

REVIEW

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

Bianca Hemmingsen, Søren S Lund¹, Jørn Wetterslev and Allan Vaag¹

Copenhagen Trial Unit, Rigshospitalet, 2100 Copenhagen Ø, Denmark and ¹Steno Diabetes Center, Niels Steensensvej 2-4, 2820 Gentofte, Denmark

(Correspondence should be addressed to B Hemmingsen; Email: biancahemmingsen@hotmail.com)

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.

European Journal of Endocrinology 161 1–9

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 glitinides, 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 (PPAR γ); 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 nitrogen 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).

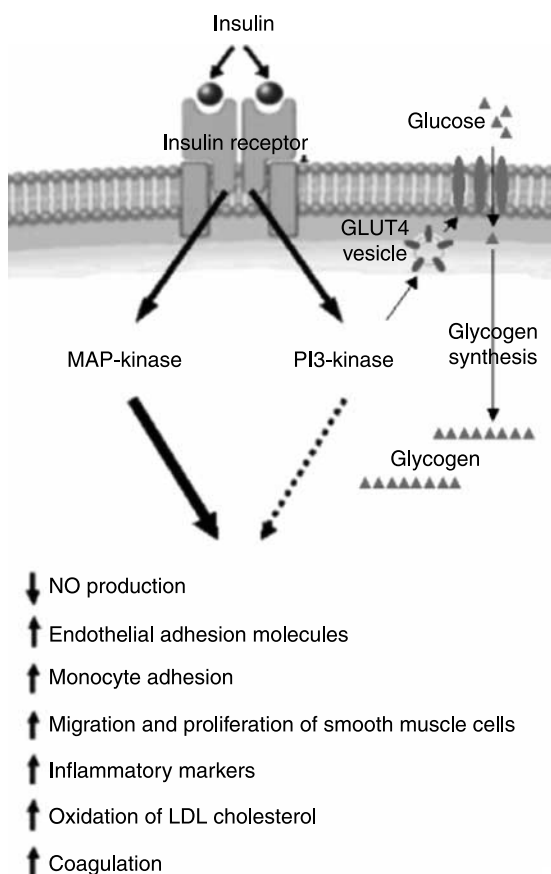


Figure 1 The effect of insulin on the vascular cells in type 2 diabetes.

Studies conducted on cell cultures and rodents have shown that insulin resistance and hyperinsulinaemia reduce NO activity and stimulate the migration and proliferation of smooth muscle cells, the expression of cellular adhesion molecules, inflammatory markers, oxidation of low-density lipoprotein (LDL) cholesterol and coagulation (7–9, 11). In addition, insulin *per se* seems to have the capacity to both increase and decrease vascular tonus (12).

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).

Table 1 Hypoglycaemic agents effect on biomarkers

Hypoglycaemic agent	Biomarkers reflecting cardiovascular risk
Metformin	Reduce endothelial dysfunction Reduce blood cholesterol Reduce inflammatory markers Reduce vascular adhesion molecules Reduce coagulation parameters
Glitazones	Reduce endothelial dysfunction Reduce inflammatory markers Reduce coagulation parameters Increase HDL cholesterol Increase LDL cholesterol Increase LDL cholesterol particle size Reduce smooth muscle cell proliferation

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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 therapy had a protective effect (21).

In the UKPDS, non-obese patients with T2D were treated with insulin or SU, but the UKPDS (and other prospective studies) did not report data for CVD risk separately in this group of patients. Hence, in non-obese patients with T2D, there is a lack of evidence that metformin or other oral hypoglycaemic agents affect CVD risk. Recent short-term trials have demonstrated a similar effect of metformin and the insulin secretagogue, repaglinide, on HbA1c in non-obese patients with T2D. Metformin treatment 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 recently published 'Hyperinsulinemia: the Outcome of its Metabolic Effects' (HOME) trial, randomly allocated 390 patients with T2D to either placebo or metformin in addition to ongoing insulin therapy.

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 PPAR γ , 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

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 Cardiac 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 $\geq 7.5\%$ 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 $\leq 8.0\%$ 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 Diamicon 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 $\geq 7.5\%$ 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 $\leq 6.0\%$ (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 2 Summary of oral hypoglycaemic agents

Oral hypoglycaemic agents	
Metformin	May be the intervention of first choice in both normal and overweight patients with type 2 diabetes Probably has a protective action against macrovascular disease
Glitazones	Is used in addition to other anti-diabetics when monotherapy or combination therapy fails The effect on macrovascular disease is not clear and the interventions are suspected of inducing heart failure and osteoporotic fractures
Metformin/sulfonylurea combination therapy	Is used when monotherapy fails The effect on macrovascular disease is not clarified
Metformin/insulin combination therapy	May be used to reduce insulin dose, weight gain and probably to protect against macrovascular disease Recent data support a protective effect against macrovascular disease, but more data are needed

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 Søgaard 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 Søgaard 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 Søgaard 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. Jorn Wetterslev and Bianca Hemmingsen declare no conflict of interest.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- 1 King H, Aubert RE & Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998 **21** 1414–1431.
- 2 Vaag A. On the pathophysiology of late onset non-insulin dependent diabetes mellitus. Current controversies and new insights. *Danish Medical Bulletin* 1999 **46** 197–234.
- 3 LeRoith D. Beta-cell dysfunction and insulin resistance in type 2 diabetes: role of metabolic and genetic abnormalities. *American Journal of Medicine* 2002 **113** 3S–11S.
- 4 Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R & Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009 **32** 193–203.
- 5 Vilsboll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O, Courreges JP, Verhoeven R, Buganova I & Madsbad S. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care* 2007 **30** 1608–1610.
- 6 de Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E & Muggeo M. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. *Diabetes Care* 1999 **22** 756–761.
- 7 King GL & Brownlee M. The cellular and molecular mechanisms of diabetic complications. *Endocrinology and Metabolism Clinics of North America* 1996 **25** 255–270.
- 8 Montagnani M, Golovchenko I, Kim I, Koh GY, Goalstone ML, Mundhekar AN, Johansen M, Kucik DF, Quon MJ & Draznin B. Inhibition of phosphatidylinositol 3-kinase enhances mitogenic actions of insulin in endothelial cells. *Journal of Biological Chemistry* 2002 **277** 1794–1799.
- 9 Nigro J, Osman N, Dart AM & Little PJ. Insulin resistance and atherosclerosis. *Endocrine Reviews* 2006 **27** 242–259.
- 10 Lusis AJ. Atherosclerosis. *Nature* 2000 **407** 233–241.
- 11 Schneider DJ, Absher PM, Neimane D, Russell JC & Sobel BE. Fibrinolysis and atherogenesis in the JCR:LA-cp rat in relation to insulin and triglyceride concentrations in blood. *Diabetologia* 1998 **41** 141–147.
- 12 Muniyappa R, Montagnani M, Koh KK & Quon MJ. Cardiovascular actions of insulin. *Endocrine Reviews* 2007 **28** 463–491.

- 13 UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998 **352** 854–865.
- 14 Davis BJ, Xie Z, Viollet B & Zou MH. Activation of the AMP-activated kinase by antidiabetic drug metformin stimulates nitric oxide synthesis *in vivo* by promoting the association of heat shock protein 90 and endothelial nitric oxide synthase. *Diabetes* 2006 **55** 496–505.
- 15 Mather KJ, Verma S & Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. *Journal of the American College of Cardiology* 2001 **37** 1344–1350.
- 16 De JJ, Kooy A, Lehert P, Bets D, Wulffele MG, Teerlink T, Scheffer PG, Schalkwijk CG, Donker AJ & Stehouwer CD. Effects of short-term treatment with metformin on markers of endothelial function and inflammatory activity in type 2 diabetes mellitus: a randomized, placebo-controlled trial. *Journal of Internal Medicine* 2005 **257** 100–109.
- 17 Holman RR, Paul SK, Bethel MA, Matthews DR & Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *New England Journal of Medicine* 2008 **359** 1577–1589.
- 18 Lund SS, Rossing P & Vaag AA. Follow-up of intensive glucose control in type 2 diabetes. *New England Journal of Medicine* 2009 **360** 416.
- 19 Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M & Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2005 **3** CD002966.
- 20 Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B & Viberti G. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *New England Journal of Medicine* 2006 **355** 2427–2443.
- 21 Mellbin LG, Malmberg K, Norhammar A, Wedel H & Ryden L. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *European Heart Journal* 2008 **29** 166–176.
- 22 Lund SS, Tarnow L, Stehouwer CD, Schalkwijk CG, Frandsen M, Smidt UM, Pedersen O, Parving HH & Vaag A. Targeting hyperglycaemia with either metformin or repaglinide in non-obese patients with type 2 diabetes: results from a randomized crossover trial. *Diabetes, Obesity and Metabolism* 2007 **9** 394–407.
- 23 Lund SS, Tarnow L, Stehouwer CD, Schalkwijk CG, Teerlink T, Gram J, Winther K, Frandsen M, Smidt UM, Pedersen O, Parving HH & Vaag AA. Impact of metformin versus repaglinide on non-glycaemic cardiovascular risk markers related to inflammation and endothelial dysfunction in non-obese patients with type 2 diabetes. *European Journal of Endocrinology* 2008 **158** 631–641.
- 24 Lund SS, Tarnow L, Frandsen M, Smidt UM, Pedersen O, Parving HH & Vaag AA. Impact of metformin versus the prandial insulin secretagogue, repaglinide, on fasting and postprandial glucose and lipid responses in non-obese patients with type 2 diabetes. *European Journal of Endocrinology* 2008 **158** 35–46.
- 25 Johnson JA, Majumdar SR, Simpson SH & Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care* 2002 **25** 2244–2248.
- 26 Kahler KH, Rajan M, Rhoads GG, Safford MM, Demissie K, Lu SE & Pogach LM. Impact of oral antihyperglycemic therapy on all-cause mortality among patients with diabetes in the Veterans Health Administration. *Diabetes Care* 2007 **30** 1689–1693.
- 27 Rao AD, Kuhadiya N, Reynolds K & Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. *Diabetes Care* 2008 **31** 1672–1678.
- 28 Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der BB, Donker AJ & Stehouwer CD. Combination of insulin and metformin in the treatment of type 2 diabetes. *Diabetes Care* 2002 **25** 2133–2140.
- 29 Kooy A, De JJ, Lehert P, Bets D, Wulffele MG, Donker AJ & Stehouwer CD. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Archives of Internal Medicine* 2009 **169** 616–625.
- 30 Caballero AE, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connor C, Logerfo FW, Horton ES & Veves A. The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. *Metabolism* 2003 **52** 173–180.
- 31 Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Scherthaner G, Schmitz O, Skrha J, Smith U & Taton J. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005 **366** 1279–1289.
- 32 Nordt TK, Peter K, Bode C & Sobel BE. Differential regulation by troglitazone of plasminogen activator inhibitor type 1 in human hepatic and vascular cells. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 1563–1568.
- 33 Pflutzner A, Marx N, Lubben G, Langenfeld M, Walcher D, Konrad T & Forst T. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. *Journal of the American College of Cardiology* 2005 **45** 1925–1931.
- 34 Deeg MA, Buse JB, Goldberg RB, Kendall DM, Zagar AJ, Jacober SJ, Khan MA, Perez AT & Tan MH. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2007 **30** 2458–2464.
- 35 Hsiao A, Worrall DS, Olefsky JM & Subramaniam S. Variance-modeled posterior inference of microarray data: detecting gene-expression changes in 3T3-L1 adipocytes. *Bioinformatics* 2004 **20** 3108–3127.
- 36 Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino RB Sr, Perez A, Provost JC & Haffner SM. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *Journal of the American Medical Association* 2006 **296** 2572–2581.
- 37 Betteridge DJ, DeFronzo RA & Chilton RJ. PROactive: time for a critical appraisal. *European Heart Journal* 2008 **29** 969–983.
- 38 Lincoff AM, Wolski K, Nicholls SJ & Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *Journal of the American Medical Association* 2007 **298** 1180–1188.
- 39 Nissen SE & Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine* 2007 **356** 2457–2471.
- 40 Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Dargie H, Komajda M, Gubb J, Biswas N & Jones NP. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol. *Diabetologia* 2005 **48** 1726–1735.
- 41 Uwaifo GI & Ratner RE. Differential effects of oral hypoglycemic agents on glucose control and cardiovascular risk. *American Journal of Cardiology* 2007 **99** 51B–67B.
- 42 Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi E, Grimm RH Jr, Probstfield JL, Simons-Morton DG & Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *New England Journal of Medicine* 2008 **358** 2545–2559.
- 43 Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompont S, de Galan BE, Joshi R &

- Travert E. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine* 2008 **358** 2560–2572.
- 44 Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG & Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. *New England Journal of Medicine* 2009 **360** 129–139.
- 45 Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P & Sherwin RS. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation* 2009 **119** 351–357.
- 46 Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, Wiley C, Selvin E, Wilson R, Bass EB & Brancati FL. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Annals of Internal Medicine* 2007 **147** 386–399.
- 47 Smits P, Bijlstra PJ, Russel FG, Lutterman JA & Thien T. Cardiovascular effects of sulphonylurea derivatives. *Diabetes Research and Clinical Practice* 1996 **31** S55–S59.
- 48 Consoli A, Gomis R, Halimi S, Home PD, Mehnert H, Strojek K & Van Gaal LF. Initiating oral glucose-lowering therapy with metformin in type 2 diabetic patients: an evidence-based strategy to reduce the burden of late-developing diabetes complications. *Diabetes and Metabolism* 2004 **30** 509–516.
- 49 Bloomgarden ZT. The Avandia debate. *Diabetes Care* 2007 **30** 2401–2408.
- 50 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P & Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New England Journal of Medicine* 2005 **353** 2643–2653.
- 51 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC & Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000 **321** 405–412.
- 52 Collins R, Armitage J, Parish S, Sleight P & Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003 **361** 2005–2016.
- 53 Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J & Pyorala K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Archives of Internal Medicine* 1999 **159** 2661–2667.
- 54 Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E & Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005 **366** 895–906.
- 55 Gaede P, Lund-Andersen H, Parving HH & Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *New England Journal of Medicine* 2008 **358** 580–591.

Received 3 April 2009

Accepted 7 April 2009