High-dose atorvastatin was superior to standard-dose pravastatin for reducing death or major cardiovascular events in acute coronary syndromes

Cannon CP, Braunwald E, McCabe CH, et al. **Intensive versus moderate lipid lowering with statins after acute coronary syndromes.** N Engl J Med. 2004;350:1495-504.

QUESTION

In patients with an acute coronary syndrome (ACS), is standard-dose pravastatin noninferior to high-dose atorvastatin for reducing death or major cardiovascular (CV) events?

METHODS

Design: Randomized, placebo-controlled trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 [PROVE IT-TIMI 22] trial).

Allocation: Concealed.*

Blinding: Blinded (clinicians and patients).*

Follow-up period: Mean 24 months.

Setting: 349 sites in 8 countries.

Patients: 4162 patients (mean age 58 y, 78% men) in stable condition who were hospitalized for an ACS (acute myocardial infarction [MI] or high-risk unstable angina) in the previous 10 days, enrolled after a percutaneous revascularization procedure (if planned), and a total cholesterol level ≤ 6.21 mmol/L (240 mg/dL) taken within the first 24 hours, or < 6 months after the onset of the ACS. Exclusion criteria included a co-existing condition that shortened expected survival to < 2 years and receipt of daily statins, 80 mg at the time of the index event.

Intervention: Daily standard-dose pravastatin (40 mg) (n = 2063) or high-dose atorvastatin (80 mg) (n = 2099).

Outcomes: Composite of major CV events: death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization with either percutaneous coronary intervention or coronary artery bypass grafting (if performed ≥ 30 d after randomization), and stroke. Secondary outcomes were coronary heart disease (CHD) death, nonfatal MI, or revascularization (if performed ≥ 30 d after randomization); and individual primary outcome components.

Patient follow-up: 99.8% (intention-to-treat analysis).

MAIN RESULTS

Pravastatin was not equivalent to atorvastatin. Patients who received atorvastatin had greater reductions in the composite endpoint; death caused by CHD, nonfatal MI, or revascularization; revascularization alone; or unstable angina requiring hospitalization than did those who received pravastatin (Table). The difference between groups did not meet the criteria for noninferiority. The upper limit of the CI exceeded the prespecified boundary (< 1.17) for showing equivalence. Groups did not differ for death from any cause (P = 0.07), death or MI (P = 0.06), stroke, or adverse effects (P = 0.11).

CONCLUSION

In patients with a recent acute coronary syndrome, standard-dose pravastatin was inferior to high-dose atorvastatin for reducing death or major cardiovascular events.

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*See Glossary.

Standard-dose pravastatin (40 mg) vs high-dose atorvastatin (80 mg) for the acute coronary syndrome at mean 24 months†

Outcomes	Atorvastatin	Pravastatin	RRR (95% CI)	NNT (CI)
Composite of major CV events	22.4%	26.3%	16% (5 to 26)	19 (11 to 62)
CHD death, nonfatal MI, or revascularization	19.7%	22.3%	14% (2 to 25)	27 (15 to 230)
Revascularization	16.3%	18.8%	14% (0 to 26)	33 (17 to 647)
UA requiring hospitalization	3.8%	5.1%	29% (5 to 47)	65 (35 to 436)

†Composite of major cardiovascular (CV) events = death from any cause, myocardial infarction (MI), documented unstable angina (UA) requiring rehospitalization, revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting (if performed ≥ 30 d after randomization), and stroke; CHD = coronary heart disease. Other abbreviations defined in Glossary; RRR, NNT, and CI provided by author.

COMMENTARY

The study by Cannon and colleagues shows that more intensive lowering of low-density lipoprotein (LDL) cholesterol with statin therapy in patients with a recent ACS reduced subsequent risk for major adverse CV events. This trial also supports the hypothesis that more aggressive LDL reduction to a target level of 60 mg/dL (1.5 mmol/L) yields greater benefit than the current guideline recommendation (LDL level < 100 mg/dL [2.6 mmol/L]).

In the ACS population, the benefit of very aggressive LDL reduction compared with moderate reduction is evident as early as 1 month after initiating therapy. This reduction would take 2 years in patients with stable coronary artery disease. In the MIRACL study, high-dose atorvastatin therapy initiated within days of an ACS diagnosis reduced recurrent ischemic events within 16 weeks (1). Early, aggressive statin therapy in patients with ACS has a powerful role in "passivating" the unstable and vulnerable plaque(s).

The subgroup analysis in the study by Cannon and colleagues showed a less prominent benefit in patients with lower baseline LDL levels and previous statin therapy. The results fall between those of the CARE trial in which a lack of benefit was observed in patients with baseline LDL level < 125 mg/dL (3.2 mmol/L) and those of the Heart Protection Study in which a consistent benefit was observed regardless of baseline LDL level (2, 3). Patients with lower baseline LDL levels or previous statin therapy would be expected to accrue less absolute benefit because they have a lower baseline risk. Therefore, current practice recommendations for patients with ACS should include obtaining a lipid and liver profile on hospital admission, and initiating or intensifying statin therapy to achieve a target LDL level < 70 mg/dL (1.8 mmol/L) (4), if no contraindication exists.

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