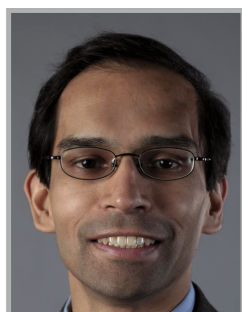


Cardiovascular complications in diabetic patients



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Q Why are diabetic patients at increased risk of myocardial infarction?

■ Mosseri & Raz:

Diabetes mellitus (DM) contributes to atherosclerosis via a combination of metabolic factors, protein glycation and the release of cytokines via the inflammatory process. This results in endothelial dysfunction and a decrease in nitric oxide secretion, which promotes invasion of macrophages and oxidized low-density lipoprotein (LDL) into the vessel wall, formation of the lipid pool and proliferation of smooth muscle cells. The decrease of nitric oxide further induces vasoconstriction and a pro-thrombotic state; both play an important role in acute coronary syndromes including acute myocardial infarction (MI).

■ Bhatt:

Diabetic patients are at significantly higher risk of MI than nondiabetic patients [1,2]. There are several postulated mechanisms for this increased risk. Diabetic patients appear to have platelets that are more reactive to thrombotic stimuli. They also appear to have impaired indigenous fibrinolysis. Glycation of various proteins may also contribute to the elevated atherogenic risk.

Q Are there any other cardiovascular conditions that affect diabetic patients more than nondiabetic patients?

■ Mosseri & Raz:

In addition to atherosclerosis and acute coronary syndromes, diabetic patients are affected by the following conditions:

Diabetic cardiomyopathy

This term relates to structural and functional changes in the myocardium of diabetic patients not secondary to coronary

artery disease or hypertension. Among implicated mechanisms are disturbances in intracellular calcium, activation of the renin–angiotensin–aldosterone system, oxidative stress, metabolic changes and mitochondrial dysfunction. The histological finding is interstitial and perivascular deposition of collagen that undergoes glycation and crisscross linking, with resultant stiffening of the myocardium. The initial clinical presentation is diastolic dysfunction followed by systolic dysfunction.

Congestive heart failure

Congestive heart failure is more prevalent in diabetic patients compared with nondiabetic patients. Contributors to congestive heart failure in diabetic patients include epicardial coronary artery disease, small coronary artery disease, diabetic cardiomyopathy and hypertension with left ventricular hypertrophy.

Cardiac autonomic neuropathy

Damage to the autonomic innervations of the heart occurs in 40–50% of diabetic patients. It may be responsible for an increased pain threshold and silent ischemia. When manifested with disturbed heart rate variability it is related to advanced coronary artery disease. QT prolongation is a manifestation of diabetic cardiac autonomic dysfunction and might explain sudden death in some patients. Sinus tachycardia due to autonomic dysfunction is also prevalent in diabetic patients.

■ Bhatt:

In addition, patients with DM often have dyslipidemia and hypertension, which are known risk factors for heart disease. In

addition to their increased risk of MI, diabetic patients are also at increased risk of stroke and peripheral arterial disease.

Q Recent research has suggested that even people under the age of 25 years with diabetes are at a significantly increased risk of heart attack, how may this affect their lifestyle compared with nondiabetic peers?

■ **Mosseri & Raz:**

Such young patients generally have Type 1 DM. These patients are at especially increased cardiovascular risk. However, since their DM is relatively new, their vascular damage may be miniscule, and therefore, preventive treatment might be very effective. Indeed, this is the only group in which tight glycemic control proved to decrease cardiac risk by 42% and MI or stroke by 58% in the Diabetes Control and Complications Trial study [3]. Smoking by itself has been known to be a marked risk factor for developing cardiovascular disease in the general population and even more so in Type 1 DM patients. It is conceivable that lifestyle modification in these young patients would be beneficial, but the clinical evidence is still lacking.

■ **Bhatt:**

It is important to treat DM with lifestyle modification as soon as it is diagnosed – ideally, even before the diagnosis of established DM is made. It does appear that in certain parts of the world, Type 2 DM is affecting even younger people than had been the case in the past. This phenomenon puts them at risk of MI at younger ages. Type 1 diabetic patients are also at risk for MI. Nevertheless, in absolute terms, the risk of MI in those under 25 years of age is very low.

Q What lifestyle changes can diabetic patients make to lower the risk of cardiovascular disease?

■ **Mosseri & Raz:**

Lifestyle changes recommended to the general population are even more important in diabetic patients because they are at increased risk. Lifestyle changes include low carbohydrate diet, low saturated fat diet and physical activity. Both help to reduce bodyweight, which is required among diabetic patients. In

addition, both are of particular importance in improving lipid profile, namely: decreasing triglycerides, increasing high-density lipoprotein and decreasing LDL. Physical activity and low salt diet help control hypertension – another sequel of insulin resistance. Smoking cigarettes doubles cardiovascular risk and therefore smoking cessation is another important component in lifestyle modification in the diabetic patient.

■ **Bhatt:**

The key lifestyle change involves loss of excess weight. In many cases, this can even prevent the development of Type 2 DM. Excess truncal obesity in particular appears to be a risk for development of DM. Control of common concomitant cardiovascular risk factors, such as hypertension and dyslipidemia, is very important.

Q Are there any pharmacological preventative treatments for diabetics at risk of heart complications?

■ **Mosseri & Raz:**

Pharmacological preventative treatments in diabetic patients are those which are aimed at controlling cardiovascular risk factors, specifically statins for hypercholesterolemia and medications to control hypertension (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are of particular importance in diabetics). Fibrates and niacin are effective in lowering triglycerides and increasing high-density lipoprotein.

The only antiglycemic medication that demonstrated promise to reduce cardiovascular complications in 342 obese Type 2 patients is metformin, in the UK Prospective Diabetes study [4]. During the past years the Action to Control Cardiovascular Risk in Diabetes, Action in Diabetes and Vascular Disease and Veterans Affairs Diabetes Trial studies failed to prove that intensive glycemic control is beneficial in prevention of macrovascular disease, including cardiac disease [4–7]. Recently, Phase II/III studies with Saxagliptin demonstrated reduced cardiovascular events, but these studies were not powered for cardiovascular end points. A large outcome multicenter study (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus trial) is currently underway.

■ **Bhatt:**

Lifestyle modification is the key to preventing DM. Weight control, through a proper diet and exercise regimen, is the safest and most effective way to prevent DM.

Q **Which of the previously mentioned treatment strategies does current research most strongly support?**

■ **Mosseri & Raz:**

Statins are probably the most established and important preventative strategy. The target LDL level in diabetic patients with cardiovascular disease should be below 70 mg% – similar to patients with known ischemic heart disease. However, global treatment of all risk factors is the most effective strategy. The STENO-2 study examined treatment of diabetic patients with a combination of aspirin and medications to reduce blood glucose, blood pressure and cholesterol blood levels. It demonstrated decreased cardiovascular events by 59%, cardiovascular mortality by 57% and total mortality by 46% [8].

■ **Bhatt:**

Statins are beneficial in the majority of patients with DM. Antiplatelet therapy is beneficial in diabetic patients with documented atherosclerosis in any arterial bed; it may have a broader role in diabetic patients who do not have documented atherosclerosis, a topic of an ongoing clinical trial [9,10]. Blood pressure control seems to be important, although it is not clear whether more aggressive blood pressure targets compared to what current guidelines suggest are beneficial for further reducing MI risk. Glycemic control – if accomplished without inducing hypoglycemic episodes – may be important for reducing cardiovascular risk, although it is not yet clear what might be the optimal target [11].

Q **Is there any difference in mortality risk in diabetic patients who suffer a heart attack as compared with nondiabetic patients experiencing heart attack?**

■ **Mosseri & Raz:**

In the Minnesota Heart Study, the case fatality rate after acute MI over 5 years was significantly higher in diabetic than in nondiabetic patients, both in men and women.

This survey also suggested that case fatality rate may be higher in diabetic women than in diabetic men [12,13].

■ **Bhatt:**

Older data suggested that the future cardiovascular risk of a patient with DM without a prior MI equalled that of a nondiabetic patient with a previous MI. The most contemporary data, however, do not support that contention [1]. In fact, patients with a history of MI are at much higher risk of a future MI than patients with DM without a prior MI. Of course, the highest risk patients are those with both DM and also a prior MI. Despite the high risk of patients with DM who sustain a MI, registry data indicate that they are undertreated [14].

Q **Does recovery from myocardial infarction differ between diabetics & nondiabetics?**

■ **Mosseri & Raz:**

The complication rate after acute MI in diabetic patients is higher than in the general population, and includes recurrent MI during hospitalization for symptomatic MI, congestive heart failure during and after hospitalization, and decreased life expectancy [15,16].

■ **Bhatt:**

Patients with DM tend to have a worse prognosis following a MI. They are more likely to sustain complications such as contrast nephropathy in the hospital and more likely to have recurrent ischemic events during follow-up. Both procedural care (coronary angiography, angioplasty/stenting and coronary artery bypass surgery) and medical care tend to be underutilized in diabetic patients with acute coronary syndromes [17].

Q **How is research in this area likely to develop over the next 5 years?**

■ **Mosseri & Raz:**

Since atherosclerosis and macrovascular complications in diabetic patients starts before the manifestation of clinical DM, and since intensive glycemic control does not prevent these complications, research is focusing on developing measures to prevent Type 2 DM, and treat other risk factors aggressively in prediabetic conditions.

An effort is being made to develop medications to control blood glucose levels that would also reduce weight, control hypertension and decrease cardiovascular events. Ease of use and safety aspects (e.g., minimizing risk of hypoglycemia) are prerequisites for such drugs. DPP-4 inhibitors and GLP1 analogs are potential candidates and are currently under investigation.

■ Bhatt:

There are several trials that are examining whether novel drugs for DM reduce the risk of ischemic events. If any of these are positive, it would be a significant advance in reducing the excess cardiovascular risk of diabetic patients. Even if these trials do not find a reduction in cardiovascular risk, if they are able to demonstrate lack of cardiovascular risk while maintaining the ability to reduce microvascular outcomes, that would still be an important step forward. Bariatric surgery appears to be very promising in improving glycemic control in obese Type 2 diabetic patients; its exact role in improving cardiovascular outcomes

will depend on ongoing studies [18]. More potent antiplatelet agents may have a particular role in diabetic patients, and ongoing studies may provide insight.

Financial & competing interests disclosure

I Raz is a member of the Advisory Board for: Novo Nordisk, AstraZeneca, Bristol-Myers Squibb, MSD and Eli Lilly. I Raz is a consultant for: AstraZeneca, Bristol-Myers Squibb, Johnson & Johnson, Eli Lilly, (Andromeda, Heal-or, Insuline, Trans-pharma, Teva-Israeli firms). Speaker's Bureau: Eli Lilly, Novo Nordisk, AstraZeneca, Roche and Johnson & Johnson. I Raz is also involved with the SAVOR study, sponsored by AstraZeneca. DL Bhatt has received research grants from AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis and The Medicines Company. DL Bhatt is also co-PI of SAVOR-TIMI 53. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

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