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ORIGINAL RESEARCH ARTICLE

Diabetes and cardiovascular disease

Carlos Guamán[1,*], William Acosta[2,3], Carla Alvarez[4], Benhard Hasbum[5]

[1] *Centro Cardiovascular Universitario, Hospital de Clínicas, Montevideo 56265, Uruguay*
[2] *Departamento de Endocrinología, Hospital de Especialidades Eugenio Espejo, Quito 272050, Ecuador*
[3] *Pontificia Universidad Católica del Ecuador, Quito 272050, Ecuador*
[4] *Departamento de Endocrinología y Metabolismo, Hospital de Clínicas, Montevideo 56265, Uruguay*
[5] *Diabetología, Academia & Investigación, San José 40502, Costa Rica*
*** Corresponding author:** Carlos Guamán, cgv0792@gmail.com

ABSTRACT

Diabetes mellitus is one of the main causes of morbidity and mortality worldwide. This group of patients generally represents a population at high or very high cardiovascular risk, which is why early risk stratification is performed, seeking to focus objectively on the pharmacological and nonpharmacological approach with an intensive strategy. Cardiovascular disease represents the main cause of mortality, but in recent years there have been advances in therapeutics that have been shown to reduce major cardiovascular events. This article reviews the interaction between diabetes, cardiovascular disease and its treatment.

Keywords: diabetes mellitus; cardiovascular diseases; hypertension; myocardial ischemia; heart failure; cardiac arrhythmias

1. Introduction

Diabetes mellitus [DM] is one of the most prevalent chronic diseases in the world; approximately 463 million adults suffer from this disease, half of whom have not been diagnosed, which generates more than 700 billion dollars in expenses for their care. Given the increase in obesity, physical inactivity and life expectancy in the population, it is estimated that by 2045 there will be more than 600 million people in the world with type 2 DM [DM2][1–3]. This disease remains underdiagnosed. The GAMI study[4] [The Glucose Abnormalities in Patients with Myocardial Infarction] demonstrated, in the context of myocardial infarction, that the oral glucose tolerance test detects new-onset DM or prediabetes in two thirds of patients.

It is estimated that in 2019 approximately 4.2 million adults aged 20–79 years died as a result of DM and its complications. Premature death and disability are also associated with a negative economic impact for countries, this is often referred to as the "indirect costs" of DM. In the United States, premature deaths are estimated to cost $19.9 billion per year to the economy, and a total of $90 billion is indirectly lost due to DM[3]. Cardiovascular pathologies are those that lead to death[5], rather than hyperglycemia per se, usually in the form of heart failure [HF], in the context of the patient with obesity and its complications, such as sleep apnea[1–3]. This article provides a general review of the interaction between cardiovascular disease and DM.

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2. Cardiovascular

2.1. Cardiovascular risk and diabetes

A meta-analysis of 102 prospective studies showed that DM doubles the risk of coronary heart disease [CHD], ischemic stroke, and death from vascular disease, independently of other risk factors, with a higher risk in women and at older ages[6]. The duration of the disease, poor glycemic control and the presence of microvascular complications [such as renal disease or proteinuria] increase both the relative risk of cardiovascular events and the absolute risk[7]. Even with blood glucose levels below the threshold for the diagnosis of DM, there is a risk of CHD, which increases with glucose concentration[6].

2.2. Cardiovascular risk stratification

The European Society of Cardiology Guidelines developed in collaboration with the European Society for the Study of Diabetes in 2019[2], state that patients with DM and three or more risk factors, or with more than 20 years of disease duration, have a very high cardiovascular risk [risk of death secondary to a cardiovascular event within 10 years > 10%], as well as those with cardiovascular disease or with DM and target organ damage [such as proteinuria or chronic kidney disease [glomerular filtration rate <30 ml/min]]. 10%[7,8]. Patients with type 1 DM [DM1] diagnosed in their first 10 years of life have a very high cardiovascular risk after 40 years of age, especially women[9] (**Table 1**).

Table 1. Cardiovascular risk categories in patients with diabetes. Modified from reference[2].

Moderate risk	High risk	Very high risk
Young patients [age <35 years in DM1 and <50 years in DM2] with duration of DM <10 years, no target organ damage[a] and no other risk factors[b].	Patients with DM of >10 years duration without target organ damage[a] and with any additional risk factors[b].	Patients with DM and established cardiovascular disease. Target organ damage[a] or three or more major risk factors[b] or DM1 of early onset and with more than 20 years of duration.

[a] Proteinuria, renal dysfunction [glomerular filtration rate < 30 ml/min/1.73 m^2], left ventricular hypertrophy or retinopathy.
[b] Age, hypertension, dyslipidemia, smoking, obesity.

DM2 of less than 10 years of evolution and without cardiovascular risk factors, who have a moderate risk [10-year risk of death from cardiovascular disease of 1%–5%][2]. Female patients are not protected against premature cardiovascular disease in the presence of DM, unlike that observed in the general population[10].

2.3. Cardiovascular damage assessment

Currently, the use of biomarkers such as C-reactive protein, fibrinogen, high-sensitivity troponin, or NT-proBNP in the assessment of cardiovascular risk has no clinical value[11]. On the other hand, the finding of microalbuminuria [30–299 mg/day] predicts the appearance of renal dysfunction and justifies nephroprotective interventions[12,13], which even have an impact on reducing mortality[14], so its measurement is recommended[15].

Resting electrocardiogram can detect silent myocardial infarction in 4% of patients with DM, which is associated with an increased risk of cardiovascular events and total mortality in men, but not in women[16]. In patients with DM1, increased QT interval is associated with increased cardiovascular mortality and increased resting heart rate is associated with risk of cardiovascular events in both DM1 and DM2[17]. Decreased resting heart rate variability was associated with increased risk of fatal and non-fatal CHD[18–20].

Patients with DM have a higher prevalence of coronary calcification than age- and sex-matched subjects without DM[21]. Computed tomography [CT] can noninvasively estimate atherosclerotic burden, coronary artery calcium score can modify the estimation of cardiovascular risk in asymptomatic and moderate-risk

patients[15,21].

Systematic screening for asymptomatic CAD in DM remains controversial, and to date it is only suggested that it should be considered in patients at very high cardiovascular risk[2,22]. The presence of carotid or femoral plaques detected by ultrasound was associated with increased cardiovascular events, so their diagnosis should be considered as a risk modifier in asymptomatic patients[23]. In selected cases, it is possible to use techniques such as myocardial perfusion scintigraphy or coronary CT angiography, which identifies atheromatous plaques causing significant coronary stenosis.

3. Arterial hypertension and diabetes

Arterial hypertension can be found in approximately 70% of patients with DM, due to the fact that in most of them there is a pathophysiological basis of obesity on which triggering factors act, such as hereditary elements and fat distribution, among others; the coexistence of these entities favors the appearance of earlier and more severe microvascular and macrovascular disease[24,25]. Several studies have shown that reducing systolic blood pressure [SBP] < 140 mmHg and diastolic blood pressure [DBP] < 90 mmHg reduces the risk of stroke, coronary events and renal disease[26]. If tolerated by the patient, the SBP target should be <130 mmHg, especially if there is a history of stroke[24,26]. In patients >65 years, SBP should be maintained between 130–140 mmHg. In no patient with DM should SBP < 120 mmHg or DBP < 80 mmHg be reduced[27].

The first recommendation for blood pressure reduction should be a diet low in sodium, rich in vegetables, fruits and low-fat dairy products[27]. A combination of aerobic exercise with resistance exercise reduces SBP by 7 mmHg and DBP by 5 mmHg[28]. In the Look AHEAD study a 5%–10% reduction in body weight achieved a 5 mmHg reduction in SBP and DBP[29].

If during the consultation the SBP persists >140 mmHg or DBP >90 mmHg despite non-pharmacological treatment, treatment with antihypertensive drugs should be initiated. 90 mmHg despite non-pharmacological treatment, treatment with antihypertensives should be initiated, of which any of the groups except beta-blockers is recommended first line, with better evidence for inhibitors of the aldosterone system [ACE inhibitors [angiotensin-converting enzyme inhibitors] or ARBs [angiotensin II receptor antagonists]], especially if microalbuminuria or left ventricular hypertrophy, or both, are present[27,30].

Combination therapy is usually required for adequate blood pressure control, with the most evidence-supported combination being ACEI or ARB and a calcium channel blocker or diuretic. The use of beta-blockers with diuretics is not recommended since they raise glycemia, could worsen glycemic control and should be avoided especially in patients with prediabetes. ACE inhibitors should not be combined with ARBs[27,31].

The LEADER study found a 1.2 mmHg reduction in SBP and 0.6 mmHg reduction in DBP with glucagon-like peptide-1 [GLP-1] receptor agonists[32], and a meta-analysis found that.

Sodium-glucose cotransporter type 2 [SGLT-2] inhibitors induced a 2.46 mmHg reduction in SBP and a 1.46 mmHg reduction in DBP[33].

4. Aspirin in primary prevention of coronary artery disease in diabetes

A meta-analysis of primary prevention clinical trials was published in 2009, analyzing 95,000 low-risk subjects, and found a 12% reduction in cardiovascular disease with aspirin use, but a significant increase in major bleeding[34]. The ASCEND study[35] [A Study of Cardiovascular Events in Diabetes], published in 2018, randomized 15.480 diabetic patients to receive aspirin 100 mg/day or placebo, finding an 8.5% incidence of myocardial infarction, stroke, transient ischemic attack, or death in aspirin patients and 9.6% in placebo patients [RR = 0.88; 95%CI, 0.79–0.97; $p = 0.01$], but major bleeding occurred in 4.1% of aspirin subjects and

3.2% of placebo subjects [RR = 1.29; 95%CI, 1.09–1.52; $p = 0.003$].

Based on these studies, aspirin [75–100 mg/day] can currently be recommended for primary prevention in patients with diabetes and high or very high cardiovascular risk, but in the absence of contraindications, such as a high risk of bleeding. It is not recommended in diabetic patients with moderate cardiovascular risk[2].

5. Coronary heart disease and diabetes

All the traditional cardiovascular risk factors, such as obesity, smoking, dyslipidemia, and hypertension, can be found in patients with CAD and DM. Hyperglycemia states are related to endothelial vasomotor dysfunction, abnormalities in lipid metabolism, systemic inflammation and prothrombotic state[36]. The presence of impaired fasting glucose alone is associated with a worse cardiovascular prognosis. Based on observational studies, approximately 70% of CD patients have newly detected DM or glucose intolerance, whereas only 20%–30% have known DM at the time of CD diagnosis[4].

The evidence on secondary prevention treatment in patients with DM is based on the analysis of subgroups of clinical trials, with their known limitations. However, it has been indisputably demonstrated that adequate glycemic control leads to a delay in the onset of microvascular complications and a reduction in their progression, so that early, effective and constant glycemic control is recommended in all clinical practice guidelines[2,37]. It is important to emphasize that the first intervention should always be lifestyle-related, recommending smoking cessation, a minimum of 150 minutes of aerobic exercise per week and a healthy diet[37].

A study of 753 patients from the UKPDS[38], with a mean follow-up of 10.7 years, compared conventional treatment with metformin, finding a 39% reduction in the risk of myocardial infarction, a 50% reduction in CAD, and a 41% reduction in stroke. In addition, observational and database-driven studies have shown that in the long term, metformin improves the cardiovascular prognosis of patients with DM[39,40]. However, there are no large-scale clinical studies on cardiovascular safety that have been designed to define its effect on cardiovascular events, although it has been the therapeutic basis in most of the large studies with the new oral antidiabetic drugs.

Sulfonylureas present a higher risk of hypoglycemia and there are doubts about their cardiovascular safety. The CAROLINA study[41] compared glimepiride with linagliptin [DPP-4 inhibitor] and demonstrated similar cardiovascular safety in patients with DM2. In the different studies, this group has not demonstrated a reduction in cardiovascular events. Among the main side effects of sulfonylureas are weight gain and, above all, hypoglycemia, which is more frequent than with any other oral hypoglycemic agent, raising the alarm for episodes of hypoglycemia that can trigger acute ischemic events. Caution should be exercised, as there is growing but contradictory evidence of increased mortality associated with their use[42]. Glibenclamide is the sulfonylurea associated with the highest risk of severe hypoglycemia and mortality, and gliclazide with the lowest risk, with no difference between immediate and prolonged release presentations[42,43].

The use of thiazolidinediones has been discussed. The PROactive study[44], which evaluated pioglitazone in its original publication, did not show statistically significant cardiovascular benefit, and the frequency of HF was higher, without an increase in mortality. It should be considered that the primary endpoint evaluated seven events [death from any cause, nonfatal infarction, stroke, acute coronary syndrome, lower limb amputation, coronary revascularization or lower limb revascularization]. After a meta-analysis evaluated cardiovascular events during rosiglitazone treatment in 2008[45] and found an increased risk of myocardial infarction, it was decided to modify the DM drug regulations, and since then all DM drugs must demonstrate cardiovascular safety before being approved for commercial use.

DPP-4 inhibitors have been shown to be non-inferior to placebo; sitagliptin was associated with an increased risk of HF hospitalization, in subgroup analysis it was found that the highest risk was in patients with pre-existing HF and in those with chronic kidney disease[46], so it is not recommended in these particular populations.

Within the GLP-1 receptor agonist group, the LEADER trial[32] evaluated liraglutide 0.6 mg–1.8 mg once daily versus placebo, and demonstrated a significant reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in 13% of patients during a 3.1-year follow-up. The SUSTAIN-6 study[47] found that semaglutide 0.5 mg–1 mg once weekly significantly reduced cardiovascular events by 26% and nonfatal stroke by 39% during a 2.1-year follow-up. The PIONEER-6 study[48] demonstrated non-inferiority of oral semaglutide [the only oral GLP-1 in current use] in reducing cardiovascular events, but there was a significant increase in retinopathies, such as vitreous hemorrhage or blindness. These drugs have been shown to slightly reduce SBP and cause weight loss, thus improving cardiovascular parameters[49].

SGLT-2 inhibitors have been the main protagonists in recent years. In the EMPA-REG OUTCOMES study[50], empagliflozin 10 mg or 25 mg/day was associated with a 14% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, compared with placebo, during a 3.1-year follow-up, with a statistically significant 38% decrease in cardiovascular death. But a statistically nonsignificant 24% increase in the risk of nonfatal stroke was found. A number needed to treat [NNT] of 39 was estimated to prevent one death in three years. Similar results were found with canagliflozin 100 mg–300 mg once daily; however, an increased incidence of lower extremity fractures and amputations was evident[51]. In the DECLA- RE-TIMI 58 study[52], dapagliflozin 10 mg once daily was associated with a lower rate of HF hospitalization, but not cardiovascular death in a 4.2-year follow-up versus placebo. In the CREDENCE study[53], canagliflozin was associated with decreased adverse renal and cardiovascular outcomes and HF hospitalization compared with placebo. The benefit of SGLT-2 inhibitors is not directly related to glucose lowering, and although several mechanisms have been proposed, they are still under study[54].

The ORIGIN study[55] assigned 12,537 patients with DM2 and prediabetes to treatment with insulin glargine U100 or conventional treatment, and after a follow-up of 6.2 years found no statistically significant differences with respect to non-fatal myocardial infarction, non-fatal stroke or cardiovascular mortality, but the use of insulin was associated with more hypoglycemia and weight gain. The DEVOTE 7 study[56], with 7637 patients randomized to insulin glargine U100 compared to insulin degludec, showed a higher risk of cardiovascular death, all-cause death and adverse events the older the age of the exposed individuals, showing benefit in the group treated with insulin degludec.

6. Acute coronary syndrome and diabetes

In acute coronary syndrome, approximately 20%–25% of patients are diagnosed with DM after the event[4,57]. Diagnosis is challenging given the high frequency of stress hyperglycemia, and should not be limited to the determination of fasting blood glucose; glycosylated hemoglobin [HbA1c] or an oral glucose overload test should be requested before discharge[2,4,57]. The HbA1c value is strongly related to mortality in this group of patients[58].

The CREATE ECLA GIK study[59], which included Latin American patients, evaluated the administration of a glucose-insulin-potassium infusion with a glycemia target of 126 mg/dL–200 mg/dL in 20,201 patients with ST-segment elevation acute myocardial infarction, accumulating 1,980 deaths and demonstrating no benefit, so this practice was abandoned. The DIGAMI 1 study[60] randomized 620 patients at the onset of myocardial infarction to a 5 U/h intravenous [IV] insulin infusion plus IV glucose, followed by subcutaneous insulin, for a blood glucose target of 126 mg/dl–198 mg/dl, finding a reduction in mortality at 1-year follow-

up. But there are a number of clinical trials that have found no benefit with intensive glucose control[61], and the DIGAMI 2[62] and NICE- SUGAR[63] studies indicated that episodes of hypoglycemia are harmful to the ischemic myocardium and are associated with increased risk of death and worse cardiovascular prognosis. International guidelines recommend the use of insulin in diabetics with hyperglycemia >180 mg/dL, adapting the target to the comorbidities of each patient [class IIa recommendation, level of evidence C][2].

7. Heart failure and diabetes

Patients with HF, whether with reduced [LVEF-R] or preserved [LVEF-C] left ventricular ejection fraction, have a higher risk of developing DM[64]. On the other side of the coin, the mere fact of having DM is a risk factor for future HF[65].

In observational studies of diabetic individuals, approximately 25% of patients with HF were unaware of their condition, and HF with LVEF-C [in 75% of patients] was more frequent than HF with LVEF-R [in 25%][66]. While patients without HF at the beginning of the studies were two to five times more at risk of presenting HF, with the risk increasing with an increase in HbA1c > 5.5%[64,67].

In the HF population with LVEF-R, DM is the main predictive marker of complications, having a 50%–90% higher cardiovascular mortality, regardless of LVEF[68]. It has been found that a patient with HF and prediabetes or undiagnosed DM has a higher risk of death and worse clinical outcome[66–68].

HF is associated with a state of insulin resistance, which is probably related to the higher prevalence of DM in this population. No association has been found with LVEF, but an increased risk of DM has been detected with greater severity of HF and with the use of loop diuretics[69].

In patients with DM the main causes of HF are CAD, chronic kidney disease, arterial hypertension and the different direct effects of insulin resistance and hyperglycemia on the myocardium[64,65,68,69]. In diabetic patients, CD is usually accelerated, severe, diffuse and silent, and the risk of myocardial infarction and myocardial ischemia is increased[67]. Data on diabetic cardiomyopathy come from several observational studies with small samples, so the existence of this particular type of cardiomyopathy has not been confirmed, although the occurrence of HF is probably due to complex pathophysiological mechanisms independent of the presence of CAD or hypertension[70].

The treatment of HF is the same as in the population without DM, given that the clinical trials that have tested the value of the various drugs and devices involved a representative population of patients with DM[71]. With respect to beta-blocker therapy, carvedilol may have some advantage as it has shown a favorable effect on insulin sensitivity and lipid profile, but the clinical relevance of this is still uncertain[72].

Of the new drugs for the treatment of HF, it is worth noting that sacubitrilo-valsartan was associated with a greater reduction in HbA1c and a lower rate of insulin initiation during a 3-year follow-up in patients with DM[73]. In the analysis of the subgroup of diabetic patients in the PARADIGM HF study, sacubitrilo-valsartan demonstrated a decrease in morbidity and mortality versus enalapril, but without statistical significance[74].

Regarding the blood glucose target, there is no evidence that strict control is better than less intense control, so a liberal target of HbA1c < 8% is recommended, avoiding hypoglycemia[2].

Metformin is safe in patients with moderately reduced renal function [glomerular filtration rate > 30 ml/min/1.73 m^2] and has been associated with a lower risk of death or hospitalization for HF compared to sulfonylureas and insulin; no significant increase in the occurrence of lactic acidosis has been found with other bigua-nides[75]. Sulfonylureas have been associated with increased risk of HF and mortality relative to metformin[76]. Thiazolidine-diones are not recommended[2]. Saxagliptin [DPP-4 inhibitor] was associated with

an increased risk of hospitalization for HF[46], while alogliptin, sitagliptin and linagliptin had non-statistically significant results in relation to this variable, so the use of this pharmacological group in patients with HF and DM is not recommended as first line; sitagliptin and linagliptin can be considered if necessary, with a grade of recommendation IIb, level of evidence A, as can GLP-1 agonists [lixisenatide, lira-glutide, semaglutide, exenatide and dulaglutide][2], while, as already noted, saxagliptin is not recommended in this population.

Among the new drugs, empagliflozin stands out, which reduced the risk of hospitalization for HF in patients with and without previous disease, with lower in-hospital mortality[50]. The DAPA HF study[77] randomized 4744 patients with HF to receive dapagliflozin 10 mg/day or placebo, with 55% of non-diabetic patients in each group. A statistically significant reduction of 26% in the combined endpoint [worsening HF and cardiovascular death] was demonstrated in both diabetic and non-diabetic patients. SGLT-2 inhibitors are currently recommended in patients with DM and high risk of HF, and will probably be included in clinical practice guidelines in the coming years as recommended drugs in HF in both patients with and without DM.

8. Arrhythmias and diabetes

DM is an independent risk factor for the development of atrial fibrillation [AF] due to various mechanisms such as autonomic, electromechanical and structural remodeling, and glycemic variability. With the onset of AF, there is an increased risk of acute HF due to loss of atrial contraction. The coexistence of DM and AF increases the risk of stroke and cardiovascular death[78,79].

In a patient with AF, the presence of DM increases the risk of stroke by 2%–3.5% annually[80]. Because of the benefit of more aggressive control of cardiovascular risk factors in this population, screening for this arrhythmia by pulse palpation and confirmation with electrocardiogram is recommended[2,15,81]. AF, whether paroxysmal or persistent, is an independent risk factor for stroke in patients with DM, so the use of direct oral anticoagulants [as first line because of the lower risk of bleeding] or warfarin is recommended[81].

Premature ventricular beats and nonsustained ventricular tachycardia are common in diabetic patients, and their finding should prompt the clinician to look for structural heart disease with stress electrocardiography, echo cardiography, coronary angiography or magnetic resonance imaging, as appropriate[82,83]. The risk of a cardiac event is determined by the pre-existing heart disease and not by the ectopic heartbeat[82]. In very symptomatic patients, beta-blockers or calcium channel blockers can be used, and in the absence of structural heart disease, class IC antiarrhythmics [flecainide or propafenone] or catheter ablation can be indicated[83].

The diagnosis and treatment of sustained ventricular tachycardia or ventricular fibrillation are the same as in non-diabetic patients[82,84]. Patients with prediabetes or DM have four times the risk of sudden cardiac death than non-diabetics[85]. Patients with DM and a history of myocardial infarction are at higher risk, and if LVEF < 35%, mortality increases substantially, so it is necessary to determine which patients would benefit from implantation of a cardiac defibrillator. On the other hand, QRS duration should be measured to identify candidates for cardiac resynchronization therapy[84], although an analysis of the guidelines for the recommendation of these devices is beyond the scope of this review.

In patients with HF with LVEF-R, treatment with renin-angiotensin-aldosterone system blockers, beta-blockers and mineralocorticoid receptor antagonists is recommended to reduce the risk of sudden cardiac death[71].

It has been found that both bradycardia and ventricular premature beats are more frequent during periods of nocturnal hypoglycemia, so the possibility of an association between increased nocturnal mortality and intensive glycemic control was raised[86]. It was postulated that the risk of sudden cardiac death in patients with DM may be increased by nephropathy, dysautonomia, prolonged QTc interval, hypoglycemia and

comorbidities.

9. Conclusions

Cardiovascular disease and DM share the same risk factors, and their interaction is constant. All patients with DM present significant cardiovascular risk, so the health care team in charge of their care should not minimize this association, generating strategies to optimize pharmacological and non-pharmacological treatment, in order to reduce macro- and microvascular complications, reduce cardiovascular mortality, improve prognosis and quality of life in the long term.

Therapeutics in DM is an area in constant progress; recent studies have shown that new drugs are another tool that, oriented to the pathophysiology of the disease, achieve not only a decrease in blood glucose levels but, more importantly, a decrease in major cardiovascular events. This has initiated a new era in the approach and in the possibility of improving the prognosis of our patients. We must await future ratification of the encouraging results found in randomized trials, always trying to maintain an adequate balance between cost and benefit.

Conflict of interest

The authors declare no conflict of interest.

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