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Management of Left Main Coronary Artery Disease

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Left main coronary artery disease (LMCAD) portends higher prognostic risk as a result of the large myocardial territory at risk, ranging from 75% to 100%, depending on the dominance of the left coronary circulation. Diagnosis and management of significant LMCAD continues to be a source of clinical apprehension and uncertainty. LMCAD is not uncommonly found in stable patients undergoing coronary angiography and is often associated with concomitant coronary artery disease (CAD). Current clinical practice guidelines from both the American College of Cardiology/American Heart Association and the European Society of Cardiology recommend revascularization for all patients with ≥50% stenosis of the left main coronary artery (LM), regardless of symptomatic status or associated ischemic burden.[1] The anatomic extent and complexity of CAD are major factors in deciding on the best management approach of LMCAD. For example, isolated LMCA lesions involving the ostium or shaft do well with either percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). However, distal LM bifurcation lesions or those associated with complex multivessel disease may do better with surgical revascularization. Other key elements of consideration include surgical operative risk, left ventricular function, acuity of clinical presentation, likelihood of achieving complete revascularization, and patients' informed preference.

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Medical Management of LMCAD

The use of guideline-directed secondary prevention and lifestyle interventions should be implemented and encouraged for all patients with LMCAD just as they are indicated for patients with non-LM CAD. In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial,[2] similar outcomes were observed for an initial strategy of optimal medical therapy compared with initial revascularization in patients with stable non-LM CAD. The safety of deferred revascularization in patients with stable LM disease is less well known, but current clinical practice guidelines strongly recommend revascularization in all patients with ≥50% stenosis of the LM.[1] The basis for these class IA recommendations is predicated on post hoc data derived from subgroup analyses of 185 patients with LM disease from 2 randomized clinical trials (RCTs) of patients with chronic stable angina conducted in the late 1970s and early 1980s[3,4] demonstrating the superiority of surgical revascularization over medical therapy on 5- to 10-year survival.[5–9] These early RCTs were conducted in an era when medical therapy was, by contemporary standards, limited. For example, only 66% of "medically managed" patients with LM in those early trials received β-blockers and only 19% were taking aspirin. These trials antedated the current widespread use of disease-modifying pharmacologic interventions (such as statins, inhibitors of the renin-angiotensin-aldosterone system, and more effective antiplatelet agents such as P_2Y_{12} inhibitors), which reduce adverse cardiovascular events in patients with CAD.[2,10–15]

Patients with LM disease are not a homogenous group. In fact, even antedating our current era of evidence-based optimal medical therapy, those with 50% to 70% LM stenosis or with preserved left ventricular (LV) function were found to have more favorable survival while receiving medical management alone (66% 3-year survival) compared with more severe LM disease >70% (41% 3-year survival) or with reduced LV function.[5,7] Even these older studies from 30 to 40 years ago were able to identify patients with LM disease who were at a relatively lower risk with medical therapy compared with patients with high-risk features such as >70% LM stenosis, poor LV function, elevated LV end-diastolic pressure, or prior myocardial infarction (MI).[5,7] Moreover, Conley et al[5] reported

that the 1-year survival rate of patients with nonrevascularized left main stenosis ≥70% ranged between 50% and 62% in those with a history of congestive heart failure, resting chest pain, resting ST-T–wave changes, LV dysfunction, or LV end-diastolic pressure >15 mm Hg, as compared with a survival rate ranging from 81% to 95% in the absence of these clinical variables.[5] However, the more favorable outcomes in these "lower-risk" groups reflected the abysmal outcomes of more severe LM disease or comorbidities (>50% death rate over 3–4 years).[5,7] The absolute risks in even the lower-risk categories (20–30% death rate over 3–4 years) makes even the most courageous physician nervous about deferring revascularization based on these clinical and angiographic characteristics alone regardless of significant advances in modern guideline-based medical therapy. Most contemporary large RCTs assessing clinical outcomes from medical versus revascularization therapy have excluded patients with LMCAD by design. Thus, it remains unproven whether optimal medical therapy may be a safe and appropriate therapeutic alternative to revascularization in certain, select subsets of lower-risk patients with stable LM CAD. Part of the obstinacy of our guidelines for LM disease is likely related to our poor ability to discriminate significant from nonsignificant LM disease from angiographic and clinical characteristics. Increasingly, newer invasive techniques are now being employed to help guide decision-making regarding revascularization therapies for LM disease.

Contemporary Evaluation of LMCAD

Most patients with significant LMCAD are symptomatic given the large myocardial territory it subtends. Nonetheless, angiographically significant LMCAD is incidentally found not so infrequently in stable patients undergoing coronary angiography. In the absence of critical LM stenosis or corroborating clinical presentation, the hemodynamic significance of incidental or intermediate LM lesions warrants further consideration. The reliance of our current clinical practice guidelines on angiographic lesion severity as the sole determinant of risk and the de facto threshold for CABG surgery decision-making is outdated in the current era of clinically proven noninvasive and invasive modalities in determining the functional and prognostic significance of angiographically challenging coronary lesions. In particular, visual estimates of intermediate LM stenoses (30–70%) from coronary angiography have significant interobserver variability.[16] Conversely, the reproducibility and accuracy of the angiographic assessment of LM stenosis ≥70% is excellent.[16,17] Thus, revascularization strategies based solely on the angiographic appearance of LMCAD stenosis of intermediate severity (between 50% and 70%) may be inappropriate. Aside from the unwarranted surgical risk, premature CABG for potentially noncritical lesions may ultimately be harmful to patients because of low graft patency rates in this setting and up to a 6-fold higher rate of accelerated obstruction of bypassed native coronary vessels, which renders subsequent PCI of native vessels technically challenging, if needed, for symptom relief.[18]

Noninvasively, certain high-risk features are suggestive of significant LM or equivalent disease, including: (1) Duke treadmill score ≤11, (2) stress-induced sustained ventricular tachyarrhythmia or nonsustained ventricular tachyarrhythmia >30 seconds or ST-segment elevation, (3) exercise LV ejection fraction ≤35%, (4) large reversible anterior perfusion defect (≥10% LV involvement on nuclear perfusion or ≥12.5% LV involvement on cardiac MRI) or multiple reversible perfusion defects of moderate size, (5) stress-induced LV dilation or increased lung uptake in the setting of moderate perfusion defect or large fixed perfusion defect, or (6) echocardiographic wall motion abnormality involving >2 segments developing at a low-dose dobutamine (≤10 mg/kg per minute) or at a low heart rate (<120 beats per minute).[19]

Invasively, more detailed evaluation of the anatomic severity and hemodynamic significance of clinically ambiguous LM lesions can be obtained by intracoronary imaging with intravascular ultrasound (IVUS) imaging or physiologically with pressure wire assessment of fractional flow reserve (FFR).

Use of Intracoronary Imaging in the Evaluation of Myocardial Ischemia in LM Lesions

The use of IVUS is particularly helpful in the determination of plaque extent and characteristics within the LM, as well as in determining ostial involvement of daughter branches. IVUS can provide an estimate of the ischemic burden of the LM lesion, and its use following LM PCI improves clinical outcomes.[20,21] In the multicenter prospective LITRO study[22] of intermediate LM stenosis between 25% and 60%, deferring revascularization of LM lesions with minimal luminal area (MLA) of ≥6 mm^2 (53% of lesions) was safe and associated with favorable outcomes at 2 years of follow-up (cardiac death-free survival of 97.7%). The disagreement between angiography and this IVUS criterion for a significant stenosis was substantial. One third of patients with an insignificant angiographic stenosis of <30% had an MLA of <6 mm^2, whereas 43% of patients with angiographic LM stenosis ≥50% had a prognostically favorable MLA of ≥6 mm.[22] Moreover, a cutoff value of 6.0 mm^2 also agrees with a theoretical value derived from fractal geometry. A study confirmed that the linear law was more exact than the Murray's law that largely underestimated the calculated mother-vessel diameter. Using the currently established 3.0 mm^2 as the best cutoff MLA for

the LM branches, the calculated LM-MLA cutoff by linear law was 5.8 mm.[23]

Although IVUS is good at describing the anatomical extent of disease, the LM-MLA cutoff for determining a functionally significant lesion differs between populations and thus these values need to be interpreted with caution. In a Korean study, the MLA cutoff for FFR <0.80 was 4.5 mm^2 with a sensitivity of 77% and a negative predictive value of 75%,[24] whereas another US study yielded a cutoff value of 5.9 mm^2 with a sensitivity and specificity of 93% and 94%, respectively, for an FFR <0.75.[25] The most plausible explanation for this discrepancy appears to relate to differences in the reference size of the coronary arteries. For example, the average LM-MLA in patients in the Korean study was 4.8 mm^2 versus 7.6 mm^2 in the US study. Another study comparing LM lesions between 99 white North American and 99 Asian patients showed that Asian patients had a significantly smaller LM-MLA (5.2 ± 1.8 mm^2 versus 6.2 ± 1.4 mm^2, respectively; $P<0.0001$).[26]

The other value of IVUS is to ensure stent optimization of LM PCI. IVUS can ensure adequate expansion and apposition of stents after LM PCI, which improves clinical outcomes following LM PCI, particularly in patients with distal LM lesions and those treated with a 2-stent strategy.[20]

Optical coherence tomography is another intracoronary imaging modality that is often employed for lesion characterization and PCI guidance in non-LMCAD, particularly given its higher resolution imaging. As compared with IVUS, optical coherence tomography is a light-based technology that requires a contrast flush to clear the blood column, which makes imaging of aortic ostial lesions in the LM challenging. Another drawback of optical coherence tomography use in LM imaging is its limited penetration depth (2–3 mm) as compared with IVUS (4–8 mm), given that the average LMCA diameter is 3.5 to 4.5 mm. Finally, literature regarding clinical outcomes or correlation with physiology for optical coherence tomography in LMCAD is lacking.

Use of FFR in the Evaluation of Myocardial Ischemia in LM Lesions

Whereas IVUS is a better tool for determining the anatomical extent of disease, FFR is a better tool for assessing the hemodynamically significance of an LM stenosis. A poor correlation was noted between quantitative coronary angiography and FFR, which further highlights the shortcomings of reliance on angiography alone in evaluating LM lesions.[17] Similar to non-LM lesions, angiographically intermediate LM lesions with an FFR of ≥0.80 can have revascularization deferred with favorable long-term outcomes.[17] The use of instantaneous wave-free ratio (iFR) is well established in non-LM lesions based on the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation)[27] and iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome)[28] trials, which both showed similar favorable outcomes by deferring revascularization of lesions with an iFR of >0.89. However, specific outcome studies evaluating iFR in LMCAD are warranted before iFR is liberally adopted as the sole determinant of revascularization in patients with intermediate LM lesions.

Although IVUS and FFR correlate well,[29] there are limitations to both techniques that may favor one modality over the other. For example, IVUS area measurements may be limited by distortion caused by minor differences in the rotational speed of the imaging element, a noncoaxial orientation of the catheter, or extensive arterial calcification. On the other hand, FFR may be limited by the frequent presence of significant downstream stenoses, which may underestimate or overestimate the hemodynamic significance of the LM lesion. However, this is of more concern when there is severe disease present in both the left anterior descending and circumflex arteries. Fearon et al[30] showed that when only one major branch of the left main has severe disease, downstream disease does not have a clinically relevant impact on the evaluation of intermediate LM stenosis with the pressure wire placed in the nondiseased branch. Based on their findings, if the FFR of the LM is either ≤0.80 or >0.85, then it can be assumed that the LM lesion is hemodynamically significant or insignificant, respectively. However, if the FFR is between 0.81 and 0.85, then the hemodynamic significance of the LM lesion cannot be accurately determined if the combined FFR of the LM and the downstream disease is ≤0.45.[30] In such situations, IVUS guidance is preferred.[20,21] Accordingly, in the modern era of contemporary CAD decision-making, an invasive assessment of stenosis severity is certainly complementary to a purely angiographic assessment and may be superior.[31]

Revascularization of LMCAD

Existing clinical practice guidelines continue to advocate CABG surgery as the singular class I indication for myocardial revascularization. However, more recent RCTs and registry studies in LM CAD support PCI as a reasonable alternative in select patients with less complex LM anatomy. Currently, in the US guidelines, PCI has a class IIa recommendation ("is reasonable") in select patients with isolated LM stenosis involving the ostium or shaft and without coexisting multivessel disease and the risk of surgical bypass is increased.[1] PCI has a class IIb recommendation ("may be reasonable") in patients with LM

stenosis involving the distal bifurcation or with less complex coexisting multivessel disease as defined by a low or intermediate SYNTAX score (≤33) and who have an elevated surgical risk. The current US guidelines recommend against PCI in patients who are good candidates for surgical bypass with coexisting complex multivessel disease as defined by highest tertile of the SYNTAX score (≥33).[1]

The guidelines are based primarily on the hypothesis-generating findings of the prespecified and powered subgroup of patients with LMCAD in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial,[32–34] with consideration of other smaller randomized trials that were underpowered to provide a conclusive answer on the optimal revascularization strategy including the LE MANS (Left Main Coronary Artery Stenting) trial (n=100; bare-metal stents [BMS])[35–37] and PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial (n=600; sirolimus-eluting stents).[38,39] The absence of conclusive evidence motivated the conduct of 2 large RCTs comparing CABG and PCI for LM revascularization (EXCEL [Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization] trial[40] and NOBLE [Nordic-Baltic-British Left Main Revascularization Study][41]), both of which have been recently published but not reflected in the guidelines as of yet. The Table summarizes key elements of the main RCTs comparing CABG and PCI for revascularization of LMCAD. Most have demonstrated similar intermediate and long-term outcomes of mortality or MI, albeit with consistently higher rates of repeat revascularization with PCI. Some demonstrated improved long-term survival with CABG in a select group of higher-risk patients attributable to complex coronary anatomy[33,34] or patients with diabetes mellitus and an LM equivalent of 3-vessel CAD.[42] In fact, no dedicated RCT has compared outcomes of PCI versus CABG for LMCAD specifically in patients with diabetes mellitus. In subgroup analyses of the LM RCTs, patients with diabetes mellitus had similar outcomes with PCI compared with CABG, although none of the studies were powered to show a difference. The prespecified subgroup analysis of patients with diabetes mellitus in the SYNTAX trial (including LM and 3VD) showed significantly higher rates of repeat revascularization with PCI but no difference in the composite of all-cause death, stroke, or MI.[43] Patients with LV dysfunction are another high-risk group for which data are lacking with respect to the optimal mode of revascularization, as they have been excluded from most large randomized trials of LM or equivalent CAD. Nonetheless, evidence from older trials demonstrated a clear survival advantage of revascularization over medical management in patients with LM with LV dysfunction.[5]

Hybrid bypass is another revascularization approach that combines coronary bypass using a minimally invasive direct coronary artery bypass approach of grafting the LIMA to LAD artery and PCI to the remaining vessels in an attempt to achieve the most desired aspects of each revascularization strategy.[45] While evidence in support of this hybrid approach is limited, ongoing large randomized trials such as the National Institutes of Health–funded HYBRID (Hybrid Coronary Revascularization) trial (ClinicalTrials.gov Identifier: NCT03089398) should shed further light on the theoretical benefit of this revascularization strategy.

The Heart Team Approach

Regardless of which method of revascularization is used, current guidelines stress the importance of a “heart team” approach to management of complex coronary disease including left main disease. The heart team weighs the risks and benefits of PCI, surgery, or medical treatment alone, taking into account the patient’s informed preference. Such teams typically include an interventional cardiologist, a cardiac surgeon, and a noninvasive physician to determine the appropriate management plan. The complexity and extent of coexisting CAD with the intention of achieving complete revascularization should be adequately considered in any discussions by the heart team and the patient. Major adverse cardiovascular events including mortality are higher in patients with incomplete revascularization than those with complete revascularization regardless of the revascularization strategy.[46] This may explain the findings of SYNTAX demonstrating improved outcomes with CABG in patients with more complex coronary anatomy, since complete revascularization was achieved more frequently with CABG than with PCI in SYNTAX and other studies.[34]

Several risk models are used in clinical decision-making to predict the relative impact of specific risk factors on outcomes with cardiac surgery. While none of these risk models are inclusive of all potential risk characteristics, they do offer general estimates of associated operative morbidity and mortality that help the heart team in selecting the best management option for a specific patient and to counsel patients accordingly. The most widely used surgical risk score in the United States is the Society of Thoracic Surgeons score.[47] It classifies operative risk based on predicted risk of mortality into low (<4%), intermediate (4% to <8%), high (8% to <12%), or extreme (≥12%). The heart team is particularly imperative in weighing the risks and benefits of surgery in the high- and extreme-risk population. Additional clinical factors that are not included in most risk models also need to be considered by the heart team in making management recommendations including frailty metrics, cognitive status, surgical recovery and social support, quality of life, life

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Table. Left Main Randomized Clinical Trials of PCI vs CABG in Perspective

	LE MANS[35,37]	Boudriot[44]	PRECOMBAT[38,39]	SYNTAX[32–34]	EXCEL[40]	NOBLE[41]
	Poland	Germany	North Korea	Europe/United States	United States/Europe	Northern Europe
Diabetes mellitus prevalence, %						
PCI	19	40	34	26	30	15
CABG	17	33	30	24	28	15
LVEF, %						
PCI	54 (SD=117	65 (55–70)	62 (SD=8)	N/R	57 (SD=10)	60 (55–65)
CABG	54 (SD=7)	65 (55–68)	61 (SD=9)		57 (SD=9)	60 (52–64)
Sample size, No.	105	201	600	705	1905	1201
LM disease severity	≥50% Angiography only	≥50% Angiography only	≥50% Angiography only	≥50% Angiography only	≥70% Angiographically, or 50% to 69% and hemodynamically significant	≥50% angiographically, or FFR ≤0.80
Distal LM stenosis, %						
PCI	56	74	67	58	82	81
CABG	60	69	62	64	79	81
LM disease+3VD, %						
PCI	60	11	40.7	35.1	17.2	N/A
CABG	75	17	41.0	38.1	19.4	N/A
Average SYNTAX						
PCI	25.2+8.7	24.0 (19–29)	24.4	30.2+12.7	26.9+8.8	22.5+7.5
CABG	24.7+6.8	23.0 (14.8–28)	25.8	29.6+13.5	26.0+9.8	22.4+8.0
Composite end point	Death/MI/CVA/TVR	Death/MI/ revascularization	Death/MI/CVA/TVR	Death/MI/CVA/TVR	Death/MI/CVA	Death/MI/CVA/TVR
Follow-up (longest)	10 y	1 y	5 y	5 y	3 y	3 y
Composite outcome	Noninferior (52.2% vs 62.5%)	Inferior (19% vs 13.9)	Noninferior (17.5% vs 14.3%)	Noninferior (36.9% vs 31%)	Noninferior (15.4% vs 14.7%)	Inferior (28% vs 18%)
Death	Noninferior (21.6% vs 30.2%)	Noninferior (2% vs 5%)	Noninferior (5.7% vs 7.9%)	Noninferior (12.8% vs 14.6%)	Noninferior (8.2% vs 5.9%)	Noninferior (11% vs 9%)
Stroke	Noninferior (4.3% vs 6.3%)	N/R	Noninferior (0.7% vs 0.7%)	Superior (1.5% vs 4.3%)	Noninferior (2.9% vs 2.3%)	Noninferior (5% vs 2%)
MI	Noninferior (8.7% vs 10.4%)	Noninferior (3% vs 3%)	Noninferior (2% vs 1.7%)	Noninferior (8.2% vs 4.8%)	Noninferior (8.3% vs 8.0%)	Inferior (6% vs 2%)
Revascularization	Noninferior (26.1% vs 31.3%)	Inferior (14% vs 5.9%)	Inferior (13% vs 7.3%)	Inferior (26.7% vs 15.5%)	Inferior (12.9% vs 7.6%)	Inferior (15% vs 10%)

Continued

Table. Continued

	LE MANS[35,37]	Boudriot[44]	PRECOMBAT[38,39]	SYNTAX[32–34]	EXCEL[40]	NOBLE[41]
IVUS	Recommended	Infrequent	At discretion 91%	Infrequent	Recommended 77%	Recommended 74%
FFR guidance	N/R	N/R	N/R	Infrequent	Recommended 9.0%	Recommended
Stent for PCI group	BMS DES only if ≤3.8	SES	SES	PES	EES	BES First-generation DES (7.7%)
LIMA use in CABG group, %	72	99	94	N/R	99	96
Off pump, %	1.9	46	64	N/R	29	16

3VD indicates 3-vessel coronary artery disease; BES, biolimus-eluting stent; BMS, bare-metal stent; CABG, coronary artery bypass graft surgery; CVA, cerebral vascular accident; DES, drug-eluting stent; EES, everolimus-eluting stent; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LIMA, left internal mammary artery; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not available; N/R, not required; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SD, standard deviation; SES, sirolimus-eluting stent; TVR, target vessel revascularization. Please refer to text for complete trial names.

expectancy, patient's preference and religious beliefs, and any potential concerns regarding tolerance or adherence with long-term dual antiplatelet therapy. An algorithm for managing patients with LM disease by the heart team is suggested in Figure 1.

PCI Technical Considerations

The heart team may also discuss procedural aspects of PCI and its likelihood of achieving complete revascularization if this is recommended. Even though not supported by conclusive data, the use of hemodynamic support may offer a safety net that allows for safe and complete revascularization in patients at highest risk. Most experts agree that hemodynamic support should be strongly considered in patients with reduced ejection fraction, decompensated hemodynamics (elevated end-diastolic LV pressure >20 mm Hg, systolic blood pressure <100 mm Hg, or mixed venous oxygen saturation <55%), or expected prolonged ischemic time caused by complexity of disease and/or need for atherectomy.[48]

Drug-eluting stents are preferred for LM revascularization as they offer improved survival and fewer adverse cardiovascular events compared with BMS, particularly when guided by IVUS imaging.[21,36] Although the majority of LMCAD involves the distal bifurcation, randomized trials specifically addressing the optimal PCI revascularization technique in these lesions are scarce.[49] Generally, provisional stenting has been advocated as the preferred approach in bifurcation lesions, as it is technically simpler with at least similar outcomes to a systematic 2-stent strategy.[50–52] However, this was challenged recently by the randomized DKCRUSH-II (Randomized Study on Double Kissing Crush Technique Versus Provisional Stenting Technique for Coronary Artery Bifurcation Lesions),[53] which included ≈17% LM lesions, showing that a 2-stent strategy using the double kissing (DK) crush technique (Figure 2) is superior to provisional stenting particularly in more complex lesions. More recently, a dedicated randomized trial comparing DK crush technique with provisional stenting for left main distal bifurcation lesions (DKCRUSH-V) demonstrated lower rates of target lesion failure with DK crush technique at 1 year (5% versus 10.7%, P=0.02) and stent thrombosis (0.4% versus 3.3%, P=0.02).[54] In DKCRUSH-III, the same investigators showed the superiority of the DK crush technique over culotte at 3 years with significantly lower rates of major adverse cardiac events (8.2% versus 23.7%, P<0.001) and stent thrombosis (0% versus 3.7%, P=0.007).[55] Notably, in the recent NOBLE trial, 87.7% of LM PCI involved the distal bifurcation, of which 63.3% underwent a provisional strategy, 23.9% had culotte stenting, and only 4% underwent LM stenting using the crush technique. Whether a dedicated RCT of PCI versus CABG using the DK crush technique preferentially for distal LM bifurcation stenting

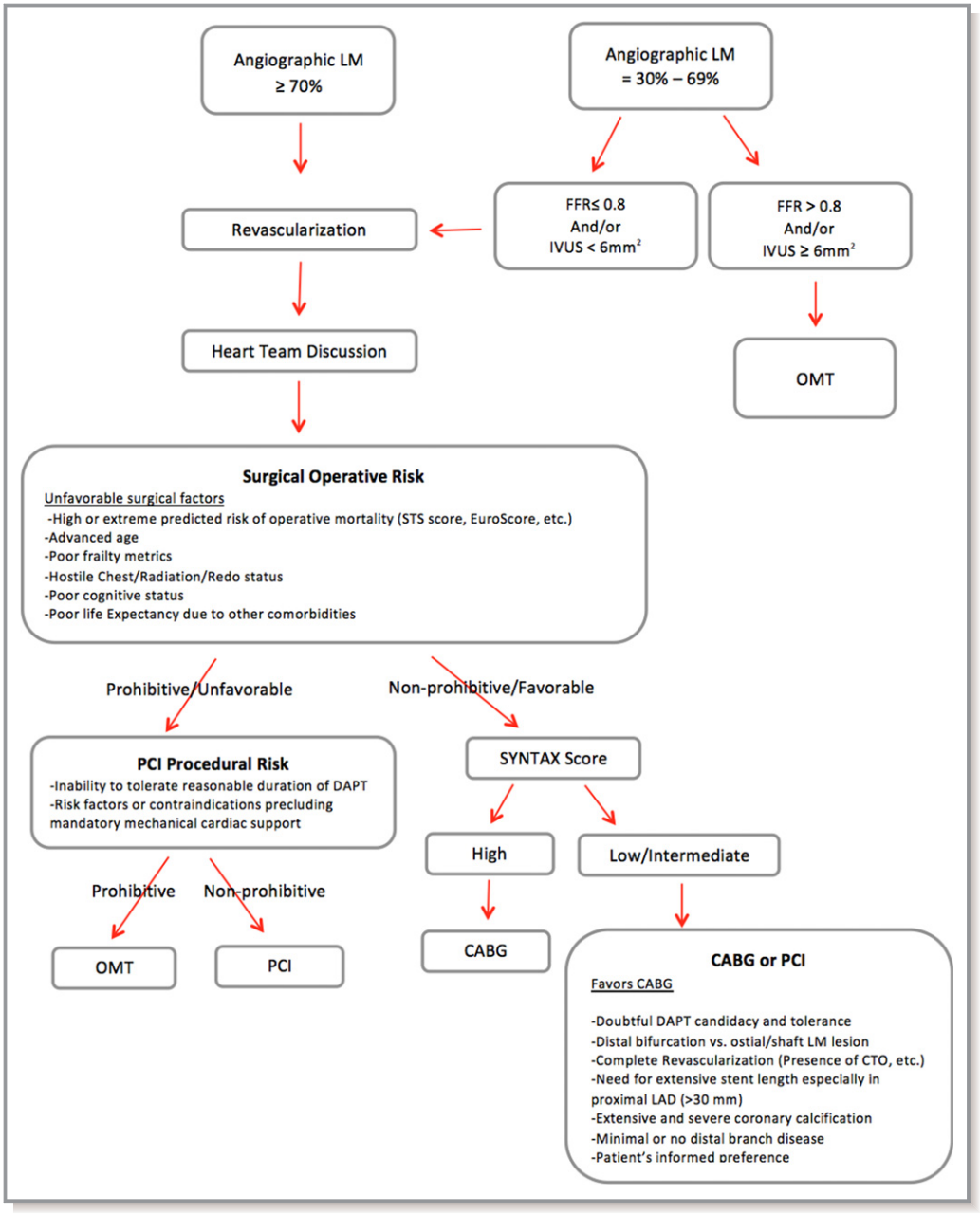

Figure 1. Proposed algorithm for heart team management of left main coronary artery (LM) disease. CABG indicates coronary artery bypass graft surgery; CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.

would demonstrate superior outcomes with PCI is thought-provoking.

Regardless of the revascularization strategy, emphasis should be placed on employing techniques shown to improve outcomes with either strategy, along with adherence to optimal medical management and lifestyle habits. Noteworthy, neither off-pump CABG[56] nor the use of bilateral internal mammary arteries[57] has been shown to improve CABG outcomes in RCTs.

RCTs of LM Revascularization

The Table summarizes the main RCTs of CABG versus PCI for LM revascularization (detailed description in Data S1). Patients had a low prevalence of diabetes mellitus compared with other PCI studies (15–30% of patients), were defined by ≥50% LM stenoses, had generally preserved left ventricular ejection fraction, and 60% to 80% had distal left main lesions. Important differences include the use of IVUS to optimize

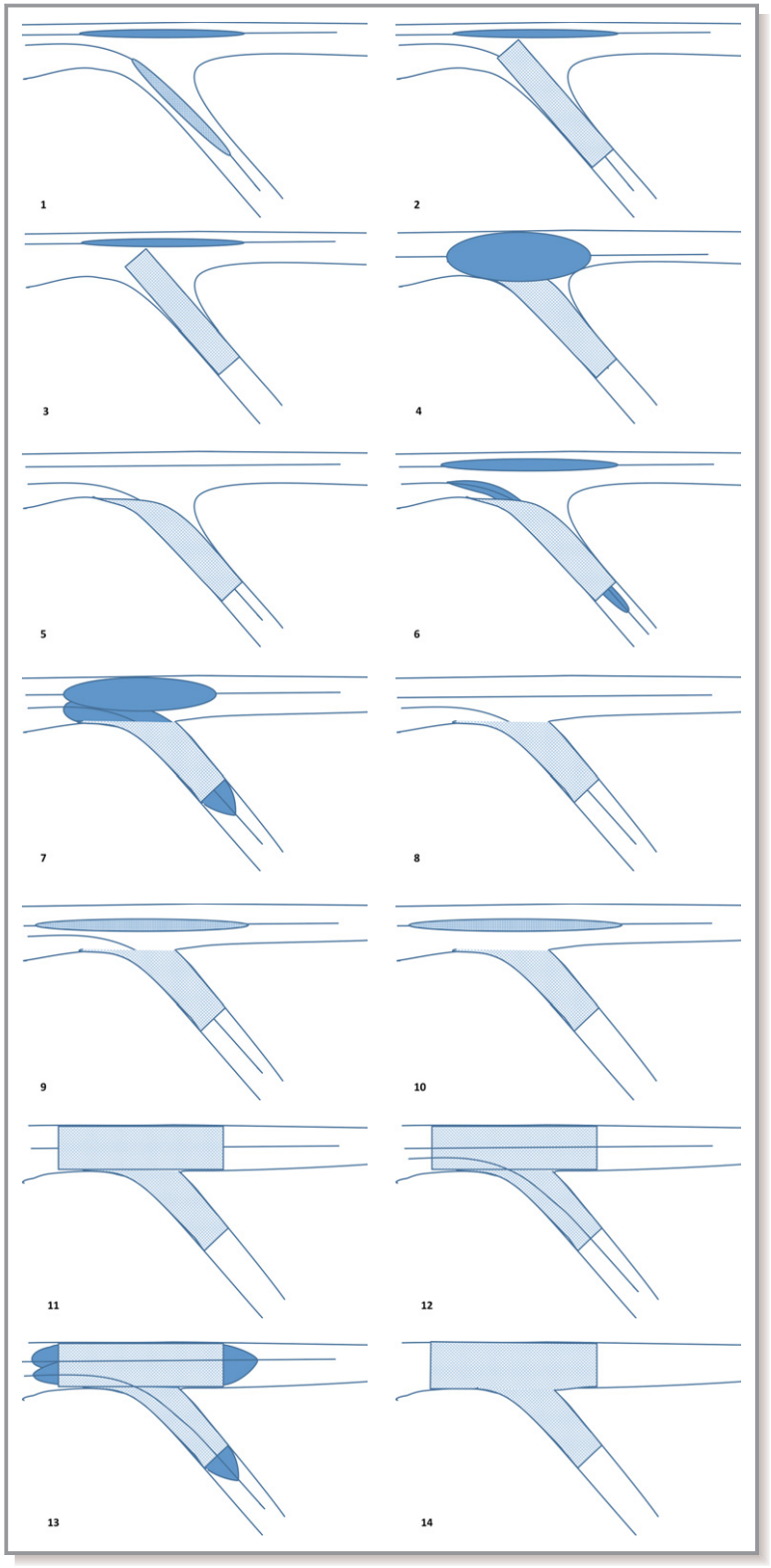

Figure 2. Step-by-step illustration of the double kissing crush 2-stent bifurcation technique.

stent deployment in the PCI group in the more recent EXCEL and NOBLE trials. Overall, they all demonstrated noninferiority of PCI as compared with CABG with respect to survival, particularly in patients with low to intermediate anatomic complexity. However, increased need for repeat revascularization after PCI continues to be the main advantage of CABG

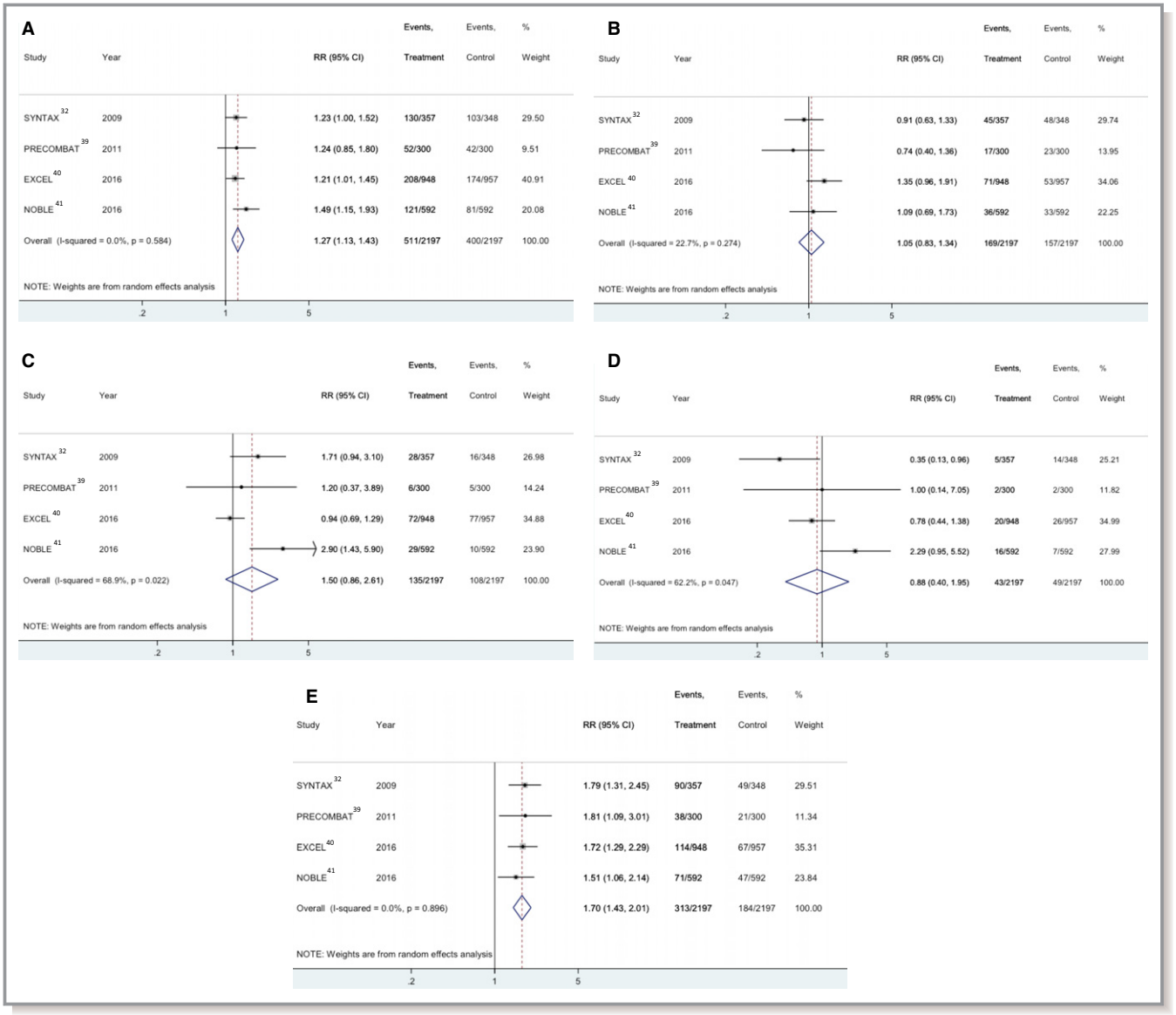

Figure 3. Pooled analyses of randomized controlled trials comparing percutaneous coronary intervention using drug-eluting stents with coronary artery bypass graft surgery in left main coronary artery revascularization. A, Pooled estimates of major adverse cardiac and cerebrovascular events. B, Pooled estimates of death. C, Pooled estimates of myocardial infarction. D, Pooled estimates of stroke. E, Pooled estimates of all repeat revascularization. CI, confidence interval; RR, relative risk. Please refer to text for complete trial names.

over PCI. Their findings are mostly consistent despite their heterogeneity including sample size, stent types, and utilization of adjunct imaging and physiologic guidance. Although there are 6 RCTs of PCI versus CABG, only 4 used drug-eluting stents and had more than 1 year of follow-up. In the LE MANS study,[35–37] 65% of the PCI group were treated with BMS, while in the study by Boudriot et al,[44] data were only presented for up to a year after randomization. Both studies were underpowered for most outcomes, with 105 patients in the LE MANS study and 201 patients in the Boudroit study. The 4 larger trials using drug-eluting stents in the PCI arm and predominantly LIMA grafts in the CABG arm were the SYNTAX, PRECOMBAT, EXCEL, and NOBLE trials. The report from the SYNTAX study is a subgroup analysis of the SYNTAX trial in patients with LM disease.[33,34]

Figure 3 shows pooled odds ratios of the 4 main RCTs employing drug-eluting stents for the end points of major adverse cardiac or cardiovascular risk, all-cause mortality, MI, stroke, and total repeat revascularization. Overall, the studies show an increased risk of major adverse cardiac or cardiovascular end points, driven not by all-cause mortality but by higher rates of MI and revascularization with PCI. However, the pooled estimate for MI had significant heterogeneity, particularly between EXCEL and NOBLE.

With the recent findings of EXCEL and NOBLE, debates have spurred reconciling the apparently disparate findings of these 2 well-conducted trials. However, an in-depth look at their design and findings reveal more consistencies than initially appreciated. Both trials enrolled similar patients but had notable differences that account for the disparate findings. Firstly, the primary end points differed between the 2 studies with repeat revascularization being excluded in EXCEL and periprocedural MI being excluded in NOBLE. Both NOBLE and EXCEL had higher rates of repeat revascularization (Figure 3E) and nonprocedural MI (Figure 3C) in the PCI groups (EXCEL: 4.3% versus 2.7%, P=0.07; NOBLE: 6% versus 2%, P=0.004) and this drove the higher major adverse cardiac or cardiovascular end point risk from PCI. In EXCEL the primary end point was death, stroke, or MI and was similar between the PCI and CABG groups. The superiority of CABG in NOBLE with regards to its composite primary end point was primarily driven by higher rates of total revascularization (15% versus 10%, P=0.03) and nonprocedural MI (6% versus 2%, P=0.004) with PCI. Similarly, EXCEL demonstrated higher rates of repeat revascularization with PCI as compared with CABG (12.6% versus 7.5%, P<0.001) as a secondary end point. The addition of stroke and revascularization for the major adverse cardiac or cardiovascular end points in EXCEL, as shown in Figure 3A, is consistent with NOBLE and higher in the PCI group.

While the rate of MI in EXCEL was similar between PCI and CABG at 3 years (8.0% versus 8.3%, P=0.64), this was primarily driven by higher rates of periprocedural MI with CABG (5.9% versus 3.6%, P=0.02). In fact, nonprocedural MI in EXCEL, the end point used in NOBLE, tended to be higher with PCI at 3 years (4.3% versus 2.7%, P=0.07) in line with the NOBLE findings (Figure 3C). In addition, the longer length of follow-up with NOBLE might have allowed for outcomes in favor of CABG to emerge. The highly anticipated 5-year follow-up data from EXCEL should shed further light on the long-term performance of PCI as compared with CABG, particularly given concerns about a signal of divergence of event curves at 3 years in favor of CABG. Consistent with other studies, mortality did not differ between revascularization strategies in both studies (Figure 3B).

Conclusions

LMCAD is one of the most challenging conditions encountered in clinical practice. Current practice guidelines in support of indiscriminate revascularization of all LM lesions ≥50% are based on older trials in an era when medical therapy was limited and before the use of invasive physiological assessment of stenosis severity. In fact, the same evidence suggests that medical management of patients at lower risk might be associated with favorable outcomes. Although smaller studies support the use of FFR and IVUS to define lower-risk groups with LM disease who could be treated by optimal medical therapy alone, larger trials assessing clinical outcomes over longer follow-up are needed to fully assess this strategy.

Current clinical guidelines strongly recommend surgical revascularization for LMCAD (class IA) with PCI considered a reasonable alternative (class II) in select patients with less complex anatomy (SYNTAX score of <33) and clinical characteristics that predict an increased risk of adverse surgical outcomes.[8] Advances in CABG and PCI techniques assessed in recent randomized trials show that PCI for LMCAD is a safe option with similar long-term survival rates to CABG surgery, particularly in those with low and intermediate anatomic risk.[34,40] However, patients with PCI need close clinical follow-up, as they may have a higher need for repeat revascularization in the future. It is expected that the results of EXCEL and NOBLE will determine the next guidelines for the foreseeable future, as forthcoming trials of this magnitude are unlikely to be pursued from economic and priority viewpoints unless marked advances in revascularization technologies emerge. Importantly, a heart team approach for shared decision-making should be the standard of care for all cases of LMCAD.

Disclosures

None.

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Key Words: coronary artery bypass graft surgery • coronary intervention • coronary revascularization • left main coronary artery disease

SUPPLEMENTAL MATERIAL

Data S1.

Detailed description of the Six Randomized Clinical Trials Comparing PCI with CABG in Left Main Coronary Artery Disease Revascularization.

LE MANS (Study of Unprotected Left Main Stenting Versus Bypass Surgery)

LE MANS was the first study to prospectively compare PCI to CABG in a randomized fashion for revascularization of LMCAD [1, 2]. This study was not powered to address differences in hard endpoints, as major adverse cardiac and cerebrovascular events (MACCE) were secondary endpoints. The study showed significant improvement of LV function with PCI as compared to CABG, which was the primary endpoint of the study. Nonetheless, PCI was associated with a lower risk of MACCE at 30 days and shorter hospitalization. Intermediate- and long-term survival and MACCE rates were similar between PCI and CABG with a trend towards higher MACCE-free survival in the PCI group [2]. Notably, this was a relatively small study of 105 patients treated primarily with BMS (65%) and first generation DES only in those with a reference diameter <3.8 mm (35%). Similarly, arterial grafts were not used consistently with the left internal mammary artery (LIMA) utilized in only 72% of cases. Overall, patients had low to moderate complexity of CAD with a mean SYNTAX score of 25, albeit the majority had distal LM and coexisting multivessel disease (Table 2).

Boudriot et al. [3]

This was a German trial that randomized 201 patients with ≥50% LMCAD to either CABG using predominantly arterial grafts (99% LIMA use) or PCI with sirolimus-eluting stents. The primary composite endpoint was freedom from MACE including death from any cause, MI, and repeat revascularization within 12 months. The average SYNTAX score was approximately 24 with two-third of the lesions involving the distal LM. This study failed to show that PCI was non-inferior to CABG with respect to the primary composite endpoint, mostly driven by higher rate of repeat revascularization in the PCI group. Nonetheless, PCI was non-inferior to CABG with respect to all cause death, MI, or both combined. Not surprisingly, the incidence of MACE in the ostial and shaft LM lesions was 1.0% as compared to 18% in the distal LM lesions within the PCI group and 5.0% versus 8.9% for CABG. An expected but noteworthy finding is that patients who underwent PCI had a significantly shorter total hospital stay (3 versus 13 days, $P<0.001$) and hospital stay after revascularization (1 vs. 8 days, $p<0.001$).

PRECOMBAT Study

PRECOMBAT was a randomized study in a South Korean population comparing PCI with sirolimus-eluting stents to CABG in patients with LMCAD, with a mean SYNTAX score of 25 [4, 5]. Advanced recommended revascularization techniques were encouraged with IVUS used in 91.2% of PCI patients and LIMA to LAD utilized in 93.6% of CABG patients. This study found that PCI was non-inferior to CABG with respect to the composite primary endpoint of mortality, MI, stroke, and revascularization at 1 and 5 years. Stroke

rate were similar between the groups; however, ischemia-driven revascularization was more prevalent in the PCI group as compared to CABG (11.4% vs. 5.5%) even though the systematic performance of follow up angiography in the PCI group may have inflated the rate of revascularization beyond what would be indicated clinically. Subgroup analysis showed that outcomes were similar including in those with diabetes and across all ranges of SYNATX score, except for LM patients with coexisting 3-vessel disease and those with LM stenosis 50-70% who seemed to fare better with CABG. In those with high SYNTAX scores ≥33, the rate of ischemia driven TVR was higher in PCI likely as a result of higher rates of incomplete revascularization due to anatomic complexity. Notably, this study was underpowered to adequately compare hard endpoints of death, stroke, and MI due to an unexpectedly low event rates.

SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) Trial

The SYNTAX trial included a pre-specified and powered subgroup of patients with LM stenosis (n=705) randomized to either CABG or PCI with 1st generation DES (TAXUS EXPRESS), with an overall mean SYNATX score of 30 [6, 7]. SYNTAX showed that there were no differences between CABG and PCI at 1 or 5 years in outcomes including all-cause death, cardiac death, and MI. However, CABG was associated with higher stroke rates while PCI was associated with higher rates of repeat revascularization. The diabetic subset had similar findings, albeit it was grossly underpowered. Notably, outcomes diverged when the extent and complexity of the overall CAD was taken into account as defined by the SYNTAX score. Patients with high SYNTAX scores (≥33) had

improved survival with CABG as compared to PCI. Again, significantly more patients treated with CABG had complete revascularization (72.5%) than patients treated with PCI (72.5% vs. 64.5%, *P*=0.02). Important to note that although the LM subset in the SYNTAX trial was sufficiently powered and pre-specified, the statistical design of the overall study was designed to test the LM subgroup only if the primary endpoint of the overall study was met, which did not occur. Therefore, LM findings of SYNTAX should be considered hypothesis generating and interpreted with caution.

EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization)

This large randomized trial was designed to specifically compare outcomes of CABG versus PCI in LM patients of low-intermediate anatomic complexity as defined by a SYNTAX score ≤32, while using contemporary everolimus-eluting stents (XIENCE, Abbott Vascular) and surgical techniques [8]. Contrary to all other studies that included patients solely based on angiographic estimate of LM stenosis ≥ 50%, EXCEL included patients with a LM >70% or 50-69% if the lesion was deemed hemodynamically significant either invasively (FFR and/or IVUS) or noninvasively. Distal LM disease was present in 80% of patients with multivessel disease in 51.3%. The procedure was guided by IVUS in 77% of cases and FFR was used in 9% of cases. PCI was found to be non-inferior to CABG at 3 years with respect to primary endpoint of death, stroke, and MI. However, again the Achilles heal of PCI appears to be the increased rate of repeat revascularization as demonstrated by a rate of 12.6% as compared to 7.5% in CABG. The increased rate of

repeat revascularization with PCI in EXCEL is consistent with most previous studies, even though the rate using contemporary stents was much lower than the rate reported in SYNTAX with first generation stents (26.7%). Notably, the rate of graft occlusion was significantly higher than the rate of stent thrombosis (5.4% vs. 0.7%) in EXCEL, whereas the rate of stent thrombosis was higher with 1st generation DES used in SYNTAX (5.1%) and similar to rate of graft occlusion (4.4%). Despite the exclusion of high SYNTAX scores by design, 24.2% of randomized patients were later determined to have high SYNTAX based on core lab assessment. Interestingly, CABG did not show benefit over PCI in subgroup of patients with high SYNTAX score, distal LM bifurcation disease, ejection fraction <50%, multivessel CAD, or younger patients. Furthermore, PCI was found to be non-inferior even in the pre-specified subgroup of diabetic patients.

NOBEL (Nordic-Baltic-British Left Main Revascularization) Study

Another highly anticipated contemporary randomized trial of CABG versus PCI for LM was recently published at the same time as the EXCEL findings, with seemingly conflicting results [9]. NOBEL included patients with visually assessed LM lesions ≥50% or those with FFR ≤0.80, and no other complex lesions such as chronic total occlusion, bifurcation, or calcified lesions. Overall, the population's average SYNTAX score was 22.5 with 81% of lesions involving the distal LM, of which one-third received a 2 stent-strategy mostly by the culotte technique, which notably has not been shown to be the superior bifurcation strategy in LMCA[10]. As compared to EXCEL, NOBEL had about 8% usage rate of 1st generation DES with Biolimus-eluting stent (BES) being the DES of

choice, which has thicker strut thickness than the XIENCE stent used in EXCEL or other currently used metallic stents in clinical practice. IVUS guidance was done in only 74% of patients and 96% underwent arterial grafting of LAD. In NOBEL, CABG was found to be superior to PCI with respect to the composite primary endpoint of all-cause mortality, MI, stroke, and repeat revascularization (29% vs. 19%). This difference was again driven primarily by a favorable rate of MI and repeat revascularization with CABG. Importantly, revascularization in PCI group was mostly driven by de-novo lesions as no significant difference in target LM revascularization was noted. Significantly, all-cause mortality and stroke were similar between the two revascularization options. The benefit of CABG was demonstrated across all ranges of SYNTAX score, keeping in mind that 87% of PCI treatments involved LM bifurcation that is known to predict worse outcome. The inconsistent use of IVUS and that fact that only half of patients had post dilation with balloons larger than 4 mm are additional drawbacks that have been suggested as explanations for the increased TVR in PCI group. It is important to note that CABG had its own unique disadvantages that are not clinically irrelevant. Aside from longer recovery period and hospital stay, patients had a 3.9% and 0.5% reoperation rate for bleeding and infection, respectively, as well as 27.5% rate of blood transfusion.

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