.

We acknowledge some limitations to our study. Firstly, having established that such a pilot study is not suited to a formal power calculation, we have a population size largely dictated by practicality and financial feasibility. Second, there are challenges to the widespread use of such AI models, including practicality of access to CTCA and sophisticated processing and clinical inertia, even if PICNIC proves its hypothesis. This represents a pilot feasibility study, and will sponsor much larger scale investigation if it achieves proof of concept. Third, given that some potentially suitable patients will undergo complete revascularization during the recruitment phase, at the discretion of the interventionist supervising their care, this will be a selected sample.

Conflict of interest

None reported.

CRediT authorship contribution statement

Michael Mahmoudi: Writing – original draft, Methodology, Investigation, Project administration, Conceptualization, Writing – review & editing. **Zoe Nicholas:** Resources, Project administration. **Richard J. Jabbour:** Data curation, Writing – review & editing. **James Shambrook:** Data curation, Software, Investigation. **Ausami**

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