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Glycaemic control in type 2 diabetes: what is the target?
By Dr Luke Bereznicki

Learning objectives
After reading this article, you should be able to:
- Outline the current management goals for people with type 2 diabetes in Australia
- Discuss the results of recent randomised controlled trials comparing tight glycaemic control with standard care in people with type 2 diabetes
- Consider how the results of these trials relate to the management of patients with type 2 diabetes under your pharmaceutical care.

Competencies addressed: 3.1.2, 3.1.3, 3.2.2, 4.2.1, 4.2.2, 4.2.3

Introduction
The number of Australians with type 2 diabetes has tripled since 1981 and continues to increase. It is projected that 1.6 million Australians will have type 2 diabetes by 2030.1 In addition to targeting blood glucose control, health professionals involved in the management of diabetes should focus on blood pressure management, cholesterol lowering and consider the use of low-dose aspirin (although this is now contentious)2 as means of reducing cardiovascular risk.4

The management of hyperglycaemia in type 2 diabetes is complicated, and combination hypoglycaemic therapy is often required to achieve and maintain target blood glucose levels. Recently the results of two major trials raised important questions about the optimal degree of glucose control required in the management of type 2 diabetes. In particular, the results of these studies question the safety of targeting low haemoglobin A1c (HbA1c) levels. The focus of this article is to review the recent evidence surrounding the optimal target for the management of hyperglycaemia in people with type 2 diabetes.

Current management goals for type 2 diabetes
People with diabetes are at elevated risk of a range of serious health problems, including cardiovascular disease, premature death, blindness, renal failure, amputations, fractures, frailty, depression and cognitive decline.5 Prospective observational studies demonstrate that the incidence of many of these outcomes are directly related to glycaemic control. Analysis of these studies shows that an increase of HbA1c of 1% is associated with an increase in the risk of cardiovascular disease by 18%, an increase in the risk of death of 12% to 14%, and an increase in the risk of retinopathy or renal failure of 37%.6-8

Glycaemia can be measured by blood glucose, or by the glycosylated level, a measure of the average blood glucose during the past two to three months. The current goals for management of type 2 diabetes, shown in Table 1, recommend a target HbA1c of 7%.9 Effective treatment of hyperglycaemia is a priority, given that strict glycaemic control reduces the microvascular complications of type 2 diabetes (e.g. retinopathy or nephropathy).6-8

Epidemiological data from the UK suggests that improving glycaemic control will also reduce the risk of macrovascular complications (e.g. cardiovascular disease), although it is recognised that improving glycaemic control is only one of a number of possible strategies to reduce the macrovascular risk associated with diabetes.

Recent evidence
Table 2 shows characteristics of four large randomised trials that compared clinical outcomes among patients with type 2 diabetes who were randomly assigned to intensive or less intensive treatment regimens.
Table 1. Goals for the management of type 2 diabetes. Taken from the RACGP Diabetes Management in General Practice Guidelines.9

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose level</td>
<td>4–6 mmol/L (fasting)</td>
</tr>
<tr>
<td>Glycated haemoglobin (HbA1c)</td>
<td>≤ 7%</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol</td>
<td>&lt; 2.5 mmol/L</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt; 4.0 mmol/L</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol</td>
<td>&gt; 1.0 mmol/L</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 1.5 mmol/L</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≤ 130/80 mmHg</td>
</tr>
<tr>
<td>Body mass index</td>
<td>&lt; 25 kg/m²</td>
</tr>
<tr>
<td>Urinary albumin excretion</td>
<td>&lt; 20 mg/L (timed overnight collection)</td>
</tr>
<tr>
<td></td>
<td>&lt; 20 mg/L (spot collection)</td>
</tr>
<tr>
<td></td>
<td>&lt; 3.5 mg/mmol (women)</td>
</tr>
<tr>
<td></td>
<td>&lt; 2.5 mg/mmol (men)</td>
</tr>
<tr>
<td></td>
<td>(albumin creatinine ratio)</td>
</tr>
<tr>
<td>Cigarette consumption</td>
<td>Zero</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>≤ 4 standard drinks</td>
</tr>
<tr>
<td></td>
<td>40 g/day (men)</td>
</tr>
<tr>
<td></td>
<td>≤ 2 standard drinks</td>
</tr>
<tr>
<td></td>
<td>20 g/day (women)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>At least 30 minutes walking (or equivalent) on 5 or more days/week</td>
</tr>
<tr>
<td></td>
<td>Total &gt; 150 minutes/week</td>
</tr>
</tbody>
</table>

a. UKPDS

The United Kingdom Prospective Diabetes Study (UKPDS) trials demonstrated that a strategy aimed at intensified control of blood glucose reduced the risk of microvascular complications in people with type 2 diabetes.10–11 UKPDS enrolled 5102 participants with newly diagnosed diabetes. Participants were 25 to 65 years old and were followed for a median of almost 11 years. 4209 patients were randomly assigned to receive either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin, or metformin) for glucose control. People in the control groups were managed by diet alone and only received treatment if their fasting blood glucose exceeded 15 mmol/L. By the end of the trials, approximately 40% to 60% of conventional management patients were treated with metformin, a sulfonylurea or insulin.

In the trial comparing conventional treatment with diet (and medication if necessary) to intensive treatment with a sulfonylurea or insulin, the intensive treatment group achieved a lower HbA1c during the trial (median HbA1c 7% compared to 7.9% in the conventional treatment group).10 The intensive-care group had a significantly lower risk of microvascular complications, but not macrovascular disease. Those in the intensive treatment group were more likely to suffer hypoglycaemic episodes.

In the trial comparing intensive treatment with metformin to conventional treatment in overweight diabetic patients, the median HbA1c was 7.4% in the metformin group and 8% in the conventional group during the trial period.11 Compared to conventional treatment, metformin reduced the risk of diabetes-related death, all-cause mortality and stroke. In this population, metformin was superior to sulfonylurea or insulin treatment, and was associated with fewer episodes of hypoglycaemia, despite a similar level of glycemic control.

Overall, the UKPDS trials demonstrated that intensified glycemic control reduced the risk of microvascular complications in people with type 2 diabetes. The results led to the current recommendation of targeting HbA1c below 7%, and the role of metformin as a first-line option in people with type 2 diabetes unless it is contraindicated.

While there is general acceptance that optimal glycaemic control will improve cardiovascular outcomes, the results of the sulfonylurea/insulin UKPDS did not provide definitive evidence that these outcomes will improve. This might have been because patients were recently diagnosed with diabetes, and so might have been at lower cardiovascular risk.

Many patients who participated in the UKPDS trials continued to be involved in post-trial monitoring. During their first five years post-trial, over 3000 patients attended annual clinics, and the remainder were followed up via questionnaire. For another five years, questionnaires were used to follow all patients. At enrolment into the post-trial phase, the median HbA1c was 8.5% in the conventional group and 7.9% in the intensive care group for the sulfonylurea/insulin trial (P < 0.001). In the metformin trial, the median HbA1c was 8.9% in the conventional group and 8.4% in the intervention group (P = 0.12). The between-group differences in HbA1c were lost after the first year of follow-up, and after 10 years the median HbA1c for people who had participated in the sulfonylurea/insulin trial was 7.7%. For those in the metformin trial, the median HbA1c was 8%. Despite this, people in the sulfonylurea/insulin intensive care group had a lower risk of any diabetes complications and microvascular complications. Interestingly, a reduced risk of myocardial infarction and mortality emerged over time, as more events occurred. People in the metformin intensive care group also had a significantly lower risk of any diabetes complication, myocardial infarction and mortality.6

Pharmacist
Table 2. Characteristics of randomised controlled trials comparing different degrees of glycaemic control in patients with type 2 diabetes. Modified from Montori et al. 2009.17

<table>
<thead>
<tr>
<th>Variable</th>
<th>UKPDS-Sulfonylurea/insulin</th>
<th>UKPDS-Metformin</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>3867</td>
<td>1704</td>
<td>10,251</td>
<td>11,140</td>
<td>1791</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>101</td>
<td>10.7a</td>
<td>3.5</td>
<td>5</td>
<td>4a</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Recent diagnosis, age 25–55 years with basal glycaemia of 6.1–15.0 mmol/L after a run-in period of diet and exercise. No history of ketonuria, vascular disease, retinopathy requiring laser treatment or ongoing coronary disease</td>
<td>Recent diagnosis, age 25–55 years with basal glycaemia of 6.1–15.0 mmol/L after a run-in period of diet and exercise. No history of ketonuria, vascular disease, retinopathy requiring laser treatment or ongoing coronary disease</td>
<td>Age 40–79 years with HbA1c &gt; 7.5% and CAD or age 55–79 and CV risk factors, BMI &lt; 45 kg/m², and no history of severe hypoglycaemia or renal impairment</td>
<td>Age &gt; 55 years and history of 1 macrovascular or 1 microvascular complication, or 1 additional CV risk factor, demonstrated adherence to the protocol run-in period</td>
<td>Age &gt; 45 years with HbA1c &gt; 7.5%, BMI &lt; 40 kg/m², and no history of CV events in the previous 6 months, advanced CHF, severe angina, or hepatic or renal impairment</td>
</tr>
<tr>
<td>Age (years) at baseline</td>
<td>53a</td>
<td>53a</td>
<td>52</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Mean baseline HbA1c %</td>
<td>7.1</td>
<td>7.2</td>
<td>8.3</td>
<td>7.5</td>
<td>9.4</td>
</tr>
<tr>
<td>CVD %</td>
<td>0</td>
<td>0</td>
<td>35</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Intervention target</td>
<td>FPG &lt; 6.0 mmol/L</td>
<td>FPG &lt; 6.0 mmol/L</td>
<td>HbA1c &lt; 6%</td>
<td>HbA1c ≤ 6.5%</td>
<td>HbA1c &lt; 6.0%</td>
</tr>
<tr>
<td>Intervention HbA1c level achieved %</td>
<td>7.0a</td>
<td>7.4a</td>
<td>6.4</td>
<td>6.5</td>
<td>6.9a</td>
</tr>
<tr>
<td>Control target</td>
<td>Best achievable FPG</td>
<td>Best achievable FPG</td>
<td>HbA1c ≤ 7.0%–7.9%</td>
<td>HbA1c per local guidelines</td>
<td>HbA1c ≤ 8.0%–9.0%</td>
</tr>
<tr>
<td>Control HbA1c level achieved %</td>
<td>7.4a</td>
<td>8.0b</td>
<td>7.5</td>
<td>7.3</td>
<td>8.4b</td>
</tr>
</tbody>
</table>

a = median, b = median achieved throughout duration of follow-up, CAD = coronary artery disease, CV = cardiovascular, BMI = body mass index, HbA1c = glycosylated haemoglobin.
b. ACCORD

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial randomised over 10,000 patients with type 2 diabetes (mean age 62 years) with a median HbA1c of 8.1% to receive intensive therapy (target HbA1c below 6%) or standard therapy (target HbA1c between 7% and 7.9%). Therapeutic regimens were individualised by the treating physician depending on the group assignment and response to therapy; any marketed anti-hyperglycaemic therapy could be prescribed. The majority of patients were male (62%) and many (36%) had a previous cardiovascular event. The median duration of diabetes in both the intensive and standard therapy groups was 10 years. At one year, stable HbA1c levels were achieved in both groups: a median of 6.4% in the intensive group and a median of 7.5% in the standard-therapy group. After an average of 3.5 years follow-up, the trial was discontinued due to a significant increase in mortality in the intensive treatment group. At this time, there was also no difference in the primary outcome of the trial, which was a composite of non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular causes. However, at the time of trial discontinuation, the risk of non-fatal myocardial infarction was reduced, despite the overall increase in mortality. Severe hypoglycaemia and weight gain of more than 10 kg also occurred more frequently in the intensive treatment group.

c. ADVANCE

The Action in Diabetes and Vascular Disease (ADVANCE) study randomised more than 11,000 patients with type 2 diabetes (mean age 66 years) with a median HbA1c of 7.5% to receive either standard glucose control or intensive glucose control (target HbA1c below 6.5%). Modified-release gliclazide was used primarily to achieve intensive control, with other antihyperglycaemic drugs added as necessary. The majority of patients were male (57%) and many had a history of cardiovascular events (32%). Similarly to the ACCORD study, the patients were not newly-diagnosed with diabetes, with a mean duration of diabetes of 7.9 and 8 years for the intensive and standard-care groups respectively. After a median duration of follow-up of five years, the average HbA1c levels were 6.5% in the intensive group and 7.3% in the standard-care group. Intensive control was associated with a significantly reduced risk of combined major macrovascular and microvascular events. However, this difference was mainly due to a reduced risk of nephropathy, and there was no effect on retinopathy or major macrovascular events, death from cardiovascular causes or death from any cause. Severe hypoglycaemia was more common in the intensive-care group.

d. VADT

Finally, the Veterans Affairs Diabetes Trial (VADT) randomised 1791 military veterans (mean age 60 years) with suboptimal response to therapy for type 2 diabetes to either intensive or standard glucose control. Most patients were male (74%), and many (40%) had already suffered a cardiovascular event. The aim of intensive treatment was to lower HbA1c by 1.5% relative to the standard-care group. At baseline, the median HbA1c level was 9.4% in each group, which was reduced to 6.9% in the intensive-therapy group and 8.4% in the standard-therapy group within the first three months of follow-up. These levels were maintained for the duration of the trial, which was a median of 5.6 years. There were no significant differences in macro- or micro-vascular outcomes between the groups. The risk of mortality was no different in the intensive group compared to the standard-care group. Adverse events (mainly hypoglycaemia) occurred more frequently in the intensive-care group.

Rationalising the recent trial results

Taking into account all of the recent major trials in this area, tight glycaemia control does not appear to reduce the risk of mortality or cardiovascular disease. The exception to this statement is the UKPDS-metformin trial. However, the UKPDS trials are older, involved patients with only newly diagnosed diabetes, achieved less glycaemic control and involved longer follow-up compared to the more recent trials. The risk of microvascular complications was reduced in the two UKPDS and ADVANCE trials. These findings are difficult to interpret, mainly because few patients developed complications and the effects varied between trials. The clearest and most consistent consequence of tight glycaemic control in these trials is that the risk of hypoglycaemia is increased two- to three-fold compared to standard care. The risk appears to increase with decreasing HbA1c targets. Weight gain also appears to be more common with intensive treatment.
The results of the aforementioned studies were recently combined in a meta-analysis.\(^1,9\) The meta-analysis showed that HbA\(_1c\) was reduced by an average of 0.9% in people receiving intensive treatment compared to standard treatment. Intensive-treatment patients had a significant 17% reduction in the risk of nonfatal myocardial infarction, although the risk of stroke and all-cause mortality was unchanged. However, the results for outcomes that were measured in each trial, such as all-cause and cardiovascular mortality, varied between trials. The increase in mortality in the ACCORD trial\(^12\) might have been due to the increased incidence of severe hypoglycaemia, the use of rosiglitazone or chance. In contrast, a mortality benefit was apparent with metformin in the UKPDS-metformin trial.\(^1,9\) The major differences in the UKPDS trial were that the population was younger, and the median HbA\(_1c\) achieved with metformin was 7.4%, slightly higher than at baseline (7.3%). While HbA\(_1c\) was relatively tight in this trial compared to the control group (8%), it is more similar to the HbA\(_1c\) levels seen in the standard-care arms of the more recent trials, particularly in ACCORD and ADVANCE (which were 7.5% and 7.3%, respectively).\(^13,15\) In fact, one conclusion from these three trials is that achieving an HbA\(_1c\) of around 7.5% provides the best balance of benefits and harms in people with type 2 diabetes compared to more intensive management (e.g. in the intensive-treatment arms of ACCORD and ADVANCE) or more relaxed management (e.g. the standard-treatment groups in the UKPDS trials). Another view is that the treatment target for HbA\(_1c\) below 7% remains appropriate, because micro-vascular outcomes might be improved with more intensive control based on the results of ADVANCE, but this has to be tempered by the potential for an increase in mortality, which was seen in ACCORD but not in ADVANCE. However, ACCORD recruited patients who were older than those studied in UKPDS and the target HbA\(_1c\) in the intervention group was achieved rapidly, which may have contributed to the risk of severe hypoglycaemia and mortality risk.

The results of the metformin UKPDS trial\(^1,9\) also highlight the importance of the choice of medication in type 2 diabetes, rather than solely basing management on the HbA\(_1c\) level. A recent systematic review of randomised controlled trials demonstrated that metformin was associated with a decreased risk of cardiovascular mortality (26%) odds reduction) compared with any other oral diabetes medication or placebo.\(^14\) This confirms the findings of the UKPDS-metformin trial,\(^1,9\) where metformin was superior to insulin or sulfonylurea treatment in overweight patients with type 2 diabetes, despite similar levels of glycaemic control. In the same systematic review, rosiglitazone was the only agent associated with an increased risk of cardiovascular morbidity or mortality, although the result was not statistically significant.\(^1,6\)

**Conclusion**

Recent randomised controlled trials do not strongly support tight glycaemic control (defined as target HbA\(_1c\) below 6% to 6.5%) as opposed to more relaxed control in type 2 diabetes (target HbA\(_1c\) between 7% to 7.9%). For younger patients with a recent diagnosis of type 2 diabetes and no history of cardiovascular disease, an HbA\(_1c\) target below 7% can still be considered, if it can be reached gradually and with a low risk of severe hypoglycaemia. Additional research is required to confirm the appropriateness of tighter glycaemic control, given the risk of severe hypoglycaemia and weight gain. An HbA\(_1c\) between 7% and 7.5% may be more reasonable and more feasible for most patients with type 2 diabetes. Ideally, HbA\(_1c\) should be as close to normal as possible without resulting in a high risk of hypoglycaemia. The current Royal College of General Practitioners guidelines for type 2 diabetes recognise that target blood glucose levels should be tempered by common sense and the need to remove symptoms, especially in the elderly, to maintain or improve quality of life.\(^7\) There is a possibility that overly intense management of blood glucose can result in severe hypoglycaemia and actually increase mortality. Achieving target levels is important, but any significant reduction in HbA\(_1c\) will improve patient outcomes.\(^1,9\)

**References**

Questions

1. Which one of the following is not a recommended target for a person with type 2 diabetes?
   a) Zero cigarette consumption.
   b) Body Mass Index < 25 kg/m².
   c) Low density lipoprotein cholesterol below 3.5 mmol/L.
   d) Total cholesterol below 4.0 mmol/L.

2. Which one of the following statements related to the United Kingdom Prospective Diabetes Study (UKPDS) is false?
   a) Intensive control of glycaemia reduced the incidence of micro-vascular complications.
   b) In overweight people, intensive treatment with metformin was superior to insulin or sulfonylurea therapy.
   c) Intensive sulfonylurea or insulin treatment was associated with a reduced risk of cardiovascular complications compared to standard treatment.
   d) Post-trial monitoring suggests that the benefits of intensive management of glycaemia persisted, despite the fact that between-group differences in HbA₁c were lost in the follow-up period.

3. Which one of the following trials found that intensive control of glycaemia increased the risk of mortality?
   a) UKPDS.
   b) ACCORD.
   c) ADVANCE.
   d) VADT.

4. Which one of the following was not an outcome of a recent meta-analysis of trials comparing intensive control versus standard control of glycaemia?
   a) A mean reduction in HbA₁c of 0.9% with intensive therapy.
   b) A significant reduction in nonfatal myocardial infarction with intensive therapy.
   c) A significant reduction in mortality with intensive therapy.
   d) No change in the incidence of stroke between intensive and standard therapy.

5. Which one of the following statements regarding intensive glycaemic therapy in type 2 diabetes is false?
   a) Metformin has been shown to result in superior outcomes compared to insulin or sulfonylureas in overweight patients at a similar level of glycaemic control.
   b) A target HbA₁c of 8.0% to 6.5% should be recommended for all patients.
   c) Intensive glycaemic control is associated with an increased risk of weight gain and hypoglycaemic episodes than standard management.
   d) There is a possibility that overly-aggressive glycaemic control is associated with an increased risk of mortality in some patients.

(A score of 4 out of 5 attracts 1 credit point.)