Medicine by the Numbers
A Collaboration of TheNNT.com and AFP

The NNT Group rating system:

Green:	Benefits greater than harms
Yellow:	Unclear benefits
Red:	No benefits
Black:	Harms greater than benefits

Tight Glycemic Control for Type 2 Diabetes Mellitus (Over Five Years)

DAVID NEWMAN, MD

TIGHT GLYCEMIC CONTROL FOR TYPE 2 DIABETES MELLITUS (OVER FIVE YEARS)

Number needed to harm = 6 for hospitalization (hypoglycemia)

Benefits	*Harms*
None were helped (prevented death, heart attack, stroke, or kidney failure) 1 in 250 was helped (prevented limb amputation)	1 in 6 was harmed (severe hypoglycemia requiring hospitalization)

Details for This Review

Study Population: Adults with type 2 diabetes mellitus

Efficacy End Points: Prevention of mortality, heart attack, stroke, kidney failure, limb amputation

Harm End Points: Hypoglycemia

Narrative: Type 2 diabetes is increasingly common in the industrialized world. The most common allopathic treatment strategy is glycemic control using A1C levels as a target. Tight glycemic control attempts to rigidly control glucose levels (typically an A1C level of 6.5% to 7.0% or lower). Standard control is less rigid and allows higher levels (usually 7.5% to 8.0%). Some experts maintain that tight glycemic control is lifesaving. There are, however, potential dangers including hypoglycemia. Additionally, the patient effort, resources, and time required for this approach are not insignificant, making its true impact far-reaching.

This summary uses a Cochrane review, updated in 2013, to address the impact of tight glycemic control compared with standard glycemic control on the outcomes of particular interest to patients with diabetes.[1] The Cochrane review includes a total of 28 trials enrolling nearly 35,000 patients.

Overall there was no improvement in deaths, heart attacks, strokes, or kidney failure with tight glycemic control. There was an improvement in limb amputation (number needed to treat = 250). Unfortunately, the most identifiable harm of tight glycemic control, hypoglycemia requiring hospitalization, was common (number needed to harm = 6). This is a linear extrapolation to five years from 12 months, 3.5% per 12 months; at 10 years, the rate would be 35% (number needed to harm = 3).

The period over which these outcomes were assessed varied. In some cases, the median period was shorter (as little as two years) despite being substantially longer in some trials for the outcome, although most were tracked for a median of five years or more.

Caveats: These are data estimates from randomized trials, which tend to represent a best-case scenario for a drug's beneficial impact. The included trials were, according to the Cochrane authors, at some risk of bias, which may magnify this effect and raises the possibility that harms may have been more significant than reported. There are no data to support the statement that tight glycemic control is lifesaving, and indeed these considerable data suggest that it is not. The median time for mortality outcomes was short, roughly two years. Over many years of using this approach, there may be an identifiable mortality benefit, although it would likely be small based on the point estimates and sequential analyses performed.

Hypoglycemia is a major problem for persons with diabetes and can be fatal or

neurologically devastating in extreme cases. Hypoglycemia did not, however, seem to increase mortality, which is reassuring, especially for those at higher risk of limb amputation.

These data should not be interpreted to mean that any attempts to control glucose levels have been proven ineffective. Although it is true that elevations in blood glucose are not the cause of type 2 diabetes, but rather a symptom of an underlying metabolic disorder, treating this measurable symptom may have benefits. Unfortunately, at this point, even this remains unproven despite being intuitively likely. Trials examining diet or lifestyle approaches vs. directed glucose control are needed to determine how beneficial treating high glucose levels is compared with other approaches.

Finally, we did not address microvascular complications in this summary because they are not patient-oriented. Nephropathy (protein in the urine) and retinopathy (retinal changes on examination) may be harbingers of later problems, and both are reduced by tight glycemic control. However, existing data argue strongly that clinically important outcomes, such as kidney failure and vision loss, occur far less often than cardiovascular outcomes, and these end points have not been shown to be impacted by tight glucose control.

This series is coordinated by Dean A. Seehusen, MD, MPH, *AFP* Contributing Editor, and Daniel Runde, MD, from The NNT Group.

This review is available from The NNT Group at http://www.thennt.com/nnt/tight-glycemic-control-for-type-2-diabetes-over-5-years/.

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REFERENCE

1. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2013;(11):CD008143. ■