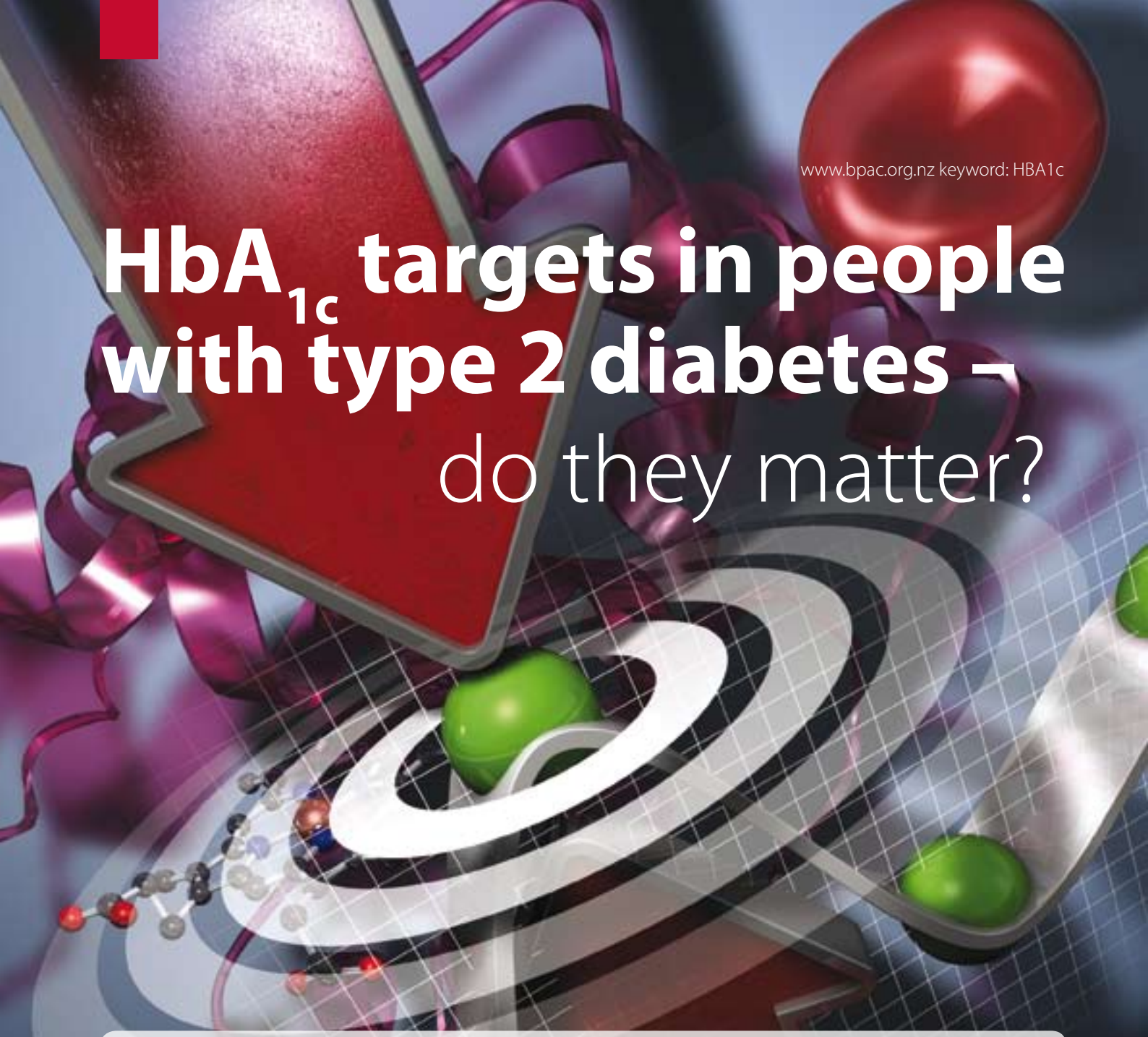
HbA_{1c} targets in people with type 2 diabetes – do they matter?



Key concepts:

- **A target HbA_{1c} should be negotiated individually, but a level of close to 7% (53 mmol/mol) seems to be an acceptable compromise for the majority of people with type 2 diabetes**
- Good glycaemic control reduces the risk of microvascular complications and may also reduce the risk of some macrovascular complications of type 2 diabetes
- Very intensive glycaemic control is associated with increased risks e.g. hypoglycaemia, weight gain and possibly increased risk of mortality
- Hyperglycaemia should not be treated in isolation when attempting to reduce cardiovascular risk
- Older people with longer duration of diabetes and who are at high cardiovascular risk may be at particular risk of harm from intensive control
- Early intervention is beneficial

The emphasis of most diabetes management guidelines was, until recently, "the lower the HbA_{1c} the better". The results of several major recent studies have generated much discussion in the literature about what a target HbA_{1c} should be, how tight intensive glycaemic control should be and which people are most likely to benefit from intensive control. Should this recent research alter the management of people with type 2 diabetes in primary care?

What is the current recommended HbA_{1c} target?

The current New Zealand guidelines for the management of type 2 diabetes, published in 2003, recommend that a target HbA_{1c} should be as close to physiological levels as possible.[1] The suggested level is preferably less than 7% or 53 mmol/mol (see below for unit conversion). In addition, the guidelines include the comment that "the lower the level of HbA_{1c}, the better".[1] Any sustained reduction in HbA_{1c} is felt to be worthwhile.

Comparison of HbA_{1c} units

Percentage units (%)	Molar units (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
8.5	69
9.0	75
9.5	80
10.0	86
10.5	91
11	97

See "Changes to laboratory reporting of HbA_{1c}" (Best Tests, Oct 2009) for further information and a method for converting between units.

What is intensive glycaemic control?

Intensive or tight glycaemic control is usually regarded as the management regimen required to achieve HbA_{1c} levels of below 6.5% or even 6.0% (48 or 42 mmol/mol). The medicines and lifestyle factors needed to reach these levels varies between clinical settings and also between research settings.

In the majority of recent clinical trials, patients randomised to intensive therapy were initiated on an oral agent that was increased or added to, if control was not achieved. Multiple agents, and often insulin, were required to achieve the target HbA_{1c}. Medicines were used that are either not available or funded in New Zealand. Standard treatment for the purposes of the trials, reflected management outlined in current local guidelines and was generally aimed at achieving a HbA_{1c} of about 1.0 – 1.5% higher than in the intensive group – usually around 7 to 8.5% (53 to 69 mmol/mol).

What are the benefits of intensive control?

There is clear evidence that intensive glycaemic control reduces the long-term risk of microvascular complications e.g. retinopathy, nephropathy and neuropathy, in people with type 2 diabetes, although it may take many years for these benefits to become apparent.[2, 3, 4]

It is less clear whether intensive glycaemic control, aimed at achieving a HbA_{1c} target of less than 6.5 or 6.0% (48 or 42 mmol/mol), can also reduce the risk of macrovascular complications, i.e. coronary artery disease, stroke and peripheral vascular disease, in people with type 2 diabetes.[5, 6]

What are the risks of intensive control?

The increased risks of intensive glycaemic control include hypoglycaemia, the possibility of hypoglycaemic unawareness, weight gain (particularly with insulin or sulphonylureas) and the potential short-term risk of worsening microvascular complications if the decrease in HbA_{1c} occurs rapidly. Patients may also find the demands of intensive glycaemic control difficult to manage. This may result in psychological stress, frustration and non-adherence especially if hypoglycaemia occurs.[7]

Results from some major trials have indicated that patients who had intensive glycaemic control were at an increased risk of death compared to patients in the standard treatment group and that there was no major reduction in microvascular complications.[5, 6]

A balance must be sought between the benefits and risks of intensive glycaemic control for the patient.

What are the current issues in the literature?

The Action in Diabetes and Vascular Disease (ADVANCE),[3] Action to Control Cardiovascular Risk in Diabetes (ACCORD)[5, 6] and Veterans Affairs Diabetes Trial (VDAT),[8] were three randomised controlled trials designed to assess the effects of intensive glycaemic control on cardiovascular outcomes. The results of these large, long-term studies have generated much debate and sparked further research.

Patients were randomly allocated to an intensive glucose lowering group or a control group with standard treatment. The HbA_{1c} targets in the intensive treatment groups were set at 6.0 to 6.5% (42 to 48 mmol/mol), which was considered to be as close to a physiological level as possible, and at 7.0 to 8.0% (53 to 64 mmol/mol) in the standard group.

Table 1 summarises some key characteristics of these trials and the overall effect on all cause mortality (primarily deaths due to cardiovascular causes).

The evidence from these three trials plus other studies is inconsistent in showing whether intensive glycaemic control has a beneficial effect on overall mortality. There was no significant change in cardiovascular or overall mortality for patients in the intensively treated groups in the ADVANCE and the VDAT trials.[3, 8] However, patients in the intensively treated group in the ACCORD study, showed statistically significant increases in both cardiovascular (35%) and overall (22%) mortality resulting in a decision to stop the trial early.[5] A trend towards increased mortality was also seen among patients in the intensively treated arm of the VDAT study although this was not statistically significant.[8, 9]

The initial results of the United Kingdom Prospective Diabetes Study (UKPDS) did not show any significant reduction in mortality in the group of patients treated with intensive glycaemic control. However after an additional ten years of follow-up there was a significant reduction in mortality in these patients, despite the intervention being withdrawn in the follow-up period.[2, 4]

Can the differences in results be explained?

Review of the major trials reveals that the characteristics of the selected patients and aspects of the design of the studies may help explain the differing results obtained.

Patients enrolled in the ACCORD, ADVANCE and VADT studies were:

- Older
- Had a longer history of diabetes at entry to the studies
- Had either a history of cardiovascular disease or multiple cardiovascular risk factors

In contrast, patients enrolled in the UKPDS study were younger, newly diagnosed with diabetes at entry and had lower cardiovascular risk.

Patients in the intensive glycaemic control group of the ACCORD study had the lowest HbA_{1c} target (<6.0% or 42 mmol/mol) and were subject to more rapid reduction

Table 1. Intensive glycaemic control in diabetes: study characteristics and results[3, 5, 8]

Study	Length of trial	No. of participants	Mean age of participants	Duration of diabetes at entry (median)	Baseline HbA_{1c}	Target HbA_{1c} (intensive group)	HbA_{1c} achieved (intensive group vs standard group)	All cause mortality (intensive group vs standard group)
ACCORD	3.5 years*	10,251	62	10 years	8.1%	<6.0%	6.4%† vs 7.5%	5.0 vs 4.0% (hazard ratio 1.22, P=0.04
ADVANCE	5 years (median)	11,140	66	8 years	7.2%	≤6.5%	6.5% vs 7.3%	8.9 vs 9.6% (hazard ratio 0.93, P=0.28)
VDAT	5.6 years (median)	1,791	60	12 years	9.4%	<6.0%	6.9% vs 8.4%	11.4 vs 10.5% (hazard ratio 1.07, P=0.62)

*mean, trial stopped early

† rapid reduction to this target

Mortality in the ACCORD study

The cause of the increased mortality observed in the intensively treated patients in the ACCORD study is not known. Several contributing factors have been proposed, including:[10, 11]

- Patient characteristics – patients were older, had a longer history of diabetes and had higher cardiovascular risk
- Study design – an aggressive regimen was used to lower HbA_{1c} within a short time frame and multiple medications were initiated to achieve the HbA_{1c} target, more so than in the ADVANCE trial
- Patient outcomes – patients in this study had higher rates of hypoglycaemia and higher weight gain (average of 3.5 kg)
- Medications used – glitazones (see below) were one of a number of medications prescribed to help achieve target HbA_{1c} levels.

There is evidence that glitazones (particularly rosiglitazone), as used in the ACCORD study, are associated with an increased risk of cardiovascular events and death.[12, 13] Glitazones are not recommended for use in people with heart failure (current or previous), ischaemic heart disease or peripheral vascular disease.[14, 15] There is also an increased risk of heart failure and cardiac ischaemia if a glitazone is used in combination with insulin. Specialist advice is recommended if a glitazone is being considered.

The ACCORD study also used some other newer medicines for glycaemic control, including dipeptidyl peptidase-4 inhibitors (DPP4) and glucagon-like peptide-1 (GLP-1), that are not currently funded in New Zealand.

in HbA_{1c}. Any available anti-diabetic medicines or combinations of up to five medicines were used to achieve these results. Intervention strategies in the other studies were less aggressive and fewer medicines were used to reduce glucose levels.

The length of the studies also varied. UKPDS trial results have now been reported for patients followed for ten years (median) while patients in the ADVANCE and VADT trials were followed for five years. Patients in the intensive glycaemic control group of the ACCORD study were followed for 3.5 years only, because this arm of the study was terminated early, due to the increase in mortality.

Do the results of the recent trials mean that guidelines for people with type 2 diabetes should be revised?

In light of conflicting evidence of the benefit of intensive glycaemic control on mortality, some researchers have suggested that guidelines may need to be revised to include a minimum value for HbA_{1c} rather than advocating "the lower, the better".[16]

A target HbA_{1c} should be negotiated individually, but a level of close to 7% (53 mmol/mol) seems to be an acceptable compromise for the majority of people with type 2 diabetes and this is consistent with the current New Zealand guideline.[1] Aiming for a HbA_{1c} below 6% appears unwise.[7] Intensive glycaemic control may do more harm than good for some people.

What do the results of the studies mean for people with type 2 diabetes?

Achieving good glycaemic control is beneficial for all people with type 2 diabetes, particularly for preventing microvascular complications. Macrovascular complications may also be reduced in the longer term i.e. after more than eight to ten years.

The key messages from the current evidence are that:

- Hyperglycaemia should not be treated in isolation

when attempting to reduce cardiovascular risk. Managing hypertension and lowering lipid levels may be easier to achieve and result in a more rapid improvement in outcomes than optimal glycaemic control.

- Early intervention is likely to be beneficial
- HbA_{1c} targets should be individualised – no one level will suit all people

Treat all cardiovascular risk factors

Achieving good glycaemic control is only one aspect of the overall treatment of diabetes, therefore hyperglycaemia should not be targeted in isolation.

All people with type 2 diabetes are at increased risk of cardiovascular disease. Preventing macrovascular complications relies on a comprehensive approach that assesses and targets all cardiovascular risk factors, e.g. blood pressure, lipids, smoking, weight, exercise and family history. The prevention of microvascular complications, e.g. retinopathy and nephropathy, also relies on management of other risk factors such as blood pressure.

Early intervention is important

The evidence suggests that intensive glycaemic control appears to be most beneficial for reducing the development of both microvascular and macrovascular complications in people who are younger, and are newly diagnosed with type 2 diabetes, and have low cardiovascular risk. However, in practice many newly diagnosed patients may already be at higher cardiovascular risk, as this can increase with "pre-diabetes".

Early initiation of intensive therapy to achieve a target HbA_{1c} of 6.0 to 6.5% (42 to 48 mmol/mol) is recommended for newly diagnosed patients with low cardiovascular risk, particularly if the anti-diabetic medication initiated is metformin and good glycaemic control can be achieved without the risk of hypoglycaemia.[3]

Steno-2 study shows mortality benefits after 13 years

The Steno-2 study investigated the effects of intensive management of multiple cardiovascular risk factors in patients with type 2 diabetes.[17] The multiple targets for treatment were a HbA_{1c} of < 6.5% (48 mmol/mol), fasting total cholesterol of < 4.5 mmol/L, fasting triglyceride level of < 1.7 mmol/L and a blood pressure of < 130/80 mmHg. In addition, patients received low dose aspirin, an ACE inhibitor (regardless of their blood pressure level), education and behavioural modification.

Results after the first eight years showed a reduction in microvascular complications only. However, after 13 years (approximately 7.5 years of treatment and 5.5 years of follow-up) there was a 20% decrease in the risk of death from any cause. N.B. Mortality curves only separated after the treatment period, very similar to the results seen in the UKPDS follow-up study.[4]

At the time of diagnosis with type 2 diabetes, patients should be given practical and motivational advice about lifestyle and diet. Consider also initiating metformin (see sidebar) rather than waiting for patients to fail to achieve their glycaemic target with lifestyle measures.

The benefits of early intervention may be explained by the "legacy effect" or "metabolic memory".[19, 20] This has been proposed as an important factor to consider when treating patients with type 2 diabetes, and may explain the improvement in macrovascular complications reported in studies with long term (greater than ten years) follow-up.[4, 17]

The "legacy effect" refers to the concept that intensive control initiated early in diabetes results in beneficial effects that persist for years and therefore reduces long term complications. Conversely, poor glycaemic control leads to the development of complications due to the chronic hyperglycaemic environment. Possible mechanisms for this include higher levels of free radical production and an increase in oxidative stress and endothelial dysfunction. The result is a complex and vicious cycle of damage which ultimately leads to complications of chronic diabetes. If intensive control is initiated after a period of poor glycaemic control it appears that the benefits for cardiovascular health are less, at least in the short term (approximately less than ten years).

Metformin is the initial medication of choice for people with type 2 diabetes

Metformin use is recommended because it:

- Does not cause weight gain
- Does not cause hypoglycaemia
- Reduces insulin resistance
- Reduces cardiovascular risk[2]
- Is low cost
- Has a long history of effectiveness and a good safety profile

For the majority of patients, these advantages outweigh the disadvantages which may include:[18]

- Gastrointestinal intolerance (5–20%)
- Lactic acidosis (very rare < 1/10,000, risk increases with renal insufficiency and age)
- A mild reduction in vitamin B12 and folate levels

See "Folate deficiency with metformin" (BPJ 16, Sep 2008) for further information.

Individualise targets

The evidence suggests that what is "good" glycaemic control for one person will not necessarily be the same for another person.

Body weight may influence both the focus of a diabetic treatment plan and the choice of medication if required, e.g. metformin when BMI is increased. People with diabetes who are overweight are at higher cardiovascular risk and require more intensive management of all cardiovascular disease risk factors.

A HbA_{1c} target of 6.0 to 6.5% (42 to 48 mmol/mol) may be appropriate and safe in a younger, newly diagnosed patient with low cardiovascular risk but an older patient with a longer history of diabetes who is at high cardiovascular risk, may be at risk of harm from intensive or tight control that aims for a target HbA_{1c} in this range.

Older patients are also likely to have a higher risk of co-morbidity, an increased risk of hypoglycaemia and an increased risk of drug-related adverse effects and interactions. A patient with existing macrovascular complications or who is at high risk of complications should have a less stringent HbA_{1c} target and the HbA_{1c} should be reduced to this target level more slowly.

Most researchers and specialist clinicians now advise that intensive glycaemic control to achieve a HbA_{1c} target of ≤ 6.0% (42 mmol/mol) should not be universally recommended.[21, 22]

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