Chapter

Current Status, Perspectives, and Future Directions of Multivessel Disease and Left Main Coronary Disease: Its Treatment by PCI or Surgery

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Abstract

MVD has evolved from an era where it was mandatory to treat all lesions, even very thin vessels. With the advent of more realistic anatomical scores such as the ERACI score and the gradient measurements with the fractional flow of reserve (FFR) and instantaneous wave-free ratio (iwFR), a more conservative era has begun, which benefits the patient in the long-term follow-up. The treatment of the LMCA remains a challenging lesion because of the amount of irrigation. It can be divided the treatment of the LMCA with a low or high ERACI score, in the first group is where the PCI has gained in confidence and dedication in addition to knowledge and bifurcation techniques. The second group with high score can only be performed in centers with high PCI experience, since their alternative will always be surgical as the first choice. The revascularization in MVD with STEMI, the priority is the culprit vessel and then evaluate the underlying lesions, an invasive or with a functional test in the short term. The patient with DM is a singular patient, and its treatment should always be evaluated by a multidisciplinary team. We believe that patients with low ERACI score have the possibility of being treated with PCI, but patients with high score are surgical.

Keywords: MVD, PCI, CABG, DM, MI, LMCA, MACCE, BMS, DES

1. Multivessel disease

1.1 Introduction

The revascularization of multivessel disease (MVD) has advanced considerably and has gone through periods where angioplasty with the advent of conventional stents (BMS) was competitive with surgery [1]. After the incorporation of drug-eluting stents (DES) with the significant reduction of the revascularization of the treated vessel, it was thought that the percutaneous coronary intervention (PCI) would be superior to coronary artery bypass graph (CABG), with the advent of the SYNTAX trial [2], which also incorporated an anatomical score that revolutionized the way of stratifying the patients. Although this trial used stents that are not

currently marketed, called first-generation DES, later came trials with second-generation stents that also failed to achieve the desired results [3]. An important element was the incorporation of the in vivo functional study of the lesion and its relation with the prognosis, which is the fractional flow of reserve (FFR) [4] and their instantaneous wave-free ratio (iwFR) [5], which gave a physiological view of the coronary disease and its treatment, although its use in stable patients such as the ORBITA trial [6] failed both by design and by results, since 85% of patients are finally revascularized, and the first randomized trial to assess functional lesion testing before CABG found patients who underwent FFR before CABG experienced similar rates of graft failure at 6 months as those who received angiography-guided by surgery [7]. We re-evaluated the SYNTAX score [8] first, and thus we generated an ERACI score [9] more in line with the modern treatment of severe and rational injuries at the time of complete revascularization, targeting medium-to-large caliber vessels, since only 70% lesions were included and vessel lesions larger than 2 mm were included.

1.2 Main trails of PCI vs. CABG and meta-analysis in MVD

In our Argentine Randomized Trial of Coronary Angioplasty With Stenting vs. Coronary Bypass Surgery in Patients With Multivessel Disease (ERACI II) 1, where patients were randomized to PCI with BMS vs. CABG after 5 years of follow-up, there were no significant differences in the mortality of all causes, PCI 7.1% vs. CABG 11.5%, $p = 0.182$. In terms of nonfatal MI, the incidence was 6.2% in the CABG group and 2.8% in the PCI group ($p = 0.128$), where a significant difference was observed in the need for new revascularization, 7.2% in the CABG group and 28.4% in the PCI group ($p = 0.0002$). MACCE was also larger in the PCI group than in the CABG, 24.5% vs. 34.7% ($p = 0.019$). A high rate of patients was asymptomatic without significant differences in both groups. The first randomized trial of patients with first-generation DES vs. CABG and with the creation of an anatomical score to assess severity divided the patients into three groups. This score was based on obstructions of at least 50% in vessels greater than 1.5 mm. Although this very basic score served to stratify patients, the SYNTAX study [2] compared CABG and PCI, followed by placement of paclitaxel-eluting stent in patients with MVD or left main disease (LMCA) or both. At 5 years of follow-up, it was observed that the MACCE between the two groups was significantly higher for the PCI group 37.3% than with the 26.9% CABG ($p < 0.0001$). The MI and the TVR was significantly higher in the PCI group than with surgery, but the mortality of all causes as well as the stroke was not significantly different between the two groups. When analyzed by groups, in the SYNTAX of low score ≤ 22, the MACCE was similar between both groups, but when analyzing intermediate scores 23–32 and high ≥ 33, it was significantly higher with PCI commensurate with CABG. The randomized trial was subsequently carried out with the so-called second-generation DES. In the Randomized CABG and Everolimus-Eluting Stent EES Implantation in the Treatment of Patients with MVD, the BEST trial [3] was performed in 27 sites in East Asia and showed PCI with placement of EES. This study had as its primary end point the composite events of death, MI, and TVR. At 2 years of follow-up, it was observed that there were no significant differences with 11% events in the PCI group compared with 7.9% in the CABG group ($p = 0.32$ for non-inferiority). In the long-term follow-up (4.6 years on average), the events of the primary end point occurred in 15.3% of patients in the PCI group and in 10.6% of those in the CABG group ($p = 0.04$). This is due to an excess of new interventions in the PCI group, since the TVR was significantly higher in the PCI group (11.0% vs. 5.4%, $p = 0.003$). There were no significant differences in mortality between the two groups, 6.6% in the PCI group and

5% in the CABG group (p = 0.30), as well as with the stroke (2.5 and 2.9%, respectively; p = 0.72). The MI was higher in the PCI group than the CABG 4.3% vs. 1.6%, respectively p = 0.02. A recent meta-analysis of Brazilian origin [10] that includes randomized clinical trials (RCT) of multivessel disease performed a group analysis. They identified a total of 15 RCT that satisfied the requirements. The following results were obtained in the pooled data (n = 12,781). Thirty-day mortality and stroke were lower with PCI (1% vs. 1.7%, p = 0.01; and 0.6% vs. 1.7%, p < 0.0001). There was no difference in 1- and 2-year mortality (3.3% vs. 3.7%, p = 0.25; 6.3% vs. 6.0%, p = 0.5). Long-term mortality favored CABG (10.6% vs. 9.4%, p = 0.04), particularly in trials of DES era (10.1% vs. 8.5%, p = 0.01). In diabetics (DM) (n = 3274) long-term mortality favored CABG (13.7% vs. 10.3%, p < 0.0001). In six trials of LMCA (n = 4700), there was no difference in 30-day mortality (0.6% vs. 1.1%, p = 0.15), 1-year mortality (3% vs. 3.7%, p = 0.18), and long-term mortality (8.1% vs. 8.1%) between PCI and CABG. The incidence of stroke was lower with PCI (0.3% vs. 1.5%, p < 0.001). DM and a high SYNTAX score were the subgroups that influenced more adversely the results of PCI (**Table 1**).

1.3 "Functional" complete or anatomic complete revascularization

The fractional flow reserve allows to measure the functional capacity of a stenosis, and if it establishes a threshold of 0.80 (which is equivalent to a maximum intracoronary pressure drop of 20%), it determines a degree of ischemia. In fact, the use of this guide in patients with MVD showed that residual angiographic lesions that were functionally nonsignificant did not cause worse evolution [11] and thus indicated that they do not need treatment, giving a complete revascularization (CR) functional rather than anatomical, since the degree of injury is less important than its functional impact, as well as the magnitude of the territory that irrigates. However, the concept of "functional" CR with PCI was introduced many years ago even when FFR was not available. The ERACI I one of the first randomized clinical trials between PCI and CABG in MVD [12] showed similar outcomes in patients with complete "functional" revascularization achieved with PCI and guided by noninvasive tests and in those with complete "anatomic" revascularization achieved with CABG.

1.4 ERACI risk score

The ERACI IV study [13] was a multicenter, observational, and prospective registry with a second-generation DES in patients with MVD and LMCA. We built a score based on our experience in the treatment of patients with more realistic MVD; since our group led by Dr Rodriguez et al. aimed to treat more critical vessel lesions that irrigate a significant territory, based on this concept we created the ERACI score (ES) by modifying the SYNTAX score (SS), as well as the difference between the treated and residual lesions, their corresponding residual ES or residual SS. This reformulated score included lesions greater than or equal to 70% in vessels larger than 2 mm. The analysis of the bifurcations and CTO was preserved as in the previous score. We included in a novel way the restenosis of the treated vessel that was cataloged as a severely calcified lesion. The rest of the variables were preserved as in the previous score [9] (**Figure 1**). The rationality of this revised score was previously published in our *Journal of Interventional Cardiology* of Argentina (RACI) 3 years ago [9]. With this new modality of scoring with the ES in the ERACI IV study, more than half of the patients had a low ES, and only 17% of the patients had a high score, in contrast to the SS that 34% of the patients were with a high score. The first analysis of this data is that with this score patients are re-categorized into a lower-risk group so they could be treated with either PCI or CABG. When we analyzed the residual untreated

Study	Origin	Date	N	MVD	Characteristics	UA	EF	Off-pump	DM	Outcome
AWESOME [76]	USA	1995–2000	454	2v and 3v	BMS, CABG previous	36	45	0	32	Survival rates for CABG and PCI were 79% versus 80% at 36 months (log-rank test, p = 0.46)
ARTS [77, 78]	International	1997–2000	1205	2v and 3v	BMS, majority 2v	30	61	0	21	Event-free survival at 5 years: 58.3% for PCI vs. 78.2% for CABG (p < 0.0001)
ERACI II [1]	Argentina	1196–1998	450	2v and 3v	BMS, majority UA	92	ND	0	17	Freedom from MACE at 5 years was lower with PCI than with CABG (65.3% vs. 76.4%; p = 0.013)
SOS [79]	Europe and Canada	1995–1999	988	2v and 3v	BMS, majority 2v	33	Nd	3	15	At a median follow-up of 6 years, 53 patients (10.9%) died in the percutaneous coronary intervention group compared with 34 (6.8%) in the CABG group (HR, 1.66; 95% CI, 1.08–2.55; p = 0.022)
MASS II [80]	Brazil	1995–2000	408	2v and 3v	BMS, clinical arm	36	65	0	30	The 10-year survival rates were 74.9% with CABG, 75.1% with PCI, and 69% with MT (p = 0.089)
LEMANS [29]	Poland	2001–2004	105	LMCAD	BMS and DES, DES if LM < 3.8	32	53	0	25	At 10 years, the mortality of PCI vs. CABG was (21.6% vs. 30.2%; p = 0.41) and MACCE (51.1% vs. 64.4%; p = 0.28)
SYNTAX [2]	Europe and USA	2005–2007	1800	LM and 3v	DES Taxus	28	Nd	15	35	5-year MACCE in all: 37.3% for PCI vs. 26.9% for CABG (p < 0.001) 5-year MACCE in 3 VD: 37.5% for PCI vs. 24.2% for CABG (p < 0.001)
CARDia [74]	UK	2002–2007	510	2v and 3v	BMS and DES, only DBT	22	59	31	100	At 1 year of follow-up, the composite rate of death, MI, and stroke was 10.5% in the CABG group and 13.0% in the PCI group (HR, 1.25; 95% CI, 0.75–2.09; p = 0.39)
Boudriot et al. [81]	Germany	2003–2009	201	LMCAD	DES (Sirolimus)	ND	ND	46	30	At 1 year of follow-up, the combined primary end point was 13.9% of patients after surgery, as opposed to 19.0% after PCI (p = 0.19 for non-inferiority)
PRECOMBAT [28]	Korea	2003–2009	600	LMCAD	DES (Everolimus)	45	60	64	42	At 5 years, MACCE in PCI group and the CABG group (cumulative event rates of 17.5% and 14.3%, respectively; HR, 1.27; 95% CI, 0.84–1.90; p = 0.26)

Study	Origin	Date	N	MVD	Characteristics	UA	EF	Off-pump	DM	Outcome
FREEDOM [67]	International	2005–2010	1900	2v and 3v	DES, only DBT	30	65	19	100	The primary outcome occurred more frequently in the PCI group (p = 0.005), with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group
Va-Cards [73]	USA	2006–2010	198	2v and 3v	DES, only DBT	Nd	Nd	Nd	100	At 2 years, all-cause mortality was 5.0% for CABG and 21% for PCI (HR, 0.30; 95% CI, 0.11–0.80); nonfatal myocardial infarction was 15% for CABG and 6.2% for PCI (HR, 3.32; 95% CI, 1.07–10.30)
BEST [3]	Korea	2008–2013	880	2v and 3v	DES (Everolimus)	42	59	64	45	MACE at 4.6 years: 15.3% for PCI vs. 10.6% for CABG (p = 0.04)
EXCEL [31]	International	2010–2014	1905	LMCAD	DES (Everolimus)	37	57	29	25	At 3 years, a primary end-point event had occurred in 15.4% in the PCI group and in 14.7% in the CABG group (p = 0.02 for non-inferiority; HR, 1.00; 95% CI, 0.79–1.26; p = 0.98 for superiority)
NOBLE [30]	Europe	2008–2015	982	LMCAD	DES (Biolimus)	18	60	16	18	Kaplan-Meier 5-year MACCE was 28% for PCI and 18% for CABG (HR, 1·51; 95% CI, 1·13–2·00; p = 0·0044)

AWESOME, Angina With Extremely Severe Outcomes; ERACI II, Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multivessel Disease; MASS II, Medicine, Angioplasty, or Surgery Study; ARTS, Arterial Revascularization Therapies Study; SOS, Stent or Surgery trial. SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; CARDia: Coronary Artery Revascularization in Diabetes; Le Mans, Left Main Coronary Artery Stenting; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus; Va-Cards, Coronary Artery Revascularization in Diabetes in VA Hospitals; BEST, Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL, Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE, Nordic-Baltic-British Left Main Revascularization Study [81]. DES, drug-eluting stents; BMS, bare-metal stent.
Modified from "Stent versus Coronary Artery Bypass Surgery in Multi-Vessel and Left Main Coronary Artery Disease: A Meta-Analysis of Randomized Trials with Subgroups Evaluation" (Pedro José Negreiros de Andrade, João Luiz de Alencar Araripe Falcão, Breno de Alencar Araripe Falcão, Hermano Alexandre Lima Rocha)

Table 1.
Overview of the main trials of MVCAD and LMCAD.

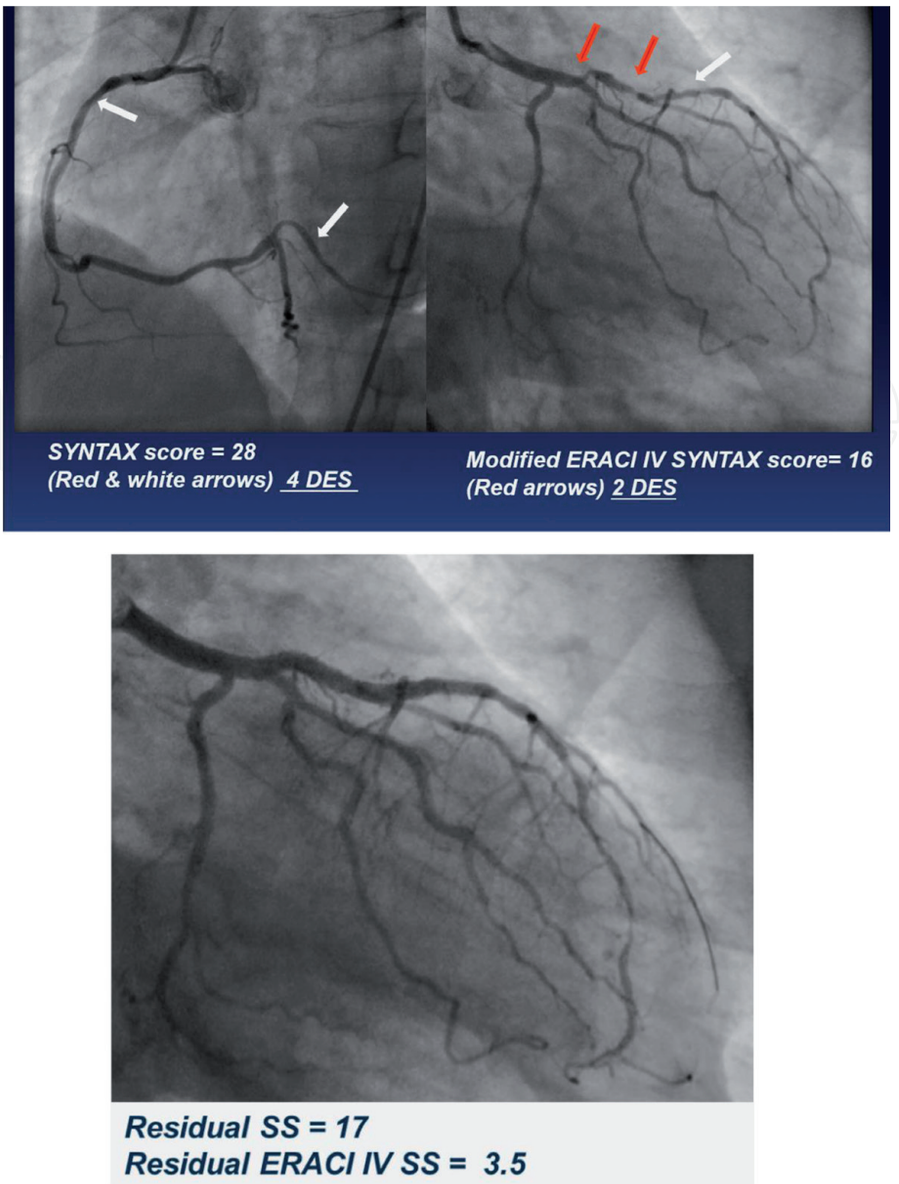

Figure 1.
Modification of the SYNTAX score by ERACI score, with residual SYNTAX and ERACI scores and its implications. SYNTAX score = 28 points (red and white arrows). Hypothetically the patients need 4 DES. Modified ERACI score, in the ERACI IV, the SYNTAX score (only the red arrows) was 16 points = patient received 2 DES. The residual ERACI score was 3.5. If the patient was scored with the SYNTAX score, he would have had 17 residual SYNTAX score.

lesions between these two scores, we also found significant differences between these two groups of patients since with RSS it was 8.7 ± 5.9 vs. and with RES it was 3.5 ± 4.6, p = 0.003. In addition, reasonably incomplete revascularization was defined, defined by a residual of ≤5 (**Table 2**). If we take the RSS, only 35% of the patients reached this goal, but if we analyze it with the RES, they reached 80%, which suggests that most patients achieved a functional rather than an anatomical revascularization (**Table 2**). This could be corroborated in the long-term follow-up where these patients had a MACCE less than 10% at 3 years of follow-up. In addition, this score was validated in another trial of our group called the WALTZ registry [14]. A total of 201 real-life patients were included prospectively, in 11 centers in the Argentine Republic using the same criteria of ERACI IV. The study design, as well as the rationale, was previously published [15]. When we performed the analysis regarding the scores, we found a significant difference with respect to the baseline (SS 11.8 + 6.8 vs. ES 7.8 + 5.3, p = 0.0016), and the same happened with the residual (RSS 5.4 + 5.6 vs. RES 1.3 + 2.9, p < 0.001). The analysis that we carry out is that the presence of

	SYNTAX score	ERACI score	P value
Number of patients (n)	225	225	
Low group	33.8%	54.8%	< 0.001
Intermediate group	32.4%	27.9%	= 0.35
High group	33.8%	17.2%	<0.001
Baseline mean	27.7 ± 11.3	22 ± 11.02	=0.0004
Residual mean	8.7 ± 5.9	3.5 ± 4.6	=0.003
Residual ≤5	35%	80%	<0.001
Residual <8	48%	93.5%	=0.002

From "Lowering Risk Score Profile During PCI in Multiple Disease is Associated with Low Adverse Events: The ERACI Risk Score" (Alfredo E. Rodriguez, Carlos Fernandez-Pereira, Juan Mieres, Hernan Pavlovsky, Juan del Pozo, Alfredo M. Rodriguez-Granillo, David Antoniucci, On behalf of ERACI IV Investigators)

Table 2.
Differences in baseline and residual risk scores: ERACI IV registry.

neoatherosclerosis [16] that we believe is also present in the second- and third-generation stents is a growing concern, which is why this more rational strategy of the use of these devices can lead to better results long term. When we look closely at the results of the Syntax II study where iwFR was used, we can verify that the conservative strategy is beneficial [17]. When we compare the PCI group guided by the iwFR with the SYNTAX I in the PCI group, we find a decrease in MI and MACCE, similar to the SYNTAX I CABG group. SYNTAX II treated fewer lesions per patient than SYNTAX I (2.6 vs. 4, $p < 0.001$) and then implanted fewer stents per patient (3.8% vs. 5.2%, $p < 0.001$) despite the fact that the two groups of patients were scored similarly, with SS ($p = 0.16$). These results are consistent with our ERACI IV trial. We also have to recognize that the FFR analysis has numerous limitations, among them it can be technically difficult in segments of diffuse disease, tandem lesions and bifurcation lesions. When performed in patients with severe aortic stenosis, the evaluation is more complex to analyze. Also you have to assume the cost of catheters that cannot be ignored. It is also important to mention that studies of CABG guided by FFR [18] have not achieved the expected results when compared when guided by angiography, and studies such as FAME 2 comparing optimal medical treatment vs. guided PCI have not observed reduction in MI or long-term mortality [19].

1.5 Guidelines

The evidence suggests that in MVD without DM and low anatomical complexity, PCI and CABG achieve similar long-term outcomes with respect to survival and the composite of death, MI, and stroke, justifying a class I recommendation for PCI. Consistent results were also obtained for patients with MVD in the recent individual patient-level meta-analysis. Thus, the previous class III recommendation for PCI in MVD and intermediate-to-high complexity was maintained [20]. The intermediate and high SYNTAX scores are associated with better evolution with the CABG. Although this score is very limited and impractical for its application, its use for making decisions in patients with MVD is reasonable [21]. The ERACI score could be more rational for making decisions due to being more realistic and conservative [9].

1.6 Ongoing trials

The Prospective Multicenter Registry of Hybrid Coronary Artery Revascularization Combined with Surgical Bypass and Percutaneous Coronary Intervention Using

Everolimus-Eluting Metallic Stents evaluates the efficacy of hybrid coronary revascularization (HCR) combining CABG and PCI in the treatment of MVD. CABG is to be performed in the left anterior descending artery and the left circumflex artery using only arterial grafts, whereas PCI is to be conducted for the treatment of the right coronary artery with everolimus-eluting stents (EESs) [22]. The Comparison of One-stop Hybrid Revascularization vs. Off-pump Coronary Artery Bypass for the Treatment of Multi-vessel Disease combines minimally invasive direct CABG and PCI to be performed in the hybrid operating suite, an enhanced operating room equipped with radiographic capability [23].

1.7 Conclusions

In our long experience in the treatment of MVD for more than two decades and according to our score, we believe that the stratified treatment can be divided into two groups, patients with low and intermediate scores in whom the results of PCI are comparable with surgery. The other group of patients are those with high scores, we think that the current state-of-the-art CABG is the treatment of choice. However, with the increase in stent technology this difference can be reduced.

2. Left main coronary artery disease

2.1 Introduction

LMCA is a disease with significant morbidity and mortality, since it threatens a large myocardial territory. LMCA stenosis occurs in approximately 15% of patients with symptomatic ischemic heart disease [24]. The most common cause of LMCA disease is atherosclerosis, which is rarely focal and involves bifurcation in 80% of cases, which usually extends from the LMCA to the LAD [25]. In the beginning, the treatment of choice for this disease was the CABG [26]. However, after the introduction of PCI, there was a growing interest in the treatment of the LMCA. Both European [20] and American [21] guidelines recommend CABG (class I) as the treatment of choice for LMCA in patients with low risk score. These recommendations were based mainly on the results of the LMCA subgroup analysis of the SYNTAX trial (705 patients) that showed no differences in the MACCE between CABG and PCI in patients with LM disease [27]. Patients treated with PCI had a lower stroke but a higher revascularization rate than CABG. The results of the PRECOMBAT trial [28] compare PCI to CABG in the treatment of LMCA. The two groups did not differ significantly in MACCE. Ischemia-driven revascularization occurred more frequently in the PCI group than in the CABG group. In addition, the LE MANS trial [29] with a 10-year follow-up compared PCI and CABG in patients with LMCA with low or medium SYNTAX score. The primary end point was the left ventricular ejection fraction (LVEF) that was slightly higher in the PCI group than the CABG group. The introduction of new-generation DES with proven efficacy and safety prompted the design of two large randomized trials: the Nordic-Baltic-British Left Main Revascularization Study (NOBEL) [30] and the Evaluation of Xience versus Coronary artery bypass surgery for Effectiveness of Left main revascularization (EXCEL) trial [31]. It is important to note that, when an LMCA PCI is performed, there is a greater awareness of the need to achieve optimal procedural results by using the available technologies, including the most effective stents, intravascular evaluation of image, and physiology. And when one faces a real bifurcation with a Medina classification [32], it is necessary to use two stents. It would seem that the best technique is double kissing balloon with crush (DKC) [33].

2.2 Main trials of the LMCA

LE MAS trial, [29] in this prospective, multicenter trial, randomly assigned 105 patients with LMCA with low and medium complexity of coexisting coronary artery disease according to SYNTAX score to PCI with stenting (n = 52) or CABG (n = 53). DES were implanted in 35%, whereas arterial grafts to the left anterior descending artery were utilized in 81%. This study is very interesting because it offers a 10-year follow-up, which as a primary end point was the evaluation of the ejection fraction between PCI and CABG in the treatment of LMCA. Although there were no significant differences, there was a tendency in favor of PCI (54.9 ± 8.3% vs. 49.8 ± 10.3%, p = 0.07). Regarding mortality, MI, and TVR, there were no statistical differences between the two groups, although there was also a trend of greater MACCE-free survival in the PCI group (34.7% vs. 22.1%, p = 0.06; reason risk, 1.71; 95% confidence interval (CI), 0.97–2.99). The Nordic-Baltic-British Left Main Revascularization Study [30] is a prospective, randomized, open-label, non-inferiority trial done at 36 centers in Europe. Patients were randomized to CABG or PCI. LMCA were visually assessed with diameter ≥ 50% or fractional flow reserve ≤0.80 in different segments of the left main coronary artery. SYNTAX score was calculated and all patients with low, medium, and high score were included. Patients were treated with the intention of achieving CR. Biolimus-eluting stent was the recommended stent in this trial. Distal bifurcation lesions could be treated with various techniques preferably by the "culotte" technique. IVUS was strongly recommended pre- and post-stent deployment. In the CABG group, the left internal mammary artery was recommended for revascularization of the left anterior descending coronary artery, and for the other lesions, saphenous venous grafts, free arterial grafts, or the right internal mammary artery could be used. The primary end point was a MACCE. About 1184 patients were included in the analysis (592 patients in each group). The SYNTAX scores were similar between the two groups (22.4 in the PCI group and 22.3 in the CABG group). CABG was performed with the on-pump technique in 84% of patients, and 96% of patients underwent arterial grafting of the left anterior descending artery. Kaplan-Meier estimates of MACCE were significantly higher in PCI (28%) than in CABG (18%). The rate of MI and revascularization was significantly higher in PCI group than in CABG, but the overall mortality and stroke were not statistically significant. At 30 days, the stroke rate in PCI group was significantly less than in the CABG group, but this difference was not seen at 1- and 5-year follow-up. The EXCEL trial [31] was a prospective randomized open-label, non-inferiority trial undertaken at 126 centers in 17 countries around the world. Patients were randomized to receive either CABG or PCI. Patients who had stable and unstable angina were included in the study; however patient who were having MI were excluded. Patients were included if they had LMCA of 70% assessed visually or 50–70% determined by means of invasive or noninvasive methods. SYNTAX score was determined and patients who had score of higher than 33 were excluded. CR was the intention of treatment in both groups. A second-generation DES EES was used in this study. Distal bifurcating lesions were treated with a two-stent strategy using various techniques. CABG was performed both on- and off-pump, with the aim of CR for vessels with 50% stenosis. Arterial grafts were strongly recommended. The primary end point was MACCE at 3 years. The intention-to-treat (ITT) analysis was used in this trial. A total of 1905 patients underwent randomization, 948 were assigned to the PCI group and 957 to the CABG group. The SYNTAX score according to assessment at local sites was low (≤22) in 60.5% of the patients and intermediate (23–32) in 39.5% of the patients. Distal LMCA was present in 80.5% of the patients. IVUS imaging guidance was used in nearly 80% of the patients in the PCI group. There was no

difference between the two groups in respect to the primary composite end-point event of death, stroke, or myocardial infarction at 3 years (15.4% of the patients in the PCI group and in 14.7% of the patients in the CABG group). At 3 years, the composite end-point event of death, stroke, myocardial infarction, or ischemia-driven revascularization had occurred in 23.1% of the patients in the PCI group and in 19.1% of the patients in the CABG group. Ischemia-driven revascularization during follow-up was more frequent after PCI than after CABG (in 12.6% vs. 7.5% of the patients, $p < 0.001$). Stent thrombosis occurred in only 0.7% of patients within 3 years after the procedure and was less common than symptomatic graft occlusion. In the Premier of Randomized comparison of Bypass surgery versus Angioplasty using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) [28] trial was a randomized study where 600 patients with LMCA went to PCI with a first-generation of DES or CABG. The primary end point was the combined events, MACCE, at 5 years of follow-up 17.5% were observed in the PCI and 14.3 % in the CABG group, $p = 0.26$. Regarding the mortality of all causes, MI or stroke, there were no significant differences. The TVR was more frequent with PCI than with CABG (11.4% vs. 5.5%, $p = 0.012$).

2.3 Analysis of the two principal trials

As we could see in these last two studies on PCI and CABG in the LMCA, we can see that the NOBLE [30] study included higher-risk patients and used a pharmacological stent with biodegradable polymer. In addition to the fact that the most frequently used technique was "culotte" by recommendation, the use of IVUS was only 75% in post PCI patients, and only 55% of the kissing balloon was performed. In addition the use of the proximal optimization (POT) was not specified, and first-generation stent was also used in 8% of patients. In the EXCEL study [31], a second-generation stent was used in patients with low and intermediate SYNTAX scores, and the amount of IVUS used reached 77%. The use of POT was also not specified, no special bifurcation technique was recommended, and the use of kissing balloon was also not specified (**Table 3**).

2.4 Meta-analysis

The objective was to compare clinical results and safety during short- and long-term follow-up by conducting a meta-analysis of large pooled data from randomized controlled trials and updated observation. The primary outcome was MACCE, MI, stroke, all-cause mortality, and revascularization after at least 1 year of follow-up. A subgroup analysis was also performed with a follow-up of over 5 years. A total of 29 studies with 21,832 patients (10,424 with PCI and 11,408 with CABG) were analyzed. At 1-year follow-up there was a significant difference in favor of the CABG in MACCE, TVR, and MI, but the stroke was significantly lower in the PCI group. In the 5-year group analysis, it showed similar results except that the MACCE showed no inferiority in the PCI group. This meta-analysis concludes that the PCI for the LMCA can be applied in carefully selected patients. The MI and the TVR remain worrying, although we must consider that most of these studies have used first-generation DES [34].

2.5 PCI strategy and technique

Angioplasty is a specialty where the practice generates a greater capacity to solve problems during the procedure. It has been seen that those operators who perform at least 15 PCI of LMCA per year in 3 consecutive years obtain better results [35].

	EXCEL	NOBLE
Inclusion criteria	- Unprotected left main coronary artery (ULMCA) disease or left main equivalent disease - Clinical and anatomic eligibility for both PCI and CABG as agreed to by the local heart team - Silent ischemia, stable angina, unstable angina, recent MI with normalization of CK-MB prior randomization - In addition to randomized patients, it also includes universal registry	- Stable, unstable angina pectoris, or acute coronary syndrome - Significant ULMCA with no more than three additional noncomplex PCI lesions - Patient eligible to be treated by CABG and by PCI
Main exclusion criteria	- Prior PCI of the left main at any time prior to randomization or prior PCI of any other (non-left main) coronary artery lesions within 1 year prior to randomization - Prior CABG - Need for any concomitant cardiac surgery - Inability to receive dual antiplatelet therapy for at least 1 year - Pregnancy or intention to become pregnant - Life expectancy less than 3 years	- ST elevation infarction within 24 h - Patient is too high risk for CABG - Expected survival less than 1 year - Allergy to aspirin, clopidogrel, or ticlopidine
Angiographic exclusion criteria	SYNTAX score ≥ 33 - Visually estimated left main reference vessel diameter < 2.25 mm or > 4.25 mm (post-dilatation up to 4.5 mm is allowed)	- CABG clearly better treatment option (LMCA stenosis and > 3 or complex additional coronary lesions)
Primary end point	- Death, MI, and stroke	- Death, stroke, non-procedural MI, and new revascularization (PCI or CABG)
Sample size	1.905	1200
Participating centers	131	36
Main results	At 3 years, a primary end-point event had occurred in 15.4% of the patients in the PCI group and in 14.7% of the patients in the CABG group	At 5 years, primary end points occurred in 28% of the patients in PCI group and in 18% of the patients in the CABG group
Conclusion	In patients with left main coronary artery disease and low or intermediate SYNTAX scores, PCI was non-inferior to CABG	CABG might be better than PCI for treatment of left main stem coronary artery disease

Modified from "NOBLE and EXCEL: The debate for excellence in dealing with left main stenosis" (Hamood Al Kindi, Amir Samaan, Hatem Hosny)

Table 3.
Comparison of EXCEL and NOBLE trials.

The PCI of the ostium and the middle third of the LMCA is technically easier if we analyze it by the ERACI score this doesn't give more than 5 points, unlike the distal third that compromises ostium of the two coronaries and presents higher ERACI scores [36]. When one faces the distal third of the LMCA, there is a totally different approach. Anyway there are different types of bifurcations, where we prefer to use the Medina classification [32]. To assess them, the provisional stent technique has become a technique with a lot of boom and has had good results compared to techniques with two stents [37]. The technique of the provisional stent has been used in up to two thirds of the branches of the LMCA. However, after two RCTs where the DKC was used as a technique, these tests presented better results than the culotte technique or the provisional stent for the treatment of bifurcations

with Medina 1,1,1 or 0,1,1 [33, 38]. In both studies, a reduction in ischemic events was observed. The decision to use a bifurcation technique with one or two stents is basically in the exact evaluation of the compromise of the origin of the left coronary circumflex or the left coronary ramus in a trifurcation. The best way to assess these vessels is with the images of the IVUS or the optimal coherence tomography (OCT) [39]. When the provisional stent technique is used and a residual obstruction of around 50% is observed, the measurement with functional study with iwFR or FFR could be considered as a complement in the decision-making of its definitive treatment. The use of kissing balloon and POT has been invoked as optimizers for this complex carrefour. Also, the post-stent images or stents of both the IVUS and the OCT are important when making decisions, since these elements clearly inform two elements that are key such as uncovered dissections or stent not well positioned [40]. The technique used in the treatment of LMCA is extremely important, just as training in true bifurcation is also difficult. Patients with true bifurcation are those who have Medina 1,1,1 or 0,1,1 and should be treated with two stents and we believe that the technique of choice is DKC. Another important element is to only include patients with low and intermediate ERACI score [17] and leave patients with high scores for very selected centers and true contraindication or patients who really refuses surgery. The use of images in diagnosis, implantation, and postimplantation has become a mandatory strategy, including the use of IVUS and optimal coherence tomography [41]. An element that has been incorporated into the technical arsenal is the technique of proximal optimization. The proximal optimization technique is a key part of treating large bifurcation lesions and will optimize results of both single- and two-stent strategies. An appropriately sized balloon should be positioned and inflated just up to the carina. When performed well, the enhanced lesion scaffolding, reduced strut mal-apposition, and improved flow dynamics are likely to translate into improved clinical results [42].

2.6 Guidelines

The evidence is clear regarding patients with low scores, where treatment with both PCI and CABG is appropriate, where there is a class I recommendation. In patients with high scores, because the evidence is much lower because many of these patients have been excluded from RCTs, the recommendation for PCI is class III, since the benefit is clearly greater with CABG. In patients with intermediate scores, due to the lack of evidence in the long-term follow-up, the recommendation remains IIa [20, 43]. When one makes a global evaluation of the LMCA and addresses the guidelines, one must also take into consideration the different portions of the LMCA such as the ostium, the middle third, and the distal third, since they have different implications, both in the technique and in the evolution of these patients, so they would probably have to be analyzed separately. Also the degree of angiographic stenosis has been changing and should not be left with the 50% obstruction that has been used universally, and perhaps it should be passed at least 70%. Although this analysis can have many deficiencies, the use of images such as IVUS or OCT or even functional studies with iwFR or FFR can be closer to a true significant obstruction. It is believed that a minimum luminal diameter of 2.8 mm or an area of < 6 mm^2 would suggest a physiologically significant obstruction [21].

2.7 Ongoing trials

Xience versus Synergy in LMCA PCI (ideal-LM), PCI of the LMCA a comparison of the newest generation of DES in combination with a short duration of

DAPT. The additional use of OCT image can be considered a standard procedure with a very low risk of major complications 0.4% [44]. VeRy thin Stents for Patients with Left mAIN or bifurcation in real life: the RAIN Multicenter Study, for coronary stents, reducing the thickness of the struts has become one of the most important innovations, since it is related to easier crushability and reduced risk of thrombosis and low rate of TVR. They performed a multicenter registry of patients treated with Biomatrix flex, Xience Alpine, Ultimaster, Resolute Onyx and Synergy. MACCE (death, MI, TLR and stent thrombosis) will be the primary end point [45].

2.8 Conclusions

In the treatment of severe LMCA in patients with low to intermediate ERACI score, the percutaneous treatment is of choice. In those with a higher score or who have total occlusions and are DM, surgical treatment is better. It is very important to evaluate each case in particular as well as work with a heart team to discuss cases that may generate controversy. The interventional cardiology must be trained in the different bifurcation techniques as well as have images such as IVUS or OCT for procedures. The implementation of the final kissing balloon and the POT in all patients is important. DKC seems to be the technique of choice in LMCA diseases with true bifurcations.

3. Patients with STEMI and MVD

3.1 Introduction

About half of the patients who enter with acute myocardial infarction with ST segment elevation (STEMI) have MVD [46]. Although it seems logical that patients with MVD have a worse prognosis, due to the extent of coronary lesions manifested by higher scores, this remains controversial. There are elements that determine that lesions at multiple sites of the coronary arteries can be complicated, and there are studies in which the multivessel PCI shows a better evolution compared to patients in whom they only receive treatment of the culprit vessel, although there are other studies they don't confirm it and consider them innocent [47], and therefore these arteries warrant treatment in much the same way one would approach any unstable lesion. An update on primary PCI for patients with STEMI (class IIb) [20, 48] by the guidelines recommends intervention of the non-culprit at the time of primary PCI if the patient is hemodynamically stable before the discharge. Subsequently, two randomized trials showed that treatment of non-culprit lesions in the acute phase reduced the risk of future adverse events. The PRAMI trial [49], CvlPRIT trial [50], and recently DANAMI-3-PRIMULTI trial [51] studied the clinical outcomes by comparing the FFR guided by CR with culprit-only PCI in STEMI and found that the composite rate of all-cause mortality, nonfatal reinfarction, and repeat revascularization was significantly lower in the CR group, which was mainly driven by a reduction in repeat revascularization. More recently, another randomized trial (COMPARE ACUTE) [52] revealed that FFR-guided complete revascularization of non-culprit arteries in an acute setting was associated with a lower risk of the composite cardiovascular outcome. We emphasized the importance of individualizing care for each patient, balancing the anticipated benefits from multivessel PCI against the potential risks.

3.2 Complete vs. incomplete revascularization

Data derived from more than 150,000 patients undergoing PCI suggest that less than 50% of all patients with MVD have CR after they have undergone percutaneous revascularization. It was observed that CR is associated with a fall in the incidence of mortality, MI, and MACCE, regardless of whether an anatomical or functional definition was used for the evaluation of IR, and perhaps the degree CR is associated with the magnitude of the risk. The association between IR and adverse clinical outcomes suggests that in patients with MVD, the degree of CR that can be achieved by PCI should be considered when discussing the choice of revascularization modality with the heart team, in addition to considering the complexity of the injury, functional significance, patient characteristics, and ERACI score [9, 53].

3.3 Randomized trials

The preventive angioplasty in acute myocardial infarction (PRAMI) study [49] was performed in five centers in the United Kingdom in patients with STEMI and MVD, where they were randomized to preventive angioplasty of non-culprit vessels vs. only PCI of the culprit vessel. It was the first of the trials that incorporated a new concept on complete revascularization in STEMI and MVD. At practically 2 years of follow-up, a reduction of more than 50% was observed on the primary end point that was the combined event of cardiac death, nonfatal MI, and refractory angina, of the patients of the preventive PCI group vs. PCI only of the culprit vessel. The study was designed to include 600 patients but was stopped early with 465 patients because the data was conclusive by the data security committee. CvLPRIT [50] (trial of primary PCI vs. complete primary injury) compared a multivessel PCI strategy in patients with STEMI (performed at the time of primary PCI or revascularization in stages before discharge) to revascularization of culprit-vessel only. In this trial, 7 centers in the United Kingdom participated, where 296 patients were included, randomization was performed by stratification between previous or non-previous infarction, and according to the time ≤3 or >3 h. The primary end point of the study was the combined events of all-cause mortality, recurrent MI, heart failure, or revascularization driven by 12-month ischemia. The result produced a reduction of primary events to more than half in the CR group (10 vs. 21%; hazard ratio (HR), 0.45; 95% CI, 0.24–0.84; $p = 0.009$). There were no differences in individual events. In the compare acute study [52] (multivessel angioplasty guided by fractional flow reserve in myocardial infarction), they included 885 patients in 24 centers in Asia and Europe, where patients with STEMI and MVD, after a primary PCI stable, were randomized to complete revascularization guided by FFR of the artery not culprit of all lesions greater than 50% vs. angioplasty only of the culprit vessel. The FFR was performed in both groups, but its results were blind to operators and patients in the culprit vessel group only. The primary end point of the study was the MACCE at 1 year, which was significantly better in the FFR-guided group (7.8% vs. 20.5%) than in the culprit vessel only (HR, 0.35; 95% CI, 0.22–0.55; $p < 0.001$). This was at the expense of revascularization without changes in mortality or MI. The DANAMI-3-PRIMULTI [51] (The Third Danish Study of Optimal Acute Treatment of Patients With STEMI: Primary PCI in Multivessel Disease) was conducted at two university centers in Denmark, where they randomized 627 patients with STEMI and MVD after a successful primary PCI of the culprit vessel to a complete revascularization guided by FFR compared to conservative treatment. The primary end point was MACCE, which was composed of death, nonfatal MI, and revascularization driven by ischemia. After an average follow-up of 27 months, it was observed that the FFR group presented a MACCE of 13% vs. 22% in conservative treatment (HR, 0.56; 95%

CI, 0.38–0.83; p = 0.004). This result was due to an excess of revascularization driven by ischemia in the conservative group. In the PRAGUE-13 trial [54], Ota Hlinomaz et al. in a university hospital in the Czech Republic randomized 214 patients with STEMI and MVD, who had an obstruction of at least ≥70%, to a group with CR day 3–40 after primary PCI compared with conservative treatment, where the primary end point was MACCE that was composed of death from all causes, nonfatal MI, and stroke, and after a mean of 38 months showed no significant differences in both groups, (16% in CR vs. 13.9 in conservative treatment; HR, 1.35; 95% CI, 0.66–2.74; p = 0.407). CULPRIT-SHOCK [55] was a study that surprised in terms of results and gave new directives in the treatment that we had been doing in this pathology, this multicenter study was carried out in 83 centers in Europe that included 706 patients with cardiogenic shock, with SETEMI and NSTEMI, at CR compared to the treatment of the culprit vessel only (CVO), whose primary end point was mortality and renal failure with dialysis at 30 days. The combined event occurred in 55.4 in the CR vs. 45.9% in the treatment of the CVO, (relative risk, 0.83; 95% CI, 0.71–0.96; p = 0.01). A significant difference in mortality between the two groups was also observed (CR 51.5 vs. CVO 43.3%; relative risk, 0.84; 95% CI, 0.72–0.98; p = 0.03).

3.4 Score to evaluate the treatment in MVD with MI

Hae Chang Jeong et al., developed a new Score to predict combined events in patients with AMI and MVD, the CONVERSE score, based on the PCI registry of nine centers in universities in Korea, in a registry of 5025 patients, evaluated 2630 patients who AMI and MVD had presented, and they were divided into two groups those who were treated CVO that were 1029 patients vs. those with PCI of MVD 1601, for this they used 8 variables that had been predictors of events in a previous study [56]. The variables were patients with arterial hypertension, diabetes, age over 65 years, deterioration of EF, heart failure in presentation, chronic renal failure, elevated CRP plasmatic, anterior descending or LMCA as culprit vessel, each variable awarded a point, the elevation above 3 points in these patients were in linear relationship with the elevation of the MACCE [57].

3.5 Meta-analysis of MVD in STEMI

In this meta-analysis of 10 trials with 2285 patients. Among the three complete revascularization strategies, that is, during the procedure index, during hospitalization or after discharge vs. treatment of the culprit vessel only, it was associated with MACCE reduction (reference rate ratio [RR], 0.57; 95% CI, 0.42–0.77), due to a lower rate of emergency revascularization. Mortality of all causes and spontaneous reinfarction was similar between the two groups. There were no differences between the different types of strategies at the time of revascularization in patients with CR [58].

3.6 An algorithm for the management of STEMI patients with MVD

Figure 2 [59].

3.7 Guidelines

MVD PCI treatment during STEMI is considered strongly indicated when there are critical lesions or associated thrombotic lesions when the culprit vessel has already been treated if there is persistent ischemia. When there is cardiogenic shock, the only treatment of the culprit vessel is the treatment of choice [20]. Patients with stable STEMI and MVD after a primary PCI the recommendation of multivessel PCI

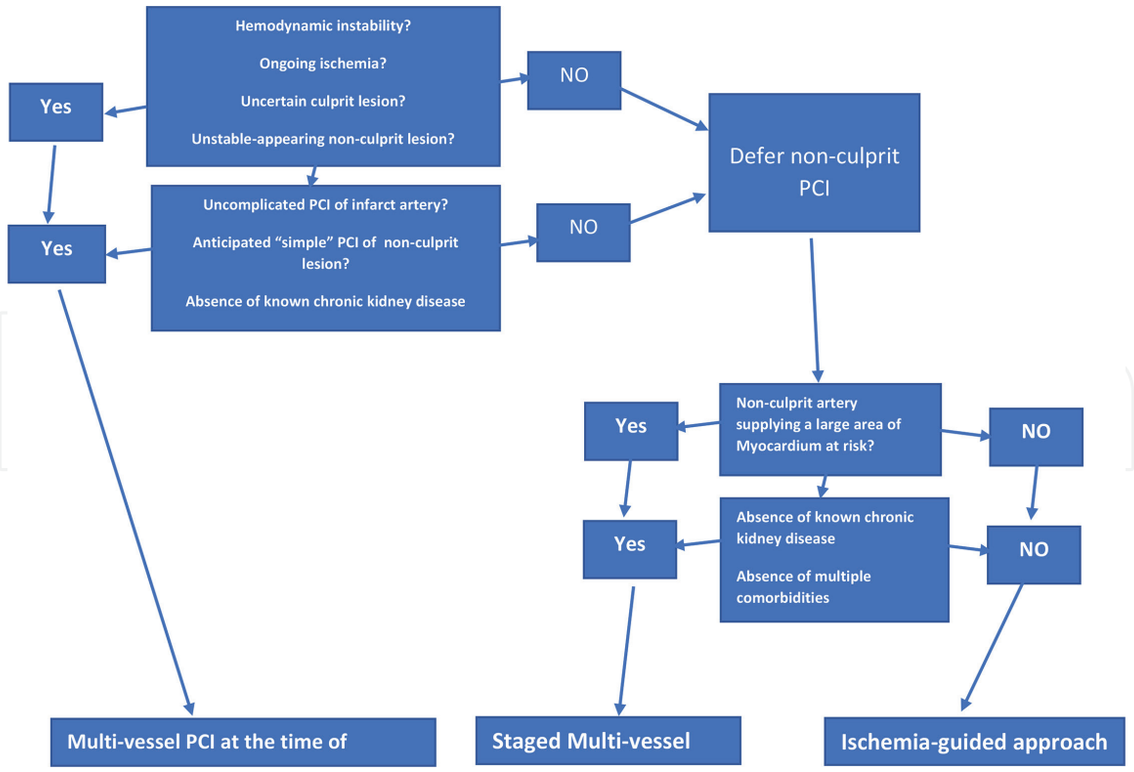

Figure 2.
Algorithm for the Management of STEMI Patients With MVD. Modified from "The Management of MVD in STEMI: The Science and Art of Decision-Making in STEMI" (Feb 07, 2018) (Jacqueline E. Tamis-Holland, MD, FACC; Addi Suleiman, MBBS).

has been updated to a Class IIB, this could be done at the time of the primary index or in stages during hospitalization or after discharge [48].

3.8 Ongoing trials

The COMPLETE [60] (Complete vs. Culprit-only Revascularization to Treat Multi-vessel Disease After Primary PCI for STEMI) trial will compare the outcomes of approximately 3900 patients randomized to a strategy of staged multivessel PCI or culprit-only revascularization. The FULL REVASC [61] (FFR-Guidance for Complete Non-Culprit Revascularization) This trial intends to evaluate the CR in about 4000 patients with STEMI or not with very high risk in patients of MVD guided by FFR during the same hospitalization of the index procedure, to evaluate clinical results.

3.9 Our experience

We were the precursors in the treatment of primary PCI in acute infarction as revealed by one of the first randomized trials with stent in acute myocardial infarction, our trial GRAMI [62]. In our daily practice we try to identify culprit vessel. If we have a territory where we find two vessels with critical lesions, we treat them. If the patient presents a critical lesion in another territory, we defer to perform it pre-discharge. We also consider the amount of territory that this vessel irrigates as well as its renal function when making the decision with the heart team.

3.10 Conclusions

Multivessel PCI both during the index procedure and in stages in stable patients is safe and could lead to better long-term results at the expense of reducing emergency

revascularization without altering mortality. The PCI of associated intermediate or very complex lesions at the time of STEMI is contraindicated. In cardiogenic shock and MVD, the treatment of the culprit vessel is only the indication. When one faces a patient with STEMI and MVD, the analysis of a heart team, where the scores are analyzed, the clinical status, the comorbidities, as well as the common sense should define the opportunity of the treatment of the non-culprit critical lesions.

4. Diabetes and multivessel disease

4.1 Introduction

DM is a global health problem; about 10% of adult patients will have the disease, and a quarter of all revascularized patients globally have DM [63]. However, patients with DM compared to nondiabetics have more MACCE and chronic heart failure. In addition, these patients have diffused and segmental disease, which puts them at greater risk of events regardless of the revascularization selected [64, 65]. PCI is limited by a higher rate of repeat revascularization and a worse clinical outcome in DM patients than with nondiabetic patients. CABG carries a greater morbidity, increased length of stay, and longer recovery times. However, both strategies have been improved during the last decade. In particular, the introduction of DES [66] has dramatically changed the landscape for PCI, with a significant reduction in the rate of restenosis especially the so-called second-generation stents that can reduce the gap [67]. The FREEDOM trial [68] demonstrated lower rates of major adverse cardiovascular events in patients with stable ischemic coronary disease who were assigned to CABG than with PCI using DES of first generation, at long-term follow-up. It is evident that this pathology carries a high atherogenic risk, and its current treatment is of surgical competence. Even so, we think that patients with a low ERACI score [17] are good candidates for PCI treatment, and the arrival of the new generation stents of Ultrathin-Strut DES [69] could reduce the gap that was created.

4.2 FREEDOM, critics, and main trials

This trial [68] has become the most important among patients with diabetes and type of revascularization as well as follow-up, which was carried out worldwide in 140 centers that included 1900 patients with DM with MVD who were randomized to PCI with DES from first generation or CABG and its long-term follow-up of at least 5 years. The primary end point was the combined mortality events of all causes, nonfatal MI, and stroke, such as MACCE. The MACCE was significantly in favor of the CABG (18.7% vs. 26.6%, $p < 0.005$), there was also a decrease in the mortality of all causes (10.9% vs. 16.9%, $p = 0.049$), the stroke was lower in the PCI group (2.4% vs. 5.2%, $p = 0.03$), and the revascularization of the treated vessel was highly significant in favor of the CABG almost three more times on the first year of follow-up. The nonfatal MI was almost double with the PCI group [68]. When the quality of life was evaluated, it was although slightly significantly better with surgery than with PCI; this is due to the amount of repeated revascularization. So, this study showed strong data and full impact on revascularization guidelines [70]. Also with respect to FREEDOM, a study of hospital costs was carried out; it was also favorable for surgical treatment vs. percutaneous treatment [71].

The study showed that the outcomes were significantly lower among patients randomized to CABG (18.7%) than patients randomized to PCI (26.6%) (**Figure 3A**). A closer look at how these rates were derived is warranted. A total of 1900 patients (953 in the PCI group and 947 in the CABG group) were enrolled

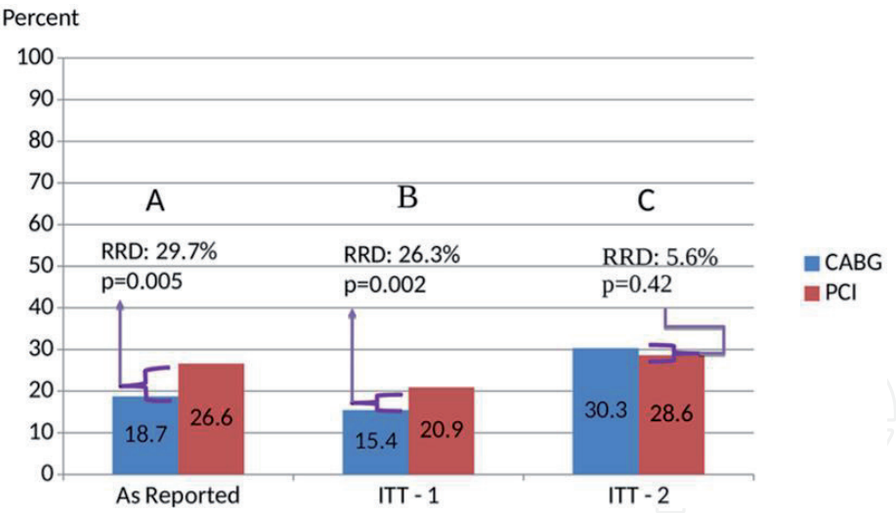

Figure 3.
A.B.C. FREEDOM trial results comparing ITT analyses. CABG, coronary arterial bypass graft surgery; ITT, intention-to-treat analysis; PCI, percutaneous coronary intervention. From "Critical appraisal of cardiology guidelines on revascularization: clinical practice" (David R Dobies and Kimberly R Barber).

and randomized. However, for the 5-year outcome rates, the denominator was 752 for PCI and 781 for CABG. These numbers are not the group totals but rather the number of patients remaining at risk at the end of the study. The number of events and the number remaining at risk are independent of each other. A basic occupant of a rate is that the subjects in the numerator are included in the denominator. The percentages the authors report are not rates; they are ratios and are very misleading. Calculating the events among the number randomized in each group results in a relative difference of 26% that is less significant than reported (**Figure 3B**). We would have more confidence in these recalculated rates if the study included all subjects in the denominator and accounted for outcomes on all subjects. They do not include the 214 (11.3%) patients lost to follow-up for whom we have no outcome data. This study also experienced a significant differential in attrition by group. The CABG group had twice the patients lost to follow-up (14.9%) as the PCI group did (7.7%). Revising the comparison by adding in the lost patients as events and calculating it with an intention-to-treat analysis (attributing events to the group of original assignment), we get a very different picture for the 5-year outcome (**Figure 3C**). The relative 5% difference is not significant (p = 0.42). This finding is in line with the 2-year composite outcomes in which the study authors observed no difference in outcome rates (13.0% vs. 11.9%, p = 0.51). The 5-year finding is significantly biased by the differential FREEDOM trial results comparing ITT analyses [72]. Other points of FREEDOM, which used first-generation stents that are currently discontinued, we remember presented a high rate of thrombosis stent [73]. Also in the trial a great geographical disparity was observed, since this difference marked by the study only was able to observe in the United States and the other centers in the randomization, and there were no significant differences outside of North American centers [68]. VA CARDS trial [74] is a study of veteran hospitals in the USA, in 22 centers, and included diabetic patients with MVD and 198 patients to be revascularized to PCI with DES or CABG with a 2-year follow-up. The primary end point of the study was the combined death events of all causes and nonfatal MI. The study was stopped early due to very slow recruitment by enrolling a quarter of the pre-established patients, which did not produce the power necessary for the evaluation of events. Within the study, it was observed that mortality in the 2-year PCI group reached a very high number up to 21% vs. 5% for CABG, while mortality was very high in the CABG group up to 15% compared with 6.2% for the PCI. This study

was inconclusive. CARDia trial was a randomized study conducted in 22 centers in the United Kingdom and 2 centers in Ireland. Where Diabetic patients with MVD and patients with complex single lesion defined as ostial or proximal lesion of the anterior descending artery, which did not include LMCA between PCI or CABG, BMS was initially used, but when available the DES were used with the Axicimab adjuvant. A total of 510 patients were included, in which the primary end point was the MACCE, which included death of all causes, MI, and stroke. The study was non-inferior and with a 1-year follow-up. After 1 year the MACCE was 10.5% in the CABG group and 13% in the PCI group (HR, 1.25; 95% CI, 0.75–2.09; p = 0.39); the mortality of all the causes were the same in both groups of 3.2% (HR, 0.98; 95% CI, 0.37–2.6; p = 0.97). Although the study did not reach non-inferiority, it made the PCI as feasible [75].

4.3 Meta-analysis of MVD and DM

In this meta-analysis of the individual database of patients, where they analyzed 11 trials of patients with MVD followed in the long term, who were randomized to PCI or CABG, in the subgroup of patients with DM, it was observed that mortality was significantly higher in patients with PCI 15.7% than with CABG, which was 10.7% (p = 0.0001), while no differences were found among non-DM patients, 8.4% for CABG and 8.7% in the PCI group (p = 0.81) [43].

4.4 Our experience

In the ERACI III registry [76] which included 3 cohorts of 225 patients in each group with multiple MVD and PCI with DES, PCI with BMS, and patients with CABG, we analyzed the results of the subgroup of diabetic patients in each group at 3 years of follow-up. The incidence of MACCE at 3 years was significantly higher in diabetics than nondiabetics (RR, 0.81 [0.66–0.99]; p = 0.018). Higher rates of death and nonfatal AMI and a trend toward increased TVR, among others, were the principal determinants of increased MACCE. When stratified by treatment modality, MACCE rates among diabetics at 3 years were 36.2% in the DES arm, 43.6% in the BMS arm, and 30.8% in the CABG group (p = 0.49). There was a nonsignificant trend toward more death and nonfatal MI among diabetics in the ERACI III-DES cohort (19.1%) than in the BMS (12.8%) or CABG (15.4%) arms of ERACI II. Just as in the FREEDOM trial, the only stents used were the first-generation stents. Another limitation is that it was not a randomized trial, but they were two well-followed cohorts.

4.5 Can newer generation DES bridge the gap?

A total of 69 randomized trials that enrolled 24,015 diabetic patients with a total of 71,595 patient-years of follow-up satisfied our inclusion criteria. When compared with CABG (RR = 1.0), PCI with paclitaxel-eluting stent (RR = 1.57 [1.15–2.19]) or sirolimus-eluting stent (RR = 1.43 [1.06–1.97]) was associated with an increase in mortality. However, PCI with EES (RR = 1.11 [0.67–1.84]) was not associated with a statistically significant increase in mortality. In PCI with EES (RR = 1.31 [0.74–2.29]), the excess repeat revascularization was not statistically significant although the point estimate favored CABG. CABG was associated with numerically higher stroke. In patients with DM, evidence from indirect comparison shows similar mortality between CABG and PCI using EES. CABG was associated with numerically excess stroke and PCI with EES with numerically increased repeat revascularization [67].

4.6 Guidelines

Overall current evidence continues to favor CABG as the revascularization modality of choice for patients with diabetes and multivessel disease. When patients present with a comorbidity that increases surgical risk, the choice of revascularization method is best decided by multidisciplinary individualized risk assessment [20].

4.7 Conclusions

In this group of patients at high risk of diffuse coronary disease, there is evidence that patients with high scores are no doubt that surgery is the first option, although the only definitive evidence is FREEDOM despite its criticisms. Since the other studies could not be completed or did not show long-term follow-up, in patients with low scores, we believe that second-generation stents and perhaps new ultra-thin DES stents could shorten the gap between surgery events and angioplasty.

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