Chapter

Percutaneous Coronary Intervention in Diabetic Patients

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Abstract

Cardiovascular disease (CVD) is responsible for 30% of deaths worldwide and is the leading cause of premature mortality in patients with diabetes mellitus (DM). One of the main contributors to the increased atherothrombotic risk in DM patients relates to their pro- inflammatory and prothrombotic status that involves abnormalities in endothelial and vascular smooth muscle cells, in platelet function and the coagulation cascade. The characteristics of CAD in diabetic patients is distinctive and infers an increased risk. Likewise, CAD in diabetics is characterised by being diffuse, affecting the left main stem more frequently, involving multiple vessels, and also affecting the distal coronary tree. Percutaneous coronary intervention in diabetics has been shown to have less favourable long-term clinical outcomes, compared to non-diabetics. With the advent of improved stent designs and antiplatelet drugs; the percutaneous coronary intervention (PCI) results have improved in the diabetic population. However, one of the main determinants of poorer outcomes in DM is the progression of atherosclerosis, which is more pronounced in diabetics and remains the primary cause of cardiac events at one year follow up after percutaneous revascularisation. Whilst new generation of drug-eluting stents has narrowed the gap between surgery and PCI in diabetic patients, coronary artery bypass grafting (CABG) remains the gold standard in diabetics with diffuse multivessel coronary artery disease.

Keywords: diabetes mellitus, coronary artery bypass grafting, percutaneous coronary intervention, antiplatelet drugs, drug-eluting stents

1. Introduction

The prevalence of diabetes mellitus has increased exponentially, from 108 million in 1980 to 422 million worldwide in 2014 [1]. Cardiovascular diseases (CVDs) constitute the number one cause of mortality globally, representing 30% of all global deaths [2]. Cardiovascular disease is the leading cause of morbidity and premature mortality in patients with diabetes mellitus (DM) [3–6]. A meta-analysis of 102 prospective studies (The Emerging Risk Factor Collaboration) showed that DM in general, confers an increased risk for developing vascular disease compared to non-diabetic patients [7]. DM increases the risk of coronary heart disease, stroke, and peripheral arterial disease by between two and four-fold. The increased risk is independent of, and additional to other cardiovascular risk factors [7–10].

It has been reported that between 20 and 30% of patients with coronary artery disease have known DM, and up to 70% have newly detected DM or impaired glucose tolerance [11]. Importantly, the risk of myocardial infarction (MI) is three to five times higher in type 2 DM. A diabetic patient with no history of MI has the same long-term risk as a non-DM subject with a past history of MI [12]. For these reasons, DM is considered to be a "coronary heart disease equivalent" [13]. The anatomical pattern of coronary artery disease (CAD) in patients with DM influences the prognosis [11]. The extension of CAD in diabetic patients exhibits distinctive characteristics that infer an increased risk. Likewise, CAD in diabetics is characterised by being diffuse, affecting the left main stem more frequently, involving multiple vessels, and also affecting the distal coronary tree [14]. CAD typically progresses more rapidly in diabetic compared with non-diabetics [15]. Furthermore, patients with DM have more associated comorbidities, such as peripheral artery disease, cerebrovascular disease or chronic kidney disease, which influence outcomes after coronary revascularisation [11].

The indications for myocardial revascularisation, for both symptomatic and prognostic reasons, were the same in patients with or without DM [16]. The anatomical pattern in which diabetes affects patients, combined with an increased risk of stent failure (restenosis and stent thrombosis), in conjunction with the "Prothrombotic State" that characterised these patients, resulted in poorer outcomes following revascularisation in general. However, it is particularly evident following percutaneous revascularisation.

Three randomised clinical trials compared percutaneous coronary intervention (PCI) vs. coronary artery bypass graft surgery in patients with DM, using mainly first-generation drug-eluting stents (DES) [11]. With this in mind, safety concerns following PCI have surfaced, specifically with the use of first-generation DES, as diabetes has emerged as an independent predictor of stent thrombosis (ST) [17]. Recently, new generation DES platforms were designed and have demonstrated improved safety outcomes, compared to the first generation. Thus, coronary artery bypass grafting has been the revascularisation treatment recommended in diabetics with multivessel disease.

Although the advent of drug-eluting stents has narrowed the gap between surgery and the percutaneous treatment, the former remains the gold standard in diabetics with diffuse coronary artery disease.

One of the main determinants of poor outcomes in DM is the progression of atherosclerosis, which is more pronounced in diabetics and remains the main cause of cardiac events at one year follow up, after percutaneous revascularisation. This review focuses on all the aforementioned issues, which affect diabetic patients, as well as any updates to the current evidence regarding the different modalities of revascularisation in this special population.

2. Vascular abnormalities and atherothrombotic risk in diabetic patients

DM is linked to an increased atherothrombotic risk. In fact, diabetics with coronary artery disease suffer a higher rate of recurrence following their index MI [18]. Atherothrombotic disease is accelerated in subjects with both type 1 and type 2 diabetes, with diverse underlying mechanisms, despite the common characteristic of hyperglycaemia. The main feature of type 2 DM is insulin resistance, which precedes the development of hyperglycaemia [19]. Contrastingly, in type 1 diabetes, hyperglycaemia is the dominant feature with insulin resistance appearing at later stages, in patients who develop renal disease [20].

One of the main contributors to the increased atherothrombotic risk in DM patients relates to their pro- inflammatory and prothrombotic status that involves abnormalities in endothelial and vascular smooth muscle cells, in platelet function and the coagulation cascade. Endothelial dysfunction in diabetics is characterised by a decrease in nitric oxide (NO), and also by an increase in the synthesis of vasoconstrictor prostanoids and endothelin [21]. Hyperglycaemia decreases endothelium-derived NO via multiple mechanisms, including the intracellular production of advanced glycation end-products (AGEs) and free radical formation [22, 23]. Furthermore, hyperglycaemia also produces an increase in the concentration in plasma of vasoconstrictors, such as endothelin, which is related to both the incidence of inflammation and smooth-muscle contraction and growth. Other metabolic disorders known to occur in diabetes including an increase in the circulating levels of free fatty acid, an increase in the production of free radicals or an exacerbation of dyslipidaemia, may also impair the endothelial function [24–26]. On the other hand, hyperinsulinemia [27] also plays an important role in the pathophysiological mechanisms that may contribute towards vascular disease in diabetic patients. The concentration in plasma of vasoconstrictors, such as endothelin, increases after administration of insulin to healthy subjects and patients with type 2 diabetes [28–31]. This phenomenon may be related to both the incidence of inflammation and smooth-muscle contraction and growth. In addition, hyperinsulinemia is a potent mitogen for restenosis, as it stimulates the proliferation and migration of smooth cells [32]. Previous studies have demonstrated that hyperinsulinaemia enhances the secretion of insulin during the oral glucose tolerance test, and is a predictor of restenosis after balloon angioplasty and stent implantation [33–35].

Platelets are also affected in diabetic patients. Both insulin resistance and hyperglycaemia contribute to a prothrombotic state by exerting several salient effects on both coagulation and platelet function. The effects of insulin resistance on platelet function is related to intra-cytosolic calcium levels, a mediator of platelet activation. Whilst insulin decreases the intra-cellular concentration of calcium in platelets from insulin-sensitive subjects *in vivo* and *in vitro*, it appears to increase the intraplatelet calcium concentrations in the insulin-resistant state, promoting platelet aggregation and activation [36]. Platelets obtained from diabetic subjects showed both increased adhesiveness and an exaggerated aggregation following activation [24]. In addition, reduced responsiveness of diabetic patients to antiplatelet therapy has been documented [14]. The overall picture of platelet abnormalities in DM results in the hypersensitivity of diabetic platelets to agonists. In fact, platelets in diabetic subjects appear to be in an activated state even in the absence of vascular injury, and they respond more frequently even to sub threshold stimuli. It has been shown that there is greater expression of the fibrinogen-binding glycoprotein IIb/IIIa receptor, which constitutes the final common pathway of platelet activation and allows for cross-linking of individual platelets by fibrinogen molecules and formation of thrombus [15]. Finally, there is also impairment of the coagulation cascade. Insulin resistance gives rise to increased levels of the fibrinolytic inhibitor Plasminogen Activator Inhibitor-1 (PAI-1), and hyperglycaemia induces the enhancement of thromboxane A2 production and an increase in factor VII and anti-thrombin III production [24–26].

The alteration in platelet function is especially relevant in diabetics patients treated percutaneously, as it may affect the response to antiplatelet treatment. Although, clopidogrel response variability is a multifactorial process, the mechanisms above explain why dual antiplatelet regimen with ASA and clopidogrel presents important limitations in diabetic patients. The main mechanisms in this patient cohort that explain poor response to dual antiplatelet therapy in diabetes

mellitus are antiplatelet resistance and clopidogrel response variability. Variability in antiplatelet effects following clopidogrel therapy is present in both the acute and the chronic phases of therapy [37]. Of note, diabetics requiring insulin are those who persist with the highest platelet reactivity, despite dual antiplatelet therapy [37]. This antiplatelet variability has clinical implications, such as increased rates of coronary stent thrombosis and recurrent ischaemic events after PCI in poor clopidogrel responders. Among the clinical factors involved in clopidogrel variability, diabetes mellitus has been associated with a greater prevalence of poor responsiveness [38]. Overall, the persistence of elevated platelet reactivity and reduced response to aspirin and clopidogrel therapy enhances the atherothrombotic risk of DM patients. Multiple causes have been implicated in these observations. Poor glycaemic control is an important cause of increased platelet reactivity. Hyperglycaemia leads to non-enzymatic glycation of platelet glycoproteins, causing changes in their structure and conformation, as well as alterations of membrane lipid dynamics. This may explain why platelet reactivity can be reduced with tight control of glucose levels [39].

The introduction of new regimens and antiplatelet agents may improve and overcome the variability in the response to clopidogrel. The P2Y12 inhibitors, with a more uniform and potent effect, have recently been evaluated. Prasugrel is a P2Y12 inhibitor of the third generation, with more potent and less variable antiplatelet effects compared to clopidogrel [40]. The TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet InhibitioN with Prasugrel-Thrombolysis in Myocardial Infarction) trial showed significantly reduced rates of ischaemic events, including stent thrombosis, in patients presenting with acute coronary syndromes undergoing PCI treated with prasugrel compared to clopidogrel [41]. In the subgroup analyses of diabetes population (n = 3146) the greatest risk reduction (rate of primary endpoint, defined as death from cardiovascular causes, non-fatal MI or non-fatal stroke) was observed in 12.2% of the diabetics treated with prasugrel vs. 17.0% in diabetic patients on clopidogrel with 30% relative risk reduction. Importantly, prasugrel was not associated with an increased risk of major bleedings compared to clopidogrel in these patients [42]. The functional impact of prasugrel versus clopidogrel, specifically in diabetic patients, was evaluated in the OPTIMUS-3 study. In this prospective, randomised, double-blind, crossover study, the standard-dose prasugrel was associated with greater platelet inhibition and better response profiles during both the loading and maintenance periods, when compared with double-dose clopidogrel [43].

On the other hand, ticagrelor, has a faster onset and offset of action and achieves higher inhibition of platelet aggregation compared to clopidogrel. In the RESPOND trial [44] Ticagrelor therapy overcomes nonresponsiveness to clopidogrel, and its antiplatelet effect is the same in responders and non-responders. The phase III Study of Platelet Inhibition and Patient Outcomes (PLATO) trial randomised acute coronary syndrome patients (n = 18,624) to receive either ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300–600 mg loading dose followed by 75 mg daily). In a predefined subgroup analysis of diabetic patients (n = 4662) there was a non-significant reduction of the primary endpoint [14.1% vs. 16.2%; HR 0.88 (0.76–1.03)], while no difference in major bleeding rates was found [14.1% vs. 14.8%; HR = 0.95 (0.81–1.12)] [45]. The recommendations from the recent ESC guidelines for the selection of antithrombotic therapy in diabetic patients with an acute coronary syndromes in patients presenting without persistent ST-segment elevation, state that the therapy should not differ from those without diabetes [46].

Phase III trial data on the use of factor-Xa inhibition direct oral anticoagulants for treatment of ACS has emerged. The APPRAISE-2 (Apixaban for Prevention of

Acute Ischemic Events) resulted in early termination of the study, due to an increase in Thrombolysis in Myocardial Infarction (TIMI) major bleeding in apixaban 5 mg bid (1.3%) compared with placebo (0.5%). There was no improvement in the composite of cardiovascular death, MI, or ischemic stroke with apixaban compared with placebo. Similarly, the ATLAS ACS 2-TIMI 51 (Anti Xa Therapy to Lower Cardiovascular Events in Addition to ASA with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction) study had a significant increase in major bleeding with their respective Factor Xa inhibitors compared with dual antiplatelet therapy. It was noted however, in the primary analysis of the combined dosing arms, rivaroxaban (combined dose arms) reduced the composite of cardiovascular death, MI, or stroke compared with placebo (8.9% versus 10.7%, respectively). In a secondary analysis of the efficacy and safety of rivaroxaban (2.5 or 5 mg bid) compared with placebo in a pooled subset of ACS patients from the ATLAS ACS-TIMI 46 (phase II) and ATLAS ACS 2-TIMI 51 (phase III) trials [47] showed that the addition of rivaroxaban to aspirin reduced a composite of cardiovascular death, myocardial infarction, and stroke versus aspirin alone, primarily by a reduction in the risk of myocardial infarction. However, the combined rivaroxaban dose groups were associated with higher rates of non-CABG TIMI major bleeding. The use of these strategies specifically in diabetic patients remains under investigation. In the stable cardiovascular disease setting, the Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) trial [48] investigated very low-dose rivaroxaban (2.5 mg b.i.d.) in combination with aspirin vs. aspirin alone or rivaroxaban 5 mg b.i.d. alone. Those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Greater absolute risk reductions were seen in high-risk patients, including those with diabetes.

3. Percutaneous revascularisation in diabetic patients

Since its inception, the use of percutaneous transluminal balloon angioplasty (BA) to treat coronary stenosis, diabetics have shown less favourable long-term clinical outcomes, compared to non-diabetics. Diabetes mellitus has been identified as an independent predictor of restenosis. In fact, the restenosis rate following BA in diabetics ranges between 35% and 71%, which is much higher than seen in the general population (30–35%) [49]. In addition, the pattern of restenosis is more severe, as these patients typically show more proliferative and occlusive types of restenosis. The main contributor to the restenosis process following plain BA is negative remodelling (i.e., vessel shrinkage) [50] that accounts for 73% of lumen reduction after balloon angioplasty, while plaque burden contributes 27% [51].

Coronary stenting was able to reduce the occurrence of restenosis, not only in general population but also in diabetic patients [52]. Two pivotal randomised controlled trials demonstrated the beneficial effects of stenting as compared to BA, the STRESS and the BENESTENT trials [53, 54]. The analysis of diabetic patients in these two trials revealed a significant reduction in restenosis rate (STRESS: stent 32%, balloon 42%; $p = 0.046$; BENESTENT: stent 22%, balloon 42%; $p = 0.02$) and clinical outcomes improvement at 6 months and at 4 years follow-up (including cardiac death, non-fatal MI and the need for repeat revascularization) [55]. Despite these results, restenosis rate remained higher in diabetics compared to non-diabetics. In a meta-analysis [56] of 16 studies, after stent implantation angiographic restenosis (defined as ≥50% diameter stenosis at follow-up) occurred in 550 of 2672 (20.6%) of non-diabetics as compared to 130 of 418 (31.1%) of diabetic patients

($p < 0.001$). The authors identified, among other factors, insulin treatment in type 2 diabetes, a marker of disease duration and severity, as an independent predictor of restenosis. The prevailing mechanism of restenosis after stenting is accelerated intimal hyperplasia which is especially exaggerated in diabetic patients [57]. Thus, the development of drug-eluting stent (DES) to tackle this mechanism of restenosis directly was a revolutionary development in this field. In this regard, the subgroup analysis of the two pivotal randomised trial, which evaluated the efficacy of first generation DES (Cypher® stent; Cordis, Johnson & Johnson, Warren, NJ, USA and Taxus® stent; Boston Scientific, Natick, MA, USA) showed positive results in terms of restenosis rates and in MACE [58, 59].

In the SIRIUS trial (Sirolimus-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) [60] a total of 1058 patients were randomised to either SES or BMS for the treatment of de novo coronary stenosis. The primary endpoint was target vessel failure (cardiac death, myocardial infarction and target vessel revascularisation [TVR]) at 9-month follow-up. The diabetes subgroup analysis of the SIRIUS trial included 279 patients, 131 receiving SES and 148 receiving BMS [61]. In this subgroup of patients, SES implantation demonstrated favourable results with significant reductions in restenosis rates (in-lesion 50% for BMS vs. 17% for SES), and in MACE (25% for BMS vs. 9.2% for SES). The TAXUS IV trial [62] enrolled 1326 patients that were randomised to PES or BMS for the treatment of de novo coronary stenosis. The primary endpoint was ischaemia driven TVR and the incidence of cardiac death, and MI at one year. Overall, the PES group showed a significant reduction in the occurrence of the primary endpoint (TVR 7.4% vs. 20.9%, $p = 0.0008$). The study included 155 diabetic patients (32% of the total population) and 33% of the diabetics were insulin-dependent DM. In this subgroup, the use of PES significantly reduced the risk of binary restenosis (70% reduction of in-segment restenosis). This reduction was also observed in insulin-dependent DM subjects (42.9% for BMS vs. 7.7% for PES, $p = 0.007$).

The DIABETES (Diabetes and Sirolimus-Eluting Stent) trial [63] was the first randomised multicentre controlled trial specifically designed to assess the efficacy of SES vs. BMS in diabetics. This study included 160 diabetic patients, 80 of whom received BMS, while 80 were treated with SES. Late lumen loss assessed by QCA at 9-month follow-up was the primary endpoint. The SES treated group showed a significant reduction of late lumen loss (relative reduction 87%). The study considered a sub-randomisation, according to the type of anti-diabetic treatment and the SES benefit was independent from diabetic status. This benefit was maintained up to 5-year follow-up [64]. Subsequently, 3 other randomised trials also designed for diabetic patients (SCORPIUS [65, 66], DESSERT [67] and DECODE [68]) have corroborated the same positive results of SES in reducing neointimal proliferation to mid and long-term. A meta-analysis of all available data in diabetics treated with PCI [69] demonstrated the benefit of DES in terms of restenosis and target lesion revascularisation.

Finally, other studies compared both DES in terms of efficacy (**Table 1**). The SIRTAX (SIRolimus versus pacliTAXel-eluting stents) trial [70] and the ISAR (In-Stent Angiographic Restenosis)-DIABETES trial [71] showed that SES in diabetics had lower MACE and lower late lumen loss compared with PES. The efficacy of new generation DES has also been evaluated. The everolimus-eluting stent (EES) has been tested against PES in the SPIRIT IV and V trial. In the subgroup analyses of the SPIRIT IV [72] EES compared with PES showed no difference in target lesion failure (6.4% vs. 6.9%, respectively, $p = 0.80$) or any of its components was present among diabetic patients, regardless of insulin use. In contrast, in the SPIRIT V

Trial	Type of study	Type of stent	N	Primary endpoint	Primary outcomes
SIRTAX [90]	Single-centre, controlled, single-blind trial	SES vs. PES#	250	MACE (cardiac death, myocardial infarction and ischemia-driven target lesion revascularisation)	The primary endpoint was significantly lower in the SES group. The difference between SES and PES stents was more pronounced in the DM patients.
ISAR-DIABETES [91]	P, NI trial	SES vs. PES in diabetics	250	In-segment late lumen loss (non-inferiority margin 0.16mm)	In-segment late luminal loss was greater in the paclitaxel-stent group than in the sirolimus-stent group (P=0.002)
SPIRIT V DIABETIC [92]	P, single-blind, R.	EES vs. PES in diabetics	324	In-stent late lumen loss at 8 months	EES was superior to PES for in-stent late loss at 9 months however, clinical endpoints were similar between the two groups.
ESSENCE DIABETESbis [92]	P, M, R	EES vs. SES in diabetics	300	In-segment late lumen loss at 8 months	Everolimus-eluting stents were noninferior to sirolimus-eluting stents in reducing Late lumen loss:.
ENDEAVOR IV [93]	P, R (1:1), single-blind, controlled trial	ZES vs. PES #	477	Target vessel failure at 9 months	A trend towards higher in-stent late loss with ZES as compared to PES, but with comparable clinical outcomes at 1-year follow-up.
RESOLUTE [94]	M, NI trial	ZES vs. EES #	538	Target vessel failure at 12 months	ZES was demonstrated to be non-inferior to EES
LEADERS [95]	M, assessor-blind, NI	BES vs. SES#	414	Composite endpoint*	The primary endpoint was comparable in diabetic patients

SES: sirolimus-eluting stent; BMS: bare metal stent; PES: paclitaxel-eluting stent; DM: diabetes mellitus; EES: everolimus-eluting stent; ZES: zotarolimus-eluting stent; BES: biolimus-eluting stent; MACE: major adverse cardiac events; TVF: target vessel failure; TVR: target vessel revascularisation; P: prospective; NI: non-inferiority trial, R: randomised; M: multicenter.
[*]Composite endpoint of cardiac death, myocardial infarction and clinically-driven target vessel revascularisation at 9 months.
[#]Diabetic subgroup.

Table 1.
Randomised controlled trials comparing drug-eluting stent vs. drug-eluting stents in diabetic patients.

Diabetic Study Everolimus-eluting stent was superior to PES for in-stent late loss at 9 months, however, clinical endpoints were similar between the two groups [73]. Interestingly no stent thromboses (Academic Research Consortium definite and probable) were seen at 1 year with EES, compared with 2 of 104 (2%) with PES (P = 0.11). The efficacy of the zotarolimus-eluting stent (ZES) has been assessed in the Endeavour IV trial against PES [74] and the Resolute™ [75] stent a new generation ZES against EES. In these studies, ZES was comparable with PES and non-inferior to EES. Finally, the biolimus-eluting stent (BES) has been compared to SES in the LEADERS all-comer trial. BES appeared to be non-inferior to SES with regard to the primary endpoint in the subgroup of diabetics [76].

The effectiveness of different DES platforms has been addressed in the Swedish Angiography and Angioplasty Registry (SCAAR) [77]. Data on restenosis from 2004 and 2008 was collected. Four DES types qualified for inclusion. In total, 35,478 DES were implanted at 22,962 procedures in 19,004 patients and 1807 restenosis events were reported over a mean 29-month follow-up. In the entire study population, the restenosis rate per stent was 3.5% after 1 year and 4.9% after 2 years. The adjusted risk of restenosis was higher in patients with DM, compared to patients without DM (relative risk [RR]: 1.23, 95% confidence interval [CI]: 1.10 to 1.37). In patients with DM, restenosis was twice as frequent with the ZES stent compared with that in SES and PES types.

Another important aspect in the use of DES is the safety, especially in diabetic patients. Safety of DES mainly refers to the incidence of ST, MI or death during follow-up. Diabetes has been identified as an independent predictor of ST in many registries with the use of first-generation DES (SES and PES) [17, 78]. In a large multicentric registry 66 of more than 15,000 patients treated with SES, the overall incidence of stent thrombosis at 1 year was 0.87% and the most potent independent predictor of thrombosis was the insulin-dependent DM [78]. Diabetic patients, as mentioned previously, exhibit specific pathophysiological factors as well as unfavourable angiographic parameters, which confers an especially high risk of thrombosis.

A Swedish Registry (SCAAR) compared diabetic patients treated with DES to those treated with BMS. The median follow-up was 2.5 years. This study included 4754 patients who received at least one DES and 4956 patients that received only bare metal stents (BMS) at the index procedure. The study showed that restenosis was halved by DES in diabetic patients with stable or unstable coronary disease, compared with BMS [RR, 0.50 (95% CI, 0.35–0.70)] and was associated with a higher adjusted RR of MI, [RR 5.03 (95% CI, 4.25–5.97)] [79]. Similar results were observed in a meta-analysis of individual patient data from four randomised trials reporting on the use of SES in diabetics [80]. This meta-analysis included 583 patients (SES vs. BMS; median follow-up of 4.2 years). There was a significant reduction in the overall hazard of MACE (hazard ratio, [HR] 0.48, 95% confidence interval [CI] 0.36–0.63, P < 0.001) with SES. The overall hazard of death (HR 0.91, 95% CI 0.59–1.41, P = 0.68), as well as death or MI (HR 0.77, 95% CI 0.54–1.09, P = 0.14), was not significantly different between the groups. No significant differences were observed regarding ST (HR 0.50, 95% CI 0.15–1.69, P = 0.26) [80]. Reassuring data also comes from the Massachusetts Data Analysis Registry that included 6008 diabetics treated between April 2003 and September 2004. After propensity score-matched risk analysis, the use of DES was associated with a significantly lower rate of death, MI and TVR [52].

New generation EES stent showed a safety benefit as compared to PES in the Spirit V- diabetic randomised trial at 1 year; the composite of death and MI was reduced by EES (9.6% vs. 3.7%; p = 0.04) as well as the thrombosis rate (1.9% vs. 0%; p = ns) [73].

Data concerning safety of BES in diabetics comes from a sub-study from the LEADERS trial. Among insulin-dependent diabetics, the rate of all-cause death and cardiac death was 0% after BES implantation, compared to 9.1% and 6.5% respectively, after SES implantation at 12 months follow-up ($p < 0.01$) [76].

Finally, the Resolute™ stent showed a higher incidence of definite ST at 1-year follow-up, compared to EES (1.2% vs. 0.3%; <0.01) in the all-comer RESOLUTE trial [81].

4. Multivessel disease in diabetics

Based on the current evidence, coronary artery bypass graft (CABG) is the treatment of choice for diabetic patients with multivessel disease [82]. However, since the inception of percutaneous coronary intervention, numerous trials have been designed to evaluate the efficacy of PCI versus CABG in patients with multivessel disease. In the following section, we will discuss the various trials that have compared surgical revascularisation to percutaneous intervention, beginning with balloon angioplasty and continuing to the modern DES era.

4.1 Trials comparing CABG and BA

Four trials designed to compare the efficacy of CABG versus BA have reported data on the subgroup of patients with diabetes mellitus: the EAST study, the BARI study, the CABRI trial and the RITA trial (**Table 2**) [83–86]. The only study that showed a significant benefit in survival of diabetic patients treated with CABG compared with BA, was the BARI trial. On the basis of these results, a clinical alert to US physicians from the National Heart, Lung, and Blood Institute, was published in Circulation 1995 and concluded that CABG should be the preferred treatment for patients with diabetes on drug or insulin therapy, who have multivessel coronary artery disease and require a first coronary revascularisation procedure.

Trial	Inclusion/exclusion criteria	Primary endpoint	Number diabetics included	F-U	Primary endpoint in DM
BARI [80]	Angina or severe ischemia, CAD amenable for BA or CABG	10-year survival	CABG DM: 180 BA DM: 173	7.8	PTCA 45.5% vs. CABG 57.8%, p = 0.025).
EAST [79]	MV CAD, no previous Rev; no LMS stenosis, no CTO, no LVEF ≤25%	3-year death, MI	CABG: 41 BA: 49	8-10.5	CABG: 75.5% BA: 60.1% *p*= 0.23
CABRI [82]	Age ≤76, MV CAD + clinical evident ischemia; no previous Rev, LMS stenosis, LVEF ≤25%, stroke, HF	Mortality	CABG: 60 BA: 64	4	CABG: 12.5% BA: 22.6% *p*= 0.01
RITA [81]	>50-70% coronary stenosis SA or UA, *de novo* single or MV CAD suitable for BA or CABG	5-year death, non fatal MI	CABG: 33 BA: 29	6.5	CABG: 16% BA: 17% *p*= 0.64

Table 2.
Randomised Controlled Trials comparing Balloon angioplasty versus CABG in patients with multivessel disease.

4.2 Trials comparing CABG versus PCI with bare metal stents

There are four randomised trial that compared the outcomes from bypass surgery versus coronary stenting in patients with multivessel disease: the ARTS, the AWESOME trial, the SOS and the ERACI II trial. Only the first two trials analysed the diabetic subgroup separately, and neither showed any survival benefit. The ARTS (Arterial Revascularisation Therapy Study) trial reported a reduced event-free survival at 1 year in diabetics treated with stenting, as compared with those treated with CABG (63.4% vs. 84.4%, p = 0.001) [87]. This difference was largely due to a significant increase in repeat revascularisation in the stent group. Of note, the rate of complete revascularisation in patients who underwent PCI was only (70.5%) compared with those who had CABG (84.1%). Conversely, the rate of death and MI in diabetic were similar between groups (6.7% vs. 3.1%, p = 0.29 and 6.3% vs. 3.1%, p = 0.29, respectively). In addition, a trend towards an increase in the rate of cerebrovascular events was observed in the CABG group (1.8% vs. 6.3%, p = 0.009). At five years, there was no significant difference in mortality between the two groups. However, it was noted, that the rate of myocardial infarction was highest in the BMS arm, compared with CABG arm (11.0% vs. 5.2%). The AWESOME trial (Angina With Extremely Serious Operative Mortality Evaluation Trial) randomised 454 patients with multivessel disease to either CABG or stenting. Among diabetics, the respective CABG and PCI 36-month survival rates were comparable (72% for CABG vs. 81% for PCI) [88]. A collaborative analysis of data from ten randomised trials to compare the effectiveness of CABG with PCI (six trials used balloon angioplasty and four trials used with bare-metal stents), in patients with multivessel disease, showed that patients with diabetes (CABG, n = 615; PCI, n = 618), mortality was substantially lower in the CABG group than in the PCI group (HR 0.70, 0.56–0.87) [89].

In summary, despite these trials demonstrating a reduced need for subsequent revascularization following PCI with stents as compared to BA, the need for repeat revascularization remained significantly higher when compared to CABG in the diabetic population with multivessel disease. Moreover, the rate of myocardial infarction in diabetics was higher at long-term follow-up with the use of stents as compared to CABG. Thus, in the BMS era, revascularisation of diabetic patients with multivessel disease, CABG remained the first option of revascularization in patients suitable for surgery.

4.3 Trials comparing CABG and DES

The data available in the current era of DES comes from a combination of registry data, subgroup analysis from two randomised trials (the SYNTAX trial and the EXCEL trial) and two randomised trial performed specifically in diabetics patients. Beginning with the registry data, there are two multicentre registries that report data for diabetic patients treated with DES: the ERACI-3 and the ARTS 2 registries. Both registries compared a current cohort of patients with multivessel disease treated with drug-eluting stents with the historical cohort of patients from ERACI 2 and ARTS 1 trial respectively; treated with either CABG or conventional BM stenting. The ARTS 2 registry was a single arm trial that included 607 patients with multivessel disease treated with SES. The ARTS I and II studies included 367 diabetic patients (SES: 159, CABG: 96, and BMS: 112); at the 5-year follow up, the rate of major adverse cardiovascular and cerebrovascular events were significantly higher in patients treated with BMS (BMS 53.6% vs. CABG 23.4% vs. SES 40.5%; p < 0.01 for SES vs. BMS and SES vs. CABG). There was no significant difference in mortality among all 3 groups. There was an advantage of CABG over SES in

reducing repeat revascularisation procedures; interestingly revascularisation rate of patients treated with SES at 5 years approached that of patients treated with BMS although remained significantly lower. This "catch-up" phenomenon was not apparent in the non-diabetic population [90].

In the diabetic subgroup of ERACI-3 registry [91], MACCE rates at 3 years were 36.2% in the DES arm, 43.6% in the BMS arm, and 30.8% in the CABG group ($p = 0.49$). Of the components of MACCE, TVR was the only one that differed significantly across the three groups: drug-eluting stent (21.3%), bare metal stent (38.5%), and CABG (15.4%); $p = 0.048$. There was a non-significant trend towards more death and non-fatal MI among diabetics treated with DES (19.1%), than in the bare metal stent (12.8%) or CABG (15.4%) cohort of ERACI-2. Sub-acute late-stent thrombosis occurred more frequently in DES-treated patients, compared with BMS patients ($P = 0.008$).

Another registry [92] compared DES implantation with off-pump CABG. This study addresses the effect of DES versus off-pump CABG, on 1-year outcome of diabetic patients with multivessel disease and critical stenosis, involving the proximal left anterior descending coronary artery, who underwent elective myocardial revascularisation. Following propensity score analysis, adjusting for baseline differences between the 2 cohorts, DES increased the risk of 12-month MACCE (HR 1.88, 95% CI, $p = 0.020$). This was due to the higher rate for repeat revascularisation in the DES group (19% vs. 5%, HR 2.05, 95% CI, $p = 0.001$). In contrast, there was no difference in the rate of the composite endpoints of death, MI, and stroke (DES group 13%, CABG group 12%; adjusted analysis, HR 0.80, 95% CI, $p = 0.40$). On the other hand, the New York registry [93] showed a trend towards improved outcomes in diabetic patients treated with CABG ($n = 3256$), compared with DES ($n = 2844$) (or for death or MI at 18 months 0.84, 95% CI 0.69–1.01; $p = 0.07$).

The SYNTAX (Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) trial randomly allocated 1800 patients with left main and/or 3-vessel coronary artery disease to PES implantation or CABG. In the subgroup of patients with DM ($n = 452$), MACCE rate was significantly higher at 1 year with PES than with CABG (26.0% vs. 14.2%; RR 1.83 [1.22–2.73]; $p = 0.003$), at the expense of higher repeat revascularisation with PES (6.4% vs. 20.3%; RR 3.18 [1.77–5.71]; $p < 0.001$). Safety endpoint (death, stroke or MI), as well as symptomatic graft occlusion or stent thrombosis rates were comparable between treatment arms. Of note, in patients with SYNTAX score > 33, death rate was significantly higher with PES (13.5% vs. 4.1%; $p = 0.04$) [94].

There are two randomised trials comparing DES and CABG in patients with diabetes. The CARDIA trial (Coronary Artery Revascularisation in Diabetes) [95] is a non-inferiority trial, comparing optimal PCI with modern CABG, as a revascularisation strategy for patients with diabetes who have multivessel or complex single-vessel coronary disease. The 1-year results of the CARDIA trial did not demonstrate the noninferiority of PCI versus CABG for revascularisation of diabetic patients. At 1 year, the primary endpoint (composite of death, non-fatal MI and non-fatal stroke) was comparable between arms (10.5% in CABG vs. 13.0% in PCI arm; $p = 0.39$), only further revascularisation was significantly higher in the PCI arm (2% vs. 11.8%; $p < 0.001$). Although this study was the first randomised trial that compared the two revascularisation strategies in diabetic patients, it was underpowered for the primary composite outcome. Therefore, further information on optimal strategies for coronary revascularisation in diabetic patients is needed.

The FREEDOM trial (Future Revascularisation Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) is a randomised trial, in which patients with diabetes and multivessel disease were randomly assigned to undergo multivessel PCI using DES versus bypass surgery and followed

for up to 5 years. At 5 years follow-up, the primary outcome: a composite of death from any cause, nonfatal myocardial infarction, and nonfatal stroke occurred more frequently in the PCI group, compared with the CABG group (26.6% vs. 18.7%; p = 0.005). The benefit of CABG was driven by differences in rates of both myocardial infarction (P < 0.001) and death from any cause (P = 0.049). Cardiac death was not significant (p = 0.12). Stroke was more frequent in the CABG group than in the PCI group (2.4% vs. 5.2%; p = 0.03) [96].

The BARI 2 Diabetes (BARI 2D) [97] is a randomised, open, controlled, multicentre trial that compared optimal medical management with prompt revascularisation (PCI or CABG) in patients with type 2 DM and stable coronary disease. The primary endpoint was death from any cause. At 5-year follow-up, survival rate was comparable between groups (88%) with no difference in MACE or death. Patients treated with CABG showed much greater atherosclerotic burden and more lesions than the PCI stratum. Prompt revascularisation significantly reduced the MACE rate in those patients treated with CABG, largely because of a reduction in MI events, but not among those selected to undergo PCI as compared to optimal medical treatment. However, up to 42% of the patients allocated to optimal medical therapy required coronary revascularisation with PCI during the 5 years of follow-up [97].

A recent meta-analysis of 11 RCTs [98], involved 11,518 patients allocated to PCI or CABG. The 5-year all-cause mortality was 11.2% after PCI and 9.2% after CABG (HR 1.20, 95% CI 1.061.37; P = 0.0038). Among patients with DM, mortality rates were 15.7% in PCI and 10.1% in CABG (HR 1.44, 95% CI 1.201.74; P = 0.0001). Conversely, this difference was not found among non-diabetic patients.

There have been a number of studies comparing outcomes of CABG and PCI that involved the use of newer-generation DES. A large meta-analysis including 8095 patients with DM showed a significant reduction in MI, stent thrombosis, and MACE, with newer-generation everolimus-eluting stents, compared to first generation DES [99]. Data from the Randomised Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) study [100], showed that the outcomes were poorer in the PCI group, with the rate of the primary outcome of death, MI, or TVR at two years significantly higher (19.2 vs. 9.1%; *P* = 0.007). In a subgroup analysis of 505 patients with DM, in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation (EXCEL) trial [101], the investigators reported the rate of the primary outcome of death, MI or stroke at three years occurred in 21.2% of patients in the PCI arm and 19.4% in the CABG arm (HR 1.04, 95% CI 0.70–1.55). In conclusion, is clear that we are yet to determine whether the newer generation DES will begin to narrow the divide favouring CABG for patients with DM and multivessel disease, and additionally, that further dedicated randomised control trials are needed.

5. The importance of atherosclerosis progression in the long-term outcome after myocardial revascularisation

Atherosclerotic coronary artery disease is a chronic condition that is not limited by revascularisation. The short and long-term outcomes in patients undergoing both percutaneous and surgical revascularisation, are not only determined by stent or graft failure, but also by atherosclerotic disease progression in other territories. A paucity of data exists regarding the impact of atherosclerosis progression on the outcome of patients after revascularisation, and this is particularly evident in

patients with diabetes. The current data regarding atherosclerosis progression after percutaneous revascularisation is limited. One of the studies that address this issue was the study conducted by Cutlip et al. [102] This study included 1228 patients treated with BMS. The cumulative incidence of restenosis events, non-restenosis events, and the overall composite end point up to 5 years was evaluated. In this study, it was demonstrated that the events relating to restenosis increased during the first year, however there was a virtual absence of restenosis thereafter. On the other hand, the rate of non-restenosis events increased during the first year, in parallel to the restenosis events but continued to increase out to 5 years. The two factors that were independently associated with an increased risk of restenosis and non-restenosis events were diabetes and multivessel disease.

Zellweger et al. [103] studied the importance of 5-year coronary disease progression after successful DES stenting. This is a sub-study of the Basket trial and involved 428 consecutive patients randomised to drug-eluting versus bare-metal stents, with successful stenting documented by freedom from symptoms/events and non-ischaemic perfusion defects (PDs) after 6 months. Rest and stress scintigraphy scans were repeated after 60 months. Late events and new perfusion defects in areas remote from stented vessels were recorded. At 5 years follow-up, 37.1% of all events were due to remote MI, or remote repeat revascularisation. In addition, asymptomatic remote perfusion defect accounted for 37.5%. There is also information about the impact of atherosclerosis progression derived from large randomised trials comparing DES vs. BMS. In the 5-years of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial, 28% of MI were located in non-target vessels. In addition, 64% in the SES group and the 42.% in the BMS group of all target vessel revascularisation were non performed in the target lesion [104]. In the 5-year TAXUS IV Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent trial: 45% of all revascularisation in the PES group were due to non-target lesion TVR [105].

The progression of atherosclerosis in diabetics has been specifically assessed by Rozeman et al. [106]. This study included 248 patients (55 diabetics/193 non diabetics) and evaluated the percentage of arteries with new narrowing's at follow-up angiography following angioplasty. The authors observed that the percentage of new narrowing was more often in diabetic patients compared to non-diabetics (14.8 vs. 9.4%; $p = 0.03$) and particularly in the arteries previously treated with angioplasty (13.6 vs. 8.5; $p = 0.01$). The 5 year follow-up of the DIABETES (DIABETes and sirolimus-Eluting Stent) trial, showed that the need for new revascularisation in the SES group was due equally to restenosis and progression of atherosclerosis in other territories [64]. On the other hand, surgical revascularisation also have disease progression [107]. It has been described that the progression is primarily in the proximal segment before the anastomosis (74%) and the majority was proximal coronary occlusion (78%). This pattern of atherosclerosis progression may be mostly asymptomatic in patients with a patent graft and prevents future events due to plaque rupture in the proximal segment of the artery.

This data suggested that the clinical implication of atherosclerosis progression is different in the two-revascularisation strategies and negatively affects patients treated percutaneously, particularly after the first year of clinical follow-up. This has to be taken into account, when comparing long term results of stent implantation versus CABG in patients with multivessel disease. Improvements in both the stent platforms and the adoption of new drug coatings have improved the outcome of patients treated with PCI. However, it is critical, particularly in the diabetic population to improve the secondary prevention strategies to decrease the occurrence of events due to atherosclerosis progression.

6. Current recommendations for revascularisation in diabetics

Contemporary guidelines place emphasis on the long-term survival benefit conferred by CABG, for treatment of diabetics with multivessel disease. A clinician's judgement on the revascularisation strategy remains an important factor. Although PCI with DES has narrowed the gap with surgery, following the results of the FREEDOM trial in CABG-eligible diabetic patients multivessel disease, CABG remains the gold standard treatment [16, 96] (**Tables 3** and **4**).

Recommendations according to the extent of CAD	CABG		PCI	
	CLASS	LEVEL	CLASS	LEVEL
One vessel CAD				
Without proximal LAD stenosis	IIb	C	I	C
With proximal LAD stenosis	I	A	I	A
Two vessel CAD				
Without proximal LAD stenosis	IIb	C	I	C
With proximal LAD stenosis	I	B	I	C
Three vessel CAD				
With low disease complexity (SYNTAX score 0-22)	I	A	IIb	A
With intermediate or high disease complexity (SYNTAX score >22)	I	A	III	A
Left main CAD				
With low disease complexity (SYNTAX score 0-22)	I	A	I	A
With intermediate disease complexity (SYNTAX score 23-32)	I	A	IIa	A
With high disease complexity (SYNTAX score ≥ 33)	I	A	III	B

CABG = coronary artery bypass graft; CAD = coronary artery disease; DM = diabetes mellitus; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

Table 3.
Recommendations for the type of revascularization in patients with diabetes with stable coronary artery disease, suitable coronary anatomy for both procedures, and low predicted surgical mortality. Adapted from 2018 ESC/EACTS Guidelines on myocardial revascularization.

Recommendations	Class	Level
It is recommended that the same revascularisation techniques are implemented(e.g. the use of DES and the radial approach for PCI, and the use of the left internal mammary artery as the graft for CABG) in patients with and without DM.	I	A
It is recommended that renal function should be checked if patients are taking metformin immediately before angiography and that metformin should be withheld if renal function deteriorates.	I	C
Optimal medical therapy should be considered to be the preferred treatment in patients with CCS and DM unless there are uncontrolled ischaemic symptoms, large areas of ischaemia or significant left main or proximal LAD lesions.	IIa	B

CABG = coronary artery bypass graft; CCS = chronic coronary syndromes; DES = drug-eluting stent; DM = diabetes mellitus; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention.

Table 4.
Recommendations for coronary revascularisation in patients with diabetes. Adapted from 2018 ESC/EACTS Guidelines on myocardial revascularization.

7. Conclusions

Diabetic patients are a very high-risk population. The unfavourable anatomy and the prothrombotic state contribute to the poor acute and midterm outcome following percutaneous revascularisations. With the advent of DES, improved stent designs and antiplatelet drugs; the rate of TLR and MACE has also improved in diabetic patients; however, it remains higher in comparison to non-diabetic patients. We have underestimated the impact of atherosclerosis progression in the appearance of late events after PCI, particularly in patients with diabetes. Whilst it is clearly evident that both aggressive secondary prevention and lifestyle modification are mandatory to alter the natural history of CAD in this group, the gold standard for diabetic patient with complex multivessel disease is surgical revascularisation.

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