

Contemporary management of type 2 diabetes: blood glucose-lowering therapies and glycaemic targets

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Recent trials and meta-analyses have raised questions about choice of therapy and use of strict glycaemic targets

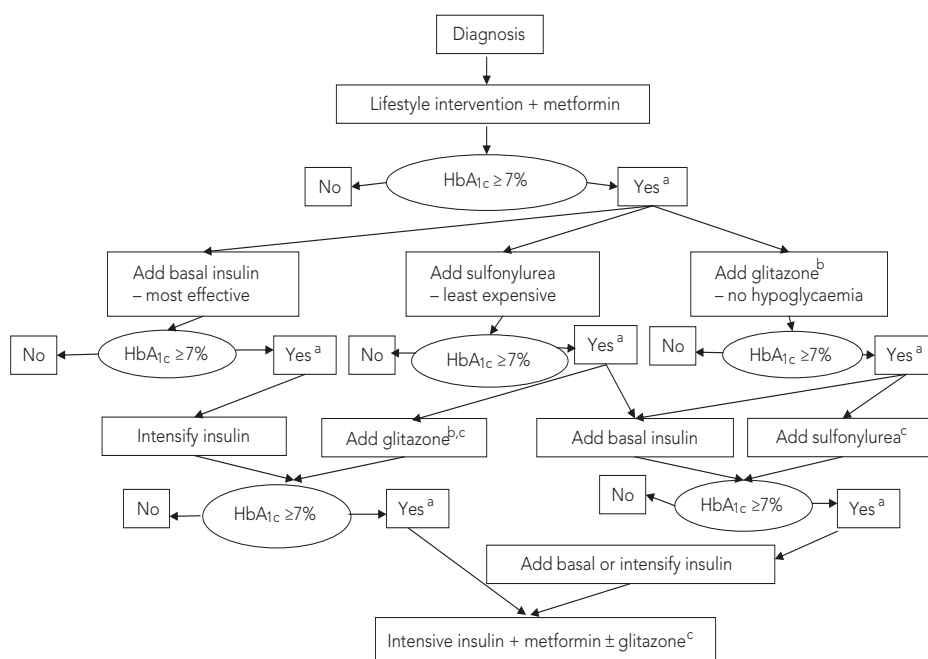
In August 2006, representatives of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) published a consensus algorithm for glycaemic management of type 2 diabetes.¹ The algorithm provoked debate, but the authors defended their recommendations,² including the introduction of metformin at diagnosis and the addition of insulin, sulfonylureas or glitazones as second-line therapy if satisfactory glycaemic control is not achieved. The glycaemic target at this and later stages of therapeutic intensification was a glycated haemoglobin (HbA_{1c}) level less than 7.0%. However, based on epidemiological data from studies suggesting no threshold for microvascular or macrovascular benefit, including pooled results from the United Kingdom Prospective Diabetes Study (UKPDS),³ organisations such as the ADA suggested more stringent goals — including a normal HbA_{1c} level (<6.0%) — if the clinical situation allowed this.⁴

The first challenge to the applicability of the algorithm came when the results of A Diabetes Outcome Progression Trial (ADOPT) were published at the end of 2006.⁵ These confirmed the durable glycaemic efficacy of rosiglitazone monotherapy but showed an unexpected increase in distal fractures in women, which was subsequently also reported for pioglitazone,⁶ the other agent in the class. Then, in May 2007, a meta-analysis of published

and unpublished trial data revealed a significant 43% increase in risk of myocardial infarction with rosiglitazone relative to other therapies for type 2 diabetes.⁷ Although the validity of this analysis is debated,⁸ pioglitazone appears to have no such deleterious cardiovascular effects and may reduce all-cause mortality.⁹ The ADA/EASD consensus algorithm was updated in early 2008 to include warnings about the association between rosiglitazone and myocardial infarction, as well as the risk of fracture with both glitazones (Box 1).¹⁰

Three recent large-scale randomised controlled trials investigated whether the 7.0% HbA_{1c} threshold recommended in the ADA/EASD algorithm should be lowered. In the glycaemic control arms of the Action to Control Cardiovascular Risk in Diabetes (ACCORD)¹¹ and Action in Diabetes and Vascular disease: preterAx and diamicroN modified release Controlled Evaluation (ADVANCE)¹² trials, and in the Veterans Affairs Diabetes Trial (VADT),¹³ type 2 participants who were at high vascular risk were randomly assigned to either conventional or intensive therapy. The target HbA_{1c} level in the intensive arm was <6.0% in both ACCORD and VADT, and ≤6.5% in ADVANCE. Median HbA_{1c} levels achieved at close of the trials were 6.4%, 6.9%, and 6.5%, respectively, compared with a median ≥0.7% greater HbA_{1c} in the respective conventional therapy groups.¹¹⁻¹³ Although ADVANCE

1 Updated algorithm for the metabolic management of type 2 diabetes from the ADA and EASD (2008)¹⁰



Reinforce lifestyle intervention at every visit.

^a Check HbA_{1c} every 3 months until HbA_{1c} is <7%, and then at least every 6 months.

^b Associated with increased risk of fluid retention, congestive heart failure and fractures. Rosiglitazone, but probably not pioglitazone, may be associated with an increased risk of myocardial infarction.

^c Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and lower expense.

ADA = American Diabetes Association.

EASD = European Association for the Study of Diabetes.

HbA_{1c} = glycated haemoglobin.

Source: Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: update regarding the thiazolidinediones. *Diabetologia* 2008; 51: 9 (Figure 1). Reproduced with kind permission of Springer Science+Business Media.

2 Recommendations for glycaemic management of type 2 diabetes based on consensus guidelines and recent trial data

- A glycated haemoglobin (HbA_{1c}) level < 7.0% remains an appropriate target when using established blood glucose-lowering therapies
- There are possible deleterious effects of attempting to achieve normoglycaemia (HbA_{1c} level < 6.0%), which may include death due to cardiovascular causes associated with hypoglycaemia
- Prescribe metformin at diagnosis
- Add insulin, a sulfonylurea or a glitazone* as second-line therapy (see algorithm to aid choice, Box 1)
- Use triple therapy if necessary (ie, initiate insulin or add a second oral agent)*
- Intensify insulin therapy (continue metformin ± glitazone) as the final therapeutic option
- Use glitazones only when increased risks of osteoporosis, cardiac failure and myocardial infarction (rosiglitazone) have been considered carefully

* Pharmaceutical Benefits Scheme restrictions to subsidised glitazone therapy may apply. ◆

used sulfonylurea-based intensive treatment,¹² other therapies could be added as needed. In ACCORD and VADT, there was no uniform management strategy, but most intensively treated patients were prescribed rosiglitazone and insulin.^{11,13}

Despite differences in the components of the primary endpoints between these trials, intensive therapy was not associated with significant macrovascular benefit. In addition, a 22% increase in all-cause mortality in the ACCORD intensive group, detected 18 months before close of the trial, resulted in all patients being transferred to less intensive glycaemic control for the remainder of the ongoing blood pressure and lipid treatment arms.¹¹ Microvascular endpoint data are not yet available for ACCORD and VADT,^{11,13} but ADVANCE data show significant reduction in new or worsening nephropathy but no effect on retinopathy with intensive therapy.¹²

The lack of effect of intensive glycaemic control on cardiovascular disease in these trials appears to be at odds with epidemiological data, especially from the UKPDS.³ It is possible that better contemporary management of non-glycaemic cardiovascular risk factors, with increased use of statins, angiotensin-converting enzyme inhibitors, β -blockers and antiplatelet agents, attenuates the benefits of improved glycaemic control. For example, fewer than 2% of UKPDS patients took lipid-lowering therapy during the trial — which closed in 1997 — compared with more than 50% of ACCORD and ADVANCE patients at the end of these studies.^{11,12} Although overt hypoglycaemia was not implicated in the increased mortality in ACCORD,¹¹ it was linked to later cardiovascular events in VADT¹³ and it is also possible that unrecognised low blood glucose concentrations contribute silently to a higher than expected cardiovascular event rate in intensively treated patients. In addition, as suggested by ACCORD subgroup analyses,¹¹ established atherosclerosis may be refractory to glycaemic intervention. A further possibility is that, in contrast to statin studies, in which benefit is evident early, the cardiovascular effects of glycaemic improvement only manifest many years later. This “legacy effect” has been reported in type 1 diabetes¹⁴ and may not have

been detected in ACCORD, ADVANCE and VADT as average duration of follow-up was ≤ 6 years.

What are the lessons from what some might regard as an “annus horribilis” for research into type 2 diabetes management? One is the clear need for carefully designed and adequately powered studies that assess the long-term efficacy and safety of new treatments from both metabolic and cardiovascular standpoints. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study might provide endpoint data that help overcome the limitations of rosiglitazone meta-analyses. However, despite an interim unblinded review of data from the study,¹⁵ and post-hoc ACCORD¹¹ and VADT¹³ analyses that did not suggest increased risk in rosiglitazone-treated patients, it is likely that larger studies will be needed for a valid assessment of the cardiovascular effects of this drug. With new therapies now available in Australia — sitagliptin (a dipeptidyl peptidase-4 inhibitor) and exenatide (a glucagon-like peptide-1 mimetic) — it would be reassuring for prescribers to know that long-term, large-scale safety surveillance of these agents was in progress. It is hoped that such trials will not be viewed as too expensive or logistically difficult, and that the government, pharmaceutical industry, hospitals, academic institutions and consumer organisations will work together to ensure their viability.

In the case of glycaemic targets, ACCORD, ADVANCE and VADT were necessary because the relative cost, inconvenience and rates of side effects (including hypoglycaemia) associated with intensive treatment needed to be weighed against cardiovascular and mortality benefit using “gold standard” randomised trial methodology. Their overall findings support the conservative glycaemic target (HbA_{1c} < 7.0%) used in the consensus algorithm¹⁰ (Box 2). However, further analyses of their data — especially those relating to microangiopathy, together with post-trial follow-up — could allow a more complex treatment algorithm to be developed, with some well defined patient groups benefiting more from achieving HbA_{1c} levels close to or below 6.0% than others.

In the meantime, evidence is emerging of the importance of optimal management of non-glycaemic vascular risk factors in patients with diabetes. For example, the recently published Steno-2 study found short- and long-term morbidity and mortality benefits from multifactorial interventions including multiple drug combinations of renin-angiotensin system blockers, aspirin and lipid-lowering agents in addition to appropriate lifestyle modification.¹⁶ Indeed, at present the ADA recommends placing less emphasis on concerted efforts to achieve normal HbA_{1c} levels, and more on optimal management of non-glycaemic vascular risk factors.¹⁷

Competing interests

I have served on Advisory Boards for, and received speaker fees and travel assistance to attend meetings from, Eli Lilly (distributor of pioglitazone and exenatide), GlaxoSmithKline (manufacturer of rosiglitazone) and Merck Sharp and Dohme (manufacturer of sitagliptin). I have also received speaker fees and travel assistance to attend meetings from Alphapharm (manufacturer of metformin) and Servier Laboratories (manufacturer of gliclazide).

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