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MANAGEMENT OF ACUTE CORONARY SYNDROMES (H JNEID, SECTION EDITOR)

Revascularization Strategies for Non-ST-Elevation Myocardial Infarction

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Abstract

Purpose of Review Non-ST-elevation myocardial infarction (NSTEMI) is an urgent medical condition that requires prompt application of simultaneous pharmacologic and non-pharmacologic therapies. The variation in patient clinical characteristics coupled with the multitude of treatment modalities makes optimal and timely management challenging. This review summarizes risk stratification of patients, the role and timing of revascularization, and highlights important considerations in the revascularization approach with attention to individual patient characteristics.

Recent Findings The early invasive management of NSTEMI has fostered a reduction in future ischemic events. Risk calculators are helpful in determining which patients should receive early invasive management. As many patients have multivessel disease, identifying the true culprit lesion can be challenging. Special attention should be given to those at the highest risk, such as diabetics, patients with renal failure, and those with left main disease.

Summary In patients with acute coronary syndrome, the decision and mode of revascularization should carefully integrate the patient's clinical characteristics as well as the complexity of the coronary anatomy.

Keywords Non-ST-elevation myocardial infarction · Revascularization · Review

Introduction

Non-ST-elevation myocardial infarctions (NSTEMI) represent a major subset of acute coronary syndromes and are a significant cause of morbidity and mortality for hundreds of thousands of US patients annually [1]. Data to support early invasive management have been adopted for over a decade, with evidence pointing to a reduction in subsequent ischemic events [2, 3]. Whether patients are treated with an early or ischemic-guided approach, coronary revascularization commonly ensues. Determining the mode of revascularization, be it percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) depends on patient-specific as well as anatomic considerations. Patient-specific factors include presence of diabetes, renal insufficiency, cerebrovascular disease, and other comorbidities that influence operative risk. Anatomical considerations primarily address feasibility of PCI, success rates, and risk of subsequent target vessel failure. Presence of left ventricular dysfunction and/or valvular abnormalities are other variables that play a significant role in decision-making.

Once all variables have been analyzed, a discussion with the patient regarding the benefit of revascularization and the risk of complications should follow. A shared decision-making process ensues. Depending on the anatomical details and application of the contemporary evidence, surgical revascularization may be a reasonable option, so the decision-making process should then incorporate a surgical opinion, what has typically been labeled the heart team approach. The ultimate goal is to provide a safe intervention (in this case a revascularization modality) that not only alleviates symptoms, but also decreases future morbidity and mortality. Traditionally, CABG has been the preferred method of

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revascularization for patients with extensive disease and specific comorbidities while percutaneous coronary intervention (PCI) has been preferred for patients with discrete coronary lesions. With advances in PCI equipment and techniques, these traditional and binary guidelines have been challenged. Drug-eluting stents (DES), particularly the second and third-generation devices have significantly reduced the risk of complications and target vessel failure [4, 5]. Potent antiplatelet therapies and high-potency statins not only contribute to early success but provide significant reduction in subsequent risk of ischemic events [6, 7]. Table 1 not only demonstrates the shifting clinical practice with higher percentages of patients referred to revascularization but also the steady increase in proportion of patients revascularized by PCI.

It is important to recognize that most randomized-controlled trials comparing the two modalities have a patient population who are eligible for both modes of revascularization, and thus often only address a subset of "real-world" patients. This paper will attempt to contemporize practical revascularization strategies and principles important to the management of NSTEMI.

Optimal Timing of Revascularization

The 2014 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Management of Patients with NSTEMI recommend combining clinical history, physical examination, electrocardiogram (ECG), and cardiac biomarkers to make a rapid determination of the likelihood of obstructive coronary artery disease [8••]. Risk stratification after a diagnosis of NSTEMI is made a crucial first step in the management of such patients as risk stratification not only guides the heart team's decision on timing of revascularization but also provides patients with information regarding their prognosis. Patients with NSTEMI are at a widely varying risk of morbidity and mortality. The Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) scoring systems are two traditional models which have been used to facilitate triage and decision-making in NSTEMI patients [9, 10]. The more contemporary HEART score, which is predictive of the 6-week risk of major adverse cardiac events, may provide better prediction of events compared with TIMI and GRACE models [11, 12]. Furthermore, high-sensitivity troponin assays may help accelerate the management of patients as dynamic changes in troponin levels during serial sampling can help distinguish ischemic from non-ischemic causes of chest pain and mild cardiac enzyme leak. Incorporation of a high-sensitivity troponin should be embedded into the chest pain algorithm from the time the patient is seen in the emergency department. The rule-out safety and rule-in performance of a 0 and 1-h high-sensitivity troponin assessment demonstrated a sensitivity of 99.4% with a negative predictive value of 99.8% [13].

After initial risk assessment has been performed, the clinician's next step is to triage patients towards one of two broad pathways: an early-invasive or ischemia-driven pathway. While the aforementioned risk stratification tools can provide some level of decision-making support, individualization of management based on an overall clinical picture is paramount. It is important to identify unstable patients early and proceed with angiography on a more urgent/emergent (within 2 h) basis. These include those with persistent angina despite intensive attempts at medical therapy, dynamic ECG changes, hemodynamic instability, electrical instability, or those with severe left ventricular dysfunction or overt heart failure. Most stable NSTEMI patients will undergo a routine early invasive approach utilizing coronary angiography within 24–48 h of hospitalization. The ischemia-guided approach is practical for patients at low risk for in-hospital mortality and typically have no concerning ECG findings or only minimally detectable elevation in cardiac biomarkers.

Several studies have demonstrated that early angiography and revascularization are known to reduce the risk of

Table 1 Trends of revascularization in selected landmark acute coronary syndrome studies

Study	Year	Enrolled patients	% of cohort revascularized	PCI	CABG
TIMI IIIB	1995	1473	4.1%	59.0%	49.2%
VANQWISH	1998	920	36.4%	45.7%	54.3%
FRISC II	1999	2457	57.2%	52.8%	47.2%
TACTICS-TIMI 18	2001	2220	54.8%	65.4%	34.6%
CURE	2001	12,564	37.6%	56.2%	43.8%
RITA-3	2002	1810	43.0%	60.8%	39.2%
SYNERGY	2004	9978	65.7%	71.5%	28.5%
ACUITY	2006	13,819	67.5%	83.5%	16.5%
EARLY-ACS	2009	9406	72.1%	81.9%	18.1%
TIMACS	2009	3031	71.7%	80.1%	19.9%
PLATO	2009	18,624	74.5%	86.3%	13.7%

refractory ischemia, recurrent myocardial infarction, repeat hospitalization, and death [2, 14, 15] (Fig. 1).

According to the CathPCI Registry, more than 70% of all PCI procedures performed in 2017 were in patients with unstable angina (UA) or NSTEMI [16]. While coronary angiography in the setting of NSTEMI has increased, as per Medicare Provider Analysis and Review, there has been only a modest increase in the percent of NSTEMI patients receiving PCI during initial hospitalization (from 21.3% in 2002 to 33% in 2014). Roughly 8–10% of patients will undergo CABG, while the remainder receive conservative best-practice medical therapy [17]. Additionally, 32–40% of patients with a NSTEMI will undergo PCI [16]. The exact timing of PCI in hemodynamically stable NSTEMI patients remains a subject for debate. Earlier randomized trials demonstrated no difference in extent of myonecrosis or major adverse events between those treated within the first 2 h vs 24–48 h [18]. Another prospective randomized trial compared immediate (< 2 h), early (10–48 h), and selective angiography, again demonstrating no difference in major ischemic events at 6 months [19]. However, more recent data point to a reduction in major ischemic events, mostly new myocardial infarctions, in those subjected to angiography and revascularization within the first 2 h. In the RIDDLE-NSTEMI trial, 323 NSTEMI patients were randomized 1:1 to an immediate-intervention group (< 2 h after randomization) and a delayed-intervention group (2 to 72 h). The primary endpoint was the occurrence of death or new myocardial infarction (MI) at 30-day follow-up. That was achieved less frequently in patients undergoing immediate compared to delayed intervention (4.3% vs. 13%, $p = 0.008$), the difference primarily driven by excess new infarctions in the delayed intervention group [20]. A meta-analysis of eight randomized clinical trials addressing early versus delayed angiography and including more than 5000 patients followed for a median of 180 days does not show improved survival in all comers. It does however suggest that early angiography contributes to improved survival in certain subsets of high-risk patients such as those with positive biomarkers, higher GRACE scores, diabetes, or age of 75 years or older [21] (Fig. 2).

Current guidelines do not offer recommendations regarding the optimal timing of CABG in patients with NSTEMI. Early retrospective studies found that when CABG was performed earlier in patients with NSTEMI, there was a trend towards more significant in-hospital mortality, heart failure, MI, and cardiogenic shock [22–25]. However, in the largest cohort of patients who underwent CABG for NSTEMI, immediate CABG (performed within 24-h of diagnosis of NSTEMI) had similar long-term outcomes compared to delayed CABG (72 h after presentation) despite patients having higher risk profiles [26]. As NSTEMI is characterized by non-transmural necrosis, early revascularization may limit infarct expansion and possible progression to transmurality. However, randomized trial evidence for such findings after CABG for NSTEMI patients is not currently available.

Considerations for Revascularization

In single and most two-vessel disease patients, it is typically easier to decide in favor of a PCI approach to revascularization. However, when multivessel revascularization is necessary, strong consideration should be given to a surgical approach. As discussed, clinical and anatomic variables in addition to patient preferences all play a role in the shared decision-making process. Diabetes, for example, is an important clinical variable that should guide management and is

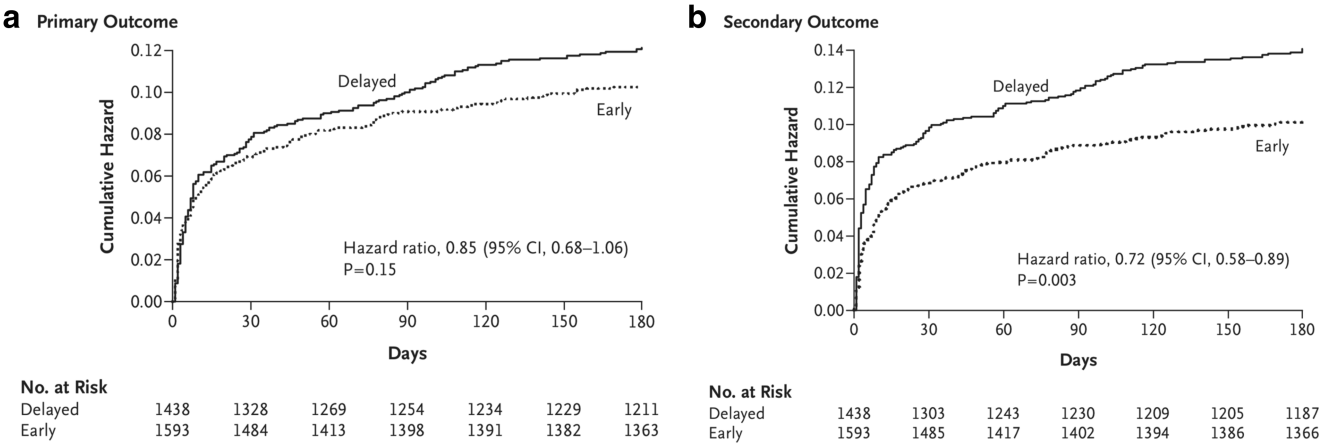

Fig. 1 Outcomes of early vs. delayed invasive approach to management of ACS patients in the TIMACS study. The difference in the composite primary outcome of death, myocardial infarction, or stroke in the early-intervention and delayed-intervention group did not reach statistical significance (panel **a**). However, early intervention was associated with strong and statistically significant reduction in the risk of the composite secondary outcome of death, myocardial infarction, or refractory ischemia, compared with the delayed intervention group (panel **b**). (From Mehta SR, et al. N Engl J Med. 2009;360(21):2165–75, Copyright © 2009 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society) [2]

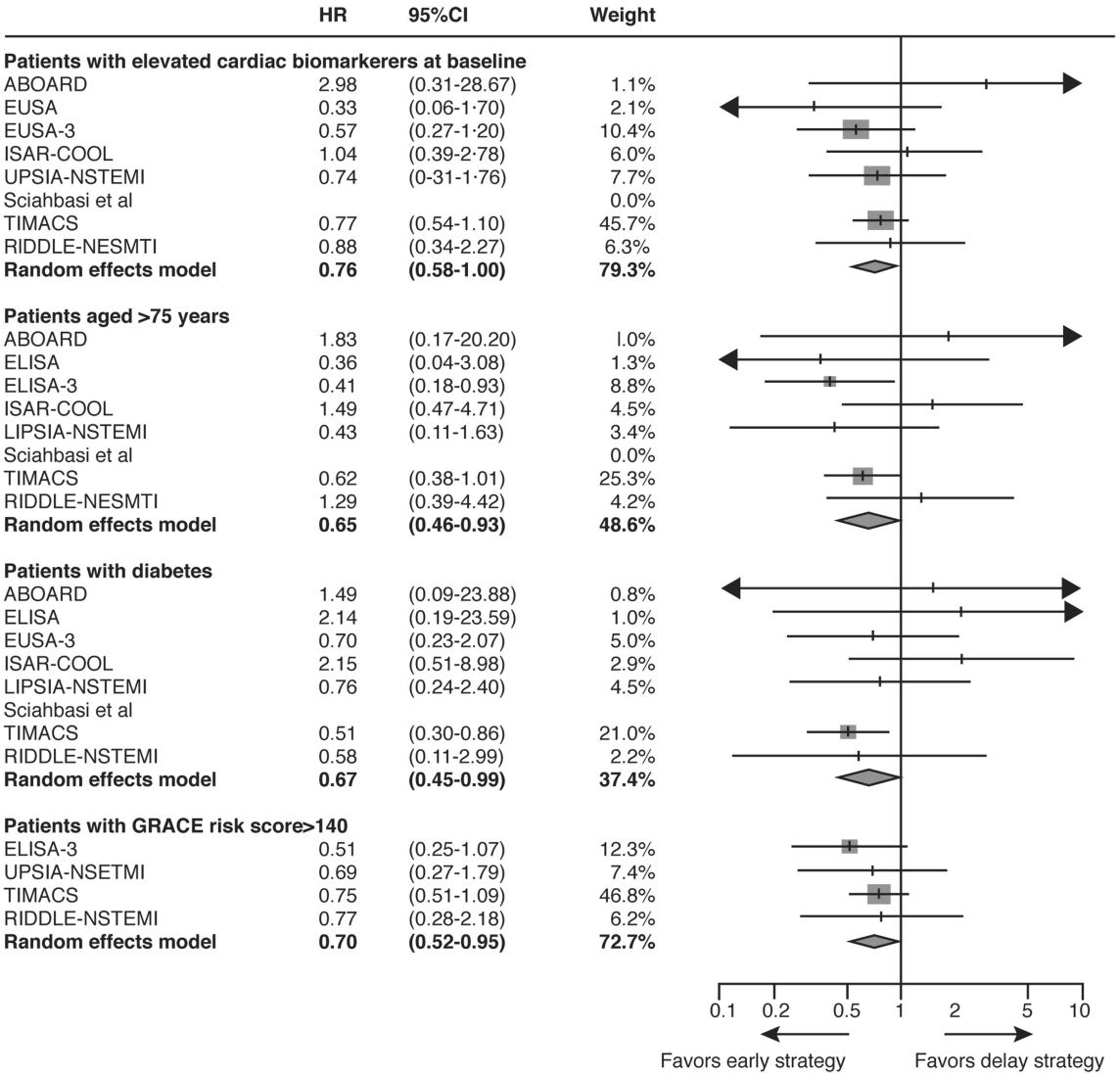

Fig. 2 Survival benefit of early invasive approach demonstrated in high-risk ACS patient subsets. In a meta-analysis of 5000 ACS patients enrolled in 8 randomized trials, an early invasive approach was not associated with survival benefit for all comers. However, survival benefit was statistically significant in pre-specified high-risk subgroups such as shown here (positive biomarkers, diabetes, elderly, high GRACE score). (Reprinted from *The Lancet*, Jobs A, et al. Lancet. 2017;390(10096):737–46, with permission from Elsevier) [17]

discussed in detail below. In patients eligible for either approach, long-term mortality is comparable with both strategies; however, rates of subsequent myocardial infarction and need for repeat revascularization are higher with PCI in most patient subsets with multivessel intervention [27, 28]. Patients who have concomitant valvular disease may be more appropriate for surgical correction, though a hybrid PCI/valve surgery management strategy is certainly a consideration. We will now focus on specific patient populations as well as general considerations regarding revascularization strategies.

Complete Vs Culprit-Only Revascularization

The incidence of multivessel CAD ranges from 29 to 60% [29, 30] and a crucial benefit afforded by CABG is the completeness of revascularization. Insights from the Bypass Angioplasty Revascularization Investigation (BARI) and the Arterial Revascularization Therapies Study demonstrated that incompletely revascularized patients tended to suffer from recurrent angina and need for repeat revascularization; this was largely driven by worse baseline clinical and angiographic characteristics [31, 32]. This conclusion is based on all-comers to the trials and information regarding how many NSTEMI patients were represented is unavailable. Multivessel PCI, however, has been shown to be safe in patients with NSTEMI, and patients treated with such an approach had similar rates of mortality and MI compared to those who underwent culprit-only PCI at 30 days and 6 months along with lower rates of repeated revascularization at 6 months of

follow-up [33]. It is challenging, however, to identify culprit lesions by angiography alone in patients with NSTEMI, and guideline documents are often lacking.

Several tools can be used to help guide the completeness of revascularization. The Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial attempted to develop a more stratified approach for assessing revascularization options [34]. While it is a commonly employed tool for the interventionalist managing a patient with multivessel disease, its utility in the setting of NSTEMI is debatable as patients with acute myocardial infarction were excluded from the SYNTAX patient cohort. Another useful tool is fractional flow reserve (FFR) where deferred revascularization in lesions above a cutoff of 0.75 is associated with lower major adverse cardiovascular events [35]. Utilizing FFR in the setting of NSTEMI has been confirmed with similar predictive value [36]. Tools such as the SYNTAX score and FFR while helpful should again be used in light of the clinical judgment along with the risk versus benefit ratio always being considered.

If PCI is selected as the mode of revascularization, achieving complete revascularization in a single setting versus a staged fashion is a consideration. Conclusions from the Single-Staged Compared with Multi-Staged PCI in Multivessel NSTEMI Patients Trial (SMILE) supported one-stage over multistage revascularization in terms of reduced major adverse cardiac events. Although the staged procedures were completed within 7 days, the increased event rates in the staged PCI group were mainly attributable to an unexplained higher incidence of target vessel revascularization beyond the first 6 months [37]. As mentioned before, identifying culprit lesions in the setting of an NSTEMI with multivessel disease can be difficult and staging an intervention may lead to the possibility of performing the sentinel PCI on a non-culprit vessel. If complete revascularization can be achieved in a fashion that limits procedure time, exposure to high contrast volumes, and exposure to excess fluoroscopy, single-sitting PCI should be considered.

Diabetic Patients

Coronary artery disease is accelerated in diabetic patients as it is a pro-atherogenic condition due to increased endothelial dysfunction, more dyslipidemic states, increased platelet aggregation, and impaired fibrinolysis [38]. Roughly 25% of patients undergoing coronary revascularization have diabetes mellitus, though this percentage may be increasing in the last decade [39]. Regardless of the mode of revascularization, outcomes in diabetic patients are generally inferior to those in non-diabetics. Patients with diabetes undergoing CABG typically suffer from poor graft conduits and accelerated rates of venous bypass occlusion not to mention higher perioperative risks, while PCI outcomes are affected by high restenosis rates. The BARI trial sets the precedent demonstrating improved long-term survival with CABG [40]. These results were corroborated in the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus) trial which compared CABG with first-generation paclitaxel-eluting stents and the BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trial which compared CABG to second-generation everolimus-eluting stents [41, 42•]. In a Canadian study examining the applicability of the FREEDOM trial data to the general population, about 5000 patients in a province-wide registry coronary revascularization (3047 PCI and 1802 CABG procedures) were followed for major cardiac and cerebrovascular events for 5 years. As expected, there was a significant advantage of CABG over PCI in reducing death and ischemic events. At 30 days, there was a significant interaction between the mode of revascularization and clinical presentation, with ACS patients benefiting from CABG much earlier than those presenting with stable disease (odds ratio for major events 0.49 [CI: 0.34 to 0.71]), whereas stable patients' event rates were not affected by revascularization strategy (odds ratio: 1.46 [CI 0.71 to 3.01]; p for interaction < 0.01). After 5 years, the advantage of CABG over PCI was almost equally noted in ACS and stable patients [43] (Fig. 3).

Despite the preponderance of evidence favoring CABG, the door for PCI is not completely closed in these patients as single and possibly double-vessel disease patients can benefit from PCI. Current antiplatelet therapies and aggressive secondary preventative strategies post-revascularization were not available or readily employed in previous studies.

Chronic Kidney Disease

Chronic kidney disease (CKD) represents a major independent risk factor for adverse outcomes in patients with acute coronary syndromes [10]. Patients with CKD, however, are more likely to be managed conservatively with revascularization reserved on for instances of recurrent myocardial ischemia. Furthermore, CKD patients are often excluded from major clinical trials making comparisons of PCI to CABG difficult to assess. Regardless of the mode of revascularization, outcomes in patients with CKD are less than ideal. In a patient undergoing CABG, CKD is an intrinsic adverse prognostic factor with markedly worse outcomes when compared to patients with normal renal function [44]. Patients with CKD undergoing PCI are affected by higher rates of restenosis on top of the ever-present risk of contrast-induced nephropathy [45, 46]. The only major randomized, prospective trial to assess differences between CABG and PCI in CAD patients with CKD was a subset of the ARTS trial. The two modes of revascularization demonstrated equivalent rates of death, MI, or stroke, though PCI was inferior with regard to reintervention rates; however, acute MI patients were excluded from the cohort [47].

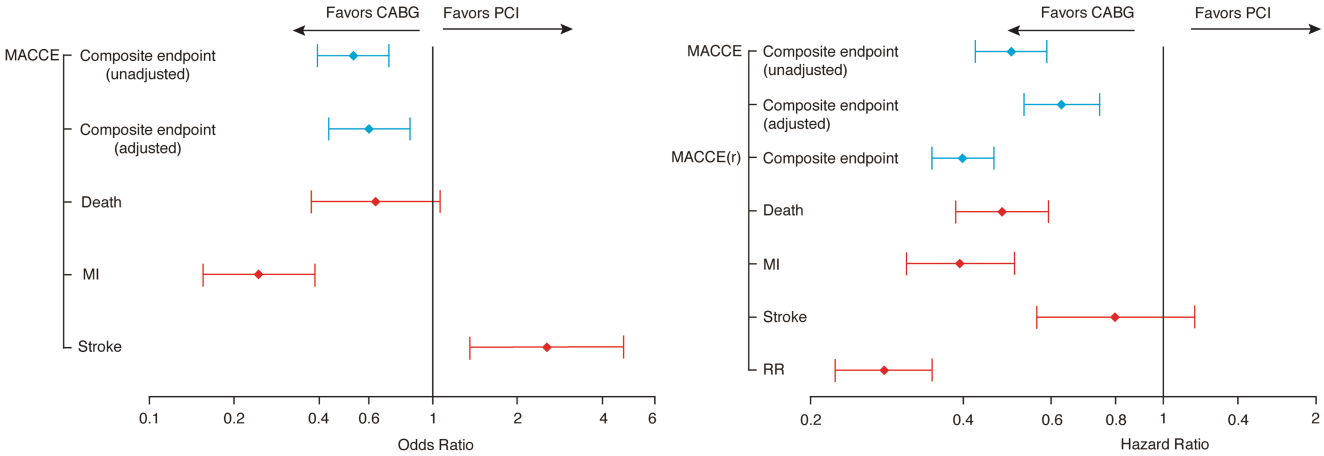

Fig. 3 Diabetics with ACS and multivessel disease in a real-life province-wide database. Left panel: The early impact of revascularization modality on the primary outcome (major adverse cardiac or cerebrovascular events, MACCE, a composite of all-cause death, nonfatal MI, and nonfatal stroke) and secondary outcomes (the individual components of MACCE) expressed as odds ratios (ORs). The ORs for primary outcome of MACCE were adjusted for age, sex, presentation (ACS vs. stable disease), urgency (emergent, urgent vs. elective), and LVEF (> 50%, 30–50% vs. < 30%). The ORs for MACCE (unadjusted and adjusted) as well as for each of the component outcomes (except for stroke) favored CABG over PCI as the revascularization mode of choice for these patients. Right panel: The late impact of revascularization modality on MACCE, its individual components, repeat revascularization post-discharge (RR), and a composite of MACCE plus RR [MACCE(r)] expressed as hazard ratios (HRs). The HRs for unadjusted and adjusted MACCE, RR, MACCE(r), and individual components of MACCE significantly favored CABG compared to PCI as a revascularization modality. (Reprinted from Ramanathan K, et al. J Am Coll Cardiol. 2017;70(24):2995–3006, with permission from Elsevier) [39]

Left Main Coronary Disease

Significant (greater than 50% narrowing) left main CAD is found in 4–6% of all patients who undergo coronary angiography, and 10.7–11.2% of left main PCIs are performed in the setting of NSTEMI [48, 49]. Standard of care for patients with significant unprotected left main coronary disease is CABG as it confers significant survival benefit on repeated studies [50–52]. This concept was further validated in the Nordic-Baltic-British Left Main Revascularization Study (NOBLE) in which 17–18% of the cohort represented patients with acute coronary syndromes (not STEMI) [53] Revascularization by CABG was shown to be superior to PCI even for left main stenosis with low-intermediate SYNTAX scores (< 32) though this was mainly driven by the need for repeat revascularization included in the composite outcome. Patients with NSTEMI represented 13.2% of the total cohort in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial which demonstrated the non-inferiority of second-generation DES to CABG based on a primary composite endpoint of all-cause mortality, MI, and stroke [54•]. Comparisons of CABG to PCI in these studies did not account for the even newer advancements in stent technology, procedural technique, and medical therapy including antithrombotic strategies. Furthermore, PCI should be considered in settings where surgery carries prohibitive risk including cardiogenic shock. Given the clinical equipoise presented with low-intermediate left main disease, patient preference along with the heart team approach should be a crucial influence towards decision-making.

Cardiogenic Shock

Cardiogenic shock is typically seen in the context of STEMI, which causes acute left ventricular dysfunction from continued cardiac myocyte ischemia and necrosis. Cardiogenic shock can complicate either a large STEMI or NSTEMI, and while mortality was traditionally thought to be similar between the two groups [55, 56], contemporary data demonstrates the short-term mortality of NSTEMI-related shock is higher [57]. The reason for comparable mortality rates is likely because NSTEMI patients are older with more comorbid conditions including previous MI, heart failure, renal dysfunction, and peripheral vascular disease. Though NSTEMI patients in shock are more likely to have recurrent ischemia, they are less likely to undergo coronary angiography [55]. Nearly two thirds of patients in the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO)-IIb trial who developed shock in the setting of NSTEMI had three-vessel disease. Only a small fraction of patients, however, received revascularization. Percutaneous coronary angioplasty was associated with improved mortality at 30 days whereas patients who underwent CABG had worse outcomes [56]. Extrapolating these findings in the approach to the current era of

revascularization should be cautioned as the advancement of technology and medical therapy has made significant strides.

Dual Antiplatelet Therapy

One of the major concerns cardiothoracic surgeons may have in performing CABG in patients with NSTEMI is the increased risk of bleeding, a result of the push towards upstream use of oral antiplatelet medications, namely $P2Y_{12}$ inhibitors. Aspirin confers only a modest increase in bleeding risk for CABG, and preoperative aspirin is known to reduce operative morbidity and mortality [58–61]. While current recommendations are to withhold $P2Y_{12}$ inhibitors from 5 to 7 days in patients undergoing elective surgery because of the known associated risks of bleeding and need for transfusion, the risk of bleeding and transfusion should be weighed against the risk of delaying surgery [8••]. Previous studies have shown that performing CABG on clopidogrel therapy increases the risk for transfusions but does not increase mortality or the rate of re-operation for bleeding [62].

Hybrid Revascularization

Hybrid coronary revascularization (HCR) combines the principal benefit of CABG (minimally invasive grafting of an internal mammary artery to the left anterior descending) with PCI of the remaining vessels. With this approach, the durability of an arterial bypass conduit is married with the decreased invasiveness of PCI. The most traditional approach to HCR involved minimally invasive direct coronary artery bypass of the left internal mammary artery (LIMA) to the left anterior descending (LAD) coronary artery followed by PCI to the non-LAD vessels, often in a staged fashion.

Performance of PCI prior to CABG allows surgery to be an adequate bailout in the event of sub-optimal PCI but also minimizes global ischemia during occlusion of the LAD for anastomosis. For NSTEMI, PCI of a culprit non-LAD vessel can be performed first, followed by surgical revascularization including the LAD at a time dictated by the patient's clinical variables. This approach, however, may require the surgeon to be comfortable with operating on dual antiplatelet therapy. The alternative approach, where PCI is performed following CABG of the LIMA to LAD, is appealing in the drug-eluting stent era as dual antiplatelet therapy (DAPT) can be continued long term. Furthermore, the assurance of a protected LAD may provide confidence for the interventionalist to tackle lesions that are more complex and potentially mitigate the need for adjunctive mechanical circulatory support. This approach for the surgeon does require deliberate avoidance of prolonged global myocardial ischemia from long pump runs as well as careful attention to hemodynamics. Simultaneous CABG and PCI in one setting within hybrid operating suites is another alternative allowing for immediate complete revascularization but requires collaborative efforts between the interventionalist and the surgeon balancing the need for antithrombotic management and minimizing the risk of perioperative bleeding.

The results of a prospective cohort, 11-center National Institutes of Health-funded study, were largely disappointing with no significant difference in the rate of major adverse cardiac events at 12 months [63]. Notably, myocardial infarction only represented subset of all patients. A randomized trial with long-term outcomes, the Hybrid Revascularization Observational Study, is currently comparing the effectiveness of multivessel PCI with HCR.

Considerations for PCI

If PCI is selected as the preferred revascularization strategy for a patient, the subtleties and nuances in procedure technique are numerous. Some approaches are worth reviewing including vascular access. Though the benefits of radial access have been highly touted, and adoption is increasing (10.9% in 2011 to 25.2% in 2014), only a quarter of overall PCIs in the USA were performed from a transradial approach [64]. This percentage has now exceeded 33% in the CathPCI Registry. Several factors are at play including a steeper learning curve, which can result in longer procedure times and greater radiation exposure. Interventionalists, however, should push for increased transradial access for PCI as it is associated with a similar rate of procedural success, reductions in the risk of bleeding and vascular complications, lower costs, and improved patient satisfaction, and improved mortality [65]. A recent meta-analysis pooling 22,843 patients across a spectrum of coronary artery disease found significant reductions in all-cause mortality for patients with NSTEMI on subgroup analysis [66].

Chronic total occlusions (CTO) are common in patients with NSTEMI and represent and independent predictor for mortality and reduction in left ventricular function [67]. The reason why concurrent CTOs may affect prognosis in NSTEMI patients may be in part related to the higher risk profile of CTO patients in general (older age, previous MI, reduced left ventricular function). In one study, the presence of a CTO in patients with NSTEMI independent from that of the infarct-related artery was associated with higher 30-day, 6-month, and 1-year mortality [68]. Notably in this study, the presence of a CTO did not affect the extent of either percutaneous or surgical coronary revascularization. The steep learning curve, technical difficulties, and lower procedural success for CTO PCI may favor complete revascularization via CABG in the correct clinical context.

Conclusion

Patients with NSTEMI represent a challenge for the cardiologist to individualize patient care and provide timely revascularization that will maximize benefit while minimizing exposure to harm. Risk assessment should be performed as soon as a diagnosis of NSTEMI is made with prompt decision-making regarding the need for invasive assessment of coronary anatomy. Recent evidence supports an early invasive approach in most patients, with evidence of reduced mortality and adverse ischemic outcomes in high-risk subsets. The decision to revascularize and the mode of revascularization should carefully integrate the patient's clinical characteristics as well as the complexity of the coronary anatomy.

Compliance with Ethical Standards

Conflict of Interest Bennet George, Naoki Misumida, and Khaled M. Ziada declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This review complies with all ethical standards for clinical research on human subjects. This article does not contain any studies with human or animal subjects performed by any of the authors.

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ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Treatment of Unprotected Left Main Stenosis

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Abstract

Purpose of Review This article reviews the latest data on unprotected left main (ULM) percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) surgery, with a focus on the NOBLE and EXCEL trials.

Recent Findings In EXCEL trial, the primary endpoint at 3 years was 15.4% in the PCI group and 14.7% in the CABG group ($p = 0.02$ for non-inferiority of PCI versus CABG). In NOBLE, the primary endpoint at 5 years was 28% and 18% for PCI and CABG, respectively (HR 1.51, CI 1.13–2.0, which did not meet the criteria for non-inferiority of PCI to CABG; p for superiority of CABG was 0.0044). Higher repeat revascularization and non-procedural myocardial infarction were noted in PCI group but there was no difference in all-cause or cardiac mortality between the two groups.

Summary A heart team approach with appropriate patient selection, careful assessment of LM lesions, and meticulous procedural technique makes PCI a valid alternative to CABG for ULM stenosis.

Keywords Left main · Percutaneous coronary intervention · Coronary artery bypass graft

Introduction

The left main (LM) coronary artery supplies up to 84% of the left ventricular myocardium [1]. Therefore, high-grade unprotected (i.e., not protected by a patent bypass graft) left main (ULM) stenosis places a large myocardial territory at risk for ischemia [2]. Significant ULM stenosis, defined as > 50% diameter stenosis, is noted in approximately 5% of patients undergoing coronary angiography for any reason, and up to 25% of those with acute coronary syndrome (ACS) [2]. Medical therapy alone is inferior to CABG in patients with significant ULM stenosis [3]. A meta-analysis of 8 trials including 4850 patients demonstrated that coronary revascularization in addition to medical therapy resulted in a 79% and

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80% relative risk reduction in 5-year mortality with CABG and PCI, respectively, compared to medical therapy alone [4]. Stent restenosis was a significant drawback to the use of balloon angioplasty or bare metal stents. This issue has been largely overcome with drug-eluting stents (DES) [5]. Further advancements in stent technology led to the development of second-generation drug-eluting stents (DES2). These stents have thinner struts (80–90 μm) composed of cobalt or platinum alloy in comparison to the first generation (DES1) (sirolimus- and paclitaxel-eluting stents) that had much thicker, 130–140 μm, stainless steel struts [6]. Basic laboratory and histopathological data reveals thinner struts exhibit more complete endothelialization compared with thicker struts with lower likelihood of intimal hyperplasia [6]. Vessels treated with DES2 experienced lower target lesion revascularization compared to DES1. Therefore, outcomes with DES2 are hypothesized to be improved as compared with CABG. This paper summarizes the current body of RCT data comparing PCI with CABG for ULM stenosis, with a focus on the two recent RCTs which exclusively utilized DES2.

Discussion of Available Trial Data

Currently published randomized controlled trials (RCT) on PCI versus CABG are summarized in Table 1. Approaches in choosing PCI versus CABG for ULM stenosis in different clinical scenarios are outlined in Table 2.

Four RCTs comparing PCI with DES1 and CABG for ULM stenosis were published between 2008 and 2011. These included LEMANS (2008), SYNTAX-LM (2010), a study by Boudriot et al. (2011) and PRECOMBAT (2011) [10, 12•, 13, 14].

Four Previously Published Randomized Trials

In the LEMANS trial, patients were randomized to PCI received either DES1 (35%) or bare metal stents (65%) versus CABG. The initial study was reported in 2008 with the 10-year follow-up of this trial published recently [9, 13]. There were no differences in mortality, myocardial infarction (MI), stroke, and repeat revascularization (RR) between PCI and CABG at 10 years in patients with low to moderate complexity disease. The probability of very long-term survival up to 14 years was comparable in the two groups, although there was a trend for higher major adverse cardiovascular and cerebrovascular event (MACCE)-free survival with PCI [9]. Boudriot et al. randomized patients to PCI with sirolimus-eluting stents (DES1) or CABG. PCI was non-inferior to CABG for 12-month MACCE-free survival but was associated with a higher RR rate [10]. The PRECOMBAT study recently reported 5-year outcomes and showed no difference in MACCE between PCI with sirolimus-eluting stents (DES1) and CABG, with higher ischemia-driven target vessel revascularization with PCI [11•]. The LM cohort of the 1800 patients included in the SYNTAX trial consisted of a pre-defined and adequately powered group of 705 patients [12]. There was no difference in MACCE between PCI with paclitaxel-eluting stents (DES1) and CABG at 5 years in the entire LM cohort [15]. However, RR was more common, and stroke was less common with PCI. MACCE and cardiac death were significantly higher in patients with SYNTAX score > 33, who underwent PCI compared with CABG.

Recently Published EXCEL and NOBLE Trial

The EXCEL and NOBLE trials were reported in 2016 and are the only RCTs in which CABG was compared with DES2 for the treatment of ULM stenosis [7••, 8••].

With 1905 patients in 17 countries at 126 centers, EXCEL is the largest ULM PCI trial published to date [7••]. In contrast to the SYNTAX trial which used DES1, DES2 were used in EXCEL. Patients with ULM with stable angina (60%) or ACS (40%) were randomized to PCI or CABG. SYNTAX score was $\leq$ 22 in 32%, 23–32 in 43%, and $\geq$ 33 in 25% of patients in the PCI group. The DES2 used in this trial was fluoropolymer-based everolimus-eluting stent (XIENCE, Abbott Vascular). In the PCI group, 82% of cases involved the LM bifurcation. Intravascular ultrasound (IVUS) was used in 77% of cases. The primary composite endpoint of death, stroke, or MI at 3 years was 15.4% in the PCI group and 14.7% in the CABG group ($p = 0.02$ for non-inferiority of PCI versus CABG; hazard ratio 1.00, 0.79, to 1.26; $p = 0.98$ for superiority). Outcomes at 30 days were superior with PCI due to fewer MI (3.9% vs. 6.2%, HR 0.63, 0.42–0.95, $p = 0.02$) [8••]. Of note, PCI offers the advantage of avoiding surgically related complications of CABG (the secondary endpoints of major bleeding, infections, arrhythmias, and reoperations 8.1% in the PCI group vs. 23.0% in CABG group, $p < 0.001$) [8••].

NOBLE was a European trial conducted at 36 sites including 1201 patients [7••]. Patients with ULM and up to three additional noncomplex lesions, with stable angina (82%) or ACS (18%), were randomized to PCI or CABG. Patients with complex multivessel coronary artery disease (CAD), chronic total occlusions, and bifurcation lesions requiring two stents were excluded. The DES2 used in this trial was the biolimus-eluting stent (Biomatrix Flex, Biosensors, Morges, Switzerland). In the PCI group, 88% of cases involved the LM bifurcation, and a two-stent approach was used in 35% cases. The majority (55%) underwent treatment of just the LM, whereas 33% had one additional lesion and 9% had two additional lesions treated. Post-PCI IVUS was used in 74% of cases [7••]. The primary endpoint was MACCE at 5 years, defined as the composite of all-cause mortality, stroke, RR, or non-procedural MI. MACCE were 28% and 18% for

Table 1 Summary of currently published randomized controlled trials on PCI vs CABG for left main coronary artery disease

Trial and term	Number of patients	Mean SYNTAX score	Secondary endpoint				Primary endpoint			
			Outcome	CABG	PCI	*p*	Outcome	CABG	PCI	*p*
NOBLE 2017	N 1201 DM 15%	22	Repeat revascularization	10%	16%	0.032	Composite: Repeat revascularization	19%	29%	0.007
5 years [7••]	ACS 17%						Death			
			Stroke	2%	5%	0.073	Stroke, non-procedural MI			
			Death	9%	12%	0.77				
			MI (non-procedural)	2%	7%	0.004				
EXCEL 2017 3 years [8••]	N 1905 DM 29%	21	Ischemia-driven revascularization	7.5%	12.6%	0.001	Composite: death, stroke, or MI.	14.7%	15.4%	Non-inferiority = 0.02 Superiority = 0.98
	ACS 24%		Stroke	2.9%	2.3%	0.37				
			Death	5.9%	8.2%	0.11				
			MI	8.3%	8%	0.64				
			Composite	19.1%	23.1%	Non-inf 0.01				
LEMANS 2008–2016	N 105 DM 18%	Not reported	Repeat revascularization (10 years)	31.3%	26.1%	0.39	Left ventricular ejection fraction LVEF change at 1 year	0.5± 0.8%	3.3± 6.7%	0.047
1 and 10 years [9]	ACS not reported		Stroke (10 years)	6.3%	4.3%	0.58				
			Death (10 years)	30.2%	21.6%	0.41				
			MI (10 years)	10.4%	8.7%	0.68				
			Composite	62.5%	52.2%	0.42				
Boudriot et al 2011	N 201 DM 36%	23	Repeat revascularization	5.9%	14%	Non-inf 0.19	Death, MI, or repeat revascularization at 1 year.	13.9%	19%	Non-inferiority = 0.19
1 year [10]	ACS not reported		Death or MI	7.9%	5%	Non-inf < 0.001				
			Death	5%	2%	Non-inf < 0.001				
			MI	3%	3%	Non-inf 0.002				
PRECOMBAT 2011	N 600 DM 32%	25	Repeat revascularization (5 years)	7.3%	13%	0.02	Death, stroke, MI or Ischemia-driven target lesion revascularization (1 year)	6.7%	8.7%	Non-inferiority = 0.01
1 and 5 years [11]	ACS 45%		Stroke (5 years)	0.7%	0.7%	0.99				
			Death (5 years)	7.9%	5.7%	0.32				
			MI (5 years)	1.7%	2%	0.76				
			Death, stroke, or MI (5 years)	9.6%	8.4%	0.66				
			Death, stroke, MI, or ischemia-driven target lesion revascularization (5 years)	14.3%	17.5%	0.26				
SYNTAX-LM 2010	N 705 DM 25%	30	Repeat revascularization (5 years)	15.5%	26.7%	< 0.001	Death, stroke, mi, or repeat	13.6%	15.8%	Non-inferiority = 0.19

Table 1 (continued)

Trial and term	Number of patients	Mean SYNTAX score	Secondary endpoint				Primary endpoint			
			Outcome	CABG	PCI	*p*	Outcome	CABG	PCI	*p*
1 and 5 years [12]	ACS 30%		Stroke (5 years)	4.3%	1.5%	0.03	revascularization (1 year)			
			Death (5 years)	14,6%	12.8%	0.53				
			MI (5 years)	4.8%	8.2%	0.10				
			Death, stroke, or MI (5 years)	20.8%	19%	0.57				
			Death, stroke, mi, or repeat revascularization (5 years)	31%	36.9%	0.12				

ACS acute coronary syndrome, *DM* diabetes mellitus, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft

PCI and CABG, respectively (HR 1.51, 1.13–2.0, which did not meet the criteria for non-inferiority of PCI to CABG); *p* for superiority of CABG over PCI was 0.0044. Interestingly, 1-year MACCE rates were similar in PCI and CABG. Higher RR (15% for PCI vs. 10% for CABG (HR 1.50, 1.04–2.17, $p = 0.0304$) and non-procedural MI (6% for PCI vs. 2% for CABG (HR 2.87, 1.40–5.89, $p = 0.0040$) were responsible for the higher MACCE rates with PCI. RR was due to new lesions in non-stented segments rather than for the treated LM lesion [7••]. There was no difference in all-cause or cardiac mortality between the two groups. SYNTAX score was not associated with MACCE in the PCI group. While early stroke was more common in the CABG group, an unexpected, numerically higher rate of late stroke was noted in the PCI group, with no overall difference in the two groups at 5 years [7••].

The findings of NOBLE are similar to those of the SYNTAX trial but differ from the findings of EXCEL. The disparity in the conclusions between NOBLE and EXCEL may be partly due to differences in study design, endpoints, and the type of stent. The absolute margin for non-inferiority in EXCEL was 4.2%, compared with a 35% relative non-inferiority margin in NOBLE [16]. The primary endpoint assessment was changed from 5 years to 3 years in the NOBLE trial due to low event rates, and Kaplan Meier estimates were used to report 5-year outcomes [7••, 8••]. These estimates could have been affected by a change in risk for patients entering the study at different time points. Importantly, RR (which is uniformly lower in patients treated with CABG compared with PCI) was included in the primary composite endpoint in NOBLE, but not in EXCEL [7••]. Periprocedural MI, defined as creatine phosphokinase elevation > 10 × upper limit of normal, was included in the composite endpoint in EXCEL, whereas it was not included in NOBLE. A thin-strut everolimus-eluting stent was used in EXCEL compared with a thicker-strut biolimus-eluting stent was used in most patients in NOBLE. The higher incidence of stroke, between 1

Table 2 Approaches in choosing PCI versus CABG in different clinical scenarios

Clinical situation	PCI	CABG	Evidence
Limited life expectancy	Favors PCI		Similar 1-year MACCE between PCI and CABG in NOBLE trial
Complex LM bifurcation stenosis		Favors CA-BG	Despite a low SYNTAX score, CABG may offer an advantage over PCI for this lesion subset
Isolated ostial or shaft LM stenosis with low SYNTAX score	Favors PCI		

LM left main, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *MACCE* major adverse cardiac and cerebrovascular events, *NOBLE* Nordic-Baltic-British Left Main Revascularization trial

and 5 years, among PCI treated patients in NOBLE contributed to the better composite outcome with CABG in NOBLE. This finding is difficult to explain but may have been related to discontinuation of dual antiplatelet therapy at 1 year. In EXCEL, the rates of stroke at 3 years were comparable between PCI and CABG [8••].

The divergence of outcome curves between PCI and CABG often becomes evident in later years, when the incidence of de novo lesions increases. This results in higher MI and RR in patients treated with PCI. On the other hand, saphenous vein graft degeneration is a continuous process and this may influence even longer term (10 years) follow-up. Longer term follow-up of the NOBLE and EXCEL might be important in understanding the relative strengths and weaknesses of PCI and CABG for LM disease.

Post NOBLE and EXCEL Meta-analyses

Giacoppo et al. conducted a meta-analysis of 4 RCTs: SYNTAX-LM cohort, PRECOMBAT, NOBLE, and EXCEL [17]. Comparable rates of the composite outcome of all-cause death, MI and stroke at the longest available follow-up were noted in the PCI and CABG groups (HR 1.06, 0.90–1.24, $p = 0.48$). The highest relative weight in this meta-analysis was from the EXCEL trial. A moderate degree of heterogeneity was noted, due to NOBEL, which was the only trial favoring CABG. PCI was associated with a significantly higher risk of RR compared with CABG (HR 1.70, 1.42–2.05, $p < 0.001$), with no difference in RR risk between DES1 and DES2. Palmerini et al. performed a meta-analysis of six RCTs comparing outcomes between PCI with DES2 and CABG with a total of 4686 patients [18]. Similar to the findings of EXCEL, PCI was associated with significantly better 30-day outcomes compared with CABG: all-cause death or MI (OR 0.69, 0.49–0.98, $p = 0.04$), and stroke (OR 0.36, 0.16–0.82, $p = 0.007$). A significant interaction was noted between time and treatment effect, and PCI associated with lower MI and stroke in the first 30 days and CABG associated with lower MI and RR thereafter [18]. At a median follow-up of 39 months, there was no difference in individual outcomes of all-cause death, cardiac death, or stroke. A significant interaction was also noted between cardiac death and RR with the SYNTAX score, such that the upper SYNTAX score tertile (> 33) was associated with increased cardiac mortality and RR with PCI. One strength of this meta-analysis was that there was no significant heterogeneity noted between trials for the long-term outcomes of all-cause or cardiac mortality [18]. Sardar et al. performed another comprehensive meta-analysis of data from five RCTs (one additional study was included to the previous meta-analysis) comparing PCI with DES versus CABG for ULMCA stenosis and demonstrated a similar risk of all-cause mortality, cardiovascular death, MI, stroke, and the combined risk of death, MI, or stroke (MACE) in the 2 treatment groups [19]. However, the risk of any revascularization or TVR was significantly higher in the PCI with DES group [19]. Another recently published meta-analysis using individual patient level data on 11,518 patients from 11 trials, of which 4478 patients had ULM disease, demonstrated no benefit of CABG over PCI in a 5-year mortality (HR 1·07, 0.93–1.91; $p = 0.65$) [20]. Interestingly, the presence of diabetes and the SYNTAX score did not influence 5-year outcomes in the ULM group [20].

Impact of DES Generation

PCI outcomes have improved significantly from the DES1 era to the current era of DES2. In the EXCEL trial, stent thrombosis was noted in only 0.7% of cases and was lower than the rate of symptomatic saphenous vein graft occlusion [7••, 8••]. In contrast, stent thrombosis with DES1 use was high and similar to rates of saphenous vein graft occlusion in the SYNTAX trial [12•]. Stent thrombosis rate associated with the biolimus-eluting stent in NOBLE was also significantly higher at 3% compared with EXCEL in which a thinner-strut stent was used [7••, 8••]. However, DES2 have not had a significant impact on the rate of RR following ULM PCI. In the meta-analysis by Giacoppo, the risk of RR was not influenced by DES generation [17, 18]. This can be hypothesized that RR may be due to progression of de novo disease outside the stented segment. This offers a clear advantage for CABG which bypasses long segments of diseased coronary artery, whereas stents have no effect on de novo lesions.

Left Main Revascularization Guidelines Overview

The 2017 ACC/AHA/SCAI appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease give a class I recommendation for a heart team approach prior to both CABG and PCI in patients with ULM stenosis [21]. Calculation of the SYNTAX score is a class IIa recommendation. PCI for ULM stenosis is a class IIa recommendation if anatomic complexity associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score < 22, ostial or trunk left main stenosis, and clinical characteristics that predict a significantly increased risk of adverse surgical outcomes) (such as STS-predicted risk of operative mortality $\geq$ 5%) are present. A class IIb recommendation is given for PCI if there is bifurcation disease, or a SYNTAX score of 23–32 and CABG morbidity is high or if STS score > 2%. PCI is rated class III or harmful if unfavorable anatomy for PCI is present in patients who are good candidates for CABG. The 2018 ESC guidelines on myocardial revascularization give a class I recommendation for ULM PCI if SYNTAX score < 22, class IIa for SYNTAX score between 23 and 32, and class III for SYNTAX score $\geq$ 33 [22].

Left Main PCI: "The Pearls Are in the Details"

Role of the Heart Team

A heart team approach is recommended by the 2011 ACC/AHA PCI guidelines [23]. In addition to technical feasibility, the likelihood of achieving "complete revascularization" with either approach should be assessed. The 2018 ESC guidelines recommend completeness of revascularization should be prioritized, when considering the decision between CABG and PCI (class I recommendation) [22].

Risk Scores for Decision Making Between PCI and CABG

Both anatomic and clinical scores have been developed and validated to predict outcomes with PCI and CABG, and hence guide decision making. While the SYNTAX score has been extensively validated as a tool of anatomic complexity and predictor of short- and long-term outcomes in patients with ULM stenosis, it does not take into account any clinical variables [24]. The SYNTAX score was not predictive of MACCE in the NOBLE trial. Rather, CABG was associated with better outcomes, compared with PCI, in the sub-group of patients with low SYNTAX score (< 22) and equivalent outcomes in patients with higher scores. This may be because most patients in the NOBEL trial had bifurcation LM stenosis. In such a patient group, the SYNTAX score can be low even in the presence of an isolated complex bifurcation LM stenosis as defined previously. Such patients may have improved outcomes with CABG. This represents a limitation of the SYNTAX score in guiding treatment selection in patients with LM CAD, compared with its utility in patients with non-left main multivessel CAD. This is highlighted by the fact that a variable interaction between SYNTAX score and PCI outcomes was noted in different RCTs. In the SYNTAX trial and the meta-analysis by Palmerini et al., significant differences were noted in PCI outcomes based on the SYNTAX score tertiles, whereas no interaction was noted in PRECOMBAT, EXCEL, and NOBLE. Other risk scores which take clinical variables into account in addition to anatomic variables in the SYNTAX score have been developed and validated. These include the SYNTAX II, Clinical SYNTAX Score (CSS), and the Global Risk Score [25–27]. The SYNTAX score II adds clinical factors, namely gender, age, chronic obstructive pulmonary disease, peripheral vascular disease, left ventricular ejection fraction (LVEF), and creatinine clearance to the SYNTAX score [25]. Diabetes is an important co-morbidity which favors CABG over PCI in multivessel CAD but is not associated with a significant effect on 5-year mortality for LM disease in the absence of significant multivessel CAD [28].

Role of Intravascular Ultrasound and Fractional Flow Reserve

In a study comparing IVUS and fractional flow reserve (FFR), an IVUS-derived minimum cross-sectional area (MLA) < 5.9 mm^2 correlated with an ischemic FFR [27, 29]. Therefore, in most cases, a MLA $\geq$ 6 mm^2 indicates that LM revascularization can be safely deferred. An MLA < 4.5 mm2 has been proposed to indicate a significant stenosis in the case of an isolated ostial or shaft stenosis [30]. FFR can also be used in place of IVUS to determine if significant flow limitation is present, and a value of 0.80 or lower is abnormal. The details on technical issues and interpretation are beyond the scope of this review. Briefly, in the presence of the downstream branch stenosis in addition to LM stenosis, placing the FFR wire into a non-stenotic branch vessel will allow measurement of the true FFR as long as the stenosis in the other branch vessel is not severe. [31]. However, in case of ambiguity, the LM MLA can be assessed with IVUS to guide decision making.

ULM PCI—Technical Issues

The details of how to perform ULM PCI are key to optimal outcomes [16, 32]. However, a complete discussion of this topic is beyond the scope of this review. The 2018 ESC guidelines provide a class IIa recommendation for an annual operator volume for left main PCI of at least 25 cases per year [22]. The DK-CRUSH V study showed lower rates of target vessel failure, target vessel MI, and stent thrombosis in 482 patients, with true bifurcation lesions of the distal LM, randomized to DK-CRUSH versus provisional stenting (PS) [33]. Absolute benefit of the two-stent approach was greater in patients with complex LM bifurcation stenosis compared with simpler lesions. The most recent consensus statement from the European Bifurcation Club recommends a provisional approach for the side branch in most cases of distal LM bifurcation lesions [34]. The DK-CRUSH technique has shown superior outcomes compared with culotte or provisional stenting in patients with true LM bifurcation lesions [33, 35]. DK-CRUSH technique is preferred over provisional T-stenting in true LM bifurcation with a class IIb recommendation in the 2018 ESC guidelines [22]. The EBC MAIN trial is highly anticipated among ULM PCI operators. The hypothesis is that the single stent provisional approach is better than planned two-stent approach [36]. Regardless of the technique, stent optimization by using pre- and post-PCI IVUS, and ensuring adequate minimum stent cross-sectional area using a proximal optimization technique and final kissing balloon inflation (FKBI) in cases of a two-stent strategy, is mandatory for improved outcomes. Selection of an appropriately sized stent with high-pressure post-dilatation is key in LM ostium stenosis. IVUS guidance was associated with a significant improvement in a 3-year mortality compared with angiographic

guidance in propensity-matched patients [37, 38]. Finally, risk assessment to determine the safety of PCI is crucial. Adequate hemodynamic support should be considered prior to complex distal left main PCI, especially in the presence of an occluded or non-dominant right coronary artery, left ventricular ejection fraction $\leq 35\%$, multivessel CAD, need for atherectomy, or significant comorbidities that may lead to hemodynamic instability during procedure.

Conclusions

Favorable outcomes of ULM PCI with newer generation DES may affect treatment decisions of CABG versus PCI. CABG offers the advantage of bypassing long segments of disease. In patients treated with PCI, de novo lesions outside the stented segments can lead to recurrent MI and the need for RR. Higher rates of residual angina in patients treated with PCI can also contribute to higher rates of repeat revascularization. Despite these limitations, excellent outcomes can be achieved with PCI, in properly selected patients with ULM stenosis. Advances in stent design and technology (such as newer generation DES) and PCI technique (high-pressure stent deployment and IVUS guidance) have contributed to the improved efficacy of PCI. Improved safety, with low 30-day mortality ($< 0.5\%$) and procedural MI (5%), have been reported with PCI in RCTs. The availability of mechanical circulatory support devices, although less extensively studied in these trials (only 5.2% of patients in Excel trial received mechanical circulatory support), may also improve the safety of PCI in this setting. At the same time, surgical techniques have also improved as reflected by lower rates of stroke and death in a more contemporary trial like EXCEL. A heart team approach with appropriate patient selection, careful assessment of LM lesions, and meticulous procedural technique makes PCI a viable option for ULM stenosis. With advances in stent technology and deployment techniques in complex and high-risk ULM disease, further studies are needed to validate the current optimism for PCI as a valid alternative to CABG or perhaps as part of a hybrid revascularization strategy with CABG.

Compliance with Ethical Standards

Conflict of Interest Yasir Taha, Rajan A.G. Patel, Jayant Bagai, Rajesh Sachdeva, Gautam Kumar, and Timir K. Paul declare that they have no conflict of interest.

Anand Prasad reports the following: Speaker: AstraZeneca, Abiomed, Gilead; Consultant: Osprey Medical, GE; Research: ACIST Medical, Medtronic.

Sandeep Nathan has served as a consultant for Medtronic, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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