THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

High dose versus standard dose statins in stable coronary heart disease

The question *"Do the benefits of high dose versus standard dose statins outweigh the harms in men and women with stable coronary heart disease?"* is important and remains unanswered in published systematic reviews. [1,2,3] This Letter attempts to answer that question using the latest Cochrane methodology and focusing on outcomes that are most relevant and meaningful for patients, total mortality and total mortality and serious morbidity [total serious adverse events (SAEs)].[4]

Methods

Studies: Randomized controlled trials (RCTs) enrolling ≥ 1000 participants followed for at least one year.

Participants: Patients with stable coronary heart disease (CHD) [stable angina or previous myocardial infarction]. Patients with acute CHD or coronary syndrome were excluded.

Intervention: High dose statin monotherapy defined as doses expected to reduce low density lipoprotein-cholesterol (LDL-C) by approximately 50% or more.[5]

Control: Standard dose statin monotherapy defined as pravastatin 40 mg or simvastatin 20-40 mg (doses shown to reduce total mortality in placebo-controlled RCTs), [6,7,8] or LDL-cholesterol lowering equivalent doses of other statins.[5]

Outcomes: Total mortality, total people with at least one SAE, hospitalization, disabling stroke, non-fatal myocardial infarction (MI), withdrawals due to adverse effects, and myopathy.

Search Strategy: We searched MEDLINE, MEDLINE In-Process, EMBASE, and CENTRAL from December 2010 to August 2012 (a comprehensive search [2] was done up until December 2010).

Risk of Bias Assessment: We applied the methodology of the Cochrane Collaboration and GRADE Working Group to assess risk of bias for each trial as well as the quality of the overall evidence.

Results and Clinical Implications

Three RCTs (IDEAL[9], TNT[10], SEARCH[11]) met the inclusion criteria studying 30,953 participants. The majority of participants (87%) had a history of myocardial infarction; (13%) had a history of angina with objective evidence of atherosclerosis or coronary revascularization.

The mean age of participants ranged from 60 to 64; 82% of participants were male, and 97% were Caucasian. The duration of follow-up ranged from a median of 4.8 years to a mean of 6.7 years. The standard doses in the three RCTs were atorvastatin 10 mg, simvastatin 20 mg and simvastatin 20-40 mg; the high doses were atorvastatin 40-80 mg, atorvastatin 80 mg and simvastatin 80 mg. The interventions tested in these RCTs were pre-specified statin doses, not pre-specified LDL-C targets.[12,13] All 3 RCTs were either fully or partially sponsored by the pharmaceutical industry.

In the 3 RCTs, high dose statins had no effect on total mortality as compared to standard dose statins, RR 0.99 [0.93, 1.06] (Table and Appendix, Fig. 3). Only one RCT reported total people with at least one SAE; high dose statin compared to standard dose statin had no effect, RR 1.00 [0.98, 1.01] (see Table). None of the RCTs reported total people with at least one hospitalization or disabling stroke. **These data plus missing SAE data were requested but not provided.**

In the 3 RCTs, high dose statins reduced non-fatal MI, RR 0.83 [0.76, 0.91], ARR 1.2%, as compared to standard dose (Table and Appendix, Figure 4). We were interested in a breakdown of MI by type: "silent" myocardial infarctions, peri-procedural myocardial infarctions, and clinical myocardial infarctions resulting in hospitalization. **These non-fatal MI data detailed by type were requested but not provided.**

Only one RCT[10,14] provided sex-specific data (1,902 women, 8,099 men) for total mortality and non-fatal MI. See Table. **Sex-specific data from the other trials were requested but not provided.**

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822•0700
Fax: 604 822•0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

In the 3 RCTs, withdrawals due to adverse effects were increased with high dose statins as compared to standard doses, RR 1.45 [1.34, 1.58], ARI 2.5% (Table and Appendix, Figure 9).

The majority of participants (93%) were enrolled only if they demonstrated pre-randomization tolerance to a standard statin dose. Patients specifically at higher risk for myopathy, (e.g. older adults, women, patients with low body mass, patients receiving interacting medications)[15] were either excluded or under-represented.

Only 24% of participants were aged 70 or older, those over the age of 80 were excluded from enrolment, and less than one in five participants were women, thus limiting the generalizability of the results. It has been previously demonstrated that methodological limitations affecting randomization, allocation concealment, and blinding in RCTs significantly impact effect estimates for subjectively-assessed outcomes such as cardiovascular events but not objective outcomes, such as total mortality.[16,17] Applied to these trials, the lack of or unclear blinding of participants, clinicians, or outcome assessors to treatment assignment or lipid parameters could lead to an exaggeration of the effect estimate for non-fatal MI by 22% (RR 0.78, 0.65-0.92).[16] The implication of this is that the demonstrated reduction in non-fatal MI could be a result of bias and not a real effect.

RR = relative risk, ARR = absolute risk reduction

ARI = absolute risk increase

The draft of this Therapeutics Letter was submitted for review to 50 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

Table: Effect of high dose versus standard dose statins

Outcome	#Participants	RR [95% CI]	ARR/ ARI [a]
Total Mortality	30,953	0.99 [0.93, 1.06]	--
Total Mortality: Men	8,099	0.95 [0.80, 1.14]	--
Total Mortality: Women	1,902	1.32 [0.90, 1.92]	--
Total Serious Adverse Events	12,064	1.00 [0.98, 1.01]	--
Non-Fatal Myocardial Infarction	30,953	0.83 [0.76, 0.91]	1.2%
Non-Fatal Myocardial Infarction: Men	8,099	0.80 [0.67, 0.95]	1.3%
Non-Fatal Myocardial Infarction: Women	1,902	0.75 [0.50, 1.13]	--
Withdrawals due to Adverse Effects	30,953	1.45 [1.34, 1.58]	2.5%

[a] – absolute effect not calculated if not statistically significant.

Conclusions

In patients with stable CHD who tolerate a standard dose of a statin:

• High dose statins do not reduce mortality as compared to standard dose statins, RR 0.99 [0.93, 1.06].

• High dose statins reduce non-fatal MI as compared to standard dose statins, RR 0.83 [0.76, 0.91], ARR 1.2%, but this is not reflected in a reduction in total SAEs, RR 1.00 [0.98, 1.01].

• In women high dose statins numerically increased total mortality, RR 1.32 [0.90, 1.92] and numerically reduced non fatal MI, RR 0.75 [0.50, 1.13] as compared to standard dose statins.

• High dose statins increased withdrawals due to adverse effects, RR 1.45 [1.34,1.58], ARI 2.5%, as compared to standard dose statins.

• Because of the lack of effect on mortality and total SAEs there is no net health benefit from prescribing high dose statins over standard dose statins.

References

1. Cholesterol Treatment Trialists' (CTT) Collaboration. *Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials*. Lancet 2010;376:1670-81
2. Mills E, O'Regan C, Eyawo O, et al. *Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of > 40 000 patients*. Eur Heart J 2011;32:1409-15
3. Ribeiro R, Ziegelmann P, Duncan B, et al. *Impact of statin dose on major cardiovascular events: a mixed treatment comparison meta-analysis involving more than 175, 000 patients*. Int J Cardiol 2011; Dec 20, epub ahead of print
4. Therapeutics Initiative. *Do statins have a role in primary prevention? An update*. Therapeutics Letter. Mar-Apr 2010;77:1-2. http://www.ti.ubc.ca/letter77
5. FDA Drug Safety Communication: *New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Relative LDL-lowering Efficacy of Statin and Statin-based therapies*. http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm#Relative
6. *Scandinavian Simvastatin Survival Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease:* The Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-89
7. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *Prevention of cardiovascular disease events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels*. N Engl J Med 1998;339:1349-57
8. Heart Protection Study Collaborative Group. *MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomized placebo-controlled trial*. Lancet 2002;360:7-22
9. Pedersen T, Faergeman O, Kastelein J, et al. *High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction*. JAMA 2005;294:2437-45
10. LaRosa J, Grundy S, Waters D, et al. *Intensive lipid lowering with atorvastatin in patients with stable coronary heart disease*. N Engl J Med 2005;352:1425-35
11. SEARCH Collaborative Group. *Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomized trial*. Lancet 2010;376:1658-69
12. Therapeutics Initiative. *Do statins have a role in primary prevention?* Therapeutics Letter. Apr-Jun 2003;48:1-2. http://www.ti.ubc.ca/letter48
13. Hayward R, Hofer T, Vijan S. *Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem*. Ann Intern Med 2006;145;520-30
14. Wenger N, Lewis S, Welty F, et al. *Beneficial effects of aggressive low-density lipoprotein cholesterol lowering in women*. Heart 2008;94:434-39
15. Abd T, Jacobson T. *Statin-induced myopathy: a review and update*. Expert Opin Drug Saf 2011;10:373-87
16. Savovic J, Jones H, Altman D, et al. *Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials*. Ann Intern Med 2012;157:429-38
17. Wood L, Egger M, Gluud L, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 2008;336:601-5