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Review

Modality Selection for the Revascularization of Left Main Disease

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ABSTRACT

The management of severe left main (LM) disease remains controversial and continues to evolve as new evidence emerges. Patient selection for coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) relies on both predicting mortality with CABG from clinical characteristics using the Society of Thoracic Surgeons (STS) risk score and anatomical complexity, using the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score. LM stenting techniques continue to evolve; for bifurcation lesions, the use of the double-kiss crush technique may reduce the incidence of late target vessel revascularization. In patients with acute coronary syndrome (ACS) complicated by cardiogenic

RÉSUMÉ

La prise en charge de la sténose du tronc commun de l'artère coronaire gauche (ACG) demeure une controverse, mais continue d'évoluer en fonction des nouvelles données probantes. La sélection des patients pour le pontage aortocoronarien (PAC) ou pour l'intervention coronarienne percutanée (ICP) repose sur la prédiction de la mortalité après le PAC à partir des caractéristiques cliniques établies par le score de risque de la Society of Thoracic Surgeons (STS) et de la complexité anatomique établie par le score SYNTAX (*Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery*). Les techniques d'implantation d'endoprothèses dans l'ACG continuent d'évoluer. Pour les lésions de bifurcation, l'utilisation de la technique

The management of severe coronary artery disease (CAD) of the left main (LM) remains controversial and an area of intense investigation. LM disease is found in approximately 5% to 10% of patients who undergo diagnostic coronary angiography. Given the large territory of myocardium supplied by the LM, the mortality rate for untreated significant disease is higher than 50% at 5 years.[1] The optimal management of LM disease requires a thorough understanding of the anatomical considerations, patient physiological factors, and the benefits and limitations of both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Although the management of LM disease was once under the sole purview of cardiac surgery, PCI has been increasingly adopted for some patient groups on the basis of observational studies and, more recently, evidence from several randomized clinical trials (RCTs). The purpose of this review is to provide a comprehensive summary of the revascularization from both a cardiology and a cardiac surgery perspective.

Patient Selection for CABG and the Role of Surgical Risk Scores

LM disease is present in almost a third of patients undergoing CABG in the Society of Thoracic Surgeons (STS) National Database of more than 1.4 million isolated cases of

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shock, PCI is likely the first-line option in those with anatomically amenable disease, whereas all other stable non–ST-elevated ACS should be treated similar to stable ischemic heart disease. Outcomes comparing CABG and PCI have been recently examined in 2 large randomized clinical trials. In general, early outcomes of periprocedural myocardial infarction and stroke favoured PCI or were not different from outcomes with CABG. However, the conclusions of both trials are at present discordant with respect to late major adverse cardiac and cerebral events; additional follow-up of the trial patients is important for informed patient decision making. The appropriate mode of revascularization should be selected according to patient clinical characteristics and the complexity of the coronary lesions according to European and American guidelines. In those with low or intermediate SYNTAX scores, particularly with high surgical risk, PCI may be preferred to CABG in most other scenarios. A multidisciplinary heart team is recommended to help individualize revascularization decisions.

du *double-kiss crush* peut réduire la fréquence de la revascularisation tardive du vaisseau cible. Chez les patients atteints d'un syndrome coronarien aigu (SCA) compliqué d'un choc cardiogénique, l'ICP est probablement l'option de première intention chez les patients qui ont une maladie favorable à son exécution sur le plan anatomique, tandis que tous les autres patients atteints d'un SCA stable sans sus-décalage du segment ST devraient être traités de la même façon que les patients atteints d'une cardiopathie ischémique stable. Les résultats cliniques sur la comparaison du PAC et de l'ICP ont récemment fait l'objet de 2 grandes études cliniques à répartition aléatoire. En général, les premiers résultats cliniques de l'infarctus du myocarde et de l'accident vasculaire cérébral en phase péri-opératoire favorisaient l'ICP ou n'étaient pas différents des résultats cliniques en lien avec le PAC. Toutefois, les conclusions des deux études montrent à l'heure actuelle une incohérence par rapport aux événements indésirables cardiaques et cérébraux majeurs tardifs. Il est important d'offrir un autre suivi aux patients de l'étude pour leur faire prendre une décision éclairée. Le mode de revascularisation appropriée devrait être choisi selon les caractéristiques cliniques et la complexité des lésions coronaires des patients en se basant sur les lignes directrices européennes et américaines. Chez les patients qui ont des scores SYNTAX faibles ou intermédiaires, et un risque chirurgical particulièrement élevé, on peut privilégier plutôt l'ICP que le PAC dans la plupart des autres scénarios. Une équipe multidisciplinaire en cardiologie est recommandée pour faciliter les décisions individualisées en ce qui a trait à la revascularisation.

CABG.[2] Physiological and anatomic considerations are in play when it comes to decision making for selecting a revascularization strategy for LM disease. Two clinically based risk models are the mainstay for assessing the predicted perioperative surgical mortality: the **Euro**pean **S**ystem for **C**ardiac **O**perative **R**isk **E**valuation (EuroSCORE) II (www.euroscore.org/calc.html) and the Society of Thoracic Surgeons (STS) score (http://riskcalc.sts.org).[3-5] However, the important randomized trials that have resulted in the current revascularization management of patients with LM coronary disease (**Syn**ergy Between PCI With **Tax**us and Cardiac Surgery [SYNTAX], **Pre**mier of Randomized **Com**parison of **B**ypass Surgery versus **A**ngioplas**t**y Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease [PRECOMBAT], **E**valuation of **X**IENCE vs **C**oronary Artery Bypass Surgery for **E**ffectiveness of **L**eft Main Revascularization [EXCEL], **No**rdic-Baltic-**B**ritish **Le**ft Main Revascularisation Study [NOBLE]) used the first Euroscore for predicting surgical risk.[6-8] In these studies, the mean EUROSCORE was 3.8 or less, and its use has been shown to overestimate predicted mortality compared with the STS score and EuroSCORE II.[3-5] This means that, as with other randomized trials in revascularization, the randomized patients were generally a low-risk cohort. In addition, all patients were deemed suitable for CABG or PCI candidates *a priori*. Therefore, the generalizability of the findings and derived recommendations beyond the study population is unclear, and real-world decision making should take that into consideration. In general, the risk models are good when applied at a population level but are inherently limited when applied to individual patients and surgeons. Certain extreme or unusual surgical risk profiles, indeed, can never be accurately adjusted for in the risk models. Hence, the importance of appropriate management strategies should be tailored for any given patient.

CABG and anatomical risk scores

As for the anatomic complexity of the coronary lesions, a high ($\geq$ 33) SYNTAX score favours CABG over PCI.[9] Both can provide comparable short- to mid-term outcomes in patients with LM disease and lower coronary lesion complexities.[9] Weighting of LM lesions in the SYNTAX score is much higher than that of the remaining coronaries and thus contributes substantially to the total score. In addition, the SYNTAX II score was developed to encompass both the anatomical SYNTAX score and clinical characteristics in predicting 4-year mortality after PCI or CABG.[10] However, the validity of this score remains controversial;[11] thus, most clinicians rely on the SYNTAX score to assess anatomical risk and the STS score to assess patient characteristics on early mortality. Other scoring systems exist to specifically qualify the anatomic complexity of the LM lesion but are of limited value for the cardiac surgeon and have no impact on CABG feasibility or long-term success.

Arterial grafting and LM disease

Venous graft attrition over time is the "Achilles heel" for CABG, and supplementing or substituting venous for arterial grafts have offered the potential to improve the durability of CABG and maintain a relative advantage over PCI.[12-14] Recent evidence supports the use of radial grafts in CABG because of their superior longer-term patency rate and associated clinical outcomes compared with venous grafts.[15] The

evidence for using a second internal thoracic graft has been primarily derived from large retrospective studies.[16,17] A meta-analysis of 9 observational studies of more than 15,000 patients demonstrated that bilateral internal thoracic artery (BITA) was associated with a significant reduction in mortality (hazard ratio [HR] 0.79; 95% confidence interval [CI], 0.75-0.84) compared with single internal thoracic artery (SITA).[18] However, these findings have not been corroborated in a large randomized trial.[15,19] In the **A**rterial **R**evascularization **T**rial (ART), 3102 patients were randomized to BITA vs SITA grafting strategies, and no difference was found at 5-year follow-up for the primary endpoint of a composite of death, MI, or stroke (HR 1.04, 95% CI, 0.81-1.32) or at 10 years (HR 0.96, 95% CI, 0.82-1.12; $P = 0.62$) in the intention to treat analysis.[19,20]

The appropriate grafting strategy for patients with isolated ostial or midshaft LM disease and without downstream stenosis of the left anterior descending (LAD) artery or circumflex systems is uncertain. Competitive flow is known to affect graft patency, and arterial grafts are particularly at risk. Bypassing an isolated moderate LM lesion using arterial grafts is less of a concern when using an internal thoracic graft than it is for a radial graft. In a small cohort study with late angiographic follow-up, all ITA grafts to both the LAD and circumflex arteries were fully patent without evidence of string sign.[21]

Off-pump vs on-pump for LM disease

There is now a general acceptance among the cardiac surgical community in Europe and North America that on-pump CABG is the default approach for multivessel CABG because of the concerns about the potential for compromised long-term outcomes that may be associated with off-pump CABG.[22,23] The likely explanation for the disparity in outcomes is related to suboptimal graft patency or less optimal completeness of revascularization.[24] Off-pump CABG may have a role in certain high-risk patients, especially in those with ascending aortic disease, which precludes aortic clamping.[25] Although Chikwe et al. showed no difference in mortality in the general population despite surgery being performed by experienced off-pump surgeons,[23] Puskas et al. showed, in analysis of more than 14,000 patients from 3 US institutions, that those in the highest quartile of predicted risk for mortality had a mortality benefit with off-pump CABG compared with on pump (odds ratio [OR] 0.45, 95% CI, 0.33-0.66; $P < 0.0001$).[26] Although early mortality may be reduced in this group, the late survival benefit of off-pump CABG was shown to be neutralized at 5 years in a meta-analysis of RCTs and observational studies in the general population.[22] Furthermore, a recent network meta-analysis of 37,720 patients demonstrated that an anaortic off-pump technique reduced the risk of postoperative stroke compared with off-pump with a Heartstring device (Maquet, Rastatt, Germany), off-pump with a partial clamp, or traditional on-pump CABG.[27]

Overview of LM Stenting Techniques

PCI has been increasingly adopted in clinical practice, particularly in favourable anatomical settings. Data from the **I**nterventional **R**esearch **I**ncorporation **S**ociety-Left **MAIN** Revascularization (IRIS-MAIN) registry showed a progressive adoption of PCI in patients with LM disease that increased from 25% in the time period between 1995 and 2002, to 61% in the period between 2007 and 2013.[28] From an anatomic standpoint, LM disease represents a heterogeneous anatomical cohort of patients with an ostial or midshaft disease as well as more complex disease involving bifurcation or trifurcation of the distal part of the artery. The ostial or midshaft LM disease can often be treated with a single-stent approach, whereas bifurcation LM disease frequently requires a complex 2-stent procedure with a creation of a neocarina. Although ostial/midshaft is more anatomically favourable, more than 80% of patients in the EXCEL and NOBLE trials had distal LM bifurcation or trifurcation disease.[7,8] In early trials of LM stenting, the most commonly used PCI technique for LM was provisional culotte or T-stenting.[29,30] The adoption of these techniques was derived from trial data of bifurcation stenting in non-LM lesions as well as generally favourable outcomes of small retrospective LM disease cohorts treated with PCI. Therefore, in recently performed RCTs of PCI vs CABG for LM disease, no specific PCI technique was typically required, although the use of culotte stenting technique was encouraged in the NOBLE trial.[7-9]

Crush vs culotte stenting in LM disease

More recently, "crush" bifurcation stenting has emerged as an alternative to culotte stenting, as the technique affords full stent coverage of the neocarina. Initially, crush stenting was not widely adopted, owing to variable results in non-LM lesions undergoing bifurcation stenting.[31,32] However, modification of the crush technique into the "double kissing" (DK) crush technique has made it an attractive bifurcation stenting option for complex LM anatomy.[33] The DK crush technique involves first stenting a side branch, followed by balloon crush, first kissing balloon inflation, main vessel stenting, second kissing balloon inflation, followed by proximal balloon optimization technique. The DK crush technique was initially tested in the DK Crush vs Culotte Stenting for the Treatment of Unprotected Distal Left Main Bifurcation Lesions-III (DKCRUSH-III) trial.[34] In this trial, 419 patients were randomized to undergo PCI with drug-eluting stents, using either the culotte or DK crush technique. The composite rate of cardiac death, myocardial infarction (MI), or target vessel revascularization (TVR) at 1 year was significantly higher in the culotte group compared with the DK crush group (16.3% vs 6.2%; $P = 0.001$). This difference was mainly driven by higher rates of TVR in the culotte cohort (11.0% vs 4.3%, $P = 0.016$). The benefit of the DK crush technique was even more pronounced in those with more complex lesions of SYNTAX scores > 22. The superiority of DK crush over culotte technique was also noted during the longer 3-year follow-up of DKCRUSH-III patients.[35] Retrospective registries have also suggested low short- and long-term event rates associated with the DK crush technique for LM disease.[36,37]

Planned vs provisional stenting

The DKCRUSH-V trial sought to demonstrate superiority of a planned 2-stent DK crush technique vs provisional

stenting in LM bifurcation PCI.[38] This trial randomized 482 patients showing significantly lower rates of a composite endpoint of cardiac death, target vessel MI, or clinically driven target lesion revascularization (TLR) at 1 year in patients undergoing DK crush vs provisional stenting (5.0% vs 10.7%; $P = 0.02$). The secondary endpoints, including target- vessel MI (2.9% vs 0.4%; $P = 0.03$) and definite or probable stent thrombosis (3.3% vs 0.4%; $P = 0.02$), were significantly higher in the provisional stenting group, whereas clinically driven TLR (7.9% vs 3.8%; $P = 0.06$) and angiographic restenosis within the LM complex (14.6% vs 7.1%; $P = 0.10$) showed trends toward superiority of the DK crush technique. Similar to the DKCRUSH-III trial, the reduction in target lesion failure in the DK crush group was particularly notable in those with complex lesions. Given the data from these trials, the best contemporary evidence-based approach to distal LM artery stenting should be the planned DK crush technique, which is associated with lower rates of in-stent restenosis, stent thrombosis, and other adverse events. Recent trials (NOBLE and EXCEL) have not incorporated DK crush technique in the majority of treated patients. Therefore, long-term outcomes in the PCI groups compared with CABG patients in these trials may have been different if DK CRUSH technique were widely used. However, this hypothesis needs to be tested in properly conducted RCTs.

Image guidance and LM stenting

Angiography as sole diagnostic modality for LM disease is limited by several factors, including the presence of a short vessel segment, the lack of a reference vessel, possible foreshortening, plaque eccentricity and remodelling, overlapping with daughter branches, and potential for missed ostial disease.[39] Intravascular ultrasound (IVUS) has been validated for assessment of intermediate LM stenosis, and, typically, a minimal lumen area < 6.00 mm^2 is associated with significant LM disease. In a multicentred Spanish study, de la Torre Hernandez et al.[40] prospectively validated IVUS criteria validated IVUS criteria by deferring revascularization by either CABG or PCI in patients with a minimal lumen area equal or larger than 6.00 mm^2. At 2-year follow-up, patients in whom revascularization was deferred have similar rates of cardiac death, MI, or any revascularization compared with those who underwent PCI or CABG.[40] Intravascular imaging should be used not only for diagnostic purposes but also to guide and optimize stenting technique.[41] A recent meta-analysis have showed a significant benefit in reducing adverse events, including death, TLR, and stent thrombosis, in patients undergoing LM PCI with the use of IVUS.[42] Given these findings, intravascular imaging guidance was frequently used in recent RCTs: 74% in NOBLE and 80% in EXCEL trials. The use of intravascular imaging should be strongly considered in all LM PCI procedures to ensure proper expansion and apposition of coronary stents. Optical coherence tomography (OCT) provides superior resolution compared with IVUS and has been associated with increased detection of stent malapposition and edge dissections. However, randomized studies comparing OCT with IVUS in LM PCI are lacking. The impact of OCT on long-term clinical outcomes after LM PCI needs to be examined further.

The use of fractional flow reserve (FFR) to assess an equivocal LM lesion presents unique challenges compared with other coronary vessels.[43] Ostial disease may falsely raise FFR, as the catheter pressure may be dampened, and the use of intracoronary adenosine is difficult in these cases.[44] Furthermore, the presence of significant moderate or severe downstream stenosis of the LAD or circumflex arteries may alter the FFR measurement of the LM.[45] Given these challenges, the evidence to support the use of FFR in assessing lesions of intermediate severity in LM disease is sparse. In both the **F**ractional Flow Reserve vs **A**ngiography for **M**ultivessel **E**valuation (FAME) I and II studies, patients with LM disease were excluded.[46,47]

LM Disease in Acute Coronary Syndrome/Cardiogenic Shock

The discussion regarding revascularization in patients with LM disease revolves primarily around the treatment of patients with stable ischemic heart disease. However, LM disease is found in 5% to 7% of patients admitted with an acute coronary syndrome (ACS)/acute MI (AMI).[48] A culprit LM thrombosis for ACS/AMI, however, is a much rarer event (0.6% to 0.9%),[49] is more often detected in patients with ST-segment elevation MI (STEMI) and frequently results in severe LV dysfunction, with cardiogenic shock (CS).[50]

In clinically stabilized patients with ACS/AMI and LM disease, the modality of revascularization should be chosen as in patients with stable ischemic heart disease. In patients with hemodynamic instability, instead, urgent or emergent coronary revascularization is crucial to increase survival. The **Sh**ould We Emergently Revascularize **O**ccluded **C**oronaries for Cardiogenic Sho**ck** k (SHOCK) trial included 40% of patients with LM disease, showed significant survival improvement at 6 months in patients with AMI and CS undergoing immediate vs deferred coronary revascularization by either PCI or CABG surgery.[51] In clinical practice, however, it is reasonable to consider PCI as the first treatment option in these critical patients, as it can be performed immediately after angiography, with potential larger myocardial salvage and LV function recovery.

The efficacy of primary PCI in patients with ACS/AMI and LM disease is also supported by observational studies. Among patients enrolled in a large prospective registry, undergoing PCI of LM disease for STEMI or non-ST elevation ACS (NSTE-ACS), mortality was 28.3% and 8.9% at 30 days, and 37.6% and 19.5%, at 1 year, respectively. In patients with CS, however, 1-year mortality was 65% and 30%, respectively.[52] Similar data have been reported in a recent small study.[50] Optimization of PCI, including early mechanical support device use in CS, revascularization of the culprit vessel only,[53] and imaging guidance[54] might increase PCI effectiveness. Although the majority of patients with NSTE-ACS often undergo PCI, in up to 10% of patients presenting with NSTE-ACS, urgent CABG is required.[50]

Adjuncts in cardiogenic shock

Several adjunctive devices (eg, intraaortic counterpulsation, mechanical LV support devices, thrombectomy) have been proposed to improve PCI efficacy, although their benefits have been controversial, disappointing, or are still under scrutiny.[54] Although primary PCI is the leading treatment of LM disease in ACS/AMI, CABG constitutes the only

possible revascularization strategy in patients not suitable for PCI, PCI failure, or in those with mechanical complications. Furthermore, available data suggest that, on the whole, CABG may compare well with PCI in presence of CS, although PCI typically can be performed much more expeditiously.

In the "revascularization arm" of the SHOCK trial, 63% and 37% of patients were treated with PCI and CABG, respectively. Despite a worse coronary picture, CABG patients had 30-day mortality similar to PCI (42.1% vs 45.3%, respectively).[51] In the small subgroup of patients with LM disease, 1-year survival was 47.4% and 30% in the 2 groups, respectively ($P = 0.45$). However, the use of an intra-aortic balloon pump (IABP) to support hemodynamics may not be sufficient for those in refractory cardiogeic shock. A comparison of IABP with Impella 2.5 (Abiomed, Danvers, Massachusetts), a temporary percutaneous left-ventricular assist device (VAD) in a small RCT has not shown to improve 30-day mortality.[55] Furthermore, data to support the use of more invasive short term mechanical support such as TandemHeart (CardiacAssist, Inc., Pittsburgh, Pennsylvania), extracorporeal membrane oxygenation, and temporary VADs is sparse, with use likely limited to specialized centres. In the STS database, operative mortality of LM disease in patients with ACS/AMI undergoing urgent, emergent, and salvage CABG was 18.1% overall, although increased from 10.3% to 18.6% and 53.3% in the 3 subgroups, respectively.[56] In a retrospective analysis of 67 patients from 2 European institutions over 11 years, hospital survival for emergent CABG for cardiogenic shock after AMI was 86%, and late survival for those who survived to discharge was 74% at mean follow-up of 6 years.[57] Surgery remains scarcely used in this setting, likely mainly because of limited availability of emergency surgery teams and surgeon reluctance to operate on very high-risk patients.

Comparative Outcomes Among Medical Therapy, PCI, and CABG for LM

Medical therapy as a sole therapeutic approach is not recommended for patients with angiographically defined LM coronary artery stenosis graded at a severity of more than 50%. This realization came after the publication of a meta-analysis by Yusuf et al.,[1] in which CABG was found to be associated with a 3-fold reduction in death due to LM coronary artery stenosis (OR 0.32, 95% CI, 0.15-0.70; $P = 0.004$), despite more than 65% of patients initially treated with medical therapy having crossed over to surgery by 10 years. As such, $>$ 50% LM coronary artery stenosis constitutes a Class I indication for revascularization, unless survival or quality of life is threatened by other important medical conditions or compelling situations.

Six randomized clinical trials—LE MANS, SYNTAX, PRECOMBAT, NOBLE, and EXCEL— and a study by Boudriot et al. have enrolled patients to undergo PCI or CABG for the treatment of LM disease, either as an isolated lesion or in the presence of additional CAD.[6-8,29,30,58] The earliest study, Left Main Coronary Artery Stenting (LE MANS), randomized 105 patients to PCI (n = 5 2) or CABG (n = 5 3) with low to intermediate SYNTAX score and found no difference between the 2 groups in the composite endpoint of mortality, MI, TVR, and stroke (51.1% vs 64.4%, $P = 0.28$) at 10-year follow-up.[59] Several limitations precluded definitive conclusions from this study: mainly, the small sample size and the low use of the LITA to LAD graft (80%). The more recent and larger studies also generally failed to show a clear advantage between the 2 modalities; however, these trials were largely underpowered and only provided follow-up of 4 years or less (Table 1). All trials denoted a higher incidence of repeat revascularization with PCI and all studies, except PRECOMBAT, showed that PCI was associated with a significantly higher rate of MI.

Two recent clinical trials comparing new-generation drug-eluting stents and CABG in the setting of LM disease have been published. In the EXCEL trial, 1905 patients with LM disease and SYNTAX score of $\leq$ 32 were randomly assigned to PCI with everolimus-eluting stents or CABG. At 3-year follow-up, the primary composite endpoint of death, MI, or stroke occurred at similar rates between PCI and CABG (15.4% vs 14.5%, $P = 0.98$). Importantly, there was no significant difference in the rates of individual endpoints including mortality (8.2% vs 5.9%, $P = 0.11$), MI (8.0% vs 8.3%, $P = 0.64$), and stroke (2.3% vs 2.9%, $P = 0.37$). Although the overall results of the EXCEL trial suggest equipoise between the 2 techniques, PCI provided better results, particularly in the early period after intervention, whereas CABG showed a trend toward improved late outcomes. Although periprocedural MI was significantly lower among PCI patients compared with CABG (3.8% vs 6.0%, $P = 0.03$), subsequent spontaneous events were more frequent with PCI (4.3% vs 2.7%, $P = 0.07$). In addition, definite stent thrombosis or symptomatic graft occlusion was significantly lower among patients allocated to PCI compared with CABG (0.7% vs 5.4%, $P < 0.001$), although in the older SYNTAX trial, the composite of stent thrombosis and graft occlusion occurred at similar rates for patients treated with PCI and CABG (5.1% vs 4.4%, $P = 0.70$).[60] In contrast, findings from the NOBLE study demonstrated PCI was inferior to CABG, resulting in a higher incidence of the primary outcome of major adverse cardiovascular events (MACCE), a composite of death, nonprocedural MI, stroke, or repeated revascularization (29% vs 19%, HR 1.48, 95% CI, 1.11-1.96, $P = 0.0066$) at 5 years.[8] These findings were driven by high rates of nonprocedural MI (7% vs 2%, $P = 0.0040$) and repeated revascularization (16% vs 10%, $P = 0.032$) in the PCI group. Although 3-year results from EXCEL did not appear consistent with that of NOBLE, a Landmark Analysis of 4-year results of the EXCEL trial was recently presented at the annual Transcatheter Cardiovascular Therapeutics meeting in San Diego, California, in September 2018. The primary endpoint of death, stroke, or AMI was higher in CABG compared with PCI at 30 days (7.9% vs 4.9%, $P = 0.008$) but was lower from 30 days to 4 years in the CABG group (10.1% vs 14.8%, $P = 0.003$). This finding was driven by lower rates of death (6.5% vs 9.4%, $P = 0.02$) and AMI (3.0% vs 5.7%, $P < 0.006$) at 4 years in the CABG arm. However, the difference in mortality was driven by increased rates of noncardiovascular fatalities (5.3% vs 3.3%, $P = 0.03$), especially due to malignancy and infection in the PCI arm. Thus, the initial published findings from NOBLE and EXCEL were discordant, whereas later results appear consistent with each other, despite caveats.

Table 1. Early and late results of recent clinical trials comparing PCI to CABG in LM disease

Trial	Median follow-up	Interventions	Early outcomes: Mortality	Early outcomes: Stroke	Early outcomes: MI	Late outcomes: Mortality	Late outcomes: Stroke	Late outcomes: MI	Late outcomes: MACCE	MACCE Definition
SYNTAX	5 years	DES	39/903 (4.4%)	5/903 (0.6%)	43/903 (4.8%)	123/903 (13.7%)	20/903 (2.2%)	83/903 (9.2%)	330/903 (36.7%)	Death from any cause, stroke, myocardial infarction, or repeat revascularization
		CABG	30/897 (3.5%)	19/897 (2.2%)	28/897 (3.3%)	94/897 (10.6%)	31/897 (3.5%)	33/897 (3.7%)	226/897 (25.4%)	
PRECOMBAT	5 years	DES	-	-	-	17/300 (5.7%)	2/300 (0.7%)	6/300 (2%)	52/300 (17.5%)	Death from any cause, MI, repeated revascularization, or stroke
		CABG	-	-	-	23/300 (7.9%)	2/300 (0.7%)	5/300 (1.7%)	42/300 (14.3%)	
EXCEL	3 years	DES	9/948 (1%)	6/948 (0.6%)	37/948 (3.9%)	71/948 (8.2%)	20/948 (2.3%)	72/948 (8%)	137/948 (15.4%)	Death from any cause, stroke, or myocardial infarction
		CABG	10/957 (1.1%)	12/957 (1.3%)	59/957 (6.2%)	53/957 (5.9%)	26/957 (2.9%)	77/957 (8.3%)	135/957 (14.7%)	
NOBLE	5 years	DES	2/592 (< 1%)	0/592 (0%)	19/592 (0%)	36/592 (12%)	16/592 (5%)	29/592 (7%)	121/592 (29%)	Death from any cause, non-procedural MI, repeat revascularization or stroke
		CABG	7/592 (1%)	4/592 (0.7%)	16/592 (0%)	33/592 (9%)	7/592 (2%)	10/592 (2%)	19/592 (81%)	

CABG, coronary artery bypass grafting; DES, drug eluting stent; EXCEL, **E**valuation of **X**IENCE vs **C**oronary Artery Bypass Surgery for **E**ffectiveness of **L**eft Main Revascularization; LM, left main; MACCE, major cardiovascular and cerebrovascular event; MI, myocardial infarction; NOBLE, **No**rdic-Baltic-**B**ritish **Le**ft Main Revascularisation Study; PCI, percutaneous coronary intervention; PRECOMBAT, **Pre**mier of Randomized **Com**parison of **B**ypass Surgery versus **A**ngioplas**t**y Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX, **Syn**ergy Between Percutaneous Coronary Intervention With **Tax**us and Cardiac Surgery.

A recent meta-analysis of the 6 RCTs including 4700 patients demonstrated that CABG was associated with increased risk of early MACCE, composite of death, MI, stroke (HR 0.67; 95% CI, 0.49-0.92) at 30 days, whereas there was no difference in MACCE at 1-year and 3-year follow-up[61] However, repeated revascularization was higher with PCI than CABG at both 1 and 3 years. These findings suggest that early outcomes favour PCI, but late results may favour CABG. Indeed, in the EXCEL trial, PCI offered several additional advantages over CABG within the first 30 days in terms of risk of stroke (0.6% vs 1.3%, $P = 0.16$), major and minor bleeding (3.7% vs 8.9%, $P < 0.001$), major arrhythmias (2.1% vs 16.1%, $P < 0.001$), renal failure (0.6% vs 2.5%, $P < 0.001$), and prolonged intubation (0.4% vs 2.9%, $P < 0.001$). Head and colleagues recently suggested, in a patient-level meta-analysis of these trials, that the 5-year survival results of PCI and CABG appear equivalent in patients with isolated LM disease and, separately, that CABG may be associated with more strokes.[62] Prognostic factors favouring CABG vs PCI overall were diabetes and higher SYNTAX score but not specifically in the LM subgroup. However, methodological shortcomings may have enabled this conclusion, as the robust survival benefit associated with CABG appears prominent without regard to the LM disease subgroup, and this analysis did not include the late mortality results of EXCEL.[63]

Given the favourable early results of PCI compared with CABG, PCI is a reasonable alternative to CABG for patients at high surgical risk, particularly for patients with favourable anatomic characteristics for PCI and with low SYNTAX scores. That said, both NOBLE and EXCEL recruited a large proportion of patients with bifurcation lesions, and, in NOBLE, patients with low SYNTAX scores had greater benefit with CABG than patients with intermediate and high complexity).[7,8] A key unknown to our current understanding is whether the revascularization conclusions will change with further patient follow-up of the landmark studies, given that the late signal from EXCEL. Finally, it is important to note that compliance with guideline-directed medical therapy (GDMT) was poor in a meta-analysis of contemporary clinical trials and was lower in CABG patients compared with PCI patients.[51] This finding highlights the potential to further improve late outcomes for both treatment modalities, but especially for CABG, by improving adherence to GDMT.

Guidelines

In the most recent version of the 2018 European Society of Cardiology (ESC)/ European Association for Cardiothoracic Surgery (EACTS) revascularization guidelines,[64] LM disease can be managed via CABG or PCI, depending on the complexity of the disease (Fig. 1). However, it is important to note that recommendations are for patients with suitable anatomy for both PCI and CABG and low predicted surgical mortality. Calculation of the SYNTAX score in LM disease received a Class I, Level of Evidence (LOE) B recommendation in cases of LM or multivessel disease. CABG is given a Class I, LOE A for LM disease of all complexity (ie, from low to high), whereas PCI, a Class I (LOE A) for patients with low SYNTAX scores (0 to 22). For those with intermediate SYNTAX scores (22 to 32) and high SYNTAX scores (> 32), PCI is a Class IIa (LOE A) and III (LOE B) indication, respectively.

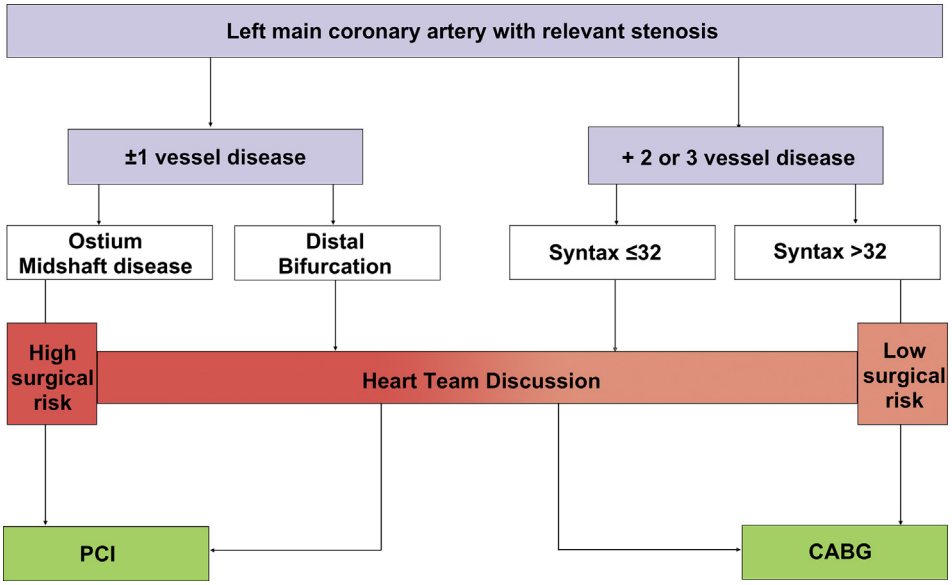

Figure 1. Treatment algorithm for the management of stable coronary artery disease with left main stenosis of > 50% and proof of ischemia. CABG would be indcidated in most patients unless prohibitive or high surgical risk as discussed by the heart team. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. Adapted from Kolh et al. with permission from Elsevier.[67]

Similarly, in the American College of Cardiology (ACC)/American Heart Association (AHA) 2017 guidelines on stable ischemic disease, PCI is reserved for those with "low risk of PCI procedural complications" coupled with "a high likelihood of good long-term outcome" and those who are at significant risk of adverse surgical outcome (Class IIa, LOE B).[65] Furthermore, PCI has a IIb recommendation (LOE B) for those with low to intermediate risk of PCI procedural complications and intermediate to high chance of a good long-term outcome along with increased risk of adverse surgical outcome. Once again, there is harm with PCI (Class III, LOE B) for those with unfavourable PCI anatomy but good candidates for CABG.

The 2018 European Guidelines recommend the use of the STS score to assess in-hospital morbidity and mortality (Class I, LOE B) over the use of the EuroSCORE II (Class IIb, LOE

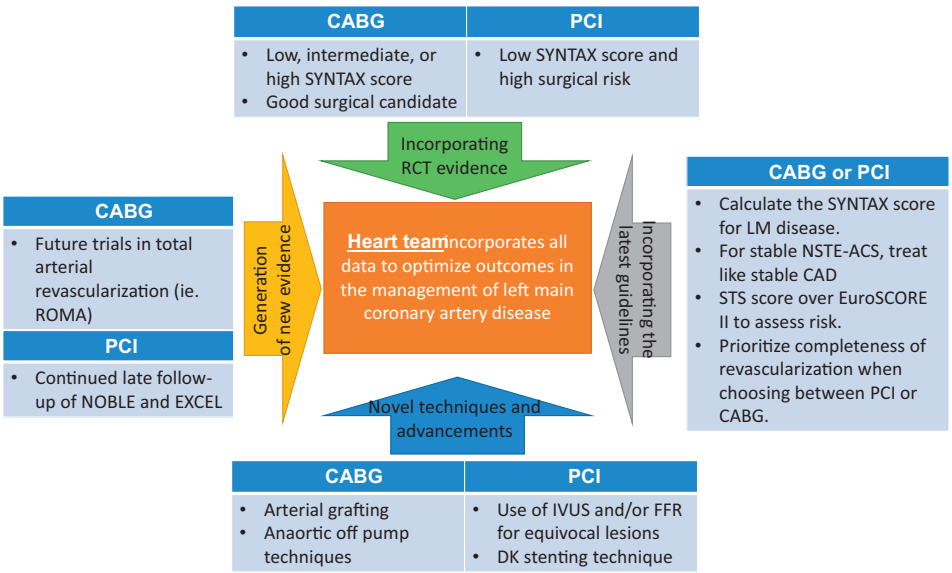

Figure 2. A conceptual summary of all available information that should be incorporated by the heart team to optimize patient outcomes in the management of LM CAD. CABG, coronary artery bypass grafting; CAD, coronary artery disease; EuroSCORE, **Euro**pean **S**ystem for **C**ardiac **O**perative **R**isk **E**valuation; EXCEL, **E**valuation of **X**IENCE vs **C**oronary Artery Bypass Surgery for **E**ffectiveness of **L**eft Main Revascularization; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LM, left main; NOBLE, **No**rdic-Baltic-**B**ritish **Le**ft Main Revascularisation Study; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; RCT, randomized clinical trial; ROMA, **R**andomized Comparison of the Clinical **O**utcome of Single Versus **M**ultiple **A**rterial Grafts; STS, Society of Thoracic Surgeons; SYNTAX, **Syn**ergy Between Percutaneous Coronary Intervention With **Tax**us and Cardiac Surgery.

B). For patients who present with STEMI (Class I, LOE B) or ACS and CS, PCI remains the treatment of choice in those with anatomy amendable to PCI (Class I, LOE B). In patients with NSTE-ACS, the choice of the revascularization strategy should balance the clinical status and patient comorbidities with the severity of disease, in accordance to the principles for the management of stable CAD (Class I, LOE B). Regardless of the modality of revascularization, completeness of revascularization should be prioritized (Class IIa, LOE B). In summary, most patients with high SYNTAX scores should be preferentially treated with CABG, whereas those with low to intermediate SYNTAX scores may be considered for PCI if the operative risk with CABG is high. However, decision making should rely on the assessment of not only coronary anatomy but also patient characteristics, presence of diabetes, completeness of revascularization, and other conditions, highlighting the importance of a heart team approach in equivocal patients.[66]

Recommendations regarding imaging adjuncts and PCI techniques have also been made in regard to LM stenting. In the European guidelines, the use of IVUS or OCT at the time of stenting received a Class IIa, LOE B recommendation.[64] However, the guidelines further specifically point out that at the time of LM stenting, IVUS should be considered to optimize the procedure (Class IIa, LOE B). In specific lesion subsets, including true LM bifurcation, a weak recommendation is made to prefer the DK crush technique over provisional T-stenting (Class IIb, LOE B).

Several important recommendations have been made regarding surgical technique in CABG. Of particular relevance to minimize the risk of stroke for CABG, minimal aortic manipulation (Class I, LOE B), use of epiaortic ultrasound to identify atheromatous plaque (Class IIa, LOE C) before aortic manipulation and off-pump CABG by experienced operators in patients with extensive atherosclerotic disease (Class I LOE B).[64] The goals of these recommendations is to reduce the risk of perioperative stroke, which has been shown to be higher than that for PCI in recent LM disease trials. The use of the radial artery for a high-grade stenosis was recently given a Class IB recommendation, recognizing the importance of arterial grafting for enhanced late graft patency. The use of routine intraoperative graft flows should be considered (Class IIa, LOE B) in an effort to ensure complete myocardial revascularization and reduce the risk of perioperative MI.

Conclusion

CABG remains the cornerstone in the management of significant LM disease, particularly for patients with stable ischemic heart disease who are otherwise good surgical candidates. Societies have recommended a heart team approach for the selection of the most appropriate method of revascularization for any individual patient. The importance of risk stratification for both the coronary anatomy and clinical characteristics is key to the selection of appropriate treatment (Fig. 2). In those with low SYNTAX scores, PCI may be a valid option, whereas there is a weaker recommendation for PCI in those with intermediate SYNTAX scores and harm associated with high−SYNTAX-score PCI. In case of high surgical risk, PCI should be favoured over CABG. Advances in both PCI and CABG continue to improve the outcomes for patients with LM disease. The use of anaortic techniques may reduce perioperative stroke, whereas the use of arterial grafting may further improve the patient's life expectancy. The use of the DK crush technique in PCI may help reduce the incidence of late repeated revascularization, an outcome that is traditionally superior with CABG. The importance of intracoronary imaging and functional assessment of LM disease is increasingly being recognized. IVUS has the potential to aid in optimal patient selection in those with equivocal lesions at angiography. RCTs have demonstrated that PCI offers improved short-term outcomes and similar survival and MACCE-free survival in the aggregated results. The conclusions differ when individual trials are considered, and later follow-up of the EXCEL trial reveals a significant reduction in MACCE events with CABG and continued divergence of survival curves. Given the important gaps in existing evidence, a multidisciplinary heart team approach is strongly recommended regarding the most appropriate method of revascularization in any individual patient with LM disease.

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