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Controversies in type 2 diabetes

An update

Background
Controversy has emerged concerning the risks associated with glitazone therapy in type 2 diabetes, specifically bone fracture and myocardial infarction. Results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study have stimulated debate about appropriate glycated haemoglobin (HbA1c) targets.

Objective
This article examines the context for glitazone therapy in patients with type 2 diabetes, the risks associated with pioglitazone and rosiglitazone, and arguments for targeting HbA1c at the threshold of 7%.

Discussion
Pioglitazone and rosiglitazone can be employed as oral therapy in patients with type 2 diabetes and preserved endogenous insulin secretion. Potential benefits and risks of each agent should be considered. An acceptable initial target for HbA1c is 7%. Lowering HbA1c to 6.5% did not reduce macrovascular complications in patients with type 2 diabetes, but did reduce new or worsening nephropathy. Aggressive therapy aiming to lower HbA1c to <6% in patients with type 2 diabetes at especially high risk of cardiovascular disease may lead to a higher risk of mortality.

Patients with type 2 diabetes undergo a transition over time from an initial state of predominant insulin resistance to progressive impairment of beta cell function. While beta cell secretion of insulin is preserved, lifestyle measures to reduce insulin resistance are indicated, and additional drug therapy is often necessary. Metformin and sulphonylureas are common first and second line therapies. Options to intensify therapy include the use of a glitazone or an alternative agent such as exenatide, or to commence insulin.

Insulin therapy is required when beta cell insulin secretion has declined to the point where sulphonylureas and insulin sensitisers are not achieving acceptable glycaemic control.[1] Glitazones remain an option to improve glycaemic control in patients with type 2 diabetes and preserved beta cell function.

Glitazone therapy in patients with type 2 diabetes

Pioglitazone

Pioglitazone can be given once daily, orally and titrated, to the maximal dose of 45 mg/day. It is Pharmaceutical Benefits Scheme (PBS) approved for use as dual therapy with either metformin or a sulphonylurea, and also for use as triple oral therapy in combination with both metformin and sulphonylurea.

In the PROspective pioglitazone Clinical Trial In macroVascular Events (PROactive) study of patients with type 2 diabetes with evidence of macrovascular disease,[2] 89% of patients randomised to pioglitazone were able to tolerate the 45 mg dose.

Pioglitazone has a favourable effect on lipid profiles, increasing high density lipoprotein (HDL) cholesterol and reducing triglycerides.[2] In the PROactive study, pioglitazone treatment reduced the cumulative incidence of death, myocardial infarction and stroke.[2] This favourable effect was confirmed in a subsequent meta-analysis

of 19 trials enrolling 16 390 patients with type 2 diabetes, in which pioglitazone was associated with a reduced risk of death, myocardial infarction and stroke.[3]

Disadvantages include the recognised adverse effects of weight gain, peripheral oedema and an increase in diagnosis of heart failure – albeit with no increase in mortality from heart failure.[4] Also, women treated with pioglitazone appear to have a higher risk of peripheral (not hip or spine) fractures.[5]

Rosiglitazone

Rosiglitazone can be given orally and titrated to the maximal dose of 8 mg/day. It was PBS listed for dual and triple oral therapy.

In patients with type 2 diabetes, rosiglitazone has comparable efficacy overall to insulin glargine.[6] However, while reductions in glycated haemoglobin (HbA1c) with treatment are almost identical in patients with an HbA1c of 7.5–9.0% at commencement, patients with an HbA1c of 9.5–11.0% at commencement have a greater reduction in HbA1c with glargine treatment.[6]

Disadvantages of rosiglitazone include an increase in both low density lipoprotein (LDL) and HDL cholesterol levels, recognised adverse effects of weight gain, peripheral oedema and an increase in diagnosis of heart failure, although without an increase in mortality from heart failure. Women treated with r osiglitazone in the A Diabetes Outcome Progression Trial (ADOPT) study experienced an increase in peripheral but not hip or spine fractures.[7,8] Fractures occurred in both pre- and post-menopausal women, although risk of osteoporosis would be of most concern in older postmenopausal women.[9]

Rosiglitazone and risk of myocardial infarction

Two recent independent meta-analyses – one including 42 trials involving 27 847 participants[10] and one including four trials involving 14 291 patients with at least 12 months of follow up[11] – found an increase in the risk of myocardial infarction associated with rosiglitazone. In both meta-analyses, participants given rosiglitazone for treatment or prevention of type 2 diabetes had an increase in the risk of myocardial infarction in the order of a 40% excess over controls.[10,11]

There is ongoing debate as to the applicability of these findings to patients with type 2 diabetes in general, with some criticism of the meta-analysis by Nissen and Wolski on methodological grounds.[10] The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial using rosiglitazone in patients with type 2 diabetes is still underway and may provide clarification of this risk.[12]

However, until further information is available, the possible increased risk of myocardial infarction with rosiglitazone must be considered when selecting a glitazone for use in patients with type 2 diabetes.[13] This risk appears to be specific for rosiglitazone.

Glitazones in cardiac failure and macular disease

Both pioglitazone and rosiglitazone are contraindicated in patients with class III and IV heart failure. Patients with class II or worse heart failure were excluded from the PROactive study, and patients with any known congestive cardiac failure (class I–IV) were excluded from ADOPT. Therefore, as patients with heart failure are likely to be more adversely affected by glitazone associated fluid retention, any significant degree of heart failure including class II or higher could be regarded as a contraindication to glitazone use.

There have been rare postmarketing reports of new onset or worsening diabetic macular oedema with glitazones.[5,13]

Targets for HbA1c in patients with type 2 diabetes

Recent guidelines for the care of adults with diabetes include an evidence based statement that 'lowering HbA1c to an average of ~7% has clearly been shown to reduce microvascular and neuropathic complications of diabetes and, possibly, macrovascular disease'. This was accompanied by a recommendation of an HbA1c goal of <7% for nonpregnant adults with diabetes in general.[14]

In the same guidelines, a second recommendation was made on the basis of epidemiologic studies which suggested an incremental benefit (albeit small in absolute terms) to lowering HbA1c from 7% into the normal range of <6%.

The ACCORD trial

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial sought to test the hypothesis that a therapeutic strategy that targets an HbA1c level of <6% would lead to a greater reduction in the rate of cardiovascular events than a strategy that targets an HbA1c level of 7.0–7.9%.[15]

In this North American study, 10 251 middle aged and older participants with type 2 diabetes at high risk of cardiovascular disease events were randomised into a standard therapy group aiming for HbA1c 7.0–7.9% and an intensive control group aiming for HbA1c of <6% (normoglycemia). Intensive control was to be achieved with at least two or more agents from a formulary including glimepiride, repaglinide, metformin, rosiglitazone, acarbose and insulin.[16] The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death.[15]

The study incorporated parallel lipid lowering and tight blood pressure control arms, with completion planned in June 2009 to provide 4–8 years (mean 5.6 years) follow up of participants. However, on 6 February 2008, the primary sponsor of the trial, the US National Heart, Lung, and Blood Institute (NHLBI) announced the termination of the intensive control arm of the study.[17]

Higher mortality in intensive control arm of ACCORD

In the glycaemic control element of the ACCORD trial, median HbA1c achieved in the intensive treatment group was 6.4% compared with 7.5% in the standard treatment group.[17] A higher rate of mortality was noted in the intensive arm, with 257 deaths (14/1000/year) compared with 203 deaths (11/1000/year) in the standard arm. However, both rates were lower than previously reported for individuals with type 2 diabetes at high risk of heart disease

(~50/1000/year). There was no identifiable link with rosiglitazone.

The NHLBI concluded that in patients with type 2 diabetes at especially high risk for heart disease, very intensive glucose lowering treatments aimed at normalising blood glucose to an HbA1c of <6% may be detrimental.

All participants in the intensive control arm of ACCORD have been switched to standard glycaemic control, while the lipid lowering and blood pressure control arms of ACCORD are ongoing. However, these findings would be applicable only to individuals similar to the ACCORD participants, namely with type 2 diabetes for an average of 10 years and with known heart disease or at least two risk factors in addition to diabetes (including high blood pressure, high cholesterol levels, obesity and smoking). The ACCORD study did not address this issue with regard to younger people with diabetes, those earlier in the course of the disease, and those without established cardiovascular disease.

Comparison of the ACCORD and ADVANCE studies

The primary study data from ACCORD have now been published.[18] Participants in the intensive glycaemic control arm experienced more hypoglycaemia requiring assistance (16.2 vs. 5.1% in the standard therapy arm) and were more likely to gain >10 kg (27.8 vs. 14.1%). Blood pressure was slightly, but significantly, lower in the intensive arm (126.4/66.9 mmHg vs. 127.4/67.7 mmHg). Participants in the intensive glycaemic control arm were more likely to die from any cause (hazard ratio [HR]: 1.22, 95% confidence interval [CI]: 1.01–1.46) or from cardiovascular causes (HR: 1.35, 95% CI: 1.04–1.76). However, they were less likely to experience a nonfatal myocardial infarction (HR: 0.76, 95% CI: 0.62–0.92).

The primary outcome – which was a composite of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes – did not differ significantly between the two groups, although there was a trend in favour of intensive control (HR: 0.90, 95% CI: 0.78–1.04).

The Action in Diabetes and Vascular Disease (ADVANCE) study involved 11 140 patients with type 2 diabetes aged 55 years and older who had a history of major macro- or micro-vascular disease, or at least one other risk factor for vascular disease, and utilised a target HbA1c ≤6.5% with median follow up of 5 years.[19]

The intensive control group received a treatment regimen including gliclazide (modified release) and achieved HbA1c of 6.5% compared with 7.3% in the standard control group. Intensive control reduced the incidence of combined major macro- and micro-vascular events (18.1 vs. 20.0%), and major microvascular events (9.4 vs. 10.9%), primarily due to a reduction in new or worsening nephropathy (4.1 vs. 5.2%), defined as development of macroalbuminuria, doubling of serum creatinine to ≥200 µmol/L, need for renal replacement therapy, or death due to renal disease.[19] The intensive control group had more frequent severe hypoglycaemia (2.7 vs. 1.5%) and lower blood pressure (135.5/73.5 mmHg vs. 137.9/74.3 mmHg) compared with the standard control group.

While neither the ACCORD nor ADVANCE studies found any significant benefit from intensive therapy for the defined macrovascular outcomes, it is conceivable that longer duration studies may be required for this purpose.

Differences in the ACCORD and ADVANCE studies

The ACCORD and ADVANCE studies both involved patients with type 2 diabetes at increased risk of cardiovascular disease. Unlike ACCORD, ADVANCE did not find any increase in mortality with intensive glycaemic control.

The ACCORD participants (mean age 62 years) were recruited from North American centres and had higher BMI (32.2 kg/m^2) and waist circumference (106.8 cm) compared with ADVANCE participants (mean age 66 years), who were primarily from Europe, Asia, Australia and New Zealand with lower BMI (28 kg/m^2) and waist circumference (99 cm).

Participants in the intensive glycaemic control arm of ACCORD had a greater reduction in HbA1c from baseline (8.1 to 6.4%) compared with those in the intensive control group in ADVANCE (7.5 to 6.5%). The rate of hypoglycaemia requiring medical assistance in the intensive arm of ACCORD was 10.5% compared with the rate of severe hypoglycaemia (blood glucose <2.8 mmol/L and transient central nervous dysfunction or requiring assistance) of 2.7% in the intensive arm of ADVANCE.

Participants in the intensive arm of ACCORD may have received more aggressive glucose lowering therapy to achieve the comparable final level of HbA1c from a higher baseline.

Conclusion

Pioglitazone and rosiglitazone are options for oral therapy to improve glycaemic control in patients with type 2 diabetes. Until further information becomes available, patients should be informed of the possible increase in risk of myocardial infarction associated with rosiglitazone, which appears to be specific for this agent. Pioglitazone does not appear to share this risk, as data from the PROactive study and one meta-analysis indicate pioglitazone use in patients with type 2 diabetes is associated with a reduction in deaths, myocardial infarction and stroke.[2,3] Patients should be offered explanations of the risks and benefits of glitazone therapy, and be able to make individual decisions as to the suitability of this therapy.

Patients with type 2 diabetes at high risk of cardiovascular disease should have glycemic control optimised with HbA1c of 7% as an initial target. The ADVANCE study showed that targeting HbA1c to 6.5% in patients with type 2 diabetes with cardiovascular disease or risk factors reduced the incidence of nephropathy, without influencing mortality or the incidence of macrovascular complications. The ACCORD study found that intensifying treatment with multiple agents aiming for HbA1c of <6% in patients with longstanding type 2 diabetes with known heart disease, or multiple cardiovascular risk factors, did not reduce the incidence of macrovascular complications and was associated with higher mortality.

Disclosure: Bu Yeap has received research grant funding from Eli Lilly, Servier and NovoNordisk, and honoraria from Eli Lilly and

GlaxoSmithKline for speaking at educational meetings. He has received support from Eli Lilly, NovoNordisk, Sanofi-Aventis and GlaxoSmithKline to attend international scientific and educational meetings.

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