Diabetes: is it enough to control blood glucose?
Heart and Metabolism is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications.

Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.
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The prevalence of diabetes in adults worldwide was estimated to be 2.8% in 2000 and is expected to grow to 4.4% by the year 2030, with the number of adults with the disease rising from 171 million to 366 million within that time frame. The greatest relative increase will occur in the Middle Eastern Crescent, sub-Saharan Africa, and India. In developing countries, the majority of people with diabetes are relatively young, currently 45-64 years of age, in contrast to the diabetic population in developed countries, where most are at least 65 years of age. This pattern is likely to be accentuated by the year 2030. In association with increasing diabetes prevalence, increasing proportions with cardiovascular disease–related morbidity and mortality will inevitably result. The risk of myocardial infarction (MI) in diabetic patients with no previous MI is similar to nondiabetic patients that have a history of MI. Indeed, whereas the 7-year incidence rate of MI in nondiabetics with a history of MI at baseline is 18.8% (vs 3.5% in nondiabetics with no prior MI; $P<0.001$), the rate in diabetics with no prior MI is 20.2% (vs 45% in diabetics with prior MI at baseline; $P<0.001$).

Notably, vascular atherosclerotic disease in diabetics differs in several aspects from disease in nondiabetics. In diabetics, atherosclerotic involvement of arteries tends to be more diffuse, to extend to smaller vessels, and to develop earlier. Also, plaques exhibit a larger lipid-rich atheroma, greater macrophage infiltration, and more thrombosis. Furthermore, clinical manifestations of vascular atherosclerotic disease occur more frequently, present with greater severity, and carry a worse prognosis than in nondiabetics.

Accordingly, diabetes is regarded as a major risk factor for cardiovascular adverse events and a key target in preventive strategies. Unfortunately, as it clearly emerges from articles in this issue of *Heart and Metabolism*, data so far are less than encouraging. Standard antidiabetic therapies offer no protection from cardiovascular events, aggressive antidiabetic therapies are no better than standard therapies, and revascularization procedures leave diabetics at much greater risk of adverse events than nondiabetics.

A better understanding of the mechanisms of myocardial ischemia in diabetics appears necessary and urgent if we are to improve this disappointing scenario. Diabetics have an increased prothrombotic milieu, they present with diffuse and severe microvascular dysfunction, and they have an abnormal cardiac energy metabolism; these mechanisms may all contribute to precipitate ischemia and worsen the prognosis. Given this complexity of the pathogenesis of myocardial ischemia, it is naive to expect major improvements in clinical outcomes to result from inno-
vations in catheter-based techniques or from better control of plasma glucose levels.

A more comprehensive approach to ischemic heart disease is necessary, one that takes into consideration nonatherosclerotic and nonvascular mechanisms contributing to myocardial ischemia, including agents that optimize cardiac energy metabolism (ie, trimetazidine).

REFERENCES

Diabetes and ischemia: similarities in cardiac energy metabolism

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Abstract
Ischemic heart disease (IHD) and diabetes mellitus (DM) are leading causes of death worldwide. Cardiac energy metabolism is profoundly altered in both of these conditions, which can lead to permanent cardiac pathologies that include heart failure and diabetic cardiomyopathy. Diabetic hearts show an increased dependence on oxidation of fatty acids for the production of adenosine triphosphate (ATP) accompanied by an impairment of glucose oxidation. Such features resemble to a large extent the metabolic phenotype of the ischemic heart during ischemia and reperfusion. Likewise, ischemic myocardium displays the insulin insensitivity that typically exists in the diabetic heart. Other common features include reduced circulating levels of adiponectin, a cardioprotective adipokine, and an enhanced state of acetylation of specific lysine residues in enzymes and transcription factors that are essential in energy metabolic processes. Recognizing cardiac metabolism similarities between DM and IHD should help to devise and optimize metabolic modulatory therapies for comorbidity patients. ■ Heart Metab. 2015;68:4-8

Keywords: cardiac efficiency; diabetes; energy metabolism; heart; ischemia

Under normal aerobic conditions, fatty acid oxidation contributes around 70% of cardiac energy production, with the remainder being mainly provided by the oxidation of glucose.1 Fatty acids and glucose compete at several regulatory points and although fatty acid oxidation has a greater potential to produce adenosine triphosphate (ATP) compared with glucose, this comes at the expense of using more oxygen.2 In addition to the lower ATP/oxygen ratio, other mechanisms—such as mitochondrial fatty acid uncoupling and futile fatty acid cycling into and from triacylglycerol (TAG) stores—contribute to a decreased efficiency of fatty acids as energy substrates compared with glucose. As such, a greater reliance on the oxidation of fatty acids can decrease cardiac efficiency, especially under conditions of limited oxygen supply or increased workloads.1

Cardiac energy metabolism is markedly altered in both ischemic heart disease (IHD) and diabetes mellitus (DM).1 Such metabolic derangements contribute to the severity of cardiac disease. In IHD, alterations in cardiac energy metabolism contribute to the severity of the ischemic injury, whereas in DM, they can play a role in the pathophysiology of diabetic cardiomyopathy (a myocardial pathology occurring in DM that predisposes the patients to heart failure independent of vascular factors).3 In both the diabetic and ischemic heart, there is an increased reliance on mitochondrial oxidation of fatty acids compared with carbohydrates, which contributes to cardiac inefficiency and contractile dysfunction.1,3 As a result, modulation
of cardiac energy metabolism to directly or indirectly increase glucose oxidation and/or decrease fatty acid oxidation can improve heart function in IHD and DM.1

This review will focus on the similarities between metabolic profiles of ischemic and diabetic hearts, as well as metabolic modulatory approaches that are potentially beneficial.

**Energy metabolism in ischemia/reperfusion injury**

Alterations in myocardial energy metabolism during and after ischemia occur in response to acute changes in oxygen availability, as well as to changes in the exposure of the heart to circulating energy substrates and to direct deregulation of cardiac energy production processes. Due to limitations in oxygen supply, the ischemic heart increases its reliance on anaerobic glycolysis for ATP production. Unfortunately, simultaneous reductions in glucose oxidation causes an accumulation of lactate and protons in the myocardium, thus contributing to the waste of the already depleted ATP in rectifying ionic imbalances brought about by ischemia.4

During reperfusion (eg, by thrombolysis or revascularization), fatty acid oxidation becomes the predominant energy source and significantly outmatches glucose oxidation.1,4 This is mainly attributed to increased availability of circulating fatty acids accompanied by a reduced myocardial uptake of glucose secondary to sympathetic discharge, which stimulates lipolysis from adipose tissue and decreases insulin secretion and sensitivity.4 Furthermore, during ischemia, the concentration of cardiac malonyl-Coenzyme A (malonyl-CoA), an inhibitor of fatty acid β-oxidation through its action on carnitine palmitoyltransferase I (CPT I), dramatically decreases as a result of decreased synthesis and maintained degradation (Figure 1).5 The resultant increase in fatty acid oxidation inhibits glucose oxidation by depressing the activity of the rate limiting enzyme of glucose oxidation, pyruvate dehydrogenase (PDH).4 This occurs while glycolysis is not proportionally suppressed, leading to lactate and proton production that contributes to contractile dysfunction.1,4,5

**Energy metabolism in the diabetic heart**

The diabetic heart is overly reliant on fatty acid oxidation as a source of energy, due to elevated levels of circulating fatty acids and upregulation of proteins involved in fatty acid uptake, transport, and oxidation.1 While some of these alterations occur secondary to defective insulin signaling,6 others are a result of local myocardial derangements.3 This includes increased expression of lipoprotein lipase (which liberates free fatty acids from circulating TAG) in states of insulin resistance. Increased lipid accumulation, such as diacylglycerols (DAG), therefore occurs, which may lead to decreased cardiac efficiency and function.

**Abbreviations**

ACC: acetyl-Coenzyme A carboxylase; DM: diabetes mellitus; I/R: ischemia/reperfusion; IHD: ischemic heart disease; MCD: malonyl-Coenzyme A decarboxylase; MI: myocardial infarction; PDH: pyruvate dehydrogenase;

Diabetes and ischemia: similarities in cardiac energy metabolism

**Fig. 1 Cardiac energy metabolism similarities in diabetes and ischemic heart disease.** Diabetic and ischemic hearts share many metabolic characteristics produced by collaborating and interconnecting pathways and mechanisms. The hallmark of diabetic and ischemic/reperfused hearts is the increased metabolism of fatty acids, particularly β-oxidation, which in the face of impaired glucose oxidation and insulin sensitivity can lead eventually to reduced cardiac efficiency and function. Also, circulating adiponectin, a “good” adipokine, is reduced in both diseases, thus contributing to insulin resistance and cardiac dysfunction. Additionally, the lysine acetylation status of myocardial proteins is generally increased and may contribute to and result from the increased reliance on fatty acid as an energy substrate.

**Abbreviations:** ACC, acetyl-Coenzyme A carboxylase; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; CoA, Coenzyme A; FA(s), fatty acid(s); MCD, malonyl-Coenzyme A decarboxylase; PPAR, peroxisome proliferator-activated receptors.
lipotoxicity-induced cardiac dysfunction and diabetic cardiomyopathy. Altered regulatory processes of fatty acid $\beta$-oxidation also contribute to the increased fatty acid $\beta$-oxidation in the diabetic heart. This includes a decrease in cardiac malonyl-CoA levels, as well as upregulation of several proteins involved in fatty acid $\beta$-oxidation. Of note, fatty acids are natural ligands of peroxisome proliferator–activated receptors (PPARs), thus increasing their activity in the fatty acid–overwhelmed diabetic myocardium. Enhanced uptake and oxidation of fatty acids results in inhibition of glucose uptake and utilization by the heart, which are typical characteristics of DM. PPAR-$\alpha$ also enhances the expression of PDH kinase 4 (PDK4), which phosphorylates and deactivates PDH. Furthermore, PPAR-$\alpha$ expression appears to indirectly correlate with the main cardiac glucose transporter, GLUT4, thus decreasing both glucose uptake and oxidation.

What is common between ischemia and diabetes mellitus?

Common metabolic aspects of DM and IHD include: (i) elevated levels of circulating fatty acids as a result of different, but related, hormonal perturbations, (ii) decreased myocardial malonyl-CoA levels, through distinct processes that eventually produce a similar effect of accelerated mitochondrial uptake and oxidation of long-chain fatty acids, and (iii) a prevailing state of blunted glucose oxidation, by virtue of either temporary (eg, ischemia/reperfusion [I/R]) or long-lasting (eg, DM) insulin resistance that includes PDH inhibition.

Other similarities also exist. For example, protein acetylation, a posttranslational modification, is globally increased in I/R mouse hearts. This is attenuated by activation of NAD$^+$-dependent histone deacetylases, which translates into cardioprotection. Increased acetylation is also seen in the diabetic heart. Key mitochondrial proteins involved in fatty acid $\beta$-oxidation are hyperacetylated with a concomitant increase in their activities and in total fatty acid $\beta$-oxidation rates.

Another shared feature is the level, and effects of, circulating adiponectin, an adipokine that plays a key role in preventing and ameliorating insulin resistance and cardiovascular dysfunction. Circulating and cardiac levels of adiponectin and myocardial expression of cardiac adiponectin type 1 receptors are diminished in diabetic rats and negatively correlate with deterioration of cardiac structure and function with positive correlation to systemic glycemic control. Interestingly, circulating adiponectin is also reduced in coronary artery patients.

Pharmacological therapies targeting energy metabolism in DM and IHD

A potential therapeutic approach to treating both DM and IHD involves inhibition of fatty acid oxidation, which can have beneficial effects on cardiac efficiency and function. Indeed, a number of pharmacological metabolic modulators function by tilting the balance toward cardiac glucose oxidation and away from fatty acid oxidation.

Glucose-insulin-potassium therapy

Glucose-insulin-potassium (GIK) therapy is an approach based on resisting ischemic injury by rectifying glucose/insulin defects that typically occur in DM. The beneficial effects of GIK therapy on cardiac infarct size and postsischemic function are associated with increased rates of glycolysis and reduced levels of circulating fatty acids. GIK was shown to reduce mortality rates post–myocardial infarction (MI) and to reduce the composite of 1-year cardiac arrest or mortality, as well as the composite of 1-year cardiac arrest, mortality, or heart failure hospitalization. A study in diabetic MI patients showed GIK to effect a more stable cardiac index and blood potassium level, a shorter time on mechanical ventilation, less atrial fibrillation, and better glycemic control. However, other trials failed to demonstrate GIK cardioprotection, possibly due to potentiation of myocardial acidosis by disproportionally stimulating glycolysis compared with glucose oxidation.

Trimetazidine

Trimetazidine is an anti-anginal drug that directly decreases fatty acid oxidation, thereby indirectly stimulating glucose oxidation. It reduces angina attacks and nitrate consumption, and improves exercise tolerance. Trimetazidine has been shown to ameliorate cardiac dysfunction in db/db diabetic mice. It is highly recommended that trimetazidine be considered when treating diabetic patients with IHD.
Etomoxir

Etomoxir is an irreversible inhibitor of CPT I, originally designed to treat DM. It promotes the metabolic switch toward glucose oxidation and improves cardiac function post ischemia and in diabetic hearts, suggesting a potential benefit in diabetic cardiomyopathy. However, although etomoxir improved the ejection fraction and cardiac output in a small clinical trial in heart failure patients, it was associated with liver toxicity, probably due to its irreversible inhibition of CPT I, which necessitated discontinuation of the study.

PPAR-γ agonists

Thiazolidinediones (TZDs) are antidiabetic drugs that inhibit oxidation of fatty acids in the heart through reducing their circulating levels secondary to their effect on adipose tissue, where their target, PPAR-γ, has the highest expression and where they increase the sequestration of fatty acids and TAG. TZDs increase myocardial glucose uptake and oxidation and preserve postischemic cardiac function in animal models of DM. However, the use of TZDs was reported to increase the risk of MI and exacerbate heart failure in type 2 DM patients, probably as a result of their adverse effects, eg, fluid retention and peripheral edema, lipid profile derangement, and antagonism of angiogenesis.

Malonyl-Coenzyme A decarboxylase inhibitors

Malonyl-Coenzyme A decarboxylase (MCD) inhibitors produce the favored metabolic shift in normal and ischemic hearts and potentiate insulin sensitivity secondary to elevating myocardial malonyl-CoA levels and CPT I inhibition. MCD inhibitors are cardioprotective against ischemia and control blood glucose concentration in rodents.

Conclusion

IHD and DM share a number of energy metabolism similarities. Several biochemical and pathophysiological features converge to increase the reliance on fatty acid β-oxidation, accompanied by deregulated insulin and adipokine actions that favor a state of compromised cardiac efficiency, structure, and function. It is therefore important to identify the major similarities and differences among cardiac metabolic syndromes in order to devise therapeutic interventions aiming to improve cardiac health.

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Diabetes and ischemia: similarities in cardiac energy metabolism

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Stents, surgery, and optimal medical therapy in diabetes

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Abstract
The successful management of coronary artery disease in diabetic patients requires an understanding of the differences between diabetic and nondiabetic coronary disease with respect to pathophysiology and angiographic features. The impact of lesion complexity and subsequent completeness of revascularization must be considered, along with the impact of stent selection or graft use and the mode of presentation. While current evidence favors surgical revascularization in stable patients, with multivessel disease, especially those with complex angiographic coronary disease, the optimal strategy in patients presenting emergently with an acute coronary syndrome, particularly with ST-segment elevation on the electrocardiogram, requires clarification. This review summarizes the role of coronary stenting, surgery, and optimal medical therapy in the treatment of coronary artery disease in patients with diabetes in the contemporary era. ■ Heart Metab. 2015;68:9-14

Keywords: coronary artery bypass graft surgery; coronary heart disease; diabetes mellitus; optimal medical therapy; percutaneous coronary intervention

Diabetes mellitus (DM) is a powerful independent risk factor for coronary heart disease (CHD) and is increasing worldwide; approximately 25% of patients undergoing invasive angiographic assessment have DM.1-3 Diabetic patients more commonly have complex coronary artery disease with diffuse plaques involving mid and distal arterial branches and more frequently have multivessel disease (MVD). It is important to emphasize that both DM and MVD are associated with increased major cardiac events in patients with ischemic heart disease.4-6

Revascularization is indicated in patients with stable CHD who have persistence of symptoms despite medical treatment. It is also indicated in stable CHD when there is inducible ischemia on noninvasive (or invasive) testing and/or significant left ventricular impairment.7 There is a clear benefit with early revascularization in non–ST-segment elevation acute coronary syndromes (NSTEMI). In patients with ST-segment elevation myocardial infarction (STEMI), emergency reperfusion improves mortality rates. The optimal management of CHD in patients with DM also requires combination pharmacotherapy to ensure good long-term outcomes and risk prevention.

Pathophysiological changes evident in diabetic patients

The patterns of coronary artery disease in diabetes differ from those in nondiabetic patients. Necrotic cores
Coronary angiographic patterns associated with diabetes

These pathophysiological changes result in functionally significant stenoses, often angiographically evident as MVD, commonly involving distal arterial branches. This complex diffuse disease impacts upon the success of revascularization procedures. Diffuse disease is more likely to require deployment of multiple stents in long segments of small-caliber vessels and incomplete revascularization is more common both percutaneously and surgically, as a site suitable for grafting may be absent. Surgical revascularization is favored in triple-vessel disease and is recommended in diabetic patients.7 Much of the benefit of coronary artery bypass grafting (CABG) revascularization is seen primarily with arterial graft conduits.3,11 Diabetic patients have less frequently received “gold standard” surgery with bilateral mammary artery grafting, due to the risks of sternal dehiscence seen in diabetic patients.12,13

Coronary revascularization in patients with diabetes mellitus

The majority of pertinent randomized controlled trials (RCT) comparing revascularization strategies in diabetic patients alone have been reported in the last 5 years (Table I), though subgroup analysis of the BARI trial (Bypass Angioplasty Revascularization Investigation)14 15 years earlier reported an increased vulnerability of diabetic patients to late events after percutaneous coronary intervention (PCI). Key trials informing practice include SYNTAX,15 CARDia,16 VA CARDS,17 and FREEDOM6; respectively, the SYNergy between percutaneous intervention with TAXus and cardiac surgery trial, the Coronary Artery Revascularization in Diabetes trial, the Veterans Affairs Coronary Artery Revascularization in Diabetes Study, and the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease study.

Post hoc analyses from the BARI trial suggested a mortality benefit for diabetic patients with MVD with surgical revascularization, a benefit not evident in non-diabetic patients. The BARI trial was a large (n=1829) North American RCT performed in the pre-stent era where PCI patients were treated with balloon angioplasty. Rates of 5-year survival in patients with medically treated diabetes (n=357) were 65.5% for PCI and...
80.6% for CABG (P=0.003), while in the nondiabetic patients (81%) 5-year survival was the same.\textsuperscript{14}

The SYNTAX trial compared PCI with paclitaxel drug-eluting stents (DES) with CABG in patients with MVD and or left main stem disease, enrolling 1800 patients, 452 of which had diabetes. First-generation stents were used and arterial graft use was high (97.3%).\textsuperscript{15} Overall, authors found both diabetic and nondiabetic patients had higher rates of major adverse cardiac and cerebrovascular events (MACCEs) and repeat revascularization (RR) at 5 years with PCI, particularly where disease was anatomically complex. In the prespecified subgroup analysis of diabetic patients, MACCE rates at 5 years were 46.5% for PCI vs 29.0% for CABG (P≤0.001), and RR rates were also significantly higher with PCI vs CABG (35.3% vs 14.6%; P<0.001). No significant difference was seen in the composite of death/stroke/myocardial infarction (MI) or in these components individually.\textsuperscript{18}

The SYNTAX trial had a lasting impact not only because of the data generated, but also because of the development and use of the SYNTAX score, an objective scoring system to grade anatomical lesion complexity in the entire coronary artery tree. Prior to the SYNTAX score, authors primarily used the number of diseased vessels to describe the extent of coronary disease, or a modified American College of Cardiology (ACC)/American Heart Association (AHA) score to divide individual lesion complexity into 4 groups. The SYNTAX score evaluates the complexity and site of each lesion in the whole coronary tree; lesions are weighted for their site and territory within the coronary tree (Figure 1), allowing comprehensive evaluation of the territories at risk. This development is particularly important in patients with complex disease, such as diabetes, and can be used in selection of the method of revascularization, and to assess the likelihood of adverse outcomes and the impact of incomplete revascularization.

The first RCT specifically looking at diabetic patients, CARDia, enrolled patients with both MVD and complex single-vessel left anterior descending (LAD) artery disease. This was a small multicenter (n=510) trial from the United Kingdom. Patients were treated with bare-metal stents (BMS) and first-generation drug-eluting stents (DES) as they became available. This noninferiority trial was acknowledged by authors to be underpowered. It used a combined primary end point of all-cause mortality, MI, and stroke and at 1-year follow-up found event rates of 10.5% after CABG and 13.0% after PCI (P=0.39). No difference in all-cause mortality or MI was evident, but repeat revascularization was more frequent in PCI patients (11.8 vs 2%; P<0.001), and major bleeding was more common in CABG patients (6.1% vs 1.2%; P=0.009), as was nonfatal cerebrovascular accident (CVA) (2.8% vs 0.4%; P=0.066).\textsuperscript{16}

![Fig. 1](Illustrative angiogram with SYNTAX score. This diabetic patient with proximal multivessel disease, presenting with an ST-segment elevation myocardial infarction due to an occluded culprit left anterior descending artery, has an overall SYNTAX score of 34.5. Lesion 1 contributes 20.5 points weighted for a new total occlusion with thrombus in the proximal left anterior descending artery. Lesion 2, 8 points for a bifurcation lesion involving the proximal circumflex and obtuse marginal branches. Lesions 3 and 4, 2 points each for obtuse marginal branch stenoses. Lesion 5, 2 points for proximal right coronary artery stenosis.)

| Table I | Summary of randomized controlled trials comparing coronary artery bypass grafting vs percutaneous revascularization respectively. | Abbreviations: CVA, cerebrovascular accident; BMS, bare-metal stent; DES, drug-eluting stent; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NA, not applicable; NS, not significant; POBA, plain old balloon angioplasty. *5-Year follow-up data shown, with the exception of repeat revascularization and MACCE, where 1-year data only are reported. The primary composite outcome at 5 years was 18.7% vs 26.6%. **Results in the table show results for diabetic patients only. |

<table>
<thead>
<tr>
<th>n</th>
<th>Diabetes</th>
<th>Stent type</th>
<th>Primary outcome</th>
<th>Death</th>
<th>MI</th>
<th>Repeat revascularization</th>
<th>MACCE</th>
<th>CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREEDOM*</td>
<td>1900</td>
<td>100%</td>
<td>DES</td>
<td>Death + MI + CVA*</td>
<td>10.9% vs 16.3%</td>
<td>6% vs 13.9%</td>
<td>4.8%* vs 12.6%*</td>
<td>11.8%* vs 16.8%*</td>
</tr>
<tr>
<td>VA CARDS</td>
<td>198</td>
<td>100%</td>
<td>DES</td>
<td>Death + MI</td>
<td>5% vs 21%</td>
<td>15% vs 6.2%</td>
<td>NS</td>
<td>NA</td>
</tr>
<tr>
<td>CARDia</td>
<td>510</td>
<td>100%</td>
<td>BMS + DES</td>
<td>Death + MI + CVA</td>
<td>NS</td>
<td>NS</td>
<td>2% vs 11.8%</td>
<td>11.3% vs 19.3%</td>
</tr>
<tr>
<td>SYNTAX**</td>
<td>1800</td>
<td>25%</td>
<td>DES</td>
<td>MACCE</td>
<td>NS</td>
<td>NS</td>
<td>14.6% vs 35.3%</td>
<td>29% vs 46.5%</td>
</tr>
<tr>
<td>BARI**</td>
<td>1825</td>
<td>19.5%</td>
<td>POBA only</td>
<td>Death</td>
<td>19.4% vs 34.5%</td>
<td>NA</td>
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</table>
VA CARDS was another small underpowered RCT (n=198), including isolated proximal LAD artery disease or LAD artery disease with coexisting MVD; sirolimus or paclitaxel DES were used. The trial was terminated early and reported the combined primary end point of all-cause mortality and MI. At 2-year follow-up, there was no difference between groups; unsurprisingly, repeat revascularization did not differ significantly between groups. Mortality was lower in surgically treated patients (5% vs 21%; hazard ratio [HR], 0.30; 95% confidence interval [CI], 0.11-0.80). However, nonfatal MI was lower in patients treated by PCI (6.2% vs 15%; HR, 3.32; 95% CI, 1.07-10.30). VA CARDS was the only trial to mandate serial electrocardiograms and nuclear scans post revascularization, perhaps explaining why it found increased MI in surgical patients. These investigations detected clinically silent MI, probably masked by postsurgical analgesia, as all detected silent MIs were observed in surgically treated patients and represented 30% of all nonfatal MIs in CABG patients.17

The most important RCT is the FREEDOM trial, which enrolled 1900 patients with diabetes with MVD, but without left main stem disease. While second-generation DES were used the last year of randomization, most stented patients received first-generation DES; 95% of patients had ≥1 mammary artery conduit in the CABG group. At 5-year follow-up, FREEDOM found lower event rates after CABG for the primary end point (composite of death, MI, and CVA) (18.7% vs 26.6%; P=0.005), individual events of death (10.9% vs 16.3%; P=0.049), MI (6.0% vs 13.9%; P<0.001), whereas CVA was more frequent post-CABG (5.2% vs 2.4%; P=0.03). Repeat revascularization and MACCE were not reported at 5-year follow-up; at 1 year they were 4.8% vs 12.6% (P<0.001) and 11.8% vs 16.8% (P=0.004) respectively. The FREEDOM trial led to changes in guidelines with a class IA recommendation for surgical revascularization in patients with diabetes and MVD.3 The hypothesis generated by the BARI trial, that a left internal mammary artery (LIMA) conduit on the LAD coronary artery was prognostically protective took 2 decades for the FREEDOM trial to confirm. On analysis of patients with MVD not involving the LAD artery, and thus not requiring a LIMA to LAD artery graft, HRs approached 1 with broad CIs, suggesting the benefits of surgical revascularization are smaller,2 though when disease severity was divided by tertiles of the SYNTAX score, there was no P-value for interaction.

Noncomplex coronary disease

The majority of research comparing CABG with PCI focuses on triple-vessel disease. Noncomplex and single-vessel disease is predominantly treated by PCI. However, conflicting evidence exists in noncomplex MVD. Data from the SYNTAX trial18 found that patients with diabetes and SYNTAX scores <23 had similar combined rates of death, MI, and stroke (20.1% for CABG and 19.4% for PCI; P=0.79). Where the disease was complex (SYNTAX score ≥ 33), in patients with diabetes, the data strongly favored CABG. SYNTAX authors concluded that differences in MACCE were driven primarily by increased rates of further revascularization; this difference is greater in diabetic subgroups. However, subgroup analysis for the FREEDOM trial using SYNTAX scores found the combined end point death/MI and stroke in lower-SYNTAX-score patients were also significant (18.7% of CABG and 26.6% for PCI; P=0.005).3 A meta-analysis6 found that further revascularization was only increased in diabetic patients where complex lesions were treated; in noncomplex disease, rates were similar in patients with and without DM.

Optimal medical treatment in diabetic patients with coronary disease

The management of diabetes and coronary disease also must involve optimal medical therapy (OMT). Recommendations include insulin sensitization or insulin provision, statins, β-blockade, angiotensin-converting enzyme (ACE) inhibition/angiotensin II receptor blocker (ARB) use, and aspirin (or dual anti-platelet therapy [DAPT] with P2Y12 inhibitors, where an ischemic event has occurred or percutaneous revascularization has been performed).7,19 The BARI 2D (diabetes) trial, investigated whether insulin sensitization or insulin provision results in superior outcomes for patients with diabetes and MVD.3 OMT in the setting of STEMI, non–ST-segment elevation myocardial infarction (NSTEMI), and unstable angina should be used in conjunction with revascularization to improve cardiovascular outcomes, and
benefits are well established. OMT as an alternative to revascularization should only be considered in limited settings, such as stable angina. In diabetic patients, the clinician should be particularly cognizant of clinically silent, but significantly unstable, coronary artery disease seen in some diabetic patients, and objectively establish the burden of disease before considering OMT alone. It should be noted that recent and contemporary major trials of OMT vs PCI, such as COURAGE (Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation),21 BARI 2D,20 FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation), and FAME-2,22,23 required angiography to define the burden of disease before including patients. Blind selection of OMT is not supported by these trials. Revascularization is usually indicated in patients with stable CHD, when there is inducible demonstrable ischemia on noninvasive imaging, or invasive functional assessment of stenosis by fractional flow reserve (FFR), and/or significant left ventricular impairment.7,24

Unanswered questions

The impact of incomplete revascularization

In trials comparing CABG and PCI, a significant disparity is seen in completeness of revascularization favoring surgically treated patients. The importance of complete revascularization has been acknowledged in surgical literature for some time.25 There is growing interest in both defining and achieving more appropriate levels of percutaneously achieved complete or near-complete revascularization.26-28 No large multicenter RCT has assessed completeness of revascularization between techniques, or tested whether complete revascularization is superior to incomplete revascularization. However, retrospective subgroup analysis using the residual SYNTAX score to define the degree of incomplete revascularization is increasingly being employed to address this question. Defining the impact of incomplete revascularization in NSTEMI and STEMI populations may further explain poorer long-term outcomes with PCI seen in DM patients.

Second-generation DES vs CABG

BMS are associated with late restenosis due to neointimal hyperplasia. Diabetes is known to be a significant risk factor for restenosis. As a result, DES became the preferred stent choice for diabetic patients. First-generation DES were found to have significant problems with stent thrombosis, a rare but often fatal late complication, thought to be overcome with second-generation DES. None of the landmark trials listed above exclusively used second-generation DES. A recent meta-analysis found no statistically significant difference in revascularization between cobalt-chromium everolimus-eluting stents (second-generation DES) and CABG and no significant increase in mortality in diabetic patients,29 suggesting contemporary trials comparing revascularization techniques are required.

Diabetes and STEMI in MVD

Most revascularization trials only included stable patients with angina and NSTEMACS. The relevance to patients who would not have met these inclusion criteria remains uncertain and is not guided by level A or B evidence.30 The treatment of STEMI patients in emergent situations is predominantly percutaneous, to ensure timely reperfusion. However, the FREEDOM results have generated uncertainty regarding the best management for nonculprit disease in patients with DM and MVD, especially when the infarct-related artery is the LAD artery. The future treatment of nonculprit disease must be considered at the time of the index admission, because uninterrupted DAPT is recommended for 3-12 months. If the nonculprit coronary disease still meets FREEDOM entry criteria, nonemergent CABG should be considered rather than further PCI.

Conclusions

The treatment of patients with diabetes and coronary disease, identified nonemergently at angiography, should have CABG if they have MVD, especially with LAD artery involvement. However, in FREEDOM, there was no interaction between the SYNTAX score and the benefit of CABG over PCI with DES. OMT involves 4-5 secondary prevention therapies recommended for all patients with stable CHD, together with insulin sensitization and insulin provision. However, there are unanswered questions about the optimal procedural management of patients presenting with anterior STEMI undergoing successful primary PCI.
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The prevalence of diabetes mellitus has dramatically increased within the last decades in industrial countries and is expected to further increase in the coming years. In 2013, 381 million people were estimated to suffer from diabetes, and by 2030, this number may nearly double. Reasons for this phenomenon are aging populations and lifestyle changes in industrial countries, linked to reduced physical activity and increasing rates of obesity. Diabetes mellitus is associated with a multitude of organ-related complications affecting renal, vascular, brain, retinal, and cardiac functions.

Congestive heart failure as a consequence of diabetes mellitus in the absence of arterial hypertension and coronary artery disease (CAD) is referred to as “diabetic cardiomyopathy.” However, this pathologic condition is not widely accepted as a distinct entity. Rubler et al already described this disease pattern back in 1972. Since then, experimental and clinical data supporting the hypothesis that diabetes can affect myocardial function independently of ischemic heart disease have become available. In this regard,
a high proportion of patients with type 2 diabetes mellitus were found to have diastolic dysfunction and heart failure with preserved ejection fraction and without clinically evident CAD. However, the underlying pathophysiologic mechanisms are not yet fully understood. It remains unclear whether diastolic dysfunction is an intrinsic metabolic myocardial disorder with diabetes or whether it is related to impaired microvascular integrity.

Previous observational studies demonstrated that 33% of men and 45% of women with diabetes develop heart failure within 5.5 years of follow-up, independently of CAD and arterial hypertension. Once heart failure is clinically evident in such patients, they exhibit a substantially higher mortality rate compared with patients without diabetes, independent of CAD. Due to the poor prognosis of patients with heart failure and diabetes, it becomes clear that the early diagnosis of subtle myocardial dysfunction is crucial. This becomes even more important since a high number of patients with impaired systolic function and diabetes may not report specific symptoms due to physical inactivity.

Cardiac magnetic resonance for the assessment of myocardial dysfunction with diabetes

Myocardial function and deformation

Altered cardiac function with diabetes is characterized by an initial increase in left ventricular (LV) stiffness and subclinical diastolic dysfunction (for a review, see references 13 and 14). In one of the first cardiac magnetic resonance (CMR) studies, investigating the presence of subclinical myocardial dysfunction in patients with diabetes, Fonseca et al described the presence of impaired systolic and diastolic function by tagged CMR in patients with type 2 diabetes mellitus and preserved LV function. In subsequent clinical studies, patients with type 2 diabetes mellitus exhibited decreased circumferential, radial, and longitudinal systolic strain by CMR displacement encoding with stimulated echoes (DENSE), compared with age-matched control subjects. Recently, these findings were confirmed using strain-encoded (SENC) magnetic resonance imaging, which demonstrated the presence of diastolic dysfunction in patients with diabetes and preserved ejection fraction, independent of impaired myocardial perfusion reserve. Along that line, diastolic dysfunction was present in young patients with type 2 diabetes mellitus, and was associated with diabetes duration and aortic distensibility. Two other studies described paradoxically increased LV torsion in patients with type 1 and type 2 diabetes mellitus, which in both cases was attributed to small-vessel disease and impaired microvascular integrity.

An example of a patient with decreased circumferential systolic strain by CMR tagging is shown in Figure 1. In another patient, SENC demonstrates the presence of normal peak systolic strain, but reduced diastolic strain rate, in a young patient with type 2 diabetes mellitus and preserved ejection fraction (Figure 2). Higher spatial resolution allowing more accurate assessment of diastolic function can be appreciated using SENC.

Myocardial perfusion and fibrosis (LGE and T1 mapping)

A number of studies have demonstrated the presence of reduced myocardial perfusion reserve (MPR) during
Adenosine-stress CMR in patients with type 2 and long-term (>10 years) type 1 diabetes mellitus.17,20-22 Along that line, decreased MPR was previously reported in patients with type 1 diabetes mellitus and autonomic neuropathy.23 However, two further studies failed to demonstrate reduced MPR in asymptomatic patients with diabetes mellitus,18,24 indicating that microvascular dysfunction may be a relatively late phenomenon and may therefore not be the primary underlying mechanism for the development of diastolic dysfunction, which obviously occurs earlier in the disease.

An example of an asymptomatic patient with type 2 diabetes mellitus and decreased MPR during adenosine stress is shown in Figure 3.

Late gadolinium enhancement (LGE) has been reported to identify occult myocardial scarring indicative of previous infarction in patients with diabetes and without clinically evident CAD.25 The identification of such occult scarring was a strong independent predictor of adverse cardiac events. Along that line, infarct-related LGE was described in patients with diabetes and unrecognized CAD, being a robust predictor of cardiac death and myocardial infarction.26

Limited data exist, on the other hand, about the presence of non-CAD–related LGE in patients with diabetes mellitus and without CAD. Recently, Khan and colleagues demonstrated the presence of non-CAD–related mid-wall LGE in patients with diabetes mellitus.18 An example of a patient with a prominent non-CAD–related mid-wall LGE and type 2 diabetes mellitus and preserved LV function is shown in Figure 4. The prognostic significance of such findings in patients with diabetes remains to be evaluated in future clinical studies.

In contrast to LGE, which is helpful for the detection of regional myocardial fibrosis, modern T1-mapping techniques can detect and quantify diffuse myocardial fibrosis, with the T1 time being inversely related to the degree of myocardial fibrosis by histologic vali-
In this regard, an association between diffuse myocardial fibrosis by T1 mapping and diastolic dysfunction was demonstrated in asymptomatic type 2 diabetes mellitus patients. Along that line, diffuse fibrosis was reported to be an early sign of cardiomyopathy in patients with type 2 diabetes mellitus in the absence of CAD or regional myocardial scarring, eventually contributing to subclinical diastolic myocardial dysfunction.

**Myocardial triglyceride content**

Increased myocardial triglyceride content, referred to as “myocardial steatosis,” can be noninvasively assessed by cardiac resonance spectroscopy. Several clinical studies have reported the presence of myocardial steatosis in patients with diabetes mellitus. However, the presence of LV dysfunction has been rated differently in these studies. In this regard, McGavock et al reported myocardial steatosis in patients with impaired glucose tolerance and diabetes mellitus in the absence of systolic dysfunction and heart failure symptoms. Conversely, myocardial steatosis was reported to be associated with reduced longitudinal strain and strain rate in men with uncomplicated type 2 diabetes mellitus. Rijzewijk et al, on the other hand, demonstrated diastolic dysfunction in a group of patients with uncomplicated diabetes with myocardial steatosis compared with control subjects. The latter findings are in line with recent observations by our group, which demonstrated an association between myocardial steatosis and diastolic dysfunction by SENC. Cardiac steatosis and diastolic dysfunction seem to develop independently of impaired MPR in an early stage of diabetic disease, while ischemia may aggravate myocardial dysfunction in later stages, as described by Poulsen et al. Subsequently, subclinical diabetic heart disease may advance to systolic dysfunction, and ultimately progress to overt congestive heart failure, arrhythmias, and myocardial infarction. An overview of the mechanisms involved in diabetic heart disease is provided in Figure 5.

**Summary and conclusions**

Diabetes leads to structural changes in the myocardium, which may be described as diabetic heart disease. Diabetic heart disease is characterized by myocardial steatosis and impaired diastolic function in the early stages, and may be accompanied by impaired microvascular integrity and reduced systolic function in later stages of the disease. Despite the fact that impaired diastolic function may be an early marker of myocardial dysfunction with diabetes, the effect of early diagnosis on clinical outcomes still merits further investigation, in light of rather limited options for the effective treatment of such heart failure patients with preserved ejection fraction. In addition, it should be noted that perfusion abnormalities may develop in such patients, independently of the presence or absence of diabetic cardiomyopathy. During clinical manifestation, macrovascular disease and arterial hypertension are also frequently present, so that the relative contribution of myocardial versus vascular disease to the clinical phenotype cannot be discerned. CMR can enable better understanding of diabetic heart disease, through detection of alterations in myocardial function, including increased triglyceride content and impaired relaxation in early stages and...
reduced myocardial deformation and micro- as well as macrovascular abnormalities in later stages of the disease.

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Is glycemic control relevant to cardiovascular clinical outcomes?

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Abstract
In patients with diabetes mellitus (DM), cardiovascular disease (CVD) and the onset of acute coronary syndromes are more prevalent than in the nondiabetic population: the mere presence of DM can be considered an equivalent of CVD. Furthermore, in diabetic patients, the classic risk factors for CVD are present in a much more severe form. However, an important—probably the most important—risk factor for CVD is the presence of microangiopathy. The question of whether glycemic control influences cardiovascular outcomes is multifaceted and requires more than a simple “yes or no” answer. Recent data have shown that treatment regimens to decrease blood glucose levels are often unnecessarily aggressive. To overcome the issue of increased incidence of hypoglycemia, especially in elderly patients with CVD, it is essential not only to seek a glycemic target more in line with the life expectancy of the patient and the real needs of prevention, but also to use drugs that do not induce hypoglycemia. In this context, incretin hormones have been an important therapeutic innovation in the field of diabetes treatment; nonetheless, of the sulfonylureas (SUs), gliclazide modified release (gliclazide MR) has robust evidence showing it to be the one that induces less hypoglycemia and cardiovascular events. ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation) is the only megatrial that has shown a benefit in terms of microvascular disease progression. That finding is important, as not only are micro- and macrovascular disease tightly intertwined, but the former frequently predicts the latter. ■ Heart Metab. 2015;68:20-26

Keywords: cardiovascular disease; diabetes mellitus; microvascular complications; risk factors

The mechanisms leading to atherosclerosis in patients with type 2 diabetes mellitus (DM) are complex (Figure 1), and they can be both metabolic and inflammatory. Hyperglycemia is firstly associated with endothelial activation and then later with dysfunction. In the presence of the latter, endothelial cells lose vasodilatory properties, vascular smooth muscle cells constrict and proliferate, procoagulant factors increase, and proteolytic enzymes, such as matrix metalloproteinase, become more active. The regeneration of endothelial cells after endoaxialization is slower, due to reduced numbers and activity of endothelial progenitor cells derived from bone marrow. Furthermore, the end products of advanced glycation (AGE), with their specific receptors, disrupt the barrier function of the endothelium. These changes may explain the increase in vascular permeability and transport of macromolecules across the endothelium. Increased oxidative stress is among the possible mechanisms by which DM can induce
endothelial dysfunction.\textsuperscript{3} DM, in addition to the traditional dysmetabolic framework, is characterized by the presence of a chronic subclinical inflammatory process, which at the later stage of the disease may account for plaque vulnerability, and the onset of acute coronary syndromes.

**The relationships between HbA\textsubscript{1c} and cardiovascular disease**

Cardiovascular disease (CVD) is detectable even when levels of glycated hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) are well below the diagnostic threshold for DM, 6.5\% (48 mmol/mol). In the EPIC-Norfolk cohort study (European Prospective Investigation into Cancer and Nutrition-Norfolk), the relative risk of CVD mortality increased continuously, in both genders, according to HbA\textsubscript{1c}.\textsuperscript{4} Compared with a concentration of HbA\textsubscript{1c} equal to 5\%, each 1\% increase in HbA\textsubscript{1c} was associated with a 20\% increase in CVD events. A recent analysis involving participants with no previous history of CVD and DM has shown an association between CVD and HbA\textsubscript{1c}: HbA\textsubscript{1c} was better at predicting cardiovascular risk than were fasting plasma glucose and postprandial glucose levels.\textsuperscript{5} In patients with DM, for every percentage point increase in HbA\textsubscript{1c}, the relative risk of CVD was equal to 1.18 for patients with type 2 DM and 1.15 for patients with type 1. Significant coronary lesions are found post mortem in 50\% to 80\% of diabetics without a diagnosis of coronary heart disease (CHD) in life. An analysis by the Emerging Risk Factors Collaboration considered data extracted from 698,782 persons evaluated in 102 prospective studies: in patients with DM, the risk associated with ischemic heart disease was equal to 2.00; with ischemic stroke, 2.27; with hemorrhagic stroke, 1.56; and with death from CVD, 1.73.\textsuperscript{6} In a recent cohort study including nearly 2 million people with type 2 DM, it was determined that 17.9\% of patients had a first episode of CVD where symptoms of peripheral artery disease were commonly the first clinical sign.\textsuperscript{7} Due to the high prevalence of CVD in patients with type 2 DM, the mere presence of DM can be considered an equivalent of CVD.

**Microangiopathy is the most important risk factor for macroangiopathy**

Microvascular complications independently predict CHD; this is true both for nephropathy and retinopa-
Glycemic control and cardiovascular outcomes

A reduction in renal function and the presence of microalbuminuria independently associate with and predict CVD. High blood pressure is a major risk factor for microalbuminuria, which itself is a predictor of macroproteinuria and overt nephropathy. The relationship between urinary albumin excretion and cardiovascular events is positive and begins at levels of albuminuria that are lower than those considered normal. Microalbuminuria not only predicts CHD, but also cerebrovascular and peripheral artery disease. Equally important is the presence of retinopathy: the diameter of the retinal vessels is a predictor of mortality from stroke and CHD in middle-aged people. The presence of proliferative retinopathy, compared with its absence, confers a 25-fold greater risk of nontraumatic amputation of the lower limbs. The presence of some form of microangiopathy is associated with an increased incidence of a first coronary event both in men and in women. Similarly, neuropathy is a powerful predictor of events and CVD mortality. It is still debatable whether microvascular complications are mere markers or whether they can be considered an early stage of CVD. It is commonly considered that microangiopathy is a late event in the natural history of DM; however, this assumption is not entirely correct as it can be detected in the heart even in the absence of overt CHD. In light of these observations, one can hypothesize that micro- and macroangiopathy represent a continuum of what we consider diabetic angiopathy (Figure 2).

Does glycemic control reduce cardiovascular disease?

The question of whether glycemic control influences cardiovascular outcomes is multifaceted and cannot be answered by a simple “yes” or “no.” While there is much evidence that the risk of cardiovascular mortality increases with an increase in HbA1c, the intervention trials aimed to determine whether a reduction in HbA1c is associated with a reduction in CVD have offered controversial results at best.

The UKPDS trial (United Kingdom Prospective Diabetes Study) was designed to investigate whether, in new-onset type 2 DM patients, tight glycemic control can reduce both micro- and macrovascular complications. In that study, treatments with sulfonylurea (SU), metformin, or insulin reduced microvascular complications; this positive effect was noticed after the trial’s end. The UKPDS trial did not demonstrate a clear-cut positive effect on macrovascular complications from intensified glycemic control: metformin treatment reduced the risk of macrovascular disease only in a small subset of obese diabetics. However, a significant reduction in events has been shown during posttrial monitoring, thus suggesting a protective effect on macrovascular disease from intensified glycemic control when implemented immediately after clinical diagnosis.

Regrettably, the results of other large studies, such as ACCORD (Action to Control Cardiovascular Risk in Diabetes), PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events), RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in and Regulation of glycemia in Diabetes), and VADT (Veterans Affairs Diabetes Trial) seem to deny the notion that tight glycemic control might provide protection against CVD in DM patients. A recent meta-analysis reported that meticulous control of blood sugar produces a limited benefit in terms of mortality from all causes and cardiovascular mortality. The same authors argue that the benefits of an intensive treatment to control blood glucose can be offset by an increase in hypoglycemia. This has led some authors to conclude that, even today, we find ourselves in a “dark age” in terms of the treatment of diabetes. The reasons for this failure are several: the drugs used in these trials induced an increased incidence of hypoglycemia and weight gain, and the patients enrolled already had advanced CVD, a stage of the disease in which the glucose-induced damage is probably minor when compared with that due to other risk factors.

Fig. 2 High blood pressure, dyslipidemia, and inflammation are the most important risk factors for macroangiopathy. Hyperglycemia, which is the single most important risk factor for microangiopathy, potentiates the effect of the other risk factors on macroangiopathy. Moreover microangiopathy is, itself, a powerful risk factor for macroangiopathy.
In that context, numerous studies have shown that the pharmacological treatment of dyslipidemia and hypertension significantly reduce major cardiovascular events regardless of the presence or absence of CVD, both in patients with or without DM. In the STENO-2 study, a 70% risk reduction in patients with type 2 DM at high cardiovascular risk was attributed to statin treatment. Another possible reason for the poor outcome in some of the megatrials is that the HbA1c target was too ambitious for patients with comorbidities and advanced age.

Having said that, there are several demonstrations highlighting the importance of blood glucose control in DM patients. The STENO trial showed approximately a 50% reduction in cardiovascular mortality in patients with type 2 diabetes at high risk when all the major cardiovascular risks, together with antplatelet treatment, approached targets. In the VADT trial, intensive glycemic control reduced cardiovascular events in those with a lower extent of calcification in the coronary tree and in patients with disease duration of less than 15 years. The recently published follow-up of that trial shows that DM patients who were randomly assigned to intensive glycemic control for 5.6 years had 8.6 fewer major cardiovascular events per 1000 person-years than those assigned to standard therapy; however, no improvement was seen in the rate of overall survival. In support of this finding, further meta-analysis showed that randomization to intensive glycemic control reduced the risk of major cardiovascular events by 9%, mainly attributed to a reduction in the risk of myocardial infarction by 15%. The benefit was observed mainly in patients without apparent CVD. A recent analysis of the ACCORD study showed that myocardial infarction, coronary revascularization, and unstable angina were less frequent in patients randomized to intensive treatment compared with standard treatment; this advantage was lost for the lowest values of HbA1c.

Four meta-analyses conducted on several studies—UKPDS, ACCORD, VADT, and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiaMicon MR Controlled Evaluation)—showed, in spite of an average increase in the risk of hypoglycemia equal to 2.59, a 14% reduction in the risk of myocardial infarction, with no increase in mortality. The increased hypoglycemia observed in the trials is not necessarily linked to the glycemic targets achieved; it also depends on the type of treatment used. For example, the ORIGIN study (Outcome Reduction with Initial Glargine Intervention), which demonstrated a neutral cardiovascular effect on treatment with basal insulin (Figure 3), showed that the incidence of hypoglycemia was significantly lower, with the same glycemic control, in those who were randomized to insulin glargine. The PROactive study demonstrated that

**Fig. 3** Time line for efficacy and safety megatrials in type 2 diabetic patients, and their results (positive/neural) in regards to cardiovascular disease.

**Abbreviations:** ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiaMicon MR Controlled Evaluation; ALO, alogliptin; AMI, acute myocardial infarction; DM, diabetes mellitus; EXAMINE, EXamination of Cardiovascular outcomes with alogliptin versus standard care in patients with type 2 diabetes mellitus and acute coronary syndrome; FDA, US Food and Drug Administration; gliclazide MR, gliclazide modified release; MET, metformin; ORIGIN, Outcome Reduction with Initial Glargine Intervention; PIO, pioglitazone; PROactive, PROspective pioglitAzone Clinical Trial in macroVascular Events; PTM, posttrial monitoring; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in and Regulation of glycaemia in Diabetes; SAXA, saxagliptin; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus; SITA, sitagliptin; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.
the intensive compared with the standard glycemic control arm; furthermore, patients had no significant weight gain. Most importantly, patients experienced less severe hypoglycemia: <3% of intensively treated ADVANCE participants, approximately 16% of intensively treated ACCORD patients, and 21% of intensively treated VADT patients. These differences may be related to differences in therapeutic approach; in the ADVANCE trial, the number of patients on insulin treatment was significantly smaller than that in the ACCORD and VADT trials. Second, weight change in the intensively treated patients was smaller than in other trials. Third, the reduction in HbA1c levels was less aggressive in the ADVANCE trial than in ACCORD and VADT. Fourth, in both arms of the VADT and ACCORD trials, multiple drugs were employed; in ADVANCE, treatment with multiple drugs added to gliclazide modified release (gliclazide MR, a sulfonylurea) was compared with treatment with multiple drugs with no gliclazide.

The effects of gliclazide on cardiovascular safety may be explained by some particular mechanisms of action, eg, it may decrease the ongoing oxidative stress both in the vessel wall and in the kidney. Given the importance of protecting the kidney in order to avoid future cardiovascular events, that drug effect is important from a pathophysiological perspective. Gliclazide has been shown to be superior to other SUs, not only by the ADVANCE study, but also by FAST-MI (the French registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction). FAST-MI collects comprehensive data on the management and outcome of consecutive patients admitted to intensive care units for definite acute myocardial infarction over a 1-month period in France, irrespective of the type of institution to which the patients were admitted.

Of the 374 centers that treated patients with acute myocardial infarction at that time, 223 participated in the study (60%). Mortality was significantly lower in patients previously treated with SUs (3.9%) vs those on other oral medications (6.4%), insulin (9.4%), or no medication (8.4%) (P=0.014). Among SU-treated patients, in-hospital mortality was lower in patients receiving pancreatic cell–specific SUs (gliclazide or glimepiride) (2.7%), compared with glibenclamide (7.5%) (P=0.019). Monami and colleagues, in a retrospective observational cohort study performed on a consecutive series of 568 outpatients with type 2 DM treated with either glibenclamide or gliclazide, observed 33 and 11 deaths in the glibenclamide and gliclazide groups, respectively, with a yearly mortality rate of 4.3% and 2.2% (P<0.05). On Cox regression analysis, after adjustment for potential confounders, including comorbidity, glibenclamide treatment was associated with a significant increase in all-cause mortality (P<0.05). In the Danish Registry, a total of 107 806 subjects were included, of whom 9607 had previous myocardial infarction. Compared with metformin, in patients with previous myocardial infarction, gliclazide treatment was not associated with increased mortality, which was observed for glimepiride, glibenclamide, glipizide, and tolbutamide.

Recently, Simpson and colleagues investigated whether mortality and the risk of CVD events varies according to the type of SU prescribed. The relative risk of death compared with glibenclamide was 0.65 (95% confidence interval [CI], 0.53-0.79) for gliclazide, 0.83 (95% CI, 0.68-1.00) for glimepiride, 0.98 (95% CI, 0.80-1.19) for glipizide, 1.13 (95% CI, 0.90-1.42) for tolbutamide, and 1.34 (95% CI, 0.98-1.86) for chlorpropamide. Similar associations were noted for cardiovascular-related mortality. These data confirm that gliclazide is associated with a lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide.

The recent results from the ADVANCE posttrial ObservatioNal study (ADVANCE-ON) monitoring data have confirmed the cardiovascular safety of gliclazide MR. The implications of these studies are that clinicians should consider possible differences in risk of mortality when selecting a SU. In 2008, the US Food and Drug Administration (FDA) issued guidance on the assessment of cardiovascular risk for new drugs to treat type 2 DM. The first three safety studies published to date are SAVOR (Saxagliptin Assess-
ment of Vascular Outcomes Recorded in patients with diabetes mellitus), EXAMINE (EXamination of Cardiovascular outcomes with alogliptIN versus standard carE in patients with type 2 diabetes mellitus and acute coronary syndrome), and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin).34-36 These three trials, conducted in DM patients at high and very high risk, demonstrated good safety profiles for saxagliptin, alogliptin, and sitagliptin, respectively. However, in the SAVOR study, increased hypoglycemia and hospitalization for heart failure was observed in patients randomized to saxagliptin treatment. Very recently, the study EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was published: in this trial, the type 2 sodium-glucose transporter inhibitor (SGLT2) empagliflozin significantly reduced the 3-point (cardiovascular death, nonfatal acute myocardial infarction, and nonfatal stroke) major adverse cardiac event rate by 14%. This study, along with a previous study on dipeptidyl peptidase-4 (DPP-4) inhibitors, offers an additional and reassuring therapeutic approach for those with type 2 diabetes.37 We are currently awaiting a number of other trials that will evaluate the safety of DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.

Conclusions

It is clear that unnecessarily aggressive treatment to decrease blood glucose is often implemented in patients with comorbidities. To avoid the increased incidence of hypoglycemia, especially in elderly patients with CVD, it is necessary not only to seek a glycemic target more in line with the life expectancy of the patient and the real needs of prevention, but also to use drugs that do not induce hypoglycemia. The advent of incretin hormones in this context has been an important therapeutic innovation in the field of diabetes treatment; nonetheless, among SUs, there is robust evidence that glitazide MR induces less hypoglycemia and cardiovascular events. Of the megatrials, ADVANCE is the only study that has shown a benefit in terms of microvascular disease progression. This is of importance as not only are micro- and macrovascular disease tightly intertwined, but the former frequently predicts the latter. Acknowledging glycemic control to be a weak strategy for improving the cardiovascular prognosis of DM patients is necessary, not only to promote the design of innovative strategies, but also to better understand the mechanisms underlying cardiovascular events. So, to the question Is glycemic control relevant to cardiovascular clinical outcomes? the answer is yes, depending on the therapeutic approach to be used.

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Glycemic control and cardiovascular outcomes


Diabetes and cardiovascular disease

Diabetes is one of the main risk factors for cardiovascular disease (CVD), particularly atherosclerotic vascular disease, including coronary artery disease (CAD).1 In the United States, according to data from the Centers for Disease Control and Prevention, at least 68% of diabetic patients over the age of 65 die of some form of heart disease.2 Death rates related to CVD among adults with diabetes are two to four times higher than the rates for adults without diabetes.2
Management of patients with diabetes and CAD usually poses a major clinical challenge: clinically, signs of myocardial ischemia, when present, may be atypical and misleading, and silent myocardial ischemia may occur in one in five asymptomatic patients with type 2 diabetes.3 Angiographically, the accelerated atherogenesis results in more severe and extensive disease, higher incidence of multivessel disease, and small-sized vessels.4 Both diabetes mellitus and small vessel size are known to be predictors of restenosis after percutaneous coronary intervention (PCI).5 In patients with multivessel disease, although bypass surgery may be the preferred therapeutic strategy because of the greater long-term protection compared with PCI,6 this comes at the expense of a higher rate of complications, including wound healing and sternal dehiscence, compared with nondiabetic patients.7

In addition, the involvement of distal coronary artery branches reduces regional coronary perfusion and causes hibernation of myocardium that together with the abnormal glucose utilization decreases left ventricular (LV) function,8 further increasing the risk for future cardiovascular events.

Cardiac metabolism in patients with diabetes

Adenosine triphosphate (ATP) is produced via two important metabolic pathways. In the healthy heart, approximately 60% to 90% of ATP production originates from β-oxidation of free fatty acids (FFAs); 10% to 40% is produced via the glycolytic pathway.9 However, glucose utilization is hampered in the diabetic patient, particularly during periods of stress; thus, FFA oxidation is dramatically increased and can account for almost 100% of the heart’s energy production.10 FFAs are a less efficient fuel, and their oxidation in mitochondria for ATP production results in higher mitochondrial oxygen (O2) consumption compared with glucose oxidation.11 The increased uptake and use of FFAs during stress and ischemia may lead to important changes in the diabetic heart, such as (i) greater decrease in myocardial performance for a given amount of ischemia, compared with the non-diabetic heart12; (ii) diminished energy production and a parallel increase in intermediate metabolic products that are toxic for the cells13; (iii) contractile dysfunction and an increased sensitivity of the heart to injury during ischemia14; and (iv) alterations in calcium (Ca2+) homeostasis, which are responsible for the impaired systolic and diastolic functions of the diabetic heart.15 Based on these premises, modulation of myocardial FFA metabolism may be a key target for metabolic interventions in patients with CAD with or without diabetes. In the former, the benefits of such metabolic approach should be even greater that those observed in nondiabetic patients.

Trimetazidine (TMZ) selectively inhibits the mitochondrial long-chain 3-ketoacyl-Coenzyme A thiolase, resulting in inhibition of FFA oxidation and increased glucose oxidation, restoring coupling between glycolysis and carbohydrate oxidation, which leads to ATP production with less O2 consumption.16

Effects of TMZ on angina relief and left ventricular function

A recent meta-analysis including 13 studies showed that adding TMZ to other antianginal drugs was associated with fewer weekly angina attacks, less weekly nitroglycerin use, longer time to 1-mm ST-segment depression, higher total work output, and longer peak-exercise duration, compared with treatment with other antianginal drugs for stable angina.17 Another meta-analysis showed that TMZ improved systolic function and clinical symptoms in patients with chronic heart failure (HF), as shown by a significant change in systolic function, New York Heart Association (NYHA) classification, and exercise duration. A specific analysis performed in patients with diabetes and HF revealed a mean 6.19% absolute increase in LV ejection fraction.18

Effects of TMZ on cardiovascular events

TMZ is effective in reducing mortality and event-free survival in patients with HF, as recently shown by Fra-gasso et al.19 In this retrospective study comprising 669 patients with HF, the addition of TMZ on top of
optimal medical therapy showed an 11.3% improvement in global survival and an 8.5% improvement in survival for CVD death. The rate of hospitalization for cardiovascular causes was reduced by 10.4% at 5 years. In a previous meta-analysis, mortality was lower with TMZ than with placebo (7.5% vs 27.5%), yielding a 71% reduction in the risk of death in patients with HF. Finally, TMZ appeared to improve clinical outcomes in patients after acute myocardial infarction by significantly reducing all-cause mortality and major adverse cardiac events (MACEs) over 12 months.20

Cardioprotective effects of TMZ in patients with diabetes

The same benefits offered by TMZ, such as better angina control, improved quality of life, and increased exercise tolerance21,22 as well as improved cardiac function in nondiabetic patients have been documented in patients with diabetes.23,24

Patients with diabetes and any degree of renal dysfunction are at risk not only for cardiovascular events, but also for worsening of renal function after administration of iodine-based contrast media. It is known that the magnitude of the increase in the level of cardiac troponin I (cTnI) directly correlates with irreversible myocardial injury and has an important prognostic signification after PCI. In a recent study performed in patients with diabetes and mild-to-moderate chronic kidney disease,25 the use of TMZ 72 hours prior to PCI was associated with a lower rate of contrast-induced nephropathy (12% vs 28% in the control group), and lower levels of cTnI after the procedure (Figure 1).

Diabetes is one of the strongest predictors of restenosis after successful PCI with stent implantation. The role of TMZ in preventing in-stent restenosis was prospectively assessed in 635 patients (27% with diabetes) after drug-eluting stent (DES) implantation.26 TMZ given for at least 30 days after the procedure significantly reduced the incidence of stent restenosis from 11.1% to 4.2% on follow-up at 9-13 months. The incidence of MACE was also lower in the TMZ-treated group at the 1-year follow-up (6.1% vs 10.8%). Although the study was not powered enough to allow for subgroup analysis, it is tempting to speculate that patients with diabetes may derive the most benefit with TMZ after PCI, regarding the prevention of in-stent restenosis. In fact, the effect of TMZ on recurrent angina pectoris and LV structure after DES implantation in elderly patients with diabetes and multivessel CAD was recently examined.27 At the 2-year follow-up, patients in the TMZ group showed a significant improvement in the incidence and severity of angina pectoris, compared with the control group, as well as silent myocardial ischemia and angina pectoris–free survival. LV function and structure were relatively stable in patients receiving TMZ, whereas they deteriorated in the control group.

Conclusion

An evolution in the understanding of the metabolic disarray in the “diabetic heart” allowed for the emergence of a novel therapeutic target to improve the imbalance in energetic substrate utilization (FFA vs glucose). TMZ, with its unique mode of action, devoid of any discernible hemodynamic effect, may have a favorable impact on the management of patients with diabetes and CAD/HF well beyond what is so easily appreciated by patients and physicians alike: an overall improvement in quality of life, increased exercise tolerance, greater angina relief, and improved cardiac function. Because patients with diabetes represent one of the high-risk groups for cardiovascular events, all the benefits provided by TMZ already documented by clinical studies (many with a significant number of diabetic patients)—such as fewer hospitalizations,
lower rates of in-stent restenosis after PCI, and increased survival—may also be applicable to patients with diabetes. A reappraisal of how patients with diabetes and CVD should be treated is overdue: in dismissing metabolic therapy with TMZ in this scenario, we are needlessly exposing our already high-risk patients to a further increase in their risk of future cardiovascular events. At least where patients with diabetes are concerned, the common saying of “what the eye doesn’t see, the heart doesn’t grieve over” might not be true.

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Preventing cardiovascular events in diabetic patients: the case of the patient with poor distal coronary targets

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Abstract
Cardiovascular disease is a major cause of morbidity and mortality in diabetes. Hypoglycemia, a common side effect of antidiabetic therapy, is associated with an increased risk for cardiovascular disease in diabetic patients and may precipitate angina in those with underlying myocardial ischemia. Thus, the prevention and prompt recognition of hypoglycemia is highly desirable in diabetic patients, especially in those with ischemic heart disease. Moreover, ischemia due to microvascular dysfunction is a frequent finding in people with diabetes. In that setting, in which surgical or percutaneous coronary intervention are not viable options, a rational use of antianginal therapy may help maximize the cardiometabolic benefits of treatment and improve quality of life. For example, trimetazidine can significantly ameliorate recurrent ischemia with a neutral or even favorable impact on glucose metabolism in diabetic patients. We present a clinical case that illustrates the importance and usefulness of a multidisciplinary approach when treating diabetic patients with ischemic cardiac disease. ■ Heart Metab. 2015;68:31-34

Keywords: coronary artery disease; diabetes; glucagon-like peptide-1 agonists; hypoglycemia; incretin; microvascular coronary dysfunction

Up to 80% of diabetic patients die from cardiovascular (CV) disease. Multiple factors (eg, hyperglycemia, a high level of low-density lipoprotein (LDL) cholesterol, elevated blood pressure, and smoking) contribute to accelerate atherosclerosis. Yet, even after adjustment for all these factors, the relative risk of cardiac mortality remains 3 to 5 times higher in diabetics. For whatever reason, the atherosclerotic involvement in diabetic subjects tends to be more severe and more diffuse than in nondiabetic subjects. Hyperglycemia, per se, exerts a deleterious effect on endothelial function and reduces coronary flow reserve beginning in the early stages of the disease. Studies on heart microcirculatory dysfunction in diabetes suggest that microvascular disease is systemic, occurring in the heart as well, where it contributes to poorer outcome upon coronary revascularization and more common heart failure.
Case report

Miss AR is a 63-year-old diabetic woman who was referred to our diabetes center in March 2014. Her family history was positive for coronary artery disease (CAD). She quit smoking in 1993. Her medical history was significant for hypertension, hypercholesterolemia, and obesity. She had type 2 diabetes mellitus (T2DM) for 13 years, complicated by nonproliferative retinopathy, but had preserved renal function and no signs of neuropathy. She was on olmesartan, aspirin, metformin, glibenclamide, and rosuvastatin. Her weight was 86 kg (body mass index, 30.5 kg/m²). Physical examination, blood pressure (135/80 mm Hg), and heart rate (70 bpm) were normal. Her fasting plasma glucose value was 5.5 mmol/L (99 mg/dL), glycated hemoglobin A₁c (HbA₁c) was 54 mmol/mol (7.1%), and LDL-cholesterol was 2.77 mmol/L (107 mg/dL). She complained of bouts of palpitations, confusion, and chest discomfort that usually resolved with ingestion of carbohydrates. Examination of her blood glucose monitoring revealed multiple values <3.9 mmol/L (70 mg/dL), particularly at times of unpredictable physical activity. Because of recurrent hypoglycemic episodes and obesity, glibenclamide was withdrawn and liraglutide initiated at the dose of 0.6 mg daily, to be increased to 1.2 mg 10 days later. A cardiologic evaluation was also planned. Basal electrocardiogram (ECG) analysis (Figure 1) showed signs of altered reperfusion and a dipyridamole stress test was performed, which showed no signs of inducible myocardial ischemia. The rosuvastatin dose was increased to ensure attainment of target LDL cholesterol levels.

Six months later, her HbA₁c level was 47 mmol/mol (6.7%) with a 3-kg loss in body weight and no further episodes of hypoglycemia, though she still experienced chest discomfort during occasions of physical effort–associated dyspnea, which resolved spontaneously within 10 minutes. She underwent myocardial perfusion single-photon emission computed tomography (SPECT) (Figure 2), showing stress-inducible impairment of coronary blood flow reserve, whereas coronary angiography did not indicate significant epicardial coronary artery stenosis. Diltiazem was prescribed to which trimetazidine was then added with marked improvement.

Discussion

CAD is common in T2DM patients due to the concomitance of multiple CV risk factors. The role of gly-

Abbreviations


Fig. 1 Basal electrocardiogram: right bundle branch block, mild ST-segment depression with inverted T waves in aVF, DII, V₅, V₆.
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cemic control on CV risk is a matter of debate. While an association was reported in epidemiological studies, intervention to ensure strict glycemic control has lead to either no effect or a marginal one. Nonetheless, glycemic control remains key to reduce the risk of microvascular complications. Near normal HbA1c is recommended in patients with a long life expectancy, free of or with mild diabetes complications, as was the case of our patient who had nonproliferative retinopathy and no other microvascular complications. Yet, Miss AR had signs and symptoms of ischemic heart disease in spite of a minor involvement of coronary arteries. This situation may be accounted for by microvascular involvement of the myocardial vascular bed, supporting the need for strict glycemic control. However, treatment should avoid hypoglycemia, which may have been a triggering factor for angina episodes in our patient.

Hypoglycemia is associated with an increased risk for CV diseases. Several mechanisms can contribute to hypoglycemia-induced myocardial ischemia, including QT-interval elongation, hypokalemia, catecholamine discharge, platelet activation, and increased blood viscosity. Though no ECG was recorded during a hypoglycemic episode, it seems reasonable to associate the chest discomfort reported by our patient with a low blood glucose level.

The risk of hypoglycemia is greater with sulfonylureas (especially glibenclamide) than with other oral antidiabetic agents. Moreover, sulfonylureas may worsen the outcome of an ischemic insult because of nonselective interaction with vessel potassium (K⁺) channels and subsequent impairment of postischemic preconditioning.

Miss AR was then kept on metformin, but shifted from glibenclamide to liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, without significant hypoglycemic risk, owing to its glucose-dependent effect on insulin secretion and preserved glucagon response to a drop in blood glucose. GLP-1 receptor agonists may also exert extraglycemic effects. Preclinical studies have shown a reduction in the size of the infarct area upon ischemic insult, but there is no evidence that this is the case in diabetic subjects as well. A number of cardiovascular outcome studies employing GLP-1 receptor agonists are currently ongoing. ELIXA (Evaluation of LIXisenatide in Acute coronary syndrome), the first of these trials, shows CV safety of lixisenatide in high-CV-risk patients with a recent acute coronary syndrome episode.

Miss AR was symptomatic and had a positive stress test. Yet no significant coronary stenosis was documented by coronary angiography. This is compatible with heart microvascular dysfunction, a factor sufficient to precipitate myocardial ischemia as well as to impair the outcome of revascularization procedures in the case of CAD. These patients usually benefit from conventional medical therapy. Addition of trimetazidine can help reduce symptoms because of its cardioprotective properties without affecting blood pressure and heart rate. It has been suggested that trimetazidine may exert its antianginal effect by inhibiting fatty acid oxidation and improving glycolysis and glucose oxidation with a neutral or even favorable effect on glucose metabolism.

Conclusion

Miss AR’s case should encourage consideration of a “cardiologic” approach in selecting antidiabetic treatment, in order to avoid conditions (e.g., hypoglycemia)
that may precipitate CV events, and a “metabolic” approach in selecting CV therapy. Such treatment should have a neutral or even favorable effect on glucose metabolism in diabetic patients with ischemic heart disease. ■

REFERENCES

Diabetic cardiomyopathy, does it exist?

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Abstract
Diabetes mellitus markedly increases the risk for cardiovascular disease, including the risk for the development of heart failure (HF). This HF risk remains increased even after adjustment for coronary artery disease (CAD) and hypertension. Thus, the term diabetic cardiomyopathy (DC) was coined, defined as ventricular dysfunction in the absence of CAD and hypertension. While the literature about the effects of diabetes on the myocardium is increasing, a controversial discussion on the existence of DC persists. Studies both in animals and humans need to be considered to evaluate whether DC exists, and to reconsider how appropriately the term “diabetic cardiomyopathy” actually describes the direct effects of diabetes on the myocardium. In addition, type 1 and type 2 diabetes mellitus likely differentially affect the heart, which is not considered in the definition of DC. In the following article, I will briefly review the controversial discussion and arguments that may support or reject the hypothesis of the existence of DC, including the effects of the distinct types of diabetes mellitus on the myocardium.

Keywords: diabetic cardiomyopathy; diabetes mellitus; heart

In diabetes, the risk of heart failure (HF) is increased despite adjustment for coronary artery disease (CAD) and hypertension. Thus, the term “diabetic cardiomyopathy” (DC) was introduced to refer to this cardiac entity, defined as ventricular dysfunction in the absence of CAD and hypertension. While the evidence in the literature supporting the existence of DC is increasing, the debate about its existence remains controversial. Some discussion may result from the term “diabetic cardiomyopathy” per se, which may describe the effect of diabetes on the myocardium in a somewhat inconvenient way, since the conventional criteria of a cardiomyopathy, which includes ventricular dilation and impaired systolic function, are usually not met by DC. In the following paragraphs, I will briefly review the controversial discussion and the arguments that may support or reject the hypothesis of the existence of DC, including the effects of the distinct types of diabetes mellitus on the heart (Figure 1).

Diabetic cardiomyopathy in type 2 diabetes mellitus?

Numerous studies report an increased risk for HF in type 2 diabetic subjects despite adjustment for CAD, hypertension, age, sex, cholesterol, and body weight. Furthermore, Iwasaka and colleagues showed that the regional ejection fraction of the noninfarcted area following myocardial infarction is decreased in type 2 diabetic subjects, although global ejection fraction is not significantly reduced. This suggests that the non-
infarcted area is unable to compensate for the loss of function in the infarcted area.² Finally, Jaffe et al report a markedly increased incidence of pulmonary congestion in type 2 diabetic patients with previous myocardial infarction despite smaller myocardial infarct size in the diabetic cohort.³ These observations support the idea of an increased myocardial vulnerability in type 2 diabetes mellitus. The clinical features of DC are thought to include left ventricular (LV) hypertrophy and diastolic dysfunction. Diastolic dysfunction remains significant after adjustment for CAD, hypertension, and LV mass index, and this seems to be true even for subjects with insulin resistance, although several studies reported that a significant association of diastolic dysfunction and type 2 diabetes mellitus disappeared after adjustment for comorbidities.⁴,⁵ LV hypertrophy and diastolic dysfunction may increase the risk for pulmonary congestion and edema due to HF with preserved ejection fraction (HFPEF), which accounts for up to 50% of HF cases in the nondiabetic population. This may be particularly true if additional stressors are present in diabetic subjects, such as ischemic cardiomyopathy, hypertension, or impaired vascular dynamics. While there is no convincing evidence of a reduced ejection fraction in DC in type 2 diabetic patients, more sensitive measures of systolic function such as strain analysis have recently been reported to detect subclinical impairment in longitudinal and radial strain, suggestive of a mild impairment due to diabetes itself.⁶

More support for an adverse effect of diabetes on the myocardium comes from studies in rodent models. Many of these models develop cardiac dysfunction, including systolic impairment of contractile function.⁷ Since rodents are somewhat resistant to the development of CAD, this cardiac dysfunction may primarily be considered a direct effect of the diabetes-associated metabolic milieu on the myocardium. Molecular alterations in hearts of type 2 diabetic rodents include oxidative stress, increased fibrosis, alterations in myocardial energetics, impaired calcium handling, and increased inflammation, among many others.⁷ Interestingly, many of these alterations have also been observed in failing hearts, suggesting that preexisting molecular alterations in DC may indicate an already predisposed and vulnerable myocardium that may ultimately progress to overt HF if sufficient additional stressors are present. Furthermore, genetically modified mice mimicking specific effects of the diabetic milieu on the heart were helpful to clarify that and how systemic metabolic alterations (eg, hyperglycemia, hyperlipidemia, and insulin resistance) affect the heart in type 2 diabetes mellitus.⁷ Finally, it is important to mention that the few human studies that are now available confirm findings of rodent DC in human hearts, including increased oxidative stress, mitochondrial dysfunction, and altered energy substrate metabolism.⁸,⁹

**Arguments for and against the existence of diabetic cardiomyopathy**

**For:**
- Increased HF risk
- Diastolic dysfunction
- Molecular alterations similar to HF

**Against:**
- Lack of persistent systolic dysfunction
- Diastolic dysfunction persistent after multivariate adjustment?
- No significant cardiac dysfunction in long-term T1DM
- Unspecific effects due to exogenous insulin treatment?

**For:**
- Increased HF risk
- LV hypertrophy
- Diastolic dysfunction
- Subclinical systolic dysfunction
- Molecular alterations similar to HF

**Against:**
- Lack of prospective clinical trial
- Secondary effects due to hyperinsulinemia and RAAS?
- Systolic/diastolic dysfunction not specific to diabetes?
- Prognosis of subclinical cardiac dysfunction unclear

**Fig. 1** A summary of arguments that may support (for) or reject (against) the hypothesis of the existence of diabetic cardiomyopathy in type 1 and type 2 diabetes mellitus.

**Abbreviations:** HF, heart failure; LV, left ventricular; RAAS, renin-angiotensin aldosterone system; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
A major criticism regarding the existence of DC in type 2 diabetes mellitus is the lack of a prospective clinical trial showing an increased risk for HF and/or impaired cardiac function in the complete absence of confounders, eg, CAD and hypertension. However, such a study would be costly, would require a rather long-term follow-up period, and would need a large amount of patients since many diabetic patients will develop confounding comorbidities during the course of such a trial, thus making it unlikely that we could expect data on the subject anytime soon. It has been argued that the changes in diastolic function may be attributable to an increase in peripheral resistance and myocardial overload mediated by hyperinsulinemia and secondary activation of the sympathetic nervous system. Since insulin acts as a growth factor, it has been suggested that the increase in LV mass in type 2 diabetes mellitus may be due to hyperinsulinemia. Some authors argue that subclinical systolic and diastolic dysfunction that can only be detected with strain imaging is observed in many other conditions, including obesity, hypertension, and even healthy aging. Therefore, such findings, even when present, may not be specific to diabetes. Whether the subclinical form of DC is of prognostic significance still remains to be investigated.

Diabetic cardiomyopathy in type 1 diabetes mellitus?

One study has shown the risk for the development of HF to be increased in type 1 diabetic subjects, with duration of diabetes and impaired glycemic control predictive of HF. In that study, hospital admission for HF occurred in almost 1 in 30 fairly young patients with type 1 diabetes mellitus, implying that HF was a major diabetic complication in these patients. In another study, the incidence of HF in type 1 diabetic patients aged 41 to 45 years was reported to be similar to that in nondiabetic patients aged 55 to 64. Similarly, it has been proposed that diabetes alone may lead to premature aging of the heart (as a sign of DC), since values of some echocardiographic parameters of diastolic function measured in young (20-32 years) persons with type 1 diabetes mellitus correspond with the diastolic parameters of healthy men at the age of 50 and over.

Evaluating the impact of type 1 diabetes mellitus on cardiac function has been challenging, probably related to the fact that patient selection and exclusion criteria may have varied considerably between studies. While only a few studies demonstrate actual systolic dysfunction in type 1 diabetic patients, studies frequently report normal or increased LV systolic function. Most studies observe abnormal LV diastolic function, whereas some report no evidence of LV diastolic dysfunction at rest in long-term type 1 diabetes mellitus. It remains controversial whether diastolic dysfunction is due to diabetes per se, since adjustment for coexistent hypertension, CAD, autonomic dysfunction, and microangiopathy blunt the significance for diastolic dysfunction in some studies.

A recent study that observed type 1 diabetic patients over an average of 36 years demonstrated that the HF incidence was rather low, and HF and myocardial dysfunction were only observed if patients developed hypertension or CAD. Despite the presence of microvascular dysfunction and fibrosis, no significant echocardiographic differences were observed in long-term type 1 diabetes mellitus in another study. Thus, rather recent studies may argue against a relevant effect of type 1 diabetes mellitus on cardiac function. The lack of cardiac dysfunction may be related to permanent treatment with exogenous insulin, which treats potentially causative systemic metabolic alterations. It has also been argued that myocardial overload and increased peripheral resistance after the administration of exogenous insulin may cause diastolic dysfunction, as opposed to being symptoms of DC. Others discussed that in some studies, echocardiographic parameters used to diagnose diastolic dysfunction (eg, shortened E/A ratio, prolonged isovolumic relaxation time [IVRT]) were misinterpreted, since absolute values that were significantly different between diabetic and nondiabetic subjects were actually (according to echocardiographic guidelines) within the normal range for healthy people, which would not allow a diagnosis of diastolic dysfunction in the diabetic cohort.

In animal models of type 1 diabetes mellitus, cardiac dysfunction has been observed in most studies, and molecular alterations are similar to that seen in type 2 diabetic hearts, including oxidative stress, increased fibrosis, alterations in myocardial energetics, impaired calcium handling, and increased inflammation, among many others, although some differences to type 2 diabetes mellitus models exist.
ferences may be related to the different pathophysiology, such as differential effects of insulin deficiency in type 1 versus insulin resistance in type 2 diabetes mellitus on cardiomyocyte insulin signaling and downstream pathways. While animal studies support the existence of DC in type 1 diabetes mellitus, it needs to be considered that diabetic animals are usually not treated with insulin. Thus, exacerbated hyperglycemia and insulin deficiency both have a continuous impact on the heart. In contrast, even though glycemic control may vary between subjects taking insulin, insulin treatment does exist in humans, and this may ameliorate the effects both of hyperglycemia and insulin deficiency on the myocardium.

Conclusions

To answer the question of whether DC exists may require appropriate interpretation of a large amount of available literature on the topic and careful consideration of the actual meaning of the term “diabetic cardiomyopathy.” Taken together, animal and human studies show overwhelming evidence of DC in type 2 diabetes mellitus, which is a combination of various molecular alterations within the myocardium, and which may be considered a predisposition to develop HFPEF and potentially also systolic dysfunction. However, data from a prospective clinical trial to more clearly evaluate the latter issue is not yet available. Molecular alterations and cardiac dysfunction also occur in animal models of type 1 diabetes mellitus, but the interpretation of data in humans is complicated due to considerable differences in patient selection and exclusion criteria and because patients are treated with insulin, which likely ameliorates the effect of type 1 diabetes mellitus on the heart.

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Antidiabetic treatment and cardiovascular events: all a matter of perspective!

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Diabetic patients are known to be at increased risk for developing macrovascular (ie, cardiovascular disease) and microvascular complications, such as eye, nerve, and kidney disease. The pathophysiology of type 2 diabetes mellitus (T2DM) is complex, mainly characterized by insulin resistance (IR) in fat, muscle, and liver tissues, and is associated with pancreatic α- and β-cell dysfunction. Accordingly, there are numerous treatment strategies offering effective glycemic control.

However, while lowering glycated hemoglobin A1c (HbA1c)—a biomarker reflecting blood glucose concentration—is associated with beneficial effects on the microvasculature, its effects on cardiovascular outcome are a matter of continuous scientific controversy. For instance, the trials UKPDS (United Kingdom Prospective Diabetes Study) and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN Modified Release Controlled Evaluation) tested different glycemic control strategies across a wide spectrum of patients with diabetes and did not find a clear benefit in terms of myocardial infarction, cardiac mortality, and hospitalization for heart failure, among other outcomes, during active therapy. On the contrary, in the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), near-normal glycemic control was associated with significantly increased risks of death from any cause and death from cardiovascular causes.

In 2008, the US Food and Drug Administration (FDA) released a guidance statement asserting the need to assess the cardiovascular safety of some of the drugs used in T2DM. When additional data became available, the FDA issued an explicit safety communication, recommending restrictions for their use. This announcement was reversed in 2013 when further evaluation of data showed that it was uncertain whether the changes in cardiovascular risk were due to the drug or due to chance alone.Regardless of the ultimate recommendations, the safety issues highlighted by the FDA translated into a change in focus and led to the construction of noninferiority trials that aimed to assess the safety profiles of the new treatments.

Indeed, while superiority trials are performed with the aim of demonstrating that a treatment strategy is more efficacious than an established one, the purpose of a noninferiority trial is to show that a new therapy is at least as good as the existing treatment. Superiority trials can identify both harmful and beneficial effects of the new therapy. However, the lack of a significant difference in results does not necessarily imply that the new treatment is equally effective.

Recently, the results of the trials ELIXA (Evaluation of Lixisenatide in Acute coronary syndrome) and TECOS (Trial to Evaluate Cardiovascular Outcomes after treatment with Sitagliptin)—for whom inception dates back to the period when the FDA issued the safety
announcements mentioned above—were presented at the American Diabetes Association’s 2015 Scientific Sessions (accessible at http://adascisessions.ci-vi-go.com/). Each trial tested a different incretin drug versus placebo and proved neutral, with no increase in the incidence of major cardiac events in high-risk patients.

Currently, there are a number of other ongoing safety trials. As these data become available, some doubts are cropping up regarding whether such trials are the best overall strategy for improving the outcomes in diabetic patients. Determining whether a specific type of glucose-lowering drug has any additional benefit over standard of care is very difficult. The drug development industry relies on the effects that a molecule exerts on the surrogate biomarker (ie, HbA1c levels). Whether or not this translates into a clinical benefit is not necessarily predictable and should be tested with a clinically meaningful perspective.

To further complicate the subject, it should be recognized that antidiabetic drugs are in the unusual position that biologically plausible, yet contradictory, arguments could be made that (i) they might cause cardiovascular harm and (ii) they might come with cardiovascular benefit. The recently published, long-term follow-up results from the VADT (Veterans Affairs Diabetes Trial) provide data supporting the hypothesis that more intense glycemic control can improve “macrovascular” cardiac events. However, the observed benefit was modest (17% lower risk of cardiovascular events with no mortality benefit) and the time horizon quite long (10 years of follow-up).11

The results of the ELIXA and TECOS trials, although neutral, were presented with enthusiasm; the drugs did not cause harm! However, it should be stressed that these (and other trials like them to come) were mainly designed to satisfy FDA requirements and demonstrate safety, as for any new glucose-lowering drug. In this scenario, the capture of a clinically meaningful benefit becomes particularly challenging. Keeping in mind that diabetic patients are vulnerable both to cardiovascular disease and cardiovascular side effects, pharmaceutical and marketing strategies that target both effects should be prioritized.

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Alogliptin is an orally taken dipeptidyl peptidase-4 (DPP-4) inhibitor developed by Takeda Pharmaceutical Company for the treatment of type 2 diabetes under the trade name Nesina in the United States, and Vidipia in Europe. Unlike saxagliptin, alogliptin is not associated with an increased risk for hospitalization for heart failure.

**Dipeptidyl peptidase-4 (DPP-4)**
DPP-4, also known as cluster of differentiation 26 (CD26), is a multifunctional enzyme best known for its biological activity to act as a protease that cleaves dipeptides from the N-terminus of proteins immediately following a position-2 proline or alanine amino acid. Because of its ability to cleave the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), DPP-4 inhibitors have been developed to prevent degradation of GIP and GLP-1 for the treatment of type 2 diabetes. Other biological functions of DPP-4 include an association with adenosine deaminase, cell-surface co-receptor activity involved in viral entry, and the regulation of signal transduction coupled to the control of migration and proliferation of cells.

**Glucagon**
Glucagon is the principal secretory product of α-cells of pancreatic islets. Glucagon is a 29–amino-acid peptide hormone derived from proglucagon via the action of prohormone convertase 2. The primary endocrine effects of glucagon are to increase hepatic glucose production by stimulating both hepatic glycogenolysis and gluconeogenesis to counter hypoglycemia.

**Glucagon-like peptide-1 (GLP-1)**
GLP-1 is an incretin hormone synthesized and secreted from intestinal L cells. GLP-1 is derived from proglucagon via the action of prohormone convertase 1. Biologically active GLP-1 is generated from GLP-1_{1-37}, as either GLP-1_{7-37} or GLP-1_{7-36} amide, which represents the majority of biologically active GLP-1 in human plasma. GLP-1 exerts a variety of effects relevant to the regulation of glucose homoeostasis, including enhancing glucose-stimulated insulin secretion, while inhibiting glucagon secretion. In addition, GLP-1 has been demonstrated to promote β-cell proliferation, inhibit β-cell apoptosis, decrease the rate of gastric emptying, and decrease food intake.

**Incretin**
Incretin refers to gastrointestinal peptide hormones released by enteroendocrine cells of the intestinal mucosa in response to the ingestion of food (or oral glucose load). The two major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino-tropic polypeptide (GIP). Incretins enhance glucose-stimulated insulin secretion, and thus are important regulators of glucose homeostasis. In addition, a variety of extraglycemic effects of incretins have been documented, including a slowing of gastric emptying, promotion of satiety, and reductions in food intake.

**Lixisenatide**
Lixisenatide is a 44–amino-acid peptide developed by Sanofi-Aventis under the trade name Lyxumia. It is a short-acting glucagon-like peptide-1 (GLP-1) receptor agonist, administered via once-daily subcutaneous injection, and used in the treatment of type 2 diabetes. The therapeutic effects of lixisenatide (and GLP-1 receptor agonists as a drug class) include the stimulation of insulin secretion and glucose-lowering efficacy, slowing of gastric emptying, and the promotion of weight loss.

**Saxagliptin**
Saxagliptin is an orally taken dipeptidyl peptidase-4 (DPP-4) inhibitor codeveloped by Bristol-Myers Squibb and AstraZeneca for the treatment of type 2 diabetes under the trade name Onglyza. Of interest, saxagliptin was shown to increase hospitalization rates for heart failure during the “Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus-Thrombolysis In Myocardial Infarction 53 (SAVOR-TIMI 53)” clinical trial.

**Sitagliptin**
Sitagliptin is an orally taken dipeptidyl peptidase-4 (DPP-4) inhibitor developed by Merck & Co. for the treatment of type 2 diabetes under the trade name Januvia. On October 2006, sitagliptin became the first DPP-4 inhibitor approved in the United States by the US Food and Drug Administration for the treatment of type 2 diabetes.
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