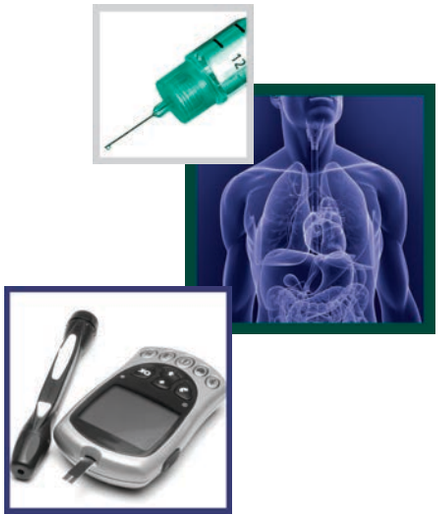
EDITORIAL



Are we overtreating cardiovascular disease in diabetic patients?



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Type 2 diabetes and other constituents of the metabolic syndrome, including dyslipidemia and hypertension, increase the risk of developing atherosclerosis and cardiovascular disease (CVD) [1]. Complications following acute coronary syndrome (ACS) are more prevalent in patients with diabetes compared with the general population. These data have prompted the medical community to treat diabetic patients more aggressively. In this article, we will review the literature and examine whether this approach has been validated for various therapeutic measures.

Glycemic control

Tight control of blood glucose in patients with Type 1 diabetes in the 2005 DCCT trial reduced the risk of heart disease by 42% and the incidence of myocardial infarction (MI) and stroke by 58% [2]. In 1998, the UKPDS demonstrated a 41% decrease in strokes (no statistical significance) and a 39% decrease in the incidence of MI in overweight patients with Type 2 diabetes treated with metformin in the intensive treatment arm compared with conventional treatment ($p = 0.01$) [3]. However, recent large randomized clinical trials have shown conflicting results. The ACCORD, ADVANCE and VADT studies examined diabetic patients whose treatment was aimed at reducing HbA1c levels to either below 6% (tight control arm) or between 7 and 7.9%. The three studies observed a slight (6–13%) decrease in the incidence of cardiovascular (CV) events in the tight control arm with no statistical significance [4–6]. The ACCORD study was stopped prematurely after 3.5 years due to a 22% excess in overall mortality and a 35% excess in CV mortality in the tight control arm. By contrast, the ADVANCE study showed a 12% reduction in mortality rates in the tight control arm compared with 7% in the other arm, which was not statistically significant.

The effect of glycemic control in acute MI has been studied. In the DIGAMI study, diabetic patients who presented with acute MI were treated with either routine or intensive glycemic control. A significant reduction in mortality within 3 years was found in the intensive control group compared with the routine control group, especially in those patients not treated with insulin before hospitalization [7]. The DIGAMI-2, however, showed no

> "...despite extensive investigations during the last two decades, the evidence that glycemic control may prevent cardiovascular events is scarce and controversial."

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difference between the intensive and routine treatment arms [8].

In conclusion, despite extensive investigations during the last two decades, the evidence that glycemic control may prevent CV events is scarce and controversial. This is true in diabetic patients treated for acute conditions, such as MI, as well as in chronic care.

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Antiplatelet aggregation in patients with diabetes

■ Aspirin

Secondary prevention

There is consensus regarding the effectiveness of aspirin in secondary prevention of CV events in the entire population, including diabetic patients [9].

Primary prevention

Diabetic patients benefited less from low-dose aspirin therapy for primary prevention of CVD compared with patients with other CV risk factors [10]. In a recently published meta-analysis, aspirin was compared with placebo [11]. There were no clear conclusions; men experienced a decrease in the risk of cardiac events (risk ratio: 0.57), but not women (risk ratio: 1.04). In a group of patients at low risk (less than 20% risk for 10 years) and patients over the age of 70 years, the decrease in CV events (the benefit from treatment) was similar to the rate of major bleeding complications. In addition, the Antithrombotic Trialists' (ATT) Collaboration concluded that, for primary prevention without previous disease, aspirin was of uncertain net value and the reduction in occlusive events needed to be weighed against any increase in major bleeds [9].

■ Clopidogrel

In the CURE trial, clopidogrel reduced the rate of cardiac events by approximately 21% compared with placebo in patients with acute coronary syndromes treated with aspirin [12]. In subgroups of patients at high risk, such as those with diabetes, there was a tendency towards benefit from clopidogrel with no statistical significance.

■ Prasugrel

The TRITON study, conducted in patients who had experienced an acute cardiac event, detected an 18% decrease in all cardiac events in patients treated with prasugrel compared with clopidogrel (all patients were treated with aspirin). Among diabetic patients, a 40% decrease in recurrent cardiac events was observed [13].

■ Ticagrelor

The PLATO study found that ticagrelor, used as an adjunct to aspirin in patients with ACS, was more efficient than clopidogrel and aspirin in reducing cardiac events, strokes and deaths, and had no excess bleeding [14]. In a subanalysis of the study, 4662 diabetic patients demonstrated a benefit from ticagrelor that was similar to that of nondiabetic patients (hazard ratio: 0.82 for death from any cause and hazard ratio: 0.65 from stent thrombosis compared with clopidogrel) without an increase in bleeding events [14].

■ Conclusion

Aspirin is accepted for secondary prevention of CV events in the entire population, including diabetic patients. Surprisingly, primary prevention has not been proven to be efficacious in this group of patients who are at a higher risk and have a greater need for protection. Studies currently underway, including the ASCEND and ACCEPT-D, are expected to shed more light on this subject by 2017. In the meantime, the American Diabetes Association (ADA), American College of Cardiology (ACC) and American Heart Association (AHA) currently recommend the following: in diabetic patients who are at an increased risk of CV events (risk more than 10% for 10 years) aspirin should be considered; and in young patients with multiple risk factors, clinical judgment must be exercised, and aspirin is not recommended in young diabetic patients with no risk factors [10].

The importance of clopidogrel is indisputable; however, in diabetic patients, drug resistance to clopidogrel is common during acute CV events. Therefore, this medication has given way to more effective and predictable P2Y12 receptor blockers such as prasugrel and ticagrelor. Clopidogrel remains a substitute for patients in whom the other agents cannot be used.

Dyslipidemia

Statin intervention trials demonstrated a reduction in CV events in the subgroups of diabetic patients similar to that found in the entire group [15]. Primary prevention statin trials included relatively small numbers of diabetic patients. The HPS showed that treating patients at high risk with simvastatin 40 mg daily was beneficial in all subgroups, including diabetic patients [16].

The CARDS trial showed the benefit of statin therapy for primary prevention in diabetic patients whose LDL cholesterol levels were 4.14 mmol/l or lower [17].

Revascularization

■ Diabetic patients with acute ST-elevation MI

Primary angioplasty reduced mortality in diabetic patients at a rate almost twice that of thrombolytic therapy [18]. Therefore, diabetic patients might be considered a special population in which primary angioplasty is recommended even more than in the general population.

■ Diabetic patients with non-ST-elevation ACS

In the TACTICS study, patients with non-ST-elevation (NSTE)-ACS (unstable angina or a non-ST-elevation MI) were randomized to primary percutaneous coronary intervention (PCI) or conservative treatment. Among diabetic patients, revascularization greatly reduced the cardiac events rate: 20.1% events in PCI patients compared with 27.7% in patients treated conservatively (27% relative reduction). Despite the fact that the natural history of coronary disease in diabetic patients who undergo ACS involves more CV events, PCI reduces mortality in these patients equally or even to a greater extent than in nondiabetic patients [19].

■ Diabetic patients with stable angina

The BARI and other studies concluded that elective coronary artery bypass graft (CABG; but not PCI) in diabetic patients improves prognosis compared with standard therapy [20]. A 10-year follow-up of a group of diabetic patients in the BARI study showed 57.8% survival after CABG compared with 45.5% in patients who underwent angioplasty (p = 0.025) [21].

In the BARI-2D study [22], 2368 patients with Type 2 diabetes and angina pectoris were randomized to invasive (percutaneous or surgical according to the treating team preference) versus conservative treatment. After 5 years of follow-up, there was no difference in mortality between angioplasty and medical therapy (88.3 vs 87.8%; p = 0.97).

In the COURAGE study, in which a third of the patients had diabetes, there was no significant difference in long-term outcomes between patients who received PCI or medical treatment [23]. More studies are underway to compare PCI using drug-eluting stents to CABG, including the Freedom trial, which is planned to include approximately 2000 patients with multivessel coronary disease who have an indication for revascularization.

■ Conclusion

In conclusion, primary PCI is the treatment of choice in all patients undergoing acute ST-elevation MI. It decreases mortality in diabetic patients by almost 50% compared with thrombolytic therapy. Therefore, in this group it is recommended even more strongly than in the general population. PCI reduces mortality in diabetic patients with NSTE-ACS at least as well as in nondiabetic patients. Patients with stable angina may be treated medically and referred for revascularization when medical treatment does not control their symptoms. Diabetic patients with diffuse coronary artery disease seem to benefit from CABG in terms of freedom from MI and combination of death, MI or stroke [22].

Heart failure in diabetic patients

The risk of developing heart failure is twice as high among men and five-times as high in women with diabetes compared with healthy age-matched peers [1]. Diabetic cardiomyopathy is a term that relates to changes in the structure and function of the myocardium in diabetic patients regardless of the existence of coronary artery disease or hypertension. It is manifested first with diastolic dysfunction [24], and systolic failure occurs at a later stage. The rate of developing new heart failure in diabetic patients is approximately 3.3% per year, 1.3-times greater than that of the general population [25]. In the ACC/AHA guidelines, the very existence of diabetes in an asymptomatic patient without structural heart disease defines him/her as being at high risk of developing heart failure [26]. The 5-year survival in patients with heart failure is 37% in patients with and 46% in patients without diabetes (p = 0.017) [14].

The treatment of heart failure in diabetic patients is similar to that recommended for nondiabetic patients and the clinical response to treatment is also similar [27,28]. The ACE inhibitor ramipril reduced the risk of MI, death and stroke, and the incidence of new heart failure in diabetic patients enrolled in the micro-HOPE study [29]. Angiotensin receptor blockers (ARBs) were found to be effective compared with

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placebo in reducing hospitalizations for heart failure in diabetic patients [30]. Administration of ACE inhibitors and ARBs to patients with hypertension and ischemic heart disease was shown to arrest new-onset diabetes [31], as well as the development of proteinuria, chronic kidney disease and CV events. There is currently no specific treatment for diabetic cardiomyopathy.

In conclusion, heart failure in diabetes is caused by the combination of coronary disease (the primary and most common factor), small coronary artery disease, high blood pressure and left ventricular hypertrophy. Its treatment is similar to that for nondiabetic patients and similarly effective, with a special role for ACE inhibitors and ARBs.

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Conclusion

Most therapeutic measures mentioned above are efficacious in preventing and treating CVD in diabetic patients and consequently improving their prognosis. These measures include: aspirin and statins for secondary prevention; prasugrel and ticagrelor in ACS; clopidogrel in ACS in a subpopulation of diabetic patients (those who are responsive to the drug); PCI during ST-elevation MI and NSTE-ACS; CABG in high-risk diabetic patients with stable coronary artery disease; and ACE inhibitors and ARBs in heart failure. In addition, PCI is effective for relieving angina in patients resistant to medical therapy.

A few measures have not proven to be clearly efficacious in improving diabetic patients' prognosis. These include tight glycemic control (both during acute MI and as a chronic treatment), aspirin for primary prevention and PCI for stable coronary disease. Are we overtreating diabetic patients with glycemic control, aspirin and PCI? Not necessarily; glycemic control is important for microvascular complications, the fulminant atherothrombotic process in diabetes might need a combination of aspirin and other antiplatelet agents rather than avoiding aspirin, but this hypothesis needs to be proven, and PCI does improve stable angina pectoris in diabetic patients, but must be confined to patients whose angina is not controlled with medications and in whom the risk of CABG exceeds the benefit.

In conclusion, when carried out according to evidence-based clinical guidelines, treatments of CVD in diabetic patients are adequate. Further investigation and understanding of the complex mechanisms involved in atherothrombotic processes in patients with diabetes should lead to even more efficient and comprehensive treatments.

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