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Revascularisation of coronary artery disease in patients with diabetes mellitus

Stéphane Cook, Stephan Windecker

Department of Cardiology, University Hospital Bern, Bern, Switzerland

Summary

Diabetes mellitus is becoming increasingly prevalent and magnifies the risk of cardiovascular complications. Endothelial dysfunction caused by oxidative stress is a hallmark of diabetes and is responsible for the ubiquitous manifestations of vascular disease in diabetics. Compared with non-diabetic patients, coronary artery disease is more severe and the clinical outcome impaired in diabetic patients undergoing revascularisation. Despite these limitations the benefit of revascularisation therapy is particularly pronounced in diabetics. The optimal revascularisation strategy (coronary artery bypass graft surgery *versus* percutaneous coronary intervention) in diabetic patients with coronary artery disease depends on clinical and anatomical considerations.

Key words: coronary artery disease; diabetes mellitus; coronary artery bypass grafting (CABG); percutaneous coronary intervention (PCI)

1. Prevalence and cardiovascular implications of diabetes mellitus

Diabetes mellitus is considered as a pandemic by the World Health Organization. During the last decade its prevalence increased [1–5] by 40% in industrialised countries (1995: 51 mio, 2005: 72 mio) and almost tripled in developing countries (1995: 84 mio, 2005: 228 mio) [6]. Along these lines, Mokdad and colleagues [7] estimated that one third of Americans born in the year 2000 will be at risk of developing diabetes mellitus during their lifetime (fig. 1) (adapted from [8]).

Epidemiological evidence suggests that diabetes mellitus amplifies the risk of cardiovascular events 4- to 6-fold [9, 10]. Cardiovascular events are responsible for 75% of all hospitalisations and 80% of all deaths in diabetic patients. Diabetic patients without previous myocardial infarction share the same risk of ischaemic adverse events as non-diabetic patients with a history of prior myocardial infarction (cardiac mortality: 2.5–2.6% per year) [11]. Accordingly, diabetes mellitus is considered as a risk equivalent to already established coronary artery disease. Moreover, diabetic women lose their gender protection against coronary artery disease and share the same cardiovascular risk as men. Diabetics make up one fourth of patients referred for coronary revascularisation, one third of patients admitted with acute coronary syndromes (ACS), and more than one third of patients presenting with cardiogenic shock.

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While some nuances in outcome are observed between patients with and without insulin-dependent diabetes mellitus, the pathophysiologic mechanisms involved are similar and hyperglycaemia *per se* is considered the culprit [12]. Thus, patients with *asymptomatic hyperglycaemia* have been found to be at increased risk for cardiovascular events. In the DECODE study [13] cardiovascular mortality in 22 514 individuals was significantly increased in subjects with asymptomatic diabetes defined as either a fasting plasma glucose >7.0 mmol/l or a 2-hour post-load plasma glucose ≥11.1 mmol/L. It is therefore of the utmost importance to screen for coronary artery disease in

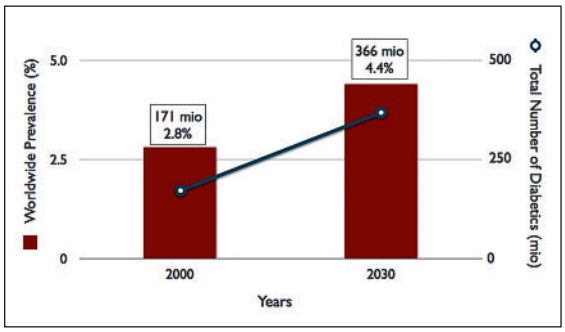

Figure 1

WHO estimate of the prevalence of diabetes during the year 2000 and projections for the year 2030 based on national surveys. Adapted from [8].

patients with known diabetes mellitus or asymptomatic hyperglycaemia, particularly in those with additional cardiovascular risk factors. A recent survey among five Swiss university hospitals reported adherence to screening for coronary artery disease in diabetic patients with at least two additional cardiovascular risk factors in less than 50%, and proper control of all cardiovascular risk factors in only 2% of patients [14]. These findings indicate the need for further improvement in screening and prevention of coronary artery disease in diabetic patients.

2. Revascularisation strategies in diabetic patients

Diabetic patients undergoing revascularisation procedures are characterised by a higher prevalence of previous myocardial infarction, congestive heart failure and arterial hypertension than non-diabetic patients [15]. Coronary artery disease is more extensive in diabetic than in non-diabetic patients, and angiographic data of the NHLBI registry showed a 56% higher prevalence of three-vessel disease [16].

As in the general population, some universal considerations influence the choice of revascularisation procedures in diabetic patients. These factors include the clinical presentation (acute coronary syndrome *versus* stable angina pectoris), coronary anatomy (extent and localisation of coronary disease, suitability for coronary artery bypass grafting [CABG] anastomoses, history of previous CABG), and left ventricular function. Apart from these disease-specific factors, other clinical characteristics influence the choice of revascularisation procedures, such as concomitant valvular heart disease, chest deformities, prior radiation exposure, peripheral artery disease and extracardiac conditions such as chronic obstructive pulmonary disease, coagulation disorders or malignancies.

3. Percutaneous revascularisation of diabetic patients

The clinical outcome in diabetic patients undergoing PCI is inferior to that in non-diabetic patients. Several aspects of diabetic coronary artery disease appear to be responsible for this observation. Coronary artery disease progresses faster and vessel size is smaller in diabetic compared with non-diabetic patients. Diabetes has also consistently been shown to be associated with higher rates of restenosis after balloon angioplasty or implantation of bare metal and drug-eluting stents. An important finding is that restenosis in diabetic patients may portend a particularly poor prognosis. Thus, the occlusive form of restenosis following balloon angioplasty has been associated not only with a significant decrease in left ventricular function but also impaired survival during long-term follow-up of 10 years [17]. Finally, diabetes constitutes an independent predictor of early stent thrombosis both in the bare metal stent and drug-eluting stent era [18]. More recently, the early outcome in diabetic patients has improved with the advent of adjunctive pharmacological therapy, including glycoprotein IIb/IIIa antagonist, pre-loading with high dose clopidogrel, and long-term thienopyridine and statin therapy. This notwithstanding, the long-term risk of death, myocardial infarction and repeat revascularisation remains nearly twice as high in diabetic as in non-diabetic patients undergoing PCI [19].

3a. Bare metal stents versus drug-eluting stents in diabetic patients

Compared with BMS, DES have significantly lowered the risk of restenosis and therefore the need for target lesion revascularisation [20]. In a pooled analysis of the ARRIVE-1 and -2 studies, Cox and colleagues demonstrated that the adjusted rate of target vessel revascularisation in 2112 diabetic patients treated with PES was similar to that in 5380 non-diabetic patients at 2 years' follow-up (TVR: diabetics: 9.8%, non-diabetics: 9.0%, p = 0.57) [21]. In 3751 pairs of patients treated with either DES or BMS in Ontario, rates of target vessel revascularisation were also significantly reduced in favour of DES in nearly all subsets of diabetic patients except for short, discrete lesions in large vessels [22]. Two randomised studies compared clinical outcome between BMS and DES in diabetic patients (DIABETES, SCORPIUS). Rates of repeat revascularisation were 2–4 times lower in diabetics treated with DES rather than BMS [23, 24]. A meta-analysis of 12 studies comparing DES with BMS in 1879 diabetic patients observed an absolute difference of 14.8% (DES: 7.3%, BMS: 22.2%, P <0.001) and a relative risk reduction of 65% in favour of DES for the endpoint of target lesion revascularisation. A collaborative network meta-analysis compared the risk of revascularisation between the two first generation DES (sirolimus-eluting stent: SES, paclitaxel-eluting stent: PES) and BMS in diabetic patients [19]. The risk of target lesion revascularisation was reduced by 71% and 62% respectively in favour of PES and SES compared with BMS in diabetic patients, similarly to that observed with non-diabetic patients. Due to the

higher baseline risk of restenosis, the absolute reduction in repeat revascularisation is more pronounced in diabetic than non-diabetic patients, and the use of DES should be strongly considered in this patient subgroup.

While the use of DES effectively reduces restenosis, concerns have been raised regarding an increased risk of stent thrombosis, thus questioning their overall safety profile [25]. Moreover, a meta-analysis of 4 early trials suggested an increased risk of death with SES compared to BMS in diabetic patients [26], a finding not confirmed in a larger analysis of 14 trials [27]. The safety and efficacy of the two first-generation DES and BMS in patients with and without diabetes was also addressed in the above-mentioned network meta-analysis [19, 28]. There were no significant differences in the risk of overall mortality, cardiac mortality or myocardial infarction among SES, PES, and BMS in both diabetic and non-diabetic patients in the overall population. However, the risk of death associated with SES was more than twice that associated with BMS in trials of clopidogrel therapy of less than 6 months' duration, whereas trials of clopidogrel lasting 6 months or longer showed no difference in risk between SES and BMS. This observation suggests that the above-mentioned increase in the risk of death associated with SES compared to BMS in diabetic patients was either due to chance or related to the restricted duration of clopidogrel therapy (<6 months) in early trials [26].

More recent evidence indicates that aggressive antithrombotic regimens may further improve clinical outcome in diabetic patients. The NAPLES study compared the use of bivalirudin alone (n = 167) versus combination therapy of heparin and tirofiban (n = 168) in 335 diabetics. The thirty-day event-free composite endpoint was significantly lower in diabetics treated with bivalirudin (12% vs 21%, p = 0.038) [29]. The DECLARE-DIABETES trial observed better outcome at two years in diabetics (n = 200 vs n = 201) treated for acute myocardial infarction and receiving triple vs dual antiplatelet therapy (aspirin + clopidogrel ± cilostazol) [30]. Prasugrel, a novel thienopyridine, which inhibits ADP-induced platelet aggregation not only faster but also to a larger extent than clopidogrel, was particularly beneficial in the subgroup of diabetic patients (ischaemic endpoint 17.0% with clopidogrel vs 12.2% with prasugrel, HR = 0.70, 95% CI 0.58–0.85, p <0.0001) without increasing the risk of bleeding in the TRITON-TIMI 38 investigation [31].

3b. Surgical revascularisation of diabetics

Similarly to PCI, the clinical outcome following CABG is worse in diabetic than in non-diabetic patients. Carson and colleagues assessed short term morbidity and mortality in a retrospective cohort study of 146 786 patients undergoing CABG in 434 hospitals in the United States during 1997 [32]. The investigators observed a higher mortality risk (3.7% vs 2.7%, adjusted OR = 1.23, 95% CI 1.15–1.32), morbidity (13.9% vs 9.1%, adjusted OR = 1.38, 95% CI 1.33–1.44) and infections (7.9% vs 5.2%, adjusted OR = 1.36, 95% CI 1.30–1.43) in diabetic compared with non-diabetic patients.

In a study of the long-term outcome following CABG in diabetic patients by Mohammadi and colleagues [33], cardiac survival at 5 and 10 years amounted to 96.4% and 90.4% among non-diabetic patients, to 95.9% and 87.0% among patients with non-insulin dependent diabetes and to 92.8% and 75.7% among insulin-dependent diabetic patients (p <0.001). Similar results have been reported in a study of 36 641 consecutive patients (31% diabetic patients) followed for a mean duration of four years [34]. In this cohort study the annual incidence of death was 3.1 deaths per 100 person-years in non-diabetic and 4.4 deaths per 100 person-years in diabetic patients. The difference was markedly increased in diabetic patients with concomitant renal insufficiency or peripheral vascular disease (9.4 deaths per 100 person-years).

Patients undergoing surgical revascularisation preferably undergo grafting with the use of the left mammary artery (LIMA). The latter affords protection from atherosclerosis and is associated with low graft failure during long-term follow-up. Tatoulis et al. [35] reported a patency rate of 98% at five years, 95% at ten years, and 88% at fifteen years. Furthermore, the survival advantage afforded by CABG in diabetic patients as observed in the BARI trial was limited to patients who received a LIMA graft. Arterial revascularisation with use of bilateral internal mammary arteries (BITA) has been shown to lower the risk of death (hazard ratio = 0.72 [0.57–0.91, 95% CI]) and need for reoperation (HR = 0.38 [0.19–0.77]) in both diabetic (N = 633) and non-diabetic patients (N = 3673), albeit at increased risk of infections [36]. While the clinical value of internal mammary artery grafts is well recognized, the use of radial artery conduits is less well established. On the one hand, radial artery grafts are associated with a better long-term patency rate in the general population. On the other hand – due to increased vasoconstriction – radial artery grafts harvested from diabetic patients are more prone to spasm and occlusion in the short term [37].

Finally, important improvements in surgical technique have been witnessed during the last decade. These include minimal invasive procedures and "off-pump" surgery to decrease manipulation of the ascending aorta with the risk of atherosclerotic emboli, as well as induction of a pro-oxidative state with activation of the complement system, which may potentially lead to multiple organ dysfunction and/or damage. This is of particular interest in diabetic patients with more extensive atherosclerosis and higher risk of perioperative infection [38].

3c. Comparative studies: percutaneous coronary intervention versus coronary artery bypass grafting in diabetic patients with stable angina pectoris

Coronary revascularisation techniques evolved dramatically during the last decade and the majority of studies comparing CABG with PCI no longer reflect current treatment standards. With the exception of one dedicated prospective, randomised controlled trial (RCT) comparing CABG with PCI specifically in diabetic patients, most of our knowledge comes from outcomes of subgroups of diabetic patients enrolled into larger RCTs comparing the two revascularisation strategies. These findings have been summarised in reviews [39] and a meta-analysis [40] (table 1). The four best-known trials comparing *plain balloon angioplasty* with CABG for patients with multivessel disease are BARI, RITA I, EAST and CABRI. The BARI trial compared balloon angioplasty to CABG in 1829 patients with multivessel disease. Although the mortality was identical between both revascularisation strategies in the overall population (PCI: 13.7% vs CABG: 10.7%, P = 0.19), at 5 years' follow-up diabetics (N = 353) treated by PCI had higher mortality than diabetics treated surgically (PCI: 35.5% vs CABG: 19.4%, P = 0.003) [41]. It is noteworthy that the survival benefit in favour of CABG was limited to patients revascularised with LIMA grafts (5-year mortality of diabetic patients treated with LIMA: 2.9%), whereas mortality in patients treated with a saphenous vein graft (18.2%) was similar to balloon angioplasty [42]. Although widely publicised, it is worth mentioning that the analysis of diabetic patients was not prespecified in the protocol but rather a post-hoc investigation, and the study was underpowered for detection of mortality differences in subgroups. A feature of note was that the findings were not confirmed in the BARI registry of 2010 patients, who were eligible for the randomised study but did not provide informed consent and were treated according to physician preference, 65% of whom underwent PCI. At seven years no difference in mortality was observed in either the overall population (PCI: 13.9% vs CABG: 14.2%, P = 0.66) or diabetic patients (PCI: 26% vs CABG: 26%, P = 0.96). Consistent with this latter observation, none of the three other RCTs comparing angioplasty to CABG (RITA-I [43], EAST [44] and CABRI) confirmed the mortality increase observed in BARI during both short- and long-term follow-up (RITA 6.5 years, EAST 8 years, CABRI [45] 4 years). Rates of repeat revascularisation were however 3–6 times higher among diabetic patients treated with PCI than among those treated with CABG in all five trials.

In keeping with the observed benefit of coronary artery stents over balloon angioplasty in terms of reduction of restenosis and need for repeat revascularisation [46, 47], several trials directly compared *bare metal stents* to CABG. The randomised AWESOME trial was performed during the transition period from balloon angioplasty to bare metal stents and compared PCI (stents: 54%) with CABG (LIMA graft: 76%) in

Table 1

Randomised controlled trials – Bare-metal stents (BMS) versus coronary artery bypass grafting (CABG) in diabetic patients with multivessel coronary artery disease.

Study	Enrolment period	Follow-up, yr	Randomised diabetics, n		PCI	CABG	Mortality			Repeat Revascularization			MACCE		
			PCI, n	CABG, n	%stent/ %DES	%arterial graft	PCI, %	CABG, %	p-value	PCI, %	CABG, %	p-value	PCI, %	CABG, %	p-value
ARTS	1997–1998	1	112	96	100%/0%	93%	6%	3%	0.29	8%	0%	<0.001	37%	26%	<0.001
	–	3	–	–	–	–	7%	4%	ns	15%	8%	0.02	41%	19%	<0.001
	–	5	–	–	–	–	13%	8%	0.27	43%	10%	<0.001	55%	25%	<0.001
AWESOME	1995–2000	5	65	79	54%/ 0%	76%	19%	28%	ns	na	na	na	na	na	na
BARI	1988–1991	5	170	173	0% / 0%	81%	35%	19%	0.002	na	na	na	na	na	na
	–	10	–	–	–	–	55%	42%	0.025	80%	19%	<0.001	na	na	na
CABRI	1988–1992	4	62	63	0% / 0%	81%	23%	13%	ns	na	na	na	na	na	na
EAST	1987–1990	3	29	30	0% / 0%	86%	7%	10%	ns	na	na	na	na	na	na
	–	5	–	–	–	–	10%	10%	ns	na	na	na	na	na	na
	–	8	–	–	–	–	40%	25%	0.23	na	na	na	na	na	na
ERACI II	1996–1998	1	39	39	77%/0%	89%	10%	10%	0.66	na	na	na	na	na	na
		5	–	–	–	–	10%	10%	0.66	na	na	na	na	na	na
MASS II	1995–2000	1	56	59	68%/0%	92%	5%	7%	0.59	na	na	na	na	na	na
		5	–	–	–	–	16%	15%	0.4	na	na	na	na	na	na
RITA	1988–1991	6.5	29	33	98%/0%	74%	7%	24%	0.09	na	na	na	17%	36%	0.06
SoS	1996–1999	2	68	74	78%/0%	81%	4%	1%	0.55	25%	5%	0.001	na	na	na
	–	5	–	–	–	–	10%	1%	0.001	na	na	na	na	na	na
	–	6	–	–	–	–	18%	5%	0.01	na	na	na	na	na	na

454 patients of whom 32% (N = 144) had diabetes [48]. A total of 1650 patients were eligible for the study but did not provide consent and were followed in the physician-guided registry. At three years' follow-up mortality was similar among PCI- and CABG-treated diabetic patients in both the randomised cohort (PCI: 19% vs CABG: 28%, P = ns) and the registry arm (PCI: 29% vs CABG: 27%, P = ns). The four other randomised clinical trials compared PCI with the use of BMS (ARTS I, SOS, ERACI II, MASS II) against CABG in patients with multivessel disease (table 1) [49–52]. All these studies lacked adjunctive pharmacological treatment including thienopyridine pre-loading and glycoprotein IIb/IIIa antagonists, and thus their applicability to today's clinical practice is limited. With the exception of the SOS trial [50], being the only trial showing increased mortality among patients (N = 988) treated with PCI compared to CABG in the overall population (PCI: 10.9% vs CABG: 6.8%, HR = 1.66, 95% CI 1.08–2.55, P = 0.02) at six years, all other studies observed similar mortality for both revascularisation strategies in the overall population. Comparison of mortality at five years showed a similar outcome among PCI patients enrolled into SOS (8.1%), ARTS I (8.0%) and ERACI II (7.1%), whereas mortality among CABG patients was much lower in SOS (4.3%) as compared with ARTS I (7.6%) and ERACI II (11.5%) in the overall population.

In ARTS I, a total of 1205 patients were randomly assigned to treatment with PCI or CABG (LIMA graft: 93%) [49]. At 5 years, while mortality was higher in diabetics (13.4%) than non-diabetics (6.8%, P = 0.03) treated with PCI, this difference was not observed among patients treated with CABG (diabetes: 8.3% vs no diabetes: 7.5%, P = 0.80). On the same lines, mortality tended to be higher with PCI (13.4%) than CABG (8.3%, RR = 1.61, 95% CI 0.71–3.63, P = 0.39) among the 208 diabetic patients, although the differences were not significant and the study was not powered to address this question. Repeat revascularisation procedures were 3–4 times more frequent among PCI-treated patients. ERACI II randomly assigned 450 patients with multivessel disease to undergo PCI (BMS: 100%) or CABG (LIMA graft: 89%) [51]. At five years' follow-up there was no difference in mortality among diabetic patients (PCI: 10.3% vs CABG: 10.3%, p = 0.96). The randomised MASS II trial compared PCI (N = 205; BMS: 68%) with CABG (N = 203; LIMA graft: 92%) and medical treatment (N = 203) in patients with multivessel disease [52]. At five years' follow-up the study showed similar mortality among diabetic patients treated with PCI (16.1%) and CABG (15.3%), whereas mortality was higher among medically treated patients (25.3%). A feature of note is that mortality was lower in diabetic patients undergoing revascularisation by either PCI or CABG than in those undergoing medical treatment in the period between 2 and 5 years' follow-up in the diabetic cohort (P = 0.04), whereas no such difference was observed in non-diabetic patients.

Bravata and colleagues reported on a systematic review comprising 23 RTCs in which 5019 patients were randomly assigned to PCI (balloon angioplasty or BMS) and 4944 patients randomly allocated to CABG [40]. A subgroup analysis among diabetic patients showed no difference in mortality between PCI (20.8%) and CABG (17.8%, P = ns). In contrast, a recent meta-analysis of individual patient data by Hlatky and colleagues comparing PCI with balloon angioplasty or bare metal stenting against CABG reported an increased risk of mortality in diabetic patients undergoing PCI (20.0% vs 12.3%, HR = 0.70, 95% CI 056-0.87, P = 0.014) [53]. A meta-analysis [54] of four trials using bare metal stents (ARTS I, SOS, ERACI II, MASS II) comprising 3051 patients compared the clinical outcome at twelve months between patients undergoing PCI with the use of BMS against CABG. A subgroup analysis in diabetic patients revealed no significant difference in mortality among patients treated by PCI (5.6%) and CABG (3.5%, HR = 1.6, 95% CI 0.72–3.6, P = 0.30). Repeat revascularisation procedures were, however, four times more common among patients treated by PCI than CABG (HR = 4.4, 95% CI 3.3–5.9). Yet another meta-analysis restricted to trials with the use of bare metal stents (rather than balloon angioplasty) showed similar rates of death, myocardial infarction or stroke in patients undergoing revascularisation by either PCI or CABG [55].

In recent years stent technology has improved further with the development of *drug-eluting stents* (DES) delivering site-specific, controlled release of therapeutic agents. Several registries have compared [56–65] clinical outcomes of patients with multivessel disease following treatment with DES or CABG to date, and are summarised in table 2 and figure 2. ARTS II was a non-randomised supplementary arm of ARTS I to determine the safety and efficacy of sirolimus-eluting stents in 607 patients with multivessel disease. Although both inclusion and exclusion criteria and the primary endpoint were similar to the RCT arm (ARTS I), patients included in ARTS II had more three vessel disease with a higher incidence of diabetes, and were treated with more and longer stents compared with ARTS I. At one year follow-up, the incidence of repeat revascularisation was 8.5% in ARTS II and therefore significantly lower compared with the historical BMS 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 for diabetics there were no significant differences between ARTS II and

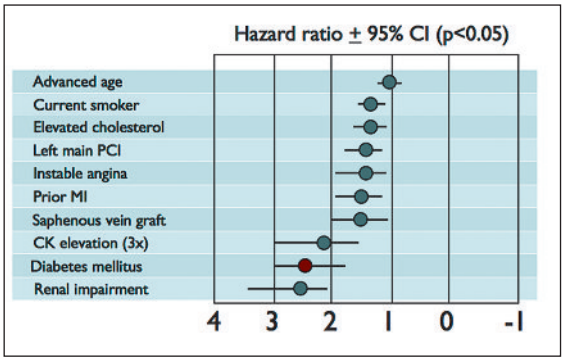

Figure 2

Impact of various risk factors – including diabetes mellitus – on late mortality following percutaneous coronary intervention. Diabetes mellitus and renal failure portend a particularly poor outcome. Adapted from [84].

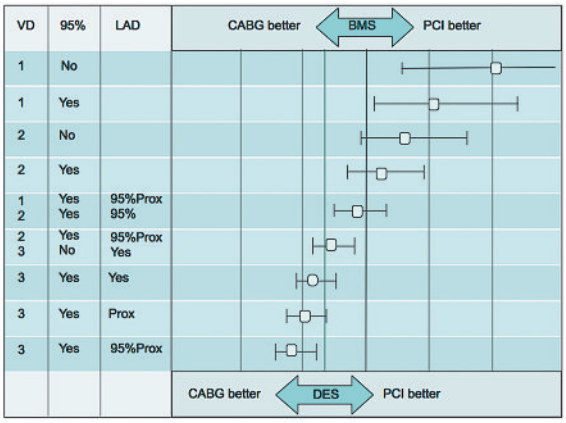

Figure 3

Adjusted hazard ratios comparing CABG and PCI with bare-metal stents (BMS) for nine coronary anatomy groups. "DES?": speculative shift in patients treated with drug-eluting stent (DES). VD: number of diseased vessels. 95%: presence of stenosis >95% coronary artery stenosis. Prox: proximal. Adapted from [85].

the CABG arm of ARTS I in MACCE at one year.

Similarly to ARTS II, ERACI III enrolled 225 patients with multivessel disease who were treated with DES and applied the same inclusion and exclusion criteria as the randomised ERACI II trial comparing BMS with CABG [59]. The rate of major adverse cardiac events at three years in ERACI III was twice as high in diabetic as in non-diabetic patients, with no differences among DES treated patients in ERACI III (36.2%) and patients undergoing CABG (30.8%) or BMS implantation (43.6%, P = 0.49) in ERACI II. The need for repeat revascularisation was lowest among patients undergoing CABG in ERACI II (15.4%), followed by DES treated patients of ERACI III (21.3%) and topped by BMS treated patients in ERACI II (38.5%, P = 0.05).

The results of both ARTS II and ERACI III trials must be interpreted cautiously in the light of the non-randomised nature of the supplementary arms. Accordingly, selection bias and confounding factors cannot be excluded and the comparison with CABG requires confirmation in prospective randomised clinical trials.

A large registry included 1680 patients undergoing revascularisation for multivessel disease at the Washington Hospital Center, of whom 1080 were treated for multivessel disease [66]. After multivariable adjustment, major adverse cardiac and cerebrovascular events were 2–3 times higher in patients undergoing PCI with DES than with CABG. The unfavourable outcome of DES-treated patients compared with CABG was mainly due to differences in revascularisation rates and was particularly pronounced in the diabetic population, with a significantly increased risk of major adverse cardiac and cerebrovascular events and mortality. A registry from Samsung Medical Center compared the clinical outcome of 831 patients with multivessel disease treated with either DES (N = 441) or CABG (N = 390) [60]. At one-year follow-up the results in diabetic patients were similar to those in the overall patient population, with no difference among DES and CABG treated patients in terms of mortality (3.8% vs 3.8%, P = 0.49) but a significantly higher rate of repeat revascularisation procedures (12.4% vs 0.5%, P <0.001) and therefore a higher rate of major adverse cardiac and cerebrovascular events (18.3% vs 4.9%, P <0.001).

Hannan and colleagues assessed the clinical outcome of patients with multivessel disease who underwent revascularisation with CABG (N = 7437) or DES (N = 9963) between 2003 and 2004 in New York State [66]. Adjusted 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 revascularisation strategy. This was in contradiction to a previous report from the same investigators comparing clinical outcome following revascularisation with BMS or CABG in New York State, where the latter group was associated with improved survival among diabetic patients with three-vessel disease [67].

The UK based CARDIA trial directly compared CABG with PCI (predominant DES use: 71%) in diabetic patients with multivessel disease in a randomised non-inferiority study. Due to recruitment difficulties, only 510 of 600 planned patients (85%) were randomised and preliminary results were presented at the 2008 European Society of Cardiology convention in Munich [68]. The primary endpoint, a composite of death, non-fatal MI and stroke assessed at one year showed a 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 with CABG (2.5%, P = 0.09). Repeat revascularisation procedures were more frequent with PCI (9.9%) than with CABG (2.0%, P <0.001) at one year follow-up. These findings are in line with the subgroup of diabetic patients (N = 512 patients) included in the SYNTAX trial, a large-scale randomised study (N = 1800 patients) comparing CABG with DES in the treatment of patients with multivessel disease [69]. The composite endpoint of death, MI and stroke at one year was similar for CABG (10.3%) and PCI (10.1%, P = 0.96) in diabetic patients, whereas repeat revascularisation and overall major adverse cardiac and cerebrovascular events were more common with the latter (PCI-MACCE: 26.0%, CABG-MACCE: 14.2%, P = 0.03) [69]. As a point of interest, a subgroup analysis according to

Table 2

Studies comparing coronary artery bypass grafting (CABG) with drug-eluting stents (DES).

	Study general characteristics		Overall population													Diabetic population								
Study	Randomised?	Follow-up, yr	Patients		Diabetics		Mortality			Repeat revascularisation			MACCE			Mortality			Repeat revascularisation			MACCE		
			PCI-DES, n	CABG, n	PCI-DES, n	CABG, n	PCI-DES, n	CABG, %	p-value	PCI-DES, n	CABG, %	p-value	PCI-DES, n	CABG, %	p-value	PCI-DES, n	CABG, %	p-value	PCI-DES, n	CABG, %	p-value	PCI-DES, n	CABG, %	p-value
Samsung Medical Center	No	1.8	441	390	163	189	2%	3%	0.17	9%	1%	<0.001	13%	4%	<0.001	4%	4%	0.49	12%	1%	<0.001	18%	5%	<0.001
Washington Hospital Center	No	1	979	701	344	257	8%	3%	0.006	na	na	na	25%	10%	<0.001	14%	2%	0.003	na	na	na	31%	9%	<0.001
RuiJin Hospital	No	2.1	235	231	75	64	3%	2%	0.77	10%	3%	0.001	15%	8%	0.03	na	na	na	na	na	na	na	na	na
Briguori et al.	No	1	–	–	69	149	–	–	–	–	–	–	–	–	–	6%	5%	0.74	19%	5%	0.001	29%	21%	0.17
UCLA-Cedars-Sinai Medical Center	No	1	–	–	102	103	–	–	–	–	–	–	–	–	–	10%	8%	0.6	20%	3%	<0.001	27%	12%	0.006
Tarantini et al.	No	2	–	–	93	127	–	–	–	–	–	–	–	–	–	4%	4%	ns	7%	4%	0.2	13%	13%	0.8
Ben Gal et al.	No	1.5	–	–	176	342	–	–	–	–	–	–	–	–	–	2%	4%	0.65	14%	1%	0.01	na	na	na
Li et al.	No	3	1834	1886	503	461	6%	4%	0.24	12%	1%	<0.001	na	na	na	8%	4%	0.03	na	na	na	na	na	na
Mack et al.	No	1.5	3089	1247	1013	437	9%	8%	0.35	14%	6%	<0.001	23%	15%	<0.001	10%	10%	0.91	15%	7%	<0.001	27%	19%	0.001
ARTS II	Single-arm trial compared with ARTS I	3	607	605	158	96	3%	4%	ns	14%	7%	<0.001	19%	16%	0.21	na	na	ns	na	na	na	28%	18%	0.09
ERACI III	Single-arm trial compared with ERACI II	3	225	225	47	39	6%	10%	0.16	14%	6%	0.002	23%	23%	ns	na	na	ns	21%	15%	0.58	36%	31%	0.49
CARDia	Yes	1	–	–	252	229	–	–	–	–	–	–	–	–	–	3%	3%	0.8	10%	2%	0.04	12%	10%	0.63
SYNTAX	Yes	1	903	897	231	221	4%	4%	0.37	14%	6%	<0.001	18%	12%	0.002	8%	6%	0.43	20%	6%	<0.001	26%	14%	0.003

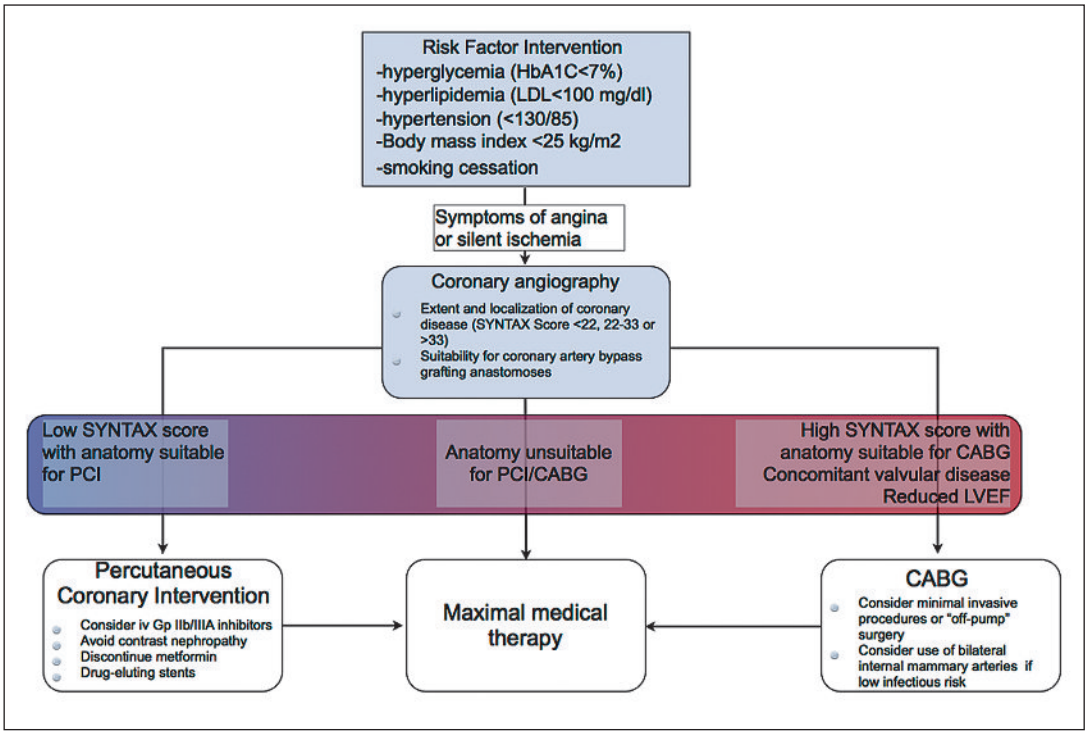

Figure 4

Flow-chart of a tailored approach for coronary revascularisation in patients with diabetes mellitus. SYNTAX score is calculated online at www.syntaxscore.com.

low, medium or high SYNTAX score (www.syntaxscore.com), revealed similar mortality in patients with a low (0–22) and medium (23–32) SYNTAX score in diabetic and non-diabetic patients, whereas mortality was increased in diabetic and non-diabetic patients undergoing PCI with a high SYNTAX score (≥33) [71].

4. Special subgroups

4a. Revascularisation of diabetic patients with acute ST-elevation myocardial infarction and cardiogenic shock

Diabetic patients experiencing acute ST-elevation myocardial infarction present later to hospital, are more likely to suffer from haemodynamic instabilities and end-organ damage, and have delayed revascularisation compared with non-diabetic patients [72]. Heart surgery in the setting of acute ST-elevation myocardial infarction remains reserved to patients with mechanical complications (papillary muscle dysfunction, rupture of the interventricular septum). The therapeutic advantage of *primary PCI* over thrombolysis appears to be particularly pronounced in diabetic patients owing to higher patency rates of the infarct-related artery (88% vs 31%, p <0.001), improved left ventricular function (LVEF 49% vs 36%, p <0.05) [73], and a significant reduction in death or myocardial infarction at 30 days (9.2% vs 19.3%, P <0.05) [74] and during long-term follow-up [73]. The value of glycoprotein IIb/IIIa antagonists in addition to standard antiplatelet therapy including aspirin and clopidogrel has been demonstrated in diabetic patients with acute ST-elevation myocardial infarction undergoing primary PCI [75]. In a meta-analysis of individual patient data from diabetic patients with ST-elevation myocardial infarction, Montalescot and colleagues reported improved survival at three years in patients treated with abciximab (22% vs 40%, P = 0.02; NNT: 6 [4–64]) [76].

Patients with acute myocardial infarction complicated by cardiogenic shock within 36 hours of symptom onset benefit from emergency revascularisation in terms of survival [77]. While the majority of patients will undergo PCI, patients with extensive coronary artery disease and those not amenable to PCI should be considered for emergency CABG. In the SHOCK trial, 30-day survival was similar in the 23 diabetic patients with cardiogenic shock referred for emergency surgery (49% of enrolled CABG patients) and the 22 patients who underwent PCI (27% of enrolled PCI patients) [78]. Accordingly, the choice of revascularisation in diabetic patients with cardiogenic shock depends on the extent of coronary artery disease and suitability for either revascularisation method.

4b. Revascularisation in diabetic patients with acute coronary syndromes (unstable angina/non-ST-elevation myocardial infarction)

Diabetes is an independent predictor of mortality (RR = 1.56; 95% CI: 1.35–1.79) in patients with acute coronary syndromes (ACS) and corresponds to the risk of non-diabetic patients who are on average ten years older [79]. Mortality in patients with ACS is twice as high in diabetic as in non-diabetic patients [80]. The European Society of Cardiology therefore allocated a high risk label to the status diabetes, suggesting that diabetic patients with ACS should be treated according to the high risk pathway, i.e., an early invasive strategy. Diabetic patients derive particular benefit from an early invasive strategy compared with conservative treatment, as demonstrated in the FRISC II [81, 82], and TACTICS-TIMI 18 [83] trials. In addition, diabetic patients with ACS benefit from adjunctive therapy with glycoprotein IIb/IIIa antagonists when undergoing revascularisation. A meta-analysis of six studies in diabetic patients with ACS showed improved survival with the use of glycoprotein IIb/IIIa antagonists [80].

Conclusions

Currently fewer than 50% of diabetic patients with additional cardiovascular risk factors undergo screening for coronary artery disease. In addition, control of coexistent cardiovascular risk factors, including blood pressure and lipid profile, using evidence-based medical therapy remains unsatifactory in diabetic patients. Optimal revascularisation of diabetic patients suffering from coronary artery disease depends on clinical and anatomical considerations. In the acute setting, including ST-elevation myocardial infarction and non-ST-elevation myocardial infarction, PCI is preferable. In patients with stable coronary artery disease, the extent of disease and non-cardiac morbidity require careful consideration. CABG remains more effective in terms of repeat revascularisation procedures and mortality in patients with advanced multivessel disease (high SYNTAX score), while PCI with the use of DES and adjunctive pharmacological treatment, including thienopyridines and glycoprotein IIb/IIIa antagonist, is a valuable alternative in patients with less extensive disease (low to medium SYNTAX score). Several ongoing trials – such as BARI-2D, FREEDOM and VA-CARDS – will clarify the relative efficacy of CABG and PCI among diabetic patients and the benefit of intensive medical treatment as compared with either revascularisation strategy. Irrespective of revascularisation strategy, intensive medical therapy with strict glucose control is mandatory and impacts on prognosis following coronary artery revascularisation.

Correspondence:
Stephan Windecker
Director, Invasive Cardiology
Department of Cardiology
Bern University Hospital
CH-3010 Bern
Switzerland
E-Mail: stephan.windecker@insel.ch

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