

Management of multivessel coronary artery disease in patients with non-ST-elevation myocardial infarction: a complex path to precision medicine

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Abstract: Recent analyses suggest the incidence of acute coronary syndrome is declining in high- and middle-income countries. Despite this, overall rates of non-ST-elevation myocardial infarction (NSTEMI) continue to rise. Furthermore, NSTEMI is a greater contributor to mortality after hospital discharge than ST-elevation myocardial infarction (STEMI). Patients with NSTEMI are often older, comorbid and have a high likelihood of multivessel coronary artery disease (MVD), which is associated with worse clinical outcomes. Currently, optimal treatment strategies for MVD in NSTEMI are less well established than for STEMI or stable coronary artery disease. Specifically, in relation to percutaneous coronary intervention (PCI) there is a paucity of randomized, prospective data comparing multivessel and culprit lesion-only PCI. Given the heterogeneous pathological basis for NSTEMI with MVD, an approach of complete revascularization may not be appropriate or necessary in all patients. Recognizing this, this review summarizes the limited evidence base for the interventional management of non-culprit disease in NSTEMI by comparing culprit-only and multivessel PCI strategies. We then explore how a personalized, precise approach to investigation, therapy and follow up may be achieved based on patient-, disease- and lesion-specific factors.

Keywords: acute coronary syndrome, culprit disease, multivessel coronary disease, non-culprit disease, non-ST-elevation myocardial infarction, percutaneous coronary intervention

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Introduction

Acute myocardial infarction (AMI) remains the leading cause of death worldwide.¹ Thankfully, with effective prevention and treatment of AMI, recent analyses have shown its incidence is in decline.^{2,3} However, despite the rate of ST-elevation myocardial infarction (STEMI) declining in the United States, the incidence of non-ST-elevation myocardial infarction (NSTEMI) has been shown to be increasing.⁴ Furthermore, although STEMI is associated with higher in-hospital and 30-day mortality than NSTEMI, mortality beyond hospital discharge is actually greater for NSTEMI.⁵⁻⁷ Contemporary data from the United Kingdom

reveal that when comparing the incidence of NSTEMI and STEMI for each decade of life, NSTEMI becomes more common beyond the age of 70.⁸ An aging population driven by a global increase in life expectancy is likely to further drive the incidence of NSTEMI, as will increasingly sensitive diagnostic testing, most notably high-sensitivity troponin assays.⁹

Despite the clear burden imparted by NSTEMI, the evidence delineating optimal treatment strategies is less established than for both STEMI and stable coronary artery disease (CAD). After initial medical management, current practice is to adopt

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an early invasive approach with coronary angiography during the index hospital admission. Seminal trials have shown lower rates of recurrent AMI and re-hospitalization after an early invasive approach compared with conservative management in NSTEMI, although a reduction in mortality rates is elusive.^{10,11} However, a large contemporary meta-analysis has suggested a mortality signal may appear with longer-term follow up,¹² and may especially apply to high-risk patients.^{11,13}

Treatment algorithms for AMI become more complex in the presence of multivessel coronary disease (MVD). Un-revascularized MVD in AMI has been shown to be associated with a greater incidence of recurrent ischemia and death at 1 year in comparison with patients with single-vessel, culprit-only disease.^{14,15} Although treatment options have been evaluated in the STEMI^{16–18} and stable CAD populations,^{19–21} showing superiority of multivessel percutaneous coronary intervention (MV-PCI) and non-inferiority of medical management respectively, there is a dearth of available evidence in the NSTEMI setting. It is essential that this be addressed due to both the large burden imparted by NSTEMI and the unique treatment conundrums it poses. For example, determining the culprit lesion can be more challenging in NSTEMI, and adopting a culprit lesion-only PCI (CL-PCI) approach may result in the unintentional treatment of a non-culprit, bystander lesion rather than a less apparent culprit plaque rupture or erosion.²²

This review will examine the implications of MVD in patients presenting with NSTEMI and summarize the evidence for and against MV-PCI compared with CL-PCI. The impact of specific patient-related, anatomical and procedural factors will be discussed. The issue of un-revascularized CAD will then be addressed in the context of the vulnerable plaque model to consider whether the integration of fractional flow reserve (FFR), intravascular imaging of coronary lesions and medical management could lead to the adoption of a personalized approach to the management of MVD after NSTEMI.

NSTEMI and the burden of MVD

The term ‘acute coronary syndrome’ (ACS) encompasses all syndromes of acute myocardial

ischemia, including STEMI, NSTEMI and unstable angina (UA). Multivessel disease is generally defined by the presence of a $\geq 50\%$ stenotic lesion (by visual angiographic assessment) in two or more major epicardial coronary arteries (Figure 1). Between 40% and 70% of NSTEMI cases^{23,24} are complicated by the finding of MVD, which is consistent across studies evaluating all ACS patients. It is unclear whether any of the traditional risk factors for atherosclerosis (e.g. smoking, hypertension, hyperlipidemia, diabetes mellitus or advanced age) contribute independently to the likelihood of MVD in NSTEMI, although chronic inflammatory conditions such as rheumatoid arthritis have been linked to higher rates of multivessel involvement.²⁵

Prognostic burden imparted by MVD

The presence of MVD in ACS has long been associated with poorer outcomes.²⁶ An early trial showed that MVD in patients with AMI receiving thrombolysis was a greater predictor of in-hospital mortality than left ventricular ejection fraction, thrombolysis in myocardial infarction (TIMI) grade flow or age.²⁷ More contemporary trials have demonstrated that MVD, and in particular three-vessel disease, is associated with a greater incidence of recurrent AMI, ischemic stroke and cardiovascular death at 1 year.^{14,15} In a Danish registry of 55,747 patients who sustained an AMI, key predictors of subsequent events at 1- and 4-year follow up were the number of vessels with severe lesions at initial presentation and the presence of left main coronary artery involvement.²⁸

Poorer outcomes are also observed in the non-ST-elevation acute coronary syndrome (NSTEMI-ACS) population, which comprises both NSTEMI and UA, with MVD. The ACUTY trial, a large, multi-center, randomized study of bivalirudin in ACS patients, determined that in patients who sustain NSTEMI-ACS and are incompletely revascularized, there is a higher rate of MI and ischemia-driven revascularization at 1 year.²⁹ In an observational study of a propensity-matched population of patients with NSTEMI-ACS and MVD, those receiving medical therapy alone experienced a greater incidence of mortality and non-fatal MI at 2 years than those treated with either PCI or coronary artery bypass grafting (CABG).³⁰ These differences remained

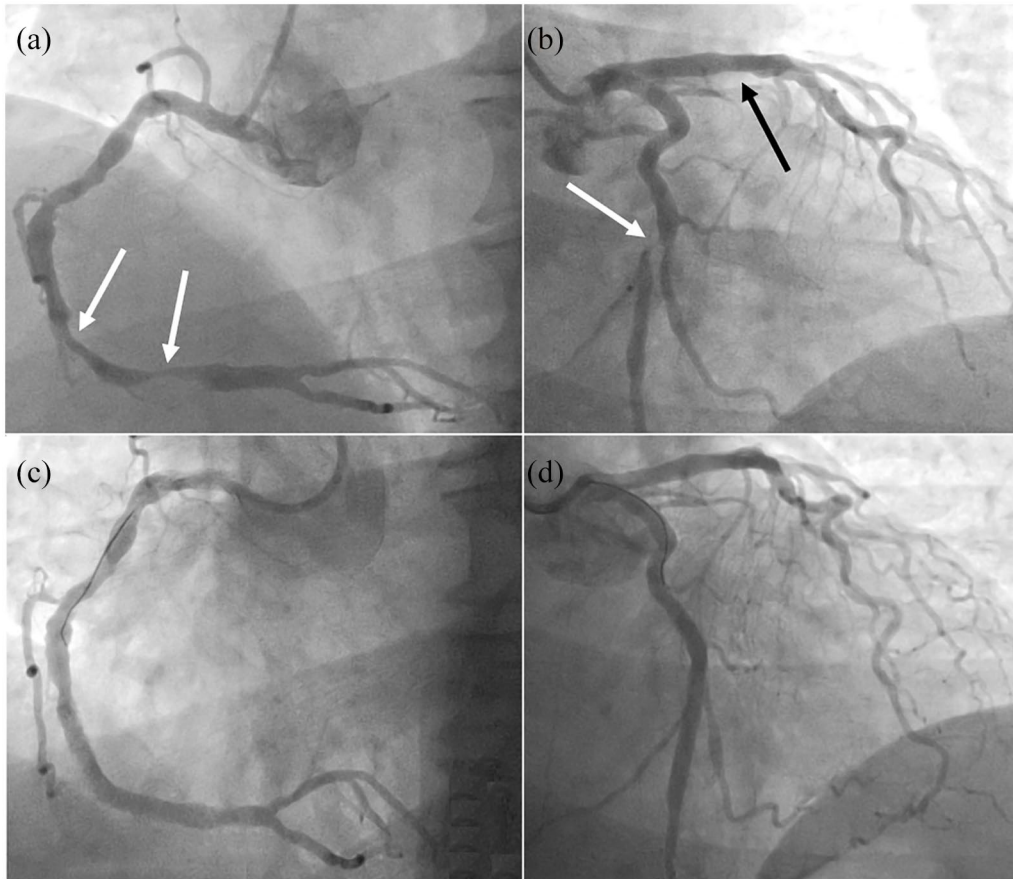


Figure 1. Angiographic images of multivessel disease in non-ST-elevation myocardial infarction (NSTEMI). A 62-year-old man presented with an NSTEMI. (a) A left anterior oblique (LAO) projection of the culprit lesion in the distal right coronary artery (white arrows). (b) A right anterior oblique (RAO) caudal projection of a severe non-culprit lesion in the left circumflex (white arrow) and mild non-culprit disease in the left anterior descending artery (LAD) (black arrow). (c) The LAO view of the culprit lesion after stenting, which was performed during the index procedure. (d) The RAO caudal view of the left circumflex artery after the non-culprit lesion was stented in a staged procedure during the index admission. Mild residual disease in the LAD was treated medically.

whether revascularization was complete or not, suggesting that some revascularization is beneficial in NSTEMI-ACS, but leaving open the question of whether complete revascularization is required.

Implications of mild and moderate non-culprit disease

While patients in the ACUTY trial with severe (>70%) non-culprit angiographic stenoses experienced the highest rates of major adverse cardiovascular events (26.4%), the inclusion of patients with non-culprit narrowings as mild as 30% only marginally attenuated the event rate to

20.4%.²⁹ This highlights the atherothrombotic risk posed by un-revascularized plaque, as well as demonstrating that risk of secondary plaque rupture or erosion is not solely determined by the severity of stenosis.

Should we treat MVD with CABG or PCI?

The data evaluating comparative effectiveness of CABG and PCI as the mode of revascularization are conflicting, derived from heterogeneous study designs and include mostly stable CAD populations. In the seminal 'SYNTAX' trial, patients with three-vessel or left main disease had a lower incidence of death, stroke, MI or

revascularization with CABG compared with those who underwent PCI.³¹ However, in the absence of these patterns of coronary disease, there is a paucity of trial data favoring a surgical approach. One large meta-analysis examining studies that deployed bare metal stents (BMSs) or used balloon angioplasty alone found that CABG did not impart a comparative mortality benefit and was associated with a higher incidence of stroke, although there was a lower rate of subsequent revascularization.³² A more recent meta-analysis examining trials that utilized both bare metal and drug-eluting stents (DESs) showed a 5-year mortality benefit with surgery over PCI in patients with MVD [8.9% versus 11.5%, hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.67–0.92], although there was no benefit in patients without diabetes.³³ Although no trials have looked exclusively at CABG versus PCI for the management of MVD in NSTEMI, propensity-matched analysis of patients enrolled in the ACUTY trial showed statistically similar mortality outcomes at 1 month and 1 year.³⁴ Given these limited data, PCI appears to be a viable alternative to CABG in a large proportion of patients with NSTEMI and MVD. However, the question remains whether MV-PCI should be pursued or whether CL-PCI suffices.

MV-PCI versus CL-PCI

It remains unclear whether MV-PCI offers incremental benefit to CL-PCI for patients presenting with MVD in the context of NSTEMI. Almost all of the studies that have looked at this question are observational, with very limited prospective, randomized data available. We identified these studies through a search of the English-language scientific literature using PubMed and MEDLINE databases. We also looked at the reference lists of meta-analyses to identify appropriate studies. We included studies that (a) directly compared MV-PCI with CL-PCI in an NSTEMI or NSTEMI-ACS population, (b) included more than 350 patients, (c) had appropriate outcome data. (Table 1). We excluded studies with (a) fewer than 350 patients, (b) more than two arms, (c) that have been published as an abstract alone or (d) have a focus on specific cohorts (i.e. elderly patients) from this table and our main discussion. Society guidelines are broad and reflect a relatively scant evidence base. Recent European Society of Cardiology (ESC) guidelines³⁵ give MV-PCI in

NSTEMI a Class IIb recommendation, while American Heart Association (AHA) guidelines,³⁶ also ascribing a Class IIb recommendation, suggest a more individualized approach without providing guidance as to what that entails.

Registry studies

Analysis from two large registries has looked exclusively at in-hospital outcomes following MV-PCI compared with CL-PCI. Brener *et al.* compared the characteristics and outcomes of 105,866 patients in the US National Cardiovascular Database Registry, who underwent CL-PCI ($n=72,048$) and MV-PCI ($n=33,818$) for NSTEMI-ACS, without propensity score matching.⁴¹ While there was more peri-procedural MI in the MV-PCI group compared with CL-PCI (1.5% versus 1.1%, $p<0.0001$), there was no difference in inpatient mortality. Those receiving CL-PCI were more likely to have presented with NSTEMI rather than UA, had higher lesion complexity [chronic total occlusion (CTO) and Type C lesion characteristics] and higher rates of culprit vessel slow-flow compared with those treated by MV-PCI. Notably, data on stent type were not presented. Similar findings were reported from a European registry of 4457 patients, of whom 1920 suffered an NSTEMI-ACS,⁴² with no significant difference for in-hospital mortality but more peri-procedural MI in patients undergoing MV-PCI compared with CL-PCI (5.3% versus 1.8%, $p<0.0001$).

A recent multi-site observational registry across London, UK, demonstrated favorable long-term outcomes for patients receiving MV-PCI compared with CL-PCI. After excluding patients with cardiogenic shock and those with prior CABG, 21,857 patients undergoing PCI for NSTEMI with at least two lesions of $\geq 75\%$ stenosis were evaluated.³⁷ In total, 11,737 (53.7%) underwent MV-PCI at the time of index angiography, with the remaining 10,120 (46.3%) undergoing CL-PCI only. In contrast to the two previously mentioned registries, crude in-hospital mortality was lower in those receiving CL-PCI compared with MV-PCI (1.5% versus 2.3%, $p=0.002$). However, after propensity matching in 19,980 patients, MV-PCI was associated with reduced 5-year mortality (HR 0.89, 95% CI 0.76–0.98). Similar results were observed in a sub-group analysis of 990 patients enrolled in the RESEARCH

Table 1. Design of selected studies comparing MV-PCI with CL-PCI in patients with MVD presenting with NSTEMI.

Study	n value	Study design	Enrolled	Clinical syndrome	MVD definition	Stents used	Left main	Chronic total occlusion	Cardiogenic shock	Timing non-culprit PCI	Previous CABG	Level of evidence	Newcastle Ottawa score
Registry data													
Rathod <i>et al.</i> ³⁷	n=21,857 CL-PCI=10,120 MV-PCI=11,737	Multi-center observational cohort study	Jan. 2005–May 2015	NSTEMI	≥75% stenosis in at least two major epicardial vessels	77% DES	Included	Excluded	Excluded	Index procedure only	Excluded	B	9
Hassamin <i>et al.</i> ³⁸	n=2864 CL-PCI=2255 MV-PCI=609	ACUITY database-linked retrospective study	Aug. 2003–Dec. 2005	NSTEMI-ACS	≥50% stenosis in at least two major epicardial vessels	84% DES	Included	Not specified	Not specified	Index admission	Included	B	7
Ibrahim <i>et al.</i> ³⁹	N=3110 CL-PCI=2287 MV-PCI=823	Retrospective sub-analysis of patients enrolled in TRANSLATE-ACS study	April 2010–Oct. 2012	NSTEMI	Significant stenoses in at least two major epicardial vessels	72% DES	Included	Not specified	Included	Not specified	Included	B	8
Onuma <i>et al.</i> ⁴⁰	N=990 CL-PCI=379 MV-PCI=611	Retrospective sub-analysis of patients enrolled in RESEARCH and T-SEARCH registries	Jan. 2000–Dec. 2005	NSTEMI-ACS	≥50% stenosis in at least two major epicardial vessels	57% DES	Included	Not specified	Not specified	Index admission	Excluded	B	9
Brener <i>et al.</i> ⁴¹	n=105,866 CL-PCI=72,048 MV-PCI=33,818	Multi-center registry-linked retrospective observational study	2000–2004	NSTEMI-ACS	≥50% stenosis in at least two major epicardial vessels ^a	Undefined	Included	Included	Not specified	Index procedure only	Excluded	B	7
Bauer <i>et al.</i> ⁴²	NSTEMI-ACS=1920 CL-PCI=1186 MV-PCI=734	Prospective, multi-center, observational registry	2005–2008	NSTEMI-ACS	≥70% stenosis in at least two epicardial vessels	51% BMS	Excluded	Not specified	Excluded	Not specified	Excluded	B	7
Kim <i>et al.</i> ⁴³	n=1919 CL-PCI=908 MV-PCI=1011	Registry-linked prospective study	Nov. 2005–June 2008	NSTEMI	≥50% stenosis in at least two epicardial vessels	92% DES	Included	Not specified	Included	Not specified	Not specified	B	7

(Continued)

Table 1. (Continued)

Study	n value	Study design	Enrolled	Clinical syndrome	MVD definition	Stents used	Left main	Chronic total occlusion	Cardiogenic shock	Timing non-culprit PCI	Previous CABG	Level of evidence	Newcastle Ottawa score
Observational data													
Shishehbor <i>et al.</i> ⁴⁴	n=1240 CL-PCI n=761 MV-PCI n=479	Single-center, prospectively enrolled, observational study	Jan. 1995–June 2005	NSTEMI-ACS	≥50% lesion in at least two epicardial vessels	BMS only	Included	Excluded	Not specified	Index admission	Excluded	B	8
Zapata <i>et al.</i> ⁴⁵	n=609 CL-PCI=405 MV-PCI=204	Institutional database-linked retrospective study	June 1996–June 2006	NSTEMI-ACS	≥70% lesion in at least two epicardial vessels	81% BMS	Included	Excluded	Not specified	Index admission	Excluded	B	7
Lee <i>et al.</i> ⁴⁶	n=366 CL-PCI=187 MV-PCI=179	Prospectively enrolled observational study	April 2003–Dec. 2006	NSTEMI-ACS	≥50% lesion in at least two epicardial vessels	DES only	Not specified	Excluded	Excluded	Index admission	Excluded	B	9

Level of evidence: derived from the American College of Cardiology and American Heart Association guidelines.

Newcastle Ottawa score: a score out of nine grading trial quality, composed of three components: selection (1/4), comparability (1/2) and outcome (1/3).

^aExpectation of MV-PCI with non-culprit lesions ≥70%.

BMS, bare metal stent; CABG, coronary artery bypass grafting; CL-PCI, culprit-lesion percutaneous coronary intervention; DES, drug-eluting stent; MV-PCI, multivessel percutaneous coronary intervention; MVD, multivessel disease; NSTEMI-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

and T-SEARCH registries,⁴⁰ which demonstrated higher rates of major adverse cardiovascular events (MACE) with MV-PCI compared with CL-PCI in the unadjusted general cohort at 30 days (HR 2.03, 95% CI 1.07–3.85), without significant difference in mortality. However, at 3-year follow up the balance had shifted in favor of MV-PCI, which was associated with much lower all-cause mortality (HR 0.55, 95% CI 0.38–0.80).

Benefits associated with MV-PCI were more uniform in a registry-linked study from South Korea,⁴³ which first showed reduced in-hospital mortality among 1919 NSTEMI patients (1.4% for MV-PCI *versus* 2.9% for CL-PCI, $p=0.025$). In extending outcomes to 1 year, this benefit was no longer significant with respect to all-cause death but was preserved for cardiac death aligning with other registry data (3.5% *versus* 6.4%, $p=0.009$). Superiority with MV-PCI at 1 year persisted with respect to MACE (12.9% *versus* 18.6%, $p=0.002$) and death or MI (HR 0.58, 95% CI 0.35–0.97, $p=0.037$). This suggests that not all benefit was derived from a reduction in the ‘softer’ clinical endpoint of repeat revascularization.

In contrast, a retrospective sub-analysis of 3100 patients³⁹ enrolled in the TRANSLATE-ACS trial showed no significant difference between the PCI approaches with respect to the composite endpoint of MACE at either 6 weeks or 1 year. A similar analysis was performed in 2255 patients with NSTEMI-ACS and MVD undergoing PCI in the ACUITY study.³⁸ No clear benefit of MV-PCI was demonstrated, and instead, a trend for higher rates of 1-year MACE (24.1% *versus* 21.7%, $p=0.11$) driven largely by peri-procedural MI. Even after multivariable analysis with propensity score adjustment for patient and procedural variables, a signal for more adverse outcomes after MV-PCI could not be definitively excluded (1-year MACE HR 1.22, 95% CI 0.96–1.55, $p=0.12$).

Single-center observational studies

A number of observational studies have also compared outcomes following CL-PCI and MV-PCI. An early study reported on 1240 patients presenting to one center in the United States between 1995 and 2005 with NSTEMI-ACS and MVD who received BMS.⁴⁴ Multivessel disease was defined as the presence of $\geq 50\%$ stenosis in at least two

major epicardial vessels. In the propensity-matched analysis, MV-PCI was associated with lower incidence of the composite endpoint of death, MI or revascularization at a median follow up of 2.7 years (HR 0.67, 95% CI 0.51–0.88, $p=0.003$). However, when evaluating the individual components of the composite, both MI and death were no longer significant, suggesting the overall benefit was driven by repeat revascularization (HR 0.59, 95% CI 0.41–0.84, $p=0.003$). This finding was supported by two other moderate-sized single-center observational studies, one primarily utilizing BMS the other exclusively using DESs. Both showed lower MACE for MV-PCI at 1 year and 36 months respectively, although in each the outcome was driven by revascularization.^{45,46}

Interpreting this information is difficult. Significant heterogeneity of the available data exists with respect to assumptions around MV-PCI and ‘complete’ revascularization, variable inclusion and exclusion criteria (particularly patients with cardiogenic shock or prior CABG), types of stents used, the severity of non-culprit disease, non-culprit lesion characteristics (e.g. presence of CTO), as well as adjustment for residual confounding factors. Results are conflicting (Tables 2 and 3). The largest and most contemporary meta-analysis from Mariani *et al.* confirmed the high degrees of heterogeneity described previously and, despite trends, failed to conclusively demonstrate reduced 12-month mortality (HR 0.79, 95% CI 0.58–1.09, I^2 67.9%) or MACE (HR 0.83, 95% CI 0.66–1.03, I^2 70.8%) with MV-PCI.⁴⁷ Importantly, this analysis was published before the large London-based registry described previously, which demonstrated significantly lower death rates beyond 6 months in the MV-PCI cohort.³⁷ Clearly, defining the optimal management approach in these patients remains hampered by a paucity of large, prospective, randomized trials and the limitations inherent to retrospective data, including strong selection bias that propensity matching cannot overcome. Even then, larger prospective trials may not pave the way forward, as they have appeared to in the STEMI cohort, owing to the pathologically varied and clinically diverse nature of NSTEMI.

Patient selection and special considerations

Identifying high-risk patients

Clear benefit from MV-PCI may yet be unearthed through better patient selection. Patients at higher

Table 2. Selected short-term outcomes of studies comparing MV-PCI with CL-PCI in patients with multivessel coronary artery disease presenting with non-ST-elevation myocardial infarction.

Study	n value	Follow-up period	Death (%)		MACE (%)		Revascularization (%)			
			MV-PCI	CL-PCI	HR/p	HR/p	MV-PCI	CL-PCI	HR/p	HR/p
Rathod <i>et al.</i> ³⁷	n = 21,857 CL-PCI = 10,120 MV-PCI = 11,737	In-hospital	2.3	1.5	0.002	4.1	3.8	0.6	1	0.015
Hassanin <i>et al.</i> ³⁸	n = 2864 CL-PCI = 2255 MV-PCI = 609	30 days	0.8	1.2	0.48	13.8	10.1	5.3	3.9	0.12
Ibrahim <i>et al.</i> ³⁹	N = 3110 CL-PCI = 2287 MV-PCI = 823	6 weeks	1.17	0.76	NR	6.58	8.92	4.01	7.23	0.0001
Onuma <i>et al.</i> ⁴⁰	N = 990 CL-PCI = 379 MV-PCI = 611	30 days	13	18.3	0.02	26.1	28	12.8	10	0.14
Brener <i>et al.</i> ⁴¹	n = 105,866 CL-PCI = 72,048 MV-PCI = 33,818	In-hospital	1.2	1.3	0.09	NR	NR	0.12	0.19	0.003^a
Bauer <i>et al.</i> ⁴²	n = 1920 CL-PCI = 1186 MV-PCI = 734	In-hospital	1.1	2.1	0.1	NR	NR	NR	NR	
Kim <i>et al.</i> ⁴³	n = 1919 CL-PCI = 908 MV-PCI = 1011	In-hospital	1.4	2.9	0.025	NR	NR	NR	NR	
Zapata <i>et al.</i> ⁴⁵	n = 609 CL-PCI = 405 MV-PCI = 204	In-hospital	1.4	0.5	0.11	2.94	2.96	0.81	NR	

^aPCI only, not CABG.
CL-PCI, culprit-lesion percutaneous coronary intervention; HR, hazard ratio; MACE, major adverse cardiovascular events; MV-PCI, multivessel percutaneous coronary intervention; NR, not reported.

Table 3. Selected longer-term outcomes of studies comparing MV-PCI with CL-PCI in patients with multivessel coronary artery disease presenting with non-ST-elevation myocardial infarction.

Study	n value	Follow-up period	Death (%)		MACE (%)		Revascularization (%)						
			MV-PCI	CL-PCI	HR/p	HR/p	MV-PCI	CL-PCI	MV-PCI	CL-PCI	HR/p	HR/p	
Rathod <i>et al.</i> ³⁷	n = 21,857 CL-PCI = 10,120 MV-PCI = 11,737	Median 4.6 years (2.2–6.2)	22.5	25.9	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hassanin <i>et al.</i> ³⁸	n = 2864 CL-PCI = 2255 MV-PCI = 609	1 year	2.9	3.2	0.54	24.1	21.7	0.11	15.2	14.4	0.38	0.38	0.38
Ibrahim <i>et al.</i> ³⁹	N = 3110 CL-PCI = 2287 MV-PCI = 823	1 year	5.7	3.75	NR	20.49	22.15	0.04	12.83	17.21	0.002	0.002	0.002
Onuma <i>et al.</i> ⁴⁰	N = 990 CL-PCI = 379 MV-PCI = 611	3 years	HR MV-PCI versus CL-PCI 0.67 (0.47–0.97)			HR MV-PCI versus CL-PCI 0.92 (0.70–1.21)			HR MV-PCI versus CL-PCI 1.19 (0.77–1.85)				
Kim <i>et al.</i> ⁴³	n = 1919 CL-PCI = 908 MV-PCI = 1011	1 year	5.4	7.9	0.064 ^a	12.9	18.6	0.002	0.6	1.7	0.052 ^b	0.052 ^b	0.052 ^b
Shishehbor <i>et al.</i> ⁴⁴	n = 1240 CL-PCI n = 761 MV-PCI n = 479	Median 2.3 years (0.2–4.3)	15	13	0.34	35	36	0.38	20	22	0.14	0.14	0.14
Zapata <i>et al.</i> ⁴⁵	n = 609 CL-PCI = 405 MV-PCI = 204	1 year	1.99	1.98	0.76	9.45	16.34	0.02	7.46	13.86	0.04	0.04	0.04
Lee <i>et al.</i> ⁴⁶	n = 366 CL-PCI = 187 MV-PCI = 179	Median 3 years (2.5–3.6)	6.1	7	0.73	19.6	32.6	0.003	13.4	28.9	<0.001	<0.001	<0.001

^aSignificant difference in cardiac death.^bTarget vessel revascularization on.

CL-PCI, culprit-lesion percutaneous coronary intervention; HR, hazard ratio; MACE, major adverse cardiovascular events; MV-PCI, multivessel percutaneous coronary intervention; NR, not reported.

risk of progressive CAD or cardiovascular events would intuitively be expected to benefit from treatment of non-culprit disease. The contemporary London-based registry showed mortality benefit where others have failed to do so, which may in part be due to their enriched NSTEMI cohort rather than the broader NSTEMI-ACS population, which also includes lower-risk UA cases.³⁷ Moreover, this study only considered non-culprit lesions with visual angiographic severity of 70%. Identification of high-risk patients could also be achieved with tools such as the TIMI, GRACE or SYNTAX scores.^{48–51} Sub-group analyses within the available data sets are mixed in this regard. A Korean registry demonstrated all-cause mortality benefit in patients with a TIMI score ≥ 4 that was not present in the overall study cohort,⁴³ while another single-center observational study from South Korea showed no change in the primary outcome of MACE when groups were risk-stratified based on SYNTAX or APPROACH scores.⁴⁶

MV-PCI and procedural implications

One potential criticism of a multivessel approach to revascularization is the potential for increasing PCI procedure time, radiation exposure, contrast loads and, ultimately, costs. Data around these important considerations are relatively scant in the NSTEMI setting. A retrospective sub-analysis showed significantly more fluoroscopy time with complete revascularization (33.9 ± 26.6 min *versus* 23.8 ± 21.4 min, $p < 0.0001$),⁴⁰ as did a single-center observational study from the United States (46 ± 190 min *versus* 25 ± 22 min, $p < 0.001$).⁴⁴ These two studies also found significantly more contrast use with MV-PCI, but unfortunately did not report rates of contrast-induced nephrotoxicity. However, other NSTEMI trials have not shown an increase in renal impairment following complete revascularization.^{41,43} An additional consideration is the propensity for peri-procedural MI. While a number of the composite endpoints mentioned previously were driven by peri-procedural MI, it remains unclear to what extent these events are prognostically important in the general literature, but particularly in the context of NSTEMI.

Impact of advancing age upon outcomes

Age may be a significant factor in considering an individual patient's suitability for MV-PCI. The threat of competing non-cardiovascular mortality

may mean MV-PCI is associated with diminishing marginal returns. In addition, there may be greater procedural morbidity for these patients. In a study of both STEMI and NSTEMI patients aged over 65,⁵² single-stage MV-PCI was associated with no significant difference in mortality at 30 days or 1 year in the NSTEMI population compared with those receiving CL-PCI, but significantly more contrast was used and longer fluoroscopy times were observed. Interestingly, the STEMI cohort had significantly more death with a single MV-PCI procedure than CL-PCI alone, contradicting the findings of recent large randomized trials in younger populations.^{16,17} One solution in the elderly may be to stage procedures, with one retrospective, observational, propensity-matched study showing that in patients aged 60 years or older with NSTEMI and MVD, the rate of cardiac death or MI at 3 years was significantly lower in the staged PCI rather than the single-stage MV-PCI group.⁵³ This was despite a relatively short mean time to non-culprit PCI (5 days) in the staged group with a majority (83.9%, 392/467 patients) having their intervention as an inpatient. The impact of staging non-culprit interventions in the general cohort is discussed in more detail later.

Angina as an outcome

A key outcome largely absent from the available data is the impact of MV-PCI upon quality of life and angina. The TRANSLATE-ACS registry did evaluate angina as a secondary outcome and showed no difference between MV-PCI and CL-PCI approaches at 6 weeks or 1 year.³⁹ In contrast, a small, single-center observational study of 151 patients showed significantly less recurrent angina and UA in those patients treated with MV-PCI.⁵⁴ Beyond angina, other patient-centered outcomes, such as quality of life or days alive out of hospital,⁵⁵ may be important metrics to capture for comparative effectiveness studies. While not traditionally considered 'hard' clinical endpoints, in a progressively more comorbid population these outcomes may represent important determinants of shared decision-making.

Anatomical considerations

Complex coronary lesions and CTO

Lesion properties need to be considered when planning non-culprit intervention, but evidence

as to how this should influence treatment approach is scarce. The distribution of non-culprit disease is important as proximal lesions in large epicardial vessels are more likely to be prognostically significant than distal vessel or branch disease. Tools such as the Gensini,⁵⁶ CASS-70⁵⁷ and Duke Prognostic⁵⁸ scores have been suggested, but their utility is debated.⁵⁹ One of the previously mentioned observational studies used Duke Prognostic scores but showed no difference in outcomes irrespective of MV-PCI or CL-PCI approach in a propensity-matched cohort.⁴⁴ Non-culprit disease located in a bifurcation may pose more risk of plaque progression or future atherothrombotic events, but bifurcation PCI is also associated with higher rates of re-stenosis and stent thrombosis.⁶⁰ Another factor to consider is lesion complexity, with 'type C' lesions characterized by length >20 mm, excessive tortuosity, severe angulation, or the presence of CTO, having been shown to be associated with greater re-stenosis rates,⁶¹ lower procedural success and greater 30-day mortality.⁶² Multivariable analysis of one previously mentioned registry comparing MV-PCI with CL-PCI in NSTEMI showed that the presence of CTO was associated with a higher likelihood of operators performing CL-PCI (adjusted OR 1.25, 95% CI 1.16–1.36).⁴¹ Interestingly, a meta-analysis of studies comparing MV-PCI *versus* CL-PCI for MVD in NSTEMI found no difference for the composite endpoint of death, AMI or revascularization, whether CTO was included in the study or not.⁴⁷ This conclusion is weakened by the fact it is derived from a sub-group analysis of broad, retrospective data and more studies looking at the clinical significance of CTO in this population are needed.

Left main CAD

A surprising number of studies of MVD in NSTEMI have included patients with significant left main disease (Table 1). Established practice has been to treat these lesions with bypass surgery. However, this has been challenged with a contemporary meta-analysis suggesting no benefit for CABG over PCI in left main disease.³³ Two prospective randomized controlled trials examining this question have now been published. The 'NOBLE' trial showed superiority of CABG over PCI with respect to MACE,⁶³ while 'EXCEL' showed that PCI was non-inferior.⁶⁴ Importantly, neither showed a significant difference in mortality. The EXCEL trial reported that the vast

majority of patients had at least one significant lesion in addition to left main stenosis, and although NOBLE did not report distribution of disease, patients in both groups had a mean of two treated lesions. However, patients with ACS were under-represented in both studies, so their applicability to the NSTEMI population is unclear. Recently, 5-year data from EXCEL were reported to show non-inferiority of PCI *versus* CABG for the composite outcome of death, stroke and MI.⁶⁵ However, it should be cautioned that there was signal for greater mortality in the PCI arm, with the Kaplan–Meier curves continuing to diverge at 5 years in favor of CABG. At this stage, any MV-PCI strategy that incorporates left main intervention in patients with NSTEMI should proceed with caution, as our understanding of the evidence evolves.

Moving beyond anatomical and angiographic assessments

The key to unearthing improved outcomes in NSTEMI patients with MVD may be through adopting a more selective strategy to non-culprit intervention and a more personalized approach to diagnosis and therapy. This may be achieved through physiological assessment of lesions and a greater emphasis on the role of vulnerable plaque in adverse outcomes, addressed using intravascular imaging and improving medical management (Figure 2).

Physiological assessment of non-culprit disease

FFR has been established as a useful tool in guiding PCI in patients with stable CAD. It has been shown to alter management of stable lesions against angiographic data alone,⁶⁶ allow for safe deferral of PCI⁶⁷ and to be associated with significantly less MACE in patients who have FFR-guided PCI compared with visual angiographic assessment⁶⁸ or medical management alone.^{69,70} However, its applicability in the setting of AMI has been debated. FFR relies upon inducing maximal hyperemia in the vascular bed distal to the stenosis being interrogated. It has been postulated that this is more difficult to achieve in infarcted tissue due to coronary microvascular dysfunction,^{71,72} although recent studies have shown that FFR in this setting may still be valid.^{73–77} Two large prospective randomized trials have looked at the use of FFR in MVD in

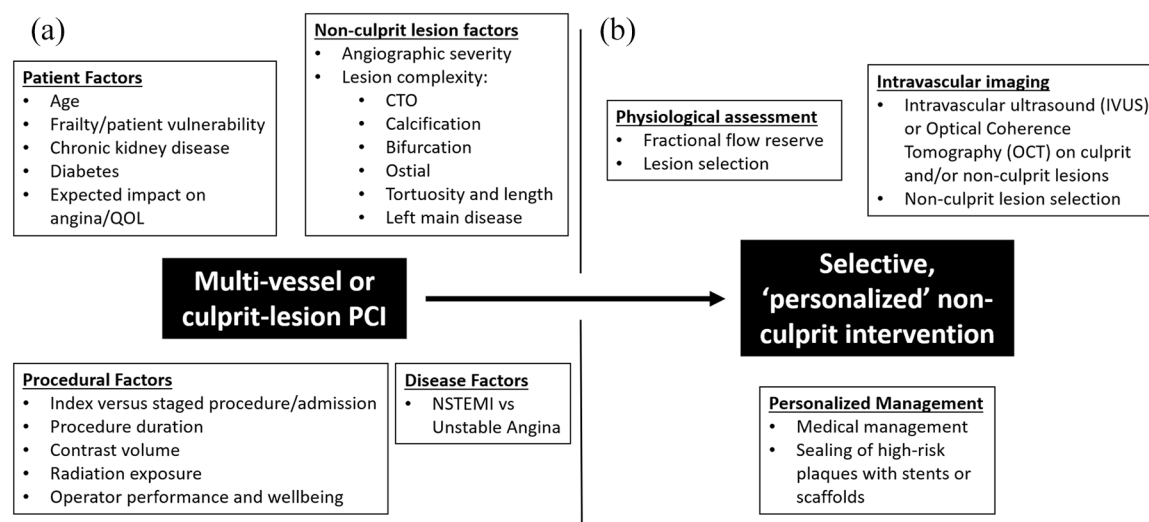


Figure 2. Factors influencing pursuit of a multivessel percutaneous coronary intervention (MV-PCI) or culprit lesion-only percutaneous coronary intervention (CL-PCI) approach and a possible pathway to a personalized approach. (a) Factors to be considered when contemplating MV-PCI after initial angiographic assessment in non-ST-elevation myocardial infarction (NSTEMI) patients with multivessel coronary artery disease (MVD). (b) Additional parameters and strategies to help achieve a 'personalized' approach to non-culprit intervention. CTO, chronic total occlusion.

patients with STEMI.^{78,79} Revascularization of infarct-related arteries alone was compared with full revascularization of physiologically significant non-culprit lesions, determined by a hyperemic FFR value ≤ 0.80 . In each study, incidence of MACE was significantly less in the FFR-guided MV-PCI group, but this was largely driven by reduced future revascularization rates.

FFR has also been postulated as a potentially valuable tool in NSTEMI, although published evidence is once again lacking. A sub-group analysis of NSTEMI-ACS patients enrolled in the FAME trial demonstrated that FFR-guided PCI led to an absolute risk reduction in MACE at 2 years of 5.1%, driven primarily by repeat MI.⁷⁶ FAMOUS-NSTEMI allocated 350 patients with NSTEMI to have FFR of all vessels with $\geq 30\%$ stenosis. After management plans had been formulated, patients were randomized 1:1 to either have their FFR findings disclosed to the treating team or not.⁸⁰ While MVD was not a prerequisite for inclusion, a majority of patients were found to have at least one lesion $\geq 30\%$ in two or more vessels (62.5% in the FFR-disclosure arm and 57.5% in the angiography-guided arm). The primary outcome was the between-group difference in the number of patients managed medically, and this

was found to differ significantly, with 40 (22.7%) patients in the FFR-disclosure group managed medically compared with 23 (13.2%) in the angiography-guided arm ($p=0.022$). Notably, the management decision at the index procedure was changed following disclosure of FFR results in 38 (21.6%) patients. This especially demonstrates the propensity for FFR to avoid overtreatment of lesions, and despite greater procedural costs FFR was shown to result in fewer stents placed, shorter procedural times, reduced contrast use and similar costs associated with the index admission.⁸⁰ Impact on clinical outcomes is more difficult to discern, with a signal toward more peri-procedural MI in the angiography-guided arm but more overall MACE in the FFR-disclosure arm. Neither result was statistically significant. The signal toward more MACE may potentially be explained by the model of vulnerable plaque, discussed in the following.

Future trials may also utilize instantaneous wave-free ratio (iFR), which obviates the need for adenosine administration, which is expensive and time-consuming. Two recent randomized prospective studies have compared iFR with FFR in a predominantly stable CAD and NSTEMI-ACS cohort.^{81,82} One showed significantly shorter

procedure times with iFR,⁸¹ while the other showed comparable procedure times but significantly more lesions evaluated in the iFR group.⁸² Both trials showed non-inferiority for iFR with respect to MACE at 1 year. Large, adequately powered trials looking exclusively at the use of FFR and iFR to guide PCI decisions in NSTEMI patients with MVD are required.

Vulnerable plaque and MVD

The common definition of MVD is based on the severity of stenosis on visual angiographic assessment. This limited approach assumes that the degree of stenosis is associated with the risk of subsequent MI and has been largely superseded by the model of vulnerable plaque.⁸³ There are three main mechanisms by which atherosclerotic plaques lead to athero-thrombosis and acute ischemia: plaque rupture, plaque erosion and calcified nodules.⁸³ Plaque rupture is considered the most common precipitating mechanism of MI. Intravascular ultrasound (IVUS) studies have shown plaque rupture in the infarct-related artery in approximately 70% of NSTEMI patients.⁸⁴ Our understanding of plaque rupture has evolved to be one of an inherently inflammatory process underpinned by disruption of thin-capped fibroatheromas (TCFAs) and subsequent thrombus formation.

Inflammation appears to be central to the risk of future non-culprit plaque rupture after initial AMI presentation.⁸⁵ The inflammatory biomarker, high-sensitivity C-reactive protein (hs-CRP) has been shown to correlate with rates of cardiovascular events.^{86,87} Notably, 40–50% of patients who are on conventional pharmacotherapy post-MI, including statins, have residual inflammatory risk as defined by hs-CRP ≥ 2 mg/dl.⁸⁸ Two studies utilizing optical coherence tomography (OCT) to image coronary plaques have shown that high levels of hs-CRP associate with the presence of TCFAs, although both were underpowered to demonstrate a temporal link to plaque rupture itself.^{89,90} Patients with systemic inflammatory conditions, such as rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus, have a higher incidence of MI,^{91–93} while transient inflammatory conditions such as influenza A are also associated with an increased incidence of AMI.⁹⁴ Indeed, the systemic inflammatory response to MI itself may also aggravate atherosclerotic plaque

inflammation, increasing the risk of subsequent thrombotic events on non-culprit lesions.⁹⁵ Thus, the vulnerable plaque model helps to understand the residual risk imparted by MVD in patients with NSTEMI, with the index plaque rupture event potentially begetting progression of atherosclerosis and subsequent ruptures at other lesion sites. Importantly, this may be a time-dependent relationship. The increased incidence of AMI after an influenza diagnosis largely disappears after 7 days.⁹⁴ As a result, it has been speculated that the potential benefit from intervening at non-culprit sites diminishes as time passes from the index AMI event.

The vulnerable plaque model also has implications for the use of FFR. In the previously mentioned FAMOUS-NSTEMI trial⁸⁰ there was a signal toward more MACE in the FFR-guided arm, where fewer stents were placed. In FAME, patients who had sustained prior NSTEMI-ACS had a higher 2-year event rate (24.2%) than the stable CAD population (18.1%).⁷⁶ This highlights the greater propensity for non-culprit plaque rupture after NSTEMI and the concern that absence of flow limitation does not equate to an absent risk of future plaque-related events. Indeed, the PROSPECT trial showed non-culprit lesions implicated in future events were frequently mild at initial angiographic assessment.⁹⁶ Conversely, in the analysis of UA and NSTEMI patients within FAME, no subsequent MIs were found to be due to previously deferred lesions.⁷⁶ Better characterization of non-culprit, non-flow-limiting plaques may hold the key to identifying those at risk of secondary events.

A question of timing

Most studies comparing MV-PCI with CL-PCI have largely excluded patients undergoing planned staged PCI procedures (Table 1). The SMILE trial, a randomized prospective study, compared outcomes in NSTEMI patients who underwent MV-PCI performed during an index procedure against those who had MV-PCI over two procedures during a single admission.⁹⁷ In total, 584 patients were assigned 1:1 to each group, with a primary outcome of major adverse cardiovascular and cerebrovascular events (MACCE) at 1 year, defined as cardiac death, all-cause death, re-infarction, re-hospitalization, target vessel revascularization (TVR) and stroke. There was a significant

reduction in MACCE in the one-stage PCI group, driven exclusively by TVR, but no significant differences in death or MI. The trial had significant limitations, including a failure to define the severity of non-culprit lesions, unclear median time to angiogram after initial presentation and a broad composite endpoint. However, most striking was an unusually high rate of TVR in the two-stage PCI arm (15.4% at 1 year), a rate that is incongruent with most other studies in the current DES era.

In contrast to SMILE, registry data have examined MV-PCI in the index procedure against a staged procedure up to 60 days in patients with NSTEMI-ACS⁹⁸ and found no significant difference in MACE between the groups in propensity-matched analysis. Recently, the COMPLETE trial, a multinational, randomized trial of STEMI patients, showed that the incidence of the co-primary outcome of cardiovascular death or recurrent MI at 3 years was lower in patients receiving complete rather than culprit-only revascularization (7.8% versus 10.5%, $p=0.004$). Notably, this effect was maintained whether complete revascularization was performed in the index procedure or staged out to a mean of 23 days.¹⁸ Extrapolating this result to NSTEMI, it seems reasonable to consider staging non-culprit interventions, although dedicated data are needed.

Intravascular imaging: the light leading us out of a dark room?

Radiofrequency IVUS is a modality that allows direct characterization of plaque and thus identification of plaque rupture.^{99,100} Three-vessel IVUS studies in patients with AMI have shown a higher rate of plaque rupture in non-culprit vessels^{89,90,101,102} than that observed in stable CAD.⁸⁴ In patients with NSTEMI this has been shown to be 16%.⁸⁴ This concept was explored in the PROSPECT trial, a prospective study that systematically examined non-culprit anatomy in ACS patients with MVD using three-vessel IVUS after successful treatment of culprit lesions.⁹⁶ A total of 697 participants were recruited and over a median follow-up period of 3 years the incidence of MACE was 20.4%. Notably, events in follow up were equally likely to arise from the initial culprit as from a non-culprit lesion. While the majority of non-culprit lesions responsible for events in follow up were angiographically mild in stenosis severity (mean $32.3 \pm 20.6\%$), greater plaque burden ($>70\%$, HR 5.03, 95% CI 2.51–10.11,

$p<0.001$) and a small luminal area ($\leq 4.0\text{ mm}^2$, HR 3.21, 95% CI 1.61–6.42, $p=0.001$) were independent predictors of events on non-culprit lesions. Furthermore, approximately half of the recurrent events at non-culprit sites occurred in the context of TCFAs and multivariable analysis found their presence was strongly associated with increased risk of future MACE (HR 3.35, 95% CI 1.77–6.36, $p<0.001$). These findings were corroborated by a subsequent analysis,¹⁰² demonstrating the vulnerability of lesions with thin fibrous caps and lipid-rich cores and suggests a potential role for IVUS in further categorizing the risk associated with non-culprit lesions.

OCT is another intravascular imaging modality that has improved our understanding of vulnerable plaques and has potential use in characterizing risk of secondary plaque rupture. Its main advantage over conventional coronary angiography and IVUS is an ability to characterize the thickness of the fibrous cap as well as improved detection of plaque rupture and erosion.^{103,104} Two small studies^{89,101} have shown a greater incidence of TCFAs in non-culprit sites of AMI patients compared with those with stable CAD. Neither was sufficiently powered to show a significant difference in the rate of plaque rupture at non-culprit sites.

Intravascular imaging in clinical decision-making

Intravascular imaging offers great promise in guiding treatment approaches for MVD (Figure 3). Establishing the mechanism of the primary event may be a key determinant, as plaque rupture at the culprit site may confer greater future risk of non-culprit events. Three-vessel OCT studies in patients with AMI have demonstrated more plaque rupture at the culprit lesion in STEMI compared with NSTEMI,¹⁰⁵ although analysis of PROSPECT showed the rate of non-culprit plaque rupture after AMI was 14.1% and did not differ significantly if the primary event was STEMI or NSTEMI.¹⁰² As IVUS of the culprit lesion was not performed before intervention, the relationship between the culprit mechanism and secondary plaque rupture cannot be elucidated. As the pathological basis for atherothrombosis in NSTEMI is heterogeneous, one application of intravascular imaging may be to define the underlying process at a patient-specific level, and thus inform an approach for non-culprit disease. The ongoing ILLUMEN-IV trial [ClinicalTrials.gov

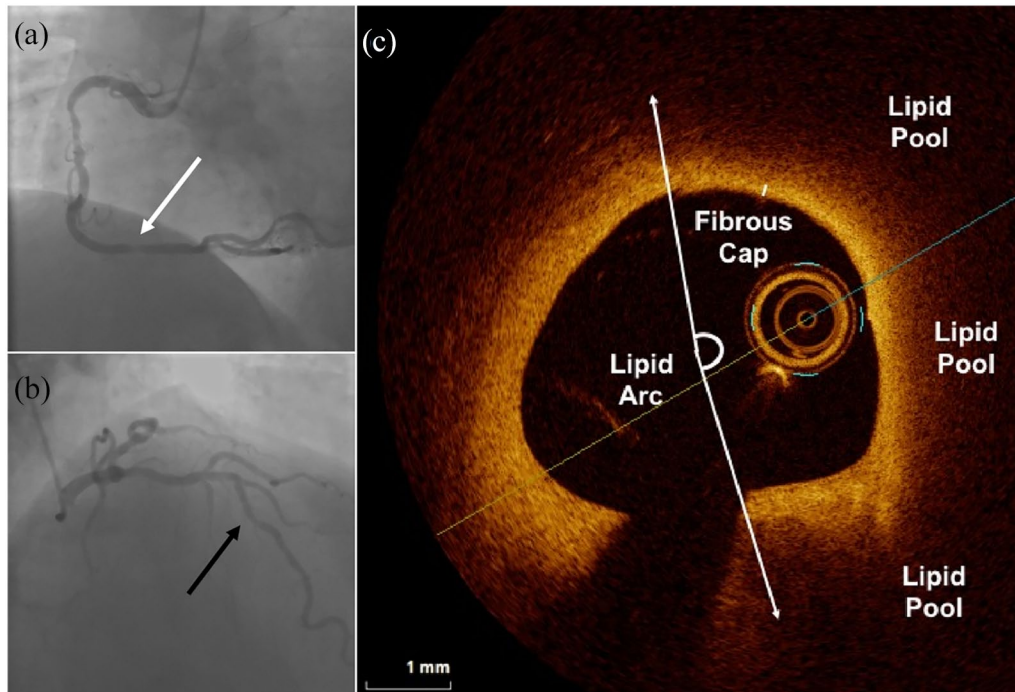


Figure 3. Imaging of a mild non-culprit lesion with optical coherence tomography. A middle-aged man presented with a non-ST-elevation myocardial infarction (NSTEMI). (a) A left anterior oblique image of the right coronary artery with a culprit lesion that was subsequently treated with a stent (white arrow). (b) A right anterior oblique cranial image of the left anterior descending artery with mild plaque (black arrow). (c) A cross-sectional optical coherence tomography image of this mild non-coronary plaque with annotation of the fibrous cap and underlying lipid pool.

identifier: NCT03507777] will examine OCT-guided PCI used in this way, but more prospective trials are needed.

How best to utilize intravascular imaging to identify non-culprit lesions at highest risk of causing future events also needs further investigation. Three-vessel OCT or IVUS in every patient with NSTEMI is unlikely to be feasible. The use of these techniques is not benign, with PROSPECT reporting a complication rate from IVUS of 1.6%.⁹⁶ PROSPECT also showed the poor specificity of IVUS, with only 26 of 595 identified TCFAs found to be the site of a recurrent event at 3.4 years, an event rate of 4.9%.⁹⁶ Even when lesions exhibited high plaque burden or reduced minimal luminal area the event rate rose to only 18.2%. Restricting routine use of IVUS and OCT to high-risk, vulnerable patients with non-flow-limiting plaques on FFR may be one way to improve this. More information is then needed to characterize the risk posed by these individual plaques. One ongoing trial is examining 35 participants with non-culprit lesions in NSTEMI

and utilizing both OCT and IVUS characteristics to develop a risk score for these lesions [ClinicalTrials.gov identifier: NCT03953040].

Once a high-risk non-culprit lesion is identified, no data currently exist on the best treatment approach, including any possible benefit from plaque sealing with stents or scaffolds. The PROSPECT-II and PROSPECT-ABSORB trials [ClinicalTrials.gov identifier: NCT02171065] are underway to partially address this crucial question. PROSPECT-II will evaluate 902 participants with three-vessel IVUS and OCT and follow patients for 3 years, whereas PROSPECT-ABSORB, an interventional sub-study, will randomize 300 participants with lipid-rich plaque to undergo PCI with a bioresorbable scaffold. Given that OCT and IVUS both have good negative predictive value for identifying lesions unlikely to cause future MACE,^{96,106} another role for these techniques may be to determine which non-culprit plaques are biologically stable, irrespective of angiographic severity, thus allowing for safe deferral of PCI.¹⁰⁷

Limitations of the vulnerable plaque model and intravascular imaging

There are some deficiencies in our understanding of the mechanistic basis of AMI that the vulnerable plaque model does not fully explain. Primarily, non-culprit plaque rupture after a primary event is clearly not the whole story around secondary events in MVD. Although one three-vessel IVUS study showed a rate of secondary plaque rupture at the non-culprit site of 79% in AMI,¹⁰⁸ that number has been shown in other IVUS and OCT studies to be only between 12% and 31%.^{89,90,101,102} Similarly, while TCFAs are more common in patients post-AMI than in those with stable coronary disease, they are still only present in 38% of non-culprit sites.¹⁰¹ Furthermore, when non-culprit plaque rupture does occur, its correlation with MACE is unclear. The cumulative incidence of MACE in patients who experienced a non-culprit rupture was the same in those patients who did not in the context of maximal medical therapy.¹⁰² This either suggests that adverse cardiovascular outcomes occur in the absence of plaque rupture or that current medical therapy is efficacious in reducing the incidence of MACE even in the face of demonstrable plaque rupture. Recent evidence also suggests a greater role for plaque erosion in NSTEMI than previously recognized,¹⁰⁹ a problem more common in women.¹¹⁰ How much relevance this has in the setting of MVD is unclear and is another area requiring future interrogation, likely best achieved through use of intravascular imaging.

An integrated invasive approach

Improved care at the bedside is limited by both a dearth of prospective randomized data in patients with NSTEMI and MVD, and the challenge of incorporating and communicating all of the previously mentioned variables into a shared decision with the patient. As we have noted, the question of whether to pursue MV-PCI or CL-PCI alone is unlikely to be answered by larger, observational analyses; instead, there is a pressing need for carefully designed and adequately powered randomized clinical trials. Such trials would enroll representative, comorbid populations with demonstrable evidence of a culprit lesion and the presence of flow-limiting, non-culprit disease (angiographically $\geq 70\%$ or physiologically proven) that was amenable to revascularization. Potential exclusion criteria might include left main disease, prior CABG or cardiogenic shock.

Randomization to either a CL-PCI or MV-PCI revascularization approach could occur at the patient level in block strata of multivariable risk (e.g. TIMI or GRACE) or instead at the hospital level in a cluster randomization design. Cross-over would need to be minimized, and secondary prevention strategies mandated per protocol. While traditional 'hard' clinical endpoints (MACE) would likely form the primary outcome, patient-centered outcomes such as quality-of-life and angina scores would be important secondary endpoints. Blinded clinical event adjudication and an angiographic core lab may add precision, and inclusion of a sham procedure may improve the integrity of the more subjective endpoints.

Results from such a trial would help inform clinical decisions that often need to be made quickly in a procedural setting after coronary anatomy is elucidated. An ideal clinical tool could utilize this trial data to identify patient characteristics and coronary anatomy, derived from both visual angiographic and FFR assessment, most suitable to a MV-PCI approach. It remains to be seen if such a tool would benefit from intravascular imaging of the culprit lesion to inform non-culprit vulnerability. The final step would be how best to apply the use of intravascular imaging techniques to non-obstructive non-culprit plaques to predict future risk, both in terms of lesion selection and therapeutic implications. This, as discussed, requires considerable further investigation.

An evolving landscape of medical management

Any integrated clinical tool informing interventional management will need to be considered in the context of an evolving landscape of medical therapy. Statin therapy has become a mainstay post-NSTEMI, being shown to reduce MACE^{111,112} in a dose-dependent manner,¹¹³ that largely correlates with the degree of reduction in low-density lipoprotein (LDL) cholesterol.¹¹⁴ The development of further systemic agents modifying plaque may significantly mitigate the risk posed by non-culprit lesions. Targeting further LDL reductions through inhibitors of proprotein convertase subtilisin-kexin type 9 (PCSK9) has been shown to lead to plaque regression,¹¹⁵ and in turn reduce MACE, primarily through reductions in non-fatal MI, stroke and revascularization.¹¹⁶ A recent randomized, double-blinded trial of canakinumab, a therapeutic monoclonal antibody

targeting interleukin-1 β , evaluated 10,061 participants with established ischemic heart disease who had well-controlled lipid profiles but an elevated hs-CRP consistent with 'residual risk'. At 2-year follow up, canakinumab was associated with fewer non-fatal MIs, strokes or deaths.¹¹⁷ Though canakinumab achieved this endpoint, it did so at the cost of a higher incidence of fatal infection and thus will not be brought to market for this purpose.

Investigation of other more accessible anti-inflammatory agents has yielded mixed results. Recently, the use of low-dose methotrexate in the Cardiovascular Inflammation Reduction Trial (CIRT) was stopped for futility at a median follow up of 2.3 years after enrolling 4786 patients with stable CAD.¹¹⁸ In contrast, the COLCOT trial found that repurposing the anti-gout drug colchicine at just 0.5 mg daily reduced MACE by 23% over a median of 2.3 years, when initiated within 30 days of AMI.¹¹⁹ Patients with multiple, high-risk coronary lesions (e.g. NSTEMI with MVD) ought to derive particular benefit from pharmacotherapies capable of mitigating atherosclerosis and its complications, either through lipid-lowering or anti-inflammatory pathways. It follows that the inclusion criteria of future clinical trials of these agents should consider enriching for these individuals. AEGIS-II, a trial of a novel parenteral HDL therapy has taken this approach, enrolling ACS patients with angiographically proven MVD [ClinicalTrials.gov identifier: NCT03473223]. If new anti-atherosclerotic drugs emerge and are successfully translated to clinical practice, current approaches to non-culprit PCI and intravascular imaging will need to be further re-evaluated. Indeed, it has been argued that advances in the medical management of atherosclerosis and thrombosis over the past 20 years have already rendered the idea of the vulnerable plaque as outdated,¹²⁰ notwithstanding further advances expected to be seen in the next 20 years.

Conclusion

The optimal revascularization strategy for patients presenting with NSTEMI and subsequently found to have MVD remains undetermined. Our current approaches have been extrapolated from the management of patients with stable coronary disease or STEMI. However, NSTEMI patients present unique clinical challenges and the available data are largely

observational, frequently underpowered for hard clinical events and, despite multivariable adjustment, unable to avoid unmeasured confounding. Large, prospective, randomized trials are needed. Even once complete, the varied pathological basis and clinical heterogeneity of NSTEMI may mean greatest benefit is unearthed through a combination of improved patient selection and further characterization of non-culprit lesions. An integrated approach that considers specific patient and anatomical factors and utilizes FFR and intravascular imaging may hold the key, with the aim of elucidating specific plaques at highest risk of causing subsequent cardiovascular events and treating them. As systemic therapies continue to emerge, the magnitude of incremental benefit derived from a lesion-based approach to revascularization in these high-risk patients remains to be seen. The answer to improving patient outcomes will almost certainly lie in a personalized, precise approach to investigation, therapy and follow up.

Author contributions

All authors contributed to the writing of the manuscript and have provided the manuscript with final approval. Authors AAW Baumann, A Mishra and PJ Psaltis were involved in the conception and design of this review article.

Conflict of interest statement

PJP has received research support from Abbott Vascular, consulting fees from Amgen and Esperion and speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Merck Schering-Plough and Pfizer.

Ethical statement

This manuscript did not require an ethical board approval because it did not contain human or animal trials.

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