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. 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)].

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.

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), or LDL-cholesterol lowering equivalent doses of other statins.

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 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, TNT, SEARCH) 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 (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.

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 (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 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.
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], ARR 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.

References

Table: Effect of high dose versus standard dose statins

<table>
<thead>
<tr>
<th>Outcome</th>
<th>#Participants</th>
<th>RR [95% CI]</th>
<th>ARR/ARI a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mortality</td>
<td>30,953</td>
<td>0.99</td>
<td>--</td>
</tr>
<tr>
<td>Total Mortality: Men</td>
<td>8,099</td>
<td>0.95</td>
<td>--</td>
</tr>
<tr>
<td>Total Mortality: Women</td>
<td>1,902</td>
<td>1.32</td>
<td>--</td>
</tr>
<tr>
<td>Total Serious Adverse Events</td>
<td>12,064</td>
<td>1.00</td>
<td>--</td>
</tr>
<tr>
<td>Non-Fatal Myocardial Infarction</td>
<td>30,953</td>
<td>0.83</td>
<td>1.2%</td>
</tr>
<tr>
<td>Non-Fatal Myocardial Infarction: Men</td>
<td>8,099</td>
<td>0.80</td>
<td>1.3%</td>
</tr>
<tr>
<td>Non-Fatal Myocardial Infarction: Women</td>
<td>1,902</td>
<td>0.75</td>
<td>--</td>
</tr>
<tr>
<td>Withdrawals due to Adverse Effects</td>
<td>30,953</td>
<td>1.45</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

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], ARR 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.