Review: Statin monotherapy is safe in hyperlipidemia except for increased risk for transaminase elevation

Kashani A, Phillips CO, Foody JM, et al. **Risks associated with statin therapy: a systematic overview of randomized clinical trials.** Circulation. 2006;114:2788-97.

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

QUESTION

In patients with hyperlipidemia, how safe is statin monotherapy?

METHODS

Data sources: MEDLINE (1966 to December 2005), EMBASE/Excerpta Medica (1980 to December 2005), the Cochrane Library, National Institutes of Health Clinical Trials Web site, Food and Drug Administration Web site, and relevant bibliographies.

Study selection and assessment: English-language, randomized, double-blind, placebo-controlled trials (RCTs) that evaluated statin monotherapy (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin) in ≥ 100 adult patients with hyperlipidemia. 35 RCTs (n = 74 102, mean age range 44 to 76 y) met the selection criteria. Follow-up ranged from 1.5 to 65 months (median 4.5 mo). Individual study quality was assessed using the Jadad scale (mean score 4.1 out of 5).

Outcomes: Myalgia, creatine kinase elevation, rhabdomyolysis, transaminase elevation, and discontinuation caused by adverse events.

MAIN RESULTS

Meta-analysis showed that groups did not differ for myalgia, creatine kinase elevation, rhabdomyolysis, or discontinuation caused by any adverse events (Table). Statin monotherapy increased the risk for transaminase elevation more than did placebo (Table). Subgroup analysis showed that atorvastatin (but not the other statins) resulted in more patients with myalgia than did placebo (n = 567, 5.1% vs 1.6%, number needed to harm 32, 95% CI 17 to 477).

CONCLUSION

In patients with hyperlipidemia, statin monotherapy increases the risk for transaminase elevation but not myalgia, creatine kinase elevation, or rhabdomyolysis.

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Statin monotherapy vs placebo for hyperlipidemia at median 4.5 months*

Outcomes	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		Statin	Placebo		
Transaminase elevation	28 (62 184)	1.5%	1.1%	30% (6 to 59)	239 (145 to 667)
Creatine kinase elevation	16 (41 457)	0.45%	0.43%	18% (–11 to 56)	Not significant
Rhabdomyolysis	20 (68 110)	0.17%	0.13%	9% (–35 to 83)	Not significant
				RRR (CI)	NNT
Myalgia	21 (48 138)	19%	19%	1% (–3 to 4)	Not significant
Discontinuation caused by any adverse events	26 (45 268)	6.1%	6.1%	4% (–3 to 11)†	Not significant

*Abbreviations defined in Glossary; RRI, RRR, NNH, NNT, and CI calculated from data in article using a random-effects model.
†Information provided by author.

COMMENTARY

The review by Kashani and colleagues provides further reassurance of the safety of monotherapy with hydroxymethylglutaryl–CoA reductase inhibitors in the management of patients at risk for cardiovascular events or death. The doses used in the included studies were typical of current practice, although study patients were commonly younger and healthier. The findings are consistent with the conclusions of the National Lipid Association Statin Safety Assessment Task Force (1). To place these findings in perspective, the mortality risk from fatal rhabdomyolysis is < 0.3/100 000 person-years, a level that is close to the background level of the disorder. Risk for serious hepatic toxicity remains minimal, and transaminase elevation is usually reversible with reduction of statin dose or termination of therapy.

Recently published work shows that generic simvastatin is cost-effective in preventing cardiovascular events across a wide range of age groups (35 to 85 y) (2), a finding that will probably result in increased use of the therapy in older patients. At the same time, treatment goals are evolving, and the drive to reduce low-density lipoprotein levels to ≤ 70 mg/dL (1.8 mmol/L) will involve higher doses of statins with potentially increased risk for adverse effects, particularly in older patients with more comorbid conditions. The bottom line is that statins are remarkably safe and effective as monotherapy. However, as we push doses higher, treat patients with comorbid conditions, and use combination therapy, we need to be aware that statins are not risk free, and prudent monitoring will be still needed.

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References

1. **McKenney JM, Davidson MH, Jacobson TA, et al.** Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006;97:89-94C.
2. **Heart Protection Study Collaborative.** Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. BMJ. 2006;333:1145.