

# Coronary artery disease: New Insights into revascularization treatment of diabetic patients

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## Abstract

Diabetes mellitus is an independent cardiovascular risk factor, considered an equivalent of coronary artery disease in terms of prognosis. A history of acute coronary syndrome is a strong predictor of another coronary episode, and cardiovascular complications are the leading cause of mortality in diabetic patients. Many patients with coronary artery disease suffer from concomitant diabetes or pre-diabetes. There are 3 strategies of coronary artery disease treatment: conservative management, coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI). Since drug-eluting stents (DES) were developed, PCI has become one of the most widespread interventional cardiology procedures performed in Europe and worldwide. Among all coronary risk factors, diabetes mellitus remains the most important predictor of unfavorable outcomes of revascularization therapy. This paper reviews the current evidence regarding revascularization in diabetic patients, with particular emphasis on PCI. A systematic analysis of clinical trials of CABG and PCI, especially with DES, was conducted.

**Key words:** stents, diabetes mellitus, coronary artery bypass graft, percutaneous coronary intervention PCI, drug-eluting stent

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A considerable proportion of individuals diagnosed with coronary artery disease suffer from diabetes mellitus or prediabetes. Previous studies have shown that 6–30% of patients with ST segment elevation myocardial infarction (STEMI) are diagnosed with diabetes mellitus on admission to the hospital. This fraction goes up to 50% if the diagnosis is based on an oral glucose tolerance test.<sup>16</sup>

Numerous studies have demonstrated that patients with diabetes mellitus have a 2–3 times higher risk of mortality due to ischemic heart disease than non-diabetic subjects.<sup>16</sup> Diabetes mellitus may remain undetected for a long period of time, and delayed implementation of treatment, not infrequently resulting from painless onset of myocardial infarction or atypical ailments as a consequence of diabetic neuropathy, is a negative prognostic factor in cardiac patients.

Disorders of carbohydrate metabolism worsen the prognosis in patients with myocardial infarction, especially STEMI. Hyperglycemia correlates with an increase in the levels of inflammatory markers, such as pro-inflammatory interleukins and the von Willebrand factor, higher concentrations of free fatty acids and hyperinsulinemia. This results in further progression of ischemia, higher incidence of life-threatening arrhythmias and an increase in the area of myocardial necrosis. Moreover, hyperglycemia, documented either on admission or during hospitalization, is a strong independent negative prognostic factor in acute coronary syndrome, both in patients with diabetes mellitus and in non-diabetic subjects.

## Atherosclerotic lesions in the coronary arteries of diabetic patients

Patients with diabetes mellitus are predisposed for early, systemic and dynamically progressing atherosclerosis, and therefore more frequently require revascularization. Individuals with diabetes mellitus are also at increased risk of multi-vessel coronary artery disease, with a tendency to involvement of the left coronary artery trunk, stenosis of distal arterial segments, the presence of atherosclerotic plaques with vascular thrombosis and calcification. Collateral circulation is usually poorly developed, and no compensatory dilation of arterial lumen is observed in the vicinity of the atherosclerotic plaque. All these disorders predispose patients to worse clinical outcomes of revascularization.<sup>17</sup>

## PCI vs CABG

Coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) with or without stents constitute alternative types of coronary

revascularization. These 2 revascularization methods are among the most widespread interventional cardiology procedures performed in Europe.

CABG remains the treatment of choice in patients with three-vessel disease, stenosis of the left coronary artery trunk and disseminated coronary artery disease, frequently associated with concomitant left ventricular dysfunction. Randomized clinical trials have shown that interventional treatment is associated with longer survival than a conservative approach. Percutaneous intervention is in turn the preferred method of revascularization in most patients with single-vessel disease, as it poses a lower morbidity risk. PCI attenuates the signs of angina and myocardial ischemia in this group of patients.<sup>10</sup>

Patients with diabetes mellitus who have undergone PCI with conventional bare metal stents (BMS) present with both clinical and angiographic evidence of restenosis significantly more often than non-diabetic subjects. Drug-eluting stents (DES) have proven to be safer than metal stents, and their implantation in patients with diabetes mellitus results in lower repeat revascularization rates of the same lesion or vessel than in diabetes-free individuals. Coronary angioplasty is associated with a decrease in intra-hospital mortality and 6-month mortality, from 20 to 7% and from nearly 35 to 12%, respectively.<sup>16</sup>

Randomized trials comparing multi-vessel PCI (with balloon angioplasty or implantation of a metal stent) and CABG have documented the superiority of the latter in patients with diabetes mellitus. CABG resulted in longer survival, a lower incidence of recurrent infarctions and less need for re-intervention in this group of patients.<sup>4</sup>

## Review of clinical trials

The FRISC-II Scandinavian randomized trial comparing invasive and non-invasive treatment of unstable coronary artery disease in a group of approximately 2500 patients documented a significant decrease in the incidence of the primary composite end-point of death and recurrent infarction after revascularization.<sup>1,8</sup>

According to data from the Munich Myocardial Infarction Registry, invasive treatment is associated with a significant decrease in the mortality of patients with myocardial infarction and diabetes mellitus.<sup>17</sup> The aim of the study was to compare the long-term outcomes of PCI and pharmacotherapy in patients with stable coronary artery disease and clinical evidence of myocardial ischemia. The study included more than 7500 patients.

Within the framework of the well-known Bypass Angioplasty Revascularization Investigation (BARI) trial assessing long-term survival in 1829 patients with multi-vessel disease and angina pectoris, a subgroup analysis was conducted to compare the outcomes of PCI and CABG in 353 individuals with diabetes mellitus and multi-vessel disease. The prognosis in patients who

underwent PCI turned out to be worse than in individuals who had surgical treatment; the 7-year survival rates for surgically-treated patients and individuals subjected to PCI were 76.4% and 55.7%, respectively.<sup>1,4</sup>

Notably, similar differences in mortality rates were not documented in the non-randomized BARI registry, which included data from patients in whom the choice of revascularization method was at the physician's discretion.

Another 3 trials comparing the outcomes of CABG and PCI in patients with multi-vessel disease and angina pectoris or clinical evidence of myocardial ischemia, i.e. the Coronary Angioplasty vs Bypass Revascularisation Investigation (CABRI), the Emory Angioplasty vs Surgery Trial (EAST) and the Randomised Intervention Treatment of Angina (RITA-1) confirmed the results of the BARI trial. However, it should be emphasized that all these trials were conducted prior to the implementation of stenting in the PCI protocol (1988–1990), i.e. in the era of balloon angioplasty.<sup>13</sup>

The BARI 2D trial, a large international randomized clinical trial including 2368 patients with a history of diabetes mellitus (10.4 years on average) compared the outcomes of intensive pharmacotherapy and the results of revascularization treatment (PCI or CABG) combined with pharmacotherapy in diabetic subjects with stable coronary artery disease. During a 5-year follow-up, all-cause and infarction-related mortality was significantly lower in persons who had undergone CABG than in individuals who received solely the optimal conservative treatment. However, no significant differences in the incidence of these endpoints were found when individuals who received only pharmacotherapy were compared with those subjected to both PCI and the medical treatment.<sup>2,3</sup>

The results of the Angina With Extreme Serious Operative Mortality Evaluation (AWESOME) trial seem to be inconsistent with the findings of the BARI trial mentioned above. The AWESOME study included solely high-risk patients, i.e. individuals with unstable angina and high surgical risk (after cardiac surgery, with a history of myocardial infarct within the previous 7 days, LVEF < 35%, age > 70 years or subjected to intra-aortic balloon counterpulsation). One third of the patients had concomitant diabetes. The 5-year survival rates for individuals who had undergone CABG or PCI were 34% and 26%, respectively.<sup>1</sup>

The 5-year multicenter SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial included 1800 patients with left main coronary artery (LMCA) disease or multi-vessel disease, randomized to CABG or PCI with DES. A subgroup analysis was conducted within the framework of this study to determine the effect of concomitant diabetes mellitus on the outcomes of PCI and CABG. The 1-year incidence of serious adverse cardio-cerebral vascular events in individuals with concomitant diabetes mellitus who underwent PCI with implantation of a paclitaxel-eluting

stent was twice as high as in diabetic patients subjected to CABG; this difference resulted mostly from a need for repeat revascularization in the former group.<sup>3</sup>

The Arterial Revascularization Therapies Study 2 (ARTS 2) registry of individuals with multi-vessel disease included data from patients with diabetes mellitus who underwent PCI with implantation of a sirolimus-eluting stent (SES), and the ARTS 1 cohort study analyzed diabetics who underwent CABG or PCI with BMS stents. A comparative analysis of these 2 studies demonstrated that the 1-year incidence of adverse events (all-cause mortality, cerebrovascular events, myocardial infarction, repeat revascularization) was markedly lower in the patients subjected to PCI with SES implantation than in the individuals from the CABG group.<sup>5</sup>

Altogether, the evidence from the clinical trials outlined above suggests that patients subjected to various types of revascularization treatment likely do not differ in terms of survival rates. However, patients with concomitant diabetes mellitus more frequently require repeat revascularization and PCI, and restenosis seems to be a significant clinical problem primarily in individuals who undergo coronary angioplasty with BMS implantation.

## PCI with stents

The implementation of drug-coated stents in clinical practice was reflected by better outcomes of percutaneous revascularization in patients with diabetes mellitus. A meta-analysis comparing the effects of drug-eluting stents (DES) and conventional bare metal stents (BMS) in subgroups of diabetic patients participating in a few clinical trials revealed that the use of DES was reflected by an 80% decrease in the relative risk of in-stent restenosis during the first year after the procedure. However, if dual antiplatelet therapy lasted less than 6 months, the mortality rates of DES-implanted patients were significantly higher than in individuals treated with BMS. In contrast, the 2 groups did not differ in terms of mortality rates and the incidence of a composite end-point (death and infarction) if dual antiplatelet therapy was continued longer than 6 months. Moreover, regardless of the duration of antiplatelet therapy, the repeat revascularization rate for the same vessel turned out to be markedly lower after DES implantation than following BMS implantation.<sup>19</sup>

Interestingly, the type of antidiabetic treatment also seems to affect the outcome of revascularization. A large clinical trial comparing the outcomes of everolimus-(EES) and paclitaxel-eluting stent (PES) implantation showed that patients who did not receive insulin were at lower risk of repeat revascularization of the same ischemic lesion after EES implantation; in contrast, the risk for repeat revascularization in individuals receiving insulin therapy was lower after PES implantation.<sup>11</sup>

These findings confirm that antidiabetic treatment, especially insulin therapy, may significantly affect clinical outcomes in patients subjected to DES implantation.

## Drug-eluting stents

Drug-eluting stents are particularly useful in coronary angioplasty in patients with diabetes mellitus. However, although their use is associated with a lower incidence of post-revascularization restenosis, it also results in a greater risk of acute in-stent thrombosis. DES implantation in patients with diabetes mellitus is associated with better angiographic and clinical outcomes than in the case of BMS. Patients treated with DES less frequently present with restenosis or recurrent myocardial infarction, and less frequently require repeat angioplasty.<sup>4</sup>

## Review of further clinical trials

The randomized multicenter trial to assess the use of the cypher sirolimus-eluting coronary stent in acute myocardial infarction treated with balloon angioplasty (TYPHOON) analyzed the safety and efficacy of a sirolimus-eluting stent in 712 patients with acute STEMI, treated with primary PCI with SES or BMS. The study showed that implantation of SES was associated with nearly twice as low 1-year incidence of a composite end-point (death, recurrent infarction, need for revascularization) as in the case of BMS.<sup>20</sup>

The Coronary Artery Revascularization in Diabetes (CARDia) study was the only clinical trial designed to compare the outcomes of CABG and PCI with BMS or DES implantation in patients with diabetes mellitus and symptomatic multi-vessel disease. The study included a total of 510 patients. The overall 1-year incidence of death, infarction and stroke in the CABG and PCI groups were 10.5% and 13% respectively, and the repeat revascularization rate amounted to 2.0% and 11.8%, respectively.<sup>3</sup>

Data from the New York revascularization registry also suggest that the outcomes in diabetic patients who undergo CABG are better than in those subjected to PCI with DES.<sup>2</sup>

The sirolimus-eluting vs paclitaxel-eluting stents for coronary revascularization SIRTAX trial was followed up 5 years later by the SIRTAX-LATE study, both of which involved a group of 1012 randomized patients with coronary artery disease and compared the outcomes of sirolimus- (SES) and paclitaxel-eluting stent (PES) implantation. The incidence of serious cardiac events in patients with diabetes mellitus turned out to be twice as high as among non-diabetics. During the first 5 years after the implantation of the stent, serious coronary events were documented in every 3<sup>rd</sup> patient with diabetes mellitus and in only 15% of non-diabetic subjects. Some evidence suggested that second-generation (SES) stents are better

than first-generation (PES) stents, and the SIRTAX-LATE study showed that SES are superior to PES in patients with diabetes mellitus.<sup>19</sup>

However, neither the Clinical evaluation of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo native coronary artery lesion (SPIRIT), a large meta-analysis of everolimus-eluting stents (EES), nor the COMPARE trial of everolimus-eluting stents and paclitaxel-eluting stents for coronary revascularization in daily practice, comparing the outcomes of everolimus- and paclitaxel-eluting stent implantation, documented any significant differences in the efficacy of the first-generation (PES) and second-generation devices (EES).<sup>19</sup>

The Randomized Evaluation of Sirolimus-eluting vs Everolimus-eluting stent Trial (RESET) was a Japanese prospective multicenter study comparing the outcomes of sirolimus- and everolimus-eluting stent implantation; it included a total of 3197 patients, among whom 45% had concomitant diabetes mellitus. Interestingly, everolimus-eluting stents turned out to be superior to sirolimus-eluting devices in individuals with insulin-dependent diabetes.<sup>11,19</sup>

An American observational prospective trial, RESOLUTE, including 1402 patients, among them 34.4% with diabetes mellitus, compared 2 types of second-generation stents (an everolimus-eluting stent and Resolute, a zotarolimus-eluting stent); the study did not find any significant differences between the 2 devices. Irrespective of the type of implanted stent, the incidence of serious adverse cardiac events was very low, and the incidence of in-stent thrombosis did not exceed 1% per year in either group.<sup>19</sup>

## The new generation of biodegradable stents

Recently, the use of a novel type of device – biopolymer-coated stents – is increasingly being reported. Preliminary evidence suggests that these devices may pose a lower risk of late in-stent thrombosis than conventional DES. DES implantation results in chronic inflammation of the arterial wall, induced by the durable polymer coating of the stent; this eventually leads to thrombosis. In contrast, the surface of the new biodegradable stents, which is exposed after the release of an antiproliferative agent, resembles the surface of conventional bare metal stents; this results in attenuation of the inflammatory process. In 2012, 3 randomized trials comparing the outcomes of treatment with biodegradable stents and sirolimus-eluting DES (ISAR-TEST 3, ISAR-TEST 4 and LEADERS) were analyzed. The meta-analysis, including data from a total of 4062 patients, showed that compared to SES, biodegradable stents have better clinical efficacy and a better safety profile during a 4-year follow-up. Moreover, the use of biodegradable stents was associated with

lower incidence of late thrombosis. However, it is unclear if the incidence of thrombosis was lower when biodegradable stents were compared with second-generation drug-eluting stents; consequently, no definite conclusions on the superiority of the former devices should be formulated until a comparative analysis of the biodegradable stents with second-generation DES has been conducted.<sup>12</sup>

## Conclusions

Diabetes mellitus is an independent cardiovascular risk factor, and cardiovascular complications constitute the leading cause of mortality in diabetic patients. Myocardial revascularization within 14 days of infarction, either STEMI or non-STEMI, results in a 53% and 64% decrease in 1-year mortality of non-diabetic subjects and diabetic patients, respectively.<sup>1</sup> This suggests that individuals with diabetes mellitus may benefit more from revascularization than patients without this condition.

Many studies have demonstrated that CABG is superior to PCI, resulting in longer survival, lower incidence of recurrent infarctions and less need for repeat intervention. Nevertheless, CABG remains the treatment of choice solely in diabetic patients with three-vessel disease, stenosis of the left coronary artery trunk and disseminated coronary artery disease, frequently associated with concomitant left ventricular dysfunction. Consequently, most individuals with diabetes mellitus are subjected to PCI. Diabetic patients are at increased risk of serious cardiovascular events after PCI. Compared to bare metal stents, the use of drug-eluting stents is associated with longer cardiovascular event-free survival and less need for repeat revascularization due to ischemia. Although several large clinical trials have shown that everolimus-eluting stents (EES) are generally safer and more efficient than paclitaxel-eluting stents (PES), this difference is not as evident in the case of diabetic patients. Thus, further research is needed to develop more efficient treatment options for high-risk patients with diabetes mellitus.

Given a choice between cardiac surgical treatment and PCI, diabetic patients are likely to prefer the latter; PCI is less invasive, raises fewer concerns, results in faster improvement of quality of life and a faster return to work, and does not require any specific form of rehabilitation. All this justifies further research on stent improvement. Perhaps biodegradable stents will constitute a solution for diabetic patients with coronary artery disease, and perhaps their use will result in lower rates of restenosis and fewer repeat revascularizations in this group.

Diabetes mellitus is becoming a pandemic and a constant increase in the incidence of this condition is expected. Consequently, awareness should also increase. Progress in research should improve the decision-making process and result in evidence-based optimization of revascularization strategies.

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