REVIEW

Oral hypoglycaemic agents, insulin resistance and cardiovascular disease in patients with type 2 diabetes

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Abstract
This article is a narrative review of the current evidence of the effects on cardiovascular disease (CVD) of oral hypoglycaemic agents that increase insulin sensitivity in patients with type 2 diabetes (T2D). In overweight T2D patients, metformin has been demonstrated to reduce CVD risk, and this beneficial effect may be conserved with the combination of metformin and insulin treatment. However, the effect of glitazones on CVD is uncertain. There is conflicting evidence from large randomized trials to support a protective effect against CVD of lowering blood glucose per se but a systematic review with meta-analysis is lacking. It may be reasonable to aim for an intervention targeting multiple CVD risk factors such as dyslipidaemia, hypertension and albuminuria in T2D patients.

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Introduction
The prevalence of type 2 diabetes (T2D) is increasing worldwide (1). Insulin resistance in peripheral tissues and inadequate compensatory insulin secretion are essential elements in the pathogenesis of T2D. Impaired insulin secretion is caused by decreased β-cell mass and the dysfunction of existing β-cells. Genetic abnormalities and intrauterine influences may also contribute to the disease process. Aspects of body composition (e.g. obesity) and lifestyle (e.g. high calorie intake and/or reduced physical activity) seem to be important for the degree of insulin resistance and thus probably for the development and progression of T2D. Insulin resistance in combination with relatively impaired insulin secretion leads to hyperglycaemia and compensatory hyperinsulinaemia (2, 3).

As T2D is a progressive disease, the glucose-lowering intervention strategy must be adjusted over time to achieve and maintain good glycaemic control (4). Patients with T2D should be recommended lifestyle interventions. This might be supplemented by oral hypoglycaemic agents, mainly metformin (which increases insulin sensitivity) and/or insulin secretagogues (sulphonylureas, SUs or glitinitides, which stimulate insulin secretion). Glitazones (which increase insulin sensitivity) and acarbose (which reduces gut glucose uptake) are less frequently recommended. If the combination of lifestyle interventions and oral hypoglycaemic agents do not achieve the glycaemic targets, insulin injections may be added, for example according to a consensus algorithm for the initiation and adjustment of therapy (4). Promising new glucose-lowering interventions indirectly stimulate insulin secretion by inhibiting the breakdown of the incretin hormone GLP1 or by increasing the incretin hormone levels by s.c. injection of a GLP1 analogue (5). The most appropriate use of incretin-based therapy in the treatment of T2D has not yet been identified (4).

The ultimate goal of T2D treatment is to reduce mortality and the risk of microvascular and macrovascular complications. The latter (mainly atherosclerosis) are the most frequent cause of increased mortality among T2D patients (6). Several studies suggest a causal association between insulin resistance and atherosclerosis (7–9). This is of clinical interest, since many patients with T2D take oral hypoglycaemic agents that affect insulin sensitivity.

The purpose of the present paper is to give a brief overview of studies focusing on the association between cardiovascular disease (CVD) and oral glucose-lowering interventions with insulin sensitizing agents.

Method
A literature search of the MEDLINE/PubMed database (from 2000 until December 2008) was conducted using the following terms: type 2 diabetes mellitus; atherosclerosis; endothelium; metformin; thiazolidinediones; peroxisome proliferator-activated receptor (PPARγ); cardiovascular disease; and mortality.
The importance of insulin resistance and/or hyperinsulinaemia in the development of atherosclerosis

Atherosclerosis is characterized by the presence of atherosclerotic plaques in the arterial wall. These contain cholesterol-filled macrophages and smooth muscle cells and might be complicated by rupture or thrombosis, resulting in clinical symptoms (10). Endothelial dysfunction (e.g. increased expression of endothelial adhesion molecules, inhibition of activity of nitric oxide (NO) and affected vasopermeability or vasomotility), transport of cholesterol into the arterial wall, oxidation of cholesterol, proliferation of smooth muscle cells and inflammation are all essential elements in the atherosclerotic process (10).

Studies have indicated a connection between hyperinsulinaemia and activation of both atherogenic and anti-atherogenic pathways (7–9). Insulin resistance in the arterial wall might lead to inhibition of phosphatidylinositol 3-kinase activity, which has anti-atherogenic effects (Fig. 1). At the same time, a compensatory increase in insulin levels might stimulate possible atherogenic signalling pathways, including the MAP kinase pathway (Fig. 1).

Metformin

Metformin reduces blood glucose levels by inhibiting hepatic glucose production and reducing insulin resistance. The plasma insulin levels are unchanged or reduced (13). Several trials indicate that metformin has anti-atherogenic effects (e.g. reduced levels of blood cholesterol, inflammatory markers, vascular adhesion molecules and coagulation parameters as well as reduced endothelial dysfunction; 13–16; Table 1).

In a substudy of the United Kingdom Prospective Diabetes Study (UKPDS), 753 overweight patients with T2D were randomized to conventional (diet) treatment or intensive glycaemic control with metformin or SU/insulin for an average of 10 years (13). Metformin resulted in lower insulin levels and improved glycaemic control compared with conventional (diet) treatment. Compared with the conventional treated group, patients allocated to metformin treatment had a significant 32% risk reduction for any diabetes-related outcome measure, as well as significant risk reductions of 39, 42 and 36% for myocardial infarction, diabetes-related death and all-cause mortality respectively. Metformin significantly reduced the incidence of CVD compared with treatment with SU/insulin independent of the achieved level of HbA1c (13). A recent 10-year follow-up study of patients who participated in the UKPDS reported continued benefit of metformin therapy (17). Metformin treatment did not reduce the number of patients with microvascular outcome measures. There are no reported data comparing CVD risk in the metformin and SU groups alone (17, 18). The benefits of metformin are supported by a systematic review with a meta-analysis (19).

In the ‘A Diabetes Outcome Progression Trial’ (ADOPT), 4360 newly diagnosed T2D patients were allocated to interventions for 4 years with rosiglitazone (a glitazone), glyburide (SU) or metformin. Although ADOPT was not statistically powerful enough to detect substantive differences in CVD risk, surprisingly, there were fewer CVD events in the glyburide group than in the rosiglitazone and metformin groups. There was no significant difference in the CVD risk between the metformin and rosiglitazone groups. In the glyburide group, however, more participants dropped out and the follow-up period was shorter (3.3 years) than in the other two groups (both 4 years) (20).
In the DIGAMI-2 trial, 1181 patients with T2D were followed for 2 years after a myocardial infarction. There were no differences in CVD mortality between the intervention groups with insulin, SU or metformin. The risk of a new myocardial infarction increased significantly with insulin therapy, whereas metformin reduced surrogate biomarkers reflecting CVD risk (i.e. reductions in body weight, insulin and cholesterol levels, markers of inflammation and endothelial dysfunction;22–24; Table 1).

In a mixed population of obese and non-obese patients with T2D, the UKPDS surprisingly reported a significant 96% increase in mortality with the combined intervention of metformin and SU compared with intervention with SU alone (13). The authors explained these differences by the observation that patients allocated to the combined intervention group were on average about 5 years older, had higher blood glucose levels and a shorter duration of follow-up than the UKPDS population overall.

Observational studies have yielded conflicting results of combined intervention with metformin and insulin secretagogues with respect to the risk of CVD (25, 26). A recently published meta-analysis indicates an increased frequency of CVD by combined intervention with metformin and insulin secretagogues compared with diet or monotherapy (27).

The participants were included regardless of body mass index (BMI). The patients randomized to metformin in combination with insulin were slightly older, had more CVD and were less often smokers than the patients randomized to placebo; other baseline characteristics were comparable (28). The primary outcome was an aggregate of microvascular disease, CVD and mortality. Secondary outcomes were CVD (fatal and non-fatal) and microvascular disease separately. The follow-up period was 4.3 years. At the end of the trial there was no significant decrease for the risk of the primary outcome. However, metformin treatment significantly reduced the risk of secondary CVD outcomes (e.g. myocardial infarction, stroke, peripheral arterial reconstruction) by 39% \( (P=0.02) \). The reduction observed in the secondary microvascular outcome was non-significant \( (P=0.43) \). The combination of insulin and metformin reduced insulin requirements and improved glycaemic control compared with combination of insulin and placebo. The changes in body weight partly explained the difference in CVD, whereas the changes in glycaemic control and insulin levels did not. The occurrence of hypoglycaemic events was comparable between both groups (29).

### Glitazones

Glitazones work by binding to the PPARγ, which increases insulin sensitivity (4). Several studies have shown that glitazones improve CVD risk biomarkers (i.e. lowering of blood pressure, triglycerides, inflammatory markers and coagulation parameters; increase in HDL cholesterol; improved endothelial function and inhibition of smooth muscle cell proliferation) (30–33). A potential pro-atherogenic effect by treatment with glitazones is an increase in LDL cholesterol (31) (Table 1). However, glitazones also increase the size of LDL particles, which theoretically makes the LDL particles less atherogenic. This effect is more pronounced in pioglitazone than rosiglitazone (34). Although both glitazones activate the same receptor, the observed differences with respect to their effects on the lipid profile may be due to the activation/inhibition of different genes (35).

A randomized trial in patients with T2D reported a reduced progression of carotid artery intimal thickness measured by ultrasound for treatment with pioglitazone compared with an insulin secretagogue (36). The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PRO-active) trial randomized 5238 patients with T2D and known CVD to add-on placebo or pioglitazone (31). The primary outcome measure (a composite of CVD events) was insignificantly reduced with pioglitazone intervention, whereas the secondary CVD outcome measure (death, non-fatal myocardial infarction and stroke) was significantly reduced (31). Pre-specified subgroup analyses from PROactive

### Table 1 Hypoglycaemic agents effect on biomarkers

<table>
<thead>
<tr>
<th>Hypoglycaemic agent</th>
<th>Biomarkers reflecting cardiovascular risk</th>
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<tr>
<td>Metformin</td>
<td>Reduce endothelial dysfunction</td>
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<td></td>
<td>Reduce blood cholesterol</td>
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<td>Reduce inflammatory markers</td>
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<td>Reduce vascular adhesion molecules</td>
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<td>Reduce coagulation parameters</td>
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<tr>
<td>Glitazones</td>
<td>Reduce endothelial dysfunction</td>
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<td></td>
<td>Reduce inflammatory markers</td>
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<td></td>
<td>Reduce coagulation parameters</td>
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<tr>
<td></td>
<td>Increase HDL cholesterol</td>
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<td>Increase LDL cholesterol</td>
</tr>
<tr>
<td></td>
<td>Increase LDL cholesterol particle size</td>
</tr>
<tr>
<td></td>
<td>Reduce smooth muscle cell proliferation</td>
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HDL, high-density lipoprotein; LDL, low-density lipoprotein.
reported a potential cardiovascular protective effect of pioglitazone in patients with T2D and previous stroke or myocardial infarction. Post hoc subgroup analyses reported similar results in patients with T2D but without known peripheral arterial disease (37).

Meta-analyses have revealed a significant increase in CVD risk with rosiglitazone treatment, whereas pioglitazone has possible cardiovascular protective effects (38, 39). This safety-jeopardizing signal of rosiglitazone has prompted the publishing of preliminary data from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia in Diabetes (RECORD) trial. This trial examines the effect of rosiglitazone in combination with either metformin or insulin secretagogues in ~4500 patients with T2D free of known CVD. Preliminary data after 3.75 years follow-up indicate that rosiglitazone treatment results in a non-significant increase in CVD risk. However, the few CVD events mean that these analyses have low statistical power. The complete data are due to become available in 2009 (40).

In addition, both pioglitazone and rosiglitazone treatment have been associated with an increased risk of congestive heart failure (31, 37, 38, 40, 41).

**Anti-diabetic treatment in general and CVD risk**

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial included 10,251 T2D patients with HbA1c ≥ 7.5% and known CVD or risk factors for CVD. The trial tested the hypothesis that intensive control of glycaemic levels, blood pressure and the lipid profile reduce the incidence of CVD and death compared with the standard treatment (42). At baseline, approximately one-third of the participants used insulin and a similar proportion had known CVD. The participants were randomly allocated to intensive glycaemic control, targeting a HbA1c level of < 6.0% or standard glycaemic control, targeting a HbA1c level of 7.0–7.9%. Combinations of all available types of anti-diabetic drugs were used to achieve the glycaemic targets. The median HbA1c level at baseline was 8.1%. After a median follow-up of 3.5 years the HbA1c level in the group allocated to intensive glycaemic control was 6.4% compared with 7.5% in the conventionally treated group. During the trial, 92% and 58% of the patients received glitazones in the intensive and in the conventional treatment groups respectively (both groups used almost exclusively rosiglitazone). About 90% of patients in both groups received metformin. Between the intensively versus the conventionally treated groups, the difference in the composite primary outcome measure of non-fatal CVD and CVD death did not reach statistical significance. However, a significantly lower frequency of non-fatal myocardial infarction was observed in the intensively treated group. Data on microvascular outcome measures have not yet been published. The glycaemic intervention arm of the trial was stopped in February 2008 because of a higher mortality rate (total and/or CVD death) in the group allocated to intensive glycaemic control compared with conventional control (257 vs 203 deaths in the intensive and conventional groups respectively). Preliminary analyses have not identified any specific cause for the higher mortality. In particular, no conclusive evidence has been found to suggest that certain oral hypoglycaemic agents or combinations thereof were responsible for the increased risk of death. Pre-specified subgroup analyses showed significant heterogeneity in the primary outcome according to known CVD or baseline HbA1c. Thus, a reduced incidence of the primary outcome was observed among participants allocated to the intensive glycaemic control with a level of HbA1c ≤ 8.0% or no known CVD before randomization. By contrast, in the groups with known CVD or baseline HbA1c of > 8.0%, the effect between interventions on the primary outcome was neutral. For total mortality, no significant heterogeneity was observed between the intervention groups with respect to known CVD or baseline HbA1c (42).

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial randomly allocated 11,140 patients with T2D and known CVD or high CVD risk to intensive or conventional glycaemic control groups (43). Unlike the ACCORD and the Veterans Affairs Diabetes trial (VADT – see below), at inclusion, the ADVANCE trial did not specify a requirement for the level of HbA1c and patients were almost exclusively insulin-naïve (1–2% used insulin at baseline). Similar to the ACCORD trial, approximately one-third of the patients had known CVD. Patients in the intensive intervention group were all treated with gliclazide (SU), in addition to any marketed anti-diabetic agent, to achieve a target level of HbA1c of 6.5% or less. In the conventionally treated group, the HbA1c target was defined by local treatment guidelines. From a median baseline HbA1c of 7.2%, after a median follow-up of 5 years, the intensive group achieved a median HbA1c of 6.4% compared with 7.0% in the conventional group. During the ADVANCE trial, only about 10–15% and 70% of the patients received intervention with glitazones and metformin respectively; the proportion of patients treated with glitazones taking rosiglitazone was not reported. This was in contrast to the ACCORD trial in which a much higher proportion of patients in the intensive glycaemic group received the glitazone intervention. The ADVANCE trial reported, in contrast to the ACCORD trial, with intensive compared with conventional glycaemic control, a significant reduction in the composite primary outcome measure of microvascular and macrovascular (non-fatal CVD and CVD death) events. Also, in contrast to the ACCORD trial, the ADVANCE trial reported no differences in CVD.
or mortality with intensive compared with conventional glycaemic control. The significant difference in the primary outcome measure in the ADVANCE trial was primarily caused by a reduction of microvascular events (nephropathy).

The VADT trial randomly allocated 1791 patients with T2D to intensive intervention versus conventional intervention (44). At inclusion, patients were required to have a level of HbA1c of ≥7.5% and, at baseline, about half of the patients used insulin and 40% had known CVD. The median baseline level of HbA1c was 9.4%. In the intensive intervention group, the target level of HbA1c was ≤6.0% (similar to the ACCORD trial) and, in the conventionally treated group, a separation of 1.5% in HbA1c compared with the intensive intervention group was aimed for. About 60–70% of the patients in the two groups received rosiglitazone; the number of metformin-treated patients was not reported (44). After a median follow-up of 5.6 years, the intensive intervention group achieved a level of HbA1c of 6.9% compared with 8.5% in the conventional group. There was no significant difference in the primary outcome measure (a composite of CVD events) between the intensive and conventional glycaemic control groups. Also, there was no evidence of increased mortality in the intensive intervention group and preliminary data indicate that intervention with rosiglitazone was not associated with higher mortality (44). However, somewhat similar to the ADVANCE trial, with intensive versus conventional glycaemic control, VADT reported significantly reduced progression of albuminuria (i.e. microvascular disease). The ADVANCE trial showed an apparently lower risk of severe hypoglycaemia than did the ACCORD and VADT trials (about 3% and 15–20% of patients had ≥1 severe hypoglycaemic episode respectively, in the ADVANCE trial and the ACCORD and VADT trials; 45).

**Discussion**

Studies conducted on cell cultures and animals indicate a possible relationship between insulin resistance, compensatory hyperinsulinaemia and the development of atherosclerosis (Fig. 1). It is unclear whether a similar mechanism exists in humans. Several studies report possible anti-atherogenic effects of oral hypoglycaemic agents that increase peripheral insulin sensitivity and thereby reduce the insulin requirement (7–9, 11–17, 22–24, 30, 32, 33; Table 1). If these effects are of clinical significance, intervention with oral hypoglycaemic agents that increase insulin sensitivity might be an attractive choice. A review of all oral hypoglycaemic agents indicates that those agents that increase insulin sensitivity are also associated with reduced CVD (metformin and glitazones; 41) – in contrast to other oral anti-diabetic agents (46).

Metformin has become the treatment of first choice, as it reduced CVD risk among overweight patients with T2D in the UKPDS (13; Table 2). Data from this study have also strongly indicated that insulin secretagogues and insulin treatment do not lead to increased CVD risk. A potential inhibition of potassium channels in the heart during SU treatment, in addition to the suspicion of a relatively pro-atherogenic effect of hyperinsulinaemia, previously gave rise to concern about increased CVD risk of treatment with insulin or insulin secretagogues (47). However, the possibility that the higher glycaemic level in the conventional (diet) treatment group increased CVD risk cannot be excluded. In turn, this might have been equalized (but not eliminated) as a result of higher (supra-physiological) plasma insulin levels and/or inhibition of potassium channels by treatment with insulin and/or insulin secretagogues. Thus, it is theoretically possible that the ‘protective’ effects of metformin against CVD as primarily observed in the UKPDS were caused by the lowering of blood glucose without a concomitant increase in plasma insulin levels.

In passing, it must be emphasized that there is no evidence to support the hypothesis that insulin and/or insulin secretagogues themselves increase the risk of CVD. Moreover, these treatments have a significant role in reducing the risk of microvascular complications in patients with T2D. The recently published 10-year follow-up from the UKPDS trial suggests that treatment with SU/insulin reduces the CVD risk and, also the risk of microvascular complications. Hence, metformin and SU/insulin may be equally effective as the treatment of first choice in patients with T2D (17, 18). Finally, the potassium channels in the heart are less affected by the newer insulin secretagogues than by those of earlier generations.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Summary of oral hypoglycaemic agents</th>
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<tr>
<td><strong>Oral hypoglycaemic agents</strong></td>
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</tr>
<tr>
<td><strong>Metformin</strong></td>
<td>May be the intervention of first choice in both normal and overweight patients with type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>Probably has a protective action against macrovascular disease</td>
</tr>
<tr>
<td><strong>Glitazones</strong></td>
<td>Is used in addition to other anti-diabetics when monotherapy or combination therapy fails</td>
</tr>
<tr>
<td></td>
<td>The effect on macrovascular disease is not clear and the interventions are suspected of inducing heart failure and osteoporotic fractures</td>
</tr>
<tr>
<td><strong>Metformin/sulfonylurea combination therapy</strong></td>
<td>Is used when monotherapy fails</td>
</tr>
<tr>
<td></td>
<td>The effect on macrovascular disease is not clarified</td>
</tr>
<tr>
<td><strong>Metformin/insulin combination therapy</strong></td>
<td>May be used to reduce insulin dose, weight gain and probably to protect against macrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Recent data support a protective effect against macrovascular disease, but more data are needed</td>
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</table>
The positive reports from the UKPDS of the effect of metformin in lowering CVD risk were supported by a meta-analysis, and in a follow-up analysis from the DIGAMI-2 trial as well as by the recent HOME trial (19, 21, 29). The reporting of lower CVD risk by glyburide intervention in the ADOPt trial was surprising, but is partly supported by the 10-year follow-up from the UKPDS. However, the data related to CVD risk in the ADOPt trial should be interpreted cautiously because of their lack of statistical power to demonstrate CVD differences and disparities in drop-out and duration of follow-up between the groups (20).

Whether a potential beneficial effect of metformin is present in all patients with T2D regardless of BMI cannot be concluded from the UKPDS. Several previous treatment guidelines have recommended insulin secretagogues as a first-line intervention in non-obese T2D patients, similarly to the UKPDS design (48). Despite the lack of trials with cardiovascular clinical outcome measures in non-obese patients with T2D, metformin is recommended by two international diabetes associations as a drug of first choice for most patients with T2D regardless of their BMI (4). In non-obese patients with T2D, trials of shorter duration have indicated that metformin and insulin secretagogues have equal glucose-lowering potentials, although metformin showed potential beneficial effects on a number of CVD risk biomarkers (22–24). Nevertheless, there is still a need for trials and systematic reviews using clinically relevant outcomes before a well-documented first-line oral hypoglycaemic agent for non-obese patients with T2D can be established. Metformin and insulin secretagogues may, with appropriate caution, be equal first-choice candidates for interventions in these patients.

It cannot be concluded from the literature whether combination therapy with metformin and SU has harmful effects, as indicated by the UKPDS (13, 25–27). At present, the international guidelines recommend combination therapy when monotherapy fails (4).

The HOME trial suggested that the potential beneficial effect of metformin on CVD was maintained when used in combination with insulin in patients with T2D (29). The HOME trial indicated that this effect of metformin therapy might at least partly have resulted from the effect of metformin to lower body weight. Although the HOME study did not clearly indicate so, the insulin sparing effect of metformin therapy might also have influenced the occurrence of CVD in that study. However, the primary composite micro- and macrovascular end point of the HOME trial was not influenced by adjunct metformin therapy (29).

There is a need for better documentation of the potential protective effect of metformin on CVD in patients with T2D, and the results from the rather small UKPDS and HOME trials need to be confirmed in new trials. There is also still a need for larger trials to clarify whether the potential protective effects of metformin on CVD are maintained in combination with insulin. Moreover, the effect of metformin therapy on microvascular disease remains uncertain.

It is still debated whether glitazones have atherogenic or anti-atherogenic effects. Trials have indicated a possible anti-atherogenic effect of pioglitazone (31, 38). The meta-analysis by Nissen et al. raised concerns about whether rosiglitazone had pro-atherogenic properties (39), but has since been criticized. Several methodological weaknesses have been highlighted, in particular the failure to state a hypothesis, exclusion of trials with zero events, analysing the number of events instead of time to events, the statistical model (using a fixed-effects model instead of the more plausible random-effects model, which would have shown that rosiglitazone had a non-significant effect on CVD). The US Food and Drug Administration concluded that the results were of concern, but did not consider the evidence sufficient to justify withdrawal of rosiglitazone from the market (46, 49). Preliminary data from the RECORD trial could neither confirm nor discount an increased risk of CVD during glitazone treatment (40).

However, glitazones are relatively expensive, increase body weight, cholesterol levels and the frequency of osteoporotic fractures. This calls for caution in the use of glitazones until their effects are clarified, with respect not only to the lowering of blood glucose levels, but also to the reduction of macrovascular disease and/or mortality (4).

A major problem in relation to the choice of anti-diabetic intervention is that it remains unclear whether there is a direct causal relationship between lowering blood glucose and the risk of developing CVD – as highlighted by the ACCORD, ADVANCE and VADT trials (42–44). In patients with type 1 diabetes, the Epidemiology of Diabetes Interventions and Complications (EDIC) study reported a reduced CVD risk as a result of lowering blood glucose (50). The post hoc analysis of the UKPDS trial also suggested such a relationship in patients with T2D (51). As emphasized by the authors of the ACCORD trial, it is not possible to separate the impact of individual events occurring after randomization (including achieved blood glucose levels, the reduction in blood glucose, administration of hypoglycaemic agents, etc.) on clinical outcomes (the same applies to ADVANCE and VADT; 42–44). Accordingly, the cause of the higher mortality rate in the intensive group of the ACCORD trial cannot be clarified and exploratory analyses have not been able to identify any specific oral hypoglycaemic agents as being potentially more harmful than others. Details of these exploratory analyses still await publication (42). In relation to the main concern of the present paper, however, it is remarkable that almost all the patients (92%) in the intensively treated group of the ACCORD trial, compared with only somewhat more than half (58%) in the conventionally treated group, received intervention with glitazones. Hence, the unequal
(by comparison with the conventional group) and small proportion of patients who did not receive intervention with glitazones in the group allocated intensive glycaemic control probably meant that there was insufficient statistical power to enable any potential harmful effect of the glitazone intervention to be demonstrated. By contrast, the proportion of patients taking metformin during the trial was similar in the two groups (~90%), which strongly suggests that the use of metformin did not explain the higher mortality in the intensive intervention group.

As outlined, the observed differences in mortality in the ACCORD compared with the ADVANCE and VADT studies cannot readily be explained. As a consequence of the ACCORD trial, targeting a level of HbA1c of 6.0% or less by using anti-diabetic polypharmacia may not be recommendable in patients with a high risk of CVD and poor glycaemic control. On the other hand, in high-risk CVD patients, the ADVANCE trial indicates a reduction in microvascular complications without an increase in CVD risk with the treatment goal being a HbA1c level of 6.5% or lower. Also, the ADVANCE trial, using the target of HbA1c of 6.5% or less in the intensively treated group, showed an apparently lower risk of severe hypoglycaemia compared with the ACCORD or VADT trials, both of which set a target of HbA1c of 6.0 or less in the intensive intervention groups.

Results from clinical trials using cholesterol-lowering therapy with simvastatin indicate an improved prognosis in patients with T2D (52, 53). Anti-hypertensive treatment has also been shown to be of major importance in the prevention of cardiovascular events in patients with T2D (54). The Steno-2 trial reported reduced mortality when using aggressive interventions targeting multiple CVD risk factors in patients with T2D with high-risk of CVD (55).

In conclusion, despite much research, it has still not been clarified which anti-diabetic interventions prevent CVD to the greatest extent in patients with T2D. Oral hypoglycaemic agents, which increase insulin sensitivity (metformin and glitazones), may have a beneficial effect on CVD risk in patients with T2D, but conclusive documentation is still unavailable, and updated systematic reviews with meta-analyses are warranted. There is uncertainty regarding the relationship between glitazones, CVD and also osteoporosis. Primarily based on the results from the UKPDS, metformin is recommended as the initial treatment in overweight and obese patients with T2D. In non-obese patients with T2D both metformin and insulin secretagogues may be the intervention of first choice. Anti-diabetic treatment should be intensified using combination therapy and insulin with the aim of achieving the HbA1c targets, but systematic reviews with meta-analyses may yield valuable knowledge about the preferred HbA1c level and drug combinations that will be of value in designing future intervention strategies. Elevated blood pressure and lipid levels should be aggressively treated independently of the anti-diabetic treatment.

**Declaration of interest**

Søren Sgaard Lund and Allan Vaag have reported equity in Novo Nordisk A/S. Allan Vaag has received funds from Novo Nordisk A/S for research. Søren Sgaard Lund and Allan Vaag have received fees from Novo Nordisk A/S for speaking and Allan Vaag has received fees from Novo Nordisk A/S for organising education. Søren Sgaard Lund and Allan Vaag are employees at the Steno Diabetes Center, Gentofte, Denmark. The Steno Diabetes Center is an independent academic institution owned by Novo Nordisk A/S and The Novo Nordisk Foundation. Allan Vaag is a member of the editorial board for European Journal of Endocrinology. Jørn Wetterslev and Bianca Hemmingsen declare no conflict of interest.

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**References**


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