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Left Main Coronary Artery Disease: Current Treatment Options

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Abstract

Significant left main coronary artery disease is defined as a greater than 50% angiographic narrowing of the vessel. In general, there are three options for the treatment of LMCA disease which include optimal medical therapy, percutaneous revascularization, or surgical revascularization, either off-pump or on-pump. It is the highest-risk lesion subset of ischemic heart disease and until recent years, coronary artery bypass grafting was the major choice of treatment. Although there is a marked increase in use of percutaneous coronary intervention in left main disease, there are still some questions about its efficacy when compared with surgery. Although bypass surgery is the gold standard, current treatment guideline recommendations canalized the treatment of this potentially lethal disease into percutaneous interventions in selected patients who had low to intermediate anatomic complexity. Left main disease with low SYNTAX scores (≤ 22) can be treated either by bypass surgery or percutaneously, whereas SYNTAX score > 32 is an indication for only coronary artery bypass surgery. The heart team should always be in collaboration, give therapeutic options to patients and decide the best treatment strategy for the welfare of the patient.

Keywords: coronary artery disease, left main coronary artery disease, coronary artery bypass surgery, percutaneous intervention, PCI, CABG, SYNTAX score

1. Introduction

Despite its short length, the left main coronary artery (LMCA) is still one of the most challenging areas of disease for both cardiovascular surgeons and interventional cardiologists today. Significant LMCA disease is defined as a greater than 50% angiographic narrowing of the vessel. LMCA disease is the highest-risk lesion subset of ischemic heart disease and until recent years, coronary artery bypass grafting (CABG) was the major choice of treatment.

Although there is a marked increase in use of percutaneous coronary intervention (PCI) in LMCA disease, there are still some questions about its efficacy when compared with CABG operations. Starting from the traditional treatment options in LMCA disease, current treatment guideline recommendations canalized the treatment of this potentially lethal disease into PCI in selected patients who had low to intermediate anatomic complexity based on some scoring systems. Patient selection for both techniques is important and directly affects the clinical outcome. In this chapter, basic characteristics of the LMCA will be discussed with recommendations of treatment options under the highlights of recent studies and guidelines.

2. Importance of LMCA

The LMCA emerges from the aorta within the sinus of Valsalva through the ostia of the left aortic cusp. It passes between the pulmonary trunk and the left atrial appendage and just under the appendage; the artery divides into the left anterior descending (LAD) and the left circumflex coronary arteries (LCx). In one third of the patients, LMCA bifurcates into LAD, LCx and ramus intermedius branches [1]. The LMCA is responsible for supplying about 75% of the left ventricular (LV) cardiac mass in patients with right dominant type and 100% in the case of left dominant type, and as a result, severe LMCA disease will significantly reduce blood flow to a large portion of the myocardium and place the patient at high risk for life-threatening events, such as LV dysfunction and arrhythmias [2].

Significant LMCA disease is defined as greater than 50% angiographic narrowing of the artery and was shown to be present in about 4–6% of all patients who underwent coronary angiography [3]. Besides, patients with unprotected LMCA (ULMCA) disease treated medically have a 3-year mortality rate of about 50% [4].

The LMCA is anatomically divided into three portions: origin of LMCA from the aorta (ostium), mid portion and the distal portion. The LMCA is different from the other coronary arteries because it has relatively greater elastic tissue content; this feature explains the elastic recoil and its high restenosis rate, following balloon angioplasty procedures [5]. Since one-third of patients have trifurcated LMCA, this anatomical feature is important because in distal LMCA stenosis, PCI is much more difficult in trifurcated lesions than the bifurcated ones [6]. In 1% of the population, the LMCA is absent, and the LAD and LCx arteries originate directly from the aorta via separate ostia.

As with other coronary artery disease, the most common cause of LMCA disease is atherosclerosis. Non-atherosclerotic causes of LMCA lesions are rare. Other reasons may be either obstructive or nonobstructive. Since it is originated directly from the aorta, any disease affecting the ascending aorta can also cause LMCA obstruction such as aortic dissection, external compression resulting from aortic aneurysm or tumor, iatrogenic injury resulting from coronary interventions or vasospasm, irradiation, syphilitic aortitis, Takayasu's arteritis, rheumatoid arthritis, aortic valve disease including malposition of prosthesis, aneurismal dilatations such as Kawasaki disease and atherosclerotic aneurysms.

There is a relationship between the length of LMCA and the LMCA segment that is diseased. In short LMCAs (<10 mm), the stenosis are more frequently localized at the ostium and then at the distal bifurcation (55 vs. 38%), in contrast to long LMCA that develops stenosis more frequently near the distal bifurcation compared to near the ostium (77 vs. 18%). The mid segment of LMS is rarely affected (5–7% of patients). Ostial LMCA stenoses are more common in women (44 vs. 20%) [7].

3. Diagnosis of LMCA disease

Most patients with LMCA disease are symptomatic. Since occlusion of this vessel compromises about 75% of blood flow to the LV, patients are at high risk of major cardiovascular events unless protected by a collateral flow. The diagnosis of LMCA disease is usually made by coronary angiography. The use of noninvasive imaging studies does not specifically distinguish LMCA from other types of coronary artery disease. Certain findings on exercise testing or, in patients with acute coronary syndromes on the electrocardiogram (ECG), are suggestive of LMCA disease. These include diffuse and severe ST-segment deviation or significant ventricular arrhythmias on ECG monitoring or hypotension during exercise [8].

Coronary angiography remains the gold standard diagnostic technique for the diagnosis of clinically important LMCA disease, although small but significant number of false-positive and false-negative results is present with inter-observer variabilities. In order to avoid precipitating myocardial ischaemia in patients with severe LMCA disease, operators try to limit the number of angiographic shots, as well as keep dye injections to a minimum: this may have an impact on diagnostic accuracy of less experienced operators. Ostial LMCA stenosis is not well shown angiographically; the diagnosis relies on detection of pressure damping on engagement of the ostia with the catheter tip and the absence of reflux of dye into the coronary sinus on injection. Detecting and quantifying stenosis of the LMCA and bifurcation rely on a normal segment for comparison: the severity of concentric stenoses of the entire LMCA may therefore be underestimated. Angiography is also poor at assessing lesion calcification. This is important firstly because where visual assessment is inaccurate, it is often because of the presence of calcification, and secondly because the presence of calcification is an important risk factor for dissection following PCI [9]. Coronary angiographic views of some patients with diagnosis of LMCA disease is shown in **Figure 1**.

In some cases, additional studies including intravascular ultrasound imaging (IVUS), fractional flow reserve (FFR) and coronary vasodilatory reserve (CVR) may be helpful for increasing diagnostic accuracy and decision-making.

IVUS is an intracoronary imaging modality that facilitates the anatomic visualization of the vessel lumen and characterizes plaques. It provides a 360° sagittal scan of the vessel from the lumen through the media to the vessel wall. It provides additional information such as minimal and maximal diameters, cross-sectional area and plaque area compared with coronary angiography alone [9]. IVUS detects calcification twice as often as angiography and is

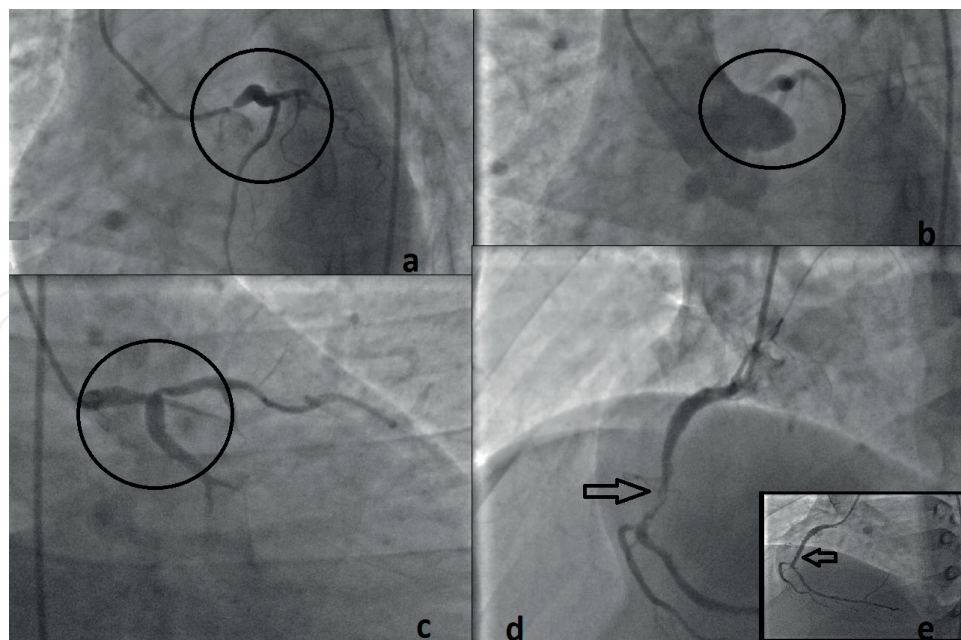


Figure 1. (a–b) Proximal LMCA stenosis at the level of aorto-ostial junction (in circles). (c–d) Acute MI patient with distal LMCA stenosis at the level of bifurcation and proximal part of LAD (in circle) and thrombosis of the RCA (arrow). (e) After thrombolytic infusion and balloon angioplasty flow in RCA is restored, patient is operated in elective conditions for left main disease.

more sensitive at detecting significant LMCA stenosis than angiography alone. IVUS may have a role in the assessment of high-risk patients and in deciding whether patients with angiographically indeterminate LMCA lesions should undergo PCI or surgery [10]. Since IVUS is an effective method to examine the coronary architecture and extent of atherosclerotic plaque with changes in vessel dimensions, it should be considered in angiographically borderline lesions as a complimentary method.

FFR is the ratio of distal coronary pressure to aortic pressure measured during maximal hyperemia which represents fraction of normal blood flow through a stenotic artery. The normal FFR for all vessels under all hemodynamic conditions, regardless of the status of the microcirculation, is 1.0. FFR values <0.75 are associated with abnormal stress tests [10]. FFR may have a role in deciding whether patients with angiographically mild or moderate LMCA disease should undergo revascularization: 56% of patients with FFR <0.75 in one study had significant LMCA stenoses [11].

CVR is the ratio of hyperemic to basal flow and reflects flow resistance through the epicardial artery and the corresponding myocardial bed. Unlike FFR, the value is affected by the coronary microcirculation and hemodynamic conditions. Although of use in the further assessment of angiographically indeterminate lesions, no studies have specifically addressed the use of this diagnostic adjunct in assessment of LMCA disease [10].

A LM pattern on exercise nuclear testing is characterized by perfusion defects in the LAD and LCx territories (i.e., reduced nuclear tracer uptake in the septal, anterior and lateral walls). It

may also be associated with a picture of “balanced” ischemia where there is uniform diminution of tracer uptake with stress, often indicative of LM with three-vessel disease. This may be accompanied by transient ischemic dilation (TID), which is considered present when the image of the left ventricular cavity appears to be significantly greater after stress as compared with that at rest [12].

More recently cardiac CT and MRI have been shown to have a high correlation with angiography for the diagnosis of LM disease. This may be particularly useful in surveillance imaging after revascularization of the LM often performed after stenting [12]. Multislice computed tomography (MSCT), also called multidetector coronary angiography, has rapidly gained in popularity and applicability. MSCT has a good diagnostic accuracy for detecting more than 50% luminal stenosis with a sensitivity of 97% (CI: 94–98%) and specificity of 86% (CI: 78–90%) compared with quantitative conventional coronary angiography [13, 14].

Cardiovascular magnetic resonance imaging (CMRI) has some advantages and limitations compared with cardiac CT imaging. Advantages of CMRI include the absence of ionizing radiation and contrast media, as well as no requirement for heart rate control with b-blockers [12]. Detection of coronary lesions in heavily calcified coronary segments by CMRI can be more reliable than by cardiac CT [15].

There is a strong association between LMCA disease and carotid artery stenosis. Carotid artery disease is present in almost 40% of patients undergoing angiography for evaluation of angina, with significant left main stem disease, compared with just 5% with single-vessel disease [16]. The AHA guidelines recommend screening all patients undergoing bypass surgery for left main stem disease to identify carotid artery disease [17].

4. Preventive and medical therapies

There are three options for treating LMCA disease: optimal medical therapy, PCI, or surgical revascularization (CABG). All patients with LMCA disease should receive preventive therapies to decrease the risk of subsequent cardiovascular events. Preventive therapies include smoking cessation, exercise, lipid lowering therapy with statins, management of diabetes mellitus with proper oral antidiabetics or insulin and achievement of target blood pressure goals with suitable antihypertensive medications. In the 1970s and 1980s, three randomized controlled trials (the Veterans Affairs Cooperative Study [18], European Coronary Surgery Study [19], and CASS (Coronary Artery Surgery Study) [20]) established the survival benefit of CABG compared with contemporaneous medical therapy without revascularization in certain subjects with stable angina. They reported a survival rate of 80–88% for CABG and 63–68% for medical treatment only. Subsequently, a 1994 meta-analysis of 7 studies that randomized a total of 2649 patients to medical therapy for CABG showed that CABG offered a survival advantage over medical therapy for patients with LMCA disease or three-vessel coronary artery disease (CAD) [21]. The studies also established that CABG is more effective than medical therapy at relieving anginal symptoms.

5. Treatment of significant LMCA disease

In general, there are three options for the treatment of LMCA disease, which include optimal medical therapy, percutaneous revascularization, or surgical revascularization, either off-pump or on-pump. Hybrid procedures may also be applied according to patient's clinical status or clinician's choice for different scenarios.

As stated above, CABG offers a survival advantage over medical therapy for significant LMCA disease since medical therapy alone has been associated with poor outcomes. CABG surgery has been accepted as the standard revascularization method for LMCA disease for several decades. In the last decade, several randomized controlled trials have shown favorable results for PCI with drug-eluting stents (DES) compared with CABG. In this title of the chapter, scoring systems for decision making and treatment strategies for LMCA disease will be discussed, mainly focusing on the surgical treatment of LMCA disease.

Compared with the early days, contemporary bypass surgery has been greatly refined. Cardiopreservation techniques have improved and nearly all patients with LMCA disease receive an internal mammary artery (IMA) graft. In addition, patients undergoing surgery are more aggressively treated medically. The outcomes are excellent. When comparing the results of CABG with PCI, the coronary stents must perform at least as well as surgery in terms of outcomes [22].

A percutaneous approach for revascularization in LMCA disease has both attractive and undesirable features. Surgery needs a long recovery period with significant potential morbidities including postsurgical atrial fibrillation, pleural effusions, infections, delayed wound healing, anemia and depression which have negative effects on patient's quality of life. A percutaneous approach is clearly more palatable to patients than surgery. For the physician, LM stem is large and easily accessible for PCI techniques. However, especially for the patients with absent collateral vasculature, balloon inflation may lead to cardiovascular collapse with ischemia. Abrupt vessel closure or subsequent stent thrombosis involving the LM stem may be a fatal event. All of these factors must be taken into account and their effect clearly understood when comparing the two revascularization methods [22].

6. Scoring systems for decision-making in LMCA disease

The assessment of patients with LMCA disease both as a candidate for surgery or PCI is often a complex procedure and best achieved by the "Heart Team" approach. When one method of revascularization is preferred over the other for improved survival, this consideration takes precedence over improved symptoms. ACCF/AHA guideline suggests that a Heart Team approach to revascularization is recommended in patients with unprotected LM or complex CAD (Class I recommendation, Level of evidence; C) [17].

Several risk stratification scores, based on either angiographic or clinical parameters, have been developed to evaluate outcomes in patients with LMCA disease who undergo bypass

surgery. Despite the use of various objective scoring systems derived from hundreds of thousands of patients, an experienced surgeon who spends time evaluating the coronary angiogram, taking a detailed history and examining the patient may provide the most accurate assessment of operative risk [22].

The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score includes factors of coronary angiographic complexity rather than clinical factors. Although the limitations of using the SYNTAX score for certain revascularization recommendations are recognized, the SYNTAX score is a reasonable surrogate for the extent of CAD and its complexity and serves as important information that should be considered when making revascularization decisions. Recommendations that refer to SYNTAX scores use them as surrogates for the extent and complexity of CAD [17].

ACCF/AHA guideline suggests that calculation of the SYNTAX and STS (The Society of Thoracic Surgeons) scores is reasonable in patients with unprotected LM and complex CAD (Class IIa recommendation, level of evidence; B). Variables which contribute to the determination of the score include dominance of the coronary artery system, number of lesions, segment involved per lesions and presence of chronic total occlusions, trifurcation, bifurcation, aorto-ostial lesions, tortuosity, calcification, thrombi, long lesions and/or diffuse disease. By the highlights of these variables, a separate number is calculated for each lesion. Then, these values are summed up to generate the total SYNTAX score. An online tool for easy calculation of the score may be found online at <http://www.syntaxscore.com>. Some of the steps illustrating the scoring are shown in **Figure 2**.

SYNTAX trial is the largest, single published study to date, comparing the outcome of PCI vs. CABG in patients with 3-vessel coronary disease and LMCA disease [23]. The higher the score, the greater is the extent and the complexity of the disease. The SYNTAX trial stratified the entire randomized population (i.e., both patients with 3-vessel and patients with left main coronary artery disease) by tercile of SYNTAX score and found that the patients in the lowest tercile (score:0–22) fared just as well with PCI as surgery, whereas those in the highest tercile (score ≥ 33) clearly did better with surgery [22, 23]. Capodanno et al. applied the SYNTAX score to a registry of 819 patients undergoing LM PCI or surgery and found that the outcomes of patients with SYNTAX score ≥ 34 was better with surgery as compared with PCI but patients with SYNTAX score < 34 had similar outcomes with surgery or PCI in terms of 2-year mortality rates [24]. They concluded that a SYNTAX score threshold of 34 may usefully identify a cohort of patients with LMCA disease who benefit most from surgical revascularization in terms of mortality.

The SYNTAX study included a subset of 705 patients with LM stem disease and their 5-year outcomes have been published [25, 26]. For the overall group with LMCA disease, there was no significant difference in the rate of major adverse cardiac and cardiovascular events (MACCE), MI, or death at 5 years in patients treated with PCI compared with those treated with surgery [26]. The rate of stroke was lower in patients treated with PCI, and the rate of repeat revascularization was lower in patients treated with surgery. When the LM cohort was divided into two groups based on the SYNTAX score, striking differences between the

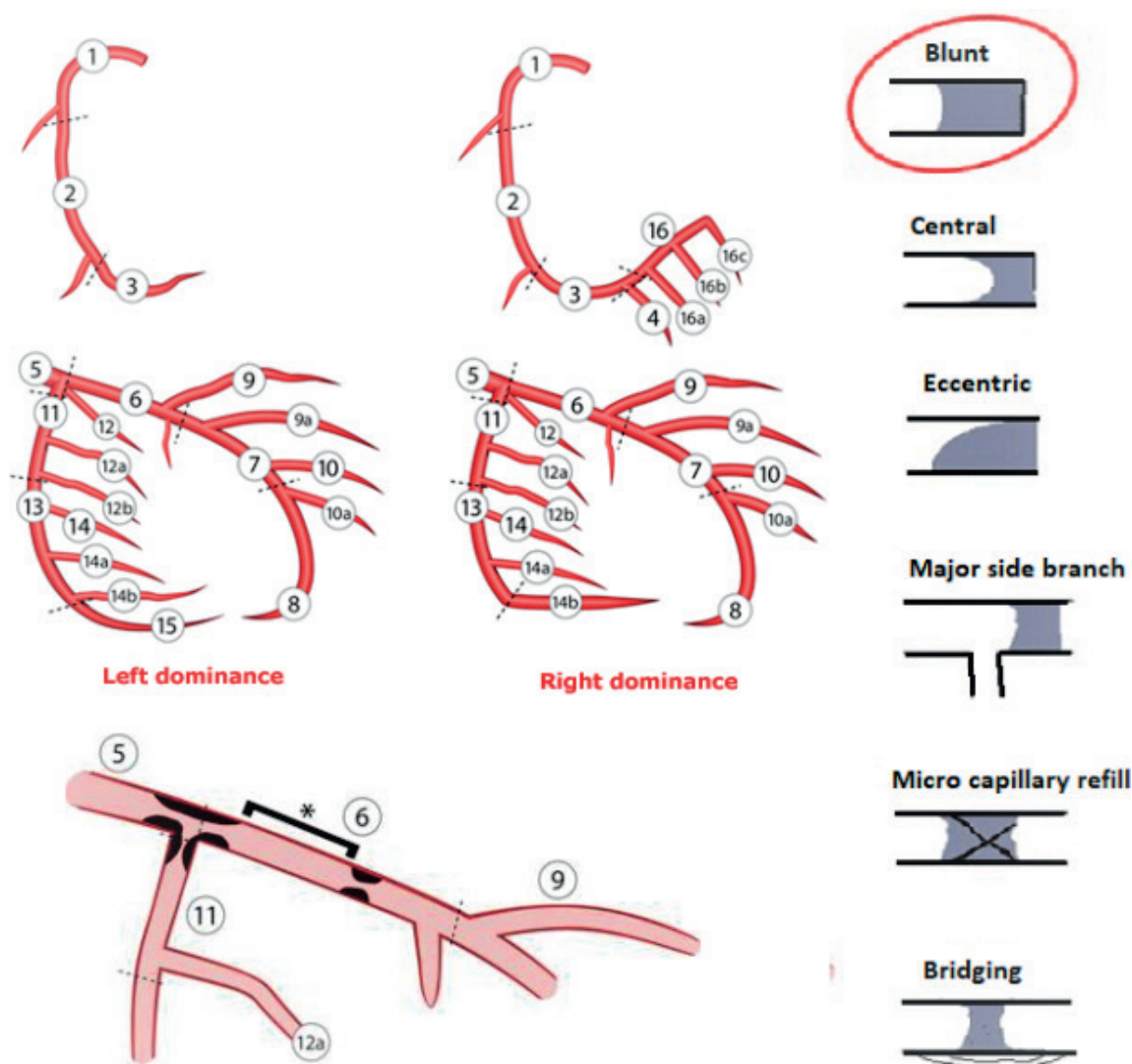


Figure 2. Some of the steps illustrating the SYNTAX scoring system; available online at: <http://www.syntaxscore.com>.

treatment strategies became apparent. For the high SYNTAX score group (≥ 33), the rate of MACCE was significantly greater in the PCI group compared with surgery. Although not statistically powered for mortality, the rate of death trended alarmingly higher in the PCI group. By contrast, for patients with scores < 33 , there was no difference in MACCE. Interestingly, in this group with low or intermediate scores, there was actually a lower mortality rate with PCI [22, 25, 26].

By-time, not only the anatomical assessment, but also the clinical status of the patients was added for better evaluation of the risk stratification, mainly on the SYNTAX score. The clinical SYNTAX score is a combination of age, creatinine and ejection fraction (ACEF) model and SYNTAX scores, and subsequent development of a logistic model has provided better risk assessment [27]. The SYNTAX II score is a combination of anatomical and clinical factors (age, creatinine clearance, LV function, gender, chronic obstructive pulmonary disease, and peripheral vascular disease) and predicts long-term mortality in patients with complex three-vessel

Recommendations according to extent of coronary artery disease	CABG		PCI	
	Class	Level of evidence	Class	Level of evidence
Left main disease with a SYNTAX score ≤ 22 .	I	B	I	B
Left main disease with a SYNTAX score 23–32.	I	B	<i>IIa</i>	B
Left main disease with a SYNTAX score > 32 .	I	B	<i>III</i>	B
Three vessel disease with a SYNTAX score ≤ 22 .	I	A	I	B
Three vessel disease with a SYNTAX score 23–32.	I	A	<i>III</i>	B
Three vessel disease with a SYNTAX score > 32 .	I	A	<i>III</i>	B

Table 1. ESC/EACTS recommendations for the type of revascularization in patients with left main coronary artery disease [30].

or LMCA disease [28]. It was found to be superior to the conventional SYNTAX score in guiding decision-making between CABG and PCI in the SYNTAX trial and subsequently validated in the drug-eluting stent for LMCA disease DELTA registry.

The STS score is a risk-prediction model, validated in patients undergoing cardiac surgery, with a specific model for CABG and combined CABG and valve surgery. It can be used to predict in-hospital or 30-day mortality and in-hospital morbidity [29]. ESC/EACTS guidelines on myocardial revascularization suggest STS score for CABG to assess short-term outcomes for CABG (Class IB recommendation) and SYNTAX score for both CABG and PCI to assess medium- to long-term (≥ 1 year) outcomes (Class IB recommendation) [30]. LMCA disease with low SYNTAX scores (≤ 22) should be treated either by CABG or PCI, whereas SYNTAX score > 32 is a contraindication for PCI. Recommendations of the ESC/EACTS guidelines for LMCA disease are summarized in **Table 1**.

7. Treatment of LMCA disease with PCI

Although surgery was and still is the main treatment option for unprotected LMCA disease, the emerging practice in PCI techniques and new materials has led to almost routine therapeutic option for a subset group of patients with LMCA disease. PCI for treatment of unprotected LMCA disease has passed through several phases. The early published experiences of balloon angioplasty for LMCA disease were associated with a high procedural mortality and poor long-term survival. In the 1980s, O’Keefe et al. reported 9.1% procedural mortality and 36% 3-year survival rate for 127 acute and elective cases with LMCA disease for coronary angioplasty [31]. In the following years, coronary stents improved the safety of PCI and also reduced the incidence of restenosis and abrupt vessel closure. As a result, these techniques were also used for a subset group of patients with LMCA disease. Initial experiences were performed with bare-metal stents and highly variable results were demonstrated according

to studied patient population. Worse outcomes were published with cardiogenic shock and who were not surgical candidates, whereas good results were obtained in elective patients who were good surgical candidates. The bare-metal stent era was characterized by high restenosis and repeat revascularization rates, and restenosis of the LM stents resulted in sudden cardiac deaths [22].

After clinical use of drug-eluting stents, a reduction in restenosis rates renewed enthusiasm for PCI in LMCA disease. At first, different series reported better outcomes with drug-eluting stents for LMCA disease but their results were limited by selection bias regarding the patient characteristics and the anatomical features of LM stem [32]. For better understanding of the results, finally properly designed, large-scale randomized controlled trials comparing PCI with drug-eluting stents to CABG surgery emerged and they provided important answers to the question of PCI vs. CABG surgery for LMCA disease [22].

PCI for LMCA may exist with a broad spectrum of clinical scenarios. The LM stem may eventually be injured and closed as a complication of diagnostic cardiac catheterization. This iatrogenic injury might not be suitable for emergency operation and this patient may suddenly become a candidate for PCI. In a similar fashion, coronary flow of the patient in the cath lab for acute MI who has an occluded LM stem may rapidly be restored by PCI rather than surgery and this may be life-saving. Different preoperative risk assessment and scoring systems may demonstrate high operative risk for the patient, or the patient himself may simply refuse the operation, which automatically puts the patient in the PCI group. The most controversial group is the group of patients who are good surgical candidates and willing to be operated. Currently, surgery is considered the standard of care for this group. Many clinicians feel that PCI should not yet be offered to this group until the results of properly performed clinical trials comparing the outcomes of surgery vs. PCI are available and show that PCI outcomes are at least equal to those with surgery [22]. If left main PCI is being considered, it should not be performed immediately after coronary arteriography. The patient should hear opinions from a multidisciplinary team prior to deciding on a revascularization strategy. Exceptions to this principle include patients who are unstable and need immediate revascularization in the catheterization laboratory or those in whom CABG is not an option for any reason [8].

In a study designed by Erglis et al. comparing drug eluting stents and bare metal stents for the treatment of unprotected LMCA disease, 103 patients with stable angina were assigned to receive either paclitaxel-eluting stent or bare-metal stent. All interventions were IVUS guided and CB pre-treated before stenting was performed in all patients. All patients were scheduled for 6-month follow-up. Follow-up analysis showed binary restenosis in 11 (22%) bare-metal stent and in 3 (6%) paclitaxel-eluting stent patients ($p = 0.021$). The findings demonstrated that implantation of paclitaxel-eluting stents was superior to bare-metal stent in the large-diameter LM vessel at 6 months [33]. By the highlights of studies and improving stent technology, drug-eluting stents are preferred in general use for LMCA disease.

In the LMCA disease, the results for distal LM were worse when compared to ostial or mid-shaft lesions. Although long-term outcomes in patients with ostial/shaft unprotected LMCA

lesions were favorable, outcomes in patients with bifurcation lesions treated with stenting of both the main and side branches appeared unacceptable [34]. The distal LMCA is the usual site of restenosis and the circumflex origin is especially vulnerable to restenosis.

In the ostial involvement, delineating the aorto-ostium by coronary angiography may be difficult and optimal stent decision may be tricky. The implantation of the stent for ostial LMS stenosis must be done with a small protrusion into the aorta to ensure adequate ostium coverage. The aorto-ostium may be very rigid due to calcium and has a tendency to recoil. In case of heavy calcification, rotational thrombectomy may help reducing calcium load, so that it helps balloon and stent expansion and prevents recoil. In most cases of ostial disease, IVUS proves very helpful to ensure coverage and proper stent expansion [22].

Distal LMS stenosis can be treated by a single-stent or by a two-stent strategy. The choice of the strategy is based on: plaque distribution, the angle between the two branches, the diameter of LAD and LCx and the presence of side branch stenosis [6]. Although the data are challenging, patients with distal LM stenosis treated with single-stent strategy have a TVR rate relatively low (<5%), nearly equivalent to patients with ostial or mid-shaft LM stenosis treated by the same strategy [35]. Provisional T-stenting is the most frequent used strategy for single-stent strategy. It consists of the deployment of a single stent from LMCA to the LAD or LCx, whichever has the highest diameter. T-stenting has an advantage that it allows placement of a second stent into the side branch if it is severely narrowed. In two-stent strategy, two stents are planned and deployed in one of several different ways (culotte method, double kissing crush, etc.) to treat both the main branch and the side branch. The lack of randomized data in this area makes it difficult to advocate one strategy over another.

In the “Intracoronary Stenting and Angiographic Results: Drug-eluting Stents for Unprotected LM Lesions” (ISAR-LM) randomized trial, comparing PCI with sirolimus-eluting stent vs. paclitaxel-eluting stent, no significant differences were reported in the composite outcome of death, MI, and TLR at 12-month follow-up. No difference was reported also in restenosis and 2-year LM-specific revascularization [36].

The best available data for long-term outcomes with stenting of LMCAD come from the EXCEL and NOBLE randomized trials. EXCEL trial assigned 1905 patients with LMCA disease of low or intermediate complexity (SYNTAX score ≤ 32) to either PCI with everolimus-eluting stents or CABG [37]. The primary endpoint, a composite of death from any cause, stroke, or MI at 3 years, occurred at a similar rate in both groups. There were no significant between-group differences in the three-year rates of the components of the primary endpoint. The secondary endpoint of death, stroke, or MI at 30 days occurred less often in patients in the PCI group due mainly to a lower rate of MI. The secondary endpoint of death, stroke, MI, or ischemia driven revascularization at 3 years occurred more often with PCI. PCI with everolimus-eluting stents was noninferior to CABG with respect to the rate of the composite endpoint of death, stroke, or myocardial infarction at 3 years.

The NOBLE trial randomly assigned 1201 patients (without ST-elevation MI) to complete revascularization with either PCI, using a biolimus-eluting stent, or CABG [38]. The primary

endpoint of major adverse cardiac or cerebrovascular events (a composite of all-cause mortality, nonprocedural MI, any repeat coronary revascularization, and stroke) at 5 years occurred more often with PCI attributable mainly to more frequent revascularization in the PCI group and a higher rate of stroke, the latter of which is not consistent with all other trials. The findings of this study suggest that CABG might be better than PCI for treatment of LM stem CAD.

Sometimes, a patient with acute MI and demonstrated three-vessel disease with involvement of LMCA disease may benefit from emergency coronary angioplasty. If the responsible vessel for acute MI is the RCA and complicated with cardiogenic shock, direct PTCA for RCA may significantly reduce in-hospital mortality and the patient may become a surgical candidate for LMCA after evaluation of the mitral valve for ischemic mitral insufficiency for possible interventions in a more stable status.

Most of the LM PCI does not require hemodynamic support, but during PCI for LMCA disease, the operator should be ready for any hemodynamic compromise, slow or no reflow or other procedural complications and take necessary precautions. These precautions include the placement of intraaortic balloon pump (IABP) or sometimes the support of percutaneous LV assist devices in poor LV functions, such as the Impella. Patients more likely to need support include those with severe LV dysfunction, occlusion of the right coronary artery, a left dominant circulation, and patients in whom the PCI procedure is likely to be complex and difficult, thus increasing the ischemic time [22]. In general, careful attention to patient's baseline hemodynamic status before and during the procedure is necessary. Patient with instable hemodynamic status or those in whom even brief balloon inflations result in hemodynamic compromise may benefit from the support. As a member of the heart team, a cardiac surgeon should always be informed before the implementation of PCI for unprotected LMCA and the surgical team should be ready for any potential complications and eventually for emergency CABG.

Patients with a patent bypass graft to either the LAD or LCx, who are considered to be "protected," may require LM intervention because of recurrent ischemia. Protected lesions are anatomically similar to those that are not previously bypassed. However, their physiology during treatment and the consequences of abrupt closure and restenosis are much more forgiving because of continued flow to the protected territory [8].

8. Surgical treatment of LMCA disease

LMCA disease is an important independent risk factor for increased mortality and morbidity at all stages of diagnosis and treatment of CAD. For several decades, CABG was regarded as the standard of care for significant LMCA disease in patients eligible for surgery. More recently, PCI has emerged as a possible alternative method of treatment for revascularization in specifically selected, especially low risk group of patients, except for the life-saving emergency high-risk groups. Besides patient characteristics, lesion location is an important factor

for the determination of treatment of choice as well as operator's experience and technical considerations. Stenting of distal stem or bifurcation lesions is technically challenging and most of the patients are presented with three-vessel disease which makes them good surgical candidates. Although the improvement in stent technology and increased experience of PCI techniques by the operators sometimes make the surgery questionable, surgery is still the "gold standard" for treatment of LMCA disease [24]. The outcomes of patients with SYNTAX score ≥ 34 was better with surgery as compared with PCI CABG surgery, which improves survival in patients with significant LMCA disease, three-vessel (and possibly two-vessel) disease, or reduced ventricular function, and prolongs and improves the quality of life in patients with LM equivalent disease (proximal LAD and proximal LCx), but does not protect them from the risk of subsequent MI. In this section, patient selection and CABG methods, as well as technical considerations, will be discussed for surgical treatment of LMCA disease. Indications of surgery for LMCA disease in ACCF/AHA guideline is summarized in **Table 2**.

By far, the most common known etiology of LMCA disease is atherosclerosis. Non-atherosclerotic causes of LMCA lesions are rare. Since atherosclerosis is a generalized disease affecting the whole arterial system in the body, its association should always be kept in mind such as carotid artery disease, cerebrovascular disease and peripheral artery disease as well as porcelain aorta which make the surgical procedure more challenging.

The incidence of sudden death in patients with critical LMCA disease means that these patients should never be thought as patients in the waiting list for elective surgery. Emergency CABG is recommended as Class I indication for patients with life-threatening ventricular arrhythmias, which is believed to be ischemic in origin, in the presence of ≥ 50 LMCA stenosis [17]. In a study by Maziak et al. [39], patients in the waiting list for CABG operations were evaluated. In this study, 281 patients over 2145 had critical ($\geq 50\%$) LM stenosis. The average time from angiography to operation was shorter in patients with LMCA disease and the presence of LMCA disease did not influence operative mortality, the incidence of low cardiac output syndrome or the incidence of perioperative MI. To examine the effect of waiting time on outcomes, patients with LMS were divided into early (operation 10 days or less after angiography) and late revascularization groups (more than 10 days). Operative mortality, low output syndrome, and myocardial infarction were similar in the early and late groups. Patients in the early group were more likely to have NYHA functional Class IV symptoms, unstable angina, or a recent preoperative myocardial infarction. He concluded that carefully selected patients with significant LMS can safely wait for operation. But, it should be kept in mind that patients with severe symptoms and recently preoperative MI should be allocated for early surgical intervention.

The "Heart Team," made up of clinical or noninvasive cardiologists, cardiac surgeons and interventional cardiologists, provides a balanced, multidisciplinary decision-making process. Formulation of the best possible revascularization approaches, also taking into consideration the social and cultural context, will often require interaction between these branches. Patients may need help in making decisions about their treatment and the most valuable advice will probably be provided to them by the Heart Team [40].

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- Class I indications
- *CABG in Patients With Acute MI*: Emergency CABG is recommended in patients with life-threatening ventricular arrhythmias (believed to be ischemic in origin) in the presence of LM stenosis $\geq 50\%$ and/or 3-vessel CAD (LoE: C)
 - *Life-Threatening Ventricular Arrhythmias*: CABG is recommended in patients with resuscitated sudden cardiac death or sustained ventricular tachycardia thought to be caused by significant CAD ($>50\%$ stenosis of LMCA and/or $>70\%$ stenosis of 1, 2, or all 3 epicardial coronary arteries) and resultant myocardial ischemia (LoE: B)
 - *CABG in Association With Other Cardiac Procedures*: CABG is recommended in patients undergoing noncoronary cardiac surgery $\geq 50\%$ luminal diameter narrowing of the LMCA or $\geq 70\%$ luminal diameter narrowing of other major coronary arteries (LoE: C)
 - *Heart Team Approach to Revascularization Decisions*: A Heart Team approach to revascularization is recommended in patients with unprotected LM or complex CAD (LoE: C)
 - *Left Main CAD Revascularization*: CABG to improve survival is recommended for patients with significant ($>50\%$ diameter stenosis) left main coronary artery stenosis (LoE: B)
- Class IIa indications
- Calculation of the STS and SYNTAX scores is reasonable in patients with unprotected LM and complex CAD (LoE: B)
 - *Left Main CAD Revascularization*:
 1. PCI to improve survival is reasonable as an alternative to CABG in selected stable patients with significant ($>50\%$ diameter stenosis) unprotected LMCAD with: (1) anatomic conditions 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 CAD); and (2) clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality $>5\%$) (LoE: B)
 2. PCI to improve survival is reasonable in patients with UA/NSTEMI when an unprotected LMCA is the culprit lesion and the patient is not a candidate for CABG (LoE: B)
 3. PCI to improve survival is reasonable in patients with acute STEMI when an unprotected LMCA is the culprit lesion, distal coronary flow is $<$ TIMI grade 3, and PCI can be performed more rapidly and safely than CABG (LoE: C)
 - Carotid artery duplex scanning is reasonable in selected patients who are considered to have high-risk features (i.e., age > 65 years, LMC stenosis, PAD, history of cerebrovascular disease (transient ischemic attack (TIA), stroke, etc.), hypertension, smoking, and diabetes mellitus) (LoE: C)
 - In the absence of severe, symptomatic aorto-iliac occlusive disease or PAD, the insertion of an IAB is reasonable to reduce mortality rate in CABG patients who are considered to be at high risk (e.g., those who are undergoing reoperation or have LVEF $<30\%$ or LMCAD) (LoE: B)
- Class IIb indications
- *Left Main CAD Revascularization*: PCI to improve survival may be reasonable as an alternative to CABG in selected stable patients with significant ($>50\%$ diameter stenosis) unprotected LMCAD with: (1) anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (e.g., low-intermediate SYNTAX score of <33 , bifurcation LMCAD); and (2) clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate-severe chronic obstructive pulmonary disease, disability from previous stroke, or previous cardiac surgery; STS-predicted risk of operative mortality $>2\%$) (LoE: B)
 - CABG to improve survival rate may be reasonable in patients with end-stage renal disease undergoing CABG for LMCA stenosis of $\geq 50\%$ (LoE: C)

Class III indications (HARM)	<ul style="list-style-type: none"> • PCI to improve survival should not be performed in stable patients with significant (>50% diameter stenosis) unprotected LMCAD who have unfavorable anatomy for PCI and who are good candidates for CABG (LoE: B)
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Abbreviations: CABG: coronary artery bypass graft; CAD: coronary artery disease; IAB: intraaortic balloon; LM: left main; LMCAD; left main coronary artery disease; LoE: level of evidence; LVEF: left ventricle ejection fraction; NSTEMI: non-ST elevation myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary revascularization; UA; unstable angina.

Table 2. ACCF/AHA guideline recommendations for left main coronary artery bypass graft surgery [17].

The hospital mortality rate for CABG surgery is approximately 1% in low-risk patients, with fewer than 3% of patients suffering perioperative myocardial infarction. The most consistent predictors of mortality after CABG are urgency of operation, age, prior cardiac surgery, female gender, low LV ejection fraction, degree of LM stenosis, and number of vessels with significant stenoses. The most common mode of early death after CABG is acute cardiac failure leading to low output or arrhythmias, owing to myocardial necrosis (often with features of reperfusion), postischemic dysfunction of viable myocardium, or a metabolic cause, such as hypokalemia. As in cardiac surgery, in general, the risk of perioperative MI increases with the degree of cardiomegaly, and in patients who have had preoperative infarction [41].

8.1. Myocardial protection for surgery in LMCA disease

The objective of any type of myocardial management during cardiac surgery should target on decreasing injury to the myocardium by combination of hypothermia, electromechanical arrest, washout, oxygen and other substrate enhancement and buffering. There is no one specific method that ideally describes the myocardial protection as in the LMCA disease. It depends on surgeon's preferences, surgical technique, and surgeon's desire for complete bloodless area during the operation, sequence and timing of proximal anastomoses and costs. The optimum strategy for myocardial protection in severe LMCA disease remains unclear not only because of different regimens, but also the advanced stenosis of the LM stem resulting in uneven distribution of the preferred cardioplegic solution, slow diastolic arrest and delayed functional recovery due to pre- and perioperative functional status of the heart in critical LM stenosis and recent MI.

The myocardial protection is achieved by either antegrade blood cardioplegia through the ascending aorta via right and left coronary ostia in the absence of severe aortic regurgitation or retrograde blood cardioplegia by a special cannula inserted into the coronary sinus through the right atrium. Severe obstructive manifestations of CAD are perhaps the best examples for the superiority of retrograde cardioplegia. These include LM lesions and acute coronary syndromes. In this specific concern of LMCA disease, the cardioplegia distribution is not even because of the proximal stenosis and may cause impaired myocardial protection. Although retrograde cardioplegia results in better distribution, myocardial cooling and more complete functional recovery of myocardium distal to coronary artery stenoses, the

presence of veno-venous shunts and thebesian channels means that distribution of retrograde cardioplegia may not effectively protect the right ventricle and posterior septum [42]. A combined approach may be a better alternative for myocardial protection where antegrade blood cardioplegia and maintained with continuous retrograde blood cardioplegia has been shown to result in reduced postoperative serum troponin I levels and rates of atrial fibrillation, compared with approaches using solely antegrade cardioplegia in patients with significant LMCA disease [43]. Patients with LMCA disease also have high incidences of involvement of RCA occlusion; so, not only the left coronary system, but also the right coronary system is impaired during antegrade cardioplegia route.

A conscious decision to use both the antegrade and retrograde routes of cardioplegia routinely, delivered in either an alternating sequential fashion or simultaneously, has evolved in the practice of some institutions. In our daily practice, we use combined antegrade and retrograde cardioplegia technique. In lack of severe aortic insufficiency, half or two-thirds of the dose is given through the antegrade perfusion cannula and the remaining solution is given through the retrograde cannula. After performing the first distal anastomosis by saphenous graft to the LCx system (mainly the best obtuse marginal artery branch), we do not wait for completion of time and perfuse the LCx from directly through the anastomosed saphenous vein graft, if the stenosis of LMCA disease is severe (**Figure 3**). In the absence of LAD stenosis, direct perfusion of LCx also allows perfusion of LAD in retrograde fashion.

Sometimes slow continuous retrograde perfusion may also be applied for better protection. Our goal is primarily good protection of the heart with as short cross-clamp time as possible. After completion of LIMA-LAD anastomosis, hot-shot with warm blood cardioplegia is given and usually the proximal anastomoses of the saphenous vein grafts to the ascending aorta is performed after the heart began to beat by the aid of side-clamp. If the aorta is severely calcified, single-clamp strategy may be used. Also, for better recovery of the heart, we also go on perfusing the heart by a line derived from the arterial cannula inserted into each saphenous vein grafts during proximal anastomosis stage.

Other preoperative prophylactic or postoperative insertion of the IABP is sometimes advisable. In addition to its use in MI with low cardiac output or shock, preoperative insertion is often helpful in unstable angina, LM disease with ongoing ischemia, and ischemia leading to ventricular arrhythmias. In the era of more complex arterial revascularization for ischemic heart disease, IABP support is helpful intraoperatively for pre-bypass support of patients with low ejection fraction [44]. When an IABP is used, it is important to understand that it is not the final therapy in terms of mechanical support for the failing heart. If the shock state persists, as evidenced by a depressed cardiac index, then some form of direct mechanical support must be implemented so as to restore adequate end-organ perfusion. Failure to adequately treat a patient in cardiogenic shock will most assuredly result in the patient's demise [41].

8.2. Type of surgery

Since the first CABG was performed in the late 1960s, the standard surgical approach has included the use of cardiac arrest coupled with CPB, optimizing the conditions for construction of

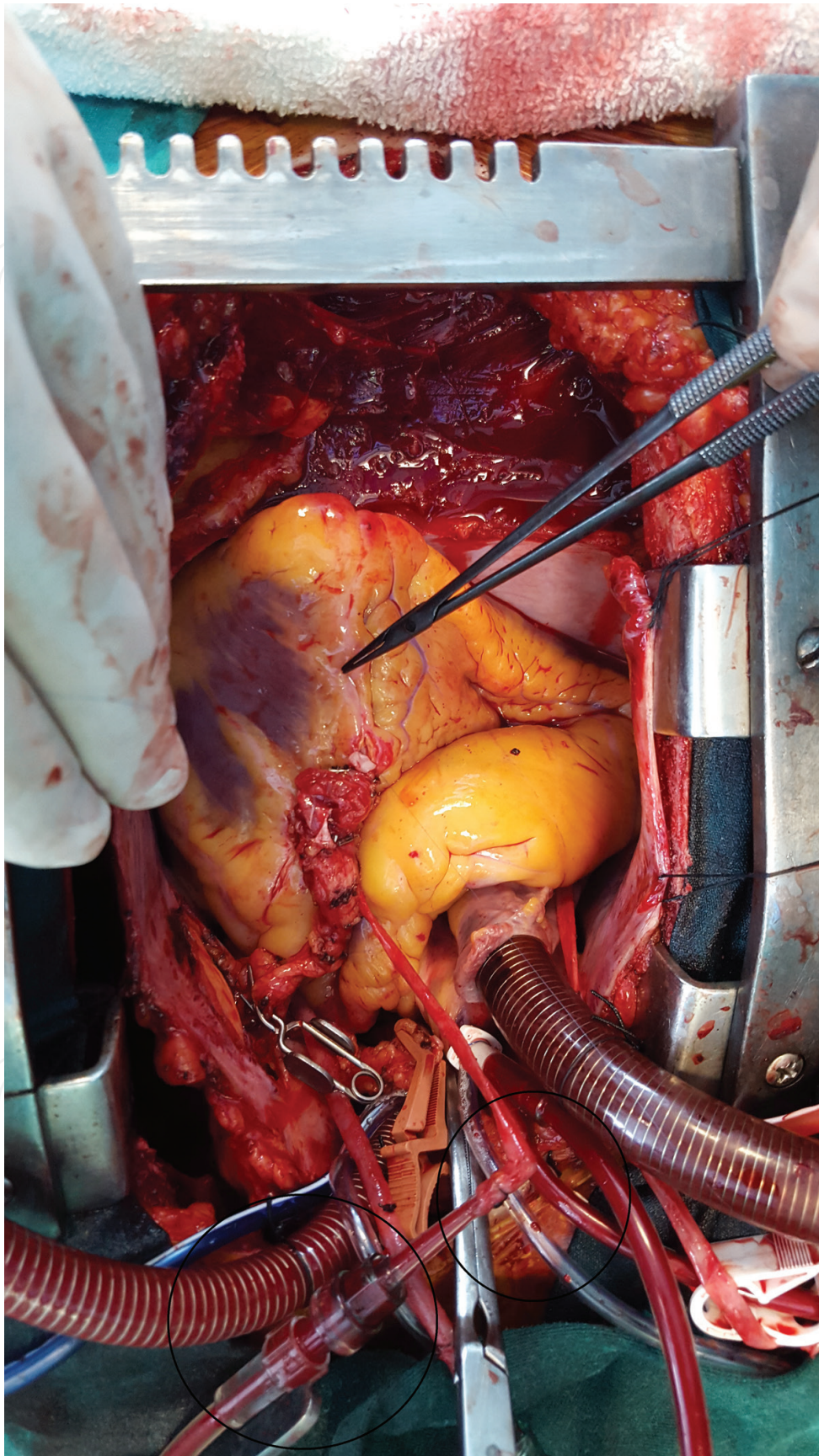


Figure 3. During on-pump bypass surgery, anastomosed saphenous vein grafts are perfused before LIMA-LAD anastomosis for better myocardial protection in left main coronary artery disease (in circle).

vascular anastomoses to all diseased coronary arteries without cardiac motion or hemodynamic compromise. Such on-pump CABG has become the gold standard and is performed in about 80% of subjects undergoing the procedure [17]. Despite the excellent results that have been achieved, the use of CPB and the associated manipulation of the ascending aorta are linked with certain perioperative complications, including myonecrosis during aortic occlusion, cerebrovascular accidents, generalized neurocognitive dysfunction, renal dysfunction, and systemic inflammatory response syndrome. To avoid these potential complications, off-pump surgical technique was developed by the aid of special cardiac stabilizing devices. This technique is also helpful in avoidance of touching the aorta which may be heavily calcified. In 2005, an AHA Scientific statement comparing the two techniques concluded that both procedures usually result in excellent outcomes and that neither technique should be considered superior to the other [45].

The LMCAD is known to be an important poor prognostic factor related to morbidity and mortality at various stages of CAD. In the past, LMCAD was accepted as a relative contraindication for off-pump CABG because of the hemodynamic compromise of the patient by changing the position of the heart. With evolving experience, some centers began to use off-pump technique in their routine daily practice and emerging number of reports in the literature have proven this method as a safe alternative to CPB. In a review article searching for studies comparing the results of on-pump CABG and off-pump CABG in patients with LMCAD, the outcomes, concerns and controversies were evaluated [46]. The majority of the studies identified showed favorable or equal outcomes of OFP when compared to conventional approach. All of the studies, apart from two, which showed lower incidence of postoperative deaths, demonstrated equal mortality rates. Stroke rates were found less in three studies. Less blood transfusions, inotropic use and length of study has been also demonstrated. The main concerns of off-pump surgery were hemodynamic instability and less complete revascularization. Main controversies were same or favorable outcomes, despite lower number of grafts with off-pump surgery, and less stroke rates, despite manipulation of aorta with side-clamping. Despite these concerns and controversies off-pump surgery has been proven to be feasible and safe as demonstrated by results from numerous studies.

Patients who have had recent MI with impaired LV and patients with dilated ventricles may not be ideal candidates for off-pump bypass procedures. Similarly, in patients with more than mild mitral insufficiency, grafting the branches of the LCx coronary artery may cause hemodynamic instability during the procedure. In such cases, surgery may be best managed by performing the revascularization procedure on the beating heart with cardiopulmonary support. The aorta is not clamped and cardioplegia is not administered. In such conditions, the heart is kept empty, providing optimal myocardial protection and hemodynamic stability (**Figure 4**).

Anesthetic management is very important during off-pump surgery. The key to avoiding conversion to emergency CPB should be proactive by preventing hypotension and low cardiac output. Intravascular volumes should be replenished before positioning the heart. The most common reason for hypotension is venous return problems. To prevent this, Trendelenburg position with turning the patient right-side may be helpful. The most important part for

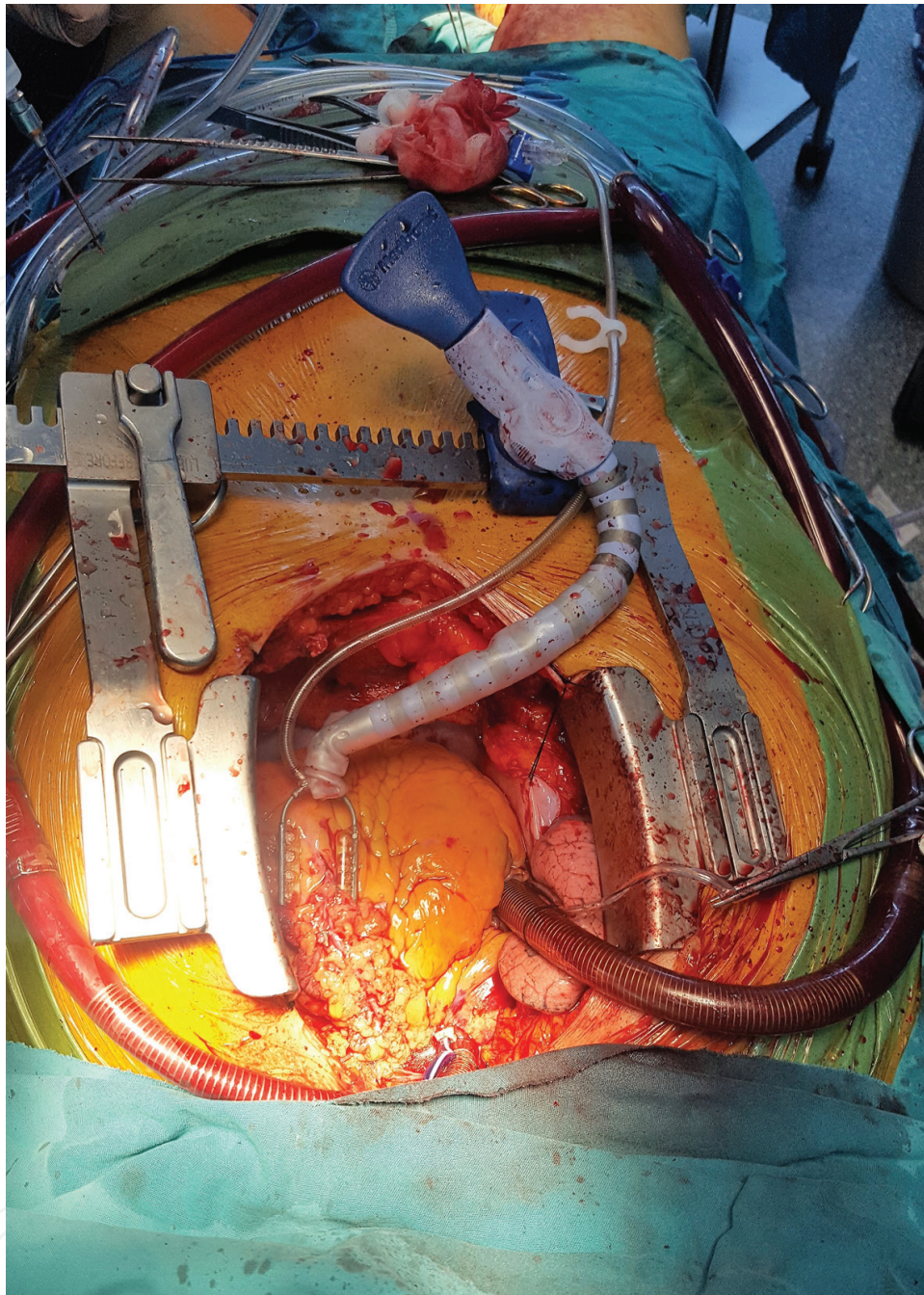


Figure 4. Cardiopulmonary bypass-assisted beating heart surgery. Note that the aorta is not clamped and cardioplegia is not administered. In such conditions, the heart is kept empty, providing optimal myocardial protection and hemodynamic stability.

positioning the heart is placement of the pericardial sutures. If the target vessel is on the left side, right side pericardial sutures should be left free and the deep pericardial sutures and the left pericardial sutures should be tightened. Generally, lifting the heart to a vertical position is relatively well tolerated. After carefully defining the target vessel, stabilizer device (e.g., Octopus System, Medtronic Inc. Minneapolis, MN) and their pads should be placed around

the vessel at diastolic phase and be fixed. After the arteriotomy, placement of intra-arterial shunt provides myocardial blood flow continuity, minimizes distal bed ischemia and helps in correct suturing. During beating heart surgery, the operative field may become dirty because of bleeding; in that case silastic tape traction from proximal and distal portion of the arteriotomy may stop bleeding and help for a bloodless area. Carbondioxide mist blower is also helpful for clear view of the operating field.

Usually anterior and the most critic vessel should be anastomosed first. In LMCA disease, after preparation of the left internal mammarian artery (LIMA), direct anastomosis to LAD provides blood flow to LV. LAD artery is usually grafted at distal one-third to one-half where the artery normally emerges from the intramyocardial location if suitable. Other LCx obtuse marginal branches can be accessed with the heart in vertical position and rotated to the right. Use of apical suction devices may help positioning the heart. In LMCA disease, positioning of the heart may cause hemodynamic instability, especially after acute MI. After LAD anastomosis, if the hemodynamic instability persists, the patient may be a candidate for hybrid approach for future PCI. The goal of the surgery should be complete revascularization in normal conditions; but any unnecessary attempts to provide complete revascularization which threatens his life should be avoided.

8.3. Conduit selection

The effectiveness of CABG in relieving symptoms and prolonging life is directly related to graft patency. Because arterial and venous grafts have different patency rates and modes of failure, conduit selection is important in determining the long-term efficacy of CABG. The LIMA is the conduit of choice for revascularization of LAD distal to the LMCA lesion. LIMA should be used to bypass the LAD artery when bypass of the LAD artery is indicated (Class I recommendation for ACCF/AHA guideline for CABG surgery) [17]. Since the atherosclerosis is an active event, anastomosis should be performed to the best distal area. LIMA provides superior short- and long-term patency and clinical outcomes to alternative conduits. Unlike saphenous vein grafts, IMA's are usually >90% patent after 10 years. They are resistant to atherosclerosis and release prostacyclin and nitric oxide, thereby causing vasodilation and inhibiting platelet function, by their endothelium studies suggesting an improved survival rate in patients undergoing CABG, when the LIMA is used rather than saphenous vein grafts to LAD. This survival benefit is independent of the patient's sex, age, extent of CAD, and LV systolic function [47]. Apart from improving survival rate, LIMA grafting of the LAD artery reduces the incidence of late MI, hospitalization for cardiac events, need for reoperation and recurrence of angina [48].

Although arterial conduits such as the radial artery have been shown to offer superior long-term patency to saphenous vein grafts, the risk of arterial graft spasm in the immediate postoperative period has discouraged some surgeons from total arterial revascularization of LMCA lesions [9]. Tatoulis et al. who analyzed 8420 patients, including 849 with significant LMCA disease, did not report adverse sequelae attributable to graft spasm in patients with LMCA disease who underwent total arterial grafting [49]. Patients should be informed before radial artery harvesting. Usually, the radial artery is harvested from the non-dominant arm of the patient. We routinely perform Doppler ultrasonography for evaluation of radial artery. The radial artery diameter >2 mm is usually suitable for a good quality conduit.

Dominance of the ulnar artery in hand should also be evaluated by modified Allen test [50]. Radial artery graft patency is best when used to graft a left-sided coronary artery with >70% stenosis and worst when it is used to bypass the right coronary artery with a stenosis of only moderate severity [51]. In technical aspects, we use radial artery grafts for >90% lesions and, during harvest, we use ultrasonic/harmonic scissors to avoid heat trauma to the vessel. After harvesting the graft, all the fasciae over the radial artery is also cleared longitudinally to prevent vasospasm (**Figure 5**). This maneuver also helps us making a better bleeding control from the side branches and provides better vessel diameter. Topical papaverine is also a good option for prevention of vasospasm.

Combination of LIMA, right IMA and radial artery may be used for full arterial revascularization processes. Some centers also prefer gastroepiploic artery either in case of inappropriate LIMA or in combination with LIMA and RIMA for full arterial revascularization concept (**Figure 6**).

Besides these arterial grafts, reversed saphenous vein grafts are commonly used in patients undergoing CABG surgery. Their disadvantage is a declining patency with time: about 10–25% of saphenous vein grafts occlude within 1 year of CABG [52]. An additional 1–2% occlude each year during the 1–5 years after surgery; and 4–5% occlude each year between 6 and 10 years postoperatively. Therefore, 10 years after CABG, 50–60% of saphenous vein grafts are patent, only half of which have no angiographic evidence of atherosclerosis [53].

Patient's age, stenosis degree of the affected coronary artery and hemodynamic status of the patient are important factors for overall graft selection. If possible, all patients with LMCA



Figure 5. Radial artery harvesting with the fascia over the artery opened longitudinally to prevent vasospasm.

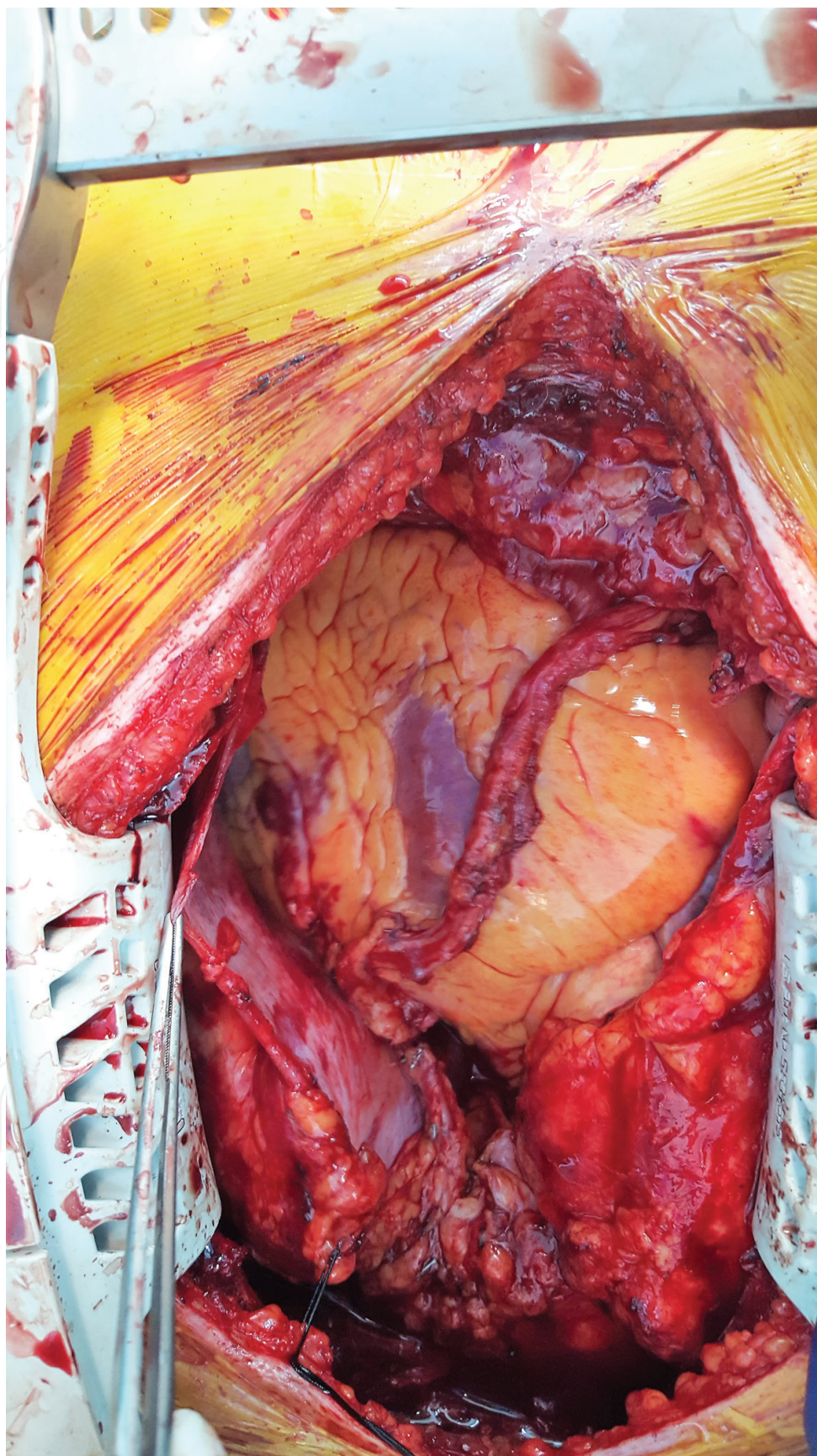


Figure 6. Arterial-only revascularization with LIMA-OM2 and RIMA-LAD anastomoses.

disease who are candidates for surgery deserve LIMA-LAD anastomosis either with on-pump or off-pump CABG surgery. Any surgeon should always target on full revascularization, but PCI should also be kept in mind. The heart team should also be in contact with LMCA patients not only before the operation, but also after the operation for future interventions or medical treatment plan.

9. Conclusion

LMCA disease is still one of the most challenging areas of disease for both cardiovascular surgeons and interventional cardiologists today. CABG offers a survival advantage over medical therapy for significant LMCA disease since medical therapy alone has been associated with poor outcomes. CABG surgery has been accepted as the standard revascularization method for LMCA disease for several decades. In the last decade, several randomized controlled trials have shown favorable results for PCI, and the emerging practice in PCI techniques and new materials has led to almost routine therapeutic option for a subset group of patients with LMCA disease. LMCA disease with low SYNTAX scores (≤ 22) can be treated either by CABG or PCI, whereas SYNTAX score > 32 is an indication for only CABG. The heart team should always be in collaboration, give therapeutic options to patients and decide the best treatment strategy for the welfare of the patient.

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