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Glucose-lowering treatment in cardiovascular and peripheral artery disease

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Diabetes-induced hyperglycemia is a causal factor for cardiovascular disease (CVD) and, specifically, peripheral artery disease (PAD). Metformin is the cornerstone drug therapy for glucose-lowering that exerts beneficial effects beyond glycemic control. New glucose-lowering drugs have recently been shown cardiovascular benefits and their impact on CVD risk is of increasing importance. Current guidelines recommend these novel therapies as second-line options for patients with diabetes and established CVD. Given the prevalence of CVD in this population, a complete understanding of the cardiovascular safety/efficacy of glucose-lowering drugs is needed. The present review provides an update overview of the anti-diabetic drugs and their impact on PAD and cardiovascular outcomes, summarizing key recent trial findings highlights their risk and benefits.

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Introduction

Diabetes mellitus (T2D) is associated with accelerated atherosclerosis occurring at different arterial districts including carotids, aorta, femoral arteries and lower extremities. Most of the atherosclerotic lesions in T2D patients are observed in the lower extremities arteries and patients with T2D also tend to present with poly-vascular atherosclerosis as compared to non-diabetic individuals and this affects their prognosis. Peripheral artery disease (PAD) in the lower extremities, namely lower extremity artery disease (LEAD), is a significant cause of morbidity and mortality worldwide. Indeed, it is known that diabetes increases the risk of both asymptomatic and symptomatic PAD, including disease with atypical symptoms [1], leading to poor outcomes [2]. In addition to diabetes, increasing age and smoking are also common risk factors associated with PAD, followed by hyperlipidemia and hypertension. Critical limb-threatening ischemia (CLTI) with risk of major amputation is around five-fold more frequent in T2D patients than in individuals without diabetes. PAD manifestations include intermittent claudication, fatigue, rest pain and, ultimately with the progression of the disease, necrosis. The quality of life of PAD patients is substantially deteriorated and is characterized by a poor prognosis. A multivariate adjusted relative risk analysis showed that duration of T2D is a potent predictor of incident PAD. Moreover, a recent large cohort study demonstrated that PAD is the most common complication observed among T2D patients with a first cardiovascular manifestation [3]. Recently, high mortality rates at 10 years and, especially in those with diabetes mellitus (DM), have been found in a cohort of patients with PAD [4].

Atherosclerosis and PAD

Lower extremity PAD is considered a manifestation of systemic atherosclerotic disease that affects the arteries of the lower limbs, specifically, the abdominal aorta, iliac, and femoral arteries, and is more likely to be found in distal vessels in the calf [5]. The pathophysiology of atherosclerosis involves complex interactions between cholesterol and vascular cells leading to atherosclerosis progression and plaque formation [6–8]. In the presence of T2D, chronic vascular damage induced by metabolic abnormalities is associated with accelerated progression of atherosclerosis, through several mechanisms that include endothelial dysfunction, inflammation and oxidative stress, abnormalities of vascular smooth muscle cell function, platelet adhesion and aggregation and hypercoagulability [9]. The initial hemodynamic consequences of atherosclerotic process in PAD involve the dilation of the arteries to preserve the flow through the vessel. Thereafter, the formation and growth of atherosclerotic plaques narrow the arterial flow lumen, reduce vascular perfusion and cause microvascular adaptation via angiogenesis [10] until vessel occlusion. When blood flow is impaired, less oxygen and nutrients reach the local tissue leading to ischemia and necrosis [11]. Then, hypoxia-induced mitochondrial injury and dysfunction result in free radical generation and oxidative stress, promoting apoptosis, muscle fiber damage and fibrosis, with its clinical complications [12,13].

Insulin resistance, DM and PAD

Insulin resistant and DM are a worldwide growing epidemic causing microvascular and macrovascular complications. Even in the early phase of insulin resistance PAD risk is increased. Indeed, high HOMA-IR (homeostatic model assessment of insulin resistance) values significantly correlate with the prevalence of PAD. Thus, poor glycemic control is an independent risk factor for PAD. Furthermore, insulin therapy is also associated with increased risk of PAD. The combination of chronic kidney disease and PAD strongly increase the risk of CVD [14]. Asymptomatic conditions during the development of PAD are also associated with a high incidence of cardiovascular events (CVE). Arterial stiffness predicted CVE specially in those patients with high CV risk such as T2D at baseline [15]. Recently, patients with PAD presented higher coronary atherosclerotic plaque vulnerability [16]. Moreover, an histological study showed that symptomatic advanced plaques frequently observed in common iliac arteries of patients with PAD are significantly associated with systemic atherosclerosis and CVE [17]. The Action in Diabetes and Vascular disease: preterAx and diamicroN modified-release Controlled EvaluatiON post-trial (ADVANCE-ON) study reported that PAD increases the risk of death and CVE in patients with T2D after ten years of follow-up [18]. Thus, the implementation of an early glycemic control in insulin-resistant patients with PAD is mandatory to reduce the risk of cardiovascular disease (CVD) and mortality.

Glucose-lowering drugs have only very recently demonstrated to reduce CVE [19••,20••,21]. Prior trials such as the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial including 11 400 patients with T2D assigned to standard treatment or intensive glucose control lead to a reduction in the primary composite endpoint of major macrovascular and microvascular events. However, this benefit was primarily due to a 21% relative reduction in diabetic nephropathy. Similarly, the Veterans Affairs Diabetes Trial (VADT) including 1791 patients with T2D randomized to standard or intensive treatment showed no significant difference in the primary composite endpoint of CVE (death, myocardial infarction [MI], stroke, heart failure [HF], surgical revascularization for coronary artery disease [CAD] or PAD, inoperable CAD, or amputation due to PAD) or secondary outcomes including new CLI. Of note, optimization of blood glucose levels prevented peripheral neuropathy and PAD in patients with T2D in the UK Prospective Diabetes Study (UKPDS), in which a reduction in HbA_{1c} of 1% was associated with a reduction in risk of 43% for amputation or death from PAD. Since intensive glucose control may increase mortality among patients with established CVD [22], a target glycated hemoglobin A_{1c} level should be tailored on the basis of age, duration of diabetes, and presence of coexisting conditions. In the past, guidelines provided a class IIa recommendation for reducing the HbA_{1c} to <7% in patients with PAD to prevent microvascular complications. Recently, the trend is for a more individualized approach to strict glycemic control. Patients with diabetes and atherosclerotic vascular disease require a multidisciplinary approach beyond glycemic control [23–26].

The worldwide epidemic of diabetes associated with increasing levels of obesity is likely to lead to a higher incidence of PAD. Patients with PAD are not optimally managed, in particular those without other concomitant CV risk factors [27,28]. It is not known whether aggressive risk factor modification decreases the risk of PAD in patients with T2D. Despite the increased rate of LEAD, diabetes-related amputation declined over the last decade [29]. However, patients with T2D randomized to intensive risk factor control or standard therapy did not show any difference after six years in the prevalence of PAD [30]. On the contrary, improvement of glycemic control reduces the incidence of peripheral vascular disease in type 1 and type 2 diabetes mellitus. An education intervention program targeted at patients with PAD promoting CV risk factor control, including diabetic glycemic control, was associated with fewer CV and limb events [31]. Thus, control of blood glucose levels, improving insulin resistance and vascular endothelial function at an early stage of atherosclerotic disease, might contribute to an overall systemic vascular protection increasing the life expectancy in patients with PAD. Hence, a better understanding of the potential benefit/risk ratio of glucose-lowering therapies in treating patients in this setting is of paramount importance. The present work will address the global safety/efficacy pattern of old and new glucose-lowering strategies in the context of most recent clinical data.

Glucose-lowering therapy

Insulin

Insulin was the first drug used for the treatment of diabetes in 1922 and remains the most potent glucose-lowering agent, required when progressive loss of β-cell function leads to poor glycemic control, particularly for patients with very high HbA_{1c} levels and advanced T2D. There are multiple barriers to the implementation of insulin treatment, including time constraints, patient compliance, and limited knowledge regarding new insulin formulations. Additionally, insulin therapy usually leads to increased body weight and risk of hypoglycemia. Despite a large amount of observational studies have suggested that insulin promotes atherosclerosis, there is no firm evidence of increased atherogenesis and CVD risk with insulin therapy. However, there are several trials including the UKPDS concluding that insulin use did not increase CV events (Table 1) [111•]. In the Diabetes Control and Complications Trial (DCCT), intensive insulin therapy reduced the onset and progression of microvascular disease without a significant reduction in CVE in