Vascular and Renal Protection in the Presence of Increased Prevalence of Type 2 Diabetes

Bruno Caramelli, Danielle Menosi Gualandro

Universidade de São Paulo – Instituto do Coração – Unidade de Medicina Interdisciplinar em Cardiologia – São Paulo, SP – Brazil

Abstract

Type 2 diabetes mellitus is currently an important risk factor for cardiovascular diseases. Therefore, diabetic patients considered at high risk should receive more aggressive preventive treatment. The intensity and severity of micro and macrovascular conditions associated with diabetes mellitus are the focus of investigation of the genetic, molecular and clinical mechanisms involved. One of the most important characteristics is that the time window for the development of atherosclerosis is smaller, showing more clearly the clinical outcomes and a potential therapeutic response. The best treatment for diabetic patients is interdisciplinary treatment through which the cardiologist and the endocrinologist investigate the consequences of the disease, any possible drug interactions and their adverse effects. The creation of a language and a common agenda for these two medical specialties can bring huge gains for the patient. The purpose of this review is to update the concepts related to the treatment and prevention of diabetes complications for non-endocrinologists.

Keywords: Diabetes mellitus, type 2; Atherosclerosis; Primary prevention; Secondary prevention; Risk factors

Introduction

Diabetes mellitus (DM) is a disease with increasing prevalence in the world population and also in Brazil. Assistance to diabetic patients has become increasingly common in medical clinics. Fatigue, irritability, tingling, blurred vision and weight loss can be among the first and main complaints. Type 2 diabetes mellitus (DM2), the incidence of which increases with age, has serious consequences for patients with serious complications mainly affecting the cardiovascular system and the kidneys.

In fact, comorbidity rates are 36.0% for diabetes and coronary disease, 33.0% for diabetes and peripheral arterial disease and 73.0% for diabetes and systemic hypertension. It is currently estimated that 2/3 of the patients with diabetes will eventually die due to complications from cardiovascular diseases. Because of these characteristics, cardiologists are in a privileged position to analyze and execute, along with endocrinologists, prevention and treatment of diabetes and its complications.

The best treatment for diabetic patients is interdisciplinary treatment, in which the cardiologist and the endocrinologist are aware of the consequences of the disease, and analyze any potential drug interactions and their adverse effects. An example of that is the demonstration of increased risk of adverse cardiovascular outcomes associated with the use of rosiglitazone in the treatment of diabetes, according to a clinical study.
The creation of a language and a common agenda for these two medical specialities — cardiology and endocrinology — can bring huge gains for the patient. The purpose of this review is to update the concepts related to the treatment and prevention of diabetes complications for non-cardiologists.

**Pathophysiology of accelerated atherosclerosis in diabetes mellitus**

There are many studies and reviews describing the metabolic and circulatory abnormalities present in DM, trying to explain the genesis and rapid progression of atherosclerosis in different vascular beds in the brain, kidneys and heart. Among the factors directly responsible are lipid abnormalities (usually hypertriglyceridemia and low HDL-cholesterol levels), systemic hypertension often associated with hyperinsulinemia and increased resistance to insulin, endothelial dysfunction, thrombophilia, glycation (formation of advanced glycation end-products — AGE) and increased oxidative stress due to reduced antioxidant capacity.13-16

This scenario gave DM the title of a major risk factor for cardiovascular diseases. Nowadays, according to the guidelines of prevention, diabetic patients are already considered of high risk and should receive special treatment and closer follow-up from diagnosis. On the other hand, the intensity and severity of microvascular and macrovascular conditions associated with DM are an opportunity to investigate the genetic, molecular and clinical mechanisms involved. Furthermore, the time window for the development of atherosclerosis is smaller, showing more clearly the clinical outcomes and a possible therapeutic response.

**Pharmacological treatment of diabetes**

Pharmacological treatment of diabetes has been practiced for a long time, but only recently the cardiovascular outcomes began to be analyzed in large clinical trials. In The UK Prospective Diabetes Study (UKPDS)17,18, a milestone for the treatment of type 2 diabetes, more than 4,000 patients with newly diagnosed DM were followed up for 10 years in 23 UK centers under treatment with insulin, sulfonylureas (chlorpropamide, glyburide and glipizide) and metformin. This study revealed, for the first time, that microvascular complications of diabetes, once deemed inevitable, could be alleviated with more rigorous control of blood glucose levels and blood pressure.19. In a subgroup of 1,704 overweight patients, from this study, it was demonstrated that the addition of metformin was associated with a lower incidence of mortality from all causes, stroke and all outcomes related to diabetes compared to patients treated solely with sulphonylurea or insulin. These results were initially focus of discussion due to the different ways of use of metformin in this study and the apparently conflicting results in each of them. However, additional findings related to weight reduction and lower incidence of hypoglycemia, both more present when intensive glucose control involved the use of metformin, added valued to the interpretation of the effects of this drug. Thus, metformin has become the drug of first choice in the pharmacological treatment of diabetes.

On the other hand, the results of UKPDS reinforced the theory of a more aggressive control of blood glucose for diabetic patients. A systematic review and a meta-analysis, however, indicated that intensive treatment with strict glycemic control does not promote any additional benefit with respect to cardiovascular and renal outcomes; is associated with a 30.0% higher incidence of cases of hypoglycemia, currently considered one of the most serious complications of treatment, especially in elderly patients.20-22.

Middle ground was then reached, recommending achieving more intense glycemic control without increasing the occurrence of hypoglycemic crises. This strategy is widely publicized in national and international treatment guidelines. At the heart of the recommendations, concerning blood glucose levels, 70-130 mg/dL during fast and <180 mg/dL two hours after lunch (postprandial) are included. Regarding glycosylated hemoglobin, the desirable goal is up to 7% for diabetic patients. For these purposes, many drugs are available, as briefly listed in Chart 1.

So far, except for metformin and, more recently, gliclazide, which will be examined, there is no conclusive scientific evidence about the benefit of other pharmacological agents on major cardiovascular outcomes in patients with diabetes. The interest also lies on the lower incidence of adverse events (safety) or on smaller or alternative outcomes. One of the most feared adverse effects, especially in the older population, is hypoglycemia. Efforts should be made to monitor its early signs and the choice of drugs and targets of serum glucose levels should be individualized. Chart 1 describes, in a simple way, the drugs that are associated with hypoglycemia although the incidence varies according to the dose, the half-life of the drug and concomitant use of other drugs.
The ischemic preconditioning phenomenon, initially described in studies with experimental animals, is one of the alternative outcomes that caught the attention of the researchers involved with the foundation of pharmacological treatment of diabetes. This is a phenomenon whereby repeating episodes of myocardial ischemia lead to a metabolic adaptation and changes in the energy matrix of cardiomyocyte so that it resists to higher intensities and periods of ischemia. Some studies have shown that metformin would have this “cardioprotective” effect\textsuperscript{24,25}. Similarly, in patients with heart failure, metformin appears to contribute to the reduction of morbidity and mortality compared to the use of sulfonylureas alone\textsuperscript{26-32}.

On the other hand, drugs such as glibenclamide and repaglinide (Chart 1) used in the treatment of type 2 diabetes mellitus promote blockage of potassium channels and stimulate insulin secretion. In the specific case of these two drugs, the mechanism of action appears to be less selective by the pancreatic beta cell and blocking could also be found on other organs such as the heart. Potassium channels are important to preserve ischemic preconditioning, a defense of cardiac cells against chronic ischemia, and could theoretically be damaged leading to higher rates of complications and cardiovascular events. Although some studies indicate this possibility by examining alternative outcomes (indirect evidence) or associations (not proving any effective causal relationship), major clinical studies showed no prejudice to the use of sulfonylureas in patients with diabetes, with or without previous heart disease, not interfering with ischemic preconditioning. There is no scientific evidence to justify contraindication to its use for these patients.

Considering cardiovascular events as the primary outcome, there is no benefit when the product added to metformin for the treatment of type 2 diabetes mellitus is a \(\alpha\)-glucosidase inhibitor (acarbose), DPP4 inhibitor or GLP-1 analogs, even in more severe patients such as those diagnosed with acute coronary artery disease\textsuperscript{33-36}. Although initial studies suggest the existence of a cardioprotective effect of new classes of antidiabetic agents, such as DPP4 inhibitors or GLP-1 analogs in the population with heart failure, two recent randomized studies have not demonstrated a reduction of cardiovascular events with these medications. In patients with diabetes and recent acute coronary syndrome (study...
EXAMINE: Cardiovascular outcomes study of alogliptin in subjects with type 2 diabetes and acute coronary syndrome)\textsuperscript{35} or with prior cardiovascular disease (SAVOR-TIMI study: Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus — thrombolysis in myocardial infarction)\textsuperscript{36}, neither alogliptin (in EXAMINE)\textsuperscript{35} nor saxagliptin (in the SAVOR-TIMI study)\textsuperscript{36} were superior to the use of placebo as a second drug added to metformin in reducing cardiovascular events in two years’ follow-up. Since these agents have low power compared to the improvement of glycemic control, are costly and present little long-term proven safety, these results indicate that they are not prioritized in this context, except when patients present unacceptable adverse effects with the use of sulfonylurea\textsuperscript{19}.

Regarding the class of glitazones, the issue is more complex and deserves explanation. Rosiglitazone was deregistered in Brazil in 2010, very quickly, with no time or opportunity to investigate the relevance and pathophysiology of small yet statistically significant effects on the cardiovascular system, increasing the incidence of myocardial infarction, for example\textsuperscript{37,38}. It was not possible to determine whether this drug would be beneficial in some situations or subgroups or if it could stand before a class effect. As opposed to what was observed with rosiglitazone, but in a different population, pioglitazone did not reveal this behavior when studied in a group of patients with diabetes and cardiovascular disease\textsuperscript{38}. Both, however, were associated with increased hospitalizations for decompensated heart failure\textsuperscript{38-39}.

Decompensated heart failure, especially in patients with diabetes, is a challenge to treat. Although the use of metformin is safe, it should be avoided in patients with poor peripheral perfusion, impaired renal function, acidosis related to circulatory shock, since there is a higher risk of intensification of acidosis and its consequences\textsuperscript{49}. In the case of sulfonylureas, it is recommended to avoid glibenclamide due to higher risk of hypoglycemia and arrhythmogenic phenomena that can accompany it\textsuperscript{19}. Thiazolidinediones can increase water retention promoting edema and worsening of the signs and symptoms of heart failure. Therefore, its use for these patients is not recommended\textsuperscript{19}. Regarding the group of incretins, which includes GLP-1 agonists and DPP4 inhibitors, although an improvement in the ventricular function observed in animal studies was initially expected, outcomes in humans are controversial. On the other hand, its use seems to have no contraindications in this population, except in the presence of severe reduction in renal function\textsuperscript{19}.

Acarbose, in turn, lacks well-designed studies to investigate its efficacy and safety in diabetic patients with heart failure. It should be remembered, however, that acarbose interacts with digoxin, reducing its serum levels\textsuperscript{41}. Dapagliflozin, the first drug in the class of sodium-glucose cotransporter enzyme 2 (SGLT2) inhibitors launched in Brazil, has not been tested in well-designed studies with respect to major cardiovascular outcomes, although there are indications for a reducing effect on blood pressure. However, SGLT2 inhibitors should be contraindicated for patients with chronic renal failure\textsuperscript{42}.

Because there was proven evidence that metformin benefits major cardiovascular outcomes, the investigators became more interested, as a drug that reduced mortality and cardiovascular complications was available. On the other hand, diabetic patients were not completely controlled. Adding a second drug in the medium and long term is very common but it is necessary to choose a very safe substance that is not associated with adverse events such as what had been observed with rosiglitazone.

Two studies recently published brought new evidence concerning the treatment of patients with diabetes mellitus and the prevention of cardiovascular complications associated with it. The first, the ADVANCE study\textsuperscript{43}, included type 2 diabetic individuals with a macro or microvascular disease who had at least one cardiovascular risk factor (age ≥65 years, history of macrovascular or microvascular disease or type 2 diabetes for more than 10 years). In this study, considered to complement the UKPDS study, participants were randomized to intensive care (gliclazide — up to 120 mg/day — associated with metformin, glitazone, acarbose or insulin) or standard care (another sulfonylurea associated with the same medications). Note that in this study all participants received optimal treatment with regard to cardiovascular risk reduction through proper control of hypertension and dyslipidemia. In fact, the average value of LDL-cholesterol was 119 mg/dL, certainly related to the use of diet and pharmacological treatment with lipid-lowering agents. Any cardiovascular benefit related to intensive care should be complementary to the use of powerful drugs already included in the prevention of cardiovascular diseases. Although it is appropriate and beneficial for patients, this observation is necessary, since
it is a population of lower risk that is less likely to reveal any differences in treatment. In the end of the study, the individuals included in the intensive treatment group involving modified release gliclazide and other drugs as required, had a reduction of 21.0% in the risk of nephropathy (3.3% vs. 3.9%, p=0.0001) and a combined decrease of 9.0% of micro and macrovascular events (15.5% vs. 16.8, %, p=0.04)\textsuperscript{43}.

After five years of follow-up, the individuals included in the ADVANCE\textsuperscript{43} study had intensive care discontinued and were followed up for five years to investigate whether the benefits were maintained (legacy effect). This second study called ADVANCE-ON\textsuperscript{44} included more than eight thousand individuals and its primary outcomes were death from all causes and macrovascular events\textsuperscript{44}. Secondary outcomes were cardiovascular death, renal retinopathy, kidney transplant and dialysis. Although any significant reduction has not been observed in the primary outcome, at the end of 10 years of follow-up in this study there was a significant reduction of 46.0% (29.0% vs. 33.0%, hazard ratio 0.54, p=0.007) of renal disease progression to dialysis or renal transplantation, indicating that the “legacy” effect, a therapeutic inheritance from those five years of intensive treatment, was maintained for up to 10 years. On the other hand, as opposed to the study with rosiglitazone, the study ADVANCE-ON\textsuperscript{44} was not associated with worsening of cardiovascular mortality. Moreover, it demonstrated efficacy in long-term glycemic control, low incidence of severe hypoglycemia (0.7%) and reduced progression to insulinization due to pancreatic failure.

**Potential Conflicts of Interest**
The authors declare that they regularly deliver lectures for medical professionals. Bruno Caramelli receives support and partnership from the pharmaceutical laboratories Biolab, Abbvie and Servier. Danielle Menosi Gualandro receives support and partnership from Servier.

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**References**


