

# Intensive and standard glucose control did not differ for major CV events or death in poorly controlled type 2 diabetes

Duckworth W, Abaira C, Moritz T, et al. *Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med.* 2009;360:129-39.

Clinical impact ratings: **GM** ★★★★★★☆☆ **C** ★★★★★★☆☆ **En** ★★★★★★☆☆

## Question

In patients with poorly controlled type 2 diabetes, how does intensive glucose control compare with standard control for reducing cardiovascular (CV) events?

## Methods

**Design:** Randomized controlled trial (Veterans Affairs Diabetes Trial [VADT]). ClinicalTrials.gov NCT00032487.

**Allocation:** Unclear allocation concealment.\*

**Blinding:** Blinded (outcome assessors).\*

**Follow-up period:** Median 5.6 years.

**Setting:** 20 sites in the USA.

**Patients:** 1791 patients (mean age 60 y, 97% men) who had inadequate responses to maximum doses of an oral agent or insulin therapy. Exclusion criteria included glycated hemoglobin (Hb) level < 7.5%, CV event in the past 6 months, advanced congestive heart failure (CHF), severe angina, body mass index (BMI) > 40 kg/m<sup>2</sup>, serum creatinine level > 1.6 mg/dL (141 μmol/L), and alanine aminotransferase level > 3 times the upper normal limit.

**Intervention:** Intensive (*n* = 892) or standard glucose control (*n* = 899). Patients were given oral metformin plus rosiglitazone (BMI ≥ 27 kg/m<sup>2</sup>) or oral glimepiride plus rosiglitazone (BMI < 27 kg/m<sup>2</sup>). The intensive-control group started with maximum doses, and the standard-control group started with half-maximum doses. Patients in the intensive-control group who did not achieve glycated Hb levels < 6% and patients in the standard-control group who did not achieve levels < 9% were started on insulin. The goal of intensive control was absolute reduction in glycated Hb levels by 1.5% compared with standard control.

**Outcomes:** First major CV event (composite endpoint of myocardial infarction [MI], stroke, CV death, CHF, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene). Secondary outcomes included all-cause mortality and microvascular complications.

**Patient follow-up:** 86% (intention-to-treat analysis).

## Main results

Groups did not differ for the composite endpoint (Table), individual components of the composite endpoint, all-cause mortality (Table), or microvascular complications.

## Conclusion

Intensive glucose control and standard control did not differ for reducing cardiovascular events or death in patients with poorly controlled type 2 diabetes.

\*See Glossary.

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## Commentary

The VADT and other studies suggest that intensive glycemic control does not reduce vascular events in patients with advanced type 2 diabetes (1, 2). Strengths of the VADT include a clear and sustained difference in HbA<sub>1c</sub> levels and good control of blood pressure and cholesterol levels. However, a major limitation was low power because of an overestimate of the incidence of the primary outcome at 6 years, leading to an inability to detect small but important differences between groups.

Patients in the VADT were mostly men, and thus the results may not be generalizable to women with type 2 diabetes. Moreover, the findings cannot be applied to patients at an earlier stage of disease. In fact, the United Kingdom Prospective Diabetes Study (UKPDS), which enrolled patients with newly diagnosed type 2 diabetes, found an enduring or “legacy” effect of tight glycemic control—reductions in risk for MI and all-cause death emerged 10 years later (3). A similar phenomenon was seen in patients with type 1 diabetes in the Diabetes Control and Complications Trial (4).

How do we reconcile findings from various studies? Findings from the UKPDS suggest that glycemic control must be started early in the course of diabetes to have an effect on CV outcomes, and it may take longer for this benefit to become clinically evident—a fact that may have contributed to negative findings of shorter studies. Until more data are available, it is reasonable to follow published guidelines (5) recommending an HbA<sub>1c</sub> level < 7% for many patients with diabetes; however, in patients with more advanced diabetes in whom the benefits of tight control are more questionable, clinicians should exercise caution and individualize therapy.

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## References

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Outcomes	Intensive control	Standard control	At a median 5.6 y	
			RRR (95% CI)	NNT
Composite endpoint‡	26%	29%	10% (-4 to 23)	Not significant
			RRI (CI)	NNH
All-cause mortality	11%	11%	6.6% (-18 to 39)	Not significant

†Abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.  
‡Myocardial infarction, stroke, CV death, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene.