

Review: Early statin therapy does not reduce the composite endpoint of death, MI, or stroke in acute coronary syndromes

Briel M, Schwartz GG, Thompson PL, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. *JAMA*. 2006;295:2046-56.

Clinical impact ratings: Emergency Med ★★★★★☆☆ Hospitalists ★★★★★★ Cardiology ★★★★★☆☆

QUESTION

In patients with recent onset of the acute coronary syndrome (ACS), does early statin therapy reduce the composite endpoint of all-cause death, myocardial infarction (MI), or stroke at 1 and 4 months?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, PASCAL (up to August 2005), Cochrane Central Register of Controlled Trials (Cochrane Library 2005, issue 2), bibliographies of relevant studies, and experts in the field.

Study selection and assessment: Randomized controlled trials (RCTs) in any language that compared statin therapy (initiated within 14 d of onset) with placebo or usual care in patients with recent onset of ACS (MI or unstable angina) who were followed for ≥ 1 month. Studies with patients who had heart transplants and those comparing 2 different statins were excluded. 12 RCTs ($n = 13\,024$, mean age range 53 to 69 y) met the selection criteria and were included in the analysis. Quality assessment of individual studies was based on concealment, blinding, and follow-up.

Outcomes: Composite endpoint of all-cause death, MI, or stroke. Secondary outcomes included the individual components of the

composite endpoint, cardiovascular death, revascularization (coronary artery bypass graft surgery or angioplasty), unstable angina (recurrent myocardial ischemia requiring hospitalization), and adverse events (myopathy, rhabdomyolysis, and liver aminotransferase level > 3 times normal).

MAIN RESULTS

Groups did not differ for the incidence of the composite endpoint at 1 and 4 months (Table). In 3 RCTs ($n = 8506$), fewer patients in the statin-therapy group developed unstable angina than did patients in the placebo or usual-care group at 4 months (Table). Groups did not differ for any other secondary endpoint at 1 and 4 months. The

statin-therapy group had higher incidences of myopathy (0.1% vs 0.06%), rhabdomyolysis (0.05% vs 0%), and liver aminotransferase level > 3 times normal (1.1% vs 0.4%) than did the placebo or usual-care group.

CONCLUSION

In patients with recent onset of the acute coronary syndrome, early statin therapy does not reduce the composite endpoint of all-cause death, myocardial infarction, or stroke at 1 and 4 months.

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Early statin therapy vs placebo or usual care for the acute coronary syndrome at 1 and 4 months*

| Outcomes | Number of trials (n) | Follow-up | Weighted event rates | | RRR (95% CI) | NNT (CI) |
|---------------------|----------------------|-----------|----------------------|-----------------------|-------------------|-----------------|
| | | | Early statin | Placebo or usual care | | |
| Composite endpoint† | 10 (12 885) | 1 mo | 4.7% | 5.0% | 7.7% (-7.5 to 21) | Not significant |
| | 10 (9469) | 4 mo | 7.5% | 8.1% | 7.4% (-6.4 to 19) | Not significant |
| Unstable angina | 3 (8506) | 4 mo | 4.8% | 6.0% | 20% (4.5 to 33) | 83 (46 to 398) |

*Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from relative risks and control event rates in article using a random-effects model.

†Death, myocardial infarction, or stroke.

COMMENTARY

It has been hypothesized that the benefits of statin therapy extend beyond low-density lipoprotein-lowering effects and include pleiotropic effects—the ability to improve endothelial function, decrease platelet aggregability, and reduce vascular inflammation. The landmark clinical trials that have led to the incorporation of statin therapy into clinical practice guidelines have indicated that the clinical benefits of statins become evident 1 to 2 years after initiation of therapy. The belief that the pleiotropic effects of statins contribute to their beneficial effects and become apparent shortly after administration to high-risk patients led to several clinical trials designed to study the early effects of statins in the high-risk period immediately following ACS.

In the meta-analysis by Briel and colleagues, the 3 largest placebo-controlled trials examined the short-term outcomes of statins in ACS. 2 trials (A to Z and PACT) showed small, nonsignificant trends toward reduced adverse events; the third (MIRACL) showed a 16% relative risk reduction in adverse events at 4 months driven by a reduction in angina requiring rehospitalization. The meta-analysis shows that statins do not reduce death, MI, or stroke in patients with ACS at 1 or 4 months, but might modestly reduce angina in the short term.

These findings should not dampen enthusiasm for initiating statin therapy in patients with ACS in the hospital. Despite their proven benefits over the long term, lipid-lowering therapy remains vastly underutilized; in-hospital initiation clearly improves long-term treatment rates and patient compliance (1). Who would hold off on recommending immediate cessation of cigarette smoking in patients with ACS because cessation is only helpful in the longer term? Lipid lowering is a critical adjunct and not an alternative to revascularization or other therapies aimed at reducing the risk for death or MI in high-risk patients. Statins ought to be initiated as soon as possible in patients with any kind of ACS, notwithstanding the excellent meta-analysis by Briel and colleagues.

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Reference

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