Review

Which is the best statin for the postoperative coronary artery bypass graft patient?

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Summary

The progression of atherosclerosis following coronary artery bypass graft (CABG) surgery results in the need for re-vascularisation therapy in a significant proportion of patients. It is well recognised that this risk can be lowered by controlling the level of low-density lipid cholesterol (LDL-C) which can be achieved easily and safely with the use of statins. The choice of which is the best statin in post-CABG patients remains unclear. It has been shown that for milligram-equivalent doses, rosuvastatin provides the greatest LDL-C reduction and greatest number of patients achieving LDL-C targets in comparison with simvastatin and atorvastatin. Rosuvastatin’s superiority over other statins in allowing patients to reach LDL-C targets has been maintained in ‘real-world’ observational studies. Rosuvastatin has also been shown to increase high-density lipid cholesterol (HDL-C) by greater proportions in comparison with other statins, providing increased anti-atherogenic effects. There are several statins currently available, some of which are now generic. However, the empirical use of generic statins does not necessarily translate into a cost-effective treatment option. This article reviews the rationale for lipid-lowering therapy in patients following CABG. We also look objectively at which is the best statin for use in the post-CABG patient, discussing effectiveness, cost and tolerability.

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1. Introduction

Coronary artery bypass graft (CABG) surgery has been a major advance in the treatment of coronary heart disease (CHD) over recent decades. It is now the most commonly performed major operation in the USA, with over 500,000 patients undergoing the procedure each year [1]. Unfortunately, due to the progression of atherosclerosis in saphenous vein grafts (SVGs), nearly one-quarter of patients 12 years after the initial operation require further re-vascularisation therapy (surgical or percutaneous) [2]. At 12 years Post-CABG, up to 60% of SVGs are occluded and only 50% of patent grafts are free from significant stenosis [3]. Elevated low-density lipoprotein cholesterol (LDL-C) is an important causative factor [4].

The Post Coronary Artery Bypass Graft Trial demonstrated that SVG disease progression can be significantly reduced with aggressive lipid-lowering therapy [5]. Treating hyperlipidaemia is both safe and easy with the use of HMG-CoA inhibitors (statins) [6]. A target LDL-C level of <100 mg dl−1 can be easily achieved with statin monotherapy [7]. There are now several brands of statins available on the market, of which some are generic. The choice of which is the best statin to use in high-risk patients remains a contentious issue.

This article aims to review the literature to determine which is the best statin to use in the postoperative CABG patient. We intend to look at effectiveness, cost and tolerability. References were selected through the use of Pubmed and Medline databases using appropriate search terms. The authors have no affiliations or financial support with the pharmaceutical industry, nor any conflicts of interest to disclose.

2. Statins

Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis. They have been shown to have the greatest lipid-lowering effects and benefits on morbidity and mortality [8–12]. Commonly used statins include simvastatin, atorvastatin, pravastatin and rosuvastatin.

3. Lipid targets

The importance of reducing cholesterol levels for the prevention of CHD is well recognised by both European and US...
The guidelines recommend an LDL-C level of <115 mg dl⁻¹ (3.0 mmol l⁻¹) in Europe. This corresponds to a total cholesterol level of <190 mg dl⁻¹ (5.0 mmol l⁻¹). In the United States, the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) has set a target of <100 mg dl⁻¹ (2.6 mmol l⁻¹) for LDL-C [5].

In the UK, the National Institute for Health and Clinical Excellence (NICE) recommends that both the primary and secondary prevention of CHD should be initiated with simvastatin 40 mg day⁻¹. In people taking statins for secondary prevention, NICE advocates increasing simvastatin to 80 mg day⁻¹ (or a drug of similar acquisition, cost and efficacy) if a total cholesterol of <4 mmol l⁻¹ or LDL <2 mmol l⁻¹ is not attained [14].

Often aggressive treatment is required to achieve lipid targets. For example, a patient with an LDL-C of 140 mg dl⁻¹ (3.6 mmol l⁻¹) will require a 29% reduction to achieve the NCEP target of <100 mg dl⁻¹ (2.6 mmol l⁻¹) [15]. The various statins have a wide range of lipid-lowering ability (Table 1). Dose titration to achieve target is also required, yet it is well documented in the literature that this seldom occurs [16].

### 4. Beneficial effects of lipid lowering following bypass

#### 4.1. SSSS and LIPID

The Scandinavian Simvastatin Survival Study (SSSS) and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial suggest a benefit below a therapeutic level of 125–130 mg dl⁻¹ of LDL-C, with diminishing gain below this level reflecting a curvilinear relationship [8,12]. Other studies have shown that aggressive treatment with a target level below 100 mg dl⁻¹ results in significantly improved outcomes following CABG [17].

#### 4.2. Post CABG Trial

The Post Coronary Artery Bypass Graft Trial is the only large randomised study of statins specifically designed to report on patients after CAGB. It was shown that patients treated aggressively with statins (LDL-C target <100 mg dl⁻¹) compared to those treated moderately (LDL-C target <140 mg dl⁻¹) had disease progression in 29% and 39% of SVGs, respectively over the 4-year follow-up period. This corresponded to a 29% lower re-vascularisation rate in the aggressively treated group (6.5% vs 9.2%, respectively; p = 0.03). Low-dose warfarin did not reduce progression of atherosclerosis [5]. The NCEP in the US has set LDL-C targets in line with these results [18]. Lowering LDL-C to 92–97 mg dl⁻¹ has also been shown to reduce atherosclerosis in the left main coronary artery compared with a moderate reduction to 131–135 mg dl⁻¹ [19].

### 5. Which is the best statin?

#### 5.1. Reductions in LDL-C

Carotid intima-media thickness (IMT) as measured with \( \beta \)-ultrasound has been well documented to be predictive of atherosclerotic disease and future coronary events [20,21]. The effects of the Atorvastatin and Simvastatin on Atherosclerotic Progression (ASAP) trial was designed to assess whether aggressive lipid lowering with atorvastatin 80 mg day⁻¹ as opposed to simvastatin 40 mg day⁻¹ could slow or reverse atherosclerotic progression. At 1 year, the mean carotid IMT was significantly reduced in the atorvastatin group, while progression was seen in the simvastatin group. The LDL-C and total cholesterol levels showed significantly greater reductions in the atorvastatin group. The HDL-C levels were seen to increase by approximately 13% in both groups [22].

A post hoc analysis from the Treating to New Targets (TNT) trials looked at whether benefit could be gained from intensive LDL-C lowering in post-CABG patients. Aggressive reductions in LDL-C to 79 mg dl⁻¹ with 80 mg day⁻¹ atorvastatin was shown to reduce cardiovascular events (cardiac death, non-fatal myocardial infarction, resuscitated cardiac arrest or stroke) by 29% and the need for repeat re-vascularisation by 30%, compared with less-intensive cholesterol lowering to a mean of 101 mg dl⁻¹ with simvastatin 10 mg day⁻¹ (Fig. 1). Total mortality however did not differ between the two groups. This was the result of reduced cardiac death but increased non-cardiac death in the 80-mg day⁻¹ group [23].

A Canadian study compared the cost-effectiveness of the most commonly prescribed statins (rosuvastatin 10–40 mg, atorvastatin 10–80 mg, pravastatin 10–40 mg and simvastatin 10–80 mg). It showed that for milligram-equivalent doses, rosuvastatin provides the greatest LDL-C reduction and greatest number of patients achieving LDL-C targets [6].

### Table 1

<table>
<thead>
<tr>
<th>Statin</th>
<th>Starting dose (mg)</th>
<th>Mean change from baseline LDL-C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10</td>
<td>−38</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10</td>
<td>−28</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10</td>
<td>−19</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>20</td>
<td>−29</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20</td>
<td>−17</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Kaplan–Meier curves for a combination of the primary end point or for coronary re-vascularisation [23].
Rosuvastatin’s superiority over other statins in allowing patients to reach LDL-C targets has been maintained in ‘real-world’ observational studies [24].

The Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin ( STELLAR ) trial findings also support that rosuvastatin is more efficacious than milligram-equivalent doses of other statins in both lowering LDL-C levels and in enabling patients to achieve NCEP ATP III LDL-C goals. In this analysis, the highest proportion of patients who achieved the European goal of LDL $<$115 mg dL$^{-1}$ ($<$3.0 mmol l$^{-1}$) were in the rosuvastatin (20 mg and 40 mg) groups (92% and 91%, respectively). The percentage of patients who met this target with the lower dose of rosuvastatin (10 mg) was similar to those on simvastatin (80 mg) and atorvastatin (80 mg) (79% vs 77% or 81%, respectively) [25].

In a retrospective analysis, Ohsfeldt et al. [26] looked at percent reductions in LDL-C, achievement of NCEP ATP III goals, treatment costs and cost-effectiveness of patients with CHD on atorvastatin, simvastatin or rosuvastatin. The majority of patients taking rosuvastatin were on 10 mg (87%), atorvastatin 10 mg (68%) and simvastatin 20 mg (57%). The mean starting dose of rosuvastatin was 10 mg, whereas the average starting dose of atorvastatin and simvastatin was 14 mg and 25 mg, respectively. NCEP ATP III guidelines recommend a target of $<$100 mg dL$^{-1}$ for high-risk patients and $<$70 mg dL$^{-1}$ for very high-risk patients (i.e., patients with cardiovascular disease and diabetes, acute coronary syndromes, etc.). Adjusted for baseline factors, the percentage of patients achieving both of these targets was significantly higher in the rosuvastatin group compared to the simvastatin and atorvastatin groups (Table 2). The smaller number of patients on rosuvastatin in this trial was expected as the study period involved market introduction of the drug. Further studies with larger numbers may be used to confirm such findings in the future.

A pooled analysis from large sets of data have shown that at starting doses of statins, rosuvastatin 10 mg has the greatest ability in allowing patients to reach both NCEP ATP III and European targets, regardless of risk category, in comparison with simvastatin 20 mg and pravastatin 20 mg (Fig. 2). As rosuvastatin significantly allows greater number of patients to achieve target levels at starting doses, the absence for the need for titration is clearly favourable [27].

Switching statins may be necessary to allow patients to reach LDL-C targets and gain further reductions in LDL-C levels. Changing from atorvastatin to rosuvastatin has been shown to help achieve the greatest percent reduction in LDL-C levels. Such a change may be necessary when greater percent reductions are required to meet individual patient care needs [13].

HDL has well-known anti-atherogenic effects such as plaque stabilisation and reversal of LDL transport from the vessel wall back to the liver. There is a strong association between low HDL levels and progression of coronary heart disease [28]. Neitzel et al. [29] showed that HDL levels were significantly lower in patients who underwent repeat operation or died 6—12 years after CABG compared with a control group who did not require re-vascularisation during the same period. Rosuvastatin produces greater improvements in lipid profile by not only lowering LDL-C, but also increasing HDL-C in greater proportions in comparison to the other statins [25,30,31]. Higher doses of rosuvastatin have been shown to increase HDL-C. In contrast, a smaller percentage increase is seen with higher doses of atorvastatin.

5.2. Cost

Rosuvastatin had been shown to provide greater treatment effectiveness at lower treatment costs than atorvastatin and simvastatin for high-risk patients in clinical practice [26,32]. In a study by Ohsfeldt et al. published in 2006, annual treatment costs for the various statins were valued at $594 for rosuvastatin, $1050 for atorvastatin and $1545 for simvastatin. Thus rosuvastatin was more effective and less expensive than both branded prices of atorvastatin and generic prices of simvastatin.

The results from Ohsfeldt’s investigation are similar to the work by Benner et al. who found that rosuvastatin was less expensive and more effective than atorvastatin, simvastatin and pravastatin. Medical costs were calculated based on drug, physician and laboratory resource, which were then multiplied by the wholesale acquisition cost of the drug and the 2005 Medicare reimbursement rates for the service. Compared to the generic lovastatin, rosuvastatin offered substantial reductions in LDL-C, HDL-C improvement, and NCEP goal achievement and therefore considered this to be a cost-effective option for high-risk patients [32]. Their conclusion was consistent with that of Morrison and Glassberg who felt statin efficacy should be the major determinant of cost-effectiveness for high-risk patients where greater cholesterol lowering is required, whereas statin cost is more

![Fig. 2. Proportions of patients who received rosuvastatin (RSV) 10 mg, simvastatin (SIM) 20 mg, or pravastatin (PRA) 20 mg and achieved NCEP ATP III LDL-C goals at 12 weeks based on pooled data. *p < 0.001 vs RSV; †p < 0.05 vs RSV [27].](https://academic.oup.com/ejcts/article-abstract/36/4/628/518496/632)

### Table 2

<table>
<thead>
<tr>
<th>Statin</th>
<th>ATP III LDL-C &lt;100 mg/dL goal</th>
<th>ATP III optional LDL-C &lt;100 mg/dL for high-risk and &lt;70 mg/dL goal for very high-risk patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>69.7% (n = 60)</td>
<td>58.1% (n = 60)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>54.8% (n = 425)</td>
<td>43.4% (n = 444)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>51.2% (n = 201)</td>
<td>36.9% (n = 207)</td>
</tr>
</tbody>
</table>

LDL-C indicates low-density lipoprotein cholesterol; ATP III: Adult Treatment Panel III.

* $p < 0.05$. 

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important for those low-risk patients who only require limited lipid reductions [33].

It is important to make note that the separate works by Benner and Ohsfeldt were published in 2005 and 2006, respectively, and were based on ‘current prices’ at the time. Recent publications have suggested that use of generic simvastatin may contribute to significant decrease in drug expenditure for statins [14,25]. While it appears that rosvastatin is the most efficacious statin in milligram-equivalent doses, providing the greatest reductions in LDL-C, current pricing of generic simvastatin has resulted in the empirical prescription of high doses of this drug (40 mg or 80 mg) for the post-CABG patient in many centres. The authors could not locate any up-to-date research reviewing at the relative cost-effectiveness amongst the statins at current prices (2008–2009). Therefore, while prescribing generic statins may not have necessarily been a cost-effective treatment option in the past, whether this remains true today is unclear.

5.3. Side effects

The common recognised side effects of statin therapy include deranged liver function tests and reversible myositis. In one study, only half of patients discharged from hospital on a statin following CABG had LFTs performed within 6 months. None of this group of patients experienced adverse muscle-related affects [34]. In the TNT trial, atorvastatin 80 mg was tolerated both in the CABG patients and in the overall population. From almost 20,000 patients, the incidence of hepatic enzyme elevation > 3 x normal was 1.43% [23]. There is currently no evidence to suggest that there are differences in adverse event rates among the statins [35–38].

6. Under-utilisation

Despite beneficial clinical outcomes with the aggressive use of statins, it is well documented that under-utilisation is an endemic problem [34]. Even in high-risk patient groups evidence shows that dyslipidaemia is not treated as the guidelines suggest [39]. In a study of 146 consecutive CABG patients, postal questionnaire revealed that 37% of patients did not have their serum cholesterol checked during the 3-year period after CABG surgery. The majority of these patients (74%) had total cholesterol greater than 5.2 mmol l⁻¹ [40]. Delacretaz et al. found that only 38% of 245 consecutive CABG or percutaneous angioplasty patients with a total serum cholesterol of 6.2 mmol l⁻¹ or more were receiving lipid-lowering therapy. In comparison, 97% of these patients were receiving anti-platelet drugs [41]. Kulik et al. found that statins are considerably underused after CABG surgery. Although prescription rates were found to be increasing over recent years, usage was still noted to be suboptimal and did not correlate with risk of coronary artery disease. Factors associated with increased statin uptake included preoperative statin use, later year of operation and additional postoperative medications. Paradoxically, a lower rate of statin prescription was seen in those at risk for further vascular events, such as patients with diabetes mellitus and a history of stroke [42]. Similar under-utilisation of statin therapy was reported in a study of 31,750 Duke University patients by Newby et al. Only 44% of patients with coronary artery disease (treated medically, percutaneously or surgically) were treated consistently with lipid-lowering therapy [43]. It is also recognised that statin drugs are not titrated as recommended to reach goals based on both national and international guidelines [15].

A substantial increase in statin initiation at hospital discharge following CABG surgery has been seen with the implementation of a discharge protocol. One such study performed by Khandera et al. showed an increase in initiation of statins from 54% in the control group to 75% in the intervention group (p = 0.001). The data also showed a corresponding beneficial trend on target achievement on LDL-C in the protocol group versus the control group [34].

7. Conclusion

There is unquestionable proof of the benefits of lipid-lowering therapy following CABG. There are currently no observational or randomised controlled trials that have evaluated outcomes post-CABG with rosvastatin compared to other statins. Current literature shows that for milligram-equivalent doses of rosvastatin has the greatest ability in allowing more patients to reach LDL-C targets. Monitoring of LDL-C levels following CABG and dose titration of statins is currently performed poorly. As rosvastatin allows greater number of patients to achieve target levels at doses of 10 mg or less, the absence for the need for titration is clearly favourable. The true cost-effectiveness of prescribing generic statins at current prices remains unclear, and the authors feel this is an area for further research.

We would therefore recommend that as post-CABG patients are high risk and achievement of low levels of LDL-C is imperative, this patient group should be on statin therapy if tolerated and have regular lipid profiles performed. The prescriber should be aware of lipid goals set by national and international guidelines and be prepared to use high-dose statins, or switch to those statins with increased efficacy if monitoring of lipid levels shows that a patient is not meeting targets.

References


