Is there an additional benefit from coronary revascularization in diabetic patients with acute coronary syndromes or stable angina who are already on optimal medical treatment?

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Submitted: 26 August 2010
Accepted: 16 September 2010

Arch Med Sci 2011; 7, 6: 1067-1075
DOI: 10.5114/AOMS.2011.26621

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Abstract

Cardiovascular disease (CVD) is common in patients with diabetes mellitus (DM) and related clinical outcomes are worse compared with non-diabetics. The optimal treatment in diabetic patients with coronary heart disease (CHD) is currently not established. We searched MEDLINE (1975-2010) using the key terms diabetes mellitus, coronary heart disease, revascularization, coronary artery bypass, angioplasty, coronary intervention and medical treatment. Most studies comparing different revascularization procedures in patients with CHD favoured coronary artery bypass graft (CABG) surgery in patients with DM. However, most of this evidence comes from subgroup analyses. Recent evidence suggests that advanced percutaneous coronary intervention (PCI) techniques along with best medical treatment may be non-inferior and more cost-effective compared with CABG. Treatment of vascular risk factors is a key option in terms of improving CVD outcomes in diabetic patients with CHD. The choice between medical therapy and revascularization warrants further assessment.

Key words: diabetes, coronary heart disease, acute coronary syndrome, coronary artery bypass graft, percutaneous coronary intervention, statin.

Introduction

Approximately 30% of patients with coronary heart disease (CHD) have type 2 diabetes mellitus (T2DM) and the prevalence of impaired glucose metabolism in this population is even higher [1-3]. Despite the considerable improvement in the management of cardiovascular disease (CVD), patients with T2DM have not benefited to the same extent as those without T2DM [4]. Possible explanations are that T2DM patients are undertreated with evidence-based medications or revascularization and/or that these treatments are less effective in T2DM [5-10].

Despite the fact that patients with T2DM account for approximately 25% of the nearly 1.5 million coronary revascularization procedures performed each year in the US, there is a relative lack of consistent data from randomized controlled trials (RCTs) comparing coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) with medical treatment alone in diabetic patients with either stable CHD or acute coronary syndromes (ACS) [11]. Therefore, the question remains whether one of the revascularization options is superior to the other in patients with T2DM. Furthermore, does revascularization provide additional benefit in diabetic patients who are on optimal medical treatment? This review considers these issues.

Search study

We searched MEDLINE (1975-2010) using the key terms diabetes mellitus, coronary heart disease, revascularization, coronary artery bypass, angioplasty, coronary intervention and medical treatment. Reference lists of the identified trials, review articles and guidelines from official societies (including those of the American College of Cardiology (ACC), American Heart Association (AHA), and Transcatheter Cardiovascular Therapeutics) were reviewed. To compare CABG surgery with PCI we identified all randomized and controlled studies which recruited patients with DM with an indication for coronary revascularization. A similar search was performed to identify all RCTs comparing the use of statins in patients with DM undergoing revascularization procedures. MEDLINE searches were also performed to identify studies, meta-analyses and review articles that addressed outcomes in patients with DM undergoing revascularization in specific situations, for example ACS or stable CHD.

Studies assessing revascularization in diabetes (Table I)

A very recent analysis of a registry from Poland reported data from 7,193 patients with ACS; 877 (12.2%) had DM on admission [10]. Diabetic patients were older and had a higher prevalence of hyperlipidaemia and previous myocardial infarction (MI) compared with non-diabetic patients ($p < 0.0001$ for all) [10]. Patients with DM were also more likely to be women, have more extensive CHD, renal failure, shock at presentation and to be admitted late ($p < 0.0001$ for all) [10]. Despite their adverse risk profile, diabetic patients were less frequently treated with primary PCI with stenting ($p < 0.0001$) [10]. Moreover, DM was independently associated with impaired epicardial reperfusion (odds ratio (OR) = 1.33; 95% confidence interval (CI) 1.07-1.64, $p = 0.009$) [10]. At mean follow-up of 524 ±194 days, patients with DM had a higher mortality rate compared with non-diabetic patients (adjusted cumulative mortality: 13.3% vs. 10.7%, adjusted hazard ratio (HR) = 1.23; 95% CI 1.04-1.46, $p = 0.013$) [10].

Regarding the optimal revascularization strategy in patients with T2DM, the Bypass Angioplasty Revascularization Investigation (BARI) trial compared CABG with percutaneous transluminal coronary angioplasty (PTCA) in 1,829 patients with multivessel CHD (64% had ACS) [12]. In a non-prespecified subgroup of diabetic patients who were being treated with insulin or oral hypoglycaemic agents ($n = 353$), the 5-year survival rates were higher in the CABG group compared with the PTCA group (80.6% vs. 65.5%, respectively; $p = 0.003$), mainly due to the lower 5-year cardiac mortality rates (5.8% vs. 20.6%, respectively; $p = 0.0003$) [12, 13]. The additional benefit of CABG was limited to the patients who received at least 1 internal mammary artery (IMA) graft; when only saphenous vein grafts (SVGs) were used, 5-year cardiac mortality was similar in the CABG and PTCA groups [12, 13]. In contrast, 5-year cardiac mortality rates did not differ in non-diabetic patients allocated to CABG or PTCA (4.7% and 4.8%, respectively; $p = 0.91$) [12]. At 10-year follow-up, angina rates were similar in the 2 revascularization strategies but subsequent revascularization rates were higher in the PTCA group than in the CABG group (76.8% vs. 20.3%, $p < 0.001$) [14]. In the subgroup of patients with treated T2DM, the CABG group had higher survival rates than the PTCA group (57.8% vs. 45.5%, respectively; $p = 0.025$) [14]. These results of the BARI trial support the use of CABG over PTCA in patients with T2DM even though this subgroup was not specified by the study protocol. In addition, there was no comparison of revascularization with medical treatment alone. Furthermore, lipid and blood pressure targets and PCI techniques as well as CABG perioperative morbidity and mortality have substantially changed since the publication of the BARI initial papers (1996-1997). The same applies to other trials performed during the same time period.

The Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) trial, published 15 years ago, also supports the use of CABG in diabetic patients [15, 16]. The CABRI trial randomized 1,054 patients (125 (11.9%) with T2DM) with symptomatic multivessel CHD to PTCA or CABG. Diabetic patients who underwent PTCA had higher mortality rates compared with non-diabetic patients (22.6% vs. 9.4%, respectively; $p = 0.001$) [15, 16]. In contrast, when CABG was performed, mortality rates did not differ significantly in diabetic and non-diabetic patients (12.5% and 6.8%, respectively; p = NS); this difference despite being nearly double was not significant, probably due to the small number of diabetic patients included in the study.

Table I. Trials assessing or comparing revascularization methods (PCI or CABG) with each other or with medical treatment in patients with CHD, focusing on those with DM

Name of the study	Aim of the study	Number of patients	Type of study	Results
POLISH STEMI registry [10]	To investigate the impact of DM on mortality in STEMI patients treated with primary angioplasty	7,193 patients with ACS; 877 (12.2%) with DM	Registry analysis with prospectively collected data	Fewer primary PCI procedures with stenting ($p < 0.0001$) and higher mortality rate in patients with DM vs. patients without DM (adjusted HR = 1.23; 95% CI 1.04-1.46, $p = 0.013$) DM independently associated with impaired epicardial reperfusion (OR = 1.33; 95% CI 1.07-1.64, $p = 0.009$)
BARI [12-14]	CABG vs. PTCA in patients with multivessel CHD	1,829; 353 with DM	RCT	5-year survival rates higher in the CABG group (80.6% vs. 65.5%, $p = 0.003$). Lower 5-year cardiac mortality rates (5.8% vs. 20.6%, $p = 0.0003$) in DM patients. Similar 5-year survival rates in the 2 groups in patients without DM. Similar angina rates in the 2 groups, but higher revascularization rates in the PTCA group (76.8% vs. 20.3%, $p < 0.001$) at 10-year follow-up. Higher survival rates in the CABG group (57.8% vs. 45.5%, $p = 0.025$) at 10 years of DM
CABRI [15, 16]	PTCA vs. CABG in patients with symptomatic multivessel CHD	1,054; 125 (11.9%) with DM	RCT	PTCA group: higher mortality rates in diabetic vs. non-diabetic patients (22.6% vs. 9.4%, $p = 0.001$) CABG group: similar mortality rates in diabetic and non-diabetic patients
Barsness *et al.* [18]	PTCA or CABG in patients with multivessel CHD	3,220; 24% with DM	Observational	Lower survival rates in patients with DM vs. those without ($p < 0.0001$). No significant differential effect of diabetes on outcome between the PTCA and the CABG group
Carson *et al.* [19]	Patients undergoing CABG	146,786; 28.4% with DM	Cohort study	Higher 30-day mortality in diabetic vs. non-diabetic patients (3.7% vs. 2.7%; adjusted HR 1.23; 95% CI 1.15-1.32, $p = 0.002$). Stroke, renal failure and infections more frequent in patients with DM
Portuguese Registry on ACS [24]	CABG ($N = 267$) vs. PCI ($N = 3,948$) or no PCI ($N = 8,773$) in patients with ACS	12,988	Retrospective analysis of a nationwide database in Portugal	Very low in-hospital mortality (1.1%) in the CABG group
MASS II [26, 27]	Medical treatment vs. CABG vs. PCI in stable multivessel CHD patients	611, 190 with DM	RCT	Similar rates of cardiac death, STEMI and revascularization in PCI and medical therapy groups and lower rates in the CABG group
RITA I [28]	PTCA vs. CABG in patients with CHD	1,011	RCT	Trend toward lower mortality in the PTCA vs. the CABG group
RITA II [29]	PTCA vs. medical treatment in patients with CHD	1,018	RCT	Greater symptomatic improvement in the PTCA group

Table I. cont.

Name of the study	Aim of the study	Number of patients	Type of study	Results
Steno-2 [31]	Intensified multifactorial intervention vs. conventional treatment in patients with DM and micro-albuminuria	160	Randomised, prospective, open, parallel trial	Lower risk of CVD (HR 0.47; 95% CI 0.24-0.73), nephropathy (HR 0.39; 95% CI 0.17-0.87), retinopathy (HR 0.42; 95% CI 0.21-0.86) and autonomic neuropathy (HR 0.37; 95% CI 0.18-0.79) with intensive treatment
BARI 2D [33, 34]	Insulin sensitization vs. insulin and intensive medical therapy with prompt coronary revascularization or at a later date in patients with DM and stable CHD	2,368	RCT	Similar 5-year cardiac mortality rates between revascularization plus intensive medical therapy and intensive medical therapy alone or between insulin sensitization and insulin provision. The MI (10.0% vs. 17.6%, $p = 0.003$), all-cause death or MI (21.1% vs. 29.2%, $p = 0.01$) and cardiac death or MI ($p = 0.03$) less frequent in the revascularization plus intensive medical therapy vs. the intensive medical therapy group
Tarantini *et al.* [38]	PCI (using exclusively DES) vs. CABG in diabetic patients with multivessel CHD	220	Retrospective with prospectively collected data	Higher prevalence of 3-vessel disease ($p < 0.001$), LAD involvement ($p < 0.001$), presence of total occlusions ($p = 0.04$) and collateral circulation ($p < 0.001$) in the CABG group. No difference in MACCE between the 2 groups at 2-year follow-up
DESIRE [40]	PCI with DES	2,084 (28.9% with DM and 40.7% with ACS)	Prospective, non-randomized single-centre registry	0.7% STEMI and 1.6% in-stent thrombosis
Tamburino *et al.* [41]	Complete vs. incomplete revascularization with PCI using DES in patients with multivessel CHD	508	Retrospective with prospectively collected data	Lower HR for cardiac death, MI or repeat revascularization (0.43; 95% CI 0.29-0.63, $p < 0.0001$), cardiac death (0.37; 95% CI 0.15-0.92, $p = 0.03$), cardiac death or MI (0.34; 95% CI 0.16-0.75, $p = 0.008$) and any repeat revascularization (0.45; 95% CI 0.29-0.69, $p = 0.0003$) with complete revascularization
Qiao *et al.* [42]	CABG vs. DES-PCI in DM patients with multivessel CHD	645	Non-randomized	Similar total mortality in the 2 groups. Lower rate of major adverse CVD events in the CABG group (HR 0.15; 95% CI 0.06-0.37, $p < 0.001$) mainly due to less repeat revascularization (HR 0.02, 95% CI 0.01-0.13, $p < 0.001$)

ACS – acute coronary syndrome, BARI – Bypass Angioplasty Revascularization Investigation, BARI 2D – BARI 2 Diabetes, CABG – coronary artery bypass grafting, CABRI – Coronary Angioplasty versus Bypass Revascularization Investigation, CHD – coronary heart disease, CI – confidence interval, DES – drug-eluting stents, DESIRE – Drug-Eluting Stents in the Real World, DM – diabetes mellitus, EAST – Emory Angioplasty versus Surgery Trial, HR – hazard ratio, IMA – internal mammary artery, LAD – left anterior descending, MACCE – major adverse cardiac and cerebrovascular events, MASS – Medicine, Angioplasty or Surgery Study, MI – myocardial infarction, OR – odds ratio, PCI – percutaneous coronary intervention, PTCA – percutaneous transluminal coronary angioplasty, RCT – randomized control trial, RITA – Randomized Intervention Treatment of Angina, STEMI – ST-elevation myocardial infarction

The Emory Angioplasty versus Surgery Trial (EAST), another "old" trial, did not show a survival (mid- or long-term) advantage for CABG in patients with multivessel CHD; however, there were no subgroup analyses in diabetic patients (23% of the study population) [17]. In an observational study with a similar population (n = 3,220; 24% with T2DM) published in 1994, diabetic patients receiving either PTCA or CABG had significantly poorer survival compared with non-diabetics ($p < 0.0001$). However, there was no significant differential effect of diabetes on outcome between patients treated with PTCA and those undergoing CABG ($p = 0.91$) [18]. A larger cohort study in 146,786 patients undergoing CABG (28.4% with T2DM) showed that the 30-day mortality was higher in diabetic patients (3.7% vs. 2.7% in non-diabetic patients; adjusted HR 1.23; 95% CI 1.15-1.32, $p = 0.002$) [19]. Stroke, renal failure and infections also occurred more frequently in patients with T2DM. Interestingly, some studies showed that pretreatment of patients undergoing CABG or PCI with statins might improve outcome [20-23]. Therefore, the lower use of statins might have influenced the results of older trials.

Some data suggest that CABG might be beneficial even in low-risk patients with ACS [24]. In a retrospective analysis of a nationwide database in Portugal (12,988 patients with ACS), 267 patients underwent CABG during the index hospitalization (group A) and 12,721 did not (group B). Group B patients were further divided into 2 subgroups: those submitted to PCI during the index hospitalization (group B1; n = 3,948) and those who were not (group B2; n = 8,773). The prevalence of T2DM was 32%, 23% and 28% in Groups A, B1 and B2, respectively. In this analysis, early CABG was associated with very low in-hospital mortality (1.1%) although it was performed in higher-risk patients and even when compared with the mortality of the lower-risk population not submitted to early CABG (2.2% in patients undergoing PCI and 6.8% in those who were not submitted to early mechanical revascularization, $p < 0.05$ vs. CABG) [24]. This report was the first to raise the issue of optimal treatment of ACS and the need for studies comparing the outcome of CABG, PCI and intensive medical treatment in patients with ACS with or without T2DM. During the last decade, PCI is gaining ground over CABG and medical treatment in patients with ACS [25]. "Rescue", "elective" and "early" PCI is extensively used for the treatment of ACS especially after the generalized use of drug-eluting stents (DES), GbIIb/IIIa inhibitors and dual antiplatelet (clopidogrel plus aspirin) treatment [25]. However, PCI is still underused in diabetic patients with ACS [10].

The studies mentioned above included patients with either ACS or stable CHD and their results have several limitations. Individual trials and meta-analyses show that in non-diabetic patients with multivessel CHD, CABG and PCI yield comparable long-term results in terms of hard endpoints (cardiac death or MI), but subsequent revascularization was more frequently necessary in patients undergoing PCI [25]. In contrast, diabetic patients appear to benefit more from CABG than from angioplasty, as shown in the BARI and CABRI trials [12-16]. These findings were also supported by the results of the Medicine, Angioplasty, or Surgery Study (MASS II) [26, 27]. MASS II randomly assigned 611 patients with stable multivessel CHD to medical treatment, CABG or PCI. In MASS II, 190 patients had T2DM (medical treatment n = 75; PCI: n = 56; CABG: n = 59). The incidence of the primary endpoint (cardiac death, ST elevation MI (STEMI) and revascularization) did not differ between PCI and continued medical therapy, whereas CABG was superior to both [26, 27]. These results seem to contradict those of the 2 older Randomized Intervention Treatment of Angina-1 and 2 (RITA-1 and 2) studies [28, 29], which compared PCI with CABG (RITA-1 [28]) and PCI with medical treatment alone (RITA-2 [29]). RITA-1 randomized 1,011 patients with CHD (45% single-vessel, 55% multivessel, 62 patients (6.1%) with T2DM) and showed a trend toward lower mortality in the PTCA than in the CABG group with no difference in total health-service costs over 5 years between the 2 strategies [28]. In RITA-2 (n = 1,018 CHD patients considered suitable for either PTCA or continuing medical treatment alone), early intervention with PTCA was associated with greater symptomatic improvement, especially in patients with more severe angina [29]. The investigators of RITA-2 suggested that when managing patients with angina, clinicians should balance these benefits against the small excess hazard of procedure-related complications associated with PTCA [29]. However, the cost of an initial strategy of PTCA exceeded that of an initial strategy of medical management by 74% over 3 years [30]. On the other hand, the Steno-2 study clearly demonstrated the value of multifactorial, target-driven, evidence-based medical intervention alone, aiming at all modifiable risk factors in patients with T2DM at high risk for macrovascular complications [31]. In Steno-2, medical treatment alone resulted in significant reductions (by more than 50%) in 7-year CVD morbidity and mortality rates [31]. Similarly, even a short-term (6-month) low-cost best practice implementation programme was associated with up to 44% reduction in estimated CVD risk in 578 patients with DM [32].

The recently published Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial provides new insight in the management of diabetic patients with stable CHD [33, 34]. In this study, 2,368 diabetic patients with stable CHD were

randomly assigned, according to a 2 × 2 factorial design, to receive (1) tight glycaemic control with insulin sensitization vs. insulin provision aiming at $HbA_{1c} \leq 7.0\%$, and (2) intensive medical management with either prompt coronary revascularization or with coronary revascularization at a later date and only if clinically indicated. The 5-year cardiac mortality rates did not differ between revascularization plus intensive medical therapy and intensive medical therapy alone (5.9% vs. 5.7%, respectively; $p = 0.38$) or between insulin sensitization and insulin provision (5.7% vs. 6%; $p = 0.76$). In the 763 patients who underwent CABG (i.e. patients with more extensive CHD), MI was less frequent in the revascularization plus intensive medical therapy group compared with intensive medical therapy alone (10.0% vs. 17.6%, respectively; $p = 0.003$). The composite endpoints of all-cause death or MI (21.1% vs. 29.2%, respectively; $p = 0.01$) and cardiac death or MI ($p = 0.03$) were also less frequent in this group [33, 34]. However, prompt coronary revascularization was significantly more expensive than medical therapy alone. The high initial costs of CABG and PCI were only partially offset by later cost savings during the 4 years of follow-up [35]. Cost-effectiveness analyses based on 4-year follow-up data favoured the strategy of medical therapy alone over prompt revascularization and the strategy of insulin provision over insulin sensitization. Overall, the BARI 2D results suggest that in patients with T2DM and stable CHD without angina, intensive medical therapy alone should be the first-line strategy. In contrast, in patients with angina that affects quality of life, intensive medical therapy and prompt CABG appears to be the preferred strategy [33-35].

Outside the context of RCTs, evidence-based medical treatment and revascularization also appear to be beneficial in diabetic patients with CHD. The recently published Euro Heart Survey on Diabetes and Heart assessed the impact of medical treatment and revascularization on mortality and CVD events in 3,488 patients with CHD (41% with T2DM) [2]. Only 44% of those with T2DM and 43% of those without T2DM received evidence-based medical treatment, while 34% and 40%, respectively, underwent revascularization. Medical treatment and revascularization had comparable favourable effects on the outcome of all patients with CHD. In diabetic patients clinical benefit was more pronounced compared with non-diabetics. A substantially lower number of diabetic patients needed to be treated for 1 year to prevent 1 death (24 in the T2DM group compared with 1,826 in patients with normal glucose metabolism) or to avoid a fatal or non-fatal CVD event (32 vs. 141, respectively) [2]. These results suggest that patients with both T2DM and CHD benefit substantially more than patients with CHD alone from combined medical treatment and revascularization.

In recent years, the outcome of revascularization procedures has been improved by the introduction of novel medical strategies such as GbIIa/IIIb inhibitors, dual antiplatelet therapy (clopidogrel plus aspirin) and aggressive statin pre-treatment [20-23] as well as by the use of DES and improved surgical methods such as multiple arterial grafting (e.g. bilateral IMA grafts [36]) and off-pump surgery [11, 25]. Therefore, the results of older studies assessing revascularization and medical treatment in patients with CHD may no longer be valid, and more up-to-date trials are needed. For example, the use of DES reduces repeat revascularization rates [11, 25]. A meta-analysis showed that DES yield better early and mid-term results compared with bare metal stents (BMS) in diabetic patients [37]. In this context, it is of interest that a very recent study comparing PCI (using exclusively DES) with CABG for multivessel CHD in diabetic patients suggested that a clinical judgment-based revascularization by DES-PCI is not associated with worse 2-year outcome compared with CABG [38]. Another study included 411 consecutive "real-world" patients (40.3% with ACS and 15% with T2DM) undergoing PCI with DES by a single operator (63.5% of the patients in 1 vessel and 36.5% in > 1 vessel) between 2003 and 2006 [39]. Only 9 patients died during the 1 to 5-year follow up. Therefore, in "real-world" patients at increased risk of in-stent restenosis with BMS, "off-label" DES implantation might reduce the risk of late complications, particularly in-stent restenosis. However, DES use might lead to acute late stent thrombosis, a serious but relatively rare complication that may be accompanied by in-stent restenosis [39]. In this context, the Drug-Eluting Stents in the Real World (DESIRE) Registry [40] recently reported long-term clinical outcomes from 2,084 patients (28.9% with T2DM and 40.7% with ACS) undergoing PCI with DES (2,864 lesions and 3,120 DES). Target lesion revascularization was performed in 3.3% of the patients during follow-up (2.6 ±1.2 years). The STEMI occurred in only 0.7% of the patients and in-stent thrombosis in 1.6% ($n = 33$). These results also suggest that the use of DES in an unselected population, including a high percentage of diabetic patients, has an acceptable rate of adverse clinical events [40].

Another recent study assessed 508 patients undergoing complete (41.7%) or incomplete revascularization (58.3%) with PCI using DES [41]. During a median follow-up of 27 months, the HR for the primary composite endpoint (cardiac death, MI or repeat revascularization) was 0.43 (95% CI 0.29-0.63, $p < 0.0001$) with complete revascularization compared with incomplete revascularization.

Complete revascularization was also associated with better outcomes in terms of the secondary endpoints: cardiac death, 0.37 (95% CI 0.15-0.92, p = 0.03), cardiac death or MI, 0.34 (95% CI 0.16-0.75, p = 0.008) and any repeat revascularization, 0.45 (95% CI 0.29-0.69, p = 0.0003) [41]. Thus, complete revascularization with DES-PCI in patients with multivessel CHD may be associated with lower rates of long-term adverse events than incomplete revascularization [41].

A recent non-randomized study from China compared CABG (n = 282) with DES-PCI (n = 363) in consecutive diabetic patients with multivessel CHD [42]. At 12 months after the index revascularization procedure, total mortality rates were similar in the CABG and DES group (3.2% vs. 3.0%, respectively; p = 0.46) [42]. However, the rate of major adverse CVD events was lower in the CABG group (7.8% vs. 17.9% in the PCI group; HR 0.15, 95% CI 0.06-0.37, respectively; p < 0.001) mainly due to less repeat revascularization (1.4% vs. 11.6%, respectively; HR 0.02, 95% CI 0.01-0.13, p < 0.001) [42]. The increased rate of repeat revascularization in the PCI group was partly due to the high restenosis rate in diabetic patients [42]. The aforementioned studies are summarized in Table I.

Comment

It is clear that diabetic patients with CHD benefit more than non-diabetic patients from medical treatment alone [2, 43], PCI with DES [2, 33, 34, 40] and CABG [33, 34, 42]. According to a recent report from the ACC [43], the following variables should be considered when deciding on the use of revascularization: a) clinical presentation (ACS or stable angina), b) severity of angina (asymptomatic, Canadian Cardiovascular Society class I, II, III or IV), c) extent of ischaemia on non-invasive testing and the presence of other prognostic factors, such as congestive heart failure or impaired left ventricular function, d) extent of medical therapy, and e) extent of anatomical disease (1-, 2- or 3-vessel disease, with or without proximal left anterior descending artery or left main coronary disease). Revascularization (CABG or PCI according to indications and individual presentation) was considered appropriate in patients presenting with ACS earlier than 12 h after the onset of symptoms as well as in patients with intolerable angina despite appropriate medical therapy and evidence of intermediate- to high-risk findings on non-invasive testing [43, 44].

Another important consideration when comparing revascularization strategies and medical treatment in diabetic patients with CHD is cost-effectiveness. We previously reported in a subgroup analysis of the GREACE (GREek Atorvastatin and CHD Evaluation) study a cost of US $6,200 per quality-adjusted life-year (QALY) gained with aggressive medical treatment vs. usual care in diabetic patients with CHD [45]. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [46, 47], which included 766 diabetic patients (34% of the study population), PCI did not decrease mortality or MI more than optimal medical therapy in patients with stable CHD. A cost-effectiveness analysis in this trial also favoured medical treatment ($6,661 for medical treatment vs. $19,605 for PCI/gained year of life) [47]. In RITA-3 cost-effectiveness analysis [48] showed that, in patients presenting with non-ST elevation ACS who were at high risk for further cardiac events, including patients with diabetes, an early interventional strategy was associated, in 95% of cases, with a gain in QALYs. The additional cost of this intervention was likely to be considered acceptable (at a threshold of $20,000 per QALY) when compared with a conservative strategy [48].

Several studies are designed to compare CABG and DES-PCI in diabetic patients. CABG is the established method of revascularization in diabetic patients with multivessel CHD, but with advances in PCI, there is some uncertainty whether CABG remains the preferred method of revascularization. The CARDia (Coronary Artery Revascularization in Diabetes) Trial [49] was designed to answer this question. The one-year results of CARDia suggest that the primary endpoint (a composite of rate of death, MI, and stroke) was similar in CABG and PCI (both BMS and DES) groups (10.5% vs. 13.0%, respectively, p = 0.39) [49]. All-cause mortality rates were identical (3.2%); however, the rate of the composite secondary endpoint of death, MI, stroke, or repeat revascularization favoured CABG (11.3% vs. 19.3%, HR 1.77; 95% CI 1.11-2.82; p = 0.02, respectively), an effect driven by a higher rate of MI in the PCI group [49]. However, when the patients who underwent CABG were compared with the subset of patients who received DES-PCI (69% of patients), the primary outcome rates were 12.4% and 11.6% (HR: 0.93, 95% CI: 0.51-1.71; p = 0.82), respectively. Thus, the one-year results of CARDia, the first randomized trial of coronary revascularization in diabetic patients, showed that DES-PCI is non-inferior to CABG [49].

Ongoing trials

Several other studies comparing CABG and DES-PCI in diabetic patients are underway, including FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals with Diabetes) [http://www.clinicaltrials.gov.], VA-CARDS (Coronary Artery Revascularization in Diabetes) [http://www.clinicaltrials.gov.] and SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) [http://www.clinicaltrials.gov.]. The results of these

trials are expected to provide valuable information on the appropriate management of very high-risk patients with both CHD and T2DM.

Conclusions

Overall, in patients with DM we should focus on intensive multifactorial intervention aiming at tight blood pressure, glucose and lipid control that can reduce both microvascular and macrovascular complications and improve survival [50-52]. The decision regarding the optimal choice of revascularization procedure in patients with DM remains to be established. Ongoing trials using the latest PCI technology combined with aggressive best medical treatment will hopefully provide clinical guidance.

Acknowledgments

This review was written independently. The authors did not receive financial or professional help with the preparation of the manuscript. The authors have given talks, attended conferences and participated in advisory boards and trials sponsored by various pharmaceutical companies.

Matilda Florentin is supported by a grant from the Hellenic Atherosclerosis Society.

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