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Current treatment of left main coronary artery disease

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SOUHRN

Pacienti s těžkou stenózou kmene levé koronární tepny (left main stem, LMS) jsou vzhledem k rozsahu postižení myokardu ve velmi vysokém riziku závažných kardiovaskulárních příhod. Po třech letech dosahuje mortalita farmakologicky léčených nemocných s významnou stenózou LMS 50 %. Za zlatý standard léčby významné stenózy LMS, zvláště při současném postižení několika koronárních tepen, je považován aortokoronární bypass (CABG). Řada studií prokázala, že perkutánní koronární intervence (PCI) může u pacientů pečlivě vybraných týmem kardiologů a kardiochirurgů představovat bezpečnou a účinnou alternativu CABG, s podobnou výslednou mortalitou. Výsledky PCI na LMS se díky neustále dále vyvíjeným technikám PCI a používáním novějších generací lékových stentů trvale zlepšují. Tyto výsledky mohou navíc dále zlepšovat nově zaváděné různé invazivní zobrazovací metody (intravaskulární ultrazvuk nebo optická koherenční tomografie), případně různé způsoby vyšetření hemodynamických poměrů (frakční průtoková rezerva). Tyto novinky v oblasti PCI LMS mohou v budoucnu vést ke změnám současných doporučených postupů v léčbě postižení kmene levé koronární tepny.

Keywords:
Coronary artery bypass grafting
Drug eluting stent
Intravascular ultrasound
Left main stem
Percutaneous coronary intervention

ABSTRACT

The patients with severe left main stem (LMS) stenosis have a very high risk of major cardiovascular events because of the extent of ischaemic myocardium. At 3rd year, the mortality rate for patients with significant LMS stenosis treated medically is 50%. Coronary artery bypass grafting (CABG) is considered the gold standard for the treatment of complex LMS stenosis, especially if it is associated with multivessel coronary disease. Many studies have showed that percutaneous coronary interventions (PCI) can be a safe and efficient alternative to CABG in carefully selected patients by the Heart Team, with similar mortality rates. The LMS PCI results have been continuously improved by the new PCI techniques developed and by the use of newer generation drug eluting stents. Furthermore, different invasive imagistic methods (intravascular ultrasound or optical coherence tomography) or haemodynamic assessment tools (fractional flow reserve) can improve the LMS PCI results. With those new developments in the technique of LMS PCI, the current guidelines about the treatment of left main coronary artery disease can be modified in the future.

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Introduction

Left main coronary artery disease is of particular importance because left main stem (LMS) is responsible for 84% of the blood supplied to left ventricle in case of left coronary dominant system [1]. The patients with severe LMS stenosis have a very high risk of major cardiovascular events because of the extent of ischaemic myocardium. So, we can say that left main coronary artery disease is the most prognostically important coronary lesion. Significant stenosis of LMS is diagnosed in 5–7% of patients undergoing coronary angiography [2]. A three-year mortality rate of 50% has been reported for the patients with significant LMS stenosis treated medically [3]. Many studies have reported survival benefits of coronary artery bypass grafting (CABG) compared to medical treatment alone in LMS stenosis and CABG has been regarded as the gold standard for the treatment of left main coronary artery disease [4–7]. Percutaneous coronary intervention (PCI) was reserved for patients with significant LMS stenosis that had a very high risk for surgery. Many improvements in interventional technologies and techniques and adjunctive pharmacotherapies have been achieved in recent years, that puts the question of whether LMS stenting is safe and efficient compared to CABG. There is a lack of randomised controlled trials of PCI versus CABG in left main coronary artery disease that takes into account the newer techniques that had demonstrated to lower the cardiovascular events (third generation drug eluting stents, kissing balloon post dilatation technique, final proximal optimisation technique, etc.) [8–12]. Therefore, we have reviewed the evidence regarding PCI and CABG in patients with LMS stenosis and we have highlighted the newer development in both treatment modalities and their potential future impact.

Particularities of left main coronary artery disease

LMS arises from left aortic sinus of Valsalva and in two thirds of patients bifurcates into left anterior descending artery (LAD) and left circumflex artery (LCx) and in one third of patients trifurcates into LAD, LCx and ramus intermedius (RI) [13]. This anatomic characteristic of LMS bifurcation is important in distal LMS stenosis because PCI poses more difficulties in a trifurcated then a bifurcated LMS. LMS is divided in three segments: ostium, mid-segment and distal-segment. The segment of LMS that is affected influences the chosen PCI technique [14]. Histologically, the LMS has more elastic fibres than other coronary arteries, which explains the higher restenosis rate after balloon angioplasty due to elastic recoil [15].

LMS has an average length of 10.8 ± 5.2 mm (range 2–23 mm) and an average diameter of 4.9 ± 0.8 mm based on 100-autopsy cases study [16]. This study found that it is a relationship between the length of the LMS and the angle between the branches in which it bifurcates. A larger angle of division is found in long LMS [16].

The most common cause of left main artery disease is atherosclerosis, as with other coronary arteries [17]. Different than LAD and LCx lesions, LMS can be involved in disorder that affects the ascending aorta. Other causes of left main coronary artery disease are: irradiation, Takayasu's arteritis, syphilitic aortitis, rheumatoid arthritis, aortic valve disease, Kawasaki disease, injury after left main coronary intervention or cardiac surgery, aortic dissection [17].

There is a relationship between the length of LMS and the LMS segment that is diseased. In short LMS (< 10 mm), the stenosis are more frequent localised at the ostium then at the distal bifurcation (55% versus 38%), in contrast to long LMS that develops stenosis more frequently near the distal bifurcation compared to near the ostium (77% versus 18%) [18]. The mid segment of LMS is rarely affected (5–7% of patients) [18]. Ostial LMS stenosis are more common in women (44% versus 20%) and are associated with larger lumen area, less calcifications, and more negative remodelling than are mid or distal-bifurcation LMS stenosis [18,19].

It is well known that atherosclerotic plaques tend to develop in low shear stress areas [20]. The part of LMS with the lowest shear stress are the lateral walls of the bifurcation, opposite to the carina. The carina is a high shear stress area, so it is frequently free of disease [21,22]. In the evolution of the atheromatous plaque, the carina can be involved later because of the concentrically extensions of the atheroma. Studies using intravascular ultrasound [23] have showed that in 90% of cases the atheromatous plaques from the distal LMS extends to the proximal LAD [20].

Evidences for medical treatment, surgery and percutaneous coronary interventions in left main coronary artery disease

Medical treatment in left main stenosis

Studies that have evaluated the medical treatment in patients with left main coronary artery disease have included a small number of patients, between 114 and 163. The reported survival rate was 49–50% in patients with LMS disease medically treated [24–26].

Bypass surgery versus medical treatment in left main stenosis

Three old studies (CASS – Coronary Artery Surgery Study; ECSS – European Coronary Surgery Study; VA – Veterans Administration Coronary Artery Bypass Surgery Cooperative Study) on CABG versus medical treatment in patients with LMS disease reported a survival rate of 80–88% for CABG and 63– 68% for medical treatment only [5,6,27].

Sabik el al. [28] have reported their 20-year follow-up of all patients with LMS disease operated between 1971 and 1998. The study which included 3 803 patients showed that the 30-day survival rate was 97.6%, with 93.6% at 1 year, 83% at 5 years and 64% at 10 years. Rates of freedom from coronary reintervention were 99.7% at 30 days, 98.9% at 1 year, 89% at 5 years, 76% at 10 years and 61% at 20 years after CABG [28].

Percutaneous coronary interventions with bare metal stents in left main stenosis

After the initial failure of balloon angioplasty in LMS stenosis and after the abandonment of PCI in this subset of

patients, the development of stenting technique allowed LMS PCI to be reconsidered as a therapeutic option. In the ULTIMA registry, which included 279 patients with LMS stenosis treated with bare metal stents (BMS), the in-hospital and 1-year mortality rates were 13.7% and 24.2% in the high-risk patients subgroup, 0% and 3.4% in the low-risk patients subgroup [29]. 46% of patients from ULTIMA registry had a major contraindication to surgery or they had high surgical risk [29]. In studies which included low risk patients at low surgical risk, in-hospital mortality rate ranged between 0–4.3% and 6–12 months mortality rate ranged between 2.5 to 10.8%, but with a high risk of restenosis (18–31%) and repeat revascularization (7.3–33.6%) [30–34].

Percutaneous coronary interventions with bare metal stents versus bypass surgery in left main stenosis

There is no randomised controlled trial studying percutaneous coronary interventions with BMS versus bypass surgery in left main stenosis. Some data can be obtained from the ASAN-MAIN (ASAN Medical Center-Left MAIN Revascularization) registry which included 100 patients with LMS stenosis treated with BMS and 250 patients treated by CABG [35]. There were no differences in the adjusted risks of death (hazard ratio [HR] 0.81; 95% confidence interval [CI]: 0.44–1.50, $p = 0.50$) and the composite outcome of death/myocardial infarction (MI)/cerebrovascular accident (HR: 0.92; 95% CI: 0.55–1.53, $p = 0.74$) between the two groups [35]. The group of patients treated with BMS had a higher rate of target vessel revascularization (TVR) (HR: 10.34; 95% CI: 4.61–23.18, $p < 0.001$) [35]. A recent analysis of the ASAN-MAIN registry has reported the temporal trends in revascularization strategy and outcomes in LMS stenosis. The outcomes of unprotected left main coronary artery PCI have significantly improved over time, with lower rates of major adverse cardiac and cerebrovascular events (MACCE), death, MI, stroke and repeat revascularization [36].

In a recently published multicenter registry analysis that compared the efficacy of DES versus BMS in the treatment of LMS stenosis the DES group had significantly lower 5-year rates of major adverse cardiac events (MACE) (19.4% vs. 31.8%, $p = 0.022$), CV death (7.0% vs. 14.7%, $p = 0.045$), and MI (5.4% vs. 12.4%, $p = 0.049$) than the BMS group. There were no significant differences in the rate of target lesion revascularization (10.9% vs. 17.8%, $p = 0.110$) and stent thrombosis (4.7% vs. 3.9%, $p = 0.758$) [37].

Percutaneous coronary interventions with drug eluting stents in left main stenosis

Drug eluting stents is one of the most important developments that boosted the utilisation of PCI in the treatment of LMS stenosis. In a meta-analysis of 1 278 patients with LMS stenosis treated with DES the mortality rate was 5.5%, the MACE rate was 16.5% and TVR rate was 6.5% [38]. The reported rates of stent thrombosis were mostly low (0–4%) [39]. The MACCE rate reported by the FRIEND registry was 10.6% at 450 days [40].

In a small study of 103 patients with LMS disease randomly assigned to BMS or DES implantation, the rate of restenosis and TVR were lower in the DES group (6% versus 22% and 2% versus 16%, respectively) [41]. An important reduction in the composite outcome of death, MI and TVR was achieved with the use of DES compared to BMS (13% versus 30%) [41]. This effect was attributable to the lower rate of repeat revascularization in the DES group.

The newer drug eluting stents are promising in term of safety and efficacy in the treatment of unprotected LMS stenosis, according to the NEST registry [42]. 154 patients with left main coronary disease were treated with everolimus- (44.2%), zotarolimus- (29.9%) and biolimus A9-eluting (25.9%) stents and they were followed up for 2 years. The MACE rate was 18.8% at 2 year follow-up and there was no case of MI or definite stent thrombosis. 4.5% of patients needed repeat revascularization of the target vessel [42]. Superimposable results were reported in a study with sirolimus eluting stents in patients with LMS stenosis after 5-year follow up [43].

Everolimus eluting stents (EES) was compared to paclitaxel eluting stents [44] in the treatment of LMS stenosis using the results of the French Left Main Taxus and the LEft MAin Xience registries [45]. After 2 year follow up, there was a reduction by 53% in target lesion failure – a composite endpoint of cardiac death, target vessel myocardial infarction and clinically driven target lesion revascularization – with EES versus PES (7.6% versus 16.3%, $p = 0.01$). The use of EES was associated with lower rates of target vessel myocardial infarction (4.1% versus 9.9%, $p = 0.04$) and target vessel failure (7.6% versus 16.3%, $p = 0.01$) [45].

In the ERACI IV study, the second generation DES has been compared with the first generation DES in patients with multiple vessel disease and unprotected left main stenosis. At one year, patients treated with second generation DES compared to first generation DES had lower incidence of death (0.4% vs. 3.1%, $4p = 0.03$), death/MI/stroke (0.9% vs. 6.7% $p = 0.001$), unplanned revascularization (1.8% vs. 8.9%, $p = 0.001$) and MACCE (2.2% vs. 12%; $p =< 0.001$). In ERACI IV, advantages were also observed in diabetics [46].

There are recent studies showing that newer DES and self-apposing stents offer a valid alternative for the treatment of the distal LMS lesions [47–49].

Overall, DES in LMS PCI are showing a good efficacy and safety profile and are recommended over BMS.

Percutaneous coronary interventions with drug eluting stents versus bypass surgery in left main stenosis

Randomised controlled trials

The first prospective randomised controlled trial on PCI versus CABG in patients with LMS stenosis was LeMans trial. The biggest limitations of this trial were the small number of patients (52 patients in the PCI group and 53 patients in the CABG group). Approximately one third of patients in the PCI group received DES, and in more than two thirds of patients in the CABG group left internal mammary artery was used. At 1-year follow-up, there was no difference between the two groups in the secondary endpoints of survival and MACCE [44].

Important data came from the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial which enrolled 1 800 patients with three-vessel or left main coronary artery disease to undergo CABG or PCI (in a 1 : 1 ratio) [50]. From the group of patients with left main coronary artery disease, 357 patients were treated by PCI with paclitaxel eluting stents (TAXUS) and 348 patients by CABG. At

1-year follow-up there was no difference between groups in the primary endpoint of MACCE (13.7% in the CABG group versus 15.8% in the PCI group, $p = 0.44$) [50]. There was a higher rate of TVR in the PCI group (11.8% versus 6.5%, $p = 0.02$) and a higher incidence of stroke in the CABG group (2.7% versus 0.3%, $p = 0.01$) [50]. This difference persisted in long-term follow-up [51]. At 3-year follow up, there were some differences between low, intermediate and high SYNTAX score groups. In patients with low and intermediate SYNTAX score there was no difference in MACCE rate between the two groups (23% in the CABG group versus 18% in the PCI group, $p = 0.33$). The MACCE rate was significantly higher for PCI in the high SYNTAX score group (21.2% in the CABG group versus 37.3% in the PCI group, $p = 0.003$) [51,52]. The same results were found after 5-year follow up [52,53]. Because this important differences were driven from subgroup analysis which is prone to biases, further well powered trials are advisable.

Recently, the results of PRECOMBAT (PREmiere of COMparison of Bypass Surgery and Angioplasty Using Sirolimus-Eluting Stents in Patients With Unprotected Left Main Coronary Artery Disease) trial were published [54]. It was a prospective and multicenter study on 600 patients with unprotected left main coronary disease randomised in a 1 : 1 fashion to PCI with sirolimus eluting stent (Cypher) or CABG. The primary composite end point of MACCE (death from any cause, MI, stroke, or ischaemia-driven TVR) was similar at 1-year and 2-year follow-up in the two groups (8.7% in the PCI group vs. 6.7% in the CABG group, $p = 0.01$ for non-inferiority and 12.2% in the PCI group vs. 8.1% in the CABG group, $p = 0.12$). The ischaemia-driven TVR rate was higher in the PCI group at two year follow--up (9.0% vs. 4.2%, $p = 0.02$) [54].

In 2015, Ahn et al. published the 5-year results of PRECOMBAT trial. During 5- year follow-up, this study did not show significant difference regarding the rate of MACCE between patients who underwent PCI with a sirolimus--eluting stent and those who underwent CABG [55].

PCI with the newer generation DES will be studied versus CABG in patients with LMS stenosis and SYNTAX score < 33 in the ongoing EXCEL trial (evaluation of Xience Prime or Xience V-eluting stent vs. CABG for effectiveness of LM revascularization) [56]. Recently, some results from the EXCEL trial have been published showing that clinical characteristics shifted long-term mortality predictions either in favour of PCI (older age, male gender and chronic obstructive pulmonary disease) or CABG (younger age, lower creatinine clearance, female gender, reduced left ventricular ejection fraction) [57,58].

Registry data

MAIN-COMPARE registry was one of the most important long-term studies comparing PCI with DES or BMS with CABG in 2 240 patients with unprotected LMS stenosis [59]. The incidence of death and the composite of death, Q-wave MI, or stroke did not differed in the PCI and CABG groups, at 3-year follow-up, regardless of the type of stent used, BMS or DES [59]. DES and BMS were associated with a 6 times and 10 times, respectively, higher risk of repeat revascularization for target vessel failure than CABG [59].

The recently published CREDO-Kyoto PCI/CABG Registry Cohort-2 results showed that the adjusted risk for death/MI/stroke was not significantly different between the group of patients with unprotected LMS stenosis treated by PCI versus the group treated by CABG in patients with low (< 23) or intermediate (23–33) SYNTAX score, whereas it was significantly higher in the PCI group than in the CABG group in patients with high (≤ 33) SYNTAX score [60].

In a subanalysis of DELTA (Drug-Eluting stent for LefT main Artery) registry, there was no difference in the rate of primary endpoint (the composite of death, stroke, and MI) in octogenarians with LMS stenosis treated by PCI with DES or CABG (32.6% vs. 30.2%, $p = 0.69$). However, the rate of target vessel revascularization was higher in the PCI group (10% vs. 4.2%, $p = 0.05$) [61]. Similar results were found in another analysis of DELTA registry that compared PCI with DES versus CABG in ostial/midshaft LMS lesions [62].

Meta-analyses

In 2010 was published a meta-analyse of 18 studies enrolling 5 483 patients with left main artery disease. 3 357 patients were treated by CABG and 2 126 by PCI with DES. There were small differences between PCI and CABG at 1-year in terms of death (PCI versus CABG, OR = 0.93, 95% CI, 0.65–1.33), MI (PCI versus CABG, OR = 1.18, 95% CI, 0.59–2.32), MACE (PCI vs. CABG, OR = 1.54, 95% CI, 0.82–2.87) and MACCE (PCI versus CABG, OR = 1.35, 95% CI, 0.99–1.84). The rate of repeat revascularization was higher in the PCI group (PCI versus CABG, OR = 6.47, 95% CI, 3.86–10.84) and the rate of cerebrovascular accidents was higher in the CABG group (PCI versus CABG, OR = 0.32, 95% CI, 0.15–0.68) [63].

Others meta-analyses have generated similar findings [64].

Percutaneous coronary interventions with bioresorbable vascular scaffold in left main stenosis

The experience with bioresorbable vascular scaffolds (BVS) for the treatment of left main stenosis is very limited. There are different case reports of LMS stenosis treated by implantation of one or two BVS with good angiographic and clinical results [65–68]. In ostial LM lesions, the use of BVS has the advantage of avoiding permanent metal struts protruding into the aorta [69]. The implantation technique of BVS is challenging in LMS stenosis because of the need of very good predilatation and progressively inflation of the stent.

Percutaneous coronary intervention versus bypass surgery in left main coronary artery disease – what actual guidelines say?

Both, American and European guidelines on myocardial revascularization state that a Heart Team approach should be used in the management of patients with left main coronary artery disease [70–72]. Any LMS stenosis > 50% have a class I A indication for revascularization based on prognostic reasons [72]. The choice of PCI or CABG is made according to the clinical features of the patient, anatomic features of LMS stenosis and surgical risk.

CABG has a class I B indication in patients with significant LMS stenosis, but PCI can be an alternative as good as CABG in carefully selected patients (Table 1) [71].

Table 1 – Indications for percutaneous coronary interventions in left main coronary artery disease according to American and European guidelines [70,71]

Class I B
Left main disease with a SYNTAX score ≤ 22 and low predicted surgical mortality [71]
Class IIa B
Left main disease with a SYNTAX score 23–32 and low predicted surgical mortality [71]
Isolated ostial or mid shaft left main disease ± 1 vessel disease in patients with stable coronary artery disease, with anatomic features associated with a low risk of PCI procedural complications[a] and clinical characteristics that predict a significantly increased risk of adverse surgical outcomes[b] (STS ≥ 5%) [70,71]
Left main disease in patients with unstable angina or non ST segment elevation myocardial infarction which are not CABG candidates [70]
Left main disease in patients with ST segment elevation myocardial infarction, with TIMI flow grade < 3, when PCI can be performed more rapidly and safely than CABG [70]
Class IIb B
Isolated distal left main disease ± 1 vessel disease [70]
Left main stenosis + 2 or 3 vessel disease in patients with stable coronary artery disease, with anatomic features associated with a low-intermediate risk of PCI procedural complications,[a] SYNTAX score ≤ 32 and clinical characteristics that predict and increased risk of adverse surgical outcomes[b] [70]
Class III
Left main disease with a SYNTAX score > 32

[a] Anatomic features that favours PCI: ostial and mid shaft left main lesions, non-calcified lesions, absence of severe tortuosity, absence of chronic total occlusions, few additional lesions on the other coronary vessel, preserved left ventricle ejection fraction.
[b] Clinical features that favours PCI: elderly patients (octogenarians), small left circumflex artery, non-diabetic patients, poor surgical candidates (distal coronary disease unfavourable to CABG), high surgical risk according to EuroSCORE or STS score, important comorbidities (e.g., moderate-severe chronic obstructive lung disease, disability from prior stroke, prior cardiac surgery), limited life expectancy, emergency clinical situations like ST segment elevation myocardial infarction or cardiogenic shock, absence of contraindications to antiplatelet therapy, patient refusal of CABG.

Risk stratification in left main stenosis

Different scoring systems have been proposed to predict clinical outcomes in patients with LMS stenosis treated by PCI or CABG.

The SYNTAX score is an anatomical risk-based score that takes into account the morphology and complexity of coronary lesions [73]. In the SYNTAX trial, patients in the lower two tertiles of SYNTAX score have non-ostial LMS lesions, isolated LMS lesions or LMS lesions associated with single-vessel disease. Patients with high SYNTAX score have multivessel disease [74]. As we have seen, SYNTAX score can predict outcomes after PCI or CABG in patients with LMS stenosis.

The logistic clinical SYNTAX score has combined the anatomical variables from the original SYNTAX score with different clinical variables. This new risk score model has a higher predictive ability to determine the 1-year all-cause death [75,76].

The Parsonnet score is an operative risk score, which include 14 clinical variables. Many studies have found that Parsonnet score can predict MACCE in patients with LMS stenosis treated by PCI [77,78].

The additive EuroSCORE is a risk model for estimating the operative mortality in patients undergoing CABG, but in some report additive EuroSCORE was an independent predictor of death or MI rate after LMS PCI [79].

The New Risk Classification Score (NERS) includes 17 clinical, 4 procedural and 33 angiographic variables. It has the ability to predict MACE at 30 days and at over 5 years follow-up in patients with LMS stenosis treated by PCI [80].

Intravascular ultrasound, optical coherence tomography and fractional flow reserve in left main coronary disease

Intravascular ultrasound

Pre-PCI IVUS can be useful in detecting the real length of the lesions, the plaque distribution and morphology and the vessel diameter [81]. Those parameters can guide the decision of treating the lesion, the choice of stent size and stent length and the technique to use [19]. In LITRO study and other studies, an IVUS-derived minimum lumen area (MLA) value < 6.0 mm^2 and an IVUS-derived minimum lumen diameter (MLD) value < 2.8 mm were associated with a fractional flow reserve (FFR) < 0.75, which was used to measure the haemodynamic significance of LMS stenosis [82,83]. There are other studies that have found different results regarding the MLA value under which a LMS stenosis can be considered hemodynamically significant [84]. Thus, the actual recommendations is to use FFR or a non-invasive stress test in patients with LMS stenosis and an IVUS-derived MLA < 6.0 mm^2 in order to decide to treat or not [85,86].

Post-PCI IVUS can be useful to determine the minimal stents areas in LMS, at the LMS bifurcation, in LAD and LCx ostium [87]. A minimal stent area (MSA) < 8 mm^2 in the proximal LMS, < 7 mm^2 in the LMS bifurcation, < 6

mm^2 in ostial LAD and <5 mm^2 in ostial LCx were associated with stent underexpansion, increased instent restenosis rate at 9 months and increased MACE rate at two-year follow up [88–91]. Separate IVUS pullbacks of the LAD and LCx are advised to accurately measure the MLA or MSA, because LCx ostial measurements cannot be reliable assessed obliquely from the LAD to LMS [92].

A recent study have highlighted the potential benefit of IVUS guided PCI in reducing MACE at 2-year follow up in elderly patients with unprotected left main coronary artery stenosis (MACE in IVUS guided PCI group versus control group 13.1% versus 29.3%, $p = 0.031$). IVUS guidance was an independent factor of survival free of MACE (HR: 0.414, CI: 0.129–0.867; $p = 0.033$) [93]. Those findings were confirmed in a recent pooled analysis of 4 registries [23].

Optical coherence tomography

Optical coherence tomography (OCT) is a safe and feasible method of assessing MLA, MSA, stent diameter and length and stent apposition in patients with LMS stenosis [94]. Newer generation OCT systems (frequency-domain [FD] – OCT) are more sensitive than IVUS in detecting stent malapposition and edge dissections in LMS stenting, but are as good as IVUS in the assessment of lumen and stent dimensions [95,96].

Three-dimensional (3D) OCT is a very good solution in obtaining information in patients with stented LMS stenosis about carina or plaque shift and side branch compromise [97]. When stenting the LMS to LAD, the lumen of LCx can be compromised primarily by carina shift, and less frequent by plaque shift, especially in LMS bifurcation with a narrow angle between the LAD and LCx. Although, FFR measurement can show a hemodynamically nonsignificant carina shift in LCX after stenting the LMS to LAD, IVUS studies have shown that a MSA > 5 mm2 in the LCx is associated with a lower rate of MACE at 2-year follow-up [90]. 3D-OCT can be used in identifying "floating struts" at the side branch ostium which can be a good place for neointimal hyperplasia [98]. Those are two reasons for the rationale of final kissing balloons post dilatation in bifurcation lesions [97].

Fractional flow reserve

FFR is a good tool to determine the severity of left main stenosis. There are studies showing that patients with intermediate LMS stenosis in which revascularization was deferred if FFR was ≥ 0.75 have the same outcomes with patients with significant LMS stenosis treated with CABG at 5-yeas follow-up [99–101].

When performing FFR in LMS lesions, we must take into account the severity of lesions in the proximal segment of LAD or LCx. FFR measurements in LMS stenosis with the pressure wire in a nonstenosed downstream vessel were influenced only when the stenosis in the other vessel is proximal and very severe [102–104].

FFR can be used to study the stenosis degree of the side branch when one stent technique is chosen for a distal LMS stenosis, with the stent being implanted from the LMS to the distal main branch. Previous studies on bifurcation lesions have showed that only in 27% of cases with a residual angiographic narrowing of ≥ 75% in the side branch ostium, the FFR measurement showed a haemodynamic significant side branch narrowing [105–107]. Probably, these results can be extrapolated to LMS lesions.

Long-term follow-up after percutaneous coronary intervention in left main stenosis

Patients with PCI with DES for LMS stenosis have comparable rates of sudden cardiac death or stent thrombosis with patients with PCI for non-LMS stenosis [108]. In DELFT registry, the rates of definite, probable and possible stent thrombosis following LMS stenting with DES were 0.6%, 1.1% and 4.4%, respectively, after three-year follow-up [109]. The ISAR-LEFT MAIN trial reported a 0.5–1.0% rate of definite or probable stent thrombosis in patients with LMS lesions [110]. Those are the reasons for the abandonment of the routine angiographic surveillance after LMS PCI.

Although, DES reduces the in stent restenosis (ISR) rate, in the context of LMS PCI in stent restenosis represents an important problem in this subgroup of patients. The principal risk factors for ISR in LMS PCI are: distal LM involvement, two stents strategies, diabetes, renal failure and stent underexpansion [111]. As we have already shown, IVUS can guide the procedure to obtain an adequately stent expansion, which can reduce the rate of ISR [89]. Multislice computed tomography can be a safe and reliable non-invasive method of excluding significant left main ISR [112].

There is no distinct recommendation for the duration of dual antiplatelet therapy after DES implantation in patients with LMS stenosis. Current guidelines should be respected in this subset of patients when considering the duration of dual antiplatelet therapy [71]. Interesting results are coming from a study on 215 patients who underwent LMS PCI with DES and platelet reactivity assessment by light transmission aggregometry at least 12 hours after a loading dose of 600 mg of clopidogrel. At 3-year follow up, the mortality and stent thrombosis rates were higher in the group of patients with a high residual platelet reactivity [113]. These results request for new studies to clarify if there is any need for tailoring the antiplatelet therapy according to platelet reactivity tests in patients with LMS PCI.

Techniques for percutaneous coronary intervention of left main stem lesions

Ostial and mid shaft left main stem stenosis

Ostial and mid shaft LMS stenosis are treated with one stent strategy [114]. The operator must pay attention at choosing the best angiographic view (anteroposterior-cranial or left anterior oblique-cranial) to adequate visualise the ostium of LMS and to proper position the stent. Techniques that help the ostial stent placement are the Szabo technique or the passage of a second coronary guide wire into the aortic root to prevent selective engagement of guiding catheter into the coronary ostium. The implantation of the stent for ostial LMS stenosis must be done with a small protrusion into the aorta to ensure adequate ostium coverage. After implantation, it is important to withdraw the balloon into the aorta and to postdilate the stent to obtain a "flared" proximal part of the stent that

ensures a good stent apposition at the ostium and facilitate the reengagement of the ostium with the catheter [19].

Distal left main stenosis

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. Different studies have showed that single-stent strategy resulted in a lower MACE rate, TVR rate and event-free survival rate at 2 years [115–117]. Patients with distal LMS stenosis treated with single stent strategy have a TVR rate relatively low (< 5%), nearly equivalent to patients with ostial or mid-shaft LMS stenosis treated by the same strategy [77,118]. TVR rates as high as 25% have been reported after the treatment of distal LMS stenosis by two-stents strategy [118,119]. Those results are reported in studies using DES in the majority of patients.

However, a recent large single centre study comparing one-stent versus two-stent technique for treatment of left main bifurcation lesions have yielded different results. At mean 4-year follow-up, rates of MACE (one stent: 9.2% vs. two stents: 11.6%, $p = 0.23$), death, MI, and target vessel revascularization were similar between groups. In multivariate propensity-matched regression analysis, two-stent technique was not predictive of MACE. The two-stents technique included in 96% of cases the final kissing balloons postdilatation. Around 50% of PCIs were guided by IVUS [120].

Recently, dedicated bifurcation stents or self-expandable stents (TRYTON, AXXESS, BiOSS, STENTYS) were used for the treatment of distal LMS stenosis. Early results are encouraging, but definite conclusions are still awaited [121–125].

Single-stent strategy

Provisional T-stenting is the most frequent used strategy. It consists of the deployment of a single stent from LMS to the LAD or LCx, whichever has the highest diameter. The stent is postdilatated in its proximal part from the LMS using proximal optimisation technique (POT) [126]. The side branch (most frequently the LCx) can be left untouched, but there are arguments for performing the final kissing balloons postdilatation (KBPD) [126]. Provisional T-stenting allows the placement of a second stent into the side branch if it is severely narrowed [85]. In a recent study, the simple crossover LMS-to-LAD stenting without opening of a strut on the LCx ostium was associated with acceptable long-term clinical outcomes [127].

Two-stent strategy

The angle between LMS branches dictates the choice of the two-stent strategy. When this angle approaches 90° the T-stenting technique is used and when the angle is < 60° strategies which generate a new carina are used, like: mini-crush, T-stenting and protrusion or V-stenting techniques. Other two-stent techniques are culotte technique and simultaneous kissing stents technique [19]. The choice of the two-stent strategy used depends on the morphology of the lesion and operator preference. The choice of which two-stent strategy to use in distal LMS stenosis has not been shown to affect 2-year survival rate and MACE rate [115,128]. Whenever the two-stent strategy is used, final KBPD is mandatory [19,128].

Discussions and future perspectives

PCI of the LMS stenosis is a challenging procedure for the interventional cardiologist, which continuously develops. Ever since the development of PCI for the treatment of LMS stenosis, there was a great dispute which is the best technique, PCI or CABG. Important studies showed that PCI can be a safe, reliable and efficient alternative to CABG in carefully selected patients with LMS stenosis, with similar mortality and morbidity rates.

In stable conditions, the selection of a patient with LMS stenosis for PCI must be done by the local Heart Team, after taking into account the anatomical, clinical and surgical risk scores (SYNTAX score, Parsonnet score, EuroSCORE, clinical SYNTAX score, logistic SYNTAX score, NERS) and patient preference. PCI for LMS disease can be a lifesaving solution in unstable conditions, like ST segment elevation myocardial infarction.

CABG remains the gold standard for patients with left main coronary artery disease and multivessel disease when the SYNTAX score is high. We should not forget that the studies evaluating PCI versus CABG in patients with LMS stenosis were conducted using first generation DES. Newer generation DES can improve the outcomes. Moreover, important progress was done in the improvement of the PCI technique for the bifurcation of LMS (POT, KBPD). There are encouraging reports showing similar outcomes between one-stent strategy versus two-stent strategy in the treatment of distal LMS stenosis when KBPD is routinely implemented and the PCI is guided by IVUS. The ongoing EXCEL trial (evaluation of Xience Prime or Xience V-eluting stent vs. CABG for effectiveness of LM revascularization) will determine the safety and efficacy of newer generation DES versus CABG in patients with LMS stenosis and SYNTAX score < 33.

LMS PCI guided by different invasive imagistic methods (IVUS or OCT) or hemodynamic assessment tools (FFR or iFFR) can improve the results of the procedure and the long-term outcomes. If locally available, those investigations should routinely been used.

The place of the BVS and dedicated bifurcation stents has still not been found in the treatment of left main coronary artery disease.

According to current guidelines, patients with less complex left main coronary artery disease can be treated by PCI and more complex LMS lesions by CABG. In the future, with the results of ongoing trails, actual guidelines can be modified.

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All authors declare that the research was conducted according to Declaration of Helsinki.

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