

# Atorvastatin at 80 mg/d reduced major cardiovascular events more than atorvastatin at 10 mg/d in stable coronary heart disease

LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352:1425-35.

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

## QUESTION

In patients with stable coronary heart disease (CHD), is intensive atorvastatin therapy (80 mg/d) more effective than moderate atorvastatin therapy (10 mg/d) for reducing major cardiovascular events?

## METHODS

**Design:** Randomized controlled trial (Treating to New Targets [TNT] study).

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

**Blinding:** Blinded (clinicians, patients, and an endpoints adjudication committee).\*

**Follow-up period:** Median 4.9 years.

**Setting:** 256 sites in 14 countries.

**Patients:** 10 001 patients 35 to 75 years of age (mean age 61 y, 81% men) who had clinically evident CHD (defined by ≥ 1 of the following: previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic CHD, and a history of coronary revascularization) and low-density lipoprotein (LDL) cholesterol level < 130 mg/dL (3.4 mmol/L). Exclusion criteria included hypersensitivity to statins, active liver disease, pregnancy, and uncontrolled diabetes mellitus.

**Intervention:** Intensive atorvastatin therapy (80 mg/d) (*n* = 4995) or moderate atorvastatin therapy (10 mg/d) (*n* = 5006) with target average LDL cholesterol levels 75 mg/dL

(1.9 mmol/L) and 100 mg/dL (2.9 mmol/L), respectively.

**Outcomes:** First major cardiovascular event defined as a composite of death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke; all-cause mortality; and persistent elevations in liver aminotransferase levels assessed every 3 months during the first year and every 6 months thereafter.

**Patient follow-up:** 100% (intention-to-treat analysis).

## MAIN RESULTS

Mean LDL cholesterol levels were 77 mg/dL (2.0 mmol/L) in the atorvastatin-80 mg group and 101 mg/dL (2.6 mmol/L) in the atorvastatin-10 mg group during treatment. The rate of first major cardiovascular events

was lower in the atorvastatin-80 mg group than in the atorvastatin-10 mg group (Table). However, the rate of persistent elevations in liver aminotransferase levels was greater in the atorvastatin-80 mg group than in the atorvastatin-10 mg group (Table). Groups did not differ for all-cause mortality (Table).

## CONCLUSION

In patients with stable coronary heart disease, intensive atorvastatin therapy (80 mg/d) was more effective than moderate atorvastatin therapy (10 mg/d) for reducing major cardiovascular events.

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\*See Glossary.

### Intensive (80 mg/d) vs moderate (10 mg/d) atorvastatin therapy in stable coronary heart disease at median 4.9 years†

Outcomes	Atorvastatin (80 mg/d)	Atorvastatin (10 mg/d)	RRR (95% CI)	NNT (CI)
Major cardiovascular event	8.7%	10.9%	21% (11 to 30)	45 (30 to 92)
			RRI (CI)	NNH (CI)
Elevated liver enzymes‡	1.2%	0.2%	568% (237 to 1227)	98 (73 to 140)
All-cause mortality	5.7%	5.6%	1% (-14 to 18)	Not significant

†Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

‡3 times upper limit of normal on 2 consecutive measurements 4 to 10 days apart.

## COMMENTARY

The TNT study by LaRosa and colleagues has answered the “lower is better” hypothesis regarding LDL reduction and CHD events. This study was designed in the aftermath of the CARE study, which suggested in a post hoc analysis that patients with CHD had no clinical benefits from lowering LDL-cholesterol below 130 mg/dL (1). The recent Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 study, in the setting of acute coronary syndrome (2), and the Reversal of Atherosclerosis with Aggressive Lipid Lowering study, in patients with chronic coronary artery disease (3), strongly suggested that the LDL goal should be reduced to < 70 mg/dL.

The TNT study also showed that aggressive LDL-cholesterol lowering with atorvastatin 80 mg/d is relatively safe, with a transaminase elevation rate of 1.2% compared with 0.2% for low-dose atorvastatin. The 5 cases of rhabdomyolysis reported also seemed not to be dose-related. Concern was raised by a nonsignificant increase in noncoronary mortality in the atorvastatin-80 mg group, but the groups did not differ for all-cause mortality. However, the TNT study was not pow-

ered to detect a difference in all-cause mortality and, for the first time in a large clinical trial in patients with baseline CHD, noncoronary mortality exceeded coronary mortality.

This is not the end of our quest to reduce coronary mortality and morbidity, because a residual cardiovascular event rate of 28% for patients receiving atorvastatin 80 mg who had LDL levels of 77 mg/dL (vs 34% for patients with levels of 101 mg/dL) was observed. Therefore, LDL lowering alone will most probably not end CHD, and global risk reduction by modifying HDL and other risk factors will continue to be an important clinical challenge.

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## References

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