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Coronary Revascularization in Diabetics: The Background for an Optimal Choice

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1. Introduction

Coronary artery disease (CAD) is more extensive and severe in diabetic than non-diabetic patients both in randomized trials and registries (see table 1 and 2). Compared with non-diabetic, diabetic patients have smaller vessel size and poorer coronary collateral vessels development. Diabetes mellitus (DM) is a major risk factor for poor outcome after percutaneous coronary intervention (PCI) and is specifically associated with higher rates of restenosis. A potential mechanism underlying this phenomenon, suggested by angiographic and ultrasonic studies, is a higher degree of late luminal loss and neointimal hyperplasia in diabetic compared to non-diabetic patients . The increased rate of restenosis in diabetic patients may have an impact on their prognosis. In a study of 603 diabetic patients undergoing balloon angioplasty between 1987 and 1995, the occlusive form of restenosis has been associated with poor survival and was an independent predictor of mortality (Van Belle 2001). Finally, DM constitutes an independent predictor of early stent thrombosis, both in the bare-metal- and drug-eluting-stent era. Current guidelines favor coronary artery bypass graft (CABG) surgery over PCI in most diabetic patients with multivessel disease (MVD). However, substantial variability exists in the current medical practice suggesting a lack of clinical consensus.

2. Clinical case: how to treat?

A 74-year-old, diabetic man without a history of cardiovascular disease was admitted because of rest angina and non ST elevation acute coronary syndrome, without significant ST segment changes at electrocardiogram and with mild hypokinesia of the mid lateral left ventricular wall at 2D echocardiography. Cardiac troponin I peaked at 10ng/L. He underwent coronary angiography (18-hour after admission) that revealed a three vessel disease. The ramus intermedium had a TIMI 2 flow (Figure 1). Left ventriculography revealed mid inferior and lateral hypokinesia with an estimated ejection fraction of 60%. Should the patient be referred for CABG surgery or treated by PCI?

3. Answers from evidence-based medicine: clinical trials

3.1 Plain angioplasty vs CABG

With the advent of coronary angioplasty, several randomized, controlled trials have compared angioplasty to traditional surgery. The first was proposed Andreas Gruentzig six

REGISTRY	TOTAL n°Pt	DM %	ALL		NO DM		DM	
			MVD%	3VD%	MVD%	3VD%	MVD%	3VD%
NHLBI PTCA Registry (1985-86) (Kip 1996)	2431	13,5	49,6	19,1	48,8	17,7	54,4	27,7
NHLBI DYNAMIC REGISTRY Phase 1- 2 (1997-99) (Laskey 2002)	4629	23	57,8	25,2	55,3	23,1	66,0	32,3
BARI Registry (Detre 1999)	2010	16,9	100	31,9	100	29,7	100	43
Northern New England CVD study (1992-96) (Niles 2001)	2766	100	100	45	0	0	100	45
(Natali 2000)	2253	11,9	40,7	18,9	38	16,7	61	35

Table 1. Prevalence of multiple vessel disease in diabetic vs non-diabetic patients in clinical registries. DM: Diabetes Mellitus, MVD: Multi-Vessel Disease; 3VD: 3-Vessels Disease

TRIAL	TOTAL n°Pt	DM %	ALL		NO DM		DM	
			MVD%	3VD%	MVD%	3VD%	MVD%	3VD%
ARTS (Serruys 1999)	1205	17,3	96,1	29	95,9	27,8	97,4	32,9
ARTS-II (Serruys 2005)	607	26,2	99,7	53,6	99,8	54,7	99,4	50,3
BARI (The BARI investigators 1996)	1829	19,3	100	41	100	40	100	46
MASS-II (Hueb 2004)	611	31,1	100	58,6	100	57,9	100	60,1
SYNTAX (Serruys 2009)	1800	25,1	100	79,5	100	78,5	100	82,6
BARI 2D (Frye 2009)	1773	100	68	32	0	0	68	32
CARDIA (Kapur 2010)	510	100	94,4	59,7	0	0	94,4	59,7

Table 2. Prevalence of multiple vessel disease in diabetic vs non-diabetic patients in randomized clinical trials. DM: Diabetes Mellitus, MVD: Multi-Vessel Disease; 3VD: 3-Vessels Disease.
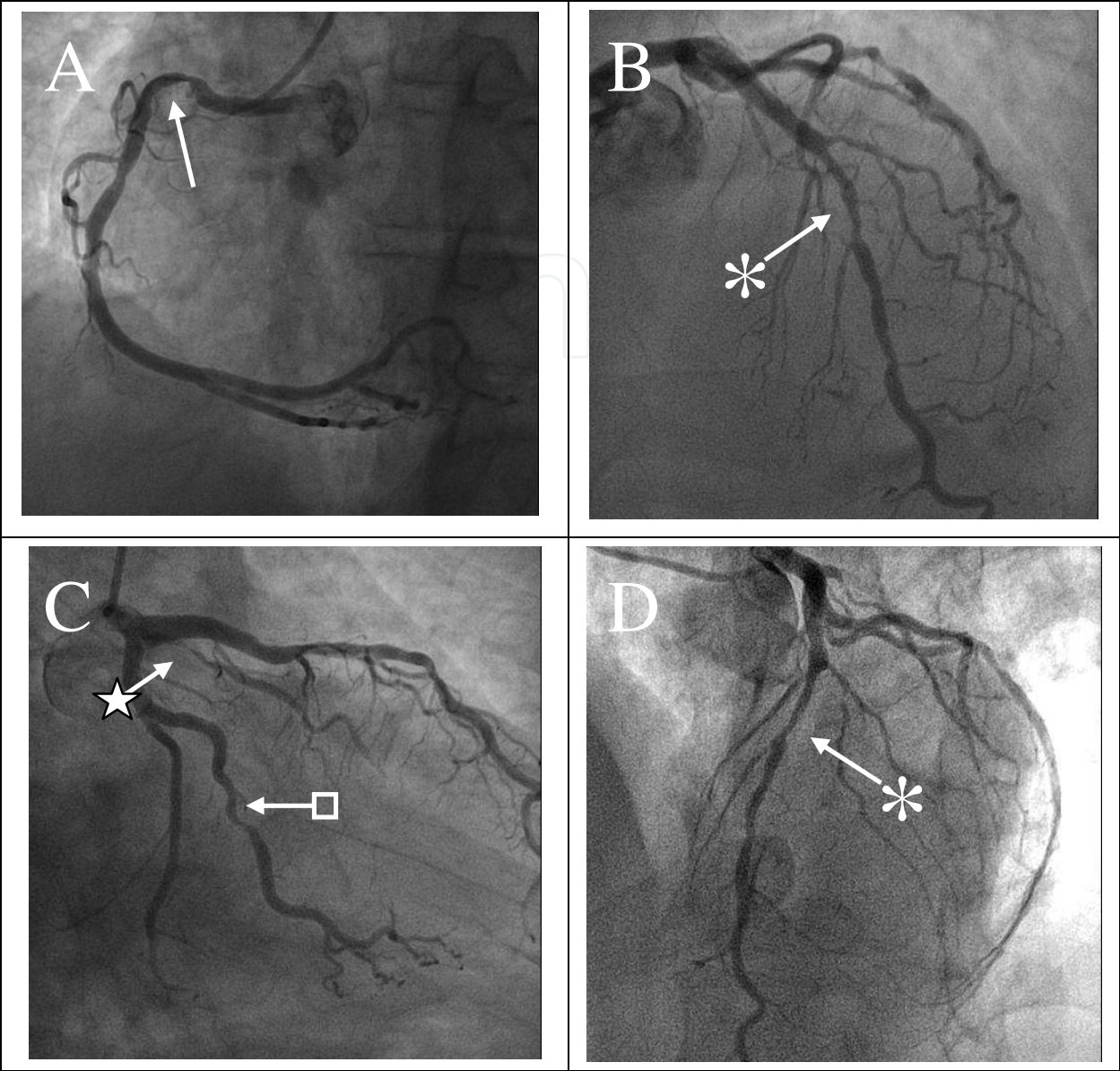
Fig. 1. A stenosis at the first tract of the right coronary artery **(A, arrow)**; a stenosis in the mid descending coronary artery (**B,D, arrows with asterisk**); a stenosis in the obtuse marginal ramus and a subocclusion of the ramus intermedium **(C, arrows with square and with star, respectively)** All the stenosis were categorized as critical by the operator by visual assessment.

years after the execution of the first procedure, when angioplasty had reached a degree of maturity. National Heart, Lung, and Blood Institute (NHLBI) funding for the first comparison of bypass surgery and angioplasty was finally obtained, and the Emory Angioplasty versus Surgery Trial (EAST) began in 1987 (King 1994). A second multicenter randomized trial, the Bypass Angioplasty Revascularization Investigation (BARI) (the BARI investigators 1996), was also approved by the NHLBI and began 1 year later. The outcomes of these two trials were consistent with other trials (Pocock 1995) confirming the overall equivalence of angioplasty and bypass surgery for patients suitable for angioplasty. However the 5-year outcome of the BARI trial demonstrated a clear advantage for surgery

in the subset of patients with DM (the BARI investigators 1997). Cardiac mortality at 5 years was 5.8% in the CABG group and 20.6% in the percutaneous transluminal coronary angioplasty group (P=0.0003). A review of the long-term results of the EAST trial showed a similar trend (King III 2000). A meta-analysis of the trials of MVD patients with 5-year follow-up, reported a risk difference for death of 2.3% (P=0.025), or, in other words, 2.3 fewer deaths in the surgery group than in the interventional group at 5 years (Hoffman 2003). At 8 years, the risk difference was 3.4 fewer deaths in the surgery group per 100 patients treated. This difference in survival did not become established until after the 3-year of follow-up. In 3 of the trials considered in this meta-analysis the diabetic population was identified. Those trials were the EAST, Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI trial participants, 1995), and BARI studies. The long-term survival in the BARI trial was mainly driven by events occurring during the follow-up period. After myocardial infarction, the patients who had undergone previous bypass surgery had a dramatically lower mortality rate than those treated with angioplasty (relative risk, 0.09; 95% CI, 0.03 to 0.29). This protective effect after myocardial infarction was much more dramatic than the effect in patients who did not have infarction. The differences in completeness of revascularization, re-occlusion of dilated arteries, or progression of disease may all have contributed to the superiority of surgery. To note, the marked benefit seen in diabetic patients was limited to that large majority receiving internal mammary artery grafting to the anterior descending coronary artery. Because internal mammary artery grafts are patent in approximately 90% of the patients in late follow-up, they may serve as a protective conduit to the most important coronary artery. On the contrary, this protection would not be afforded in the angioplasty group, even if restenosis did not occur, because of potential progression of disease or plaque rupture in that proximal or mid anterior descending vessel.

Thus, neither the BARI DM findings nor the resulting Clinical Alert (McGuire 2003), that pointed out the superiority of bypass surgery, had measurable impact on the overall clinical practice patterns because they resulted obsolete before the results were available. Moreover, the results of the BARI trial were not duplicated in the BARI registry (constituted of those patients eligible, but not randomized), where diabetic patients treated by CABG or balloon angioplasty had similar survival rate and cardiac mortality (Detre 1999). These discrepancies might be explained by differences in measured and unmeasured clinical and angiographic characteristics of the patients enrolled in the registry, who underwent revascularization not by randomization but on the basis of the clinical judgment. Therefore, the primacy of surgery in the treatment of diabetic patients with MVD began to be discussed.

3.2 Bare-metal stent vs CABG

Coronary stents represented the most important improvement in the acute outcomes of patients undergoing PCI. This is clearly shown by the comparison between the diabetic patients in the 1985–1986 NHLBI PTCA registry and the contemporary patients in the 1997–2002 NHLBI Dynamic Registry (Srinivas 2002). Stenting was used in 87.5% of the latter registry and in none of the former, and resulted in greater angiographic success (94.8% versus 78.1%), less abrupt closure (0.9% versus 2.2%) and reduction of the hard end points of death (1.9% versus 4.3%), myocardial infarction (1.0% versus 7.4%), and in-hospital CABG surgery (0.8% versus 6.2%). In stent-PCI era, there were no revascularization trials

specific to diabetic patients with MVD; however, 4 trials evaluated revascularization strategies using stent compared with CABG in such patients. They were the Arterial Revascularization Therapy Study (ARTS)(Serruys 1999), the Stent or Surgery trial (SOS) (SOS investigators, 2002), the Argentina Randomized Trial of Angioplasty versus Surgery (ERACI II) (Rodriguez 2001, 2003), and the Medicine, Angioplasty, or Surgery Study (MASS II) (Hueb 2004). Each of these was a strategy trial comparing CABG with stent-PCI. The ARTS trial was composed of 1205 patients with MVD randomized to CABG or stenting and followed up for 3 years. Overall survival without stroke or myocardial infarction was 87.2% for PCI and 88.4% for CABG. Repeat revascularization was substantially less than previous balloon angioplasty trials for patients randomized to stenting (21.2% at 1 year and 26.7% at 3 years). In this trial, however, DM was a strong independent predictor of events at 3 years. Among the 208 patients with DM, the ARTS I trial showed that mortality rate was not significantly different between stent-PCI and CABG, and the composite of major adverse events at 1 year was significantly higher in patients randomized to stent-PCI compared to CABG (81.3% versus 52.7%), mainly due to the higher incidence of repeat revascularization, while the incidence of death, myocardial infarction and cerebrovascular events was not different. When the ARTS trial was compared with the BARI trial for 1-year mortality, there was an apparent improvement among diabetic patients treated by stent. The 1-year mortality for diabetic patients in BARI randomized to surgery was 6.4%, compared with ARTS, 3.1%. Likewise, in the BARI PTCA group, the 1-year mortality in diabetic patients was 11.2%, compared with ARTS, 6.3%. A pooled analysis of the 4 stent trials failed to detect a difference at 5-year follow-up between stenting and surgery in diabetic patients with multivessel disease in term of death, myocardial infarction and cerebrovascular events, but an higher rate of repeat revascularization (6.3% CABG versus 25% stent) was observed. Such improvement in outcomes may reflect selection differences between BARI and ARTS or may reflect improving medical management of diabetic patients during the stent era. It should be emphasized that these randomized trials, however, might have introduced several selection bias. Because of the restrictive nature of enrollment, only the 5–12% of the total population was considered eligible for revascularization. Moreover, among the selected individuals, only 20–25% were diabetic; therefore, the results of these trials may not have captured the complex scenario of the impact of the clinical assessment in choosing PCI versus CABG in diabetic patients with MVD. To this regard in the MASS II trial, Pereira et al observed a reduced survival rate in the group randomized to a strategy of revascularization that differed from the choice of the physician (i.e., their physicians would not have chosen PCI or CABG for those patients) (Pereira 2006). They also found that the presence of three-vessel disease was the main predictor of the discordance between the choice of PCI or CABG made by randomization and that selected by physicians. Similarly, comparing the outcome of the BARI eligible diabetic patients with MVD treated by stent-PCI and included in the NHLBI Dynamic Registry with that of the diabetic patients randomized to plain angioplasty in the BARI trial, it is noteworthy that fewer lesions were attempted in the registry group (1.53 versus 2.56), and a dramatic decrease in abrupt closure and in in-hospital bypass graft surgery (1.9% versus 11.2% in BARI) was observed. Moreover the 1-year survival for NHLBI Dynamic Registry patients with characteristics similar to those of the BARI patients was 92.1%, compared to 93.6% and 88.1% of the BARI surgery and BARI PTCA patients respectively. These were not concurrent patient groups and may reflect either the significant differences between randomized and registry patients or the improved medical management of patients in the stent era.

More recently, a study conducted by Hannan and coworkers evaluated patients who underwent revascularization procedures in the New York's cardiac registries, to evaluate the rates of death and subsequent revascularization within three years after the procedure in various groups of patients with multivessel coronary artery disease (Hannan 2005). When the subgroup of patients with DM was analyzed, the adjusted hazard ratios for mortality were still lower after CABG than after stenting in all anatomical subgroups, particularly in the patients who had three-vessel disease and those with involvement of the proximal LAD artery. Restenosis, of course, remained the limiting Achille's heel of the PCI in diabetics. Thus, even in the stent era, although some improvements in PCI outcome were observed, CABG remained the gold standard for diabetics with significant and extensive multi-vessel CAD.

3.3 Drug-eluting stent vs CABG

The introduction of Drug-eluting stents (DES) significantly decreased the need for target-lesion revascularization, successfully addressing the problem of restenosis observed with the bare-metal stents. Two randomized studies, the Diabetes and Sirolimus-Eluting Stent (DIABETES) Trial (Sabaté 2005) and the SCORPIUS (German Multicenter Randomized Single Blind Study of the CYPHER Sirolimus-Eluting Stent in the Treatment of Diabetic Patients with De Novo Native Coronary Artery Lesions) (Baumgart 2007) study, compared clinical outcomes between bare-metal stents and DES in diabetic patients. The DES markedly reduced the rates of repeat revascularization in both studies. A collaborative network meta-analysis compared the risk of revascularization between the two first-generation DES – sirolimus- and paclitaxel-eluting stent – and bare-metal stents in diabetic patients (Stettler 2008). The risk of target-lesion revascularization was reduced by 71% and 62%, respectively, in favour of paclitaxel-eluting stent and sirolimus-eluting stent compared with bare-metal stents in diabetic patients, similarly to the results observed in non-diabetic patients. The absolute reduction in repeat revascularization was more pronounced in diabetic than non-diabetic patients, due to the higher baseline risk of restenosis, so the use of DES should be strongly recommended when PCI is the revascularization choice in diabetic patients. The diabetics in TAXUS IV (Dangas 2004), SIRIUS (the Sirolimus-Eluting Stent in de Novo Native Coronary Lesions trial)(Moses 2003), DECODE (Chan 2008), and DIABETES trials had single digit target lesion revascularization rates (7.8%) with DES versus 24.7% with bare-metal stents (Hillegass 2008). Although a recent meta-analysis of four trials suggested an increased risk of death with sirolimus-eluting stent compared to bare-metal stents in diabetic patients (Spaulding 2007), this finding was not confirmed in a larger analysis of 14 trials (Kastrati 2007). The safety and efficacy of the two first-generation DES in patients with and without DM was also addressed by others (Stettler 2007, 2008). Of note, in trials with less than 6 months duration of clopidogrel therapy, the risk of death associated with sirolimus eluting stents was more than twice the risk associated with bare-metal stents, whereas trials with clopidogrel of 6 months or longer showed no increase in risk with sirolimus eluting stents compared with bare-metal stents. This observation suggests that the above-mentioned increase in the risk of death associated with the use of sirolimus eluting stents in diabetic patients was most likely due to the restricted duration of clopidogrel therapy below 6 months in early trials.

In summary, DES demonstrate to be effective in reducing the need for target lesion revascularization and to have a similar safety profile, with comparable rates of death,

cardiac death, and myocardial infarction to bare-metal stents in diabetic patients. But can DES be advocated for the treatment of diabetics with MVD instead of CABG?

Several registries have compared clinical outcome of patients with MVD treated by DES-PCI or CABG. The ARTS II (Serruys 2005) was a non-randomized registry to determine the safety and efficacy of sirolimus-eluting stents in 607 patients with multivessel disease. In order to make the results of this registry as comparable as possible to the randomized ARTS I trial, comparing bare-metal stents with CABG, the same inclusion and exclusion criteria, the same protocol definitions, and the same primary endpoint were chosen. Nevertheless, as compared with ARTS I, patients included into ARTS II had more three-vessel disease, a higher incidence of DM, and were treated with more and longer stents. At 1 year of follow-up, the incidence of repeat revascularization was 8.5% in ARTS II and therefore significantly lower than in the historical bare-metal stents arm of ARTS I (21.3%, RR = 0.44, 95% CI 0.31–0.61), but still higher than in the historical CABG arm of ARTS I (4.2%, RR = 2.03, 95% CI 1.23–3.34). Conversely, the combined endpoint of death, myocardial infarction, or stroke was lower in ARTS II (3.0%) than the CABG-ARTS I group (8.0%, RR = 0.37, 95% CI 0.30–0.51). In a stratified analysis, diabetic patients had a higher rate of major adverse cardiac and cerebrovascular events (MACCE) (15.7% versus 8.5%, RR = 1.85, 95% CI 1.16–2.97, $P = 0.09$) and repeat interventions (13.4% versus 6.8%, RR = 1.97, 95% CI 1.16–3.34, $P < 0.01$) compared with non-diabetic patients. There were no significant differences between ARTS II and the CABG arm of ARTS I in MACCE at 1 year. More recently, the 3-year follow-up data of ARTS II have been reported and compared to the historical groups of ARTS I. Similarly to the 1-year data, MACCE were similar in ARTS II (19.4%) and the CABG arm of ARTS I (16.2%, $P = 0.21$) but they were more frequent in the bare-metal stents arm of ARTS I (34%, $P < 0.001$). Freedom from revascularization remained higher within the CABG arm of ARTS I (93.4%) followed by the DES arm ARTS II (85.5%, $P < 0.001$) and topped in the by the bare-metal stents arm of ARTS I (73.7%, $P < 0.001$). Similarly, the ERACI III study enrolled 225 patients with multivessel disease who were treated with DES and respected the same inclusion and exclusion criteria as the randomized ERACI II trial comparing bare-metal stents with CABG (Rodriguez 2007). The need for repeat revascularization was lowest among patients undergoing CABG in ERACI II (15.4%), followed by DES-treated patients of ERACI III (21.3%) and topped by bare-metal stents -treated patients in ERACI II (38.5%, $P = 0.05$). The results of ARTS II and ERACI III have to be cautiously interpreted in the light of the non-randomized nature of the study. Consistent with that, the registry data of Hannan and colleagues, who assessed the clinical outcome of patients with MVD treated by CABG ($n = 7437$) or DES ($n = 9963$) in the New York State (Hannan 2008) showed that the rates of death (HR = 0.97, 95% CI 0.77–1.20, $P = 0.75$) and death or myocardial infarction (HR = 0.84, 95% CI 0.69–1.01, $P = 0.07$) were similar for diabetic patients irrespective of revascularization strategy. This was in contradiction with the previous report from the same investigators comparing bare-metal stents to CABG, where the latter group was associated with improved survival among diabetic patients with three-vessel disease, showing a potential benefit of DES-PCI over bare-metal stent-PCI.

The UK-based CARDIA (Coronary Artery Revascularization in DM) trial directly compared CABG with PCI (predominant DES use: 71%) in diabetic patients with multivessel disease in a randomized, non-inferiority study. Due to recruitment difficulties, only 510 of 600 planned patients (85%) were randomized (Kapur 2008). The primary endpoint, a composite of death, non-fatal MI, and stroke, assessed at 1 year showed similar outcome for PCI (11.6%) and

CABG (10.2%, $P = 0.63$) with no significant differences in rates of death (PCI: 3.2%, CABG: 3.3%, $P = 0.83$) and myocardial infarction (PCI: 8.4%, CABG: 5.7%, $P = 0.25$), although non-fatal strokes tended to be less common with PCI (0.4%) than CABG (2.5%, $P = 0.09$). Repeat revascularization procedures were more frequent with PCI (9.9%) than CABG (2.0%, $P < 0.001$) at 1-year follow-up. These findings were in line with the subgroup of diabetic patients ($n = 512$ patients) included in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial (Serruys 2009), a large-scale randomized study (n = 1800 patients) comparing CABG with DES in the treatment of patients with MVD. The composite endpoint of death, MI, and stroke at 1 year was similar for CABG (10.3%) and PCI (10.1%), whereas repeat revascularization was more common with the latter [13.7% subsequent revascularization procedures with an initial strategy of multivessel DES versus 5.9% with CABG (p < 0.001)]. To note, the excess in repeat revascularization was smaller than any prior large randomized trial, in a much more complicated coronary anatomic setting. Moreover, there was a significant interaction between SYNTAX score and treatment group (P = 0.01); patients with low or intermediate scores in the CABG group and in the PCI group had similar rates of major adverse cardiac or cerebrovascular events, whereas among patients with high scores, the event rate was significantly increased in the PCI group. Thus, although PCI did not meet the test of noninferiority against CABG, the creation by the authors of a semiquantitative method (SYNTAX score) to characterize the three vessel disease might help to guide, in daily practice, the "clinical sense" to differentiate between patients and (non randomized) types of revascularization on a case-by-case basis. The prognostic role of the clinical judgment in the selection of the most appropriate strategy of coronary revascularization, already discussed in the plain angioplasty era (BARI registry) and in the bare-metal stent era (MASS II study), was confirmed by others also for DES-PCI (Tarantini 2009). Thus, in this regard, the use of SINTAX score might reduce the gap between the art and the science of the most appropriate coronary revascularization choice, and thus promises to have an important role in clinical practice.

The PCI guidelines have emphasized the long term benefit conferred by CABG in diabetic patients with MVD, but clinician's judgment on the revascularization strategy remains an important factor that is unadjustable by using standard clinical variables. This concept has been captured in the BARI 2D study (aggressive medical therapy versus revascularization)(Frye 2009), and among the diabetic patients with MVD randomized in the revascularization arm, the choice of PCI or CABG was on clinical basis and the anatomical complete revascularization was not required. The predictors for surgical choice was the presence of three vessel disease, proximal left anterior descending artery, total occlusion, complex multiple lesions (Kim 2009). The recent published appropriateness criteria for coronary revascularization (Patel 2009), developed to mimic common situations encountered in everyday practice that includes information on symptom status, extent of medical therapy, risk level as assessed by noninvasive testing, and coronary anatomy, gives to the choice of revascularization by PCI an high level of appropriateness in case of patients with DM and double vessels disease, but an "uncertainty" for diabetic patients with three vessels disease. This means that coronary revascularization may be acceptable and may be a reasonable approach for the indication but with uncertainty implying that more research and/or patient information is needed to further classify the indication .

4. Invasive physiological assessment: the role of fractional flow reserve

In patients with MVD, it is often difficult to determine which lesions are responsible for reversible ischemia. Noninvasive stress tests are often not able to accurately detect and localize ischemia. Therefore, the coronary angiogram is the standard for decision making about revascularization in such patients. In randomized trials evaluating coronary revascularization either by PCI or CABG, as well as in daily practice in most catheterization laboratories, lesions with a diameter stenosis of ≥50% on the angiogram are generally considered for revascularization. Coronary angiography, however, may result in both underestimation and overestimation of a lesion's severity and is often inaccurate in predicting which lesions cause ischemia even for lesions graded 70% to 80%. The fractional flow reserve (FFR) is an accurate and selective index of the physiological significance of a coronary stenosis that can be easily measured during coronary angiography. An FFR value of ≤0.80 identifies ischemia-causing coronary stenoses with an accuracy of >90%. In the randomized FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study (Tonino 2009), FFR-guided percutaneous coronary intervention (PCI) with drug-eluting stents was compared with angiography-guided PCI in patients with MVD. The 1-year results of this study showed that FFR guidance of PCI significantly decreased the combined end point of death, myocardial infarction, and repeat revascularization. It is noteworthy that only 46% of the patients with MVD enrolled resulted to have a functional MVD (≥2 coronary arteries with an FFR ≤0.80). This result is consistent with the results of prior studies (Sant'Anna 2007). If we compare the FAME with the SYNTAX study in which PCI was guided by angiography alone, not surprisingly, the clinical outcome was similar to that in the angiography group in the FAME study. In contrast, the clinical outcome in the FFR group in the FAME study was similar to that in the group of patients in SYNTAX who underwent coronary-artery bypass grafting (table 3).

Characteristic	Angiography--Guided PCI (N = 546)	CABG (N = 549)	Angiography--Guided PCI (N = 496)	FFR--Guided PCI (N = 509)
Mean age (yr)	65.1	64.5	64.2	64.6
Diabetes (%)	Unknown	Unknown	25.2	24.2
Unstable angina (%)	27.8	27.3	35.8	29.4
Mean EuroSCORE value	3.7	3.7	3.7	3.8
Mean SYNTAX score	14.5	14.5		
Low	17.3	17.3		
Intermediate	27.4	27.5		
High	39.8	41.0		
MACCE (%)				
All patients	19.1	11.2	15.8	11.0
Patients with low SYNTAX score	17.2	14.7		
intermediate SYNTAX score	18.6	10.1		
high SYNTAX score	7.9	6.4		
Death or MI (%)	7.9	6.4	7.9	5.1
Mean hospital stay (days)	3.5	9.3	3.7	3.4

Table 3. Characteristics of Patients and Outcomes in the SYNTAX and FAME Trials.

5. Progression of coronary disease in diabetics: the role of secondary prevention

A pooled analysis of individual patient level data from 4 second-generation stent trials pointed to the impact of progression of disease. Although not specific for diabetic patients, 5-year follow-up documented that late cardiac events were 2-fold related to the progression of the disease instead of restenosis at the originally treated site (Cutlip 2004). Events caused by the treated lesion occurred in 20.3% of the patients, most of them in the first year as result of restenosis. There were very few target lesion–specific events after the first year. Conversely, events related to untreated segments of the coronary tree continued and affected 37.9% of the patients by 5 years. At the end of 5 years, only 8.9% of patients had events limited to restenosis of the target lesion originally treated, whereas 37.9% had events that included nonrestenotic segments. The need to focus on more aggressive long-term prevention was also highlighted by a study from Denmark. A multipronged approach to prevention of vascular disease progression has gained traction in recent years. A small multifactorial intervention study in patients with type 2 DM illustrates this point (Gaede 2003). Patients were randomized to a conventional treatment according to national guidelines of Denmark or to receive intensive behavioral modification and pharmacological therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria in addition to aspirin therapy. Hemoglobin A1c values were improved in patients with the intensive therapy, and the end points of cardiovascular death, nonfatal infarction, stroke, revascularization, and amputation were reduced more than 50% (HR, 0.47; 95% CI, 0.24 to 0.73). This data was confirmed also in the more recent Action in DM and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study (Patel 2008) .The profound importance of slowing disease progression, as noted above, is also highlighted by the fact that attempts at secondary prevention efforts in past randomized trials were substandard when judged by contemporary best practice. The average Low Density Lipoprotein (LDL) levels in patients on entry to the BARI trial were virtually identical to those at the end of 5 years: 143 mg% at the beginning and 141 mg% at the end. Although there is no evidence in the BARI trial that there was a specific difference in outcomes between groups who had their lipoprotein profiles improved and those who did not, the above finding is certainly proof that secondary prevention did not approximate the more rigorous clinical standards of contemporary practice. Today, pharmacological antiatherosclerotic intervention in diabetics is directed toward the hyperinsulinemia, hyperglycemia, hypertension, hyperlipidemia, and hypercoagulability that accompany DM. In addition, the Heart Outcomes Prevention Evaluation (HOPE) (Yusuf 2004) revealed that ACE inhibitors can specifically improve vascular outcomes independently of their effect on blood pressure in the diabetic subgroup. Although the United Kingdom DM study, UKDG, indicated that aggressive glycemic control per se did not reduce large-vessel vascular events in that population (UK Prospective Diabetes Study Group 1998), there are other lines of evidence to indicate that aggressive risk factor control directed toward lipids can have positive effects on long-term outcomes. Importantly, in the Scandinavian Simvastatin Survival Study (4S) (The Scandinavian Simvastatin Survival Study Group 1994), diabetics who were placed on statins had atherosclerotic event rates comparable to those of the treated non-diabetic group: a 30% to 40% reduction compared with placebo . Moreover, a subanalysis on diabetic population of the The Lescol Intervention Prevention Study (LIPS) study (Serruys 2002) that was a multinational randomized controlled trial, showed a 51% reduction in the in major

adverse cardiac events from the routine use of fluvastatin, compared with controls, in patients undergoing percutaneous coronary intervention (PCI, defined as angioplasty with or without stents). This evidence supports the hypothesis that aggressive risk factor control will favorably influence the long-term outcomes in the diabetic population and assist in eliminating the gap between PCI and CABG patients. In addition, other treatments, including long-term dual antiplatelet therapy with aspirin and clopidogrel, show promise in minimizing atherothrombotic events in the diabetic population. Although they have not been specifically studied in the context of DM and MVD, they also hold the potential to minimize long-term events after successful revascularization.
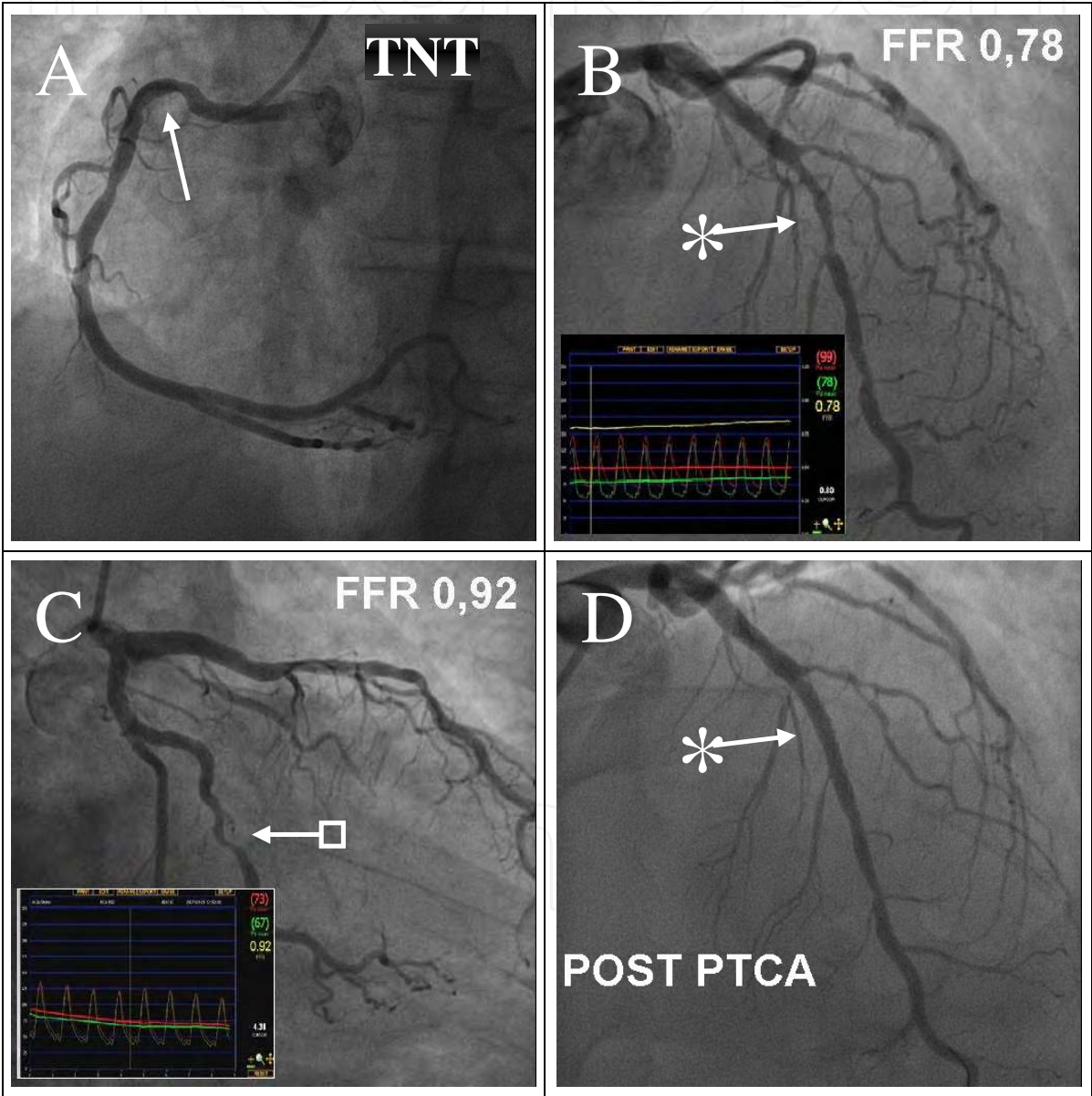
Fig. 2. The right coronary artery stenosis appeared only moderate after intracoronary nitroglicerin bolus **(A, arrow)**. The FFR was below the ischemic threshold of 0.80 **(B, arrow with asterisk)** and was stented with good angiographic result **(D, arrow with asterisk)**. The FFR of the obtuse marginal ramus stenosis was 0,92, so the lesion wasn't treated **(C, arrow with square)**.

6. Clinical case: how did we treat?

The TIMI risk score of the patients was 3 and the syntax score 13. We treated first the culprit lesion on the ramus intermedium. The lesion on the right coronary was only moderate after intracoronary nitroglicerin bolus. Then, we made a FFR estimation of the left descending artery and the obtuse marginal ramus lesions after intracoronary and intravenous infusion of adenosine (see figure 2).

Thereafter, we treated by DES-PCI only the left descending artery lesion, that resulted significant by FFR. The patient was discharged with dual antiplatelet therapy and high dosage of statin with a target of LDL < 70 mg%. At 3-year of follow-up the patients remained asymptomatic and with negative stress test.

7. Conclusions

Compared with non-diabetic, diabetic patients have more extensive atherosclerosis and a worse clinical outcome following revascularization procedures. Notwithstanding, the therapeutic benefit of revascularization is particularly pronounced in this high-risk subgroup of patients. The best strategy of coronary revascularization in diabetic patients depends on the clinical setting and anatomical factors (see figure 3).
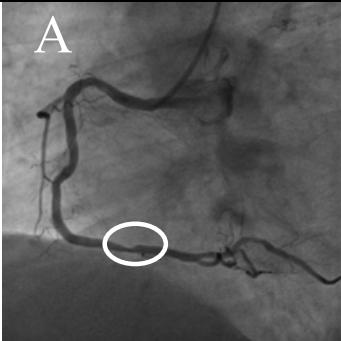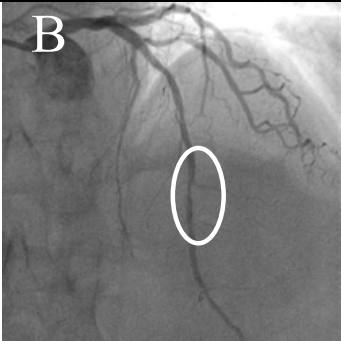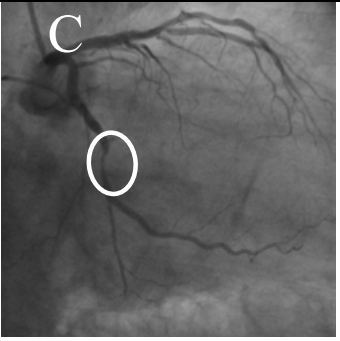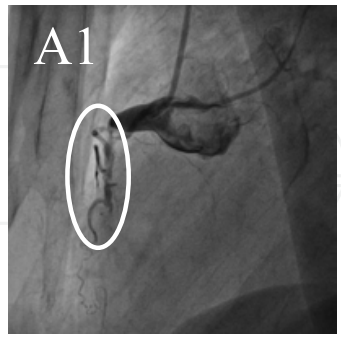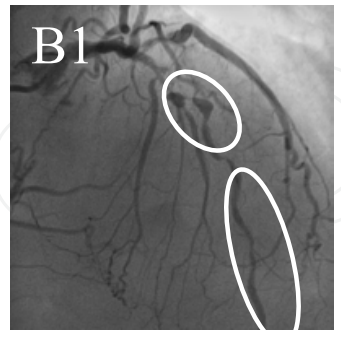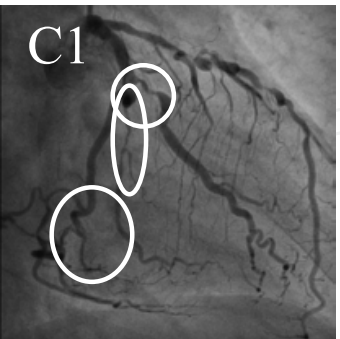
Fig. 3. Upper panel shows images of a good angiographic candidate for PCI: a stenosis on distal right coronary artery **(A)**; a stenosis on mid descending coronary artery **(B)**; a stenosis on the mid circumflex artery **(C)**. Lower panel shows images of a poor angiographic candidate to PCI: Chronic total occlusion of the right coronary artery at the first tract **(A1)**; multiple stenosis of the left descending coronary artery, also involving bifurcations and with dilated tract interposed **(B1)**; multiple stenosis of circumflex artery and its branches **(C1)**. All lesions are indicated with a circle. On the right column, the angiographic syntax score for each patient.

In the acute setting including ST-elevation myocardial infarction and non-ST-elevation myocardial infarction, PCI seems preferable as shown in AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) substudy (Sedlis 2002). In patients with stable coronary artery disease, the extent of disease and non-cardiac morbidity require more careful evaluation. CABG appears more effective in terms of repeat revascularization procedures, particularly in diffuse MVD, while DES-PCI with aggressive pharmacological treatment (i.e. thienopyridines and downstream glycoprotein IIb/IIIa antagonist) is a valuable alternative in patients with less extensive disease (see figure 3).

Although PCI did not meet noninferiority against CABG in diabetic patients with 3-vessel disease, the creation of a semiquantitative method (i.e. SYNTAX score) to better characterize the three vessel disease might help to guide, in daily practice, the "clinical sense" to differentiate between patients and (non randomized) types of revascularization on a case-by-case basis. Moreover, the use of an invasive physiological assessment can add further imformations to refine the most appropriate revascularization choice. The FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) trial (Farkouh 2008) will randomize more than 2000 diabetic patients with MVD to either multivessel DES-PCI or CABG, so will shed more light on the relative efficacy of CABG and DES-PCI among diabetic patients with three vessel disease. However, while awaiting the results of future trials, please, don't forget that stent will fix the lesion, CABG the vessel, but both won't fix the patient without aggressive medical therapy during the follow-up.

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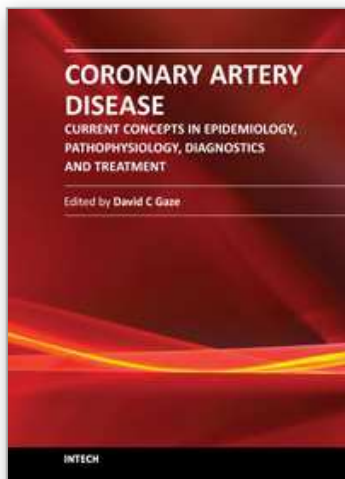
Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment

Edited by Dr. David Gaze

Cardiovascular disease is ranked as the leading cause of death world wide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antiplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease

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