Commentary: Treatment of multivessel coronary artery disease in patients with diabetes: Advocating for the best strategy

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In the paper entitled “The SYNTAX Score According to Diabetic Status: What Does This Mean for the Patient Requiring Myocardial Revascularization?” Ruel and colleagues¹ advocate that coronary artery bypass grafting (CABG) should be preferentially used over percutaneous coronary intervention (PCI) in any patient with diabetes and multivessel CAD who has a significant survival potential, regardless of the SYNTAX score (ie, even if the SYNTAX score is low or intermediate) or unless there are other contraindications to CABG.

This is a very timely statement in the context of what is already known in the treatment of stable multivessel disease, namely that CABG is the gold standard in the treatment of complex coronary artery disease (CAD) and the only revascularization treatment with a potential to prolong life.²

These considerations are supported by 2 important meta-analyses that included 111 randomized studies with more than 100,000 patients. In patients with coronary 3-vessel disease, a significant advantage in 5-year survival is observed with CABG compared with PCI. Subgroups analyses confirmed this advantage mainly in patients with diabetes, high complexity of CAD, and in those with reduced left ventricular function.^{3,4}

This knowledge has fully been integrated in the most recent guidelines on coronary revascularization from the European Societies of Cardiology and Cardiovascular Surgery. A summary is found in Figure 1.⁵ Although surgical revascularization is recommended as an IA indication for all patterns of 3-vessel coronary disease, PCI is only equivalent for SYNTAX scores <23 and only if the patient does not have diabetes.⁵

Although the guidelines have produced very clear treatment recommendations in recent years, these are frequently not implemented in clinical practice: This lead, unfortunately, to “nonevidence-based” treatment. The

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Central Message

Surgical revascularization is superior to PCI in most patients with 3-vessel CAD, left main, and in those suffering from diabetes. This position is underpinned by guideline recommendations.

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consequences of this have not only been decreasing number of patients scheduled for the most appropriate treatment despite an increasing incidence of the disease itself but also objective disadvantages for the patients, in terms of reduced survival and symptom-free survival and rates of reintervention.

Hannan and colleagues⁶ reported that of 11,000 patients with a clear-cut indication for surgical revascularization, only 50% actually received CABG. In contrast, when PCI was a possible option, more than 90% of the patients received PCI. The introduction of drug-eluting stents has markedly boosted this trend. Whereas in 2005, 80% of patients with multivessel disease involving proximal left anterior descending stenosis were treated surgically, by 2015 43% received a drug-eluting stent for this pattern of disease 2015.^{7,8}

This development did not only influence the actual number of PCI procedures, but Campos and colleagues⁹ reported that implementation of the guidelines may have significant advantages for the patients over the mid-term, with a 5.6% reduction in mortality, as shown in Figure 2.

Finally, no blame can be attributed to the referring doctors (either the family doctor or the noninvasive cardiologist) if they have been excluded from the treatment allocation process.

Current concerns regarding the referral and treatment process are the result of long-lasting professional and

FIGURE 1. Algorithm for the treatment of multivessel coronary artery disease and left main coronary artery according to the most recent guidelines. *PCI*, Percutaneous coronary intervention; *CABG*, coronary artery bypass grafting, *CAD*, coronary artery disease.

industry-derived biases. This has resulted in 3 important limitations concerning the design of trials of PCI versus CABG over the last 4 decades: (1) the unrepresentative nature of the patient populations; (2) usually short-term follow-up; and (3) occasionally, subsequent adjustment of the study design to fit expectations.

Although daily experience shows that a majority of patients suffering from CAD present with complex multivessel disease and/or left main coronary artery disease and therefore would be best treated with surgical revascularization, study populations, as shown in Figure 3, are usually completely different. A summary of 15 previous

FIGURE 2. Expected survival according to the recommendation (all patients received interventional treatment). *CABG*, Coronary artery bypass grafting; *PCI*, percutaneous coronary intervention.

Trial	N	Pop (%)	Stent	LMD (%)	3VD (%)	Proximal LAD (%)	EF > .50	DM (%)	ITA (%)
RITA	1011	4	—	0	12	—	—	6	74
ERACI	127	9	—	0	45	—	100	11	75
LAUSANNE	134	3	—	0	0	100	—	12	100
GABI	359	4	—	0	18	—	—	10	37
EAST	392	4	—	0	40	70	100	25	—
CABRI	1054	3	—	0	40	—	100	12	75
MASS	142	69	—	0	—	100	100	21	100
BARI	1829	12	—	0	41	36	100	24	80
TOULOUSE	152	3	—	0	29	—	—	14	58
SIMA	121	—	?	0	—	100	100	11	100
ERACI II	450	2	+	0	56	—	—	17	88
AWESOME	454	—	+	0	45	—	—	—	70
MASS II	408	2	+	0	41	—	—	—	—
ARTS	1205	5 ^a	+	0	32	—	100	19	93
SoS	988	5 ^a	+	0	38	45	100	14	81
SUMMARY	8826	5		0	35%	41	100	16	79
CABG (UK)				>20	>90	>90	30	25	>90

^a The 5% is estimated.

FIGURE 3. Summary of relevant studies that were used for the redaction of guidelines. *LMD*, Left main coronary artery disease; *3VD*, 3-vessel disease; *LAD*, left anterior descending; *EF*, ejection fraction; *DM*, diabetes mellitus; *ITA*, internal thoracic artery.

randomized studies that significantly influenced the guidelines shows this very clearly; altogether, only 35% of the patients in the depicted studies had 3-vessel coronary disease, only 40% had proximal left anterior descending disease, no patients had left main coronary stenosis, and all studies only included patients with a normal left ventricular function.³

One of the major advantages of the more recent SYNTAX trial was to include a population far more representative of “real-life” clinical practice, but even so, almost 41% of the whole population was deemed ineligible for randomization, and the vast majority of these were patients who went straight to CABG because of the anatomical complexity of their disease.¹⁰

A second limitation is that the large majority of studies have a very short follow-up interval and concluding statements are often reported at 1 year. In view of the long-term issues of coronary artery disease, this is clinically irrelevant in making treatment recommendations. When longer follow-up data are reported, CABG is usually superior to interventional treatment, not only in patients with complex coronary artery morphology but also in those patients in whom PCI had been thought to be equivalent.¹¹

Beside the problem of too-short observational intervals, there is another specific study design that may lead to misinterpretation of results. Although surgery has been recognized to be superior to PCI in patients with coronary 3-vessel disease, left main coronary stenosis has been increasingly treated by PCI, also in patients with a complex morphology. Within this topic, the EXCEL trial¹² was

recently criticized.¹³ Although no statistically differences could be demonstrated in term of combined end points like death, cerebrovascular accidents, and myocardial infarction at 3 years, the biochemical definition of myocardial infarction was changed shortly before assessment of the results that appeared to significantly increase the number of periprocedural incidence of myocardial infarction in the CABG group.

We believe there are 3 major explanations for the durable superiority of CABG over PCI: (1) the specific location of the bypass anastomosis; (2) the completeness of the revascularization; and (3) the expression of vasoactive substances. First, CABG is performed in the middle-to-distal coronary artery segments. This brings different advantages as compared with PCI: (1) the anastomosis is completely independent of the complexity of the stenotic lesion itself and (2) the bypass has prophylactic qualities, since the segment between the lesion and the site of the more distal anastomosis is protected against additional stenotic lesions. Further, in contrast to stents, bypass grafts enhance development of collaterals.¹⁴

Second, CABG enhances the possibility of complete revascularization. With regard to this issue, it has been demonstrated in 22,000 patients that survival is related to complete revascularization and in 31% of these patients this was achieved with arterial revascularization.¹⁵

Third, the secretion of vasoactive substances from arterial bypass grafts (especially the internal thoracic artery) has to be considered. Endothelial secretion of nitric oxide can increase blood flow through the graft, as well acting

as stabilizing coronary artery plaque and also as an antithrombotic agent. All these factors may explain the excellent patency rate of 90% after 20 years observed when the internal thoracic artery has been used.¹⁶ In contrast, drug-eluting stents inhibit the re-endothelialization process, may act as a prothrombotic, and impair the endothelial function in the more distal coronary artery tree.¹⁷

The following short conclusions may clarify the most-recognized indications for patients suffering from coronary artery disease. (1) Surgical revascularization is superior to PCI in most patients with 3-vessel CAD, left main, and in those suffering from diabetes. (2) This position is underpinned by guideline recommendations. (3) Heart teams are the most reliable method to enforce the use of guideline recommendations when they function correctly.

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