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A_{1c} and CVD – how low to go?

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

Tight glycaemic control does not seem appropriate for all patients with type 2 diabetes.

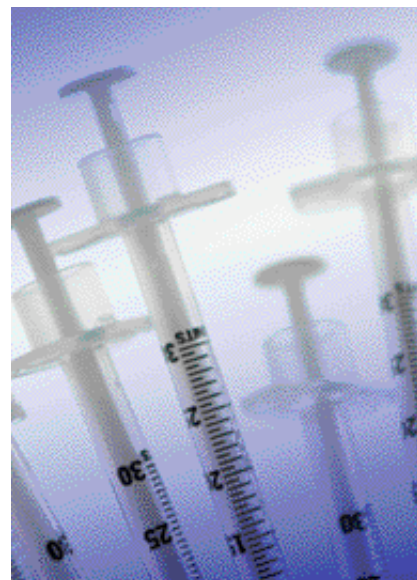
Tight treatment targets for people with diabetes have come into question with three recently published studies identifying no cardiovascular benefit of tight glycaemic control and one of these also demonstrating an increase in mortality rate. In all three studies, glycosylated haemoglobin (A_{1c}) levels were significantly reduced in individuals with or at high risk of cardiovascular disease (CVD). These studies have an impact on the target levels of A_{1c} recommended to people with type 2 diabetes.

Previous trials – DCCT and UKPDS

The Diabetes Control and Complications Trial (DCCT) for type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes showed that glycaemic control reduces the risk of microvascular complications in patients with type 1 and type 2 diabetes, respectively.^{1,2}

A subsequent analysis of the 18-year follow up of DCCT participants (the Epidemiology of Diabetes Interventions and Complications [EDIC] study) and the epidemiological analysis of the UKPDS showed that improving glycaemic control reduces the risk of macrovascular complications (CVD).^{3,4} Both these analyses suggested that a decrease of 1% in the absolute A_{1c} value was associated with a 20% decrease in cardiovascular events.

However, both the DCCT and the UKPDS showed that decreasing A_{1c} was also associated with an increase in costs in terms of hypoglycaemic events. This cost was considerably more in type 1 diabetes



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than in type 2 diabetes.⁵

In summary, as A_{1c} decreases, long-term benefits increase but short-term costs also increase. At what level of A_{1c} does cost exceed benefit?

ACCORD, ADVANCE, and VADT

Three recently published trials addressed the question of cost versus benefit for patients with type 2 diabetes – the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT).⁶⁻⁸

Table. ACCORD, ADVANCE and VADT

Trial	Target A _{1c}		Achieved A _{1c}		CVD outcome
	Control treatment	Intensive treatment	Control treatment	Intensive treatment	
ACCORD ⁶	7.0 to 7.9%	Less than 6%	7.5%	6.4%	Mortality increase
ADVANCE ⁷	'Usual'	Less than 6.5%	7.3%	6.5%	No significant difference
VADT ⁸	Less than 9.0%	Less than 6%	8.4%	6.9%	No significant difference

ABBREVIATIONS: The trials: ACCORD = Action to Control Cardiovascular Risk in Diabetes study; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation; VADT = Veterans Affairs Diabetes Trial. A_{1c} = glycosylated haemoglobin; CVD = cardiovascular disease.

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

Different inclusion and exclusion criteria were used in the three trials but in each trial participants were allocated to receive intensive treatment or control treatment. The targets for A_{1c} were different in each trial, and the actual levels of A_{1c} achieved were reasonably close to these targets.

The A_{1c} values and the CVD outcome for each trial are summarised in the Table.

The question

All three trials were addressing the same question:

‘Does a reduction of A_{1c} from the control treatment level to the intensive treatment level reduce cardiovascular events?’

The answer

And the answer is... No.

- In the ACCORD study, reducing A_{1c} from 7.5% to 6.4% increased mortality (by 22%).
- In ADVANCE and VADT, reducing A_{1c} from 7.3% to 6.5% and from 8.4 to 6.9%, respectively, did not significantly reduce cardiovascular events (a nonsignificant decrease occurred in ADVANCE and a nonsignificant increase in VADT).

So what’s the bottom line?

The current target A_{1c} level recommended in Australia is less than 7.0%.⁹

‘However, especially in the elderly, biochemical ideals should be tempered by common sense and the need to remove symptoms and maintain or improve quality of life. ... Over-zealous management can result in severe hypoglycaemia and may be associated with increased mortality.’⁹

One Australian diabetologist recommends three targets for A_{1c} :¹⁰

- A_{1c} less than 6.5% (as recommended by the International Diabetes Federation)¹¹ in those individuals with recently diagnosed type 2 diabetes (e.g. up to 10 years’ duration) and not requiring insulin

- A_{1c} less than 7.0% (as recommended by the American Diabetes Association and Diabetes Australia)^{9,12} in those individuals with longstanding type 2 diabetes and/or requiring insulin and/or with existing CVD
- A_{1c} in the range 7.0 to 8.0% in those individuals with type 2 diabetes plus severe complications and/or comorbidities.

These ‘bottom lines’ seem reasonable but there are still many questions about A_{1c} and CVD and how low to go. **MT**

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