# Atorvastatin did not prevent cardiovascular events in type 2 diabetes

Knopp RH, d'Emden M, Smilde JG, Pocock SJ. **Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN).** Diabetes Care. 2006;29:1478-85.

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

## QUESTION

In patients with type 2 diabetes, is atorvastatin more effective than placebo for preventing cardiovascular (CV) events?

## METHODS

**Design:** Randomized placebo-controlled trial (The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Noninsulin-dependent Diabetes Mellitus [ASPEN]).

**Allocation:** {Concealed}†.*

**Blinding:** Blinded (clinicians, patients, outcome assessors, {data collectors, data analysts, and data safety and monitoring committee}†).*

**Follow-up period:** Median 4 years.

**Setting:** 70 centers in 14 countries.

**Patients:** 2410 mixed primary and secondary CV prevention patients 40 to 75 years of age (mean age 61 y, 66% men, 84% white) who had type 2 diabetes for ≥ 3 years; low-density lipoprotein [LDL] cholesterol levels ≤ 160 mg/dL (4.1 mmol/L) (≤ 140 mg/dL [3.6 mmol/L] in patients with myocardial infarction [MI] or an interventional procedure > 3 mo before screening); and triglyceride levels ≤ 600 mg/dL (6.8 mmol/L). Exclusion criteria included type 1 diabetes; MI, interventional procedures, or unstable angina ≤ 3 months before screening; congestive heart failure treated with digoxin; hemoglobin $A_{1c}$ > 10%; active liver disease or hepatic dysfunction; renal dysfunction or nephrotic syndrome; creatine phosphokinase ≥ 3 times the upper limit of normal; blood pressure > 160/100 mm Hg; body mass index > 35 kg/m$^2$; placebo run-in compliance rate < 80%; hypersensitivity to study medication; and use of immunosuppressants or drugs that interact with study medication or increase risk for rhabdomyolysis with statins.

**Intervention:** Atorvastatin, 10 mg/d ($n$ = 1211), or placebo ($n$ = 1199).

**Outcomes:** Composite endpoint of CV death, nonfatal MI, nonfatal stroke, recanalization, coronary artery bypass grafting, resuscitated cardiac arrest, or worsening or unstable angina requiring hospitalization. Secondary outcomes were individual components of the composite endpoint; fatal or nonfatal MI; non-CV death; transient ischemic attack; worsening or unstable angina not requiring hospitalization; angina, ischemic pain, or acute ischemic heart failure requiring hospitalization; surgery for or new diagnosis of peripheral arterial disease; and adverse events. The study had 90% power to detect a 32% risk reduction in the primary composite endpoint.

**Patient follow-up:** 81% (intention-to-treat analysis).

## MAIN RESULTS

Groups did not differ for the primary composite endpoint or fatal or nonfatal MI (Table). Groups also did not differ for any other secondary outcome or in the frequency of adverse events.

## CONCLUSIONS

In low-risk patients with type 2 diabetes, atorvastatin did not prevent cardiovascular events.

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*See Glossary.

†Information provided by author.

**Atorvastatin vs placebo for type 2 diabetes at median 4 years‡**

| Outcomes | Atorvastatin | Placebo | RRR (95% CI) | NNT |
|---|---|---|---|---|
| Composite endpoint§ | 14% (166/1211) | 15% (180/1199) | 10% (–12 to 27) | Not significant |
| Fatal or nonfatal MI | 4.0% | 5.5% | 27% (–6 to 49) | Not significant |

‡MI = myocardial infarction. Other abbreviations defined in Glossary; individual event rates of the composite endpoint, RRR, NNT, and CI provided by author.
§Cardiovascular death (3.1% vs 3.1%), nonfatal MI (3.5% vs 4.8%), nonfatal stroke (2.6% vs 3.0%), recanalization (3.6% vs 3.9%), coronary artery bypass grafting (4.0% vs 4.1%), resuscitated cardiac arrest, or worsening or unstable angina requiring hospitalization (3.1% vs 3.0%).

## COMMENTARY

The ASPEN trial by Knopp and colleagues offers a few lessons. The low event rates among placebo-group patients further the notion that not all patients with diabetes are at high risk for CV events. This may be attributable to chance or to preferential recruitment of low-risk patients for the trial. The patients with diabetes may have been at lower risk because they had no other CV risk factors or previous events or because their risk factors were well controlled. These results advance the idea that there are "diminishing returns" when using effective interventions in lower-risk patients or in high-risk patients receiving other effective CV risk-reduction interventions. For clinicians, these results support an approach that is less focused on achieving LDL cholesterol goals and more focused on reducing overall CV risk.

A meta-analysis of randomized trials of statins in patients with diabetes that showed a 20% (95% CI 10 to 29) relative risk reduction in major coronary events in the primary prevention groups and 21% (CI 7 to 32) in the secondary prevention groups offers the best estimate of statin effects (1). The results from the ASPEN trial in a mixed prevention group are imprecise but potentially consistent with these pooled results. The decision of the data monitoring committee in this study to offer statins to participants who had CV events in both groups further impaired the trial's ability to offer clear inferences. The results in ASPEN may seem inconsistent with the CARDS trial (2), but in CARDS the effect of atorvastatin in patients with diabetes may have been inflated by the decision to stop the trial early because of an unexpectedly large treatment benefit (3).

Finally, the well-designed ASPEN trial, documenting no benefit, may highlight a form of reporting bias. Knopp and colleagues chose to submit their report to a subspecialty journal. In contrast, the CARDS trial, completed about the same time and reporting a 37% relative risk reduction in major CV events, was published 2 years ago in *The Lancet*.

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***References***

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