THERAPEUTICS

Atorvastatin reduced major cardiovascular disease events in type 2 diabetes mellitus

Colhoun HM, Betteridge DJ, Durrington PN, et al. **Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial.** Lancet. 2004;364:685-96.

QUESTION

In patients with type 2 diabetes mellitus, is atorvastatin better than placebo for primary prevention of major cardiovascular disease (CVD) events?

METHODS

Design: Randomized placebo-controlled trial (Collaborative Atorvastatin Diabetes Study [CARDS]).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, pharmacists, data collectors, outcome assessors, monitoring committee, and data analysts).*

Follow-up period: Median 3.9 years.

Setting: 132 clinical centers in the United Kingdom and Ireland.

Patients: 2838 patients 40 to 75 years of age (mean age 62 y, 68% men) with type 2 diabetes mellitus (defined with 1985 World Health Organisation criteria) diagnosed ≥ 6 months before study entry who had ≥ 1 of the following: a history of hypertension, retinopathy, microalbuminuria or macroalbuminuria, or a current smoking habit. Exclusion criteria included a history of CVD, plasma creatinine > 150 µmol/L (1.7 mg/dL), glycated hemoglobin > 12%, and < 80% compliance with placebo during the baseline phase.

Intervention: Atorvastatin, 10 mg daily (n = 1429), or placebo (n = 1412).

Outcomes: A composite endpoint consisting of an acute coronary heart disease event (myocardial infarction including silent infarction, unstable angina, acute coronary heart disease death, or resuscitated cardiac arrest), coronary revascularization procedures, or stroke.

Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

The rates for the composite endpoint were lower in the atorvastatin group than in the placebo group (Table). When individual components of the composite endpoint were evaluated, the atorvastatin group had lower rates for acute coronary events and stoke, but not for coronary revascularization (Table).

CONCLUSION

In patients with type 2 diabetes mellitus, atorvastatin was more effective than placebo for reducing the rate of major cardiovascular disease events.

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*See Glossary.

Atorvastatin vs placebo in patients with type 2 diabetes mellitus at median 3.9 years†

Outcomes	Atorvastatin	Placebo	RRR (95% CI)	NNT (CI)
Composite endpoint	5.8%	9.0%	35% (16 to 51)	32 (20 to 79)
Acute coronary events	3.6%	5.5%	35% (8 to 54)	53 (29 to 273)
Stroke	1.5%	2.8%	47% (11 to 68)	78 (42 to 411)
Coronary revascularization	1.7%	2.4%	30% (–16 to 58)	Not significant

†Composite endpoint = an acute coronary heart disease event, coronary revascularization, or stroke. Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Before the trial by Colhoun and colleagues, evidence for lipid lowering for primary prevention of CVD in patients with diabetes came only from the Heart Protection Study (HPS) (1) and subgroup analyses from trials in which treatment allocation was not stratified by diabetes status (2, 3). In CARDS, patients with type 2 diabetes and 1 other risk factor for coronary artery disease or retinopathy had a 35% relative risk reduction in CVD attributed to atorvastatin, 10 mg daily, similar to a 33% relative risk reduction in CVD with simvastatin, 40 mg daily in the HPS (1).

Participants' baseline mean low-density lipoprotein (LDL) level (3.0 mmol/L [117 mg/dL]) was unchanged in the placebo group but decreased by 31% in the atorvastatin group after 4 years. Prevention of CVD attributed to atorvastatin was of a similar magnitude regardless of participants' baseline lipid levels, which suggests that a threshold level below which statin therapy should be withheld does not exist.

These data show that substantial CVD risk reductions can be realized by achieving relative reductions in LDL levels with 1 drug at a fixed dose, but neither the CARDS nor the HPS addressed the risk or benefit for further LDL reduction with increasing doses of drugs or combinations of drugs to target "goal" lipid levels.

In CARDS and HPS, adverse events, including rhabdomyolysis, did not increase with statin therapy. Although participants in randomized controlled trials may not represent all patients seen in clinical practice, participants in CARDS had comorbid conditions similar to most patients with diabetes. The CARDS and HPS provide conservative estimates of 25% to 27% 10-year risk for CVD in untreated patients with diabetes and direct evidence of the substantial benefit and low risk of statin therapy for primary prevention of CVD.

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References

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2. **Gami AS, Montori VM, Erwin PJ, Khan MA, Smith SA.** Systematic review of lipid lowering for primary prevention of coronary heart disease in diabetes. BMJ. 2003;326:528-9.
3. **Sever PS, Dahlöf B, Poulter NR, et al.** Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361:1149-58.