

# Intensive insulin therapy reduced cardiovascular disease in type 1 diabetes

Nathan DM, Cleary PA, Backlund JC, et al. **Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes.** *N Engl J Med.* 2005 Dec;353:2643-53.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆ Cardiology ★★★★★☆ Endocrinology ★★★★★★

## QUESTION

In patients with type 1 diabetes, does long-term intensive insulin therapy (IIT) reduce cardiovascular disease (CVD) events?

## METHODS

**Design:** Long-term follow-up of patients in a randomized controlled trial (Diabetes Control and Complications Trial [DCCT] and Epidemiology of Diabetes Interventions and Complications [EDIC] study).

**Allocation:** {Concealed}†.\*

**Blinding:** Blinded (outcome assessors {and laboratory technicians}†).\*

**Follow-up period:** Mean 17 years.

**Setting:** 28 clinical centers in the United States and Canada.

**Patients:** 1441 patients 13 to 40 years of age with type 1 diabetes. Exclusion criteria were a history of CVD, hypertension (blood pressure  $\geq 140/90$  mm Hg), or hypercholesterolemia (serum cholesterol level  $\geq 3$  standard deviations above age- and sex-specific means).

**Intervention:** IIT ( $\geq 3$  insulin injections/d or an external insulin pump, with dose adjustment based on  $\geq 4$  self-monitored glucose measurements/d, to reach a target blood glucose level 70 to 120 mg/dL [3.9 to 6.7 mmol/L] before meals and  $< 180$  mg/dL

[10.0 mmol/L] after meals and glycosylated hemoglobin [HbA<sub>1c</sub>] level  $< 6.05\%$ ) ( $n = 711$ ), or conventional therapy (1 or 2 insulin injections/d) ( $n = 730$ ). At the end of DCCT (mean 6.5 y), patients in the conventional therapy group were offered IIT, and all diabetes care was subsequently carried out by the patients' own care providers.

**Outcomes:** Time to CVD events (nonfatal myocardial infarction [MI], stroke, CVD mortality, silent MI, angina, or revascularization by angioplasty or coronary artery bypass).

**Patient follow-up:** 93% (intention-to-treat analysis).

## MAIN RESULTS

At mean 17 years (the end of EDIC), fewer patients in the IIT group had CVD events than did those in the conventional therapy

group (Table). Previous allocation to IIT during the DCCT led to lower HbA<sub>1c</sub> levels than conventional therapy (7.4% vs 9.1%,  $P < 0.01$ ), but the 2 groups did not differ for HbA<sub>1c</sub> level at the end of EDIC (7.9% vs 7.8%,  $P = 0.38$ ).

## CONCLUSION

In patients with type 1 diabetes, long-term intensive insulin therapy reduced cardiovascular disease events.

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\*See Glossary.

†Information provided by author.

## Intensive insulin therapy vs conventional therapy for type 1 diabetes†

| Outcome     | Cumulative incidence at 19.6 y |                      | RRR (95% CI)  | NNT (CI) <sup>§</sup> |
|-------------|--------------------------------|----------------------|---------------|-----------------------|
|             | Intensive insulin therapy      | Conventional therapy |               |                       |
| CVD events‡ | 5.9%                           | 10.3%                | 42% (9 to 63) | 23 (12 to 352)        |

‡Cardiovascular disease (CVD) mortality, nonfatal myocardial infarction (MI), silent MI, revascularization, angina, and stroke. Abbreviations defined in Glossary; cumulative incidence, RRR, NNT, and CI provided by author.

§Number needed to treat intensively over a mean of 6.5 years to prevent 1 CVD event over a follow-up of 19.6 years.

## COMMENTARY

The DCCT showed that 6 years of IIT targeting normoglycemia markedly reduced diabetic retinopathy, nephropathy, and neuropathy in patients with type 1 diabetes. It was not designed to examine CVD events, although a trend toward reduced CVD events in the treatment group existed at the end of the active phase. The additional power provided by the passive follow-up of  $> 93\%$  of the original DCCT cohort for a further 11 years, the relatively high CVD event rate of 0.42% per person-year in the control group (compared with 0.26% in the IIT group), and the preplanned analysis of the long-term CVD effect of the intervention have confirmed the initial trend. Thus,  $\geq 6$  years of IIT reduces the long-term (17-y) risk for CVD events in patients with type 1 diabetes. Moreover, explanatory analyses suggest that the benefit of 6-year IIT was attributable to the lower HbA<sub>1c</sub> level achieved, did not require the lower HbA<sub>1c</sub> to be maintained during the 11-year passive follow-up phase, and persisted when a different definition of a CVD event was applied. Although the unblinded nature of the DCCT may have magnified the benefits of IIT if patients in the treatment group

used more ancillary cardioprotective therapies than patients in the conventional therapy group, no evidence of such co-intervention was detected in the careful analyses that were reported. CV protection can be added to the list of benefits of IIT in patients with type 1 diabetes.

The high risk for severe hypoglycemia with IIT remains an obstacle to achieving optimal glycemic control. The challenges now are to identify new ways to safely and effectively implement this approach in patients with type 1 diabetes and to determine if the benefits also apply to patients with type 2 diabetes. Several clinical trials of glycemic control in patients with type 2 diabetes will be completed by 2009 (1).

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## Reference

1. Buse JB, Rosenstock J. Prevention of cardiovascular outcomes in type 2 diabetes mellitus: trials on the horizon. *Endocrinol Metab Clin North Am.* 2005;34:221-35.