Cardiovascular safety of anti-diabetic drugs

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Cardiovascular disease is the leading cause of morbidity and mortality among patients with diabetes, underscoring the importance of choosing anti-diabetic drugs that do not increase cardiovascular risk but might reduce the risk of cardiovascular events. Most type 2 diabetic patients die from cardiovascular causes despite the beneficial effects of blood pressure (BP) and lipid-lowering medications. The prevalence of patients with cardiovascular disease and diabetes mellitus is growing exponentially. Approximately 40% of patients hospitalized with heart failure and reduced ejection fraction have diabetes mellitus. The recent trials conducted in patients with heart failure who had diabetes showed a different response to standard medication, with these patients being more prone to develop side effects than patients with the same degree of heart failure but without diabetes mellitus. Therefore, careful selection of drug therapy paying particular attention to cardiovascular safety is important in optimizing diabetic therapy. This review discusses the efficacy and safety of the most commonly prescribed anti-diabetic drugs in the context of cardiovascular impact.

Keywords Diabetes mellitus • Anti-diabetic agents • Cardiovascular disease

Introduction

Type 2 diabetes mellitus (T2DM) is a disorder characterized by insulin resistance and a progressive decline in pancreatic β-cell function associated with increasing hyperglycaemia. Defective β-cell function occurs early and can be detected in individuals with impaired fasting and/or post-prandial glucose levels. The UK Prospective Diabetes Study (UKPDS)1 indicated that by the time T2DM is diagnosed, individuals have already lost up to 50% of their β-cell function. The decline in function proceeds at 6% per year, which is 20 times greater than that explained by normal ageing. Treatment of T2DM is based on an interplay of patient characteristics, severity of hyperglycaemia, and available therapeutic options. Metformin, sulfonylureas (SUs), and thiazolidinediones (TZDs) are the most studied of the oral medications used worldwide. They play a prominent initial role in the T2DM treatment algorithm recommended by the American Diabetes Association (ADA) and the European Diabetes Association for the Study of Diabetes (EASD).2 Metformin is considered to be the first-line therapy unless it is not tolerated or is contraindicated. Second-line therapy includes SUs, TZDs, dipeptidylpeptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) agonist. Meglitinides also known as the non-sulfonylurea secretagogues and they are recommended as an alternative to SU therapy for patients with irregular meal times or late post-prandial hypoglycaemia with traditional SU therapy. While it is yet to be determined what the cardiovascular effects of anti-diabetic drugs are, the effect of improved glycaemic control on cardiovascular complications is well established, and in spite of a large and growing armamentarium of anti-diabetic drugs, the majority of patients over time fail to achieve recommended treatment goals. Cardiologists should weigh cardiovascular and other risks against the potential benefits when prescribing medications. Therefore, it is important to clearly define the benefit and risk of current anti-diabetic agents.

Metformin

Metformin is recommended as the first-line drug for T2DM by most international guidelines (Figure 1). The preference for metformin over other available drugs is based on its efficacy on blood glucose control, tolerability, and safety.3 Moreover, metformin has a favourable action on several risk factors, including lipids, body weight, and blood pressure (BP).4 Experimental studies have also shown that this drug could have beneficial effects on fibrinolysis and platelet aggregation.5 In comparison to other oral agents, metformin is regarded as the best initial choice, resulting in a decrease in glycated haemoglobin (HbA1c) better than or equipotent to SUs but without a risk of hypoglycaemia.3 The position statement of the EASD and ADA in 2012

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recommends metformin as the foundation treatment for T2DM along with diet and exercise, a stance that is also embraced by the American Association of Clinical Endocrinologists.

**Efficacy**

Up to the present, the UKPDS is the most extensive study assessing metformin compared with other treatments. It aimed to study the effect of glycaemic control on the prevention of complications, associated morbidity and mortality in non-insulin dependent diabetics. Patients with fasting plasma glucose at entry between 6 and 15 mmol/L, were randomized to sulfonylurea, insulin, metformin [only in overweight patients: body mass index (BMI) 25–29 kg/m²], or diet. At 3 years, metformin achieved the same reduction in fasting plasma glucose and HbA1c as did SU’s or insulin, but in addition it reduced fasting plasma insulin and did not induce weight gain (Table 1). Metformin was associated with fewer hypoglycaemic

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**Figure 1** Treatment regimen for type 2 diabetes mellitus patients.
The study found that the observed benefits included a 42% reduction in diabetes-related fatalities (compared with diet alone, $P = 0.017$), a 36% reduction in all-cause mortality ($P = 0.011$), 39% reduction in MI ($P = 0.01$), and a 32% reduction in any diabetes-related endpoint ($P = 0.002$). Following UKPDS, other studies have reported significant improvements of all-cause mortality and cardiovascular mortality. A retrospective analysis of patient’s databases in Saskatchewan, Canada stated significant reductions for all-cause mortality, and cardiovascular mortality of 40 and 36%, respectively. The PRESTO trial showed significant reductions of any clinical event (28%), MI (69%), and all-cause mortality (61%). The HOME trial reported a decreased risk of developing macrovascular disease. In non-diabetic patients with normal coronary arteriography but also with two consecutive positive (ST depression > 1 mm) exercise tolerance tests, an 8-week period on metformin improved maximal ST-segment depression, Duke treadmill score, and chest pain incidence compared with a placebo. A retrospective cohort study has shown that metformin therapy is a safe treatment in diabetic patients with heart failure. In hospitalized patients with heart failure, metformin was associated with lower 1-year mortality and re-hospitalization rate compared with insulin or SU2.

**Safety**

**Cardiovascular impact**

Diabetic patients are at high risk of cardiovascular events, particularly of coronary heart disease by about 3-fold. Despite the efforts at controlling blood glucose and associated risk factors, cardiovascular morbidity and mortality remain high in diabetic patients than in the rest of the population. The correct treatment of hyperglycaemia is considered one of the tools for preventing cardiovascular disease in diabetic patients. Many classes of drugs have been shown to be effective as glucose-lowering agents, at least in the short and medium term; it has been suggested that some of these molecules, including metformin, could confer a cardiovascular protection beyond the beneficial effect of the improvement of glucose control alone because of the reduction of total and low-density lipoprotein (LDL) cholesterol, triglycerides, body weight, and BP. The UKPDS demonstrated that metformin reduced the risk of fatal macrovascular complications compared with other modalities (Table 1). The study found that the observed benefits included a

**Table 1** Summary of recommendation for blood pressure and lipid control for adult with diabetes

<table>
<thead>
<tr>
<th>Management of diabetic CVD</th>
<th>Hypertension/BP control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Patients with diabetes and hypertension should be treated to a BP goal of &lt;140/90 mmHg</td>
</tr>
<tr>
<td></td>
<td>Patients with renal, eye, or cardiac damage should be treated to a BP goal of &lt;130/80 mmHg</td>
</tr>
<tr>
<td>Treatment</td>
<td>Patients with BP &gt;120/80 mmHg should be advised on lifestyle changes to reduce BP</td>
</tr>
<tr>
<td></td>
<td>For initial BP &gt;150/100 mmHg</td>
</tr>
<tr>
<td></td>
<td>Lifestyle changes (weight loss if overweight, ↓ sodium intake, moderation of alcohol intake, stop smoking, and ↑ physical activity</td>
</tr>
<tr>
<td></td>
<td>ACEI or ARB + thiazide diuretic or calcium channel blockers or β-blockers</td>
</tr>
<tr>
<td></td>
<td>If not at target (2–3 months): add β-blockers or calcium channel blocker or thiazide diuretic</td>
</tr>
<tr>
<td></td>
<td>If still not at target consider, α-blockers or vasodilators or spironolactone</td>
</tr>
<tr>
<td>Dyslipidaemia management</td>
<td>Intensify lifestyle therapy and optimize glycaemic control for patients with elevated triglyceride levels &gt;1.7 mmol/L and/or low HDL cholesterol &lt;1 mmol/L and/or LDL cholesterol &gt;2.5 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Lipid-lowering drug therapy with simvastatin 40 mg or atorvastatin 10 mg is recommended for primary prevention in patients with T2DM aged &gt;40 years regardless of baseline cholesterol</td>
</tr>
<tr>
<td>Antithrombotic therapy</td>
<td>Consider aspirin therapy (75–162 mg/day) as a primary prevention in men &gt;50 years or women &gt;60 years who have at least one additional major risk factor (family history of CVD, hypertension, dyslipidaemia, or albuminuria)</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers.
metformin; however, there is a risk of lactic acidosis, which may be fatal in a substantial number of cases. First evidence evolved from case reports on metformin treatment. Concerns about metformin-associated lactic acidosis have led to the practice of metformin discontinuation prior to diagnostic angiography and percutaneous coronary intervention. Evidence for the safety of metformin has been reported in a large randomized controlled trial (the Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach study), which compared outcomes at 1 year in diabetics taking metformin (n = 7227), to ‘usual care’, i.e. diabetics treated with a sulfonylurea, TZD, insulin, or any other non-metformin monotherapy or combination therapy (n = 1505). No cases of lactic acidosis were reported in either group. According to guidelines from the National Institute for Health and Clinical Excellence in the UK, metformin should be withdrawn if serum creatinine is ≥150 μmol/L (Table 1), or the estimated glomerular filtration rate is <30 mL/min/1.73 m². Recommendation on the timing of discontinuing metformin prior to contrast administration vary depending on which guidelines are studied, and range from discontinuation 48 h prior to the procedure, 24 h prior to the procedure, or on the day of the procedure. New data are necessary to determine whether there is a significant problem with lactic acidosis in those patients on metformin who undergo coronary angiography.

Sulfonylureas

Sulfonylurea derivatives are the oldest class of oral anti-diabetic agents and are currently used as second-line or an add-on treatment option for T2DM. These agents act on pancreatic β-cells by binding adenosine triphosphate-dependent potassium channels causing a chain of events that leads to increased insulin secretion (Table 1). Sulfonylureas have gone through several steps of development and are categorized as first-generation agents (chlorpropamide, tolvazamide, and tolbutamide), second-generation agents (glipizide and glyburide), and third-generation agent (glimepiride). The first-generation agents have longer half-lives, increased incidence of hypoglycaemia, and more drug interactions. The second- and third-generation agents have more rapid onsets of action, shorter half-lives, and lower incidence of hypoglycaemia. Consequently, the generations differ in their pharmacokinetic, efficacy, and safety profiles.

Efficacy

Sulfonylureas can be expected to reduce fasting plasma glucose by an average of 2–4 mmol/L accompanied by a decrease in HbA1c of 1–2%. In the UKPDS, treatment with SUs (glyburide or chlorpropamide) achieved an HbA1c <7% in 50% of patients at 3 years. Despite this impressive initial response, only 34% of patients maintained an HbA1c <7% at 6 years, and this number declined to 24% at 9 years. Initiation of sulfonylurea treatment in a patient recently diagnosed with T2DM who shows a random glucose >16.6 mmol/L and an HbA1c >9–10% is debatable. Due to large insulin requirements, secondary to glucotoxicity patients exhibiting blood sugars >16.6 mmol/L are unlikely to achieve acceptable glucose control with sulfonylurea monotherapy and such patients are best treated, at least initially, with insulin therapy. After a period of adequate glycaemic control, a trial of SUs to replace insulin therapy, alone or in combination with metformin, may be attempted.

Safety

Cardiovascular impact

Sulfonylureas have represented the backbone of oral therapy in T2DM; however, there are controversies in terms of the cardiovascular safety of this anti-diabetic drug. In early 1970, the report of the University Group Diabetes Program (UGDP) suggested that tolbutamide therapy was no more effective than diet alone and was associated with an increase in cardiovascular toxicity. Therefore, the UGDP discontinued therapy with the first-generation sulfonylurea tolbutamide, because of an increase in all-cause and cardiovascular mortality compared with the other treatment groups. As this led some experts to conclude that SUs, as a class, were associated with increased cardiovascular mortality, a serious consequence of this UGDP study has been condemnation of the therapeutic use of an entire class of SUs drugs. Although others criticised the design and analysis of UGDP study, the question of safety and efficacy of tolbutamide and other sulfonylurea groups of drugs were raised. Later on, the UKPDS group demonstrated that treatment with SUs showed a trend toward protection against MI rather than augmentation of cardiovascular mortality (Table 1). Nevertheless, a study by Garratt et al. reopened this controversy on cardiovascular side effects of SUs when they demonstrated increased early mortality in 67 persons taking the sulfonylurea glyburide vs. 118 using insulin or lifestyle therapy alone. This study, on the surface, seemed to condemn sulfonylureas as therapeutic agents. However, a critical reappraisal of this study reveals a few exciting facts. This study was retrospective, randomization was lacking, and the use of sulfonylureas by patients in this study was not specified. The study sample was too small to reach a decision about the cardiovascular risks of sulfonylureas. Furthermore, in the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial incident cardiovascular events with glyburide were not different from those of rosiglitazone, which was later suspended in some countries, and limited in others, for insufficient cardiovascular safety. In addition, weight gain of 2 kg is common with the initiation of sulfonylurea therapy. This may have an adverse impact on cardiovascular disease outcome. Finally, a smaller trial on patients with prior cardiovascular events showed a clear superiority of metformin over gliclazide.

Hypoglycaemic impact

The second major concern expressed with sulfonylureas is hypoglycaemia. Severe protracted hypoglycaemia is more likely with longer-acting sulfonylureas such as glyburide. The timing of hypoglycaemia tends to reflect the pharmacokinetics of the sulfonylureas. Thus, glyburide has a propensity to cause inter-prandial hypoglycaemia, whereas chlorpropamide tends to induce hypoglycaemia in the pre-breakfast period. In addition, it is possible that acute hypoglycaemia induced by sulfonylureas, may trigger ischaemia and cardiovascular events. Hypoglycaemia and rapid changes in blood glucose have been shown to increase counter regulatory hormones such as epinephrine and norepinephrine, which may induce vasoconstriction, platelet aggregation, and thereby ischaemia. Therefore, selection of appropriate agents according to each patients profile is crucial to get maximum beneficial effects (Figure 1).
Meglitinides

The meglitinides are structurally different than sulfonylureas and exert their effects via SUR-1 receptor, but act similarly by regulating ATP-dependent potassium channels in pancreatic β-cells thereby increasing insulin secretion. In the natural history of T2DM, a blunted response of the first phase of glucose-stimulated insulin release has been observed. An initial surge of insulin is essential to suppress hepatic gluconeogenesis in the post-prandial period. If this mechanism fails, post-prandial hyperglycaemia is exacerbated and the HbA1c level is adversely affected. The meglitinides were developed to address this problem. They bind to the SUR-1 receptor in much the same way as the sulfonylureas. However, this action is mediated through a different binding site on the ‘sulfonylurea receptor’ of the β-cell, and these drugs have somewhat different characteristics when compared with the sulfonylureas. Unlike the commonly used sulfonylureas, the meglitinides have a very short onset of action and a short half-life. The short half-life of these drugs potentiates the effect of the first phase of insulin secretion, but the effect on the second phase is not sustained.40 Currently approved drugs in this class and a short half-life. The short half-life of these drugs potentiates the effect of the first phase of insulin secretion, but the effect on the second phase is not sustained.40 Currently approved drugs in this class include the benzoic acid derivative repaglinide, approved in 1997, and nateglinide, a D-phenylalanine derivative, approved in 2000.41 They should be dosed half an hour prior to each meal and one of the advantages is that they can be used in renal insufficiency.

Efficacy

Due to the glucose sensitive release of insulin, meglitinides cause less hypoglycaemia in comparison with sulfonylureas. Repaglinide has been shown to improve glycaemic control over placebo in several randomized, double-blind multicentre trials.42 A double-blind, randomized, fixed-dose trial of 361 patients on a background diet was performed over 24 weeks. Following a washout period, subjects received repaglinide 1 or 4 mg with meals, or a placebo.42 From a mean baseline of 8.7%, HbA1c increased by 1.4% in the placebo group, while it decreased by 0.7 and 0.5% in the repaglinide 1 and 4 mg groups, respectively (P < 0.001). Repaglinide and nateglinide monotherapies were compared over 16 weeks in subjects uncontrolled by diet and exercise. The reduction in HbA1c values from baseline was significantly greater for repaglinide than nateglinide (1.57 vs. 1.04%), and repaglinide had more pronounced effects on reducing fasting plasma glucose and glucagon secretion, with no differences in post-prandial glucose and insulin secretion.43 Different studies have compared the efficacy of meglitinides and sulfonylureas or meglitinides and metformin. A study comparing the effects of 270 mg of nateglinide (n = 16) with 20 mg of gliclazide (n = 8) in a 12-week open label prospective study found that gliclazide was slightly more effective that nateglinide (HbA1c was 0.2% less in the gliclazide group).44 In a 24-week multicentre study, 360 mg of nateglinide was similarly effective as metformin 500 mg three times a day in terms of HbA1c reduction (−0.8% in both groups).45

Safety

Cardiovascular impact

Repaglinide has not been shown to be associated with increased mortality and cardiovascular risk compared with metformin in a large cohort of diabetic patients with or without previous MI.46 In an uncontrolled randomized study involving 112 patients with inadequately controlled T2DM not previously treated with oral hypoglycaemic agents, the use of repaglinide was associated with positive improvements in some parameters of cardiovascular risk, such as homocysteine, plasminogen activator inhibitor, and lipoprotein (a).47 The previously reported randomized controlled trial in diabetes prevention, the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, demonstrated no beneficial effect of nateglinide in stopping the progression from prediabetes to diabetes compared with placebo.48 The NAVIGATOR study group randomized 9306 adult subjects with impaired glucose tolerance (IGT) and cardiovascular disease or cardiovascular risk factors to receive placebo or nateglinide (60 mg before meals, three times daily), along with a study-specific lifestyle modification program.49 The study reported that 36.0% of participants in the nateglinide group developed diabetes while 33.9% in the placebo group progressed to diabetes after a median follow-up of 5.0 years (P = 0.05). Compared with placebo, nateglinide lowered fasting plasma glucose by 0.03 mmol/L, but increased 2-h post-prandial glucose by 0.24 mmol/L. In addition, 10% of all participants lost 5% of their baseline weight by 6 months; however, the nateglinide group had an overall higher mean body weight throughout the entire study (mean difference 0.35 kg, P < 0.001). These agents stimulate insulin secretion with a very short half-life, which confers them the advantages of not causing excessive hypoglycaemia, significant weight gain, and chronic hyperinsulinemia, which are more common with sulfonylureas.

Thiazolidinediones

Thiazolidinediones were first reported as insulin-sensitising drugs in the early 1980s by the pharmaceutical company Takeda,49 but their mechanism of action remained a mystery until the mid-1990s. The discovery of the TZDs as high-affinity PPARγ ligands was a major breakthrough in the pharmacology of PPARγ.50 Thiazolidinediones (also termed glitazones) are potent insulin-sensitizers that efficiently improve glycaemic control in T2DM patients. Three TZDs have been FDA approved for diabetes: troglitazone, rosiglitazone, and pioglitazone. However, despite clear benefits in glycaemic control, this class of drugs has recently fallen into disuse due to concerns over their side effects and adverse events. The rise and fall of TZDs is shown by their use in ambulatory diabetes visits: from 6% in 1997 to 41% in 2005 and down to 16% by 2012.51

Efficacy

Troglitazone was introduced in 1997 but withdrawn from the market in 2000 due to increased risk of liver failure from fulminant hepatitis.52 Rosiglitazone and pioglitazone were both FDA approved in 1999, but pioglitazone has become the TZD of choice for reasons described below. Thiazolidinediones lower Hb1c effectively by 1% as monotherapy in T2DM, where they particularly do not cause hypoglycaemia like insulin or insulin secretagogues (i.e. sulfonylureas), and they can be used in combination with other anti-diabetic agents.53 The first-line drug metformin is often mentioned as an insulin sensitizer, but its primary effect is suppression of hepatic glucose production, whereas its effects on peripheral insulin sensitivity are quite small, variable across studies, and absent in a meta-analysis.54 In the same analysis, TZDs have large and
consistent effects improving insulin sensitivity. Furthermore, the ADAPT randomized controlled trial showed that rosiglitazone provided more durable glycaemic control than metformin or sulfonylurea. Insulin sensitization also appears to be the mechanism whereby TZDs prevent or delay development of T2DM in individuals with pre-diabetes. The ACT NOW study involved 602 patients with IGT, pioglitazone decreased progression to T2DM by 74% over 2.4 years.56 Previous studies of patients with pre-diabetes demonstrated that troglitazone57 or rosiglitazone58 similarly decreased progression to diabetes. Since TZDs are the most potent known insulin sensitizers, patients on TZDs will require lower levels of endogenous and exogenous insulin to maintain euglycaemia. Indeed, patients using insulin who are started on TZDs typically reduce their insulin dose or even discontinue insulin injections.59

Safety
Cardiovascular impact
There is a greater concern with rosiglitazone than with pioglitazone. A retrospective analysis of data from >225 000 patients60 concluded that the use of rosiglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality in patients aged 65 years or older (Figure 1). On the basis that the risks outweigh the benefits, rosiglitazone use was restricted in the USA to patients with T2DM who were not effectively treated with other medications. In late 2013, the FDA lifted their restriction on the basis of the results from the RECORD clinical trial (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes), which failed to reproduce the results from the 2007 meta-analysis and indicated no elevated risk of heart attack or death in patients being treated with rosiglitazone vs. diabetes medications.61 Moreover, in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) clinical trials, pioglitazone treatment resulted in a non-statistically significant 10% relative risk reduction for the primary composite endpoint [all-cause death, MI, acute coronary syndrome (ACS)] and a statistically significant 16% reduction for the main secondary endpoint (death, MI, and stroke) after a mean 34.5 months in 5238 T2DM patients with established cardiovascular disease (CVD) (Table 1).62 The potential difference in heart failure risk between pioglitazone and rosiglitazone may lie in their distinct effects on lipoproteins, with pioglitazone showing a more beneficial effect (triglycerides decrease 15%, high-density lipoprotein (HDL) cholesterol increased by 10%, with no effect on LDL or in total cholesterol) than rosiglitazone (no effect on triglycerides, HDL cholesterol increased by 10%, but 5–10% increases in LDL and total cholesterol).63 This difference on lipids may reflect weaker PPARα agonism by pioglitazone.64 These and markers of heart failure risk favour pioglitazone, and two studies directly measuring atherosclerotic plaques in patients with T2DM showed benefits of pioglitazone compared with the sulfonylurea gliclazide. In the CHICAGO study, pioglitazone slowed the progression of carotid intima media thickness (CIMT),65 while in PERISCOPE pioglitazone actually led to a regression in coronary atheroma volume assessed by intravascular ultrasound.66 In the ACT NOW study of patients with pre-diabetes, pioglitazone similarly decreased progression of CIMT.67 Despite these impressive cardiovascular benefits with pioglitazone therapy, its use has also declined markedly, potentially due to ‘guilt by association’ with rosiglitazone and the description of new risks for fractures and bladder cancer.

Weight gain on thiazolidinediones: both fluid retention and oedema
Weight gain of 1–3 kg is common in patients taking long-term TZDs when used alone or in combination with other anti-diabetic agents. Greater weight gains of 4–5 kg may be seen, however, when TZDs are used in combination with insulin treatment. In a 52-week study comparing rosiglitazone to a sulfonylurea (glyburide, median dose 7.5 mg/d), a mean weight gain of 1.9 kg was observed in both the sulfonylurea group and the rosiglitazone group at the 4-mg daily dose, and a 2.9-kg weight gain was observed at the rosiglitazone 8-mg daily dose.68 Similar weight gain has been observed when rosiglitazone is added to metformin. When added to insulin therapy, however, weight gain may be more dramatic. After 6 months of treatment, weight gains of 4.1 and 5.4 kg were encountered when rosiglitazone, at the 4g and 8 mg daily doses, respectively, was added to insulin (mean dose 70 U/d), compared with a weight gain of 1 kg in patients treated with insulin alone.69 Similar increases have been observed with pioglitazone, either as monotherapy or in combination with other anti-diabetic agents.70 Clinicians are most likely to see oedema as a consequence of TZD therapy when either of the TZDs is used in combination with insulin. For instance, rosiglitazone 4 or 8 mg per day in combination with insulin was associated with a 13.1 and 16.2% incidence of oedema, respectively, compared with 4.7% in those taking insulin alone.71 Pioglitazone at 15 or 30 mg daily in combination with insulin resulted in a combined 15.3% incidence of oedema, compared with 7.0% for insulin alone.72 Therefore, the incidence of oedema is higher when either of the TZDs are combined with insulin compared with other anti-diabetic agents (Table 1). Patients should be instructed to monitor for weight gain or the presence of pedal oedema. Therefore, patients with NYHA functional class III or IV heart failure should not receive TZDs.21

Glucagon-like peptide-1
Incretins are gut hormones that potentiate insulin secretion after ingestion in a glucose-dependent manner. The two best-studied incretins, glucose-dependent insulinotropic polypeptide and GLP-1, exert their insulinotropic actions through distinct G-protein-coupled receptors highly expressed on islet β-cells.73 In addition, GLP-1 suppresses glucagon release from pancreatic α-cells, an action that is likely to be mediated through the local release of somatostatin from islet δ-cells.74 There are two current approaches to enhancing endogenous GLP-1 action in vivo. The first approach involves incretin mimetics, which are GLP-1 analogues that mimic the effect of GLP-1 but are resistant to degradation by DPP-4. Compounds in this class include exenatide and liraglutide. The second approach is to produce substances that increase the half-life of endogenous GLP-1. Agents in this class include exenatide twice daily/once weekly, liraglutide once daily, albiglutide once weekly, lixisenatide once daily, and dulaglutide once weekly injections.76 When selecting the most appropriate agent, a comprehensive review of all head-to-head data indicates that exenatide and liraglutide appear to still offer the best HbA1c and weight reduction,77 while the once weekly agents may cause less GI side effects compared with the once daily or twice daily options.
**Efficacy**

**Glucagon-like peptide-1 agonist exenatide**

Exenatide improves glycaemic control primarily by reducing post-prandial hyperglycaemia, with a modest reduction in fasting plasma glucose levels. A prominent feature of T2DM is a significant reduction in first-phase insulin secretion, the insulin normally secreted by pancreatic β-cells within 10 min after an abrupt rise in plasma glucose concentrations. Exenatide has been displayed to restore both first-phase and second-phase insulin secretion in response to a glucose bolus in subjects with T2DM. The efficacy and safety of exenatide have been assessed in placebo-controlled trials. All trials enrolled patients with HbA1c levels of 7.5–11% and BMI > 25 kg/m². In placebo-controlled trials, exenatide resulted in improved glycaemic control which was dose-related. Exenatide’s efficacy as monotherapy (5- and 10-µg twice daily dosing) was explored in previous study, which demonstrated that HbA1c levels declined steadily during the first 12 weeks of treatment and remained stable at 0.7 and 0.9% below baseline. In particular, exenatide lowers post-prandial glucose levels after breakfast and dinner to a much greater degree than after lunch. The half-life of this agent is too short for the pre-breakfast injection to also cover the lunch-related glucose excursion. In other studies, in which exenatide (10 µg twice daily) was combined with either metformin or a sulfonylurea, similar improvements in HbA1c levels, with stable values of 0.8–0.9% below baseline.80 In particular, exenatide lowers post-prandial hyperglycaemia, with a modest reduction in fasting plasma glucose concentrations. Exenatide has been displayed to restore both first-phase and second-phase insulin secretion in response to a glucose bolus in subjects with T2DM.79

**Glucagon-like peptide-1 agonist liraglutide**

Liraglutide influences the secretion of both pancreatic β and α-cells. The most important effect is the glucose-dependent stimulation of insulin secretion and reduces glucagon secretion by pancreatic α-cells, and consequently hepatic glucose production. The clinical effectiveness of liraglutide is being evaluated in the Liraglutide Effect in Diabetes, or LEAD programme. The LEAD programme has compared liraglutide with widely used classes of anti-diabetic drugs in a series of randomized, double-blind, controlled, 26-week studies in ~3800 patients with T2DM and blood glucose inadequately controlled with standard oral therapies. The data from these studies indicate that the addition of liraglutide to ongoing oral anti-diabetic drugs can significantly improve glycaemic control as well as weight loss in previously uncontrolled patients with T2DM.85 Liraglutide 3.0 mg daily has been shown to result in sustained weight loss, improved cardiovascular risk factors and improved glycaemic control in obese individuals. Hence, it is also of potential clinical value for the treatment of obesity (Figure 1). Across the LEAD trials programme, the overall rate of hypoglycaemic events observed in patients with T2DM treated with liraglutide was generally low.

**Safety**

**Cardiovascular impact**

Human studies of recombinant native GLP-1 have demonstrated cardiovascular benefits including reduced arrhythmias, improved left ventricle function, and improved endothelial function, in patients with or without diabetes and with coronary artery disease and chronic heart failure. In addition, potential reduction in CVD risk has been reported with incretin-based treatment in patients with T2DM. Clinical studies in T2DM patients indicate GLP-1 receptor agonists protect against non-glycaemic cardiovascular risk factors compared with the placebo and most standard anti-diabetic agents. Retrospective analyses of data suggested a possible reduced likelihood of having a cardiovascular event over a 1- to 4-year period among patients who were treated with exenatide twice daily compared with other glucose-lowering agents. Moreover, infusion of exenatide (0.12 pmol/kg/min) for 6 h during two consecutive days in men with T2DM and heart failure led to significantly increased cardiac index (P = 0.003) and decreased pulmonary capillary wedge pressure (P = 0.001) compared with the placebo. In addition, clinical studies of patients with T2DM have examined reductions in BP, lipid, body weight, and cardiovascular risk biomarkers, in response to liraglutide or exenatide treatment.

**Dipeptidylpeptidase-4 inhibitors**

Dipeptidylpeptidase-4 inhibition was first approved for clinical use in 2006 with the DPP-4 inhibitor sitagliptin, and thereafter, several other DPP-4 inhibitors have been introduced into clinical practice. All are oral agents taken once or twice daily and are also being developed for once-weekly administration. These agents reduce fasting and post-prandial hyperglycaemia, have a low risk for hypoglycaemia and are weight neutral. Different DPP-4 inhibitors are distinctive in their metabolism (saxagliptin and vildagliptin are metabolized in the liver while sitagliptin is not), their excretion, their recommended dosage, and the daily dosage that is required for effective treatment. They are similar, however, when comparing their efficacy regarding lowering HbA1c levels, safety profile, and patient tolerance.

**Efficacy**

The efficacy of DPP-4 inhibitors on HbA1c as monotherapy or in combination with other oral anti-diabetic agents was tested in multiple trials lasting 12–52 weeks. The treatment of T2DM with sitagliptin and vildagliptin for > 12 weeks compared with the placebo and other oral anti-diabetic drugs showed a reduction of 0.74% in HbA1c levels. This result proved DPP-4 inhibitors were only slightly less effective than sulfonylureas and as effective as metformin and TZDs in regard to reducing blood glucose. Studies on the influence of DPP-4 inhibitors on patient weight demonstrated variable results but are largely considered to be neutral (Figure 1). Studies regarding treatment with sitagliptin showed variability between 1.5 kg of weight loss in 52 weeks of therapy and 1.8 kg of weight gain in 24 weeks of therapy. Studies regarding treatment with vildagliptin showed variability between 1.8 kg of weight loss and 1.3 kg of weight gain in 24 weeks of therapy. In a meta-analysis of various
studies regarding the treatment of all three DPP-4 inhibitors, the effect of this group of drugs on weight was neutral.95

Safety
Cardiovascular impact
Lipid profile is a crucial factor of cardiovascular risk in T2DM. Twenty patients with T2DM and a body mass index between 28 and 40 kg/m² were included and randomized to receive 100 mg vil-
dagliptin or placebo.96 The results of that study indicate that DPP-4 inhibition increases post-prandial lipid mobilisation and oxidation which contributes to the reduction of cardiovascular risk. In the EXAMINE trial (EXamination of Cardiovascular outcomes with alogl
iptin versus standard of care in patients with T2DM and ACS),97 5380 patients with T2DM with either acute MI or unstable angina requiring hospitalization within the previous 15–90 days were random-
domized to receive alogliptin or placebo and followed up for 1.5 years. Alogliptin treatment did not improve the combined outcome of primary endpoints including death from cardiovascular causes, non-fatal MI, and non-fatal stroke. Similarly, in the SAVOR-TIMI trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Pa-
tients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction),98 16 492 patients with T2DM and history or at risk of CV events were followed for 2.1 years and were randomized to receive saxagliptin or placebo. In consistency with the results from EXAM-
INE, no improvements in cardiovascular outcomes were observed in treatment group compared with placebo-treated patients. It must be noted that the median follow-up period for EXAMINE and SAVOR-TIMI was 1.5 and 2.1 years, respectively, and a longer follow-
up period may be necessary to further confirm the results. Finally, the results of TECOS (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin) have clarified that increased risk of HF is not a DPP-4 inhibitors class effect.99 In TECOS, 14 671 patients were either assigned to sitagliptin or placebo in addition to their current anti-diabetic therapy. Thus, all three trials suggest that DPP-4 inhibitors are basically safe from a cardiovascular standpoint but also do not improve cardiovascular endpoints at least in the short term.

Sodium glucose cotransporter 2 inhibitors
Sodium glucose cotransporter 2 (SGLT-2) inhibitors are a new class of anti-diabetic drugs with a novel mechanism of action. They reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion.100 The first agent ap-
proved in T2DM was dapagliflozin, in late 2012, shortly followed by canagliflozin, and more recently by empagliflozin; all three are cur-
rently approved in the USA and in the European Union.101 Unlike many current therapies, the mechanism of action of SGLT-2 inhibitors is independent of insulin secretion or action and, therefore, does not depend on β-cell function. This suggests that SGLT-2 inhibitors may be effective across all stages of disease progression and carry a low risk for hypoglycaemia.21

Efficacy
All three approved SGLT-2 inhibitors induce a similar sustained urinary glucose loss of 40–80 g/day, associated with good blood glucose-lowering efficacy in T2DM (a reduction in HbA1c of 0.7
0.8% from a starting HbA1c of 8.0%) and lowering of body weight by 2–3 kg.102,103 In a large meta-analysis that included data from SGLT-2 inhibitor trials predominantly involving dapagliflozin and canagliflozin, a favourable effect on reducing HbA1c was observed with a mean difference of 0.7% when compared with placebo.104 Empagliflozin has recently been approved for use in T2DM patients. In a study of T2DM patients controlled with metformin only, HbA1c was improved by a placebo-corrected mean of 0.57 with 10 mg empagliflozin and 0.64% with 25 mg empagliflozin at 24 weeks (both P ≤ 0.001 vs. placebo).105 When empagliflozin was investigated as an add-on therapy to metformin and sulfonylure-
ea and to pioglitazone with or without metformin, similar results were obtained.105 Furthermore, in a longer-term 78-week study, 10 and 25 mg empagliflozin as an add-on therapy to patients taking basal insulin resulted in significant weight loss vs placebo (2.2 vs. 0.7 kg; P ≤ 0.01).106 Dapagliflozin was also associated with weight loss vs. weight gain with glipizide at 52 weeks in patients inade-
quately controlled with metformin (3.2 vs. 1.4 kg for dapagliflozin vs. glipizide; P ≤ 0.0001).107 In patients with moderate chronic kidney disease, the efficacy tends to be dampened and safety concerns may occur.108

Safety
Cardiovascular impact
Sodium glucose cotransporter 2 inhibitor therapy may be consid-
ered in T2DM patients with chronic heart failure with reduced ejection fraction (HFREF), because part of the SGLT-2 inhibitor mechanism includes diuresis, which leads to a preload reduction. This preload reduction is often needed in patients with HFREF.109 Another cardiovascular benefit of SGLT-2 inhibitors is the reduc-
tion of BP, in part due to the osmotic diuresis. A 3–5 mmHg reduc-
tion in systolic and 2 mmHg reduction in diastolic BP have been seen without any compensatory increase in heart rate.110 A meta-analysis of 27 randomized controlled trials shows that SGLT-2 inhibitors de-
crease systolic BP by 4.0 mmHg and diastolic BP by 1.6 mmHg.110
Also relevant for assessing CV safety is the plasma lipid profile; it turned out that canagliflozin (and also other SGLT-2 inhibitors) slightly increase the levels of both HDL and LDL cholesterol.111 This simultaneous increase of both lipoproteins might be a conse-
quence of the observed haemoconcentration and probably does not imply increased CV risk. Sodium glucose cotransporter 2 inhibi-
tors have shown beneficial effects on CV risk factors, such as BP, li-
pids, HbA1c, and weight. Whether these benefits translate into long-term reduction of CV events is unknown. According to the current knowledge from a meta-analysis of clinical trials, including an interim analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS), showed that canagliflozin does not increase the overall CV risk.112 Notably, in patients without CV disease, canagliflozin-treated patients performed numerically better than the comparator therapies in respect to major CV events. The CAN-
VAS is an ongoing trial to evaluate adverse CV events with the use of canagliflozin in diabetics with high CV risk and is expected to be completed in 2018.113 Cardiovascular effects of dapagliflozin are currently being studied in an ongoing Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58), results of which are expected to be released in
2019.144 Taken together, evidence that will define the overall balance of benefits and risks of this new drug class is anticipated within the next 5 years.

Conclusion

Anti-diabetic agents impact on cardiovascular morbidity and mortality

Patients with T2DM have an inherent, elevated risk for cardiovascular disease that likely begins well in advance of a diagnosis of chronic hyperglycaemia. Data describing cardiovascular benefits with metformin are encouraging, with studies showing reductions in any diabetes-related endpoint, diabetes-related death, and all-cause mortality. Evidence for the safety of sulfonylurea therapy is still conflicting, but compared with metformin therapy, sulfonylurea use has been associated with an increased risk of developing heart failure, especially at higher doses. Meglitinitide therapy with repaglinide has been shown to decrease cardiovascular markers including markers of inflammation, platelet activation, and lipid parameters, although less effectively than metformin. The T2D pioglitazone has also been shown to lower the composite of all-cause mortality, non-fatal MI, and stroke in patients with T2DM at high risk for macrovascular events. Thiazolidinediones use, primarily rosiglitazone, is contraindicated in patients with heart failure, as it has been shown to increase the risk of heart failure. Incretin-based therapies including GLP-1 agonists and DPP-4 inhibitors have potential positive effects on the cardiovascular system. The GLP-1 analogue exenatide is associated with a significantly decreased risk of CVD and CVD-related hospitalizations in patients with T2DM. Sodium glucose cotransporter 2 inhibitors are novel oral glucose-lowering agents though, the potential for cardiovascular benefits from the SGLT-2 inhibitors remains to be established. There is ample evidence also to suggest that a multifactorial approach to diabetes care, which targets glycaemic control in addition to treatment of hypertension and dyslipidaemia, will significantly decrease cardiovascular risk. Cardiovascular risk reduction in diabetes, rather than focusing upon glycaemic management alone, should aim to reduce plasma glucose in addition to cholesterol and BP (Table 1). The results of ongoing clinical trials will provide further evidence about the cardiovascular safety and perhaps efficacy of diabetes drugs. These trials will certainly help to further refine therapeutic guidelines in the future.

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References

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lines, and their evidence base, on risk of lactic acidosis after administration of con-

23. Czyr DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative outcomes
study of metformin intervention versus conventional approach the COSMIC

24. Mazzucca AM, Massi A, Gerbasi M. Discontinuation of metformin in the setting of
coronary angiography: clinical uncertainty amongst physicians reflecting a poor


comparison of glycemic effects of sitagliptin and sulfonylureas in elderly patients


28. Tran L, Zielinski A, Roach AH, Jende JA, Householder AM, Cole EE, Atway SA,
Amanuayn P, Accorsi ML, Sheh SW, Thompson EE. The pharmacologic treat-
ment of type 2 diabetes: injectable medications. Ann Pharmacother 2015;49:
700–714.

29. Selzter HS. A summary of criticisms of the findings and conclusions of the Feeding

30. Schwartz TB, Meiner C. The UGDP controversy: thirty-four years of conten-
trast medium for patients receiving metformin. J Am Coll Cardiol 1999;33:
119–124.

31. Riddle MC. Sulfonylureas differ in effects on ischemic preconditioning—is it time
to retire glyburide? J Clin Endocrinol Metabolism 2003;88:528–530.

32. Garratt KN, Brady PA, Hassinger NL, GR, Drzec A, Holmes JR. J Lin
Sulfonylureas drugs increase early mortality in patients with diabetes mellitus prior
direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 2015;39:
1304–1311.

33. Clemens KK, Clemens KK, McArthur E, Dixon SN, Fleet JL, Hramiak I, Garg AX.
The hypoglycemic risk of glyburide (glibenclamide) compared with modified-

34. Bontle SA. Oral antihyperglycemic treatment options for type 2 diabetes mellitus in
oral agent combination therapy for type 2 diabetes (RECORD): a multicentre,

35. Fuchar S, Efronova RA. Impact of glucose-lowering drugs on cardiovascular

36. Hong J, Chang Y, Li S, Li V, Qiu D, Dong Y, Zhou Z, Tang W, Zhao J, Cui L,

Kimball RM. Effect of metformin on the incidence of diabetes and cardiovascular

38. Fujita T, Sugiyama Y, Takei T, Sohda T, Watanavat Y, lwatsuka H, Suzuki Z. Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (ADD-3878,

39. Mansour M. The roles of peroxisome proliferator-activated receptors in the

40. Turner LW, Narrey D, Stafford RS, Singh S, Alexander GC. Ambulatory treatment of

41. Kohroser J, Matlai J, Reichel M, Hagerter B, Bonkovsky HL. Gliclazide hepatotoxicity due
to taglization: report of two cases and review of adverse events reported to the United
States Food and Drug Administration. J Am Gastroenterol 2000;95:
272–276.

42. Danne RE, Chen ER, Lazar MA. Thiazolidinediones and the promise of insulin

43. Natali A, Ferrannini E. Effects of metformin and thiazolidinediones on suppression of
hepatic glucose production and stimulation of glucose uptake in type 2 dia-

44. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Krazwitz BG,
Lachin JM, O'Neill MC, Zinman B, Viberti G. Glycemic durability of rosiglitazone,

45. Doerrsen RA, Murphy B, Schwenke DC, Banerji M, Buse JB, Buchanan GA, Buchman C,
Climent SC, Henry RR, Hodis HN, Kaschki AE, Jacek WJ, Maduiala S, Ratner RE,
1104–1115.

46. Knowler WC, Hamman RF, Edelstein SL, Barrett-Conner E, Ehrmann DA,
Walker EA, Fowler SE, Nathan DM, Kahn SE. Prevention of type 2 diabetes with
troglitazone in the diabetes prevention program. Diabetes 2005;54:
1150–1156.

47. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dincag N, Hanefeld M,
Hoogwerf B, Laakso M, Muhl C, Zibman J, Zinman B, Holman RR. Effect of rosigli-
tazone on the frequency of diabetes in patients with impaired glucose tolerance
or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:
1096–1105.

48. Yau H, Rivera K, Lomassoros R, Kuss K. The future of thiazolidinedione therapy in

Kelman RA. Risk of acute myocardial infarction, stroke, heart failure, and death
in elderly type 2 patients treated with rosiglitazone or pioglitazone. JAMA

50. Mahaffey KW, Haffner D, Dickerson S, Burns S, Turt-Ulhig S, White J, Newbey CK,
Komajda M, McMurray JJ, Bigelow R, Home PD, Lopes RD. Results of a re-
evaluation of cardiovascular outcomes in the RECORD trial. Am Heart J 2013;
166:240–249 e1.

51. Dormandy JA, Charbonnel B, Eckell DJ, Erdmann E, Massi-Benedetti M,
Moules IK, Skene AM, Tan MH, Lefebvre P, Murray GD, Stanwell E, Wilcox RG,
Wilhelmsen L, Betteridge J, Birkenfeld K, Golay A, Heine RJ, Koranyi L,
Laakso M, Molan K, Norkus A, Pirags V, Poder T, Schein A, Scherbaum WA,
Schandlher G, Schmotz O, Skrha J, Smith U, Taton J. PROactive investiga-
tors. Secondary prevention of macrovascular events in patients with type 2 diabetes
in the PROActive Study (PROActive pioglitAzone Clinical Trial In macroVas-

52. Chiquest E, Ramirez D, Fergonza R. A meta-analysis comparing the effect of
thiazolidinediones on cardiovascular risk factors. Arch Intern Med 2004;
164:2097–2104.

Association of human thiazolidinedione-proliferator-activated receptor gamma (PPAR

54. Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D’Agostino RB Sr,
Peraza A, Provost JC, Haffner SM. Effect of pioglitazone compared with glimepiride


