Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus

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ABSTRACT

- Tight glycaemic control reduces the risk of development and progression of organ complications in people with type 1 or type 2 diabetes.
- In this position statement, the Australian Diabetes Society recommends a general target glycated haemoglobin (HbA_{1c}) level of ⩽ 7.0% for most patients.
- This position statement also provides guidelines for the individualisation of glycaemic targets to a tighter or lesser degree, with a recommended target HbA_{1c} level of ⩽ 6.0% in some people, or up to ⩽ 8.0% in others.
- Individualisation of the HbA_{1c} target is based on patient-specific factors, such as the type of diabetes and its duration, pregnancy, diabetes medication being taken, presence of cardiovascular disease, risk of and problems from hypoglycaemia, and comorbidities.
- Management of diabetes also includes: adequate control of other cardiovascular risk factors, including weight, blood pressure and lipid serum levels; antiplatelet therapy; and smoking cessation.

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Type 1 and type 2 diabetes are associated with increased microvascular and macrovascular disease, disability and premature mortality. There is strong evidence from randomised controlled trials that better glycaemic control can reduce some of these diabetic complications. Improving glycaemic control is a principal goal of diabetes management. Most authorities have recommended a glycated haemoglobin (HbA_{1c}) target level of ⩽ 7.0%, largely based on the results of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), which demonstrated that intensive glucose control substantially reduced onset and delayed progression of microvascular disease in type 1 and type 2 diabetes, respectively.[1,2]

In the DCCT, tight glycaemic control, achieving a mean HbA_{1c} level of 7.0% (v 9.2% in the conventional-therapy arm), reduced retinopathy by 47%–76%, nephropathy by 39%–54%, and clinical neuropathy by 60% in participants with type 1 diabetes.[1] In the UKPDS, intensively treated people with newly diagnosed type 2 diabetes (mean age, 53 years) had a median HbA_{1c} level of 7.0% over 10 years (v 7.9% with standard treatment) and a 12% reduction in diabetes-related end points, mainly in microvascular events.[2] Additionally, in an obese subgroup of the intensive-therapy group, metformin used as first-line therapy reduced the incidence of myocardial infarction and mortality.[3] The effect was not statistically significant in participants primarily assigned to treatment with sulfonylureas or insulin.[2]

In 2008 and 2009, results of several large studies designed to examine the effect of even tighter glycaemic control on cardiovascular outcomes were published, as well as results of the long-term follow-up of UKPDS. The conflicting results of these studies have raised questions about the appropriateness of existing HbA_{1c} targets, and created confusion among clinicians. This has prompted the Australian Diabetes Society (ADS) to develop recommendations for HbA_{1c} levels, with a focus on the individualisation of targets. These will complement the soon-to-be-released National Health and Medical Research Council (NHMRC)-approved *Evidence based guideline for blood glucose control in type 2 diabetes*, which recommends a general HbA_{1c} target level of ⩽ 7.0%.[4] The ADS recommendations are shown in Box 1 and Box 2.

A more detailed version of this position statement is available on the ADS website (http://www.diabetessociety.com.au/downloads/positionstatements/HbA1ctargets.pdf). The process used to develop the document is outlined in Box 3. Our recommendations serve as a guide to assist patient management, and it is not our intention for them to be applied dogmatically.

Type 2 diabetes

Key recent studies of tight glycaemic control

ACCORD study

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, 10 251 adults with type 2 diabetes (mean age, 62 years; disease duration, 10 years) were randomly allocated to intensive therapy (target HbA_{1c} level, < 6.0% using any antidiabetic agent) or conventional therapy (target HbA_{1c} level, 7.0%–7.9%).[5] All participants had an established or increased risk for cardiovascular disease (CVD). At 1 year, the intensive-therapy group achieved a median HbA_{1c} level of 6.4%, and the conventionally treated group, 7.5%.

After 3.5 years of follow-up, the intensive regimen was discontinued because of an unexpected increase in all-cause mortality (a secondary end point) in this arm (5.0% v 4.0%; hazard ratio [HR], 1.22; 95% CI, 1.01–1.46; $P = 0.04$). At this point, the pre-specified primary outcome, which was the first occurrence of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death, was showing a non-significant trend favouring intensive control (6.9% v 7.2%; HR, 0.90; 95% CI, 0.78–1.04; $P = 0.16$). No cause for the increased mortality in the intensive-therapy group was identified, though the incidence of hypoglycaemia requiring assistance was higher (10.5% v 3.5%; $P < 0.001$). On post-hoc subanalysis, increased mortality was observed in the intensive-therapy group among participants with known CVD or HbA_{1c} levels > 8.5% at baseline. Weight gain > 10 kg was also more common in the intensive-therapy group.

The increased mortality in the intensive-therapy group has raised questions about the appropriateness of an HbA_{1c} target level near the normal range in patients with, or at high risk of, CVD.

1 Recommended glycated haemoglobin (HbA_{1c}) target ranges for adults with type 2 diabetes

	HbA_{1c} target	Rationale for recommendation	Level of evidence for target
General target	⩽ 7.0%*	UKPDS demonstrated improved outcomes with median HbA_{1c} ⩽ 7.0%; result supported by NHMRC systematic review.	I
Specific clinical situations			
Diabetes of short duration† and no clinical cardiovascular disease			
• Requiring lifestyle modification ± metformin	⩽ 6.0%*	UKPDS showed early treatment of diabetes to be beneficial. In epidemiological studies, the threshold level of HbA_{1c}, beyond which increased mortality and cardiovascular events occur, lies between 5.0% and 6.0%. Risk of hypoglycaemia is negligible with lifestyle modification or metformin.	Consensus
• Requiring any antidiabetic agents other than metformin or insulin	⩽ 6.5%*	UKPDS showed early treatment of diabetes to be beneficial. Risk of hypoglycaemia increases with use of most antidiabetic agents other than metformin, hence we do not recommend a target HbA_{1c} ⩽ 6.0% for this group. ADVANCE demonstrated reduced microvascular disease with target HbA_{1c} ⩽ 6.5%.	II
• Requiring insulin	⩽ 7.0%*	UKPDS demonstrated improved outcomes with median HbA_{1c} of 7.0% in people with newly diagnosed diabetes, including among those treated with insulin.	II
Pregnancy or planning pregnancy	⩽ 6.0%*	Observational data (albeit mainly in type 1 diabetes) demonstrate a relationship between HbA_{1c} and adverse pregnancy outcomes when HbA_{1c} levels exceed a threshold between 5.0% and 6.0%.	Consensus
Diabetes of longer duration† or clinical cardiovascular disease (any therapy)	⩽ 7.0%*	UKPDS demonstrated improved outcomes with median HbA_{1c} of 7.0%. ACCORD indicated that attempts for even tighter control in people with relatively long duration of diabetes and cardiovascular disease were associated with increased mortality. We therefore do not routinely recommend tighter control in this group.	II
Recurrent severe hypoglycaemia or hypoglycaemia unawareness (any therapy)	⩽ 8.0%	Severe hypoglycaemia is associated with significant morbidity and mortality. Risks of tight glycaemic control outweigh the benefits for such patients.	Consensus
Patients with major comorbidities likely to limit life expectancy‡ (any therapy)	Symptomatic therapy of hyperglycaemia§	Tight glycaemic control will be of no benefit, as diabetic complications take many years to develop.	Consensus

ACCORD = Action to Control Cardiovascular Risk in Diabetes study. ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial. NHMRC = National Health and Medical Research Council. UKPDS = United Kingdom Prospective Diabetes Study.
* Achievement of HbA_{1c} targets must be balanced against risk of severe hypoglycaemia, especially among older people. † In an older adult, long duration might be considered to be > 10–20 years, but for a person who develops type 2 diabetes at a young age, it may be considerably longer. ‡ Examples of major comorbidities include chronic medical conditions, such as chronic kidney disease stages 4 or 5; heart failure stages III or IV (New York Heart Association grading); incurable malignancy; and moderate to severe dementia. § Where practical, suggest blood glucose target level < 15 mmol/L to help minimise risk of infection. ◆

ADVANCE trial

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial randomly allocated 11 140 people with type 2 diabetes (mean age, 66 years; mean duration of disease, 8 years) and major macrovascular or microvascular disease, or at least one other risk factor, to intensive or standard glycaemic control.[6] The intensive-therapy group was treated with modified-release gliclazide (Diamicron MR, Servier), with the suggested sequential addition of metformin, a thiazolidinedione, acarbose and insulin as required to achieve a target HbA_{1c} level ⩽ 6.5%. The standard-therapy group was treated in accordance with local guidelines.

After 5 years, the mean HbA_{1c} level was 6.5% in the intensive-therapy group and 7.3% in the standard-therapy group. Intensive control resulted in a reduction in the primary outcome of combined major microvascular and macrovascular events (18.1% v 20.0%; HR, 0.90; 95% CI, 0.82–0.98; $P = 0.01$), which was solely due to fewer microvascular events, mainly nephropathy.

There were no differences in major macrovascular events or mortality. Severe hypoglycaemia was more common in the intensive-therapy group (2.7% of participants having at least one episode v 1.5%; HR, 1.86; 95% CI, 1.42–2.40; $P < 0.001$), with this contributing to increased hospitalisation (44.9% v 42.8%; HR, 1.07; 95% CI, 1.01–1.13; $P = 0.03$).

Veterans Affairs Diabetes Trial

The Veterans Affairs Diabetes Trial (VADT) recruited 1791 participants (mean age, 60 years; 97% male; mean duration of disease, 12 years) with suboptimally controlled type 2 diabetes to receive either intensive or standard treatment.[7] The HbA_{1c} target level was < 6.0% for the intensive-therapy group, and 8.0%–9.0% for the standard-therapy group. Stable median HbA_{1c} levels of 6.9% and 8.4%, respectively, were achieved.

2 Recommended glycated haemoglobin (HbA_{1c}) target ranges for adults with type 1 diabetes

	HbA_{1c} target	Rationale for recommendation	Level of evidence for target
General target	⩽ 7.0%*	DCCT/EDIC showed that achieving a mean HbA_{1c} of 7.0% is associated with improved outcomes.	II
Specific clinical situations			
Pregnancy or planning pregnancy	⩽ 7.0%*†	Better pregnancy outcomes (borderline significance) were achieved for intensive-therapy group of DCCT (mean HbA_{1c} of 7.4%). Observational data demonstrate a relationship between HbA_{1c} and adverse pregnancy outcomes when HbA_{1c} levels exceed a threshold between 5.0% and 6.0%, but there is a heightened risk of hypoglycaemia at such low levels. Therefore, for most women, we recommend a target HbA_{1c} ⩽ 7.0%.	II
Recurrent severe hypoglycaemia or hypoglycaemia unawareness	⩽ 8.0%	Severe hypoglycaemia is associated with significant morbidity and mortality. Risks of tight glycaemic control outweigh the benefits for such patients.	Consensus
Patients with major comorbidities likely to limit life expectancy	Symptomatic therapy of hyperglycaemia‡ and avoidance of ketosis	Tight glycaemic control will be of no benefit, as diabetic complications take many years to develop.	Consensus

DCCT = Diabetes Control and Complications Trial. EDIC = Epidemiology of Diabetes Interventions and Complications study.
* Achievement of HbA_{1c} targets must be balanced against risk of severe hypoglycaemia. † An HbA_{1c} level ⩽ 6.0% is desirable if it can be achieved safely.
‡ Where practical, suggest blood glucose target level < 15 mmol/L to help minimise risk of infection. ◆

After a median follow-up of 5.6 years, no difference was demonstrated in the primary outcome of time to the first occurrence of any one of myocardial infarction, stroke, cardiovascular death, congestive heart failure, surgery for vascular disease, inoperable coronary artery disease or amputation for ischaemia (HR, 0.88; 95% CI, 0.74–1.05; $P = 0.14$).

There was no difference in all-cause mortality (HR, 1.07; 95% CI, 0.81–1.42; $P = 0.62$). Severe hypoglycaemia was three times more likely in the intensive-therapy group, and weight gain was 4 kg greater.

UKPDS follow-up

The 10-year observational post-trial monitoring of the original randomised UKPDS cohorts has provided additional data about longer-term type 2 diabetes outcomes.[8] Upon completion of the UKPDS, all study participants were advised to aim for lower blood glucose levels than previously targeted, with 3277 patients entering post-trial monitoring.

Although the difference in HbA_{1c} levels between the intensive- and standard-therapy groups was lost within 1 year of completing the original study, the previously demonstrated reductions in risk of diabetes end points and microvascular disease persisted at 20 years. A reduction in myocardial infarction (15%; $P = 0.01$) and all-cause mortality (13%; $P = 0.007$) emerged among patients originally under intensive treatment with sulfonylureas or insulin compared with participants in the standard-treatment group, and even greater reductions were observed in those originally treated with metformin (21% in any diabetes end point; 33% in myocardial infarction; 27% in all-cause mortality). Therefore, the benefits of better glycaemic control from the time of diagnosis of type 2 diabetes persisted and strengthened. Furthermore, the cardiovascular benefits may take many years to become evident.

Key studies compared

ACCORD showed an overall detrimental effect of tight glycaemic control on mortality; ADVANCE and VADT did not show any overall effect, either positive or detrimental, of tight glycaemic control on mortality; and UKPDS showed a reduction in all-cause mortality.

A limitation of ACCORD, ADVANCE and VADT is that, compared with UKPDS, they recruited older participants at increased risk of CVD with poorly controlled diabetes. These patients may have had suboptimal control for many years, resulting in irreversible end-organ damage. Instituting tight control in such patients may have outcomes very different from those of maintaining excellent control from the outset, especially when other risk factors are addressed. Therefore, these three studies do not provide guidance for the management of younger patients, patients with lower risk of CVD or patients with longstanding, well controlled type 2 diabetes. In contrast, UKPDS indicates that maintaining good glycaemic control after achieving it early in the disease process is beneficial. However, as the cardiovascular benefits were only observed in the post-trial monitoring period of UKPDS, appropriate trials in newly presenting young patients are much needed.

Other recent epidemiological and observational data

Epidemiological and observational studies have shown a continuum of risk of diabetic complications and mortality with increasing HbA_{1c} levels. The threshold for increased risk lies within or at the upper limit of the normal range for HbA_{1c}.

Published in 2004, the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk) Study prospectively followed 10 132 individuals aged 40–79 years for an average of 6 years.[9] A

continuous increase in cardiovascular events and all-cause mortality was observed with increasing baseline HbA_{1c} levels from 5.0% upwards in men, even in the absence of diabetes. Among women, this was significant at HbA_{1c} levels > 6.0%.

Also published in 2004, a meta-analysis of prospective cohort studies in people with type 2 diabetes estimated that for every 1.0% increase in the level of HbA_{1c}, there was an 18% (95% CI, 10%–26%) higher risk of CVD.[10] For people with type 1 diabetes, the risk increased by 15% (95% CI, 8%–43%).

Follow-up UKPDS data, published in 2000, showed that each 1.0% reduction in the HbA_{1c} level was associated with a 37% decrease in risk of microvascular complications, 14% decrease in risk of myocardial infarction, and 14% decrease in risk of all-cause mortality, with no threshold effect.[11]

Management implications

The main concern arising from the ACCORD study is that tight glycaemic control in individuals with or at high risk of CVD increases the risk of death. When the results of ACCORD are considered together with those of the other trials mentioned above, there remains a clear benefit of maintaining an HbA_{1c} level $\leqslant$ 7.0% for most patients. However, the risk–benefit balance is complex, and the following conclusions can also be drawn:

- Tight glycaemic control early in the diabetes disease process is desirable and is likely to yield the greatest benefit for the prevention of microvascular and macrovascular complications, as well as overall mortality. There is no evidence that maintenance of tight glycaemic control (eg, HbA_{1c} levels < 6.0%–6.5%) in a patient with longstanding well controlled type 2 diabetes increases mortality risk.
- Attaining tight glycaemic control in advanced disease yields little, if any, benefit for macrovascular disease but is effective in retarding the development and progression of microvascular disease.
- Attempts to achieve tight glycaemic control need to be balanced against the increased risk of severe hypoglycaemia. In the UKPDS, the annual incidence of hypoglycaemia was 0.1% among participants who were treated with diet alone; 0.3% for those receiving metformin monotherapy; 1.2% for those taking sulfonylureas; 3.8% for participants taking basal insulin only; and 5.5% for those taking prandial insulin.[12] Caution is necessary when treating older people or people with CVD. When such patients are taking insulin or sulfonylureas, a low HbA_{1c} level warns of a heightened risk of hypoglycaemia. For patients prone to severe hypoglycaemia or who have hypoglycaemia unawareness, it is prudent to maintain an HbA_{1c} level > 7.0%.
- Intensive correction of HbA_{1c} levels requires caution because the risk of hypoglycaemia may be increased. This is particularly important for patients with CVD or a history of diabetes longer than 10–20 years. Weight gain is also more likely.

In light of these conclusions, practitioners need to individualise the HbA_{1c} target level, taking into consideration the presence of CVD, diabetes duration, diabetes medication regimen, comorbidities and problems with severe hypoglycaemia (Box 1). It is important to remember that the prevention of hypoglycaemia does not rely purely on adjustment of medication, but also on patient education, including instruction in blood glucose monitoring.

Type 1 diabetes

Recent data regarding tight glycaemic control

DCCT/EDIC

Upon the completion of the DCCT, follow-up of 1394 participants (96% of DCCT survivors) continued in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. Among the primary aims of EDIC were to examine the long-term effects of the earlier differences in glycaemic control on both microvascular disease and CVD. All EDIC participants were advised about intensive insulin therapy, and returned to their usual medical practitioner for diabetes care.

Subsequently, the HbA_{1c} levels converged, with the level in the original intensive-therapy group rising to 8.0% ±1.2% and the conventional group's level decreasing to 8.2% ±1.2%. The rate of progression of retinopathy,[13] nephropathy[14] and neuropathy[15] remained lower in the prior intensive-therapy group, though there was some attenuation of the effect on retinopathy after 4 to 10 years.[16] Over 17 years of follow-up in DCCT and EDIC, participants in the DCCT intensive-treatment group had a 42% lower risk of CVD events (P=0.02), and non-fatal myocardial infarction, stroke or cardiovascular death fell by 57% (P=0.02).[16]

These long-term results of DCCT/EDIC on both microvascular and macrovascular outcomes support the target HbA_{1c} level of $\leqslant$ 7.0% for people with type 1 diabetes. Situations where it is suggested that the HbA_{1c} target level should be less strict are outlined in Box 2. In particular, it is advisable that HbA_{1c} be maintained at higher levels (eg, 7.0%–8.0%) for patients who suffer severe hypoglycaemic episodes or have hypoglycaemia unawareness.

Pregnancy

Pregestational diabetes is associated with serious adverse pregnancy outcomes, such as miscarriage, congenital malformation, pre-eclampsia and perinatal death. There is a continuous relationship between elevated HbA_{1c} levels at conception and these outcomes, with increased risk at even slight elevations above the non-pregnant normal range.

A meta-analysis that included 1977 pregnant participants (the vast majority with type 1 diabetes) from seven prospective cohort

3 Consensus process used to develop this Australian Diabetes Society position statement

Aim: To develop guidelines for the individualisation of glycated haemoglobin (HbA_{1c}) targets for the treatment of diabetes mellitus in adults.

Method: Australian Diabetes Society (ADS) members were invited to make submissions to ADS Council regarding their views on HbA_{1c} targets, with a specific focus on the results of recent clinical trials. ADS Council prepared a draft position statement, taking into consideration the submissions. This was reviewed by four eminent former presidents of ADS, and further changes were made. The final version of the position statement was prepared by ADS Council. Guidelines for pregestational and gestational diabetes management were developed in collaboration with the Council of Australasian Diabetes in Pregnancy Society.

Levels of evidence: Each of the recommendations was graded according to the National Health and Medical Research Council (NHMRC) levels of evidence. ◆

studies found that for every 1 SD increase in the level of HbA_{1c} (equivalent to 0.5% where the normal range is 4.0%–6.0%), the risk of congenital malformation increased by 20%.[17] Even when the HbA_{1c} level was only 2 SD above the mean (that is, 6.0%), there was about a 50% increase in risk (absolute risk, 3%) compared with participants with HbA_{1c} levels at the population mean (5.0%). There are no detailed data defining the relationship between HbA_{1c} level and fetal outcome in type 2 diabetes, beyond the recognition that high HbA_{1c} levels in early pregnancy are associated with serious adverse fetal outcomes.[18]

The only randomised controlled trial data come from the DCCT, which included 270 pregnant participants with type 1 diabetes.[19] Women in the intensive-therapy arm had lower HbA_{1c} levels at conception than those in the control arm (7.4% ±1.3% v 8.1% ±1.7%). Despite intensification of management during pregnancy resulting in a convergence in HbA_{1c} levels between the two groups, eight congenital malformations occurred in the conventional-therapy group, compared with one in the intensive-therapy group ($P = 0.06$).

We recommend that the HbA_{1c} level at conception and during pregnancy should be ≤ 6.0%. This is achievable for many women with type 2 diabetes. Although this HbA_{1c} target is also desirable in women with type 1 diabetes, there is a heightened risk of severe hypoglycaemia with such tight glycaemic control. Therefore, unless a lower HbA_{1c} level can be achieved safely, a conservative target of ≤ 7.0% is recommended for women. Prepregnancy planning is essential. Other aspects of pregnancy care for women with pregestational diabetes have previously been outlined in the Journal.[20]

Coexistent cardiovascular risk factors

Weight control, antihypertensive therapy, lipid control and antiplatelet therapy are critical in diabetes management. The Steno-2 Study addressed multiple risk factors through control of HbA_{1c}, blood pressure and lipids, and a regimen of aspirin and angiotensin-converting enzyme (ACE) inhibitor therapy, healthy diet, physical activity and smoking cessation.[21] This long-term target-driven intervention among people with type 2 diabetes and microalbuminuria more than halved the risk of CVD, nephropathy, retinopathy and autonomic neuropathy. The UKPDS and ADVANCE also demonstrated improved outcomes with better blood pressure control.[22,23] The blood pressure target is < 130/80 mmHg, and for those with ≥ 1 g/day of proteinuria, < 125/75 mmHg. Statin therapy markedly reduces macrovascular events in type 2 diabetes.[24,25] The main lipid target is a low-density lipoprotein cholesterol level < 2.5 mmol/L for primary prevention and < 1.8 mmol/L in secondary prevention. For most people with type 2 diabetes, the high absolute risk for macrovascular disease justifies statin treatment and an ACE inhibitor (or angiotensin-II receptor blockade), even if lipids and blood pressure are in the target range. Antiplatelet therapy (especially aspirin) is indicated for secondary and, in many cases, primary prevention in those with high absolute cardiovascular risk.[26]

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Competing interests

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