Pharmacologic Therapy of Type 2 Diabetes

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KEYWORDS

• Type 2 diabetes • Metformin • Sulfonylurea • Insulin • GLP-1 analog
• DPP-4 inhibitor • SGLT-2 inhibitor

KEY POINTS

- For glycemic control, metformin is the optimal first-line therapy for most patients.
- There are many issues to consider when deciding on additional therapies, including: effects on blood sugar lowering, weight, risk of hypoglycemia, costs, and route of administration.
- In patients with renal impairment, some medications have more pronounced adverse effects, and some are contraindicated.
- Elderly patients often need adjustment in their diabetes regimens due to less aggressive glucose lowering goals, and increased sensitivity to adverse effects of certain medications.
- Do not to overlook important therapies that reduce the risk of cardiovascular disease, independent of blood sugar lowering, including statins, antihypertensives and aspirin.

INTRODUCTION

Type 2 diabetes (T2DM) is a common condition, affecting 9.3% of the US population in 2014, 21 million people with the diagnosis and an estimated 8.1 million people who are undiagnosed.[1] Treatment of diabetes and related complications can be complex. In addition to lifestyle changes, medications play an important role in controlling patients' blood glucose levels and preventing complications from diabetes including kidney failure, blindness, amputations, and heart disease. From an individual and societal standpoint, it is also an expensive disease. Medical spending attributed to diabetes per individual is significant. For a patient diagnosed at age 50, it is estimated that he or she will have an excess of $91,200 in medical spending over his or her lifetime compared to a matched individual without diabetes, with 44% of this spent on prescription medications.[2] With appropriate therapy, patients can lead full, healthy lives

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with the disease, so making informed decisions regarding pharmacotherapy for T2DM is clearly of great importance.

Treatment in Context

Prior to discussing the various pharmacologic agents that can be used to manage diabetes, one must put the medications into the context of the clinical benefits of treatment. Microvascular complications of diabetes include retinopathy, neuropathy, and nephropathy. The UKPDS (UK Prospective Diabetes Study) trial was a landmark study in treatment of T2DM, finding a reduction in microvascular complications with HbA1c lowering in patients with newly diagnosed T2DM. Patients randomized to pharmacologic treatment achieving HbA1c lowering to 7% versus 7.9% in the control arm showed a significant 25% reduction in aggregate microvascular endpoints–retinopathy requiring photocoagulation, vitreous hemorrhage, and/or fatal or non-fatal renal failure.[3] Observational UKPDS follow-up studies found evidence of a legacy effect, with persistent reduction in microvascular complications in the years following the study, despite no long-term difference in glucose control between the 2 groups.[4]

Macrovascular complications of diabetes include cardiovascular disease (CVD) and cerebrovascular accidents (CVAs). A benefit of glucose-lowering therapy in reducing the risk of these complications is less clear. A notable study, which did find benefit, is the UKPDS series of studies.[3–5] In the overweight subgroup of the original UKPDS study, patients who were treated with metformin had a statistically significant reduction in myocardial infarction (39%) in addition to all-cause death (36%).[5] In the post-trial observational follow-up study, this reduction in coronary events and all-cause death persisted (33% and 27% RRR [relative risk reduction] respectively). As well, a long-term benefit of early treatment with insulin and sulfonylureas was found (15% RRR for myocardial infarction, and 13% RRR for all-cause death).[4] However, several subsequent long-term studies failed to show benefit with intensive blood glucose lowering. In fact, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was ended early because of an excess risk of all-cause death in the intensive treatment arm (hazard ratio [HR] 1.22).[6] In contrast to the UKPDS, participants in these trials had long-standing diabetes, with established CVD or CVD risk factors, suggesting that intensive glucose control early in the course of T2DM may be important for reducing CVD risk. **Table 1** has a summary.

From the standpoint of preventing microvascular and macrovascular complications of diabetes through improved glycemic control, there are several factors to consider.

Table 1
Landmark clinical trials assessing for macrovascular benefits of glycemic control in type 2 diabetes

Long-Standing Poorly Controlled Type 2 Diabetes, Aggressive HbA1c Lowering	Newly Diagnosed Patients with Type 2 Diabetes
ACCORD: increase in all-cause death, no benefit/harm in: CV outcomes ADVANCE: no benefit/harm in CV outcomes VADT: no benefit/harm in CV outcomes during the trial, observational follow-up trial with reduction in CV events, although not CV or all-cause death	UKPDS 10 y follow-up: reduction in CV events and all-cause death with metformin treatment > insulin or sulfonylurea treatment

Abbreviations: ADVANCE, Action in diabetes and vascular disease: PreterAx and diamicron MR controlled evaluation; VADT, Veterans affairs diabetes trial.
Data from Refs.[5–8]