

# Review: Interventions that lower cholesterol levels or blood pressure in diabetic patients prevent cardiovascular disease

Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. *Am J Med.* 2001 Dec 1;111:633-42.

## QUESTION

In patients with type 2 diabetes mellitus, do medications for intensive reduction of cholesterol and glucose levels and blood pressure prevent cardiovascular disease (CVD)?

## DATA SOURCES

Studies were identified by searching MEDLINE (1966 to 2000) and bibliographies of relevant studies and reviews.

## STUDY SELECTION

2 reviewers independently selected English-language randomized controlled trials (RCTs) that compared medications for intensive risk-factor reduction with placebo or routine risk-factor reduction in adults with type 2 diabetes; had  $\geq 10$  patients in each group; followed patients for  $\geq 1$  year; and reported on  $\geq 1$  of aggregate cardiac events, cardiovascular mortality, all-cause mortality, myocardial infarction, and stroke. Exclusion criteria were nonpharmacologic treatments, absence of prespecified outcomes, or comparing therapeutic agents rather than evaluating risk-factor lowering.

## DATA EXTRACTION

Data were extracted on patients, treatment, CVD history, diabetes duration, risk-factor levels, and outcome events.

## MAIN RESULTS

7 cholesterol-lowering RCTs (2603 diabetic patients, mean age 58 y, 87% men), 6 blood pressure-lowering RCTs (7572 diabetic patients, mean age 62 y, 57% men), and 5 glucose-lowering RCTs (5159 diabetic patients, mean age 57 y, 59% men) were included. Mean follow-up ranged from 4.3 to 6.1 years for cholesterol-lowering RCTs, 2.0 to 8.4 years for blood pressure-lowering RCTs, and 1.0 to 12.5 years for glucose-lowering RCTs. Pooled results showed that lowering cholesterol levels and blood pressure reduced cardiac event rates; the lowering of glucose levels did not reduce cardiac event rates (Table). When cholesterol-lowering RCTs were classified as primary prevention

or secondary prevention, the effect remained for secondary-prevention RCTs (3 RCTs) but not for primary-prevention RCTs (2 RCTs) (Table).

## CONCLUSIONS

In patients with type 2 diabetes mellitus, medications to lower cholesterol levels or blood pressure substantially reduce cardiovascular disease (CVD). Medications to lower glucose levels appear to have less, if any, effect on CVD.

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### Intensive risk-factor reduction (treatment) vs placebo or routine risk-factor reduction (control) for aggregate cardiac events\* in type 2 diabetes at mean 1- to 12.5-year follow-up†

Risk-factor interventions	Number of studies	Events/1000 person-years		Summary rate ratio (95% CI)	Person-years needed to treat (CI)
		Treatment	Control		
Cholesterol lowering	5	30	41	0.75 (0.61 to 0.93)	106 (62 to 366)
Primary prevention	2	8	19	0.44 (0.17 to 1.2)	97 (45 to NM)
Secondary prevention	3	34	44	0.77 (0.62 to 0.96)	120 (61 to 48 560)
Blood pressure lowering	3	17	23	0.73 (0.57 to 0.94)	157 (88 to 726)
Glucose lowering	2	15	18	0.87 (0.74 to 1.01)	Not significant

\*Death from coronary heart disease and nonfatal myocardial infarction.

†Summary rate ratios were calculated using a fixed-effects model. NM = not clinically meaningful because person-years needed to treat is negative.

## COMMENTARY

Despite a well-known increase in the incidence of CVD in patients with type 2 diabetes, the relative effect of glycemic control, cholesterol lowering, and blood pressure control with medications remains controversial. In their meta-analysis, Huang and colleagues show that while cholesterol-lowering and blood pressure-lowering drugs reduced the risk for cardiac events, the risk reduction with glucose-lowering agents was not statistically significant.

The interpretation of these findings is fraught with uncertainties in view of the following caveats. First, as pointed out by the authors, the underlying cardiovascular status of patients in each of the 3 interventions differed: The percentages of patients with coronary artery disease in the cholesterol-, blood pressure-, and glucose-lowering RCTs were 89%, 32%, and 13%, respectively. Consequently, the lowest event rates in the control groups of the glucose-lowering RCTs reflected the lowest absolute risk for events in patients with such underlying disease. Only 2 of the 5 glucose-lowering RCTs, both targeted at primary prevention, provided aggregate cardiac end points. In fact, in the only secondary glucose-lowering RCT included in this analysis, the reduction in cardiovascular mortality was statistically significant. However, it was a relatively short-term RCT. Second, the mean fasting plasma glucose reduction of 29 mg/dL and mean glycosylated hemoglobin (HbA<sub>1c</sub>)

reduction of 0.9% achieved in the glucose-lowering trials may not sufficiently improve the glycemic burden. Finally, the effects of newer insulin-sensitizing agents (e.g., thiazolidinediones), with potential benefits for atherogenesis or vascular function, were not studied.

Epidemiologic evidence continues to show that the increased risk for CVD extends well into the moderately increased range of glycemia (HbA<sub>1c</sub> < 7.0%) (1). Thus far, none of the RCTs available have fully tested the glucose-lowering hypothesis. Currently, 2 large trials aiming for tighter glucose control with various pharmacologic agents, including insulin sensitizers, are being done (2, 3). Furthermore, despite evidence for reduced cardiovascular events with cholesterol- and blood pressure-lowering medications, the residual risk in diabetic patients treated to current target levels remains unacceptably high.

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## References

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