A review of high-dose statin therapy: targeting cholesterol and inflammation in atherosclerosis

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Lipid lowering with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or 'statins' has dramatically reduced morbidity and mortality in patients with established cardiovascular disease. Recently, there have been multiple studies investigating the role of high-dose statin therapy with more aggressive lipid lowering in this setting. Concomitantly, there is increasing evidence implicating a role of inflammation in the pathogenesis of atherosclerosis. These high-dose statin trials and other studies have also provided a wealth of data suggesting that statins have anti-inflammatory and anti-oxidant properties that go beyond their lipid-lowering effects. In this review, we will provide a brief overview of recent, large-scale, randomized, placebo and active controlled trials of high-dose statin therapy in the setting of stable and unstable coronary artery disease and percutaneous coronary intervention. Further, we will discuss the evidence for effects of high-dose statin therapy on inflammation and C-reactive protein.

KEYWORDS
Coronary artery disease; 3-hydroxy 3-methylglutaryl CoA reductase inhibitors (statins); C-reactive protein; LDL

Introduction

The efficacy of statins in the primary and secondary prevention of cardiovascular events mediated by reduction in low-density lipoprotein cholesterol (LDL-C) has been well established.1–5 Meta-analyses of randomized trials have demonstrated dramatic reductions in major coronary events, cardiovascular morbidity, and all-cause mortality.6 However, these early trials excluded high-risk patients, such as those presenting with an acute coronary syndrome (ACS). Further, the benefits were demonstrated in patient populations with relatively high total cholesterol and LDL-C at the initiation of therapy [for example, mean total cholesterol of 261 mg/dL and LDL-C of 188 mg/dL in the Scandinavian Simvastatin Survival Study (4S)]. The Heart Protection Study (HPS) was the first to include patients with an LDL-C of <100 mg/dL. In this trial, over 20,000 patients with coronary or peripheral vascular disease or diabetes mellitus were randomized to simvastatin 40 mg daily vs. placebo, and significant reductions in all-cause mortality, cardiovascular mortality, vascular events, and stroke were demonstrated over a 5 year follow-up period. A novel finding of the study was the consistent, nearly 25% reduction in major vascular events across all levels of initial LDL-C including <100 mg/dL.7 Patients with a mean initial LDL-C <100 mg/dL level had attained a mean level of <70 mg/dL which led to calls for a re-appraisal of target LDL-C goals.8,9 This aggressive LDL-C lowering has been studied in multiple recently published trials of high-dose statin therapy. Here, we provide a narrative overview of randomized trials of high-dose statin therapy in patients with stable coronary artery disease, ACSs, and those undergoing percutaneous coronary intervention (PCI). In addition, we briefly discuss the role of statin-mediated modulation of inflammation as a possible mechanism underlying the benefit of this therapy. Subsequent analyses of these trials provide new data in this respect.

Search strategy and selection criteria

We searched the OVID Medline database for English language randomized controlled trials of high-dose statin therapy published from 1995 to 2006 in the various settings discussed previously. We used the medical subject heading terms 'hypercholesterolaemia', 'anticholesteremic agents', 'hydroxy-methylglutaryl-CoA reductase inhibitors', 'coronary disease', 'coronary arteriosclerosis', 'angina pectoris', 'angioplasty', and 'myocardial infarction'. Inclusion criteria were the following: (i) controlled clinical trials of high-dose statin therapy vs. placebo or active control, (ii) randomized treatment allocation, and (iii) clinical primary outcome measures. High-dose statin therapy was defined as allocation of the active treatment arm to the highest currently approved dose of the particular statin used in the trial. Studies were excluded if they did not meet the primary inclusion criteria or if they included clinical outcome data but not as a primary endpoint. The search strategy and results are displayed in Figure 1.
High-dose statin therapy in stable coronary artery disease

Atorvastatin vs. Revascularization Treatment trial—1999

The Atorvastatin vs. Revascularization Treatment (AVERT) trial studied the effects of the 80 mg dose of atorvastatin in patients with stable coronary disease who were asymptomatic or had mild-to-moderate angina and were referred for PCI (Table 1). Pitt et al.\textsuperscript{10} randomized a total of 341 patients to atorvastatin or to undergo the recommended intervention and be treated with usual medical therapy which could include lipid-lowering therapies. The primary endpoint was a composite of ischaemic events including cardiac death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI), cerebrovascular accident, coronary bypass or angioplasty, and worsening angina.

After 18 months of follow-up, a 36% ($P = 0.048$, not statistically significant after adjustment for interim analysis) reduction in ischaemic events was observed in the atorvastatin group. This finding was largely driven by reduced revascularization procedures and hospitalizations for worsening angina. Time to an ischaemic event was also significantly longer in the atorvastatin arm. However, as the AVERT trial was not blinded, the degree of benefit is subject to bias.

Treating to New Targets trial—2005

The Treating to New Targets (TNT) trial was the first large-scale randomized trial to investigate the effects of 80 mg of atorvastatin in a population of patients with stable coronary artery disease and moderately elevated LDL-C. LaRosa et al.\textsuperscript{11} sought to determine whether aggressive LDL-C lowering with high-dose therapy would provide incremental benefit over moderate dose therapy. The investigators randomized 10 001 patients with stable coronary artery disease to atorvastatin 80 mg or 10 mg and followed them for a median of 4.9 years. Prior to randomization, study subjects were enrolled in an 8 week run-in period which permitted open-label treatment with atorvastatin 10 mg to ensure that then-current guidelines for LDL-C were met, a unique feature of this trial. The primary endpoint was a composite of coronary death, non-fatal MI, resuscitated cardiac arrest, or stroke.

The investigators observed a 22% reduction in the primary endpoint in the atorvastatin 80 mg arm (Table 1). The individual components of non-fatal MI [hazard ratio (HR) 0.78; 95% confidence interval (CI) 0.66–0.93, $P = 0.004$] and stroke (HR 0.75; 95% CI 0.59–0.96, $P = 0.02$) were also reduced. Of some concern, however, was that all-cause mortality was not reduced largely because of the unexpected finding of an excess of non-cardiovascular death in the high-dose arm. This difference nearly reached statistical significance.
(HR 1.25, \( P = 0.06 \)). As this trend had not been seen in previous moderate-to-high-dose statin trials in other patient populations, the authors attributed this finding to chance.

**Incremental Decrease in End Points through Aggressive Lipid Lowering trial—2005**

The Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trial, which recruited patients in Northern Europe, was similar to TNT in that 80 mg of atorvastatin was studied in patients with stable coronary artery disease.\(^{12}\) A total of 8888 patients with a history of definite MI and who met guidelines for statin therapy were randomized to atorvastatin 80 mg or simvastatin 20 mg and followed for a median of 4.8 years. The trial used an open-label blinded endpoint design. The primary outcome measure was a composite of coronary death, non-fatal MI, or revascularized cardiac arrest.

Although Pedersen et al.\(^ {12}\) observed no difference in the primary endpoint between the two groups, they found a 17% (HR 0.83; 95% CI 0.78–0.91, \( P = 0.02 \)) reduction in non-fatal MI and 23% (HR 0.77; 95% CI 0.69–0.86, \( P = 0.02 \)) reduction in coronary revascularization in patients randomized to atorvastatin (Table 1). Notably, no trend in increased non-cardiovascular deaths in the atorvastatin arm was observed, strengthening the TNT investigators’ contention regarding the finding in their trial.

**High-dose statin therapy in ACSs**

**Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial—2001**

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial was the first large-scale study to investigate high-dose atorvastatin therapy in the ACS setting (Table 2).\(^ {13}\) The trial randomized 3086 patients with unstable angina or non-Q-wave MI to atorvastatin 80 mg or placebo within 24–96 h of presentation. The primary endpoint was a composite of death, non-fatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischaemia over a follow-up period of 16 weeks.

Schwartz et al.\(^ {13}\) observed a 16% reduction in the primary endpoint in the atorvastatin arm which was largely driven by a reduction in recurrent symptomatic ischaemia (HR 0.74; 95% CI 0.57–0.95) (Table 2). A reduction in stroke was also observed (HR 0.50; 95% CI 0.26–0.99).

**Fluvastatin On Risk Diminishment after Acute Myocardial Infarction trial—2002**

The Fluvastatin On Risk Diminishment after Acute Myocardial Infarction (FLORIDA) trial randomized 540 patients to fluvastatin 80 mg daily or placebo within 14 days of acute MI. The primary endpoint of the trial was a composite of ischaemia on ambulatory ECG monitoring at 12 months or the occurrence of a major clinical event including death, recurrent MI, or revascularization during the study. No effect of fluvastatin on ischaemia or clinical events was detected over the period of the study, although as pointed out by the authors, the trial was underpowered. The results were therefore difficult to interpret, although a post hoc analysis revealed a trend towards a reduction in the primary endpoint in patients with pronounced ischaemia at trial onset.\(^ {14}\) Notably, the reduction in LDL-C in the fluvastatin arm was quite modest when compared with the active therapy arms of the other ACS trials (Table 2).

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**Table 1 Clinical trials in stable coronary artery disease**

<table>
<thead>
<tr>
<th>Trial</th>
<th>AVERT</th>
<th>TNT</th>
<th>IDEAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of publication</td>
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<td>2005</td>
<td>2005</td>
</tr>
<tr>
<td>Number of patients</td>
<td>341</td>
<td>10,001</td>
<td>8888</td>
</tr>
<tr>
<td>Treatment arms</td>
<td>Atorvastatin-80 vs. usual care</td>
<td>Atorvastatin-80 vs. Atorvastatin-10</td>
<td>Atorvastatin-80 vs. Simvastatin-20</td>
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<tr>
<td>Follow-up period</td>
<td>18 months</td>
<td>4.9 years (median)</td>
<td>4.8 years (median)</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Clinical</td>
<td>Composite(^ {ab} )</td>
<td>Composite(^ {ac} )</td>
</tr>
<tr>
<td>Baseline LDL-C (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>3.69</td>
<td>2.51</td>
<td>3.14</td>
</tr>
<tr>
<td>Placebo/moderate dose</td>
<td>3.75</td>
<td>2.53</td>
<td>3.14</td>
</tr>
<tr>
<td>%Change in LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>−46</td>
<td>−20.6(^ {d} )</td>
<td>−33.3</td>
</tr>
<tr>
<td>Placebo/moderate dose</td>
<td>−18</td>
<td>3.1(^ {d} )</td>
<td>−14.3</td>
</tr>
<tr>
<td>Primary endpoint events (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>22</td>
<td>434 (8.7)</td>
<td>411 (9.3)</td>
</tr>
<tr>
<td>Placebo/moderate dose</td>
<td>37</td>
<td>548 (10.9)</td>
<td>463 (10.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>36(^ {e} ) RRR(^ {e} )</td>
<td>0.78 (0.69–0.89)</td>
<td>0.89 (0.78–1.01)</td>
</tr>
<tr>
<td>( P = 0.048 )</td>
<td>( P &lt; 0.001 )</td>
<td>( P = 0.07 )</td>
<td></td>
</tr>
</tbody>
</table>

\(^ {a}\)Cardiac death, resuscitated cardiac arrest, non-fatal MI, cerebrovascular accident, CABG, PTCA, or angina requiring hospitalization.  
\(^ {b}\)Coronary death, non-fatal MI, or stroke.  
\(^ {c}\)Time to first occurrence of coronary death, non-fatal MI, or resuscitated cardiac arrest.  
\(^ {d}\)Change in LDL is from time of randomization until end of trial (after run-in phase where some patients were treated with open-label atorvastatin).  
\(^ {e}\)RRR, relative risk reduction. To convert values of LDL-C to mg/dL, multiply by 38.67.
**Aggrastat to Zocor trial—2004**

Phase Z of the Aggrastat to Zocor (A to Z) trial compared an aggressive with a more moderate and delayed dosing strategy of simvastatin in patients presenting with an ACS.\(^{15}\) Within 5 days of presenting with ACS, 4497 patients were randomized to either simvastatin 40 mg for 1 month followed by 80 mg or placebo for 4 months followed by simvastatin 20 mg. The primary endpoint was a composite of cardiovascular death, non-fatal MI, re-admission for ACS, and stroke. The median follow-up period was 721 days (24 months).

De Lemos et al.\(^ {15}\) found no difference in the occurrence of the primary endpoint between the two groups (Table 2). Likewise, none of the components of the primary endpoint was reduced except for cardiovascular death (HR 0.75; 95% CI 0.57–1.00). However, in a post hoc analysis, from 4 months until the end of the trial period, the authors reported a 25% reduction (HR 0.75; 95% CI 0.60–0.95) in the primary endpoint in the simvastatin 40/80 mg arm.

<table>
<thead>
<tr>
<th>Table 2 Clinical trials in ACSs</th>
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<tbody>
<tr>
<td><strong>Trial</strong></td>
</tr>
<tr>
<td>Year of publication</td>
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<tr>
<td>Number of patients</td>
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<tr>
<td>Treatment arms</td>
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<tr>
<td>Follow-up period</td>
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<tr>
<td>Baseline LDL-C (mmol/L)</td>
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<tr>
<td>Placebo/moderate dose</td>
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<tr>
<td>%Change in LDL-C</td>
</tr>
<tr>
<td>Placebo/moderate dose</td>
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<tr>
<td>Baseline C-reactive protein (mg/L)</td>
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<tr>
<td>Placebo/moderate dose</td>
</tr>
<tr>
<td>%Change in C-reactive protein</td>
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<tr>
<td>Placebo/moderate dose</td>
</tr>
<tr>
<td>Primary endpoint events (%)</td>
</tr>
<tr>
<td>Placebo/moderate dose</td>
</tr>
<tr>
<td>HR (95% CI)</td>
</tr>
</tbody>
</table>

\(^ a\)Death, non-fatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischaemia.

\(^ b\)Presence of ischaemia on ambulatory ECG monitoring or a major clinical event (cardiovascular or non-cardiovascular death, recurrent MI, or recurrent ischaemia with hospitalization or revascularization).

\(^ c\)Cardiovascular death, non-fatal MI, re-admission for ACS, and stroke.

\(^ d\)Death from any cause, MI, documented unstable angina requiring rehospitalization or revascularization, and stroke.

\(^ e\)Data presented as risk ratio.

\(^ f\)Calculated relative risk reduction.

**Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trial—2005**

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial sought to determine whether there was incremental benefit of reducing LDL-C levels to ~70 mg/dL compared with moderate pravastatin therapy with the more traditional goal of 100 mg/dL in patients presenting with an ACS. Cannon et al.\(^ {16}\) randomized 4162 patients presenting within 10 days of an ACS to atorvastatin 80 mg or pravastatin 40 mg and followed them for a mean of 24 months. The primary endpoint was the time from randomization to occurrence of death, MI, unstable angina, or revascularization.

The investigators observed a significant 16% reduction of the primary endpoint in the atorvastatin arm (Table 2). Among the individual components of the primary endpoint, revascularization (HR 0.86; \(P = 0.04\)) and recurrent unstable angina (HR 0.71; \(P = 0.02\)) were also reduced. Further, Ray et al.\(^ {17}\) recently performed a time-to-benefit analysis and demonstrated improvement in clinical outcomes as early as 30 days after randomization along with persisting long-term reductions in clinical events.

**High-dose statin therapy in PCI**

**Fluvastatin Angioplasty Restenosis trial—1999**

The Fluvastatin Angioplasty Restenosis (FLARE) trial was designed to examine the effect of high-dose statin therapy on the occurrence of restenosis following percutaneous trans-luminal coronary angioplasty (PTCA) without stenting. Serruys
et al.\textsuperscript{18} randomized 1054 patients to fluvastatin 40 mg twice daily or placebo starting 2–4 weeks prior to planned PTCA and continuing until follow-up angiography (~26 weeks). The primary outcome measure was angiographic restenosis, although clinical outcomes at 40 weeks were also assessed.

Although the investigators observed no difference in the primary outcome, a 63% reduction in death or non-fatal MI was observed [relative risk (RR) 0.37; 95% CI 0.18–0.89, \( P = 0.025 \)].\textsuperscript{18} To confirm these provocative findings, the investigators subsequently conducted the Lescol Intervention Prevention Study (LIPS) trial.

### LIPS—2002

The LIPS trial examined high-dose statin therapy in patients with stable or unstable coronary syndromes or silent ischaemia undergoing PCI. Serruys et al.\textsuperscript{19} randomized 1677 patients within days after first successful PCI with normal-to-moderately elevated total cholesterol to fluvastatin 80 mg or placebo. The primary outcome measure was a composite of cardiac death, non-fatal MI, or repeat revascularization procedure (PCI or CABG).

After a median follow-up period of 3.9 years, the investigators observed a 22% reduction in the primary endpoint in patients randomized to high-dose fluvastatin (RR 0.78; 95% CI 0.64–0.95, \( P = 0.01 \)). This reduction remained after restenosis events were excluded from the primary endpoint (RR 0.67; 95% CI 0.54–0.84).

Consistent with these findings, Chan et al.\textsuperscript{20,21} demonstrated a significant reduction in peri-procedural MI and a mortality benefit associated with statin therapy prior to PCI for stable or unstable coronary disease (excluding ST-elevation MI) in a large registry. The survival benefit predominated in patients with elevated baseline C-reactive protein levels implicating inflammation as an important determinant of outcome in this patient population.\textsuperscript{21}

### High-dose statin therapy, atherosclerosis, and inflammation

The role of inflammation in the pathogenesis of atherosclerotic coronary disease has been extensively investigated over the last 15 years.\textsuperscript{22–25} Indeed, there is at least some evidence to implicate inflammation in each step of the atherosclerotic process, from fatty streak formation to plaque progression and rupture (Figure 2). Among the numerous circulating inflammatory biomarkers that have been found to be variably predictive of cardiovascular events, the most extensively studied and controversial has been the acute-phase reactant high-sensitivity C-reactive protein.\textsuperscript{26,27} Multiple studies, including several meta-analyses, have demonstrated C-reactive protein to be an independent predictor of cardiovascular risk.\textsuperscript{28,29} Further, recent laboratory studies of intravenous C-reactive protein infusion in animal models and human volunteers demonstrated increased inflammation and atherosclerosis and activation of coagulation, providing evidence for a direct role of C-reactive protein in the pathogenesis of coronary artery disease.\textsuperscript{30,31}

Statins have been recognized to have anti-inflammatory and antioxidant properties, and it has been suggested that these so-called ‘pleiotropic’ effects may account for some of the benefits of statins beyond LDL-C lowering alone.\textsuperscript{32–35} Recent studies have shown that statins reduce inflammatory macrophage cell growth within atherosclerotic plaques, decrease superoxide production from NAD(P)H oxidase (nox1) in vascular smooth muscle cells, and increase

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**Figure 2** The role inflammation in the pathogenesis of coronary artery disease and ACSs. RAC and Rho, G-protein subunits; RA 1, Rap-activated 1; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.
endothelial nitric oxide production. In addition, they promote potent systemic anti-inflammatory effects by inhibiting the isoprenylation and translocation of Rac, a key subunit of the NAD(P)H oxidase complex that catalyses the production of superoxide (Figure 1).

The impact of statin therapy on C-reactive protein and cardiovascular morbidity and mortality was first demonstrated by Ridker et al. in analyses of the Cholesterol and Recurrent Events (CARE) and Air Force/Texas Coronary Atherosclerosis Prevention Studies (AFFCAP/TexCAPS) as well as the prospective randomized Pravastatin Inflammation/CRP Evaluation (PRINCE) trial. These studies demonstrated reductions in C-reactive protein which were largely independent of changes in lipid levels in patients treated with lovastatin (14.8%; 95% CI 12.5–17.4, \( P < 0.001 \)) or pravastatin (13.8%, 95% CI not reported, \( P < 0.001 \)). More importantly, these trials suggested that the benefit of statin therapy may extend to patients with low total and LDL-C but heightened inflammatory state as measured by C-reactive protein.

A number of clinical trials discussed in this review have provided additional data on high-dose statin therapy and C-reactive protein. The MIRACL trial demonstrated a reduction in C-reactive protein (74%; 95% CI 71–75, \( P < 0.001 \)), independent of initial LDL-C in the high-dose atorvastatin group. In a recently reported pre-specified analysis of the A to Z trial, lower levels of achieved C-reactive protein at 30 days and 4 months were found to be independently correlated with improved long-term survival. Indeed, patients with high-sensitivity C-reactive protein > 3 mg/L were at more than three-fold higher risk of death (HR 3.7; 95% CI 1.9–7.2), although those with high-sensitivity C-reactive protein of 1–3 mg/L were at greater than two-fold higher risk of death (HR 2.3; 95% CI 1.2–4.6) when compared with achieving hsCRP < 1 mg/L. This was more likely to be achieved in the aggressive dosing simvastatin arm than in the conservative arm. In subanalyses of the PROVE IT trial, it was demonstrated that patients who achieved lower C-reactive protein levels regardless of achieved LDL-C had better clinical outcomes than those with elevated C-reactive protein. Further, lower C-reactive protein levels were more often achieved with intensive atorvastatin therapy regardless of the presence of other risk factors (Table 3).

### Safety of high-dose statin therapy

Safety concerns surrounding high-dose statin therapy centre on the traditional liver- or skeletal muscle-related disturbances seen at low rates with moderate-dose statin therapy, in addition to potential new risks related to ultralow cholesterol and LDL-C levels. With the publication of these major clinical trials, along with previously published data and ongoing trials, there is now a substantial body of evidence to address these safety concerns. Atorvastatin has been the most extensively studied at high doses and so possesses the most data regarding safety and adverse effects, as summarized recently by Waters.

The incidence of hepatic enzyme elevation (defined as ALT or AST > 3 x the upper limit of normal) in patients treated with high-dose atorvastatin, simvastatin, or fluvastatin in major trials is ~0.5–3%. High-dose atorvastatin likely has slightly higher rates as seen in the IDEAL trial, and in a randomized head-to-head efficacy and safety trial against simvastatin. Discontinuation or dose reduction of the offending statin usually results in prompt resolution of the enzyme elevations.

The incidence of myopathy (defined as creatine kinase elevation of > 10 x upper limit of normal with muscle-related symptoms) and frank rhabdomyolysis in controlled clinical trials employing the use of high-dose statin therapy is rare. In nearly 12 000 patients encompassing over 40 trials of high-dose atorvastatin, there were only two cases of myopathy, whereas no cases of myopathy have been reported in controlled trials of high-dose fluvastatin. In contrast, high-dose simvastatin therapy seems to be associated with a perceptible increase, although small, in the risk of myopathy. In nearly 4000 patients in controlled trials of high-dose simvastatin, including A to Z, there were 16 cases of myopathy (0.4%), including three cases of rhabdomyolysis. The ongoing Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) secondary prevention trial of simvastatin 80 mg vs. simvastatin 20 mg in over 12 000 patients

### Table 3 Changes in LDL and C-reactive protein in randomized trials of high-dose statin therapy

<table>
<thead>
<tr>
<th>Trials</th>
<th>Baseline</th>
<th>1 month</th>
<th>3–4 months</th>
<th>Final (8–24 months)</th>
<th>Arms</th>
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<tbody>
<tr>
<td>MIRACL</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>11</td>
<td>–</td>
<td>2.9</td>
<td>–</td>
<td>Placebo</td>
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<tr>
<td>LDL (mmol/L)</td>
<td>3.21</td>
<td>–</td>
<td>3.49</td>
<td>–</td>
<td>Placebo</td>
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<td>A to Z Trial</td>
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<td>PROVE IT-TIMI-22</td>
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<tr>
<td>C-reactive protein (mg/L)</td>
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<td>2.3</td>
<td>2.1</td>
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<td>Pravastatin-40</td>
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<tr>
<td>LDL (mmol/L)</td>
<td>2.74</td>
<td>–</td>
<td>–</td>
<td>1.60</td>
<td>Atorvastatin-80</td>
</tr>
</tbody>
</table>

To convert values of LDL-C to mg/dL, multiply by 38.67.
should more definitively answer questions regarding the safety concerns surrounding high-dose simvastatin.  

Epidemiological and animal studies have suggested a link between low total cholesterol levels and risk for retinal and optic nerve damage, haemorrhagic stroke, and mortality.  

As a substantial proportion of patients treated with high-dose statin therapy will reach LDL-C levels far below 70 mg/dL, these potential hazards have come to the forefront. The IDEAL trial, along with recent analyses of the PROVE IT and TNT trials, has demonstrated no increase in the risk of these adverse events associated with ultra-low LDL-C levels. 

Data from the SEARCH trial will provide further insight regarding these potential side effects.

Discussion

The clinical trials discussed in this review provide substantial support for the institution of high-dose statin therapy in various clinical settings in the secondary prevention of coronary events. Two recent meta-analyses of high-dose statin trials have been able to quantify the benefit. Cannon et al., in a meta-analysis of high-dose statin trials including TNT, IDEAL, PROVE IT, and A to Z, demonstrated a 16% reduction in coronary death or MI with high-dose compared with moderate-dose statin therapy. Further, Bavry et al., in an analysis of high-dose statin therapy in the setting of ACS, demonstrated a 22% reduction in all-cause mortality, as well as a 25% reduction in cardiovascular mortality. Concomitantly, they provide insight into the contributions of atherogenic lipoproteins and inflammation to atherosclerotic plaque burden through analysis of statin-mediated effects on these parameters. The data linking inflammation and oxidative damage with coronary artery disease and ACSs are now mounting. Currently, C-reactive protein remains the most extensively studied marker of inflammation in coronary disease and adds incremental predictive power to traditional risk factors in predicting adverse cardiac events. Additionally, after weight loss, exercise, and smoking cessation, statins remain the best therapeutic option to mitigate inflammation in coronary artery disease. Despite this evidence, the role of inflammation, C-reactive protein, and the pleiotropic effects of statins remains quite controversial. In a recent meta-regression analysis of LDL-C-lowering trials, cardiovascular risk reduction in these trials was felt to be attributable to lipid lowering alone and not to the pleiotropic effects of statins.

The ongoing 15 000 patient Rosuvastatin in the Primary Prevention of Cardiovascular Disease Among Patients With Low Levels of Low-Density Lipoprotein Cholesterol and Elevated High-Sensitivity C-Reactive Protein (JUPITER) trial will hopefully add a wealth of data to help understand better the roles and interplay of inflammation, C-reactive protein, statins, and coronary artery disease.

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Rare coronary anomaly coexisting with atrial septal defect: contraindication to Amplatzer occluder implantation

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A 39-year-old man presented with a history of gradually progressing exertional dyspnoea. He had 2/6 systolic murmur in the second left intercostal space. ECG revealed right bundle branch block. Transthoracic echocardiography showed ostium secundum atrial septal defect (ASD) with pulmonary to systemic flow ratio of 2.5. Right ventricular systolic pressure was 47 mmHg. Prior to planned ASD closure with an Amplatzer occluder transoesophageal echocardiography (TEE) was performed (Panels A and B).

TEE confirmed the presence of ASD II. The size of the defect assessed with 3D reconstruction was 2 × 3 cm. The anatomy of interatrial septum was considered suitable for Amplatzer implantation. However, atypical linear echo-free space was noted by aortic root next to the ASD. Detailed evaluation revealed that it was most probably anomalous right coronary artery (RCA) originating from left circumflex artery (LCx) and surrounding the aortic root between the non-coronary sinus of Valsalva, the atra, and interatrial septum (Panel A).

Anomalous origin of the RCA from proximal segment of LCx was confirmed with 64-slice multislice computed tomography (MSCT) (Panel C). RCA was coursing very close to the ASD (Panel D).

Coronary angiography is not routinely performed prior to ASD closure in young persons without history of coronary artery disease. If the coronary anomaly was missed in the TEE study, the anomalous RCA could be compressed by the Amplatzer occluder, causing myocardial ischaemia or even infarction. Such complication was previously described in the literature. The patient was referred for surgical ASD closure. The surgeon was informed on the course of RCA and safely placed the sutures leaving the artery intact.

In conclusion, physicians performing TEE evaluation in ASD patients should be aware of this very rare but potentially dangerous coronary anomaly. In our opinion, in such a case, surgical strategy of ASD closure should be recommended.

Panel A. TEE showing the abnormal linear echo-free structure (RCA) located very close to the ASD.
Panel B. Three-dimensional TEE reconstruction. View from the left atrium (LA). Interatrial septum with large ASD is seen.
Panel C. MSCT. Reconstruction of the coronary arteries confirms abnormal RCA origin from the left coronary artery (LCA).
Panel D. MSCT slice showing RCA located close to the ASD.