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REVIEW

Diabetes Medications and Cardiovascular Outcomes in Type 2 Diabetes

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Introduction Patients with type 2 diabetes have an increased risk of developing adverse cardiovascular (CV) outcomes. The evidence relating to the effects of glucose-lowering medications on CV outcomes is of variable quality and there are numerous trials ongoing.

Results In this review, we summarise the available literature on CV outcomes of the following diabetes treatments: metformin, the sulfonylureas, acarbose, glucagon-like peptide 1 (GLP1) receptor agonists, dipeptidyl peptidase-4 inhibitors (DPP4i), sodium-glucose co-transporter 2 inhibitors (SGLT2i), thiazolidinediones (TZDs) and insulin.

Conclusions Insulin is required if glucose levels are very high. Otherwise, metformin, acarbose, some GLP1 receptor agonists and one SGLT2i appear beneficial for CV outcomes.

Keywords Type 2 diabetes • Major adverse cardiovascular events • Metformin • SGLT2 inhibitors • DPP4 inhibitors

Introduction

There is an approximate two-fold excess risk of vascular disease in individuals with diabetes [1]. The risk of microvascular complications (neuropathy, retinopathy and nephropathy) is related to the duration and severity of hyperglycaemia, and the risk is reduced by improving glycaemic control. However, the mechanisms driving cardiovascular (CV) disease in the diabetes population are not entirely understood. Poor glycaemic control correlates with increased CV risk, but it has not been shown that general glucose-lowering in diabetes improves CV risk.

The landscape of diabetes trials changed radically in 2007 after a meta-analysis suggesting that there was an increased risk of myocardial infarction (MI) and CV-related death with rosiglitazone [2]. After this, the Food and Drug Administration (FDA) in the United States (US) amended their approval procedures to require investigators to show that new glucose-lowering agents are tested for CV safety and do not increase CV risk [3]. Thus, modern CV trials now focus on major adverse cardiac events (MACE) as the primary endpoint. Major adverse cardiac events is a composite of non-fatal MI, non-fatal stroke and death from CV disease. The overall annual rate of MACE in type 2 diabetes (T2D) is around 2% [4].

Understanding CV risk or benefit of diabetes therapies is clearly important for management. Here, we review the major diabetes therapies and the evidence for CV outcomes. The major tissue sites of action are summarised in Figure 1.

Abbreviations: C-IMT, carotid intima–media thickness test; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; DPP4i, DPP4 inhibitors; GLP1, glucagon-like peptide 1; HbA1c, glycated haemoglobin; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiac event; MI, myocardial infarction; PAD, peripheral arterial disease; PPAR, peroxisome proliferator-activated receptor; RCT, randomised controlled trial; RRR, relative risk reduction; SGLT2, sodium-glucose co-transporter 2; SGLT2i, SGLT2 inhibitors; T1D, type 1 diabetes; T2D, type 2 diabetes; TZD, thiazolidinediones

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Metformin

Metformin is a biguanide which has been used in diabetes treatment for almost 60 years. Metformin decreases hepatic glucose production and may increase peripheral glucose utilisation [5]. It has long been considered first-line therapy for diabetes management, although we note that it was re-introduced to the US in 1995. The biguanide family had been banned there as a result of fatalities induced by another class-member, phenformin, and metformin was re-introduced after a large-series study showed no increase in the risk of lactic acidosis with metformin when used appropriately [6].

Perhaps because metformin is an 'old' drug, there are no randomised controlled trials (RCTs) designed to assess whether it has any CV risk effects. Retrospective analyses of large databases have concluded that metformin is superior to sulphonylureas in the treatment of diabetes [7–9]. It is difficult to assess whether the difference in adverse CV events seen in these trials was due to a benefit of metformin, or a deleterious effect of sulphonylurea therapy or both.

The landmark United Kingdom Prospective Diabetes Study (UKPDS) [10] was the first large study to show that intensively lowering glucose significantly reduced microvascular disease compared to conventional therapy (0.7% reduction in glycated haemoglobin [HbA1c] [~8 mmol/mol], 25% relative risk reduction [RRR], $p = 0.0099$). It studied over 5000 patients with newly diagnosed T2D from 1977–1991. Despite the beneficial effect on microvascular disease, there was no significant reduction in all-cause mortality and stroke. The RRR for MI reached borderline significance (16% RRR, $p = 0.052$).

A subgroup of 753 obese patients were randomised to receive intensive treatment with metformin or conventional treatment [11]. It was found that patients allocated to the group intensively treated with metformin, compared to conventionally treated obese patients, had a reduced risk of combined diabetes-related end points (32% decrease, $p = 0.002$), diabetes-related deaths (42%, $p = 0.017$) and all-cause deaths (36%, $p = 0.011$). In comparison, the insulin and sulphonylurea-treated groups did not show a reduced risk.

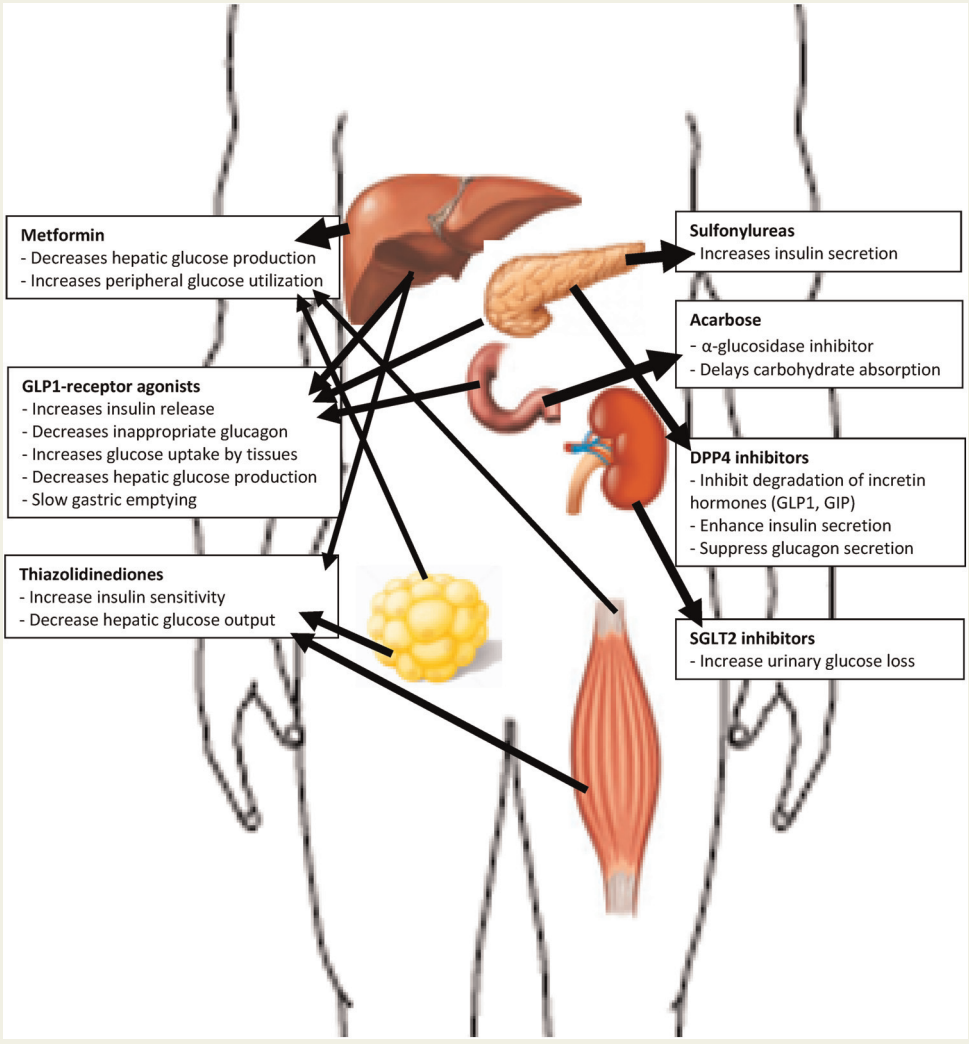

Figure 1 Oral diabetes medications and their sites of action.