Role of Statin Therapy in the Coronary Bypass Patient

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Statins have been proven to prevent or delay ischemic events in patients at risk for atherosclerotic coronary disease. Increasing evidence suggests that statin therapy is also beneficial to patients undergoing coronary revascularization. In this review statin therapy will be shown to improve vein graft patency, minimize recurrent ischemic events, and decrease the need for repeat revascularization procedures in patients who have undergone coronary artery bypass grafting.

As cardiac surgeons, we like to think that after a multivessel coronary artery bypass graft (CABG) procedure, we have prevented ischemic heart disease. However, as Grondin [1] reported in a landmark study nearly 20 years ago, atherosclerotic changes develop in the vein grafts of 45% of all CABG patients by 5 years, changes that lead to recurrent angina and acute coronary syndromes. Vein grafts are susceptible to the same changes seen in native coronary arteries, including injury to the endothelium, aggregation of platelets leading to thrombosis, and smooth muscle proliferation and migration resulting in hyperplasia and narrowing of the vessel lumen. Furthermore, progression of arteriosclerosis also occurs distal to the site of the vein graft anastomosis in 40% of patients [2]. Thus even after complete revascularization, long-term clinical outcomes are still determined by recurrence of arteriosclerosis in the vein graft and progression of disease in native coronary arteries.

Statins have been found in several studies to prevent or delay ischemic events in patients who are at higher risk for the development of arteriosclerosis [3–6]. The goal of this review is to examine the role of statin therapy in minimizing ischemic events in CABG patients. The contribution of hypercholesterolemia to the development of atherosclerotic plaque formation and endothelial dysfunction is discussed. Studies are cited to demonstrate the effects of statin therapy in the CABG patient, as well as patients with peripheral vascular disease and those undergoing percutaneous coronary revascularization and cardiac transplantation. Finally, recommendations are made for the role of the cardiac surgeon in initiating statin therapy for patients undergoing CABG procedures.

Relationship of Hypercholesterolemia to the Atherosclerotic Process

Hypertension, hypercholesterolemia, diabetes, and smoking are risk factors associated with changes in the vessel wall that are termed oxidative stress. Normal vascular endothelial function is dependent on a balance between nitric oxide (NO), which causes vasodilation, and superoxide radicals and angiotensin II, which lead to vasoconstriction [7]. During oxidative stress this balance is impaired, resulting in an increased availability of superoxide anions, which leads to a breakdown of NO. This results in abnormal flow-mediated endothelial vasodilation and hypertension. Ultimately, expression of adhesion molecules increases, resulting in increased leucocyte adhesion and increased production of plasmino-gen activator inhibitor 1 (PAI-1), resulting in acute inflammation, thrombosis, smooth muscle cell proliferation, and increased production of extracellular matrix [8]. This impaired endothelial function contributes to the formation of atherosclerotic plaques [9].

In addition to the relationship between hypercholesterolemia and plaque formation that results in the need for CABG procedures, hypercholesterolemia also impairs endothelial function, which occurs before plaque formation and may predict adverse clinic events. Endothelial vascular function can be assessed using techniques to measure flow-mediated brachial artery reactivity. The brachial artery is cannulated and following baseline measurements of flow, increased amounts of acetylcholine are administered and a dose–response curve is established. In addition to changes in flow, ultrasound may also be used to assess changes in artery wall dimensions. In response to acetylcholine, patients with normal endothelial function can augment brachial arterial flow by more than 20–25% above baseline values. However, patients with hyperlipidemia and diabetes have a significantly impaired response to the administration of acetylcholine and fail to augment blood flow, indicating the presence of impaired vascular endothelial function [10, 11]. Acutely elevated lipid levels can also affect endothelial function in normocholesterolemic individuals. Vogel and coworkers [12] showed that within 4 hours of consuming a high-fat meal, flow-mediated dilation of the brachial artery of normocholesterolemic volunteers was...
reduced by nearly 50% and was only partially restored after 6 hours.

Importance of Altered Endothelial Function in the Cardiovascular Patient

Several studies have shown the importance of abnormal endothelial function as a predictor of adverse cardiovascular events and the progression of arteriosclerosis. Hashimoto and coworkers [13] correlated abnormal flow-mediated endothelial brachial artery vasodilation with intima-media thickness (IMT) of the carotid artery, an accurate end point of systemic arteriosclerosis. Men with arteriosclerosis had significantly greater carotid artery IMT and significantly decreased flow-mediated dilatation compared with patients without arteriosclerosis. The study supports the concept that endothelial dysfunction is significantly related to arteriosclerosis. Suwaidi and coworkers [14] studied the relationship of abnormal endothelial function and future cardiac events in 157 patients found to have minimal coronary disease at the time of diagnostic catheterization. Patients with abnormal endothelial function had a significantly higher ($p < 0.05$) incidence of myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), CABG, or cardiac death during a 28-month follow-up. Similar findings were noted by Neunteufl and coworkers [15] in a group of patients having coronary angiography but found to have only minimal disease. After angiography, all patients underwent brachial artery flow-mediated vasodilation with acetylcholine. Patients with impaired endothelial function were more likely to require PTCA ($7\%$ versus $37\%, p = 0.003$) or CABG ($0\%$ versus $15\%, p = 0.009$), and twice as likely to have an MI ($11\%$ versus $20\%, p = 0.09$). These studies add further proof to the concept that abnormal endothelial function is a predictor of serious cardiovascular events.

Decreasing Low-Density Lipoprotein-Cholesterol Improves Endothelial Function

Because endothelial function is impaired by elevated low-density lipoprotein-cholesterol (LDL-C) levels, does any evidence suggest that lowering serum lipids will normalize vascular function? Tamai and colleagues [16] studied the response of brachial artery blood flow in 7 patients with familial hypercholesterolemia before and after LDL-C apheresis, a technique commonly used to lower LDL-C in these patients. After a single apheresis, LDL-C levels fell from 142 to 33 mg/dL ($p < 0.0005$). This reduction resulted in a mean increase of acetylcholine-induced brachial artery vasodilation from 15 to 42 mL/min/100 mL ($p < 0.005$). In addition, the improvement in blood flow and decrease in LDL-C level was associated with an increased production of NO metabolites. This study emphasizes the importance of hypercholesterolemia in contributing to vascular endothelial dysfunction. Furthermore, it also demonstrated that this endothelial impairment can be reversed by aggressive LDL-C reduction. Anderson and colleagues [17] studied the effect of lipid lowering in a group of patients with abnormal baseline endothelial function. After 1 year of statin therapy, LDL-C levels were significantly decreased and a significant improvement in acetylcholine-induced vasodilation was noted. Finally, Dupuis and colleagues [18] found that a $33\%$ reduction in LDL-C 6 weeks after an MI was associated with a $42\%$ increase in brachial flow-mediated dilation. These studies suggest that lowering serum lipid levels can significantly improve endothelial function.
Effects of Statins on Endothelial Function and Atherogenesis

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase and are the most effective lipid-lowering agents available to clinicians [19]. They exert their action by inhibiting the conversion of 3-hydroxy-3-methylglutaryl coenzyme A into mevalonate, which is the rate-limiting step in cholesterol synthesis [20]. In addition to inhibiting mevalonic acid synthesis, statins also decrease the synthesis of other isoprenoid intermediates involved in the cholesterol pathways such as geranylgeranyl pyrophosphate and farnesyl pyrophosphate which prevent the activation of membrane associated pathways such as Rho and Ras [21]. The reduction of these intermediate pathways is responsible for the pleiotropic effects of statins that result in clinical benefits which are independent of their lipid-lowering properties. These include improved endothelial function, a reduction in the inflammatory process, and decreased thrombosis and enhanced fibrinolysis.

Statins improve endothelial function through several pathways that affect NO availability. They decrease endothelial cell superoxide production, which inactivates NO. This occurs not only by reducing LDL, but by directly preventing the isoprenylation of P21 rac, a protein involved in the formation of the superoxide precursor nicotinamide adenine dinucleotide phosphate oxidase [22]. Statins also upregulate the expression of endothelial NO synthase [23]. NO synthase activity is inhibited by the protein caveolin 1. Statins decrease cellular caveolin levels and decrease the inhibition of endothelial NO synthase by caveolin, thus resulting in increased NO production [24]. Statins also preserve endothelial function by inhibiting the release and effects of angiotensin II and endothelin, which can alter the balance between superoxide anions and NO [25].

Statins preserve endothelial function and decrease the risk of atherogenesis by reducing the inflammatory process. They decrease plasma levels of C-reactive protein independent of reductions in LDL [26], reduce plasma levels of cytokines, and suppress cytokine and adhesion molecule expression [27]. By reducing P-selectin expression and CD18 upregulation, they inhibit leukocytes from adhering to the endothelium [28].

Statins also suppress thrombosis and enhance fibrinolysis. They reduce platelet aggregation and adhesion, thromboxane formation, and inhibit expression of tissue factors which promote platelet activations [29–34]. They promote fibrinolysis by enhancing tissue plasminogen activator synthesis and reducing tissue PAI-1 [35].

Evidence suggests that statins may modulate arterial gene expression [36]. They inhibit T-cell activation by downregulating major histocompatibility complex II, which is required for antigen presentation and T-cell activation. The resulting decrease in helper T-cell differentiation and activation leads to a reduction in proinflammatory cytokines. This effect may explain why statins may be useful in treating graft arteriosclerosis and rejection after cardiac transplantation (see below).

Finally, an exciting new mechanism by which statins preserve endothelial function is their ability to activate and mobilize endothelial progenitor cells (EPCs) after an ischemic event. Vasa and coworkers [37] treated 15 patients with angiographically stable coronary disease with 40 mg atorvastatin for 4 weeks. Statin therapy was associated with a significant increase in the number and functional activity of EPCs in these patients. Since EPCs are known to participate in the repair of the endothelium after ischemia, statins may preserve endothelial function by neorevascularization of ischemic tissue with EPCs.

Effects of Statins on Clinical Events in Patients With and Without Risk for Cardiovascular Disease

This section reviews evidence supporting the use of statins for improving long-term outcomes and reducing ischemic events in patients with and without risk for cardiovascular disease. These studies demonstrate how the potentially beneficial effects of lipid lowering and preserved endothelial function will result in better patient outcomes.

Primary Prevention Trials

The WOSCOPS (West of Scotland Coronary Prevention Study) and AFCAPS/TEX CAPS (Air Force/Texas Coronary Arteriosclerosis Prevention Study) studies were clinical trials that examined the effects of lipid lowering in adults who had no history of cardiovascular disease [4, 38]. In the WOSCOPS trial, 6,595 men with elevated cholesterol levels without any coronary events were randomized to pravastatin or placebo and were followed for an average of 5 years [38]. In the AFCAPS/TEX CAPS trial, 6,605 men and women with normal total cholesterol and LDL-C levels and without any cardiovascular disease were randomized to lovastatin or placebo and followed for as long as 5.3 years [4]. In both trials, LDL-C levels were lowered by 20% to 25%. In the WOSCOP trial, significant reductions were noted for risk of nonfatal MI (31%), death from coronary heart disease (33%), and all-cause mortality (22%). In AFCAPS/TEX CAPS, the incidence of MIs were reduced 40% (p = 0.002), any coronary events by 25% (p = 0.006), and all cardiovascular events by 25% (p = 0.003). Statin therapy also lowered the risk for coronary revascularization procedures by 33% (p = 0.0001). Both trials showed that lipid lowering with statin therapy had a substantial effect on decreasing cardiovascular events in patients who had no prior history of cardiovascular disease.

Secondary Prevention Trials

Secondary prevention trials sought to determine the effectiveness of statin therapy in patients who had already experienced a coronary event (angina or MI) and in persons who had undergone some type of revascularization procedure.

Patients With Previous Coronary Events

The 4S (Scandinavian Simvastatin Survival Study) trial followed 4,444 men and women with angina or a previous MI and elevated cholesterol levels for 5.4 years. Patients
were randomized to receive either pravastatin or placebo [5]. The CARE (Cholesterol and Recurrent Events) trial followed 4,159 patients who had experienced an MI for 5 years [39]. Patients in this trial were randomized to receive pravastatin or placebo. Pravastatin was also used in the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) study, which followed 9,014 patients with unstable angina or an acute MI [40]. In all three trials, total cholesterol and LDL-C levels were reduced by 25% to 35% and the lower lipid levels correlated with improved clinical outcomes. Nonfatal MIs were reduced by 34% in 4S and 24% in the LIPID and CARE studies. Deaths from coronary heart disease were reduced by 42% in 4S, 24% in LIPID, and 19% in the CARE trial. Mortality from any etiology was reduced by 30% in 4S, 22% in LIPID, and 8% in CARE.

The Medical Research Council British Heart Foundation Heart Protection Study (HPS) was designed to determine whether statins would be of benefit to patients with average-to-low LDL levels who were still at risk for coronary and atherosclerotic-related events due to a history of coronary artery and peripheral vascular disease, stroke, or diabetes [41]. The 20,536 patients were randomized into four groups: simvastatin 40 mg daily, simvastatin 40 mg + vitamin therapy (vitamins E and C and B-carotene), vitamin therapy without any statin, and a placebo group. The average follow-up was 5.5 years. Vitamin therapy had no effect in preventing atherosclerotic events. Patients treated with statins had a 24% (p < 0.00001) reduction in coronary death and death from other vascular disease, fatal and nonfatal strokes, and the need for revascularization procedures. These beneficial effects were observed among a broad group of high-risk patients for whom statin therapy had been uncertain. This group included women, persons older than 70 years, and patients with LDL-C levels less than 120 mg/dL.

The 4S, CARE, LIPID, and HPS trials demonstrated that statin therapy effectively improves survival and reduces ischemic events in patients with known coronary artery disease. But what about the patient who has already undergone a potentially “curative” revascularization procedure for ischemic heart disease? The next section examines the role for statin therapy in the patient who has already undergone a revascularization procedure.

**Statin Therapy in the Revascularized Patient**

The Post-Coronal Artery Bypass Graft (Post-CABG) trial was designed to determine whether statin therapy could delay or prevent the progression of atherosclerotic disease in vein grafts and thereby reduce ischemic events [42]. This multicenter trial included 1,351 patients who were 1 to 11 years from the time of their CABG. Men in the study had to have a least two patent, but not necessarily disease-free saphenous vein grafts; women had to have a least one such graft. Baseline LDL-C levels were 130 to 175 mg/dL. Patients were randomized to receive either aggressive treatment with lovastatin 80 mg/d designed to achieve an LDL-C of less than 85 mg/dL or moderate treatment using 40 mg/d with a target LDL-C of 135 mg/dL. The primary end point was the mean per-patient percentage of grafts with significant progression of atherosclerotic lesions in saphenous vein grafts (at least 0.6-mm change). Secondary end points included new graft occlusion; changes in graft luminal diameter; the incidence of MIs; and the need for repeat revascularization (CABG or PTCA). Angiograms were repeated in all patients at an average of 4.3 years from entry into the study. Patients in the moderate treatment group achieved the target LDL-C of 135 mg/dL; those in the aggressive group averaged 95 mg/dL, slightly above the targeted level of 85 mg/dL or less. Patients treated in the aggressive lipid-lowering group had less progression of atherosclerotic lesions in the vein grafts (p < 0.0001) and a reduction in new occlusions (p = 0.001) and new lesions (p < 0.001). The need for a revascularization procedure after 4 years was 29% lower in the aggressive lipid-lowering group (6.5% versus 9.2%, p = 0.03). Patients with two or more risk factors (smoking, diabetes, hypertension, high-density lipoprotein-cholesterol less than 40 mg/dL, triglycerides 145 mg/dL or higher) seem to have benefited the most from aggressive lipid lowering. Furthermore, the beneficial effects of aggressive lipid lowering continued after 7.5 years. Patients who had received aggressive lipid lowering with LDL-C levels of 100 mg/dL or lower had a 30% reduction in revascularization procedures (p = 0.006) and a 24% reduction in the composite end point of cardiovascular death, stroke, need for revascularization, and death from any cause (p = 0.001). The Post-CABG trial showed the importance of not just lipid lowering, but aggressive treatment to achieve LDL-C levels of 100 mg/dL or less in revascularized patients. The angiographic benefits of decreased progression of atherosclerotic disease, increased vein graft diameter, and improved patency translated into a reduction of clinical events and improved survival that persisted 3 years after the study was completed. This study showed that the benefits of lipid lowering are extended not only to patients at risk for cardiovascular events but also to those who have had supposedly “curative” revascularization procedures.

Another study that examined the effect of statin therapy in patients who already had a revascularization procedure was the CARE trial [39]. As noted earlier, this trial was a randomized, double-blinded study comparing pravastatin 40 mg/d with placebo in patients who survived an MI and had mildly elevated cholesterol levels. Within this trial, patients underwent PTCA (n = 1,154), CABG (n = 876), or a PTCA + CABG (n = 215) in the first 3 months after their MI. This group of 2,245 patients was also randomized to receive either pravastatin 40 mg/d or placebo during a 5-year period. Similar to the Post-CABG trial, statin therapy resulted in a significant reduction of LDL-C after 5 years (136 mg/dL placebo versus 98 mg/dL pravastatin). These figures were almost identical to the aggressive versus moderate groups reported in the Post-CABG study. It is not surprising that PTCA patients treated with statin therapy had a 43% reduction in the incidence of MI (p = 0.009) and a 39% reduction in cardiovascular death (p = 0.01). Statin PTCA patients also had a 22% reduction in the need for a repeat revascularization (p = 0.05) and a 72% reduction in the incidence of...
strokes ($p = 0.006$). CABG patients who received pravastatin had a 33% reduction in the incidence of cardiovascular deaths ($p = 0.034$). It is important to note that most patients in the CARE trial also received other therapies to reduce cardiovascular events, including aspirin, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors. Therefore, the ability to demonstrate a significant improvement in clinical outcomes makes these results even more striking and supports the concept of aggressive lipid lowering in the revascularized patient.

The beneficial effects of statin therapy in the CABG patient was also documented in two other smaller, single-center trials, which involved preoperative statin therapy. Christenson [43] evaluated the effect of using simvastatin for 4 weeks before CABG and for 1 year after surgery on the incidence of arteriosclerosis graft disease. Repeat angiography was performed 1 year after surgery. Patients treated with statins had a lower incidence of MI ($p = 0.03$) and vein graft occlusion ($p = 0.02$). Furthermore, similar to the Post-CABG trial, statin therapy prevented the development of new lesions in patent vein grafts. Dotani and coworkers [44] examined the effect of statin therapy in a retrospective study involving patients receiving statin therapy before their CABG. Preoperative statin therapy was associated with a significant reduction in the composite end point of death, MI, and unstable angina 1 year after CABG ($p = 0.006$). Unstable angina was reduced from 11% to 3% with statin therapy ($p = 0.02$). Statin treatment also reduced the incidence of arrhythmias.

### Statin Therapy as an Alternative to Revascularization

The previously mentioned trials clearly demonstrated that statin therapy has a role in the coronary patient who has already had an ischemic event or undergone a revascularization procedure. But can statin therapy also be used as an alternative to revascularization procedures in patients with stable coronary artery disease? The AVERT (Atorvastatin versus Revascularization Treatment) study was undertaken to assess whether aggressive lipid-lowering therapy could be used as an alternative to percutaneous catheter-based therapy in patients with stable coronary artery disease [45]. The study included 341 patients with stable angina and documented coronary artery lesions (at least 50%) that could be treated with percutaneous revascularization. Patients were excluded if they had acute and unstable syndromes, significant left main disease, ejection fractions of 0.40 or less, or New York Heart Association class III or IV heart failure symptoms. Patients were randomized to receive atorvastatin 80 mg/d or to undergo PTCA plus standard antianginal therapy. In fact, 71% of patients in the PTCA group also received a statin; however, those patients did not receive high, aggressive doses. At the end of the 18-month follow-up, the statin group had a 46% reduction in LDL-C compared with a 18% reduction in the PTCA group ($p < 0.05$). The absolute LDL-C levels were strikingly similar to the values seen in the Post-CABG and CARE trials: 95 mg/dL in the statin group and 135 mg/dL in the PTCA group. At the conclusion of the study (18 months), patients treated with atorvastatin had a 36% reduction ($p = 0.041$) in the incidence of ischemic events, most notably the need for a second revascularization and rehospitalization for worsening angina. Furthermore, high-dose statin therapy was well tolerated, as no significant differences were noted in elevation of liver function studies or the incidence of myositis. In summary, the AVERT trial showed that aggressive statin therapy may be used in patients with stable coronary disease as an alternative to PTCA. It also suggested that statins may not only prevent the progression of atherosclerotic changes in vein grafts, but may also have a protective effect on native coronary vessels with obstructive lesions.

### Statin Therapy for Acute Coronary Syndromes

The trials reported in the previous sections have shown convincing evidence that statins reduce cardiovascular morbidity, mortality and the need for repeat revascularization in patients who are at high risk for developing cardiovascular disease, in those patients who have already experienced a coronary event, and in patients who have already undergone coronary revascularization. However, the role of statin therapy for patients with acute coronary syndromes was still unknown. By design, previous studies had excluded patients with unstable angina and acute MI’s. However, it is during acute coronary syndromes that patients may experience increased mortality and ultimately recurrent ischemic events. The MIRACL (Myocardial Ischemic Reduction With Aggressive Cholesterol Lowering) trial sought to determine whether early and intensive lipid lowering with statin therapy could reduce early ischemic events in patients with acute coronary syndromes [46]. The study included 3,086 patients with unstable angina or a non-Q wave MI. Patients were randomized to receive either atorvastatin 80 mg or placebo. Treatment was initiated 24 to 94 hours after hospitalization and continued for 16 weeks. Patients were excluded if a PTCA or CABG were performed during this hospitalization, or in the previous 6 months, or if they had experienced a Q wave MI within the preceding 4 weeks. At the start of the study, both groups had a mean LDL-C of 124 mg/dL, but at the end of the 16-week follow-up period, LDL-C was 135 mg/dL in the placebo group versus 72 mg/dL in the atorvastatin group, nearly a 40% reduction. These values are similar to the Post-CABG and CARE trials [39, 42]. It was not surprising then that patients treated with atorvastatin had a 26% reduction in repeat hospitalizations due to worsening angina ($p = 0.02$). Patients taking atorvastatin also had 50% reduction in strokes ($p = 0.045$). The MIRACL study showed that early intensive statin therapy during acute coronary syndromes reduced ischemic events within a relatively short period of therapy. Furthermore, this improvement was seen in a group of patients that presented with relatively normal baseline LDL-C levels. As in other lipid trials (Post-CABG, CARE, AVERT), this intensive statin therapy was well tolerated.
Only 2.5% of patients had a rise of liver function tests (LFTs) and this returned to baseline when the statin was discontinued. This study provided evidence to support the use of statin therapy, not only to prevent ischemic events, but also to treat patients during acute coronary syndromes.

The MIRACL trial supports earlier trials of primary and secondary prevention using statin therapy to decrease the incidence of recurrent coronary ischemic events. In a recent review of the use of statins in the treatment of acute coronary syndromes, Waters and Azar [47] suggested that all patients be started on a statin as soon as possible after their admission to the hospital once a baseline lipid profile is obtained. Larger clinical trials will need to be performed to determine the ultimate role of statins in acute coronary syndromes, as well as the dosages required to achieve these beneficial effects.

Statin Therapy May Enhance Myocardial Protection During Coronary Revascularization

The favorable outcomes in the MIRACL study prompted us to investigate the role of statins to enhance myocardial protection during coronary revascularization [48]. We hypothesized that the favorable effects of statins on endothelial function, inflammation, and fibrinolysis might decrease ischemic damage during coronary revascularization for unstable coronary syndromes. Twenty pigs underwent isolated coronary occlusion for 90 minutes, followed by 45 minutes of cardioplegic arrest and 180 minutes of reperfusion. Ten animals received atorvastatin (40 mg qd) for 21 days before surgical intervention, at a dose similar to the MIRACL and AVERT trials for a 70 kg patient. The other group of pigs received no statins. During the 90 minute period of coronary occlusion, statin-treated animals received fewer cardioversions for ventricular tachycardia and fibrillation ($p = 0.0001$). This is similar to studies in patients with implantable defibrillators which showed that patients receiving statins have a 40% reduction in the incidence of ventricular tachycardia or fibrillation [49]. It is postulated that the beneficial effects of statins stem from their reduction of superoxide free radicals and free fatty acids which contribute to sarcoplasmic injury, intracellular calcium overload, and alterations in transmembrane ion channels which affect ventricular conduction and excitability. Statin-treated animals also had higher wall motion scores ($p = 0.01$), lower infarct size ($p = 0.0001$), and better preservation of coronary endothelial vasomotor function ($p = 0.01$). These beneficial effects occurred in the absence of changes in serum cholesterol or LDL-C levels, suggesting that these beneficial effects of statins were the result of pleiotropic properties. The favorable effects of statin pretreatment before coronary revascularization was also observed by Chan and coworkers [50] in a retrospective study involving 5,052 patients undergoing PTCA. Patients receiving statin therapy before their PTCA had a significant reduction in mortality that persisted for up to 6 months. Similar results were noted by Walter and coworkers [51], who found that the initiation of statin therapy immediately after stent insertion significantly improved 6-month clinical outcomes in patients with unstable angina. Furthermore, in another series, this same group found that patients with elevated C-reactive protein levels during their stent implementation had a decreased risk for major cardiac events if they received statin therapy [52]. This result provides further evidence that statins may decrease ischemic events because of their role in decreasing the inflammatory response. Along with the MIRACL trial, these studies suggest that statins may also have an important role in decreasing ischemic damage during acute coronary syndromes and coronary revascularization. They may also confer additional protection for patients undergoing CABG surgery irrespective of their baseline cholesterol and LDL-C levels.

Beneficial Effects of Statins in Cardiac Transplant Patients

Recent studies have demonstrated improved outcomes in cardiac transplant patients receiving statins during the postoperative period. Kobashigawa and coworkers [53] randomized patients to receive pravastatin 40 mg versus no statin therapy. Statin-treated patients had improved survival (98% versus 78%; $p = 0.025$) and fewer episodes of cardiac rejection and hemodynamic compromise (3% versus 14%; $p = 0.005$) at 1 year. Wenke and coworkers [54] studied the effects of simvastatin (5 to 20 mg) compared with diet during an 8-year period. Patients in the statin group had better long-term survival ($p < 0.006$) and a lower incidence of graft vessel disease ($p < 0.02$). Keogh and coworkers [55] randomized patients to pravastatin 40 mg po qd with simvastatin 20 mg po qd during a 1-year follow-up. Survival (97.6% pravastatin versus 83.7% simvastatin; $p = 0.078$) and immunosuppressive-related mortality (2.4% pravastatin versus 15.6% simvastatin; $p = 0.06$) tended to be better in the pravastatin group. Finally, Mehra and coworkers [56] studied survival and allograft rejection profiles of pravastatin (20 mg qd) versus simvastatin (10 mg qd). Both statins improved survival at 1 year compared with the no-statin group ($p = 0.04$). No difference was noted between the two statins in terms of survival or immunosuppression.

These studies support the concept that statin therapy started immediately after heart transplantation improves survival and may decrease rejection and graft arteriosclerosis. Reduction in LDL-C with statins has been associated with significant increases in the unbound fraction of cyclosporine, which may limit severe rejection episodes. Low-dose statin therapy is safe and appears to enhance clinical outcomes after cardiac transplantation. It is unclear, however, whether using high-dose statins to achieve LDL-C levels of 100 mg/dL or less in the CABG patient is safe after cardiac transplantation. In the study by Keogh and colleagues [55], increasing the dose of simvastatin to 40 mg/d was associated with an increased incidence of side effects including rhabdomyolysis. Further clinical studies will be necessary in the cardiac
transplant population to determine the risks and benefits of high-dose statin therapy in these patients.

Statins and Noncardiac Vascular Surgery
Statin therapy may also play an important role in decreasing ischemic events in patients undergoing noncardiac vascular surgery. To evaluate the effect of statin use and perioperative mortality, Poldermans and coworkers [57] performed a case-controlled study among 2,816 patients who underwent vascular surgical procedures. Patients who received a statin were less likely to have a cardiovascular mortality after their vascular surgery procedures. The effects of pretreatment with statins following noncardiac vascular surgery was also studied by Durazzo and coworkers [58] in a prospective, randomized, double-blind trial involving atorvastatin (20 mg/d) 30 days before surgery. The incidence of cardiovascular events (death, MI, unstable angina, and stroke) was significantly less ($p = 0.022$) in patients treated with atorvastatin during the 6-month follow-up. These studies strongly suggest that statin therapy is associated with improved outcomes in patients undergoing major noncardiac vascular surgery.

Statin Therapy Reduces Stroke Incidence
Clinical trials have demonstrated that statins reduce the incidence of strokes in patients with both normal and elevated cholesterol levels. In the CARE trial, researchers observed a 32% reduction in strokes or transient ischemic attacks among patients receiving pravastatin [59]. The LIPID study revealed a 19% reduction in strokes in patients with a wide range of cholesterol levels treated with pravastatin [40]. In the MIRACL trial, a 50% reduction in strokes was noted after only 16 weeks of treatment with atorvastatin [46]. A meta-analysis of 13 primary and secondary prevention lipid trials involving 20,303 patients revealed that treatment with various statins led to a 31% reduction of strokes [60]. The HPS, which involved more than 20,000 patients with diabetes and coronary heart disease, demonstrated a 27% reduction in stroke with simvastatin in patients with elevated, normal, and even low LDL-C levels [41]. This benefit was seen in all types of patients, including women, the elderly, and patients with diabetes.

The neuroprotective effects of statins appears to be due to mechanisms that are not related to their cholesterol-lowering properties. Linear regression analyses of percent reduction in cholesterol and the incidence of strokes shows no correlation between these two factors [60]. The neuroprotective effects of statins are most likely the result of their preservation of endothelial function and their anti-inflammatory, antioxidant, and antithrombotic effects [61].

Role of the Cardiac Surgeon in the Implementation of Statin Therapy
Despite increasing evidence to support the beneficial effects of statins in cardiovascular patients, cardiac surgeons have been reluctant to initiate statin therapy during the preoperative or postoperative period. There are concerns that the surgeons will not be observing the patients for their long-term care, that it is the responsibility of the cardiologist or referring physician to initiate lipid-lowering therapy, and that statins may have side effects that will influence patient outcomes. However, data now show that early institution of statin therapy after a cardiovascular event confers increased protection and improves long-term outcomes. Muhlestein and coworkers [62] studied the effects of in-hospital prescription of statins versus postdischarge prescriptions in 600 patients hospitalized after episodes of acute coronary syndromes. Patients who received a prescription for a statin on discharge from the hospital had better long-term compliance (77% versus 40%; $p < 0.0001$). Even more importantly, patients who received a statin on discharge had a reduced mortality rate (15.7% versus 11.7%; $p = 0.05$.) The effect of early statin therapy in clinical outcomes was even more impressive in the Cardiac Hospitalization Arteriosclerosis Management Program (CHAMP) [63]. This trial consisted of the institution of aspirin, statins, ACE inhibitors, and β-blockers for patients after an acute MI before discharge from the hospital. Compared with before the initiation of the CHAMP program, the use of statins increased from 6% to 86% ($p < 0.01$). At the 1-year follow-up, compliance with the statin therapy was 91%; 58% of CHAMP patients had an LDL-C level of 100 mg/dL or less compared with 6% of pre-CHAMP patients. The improved use of statins in combination with the other cardioprotective therapies was associated with significant reduction in the rates of deaths, nonfatal MI, and repeat hospitalization (14.8% versus 6.4%; $p < 0.01$), which persisted during an 8-year period [64].

Starting patients on lipid-lowering therapy in the hospital after surgery has many advantages. The message is conveyed to the patient that this is an important therapeutic intervention that may prevent another surgery or the need for rehospitalization. The surgeon has the opportunity to consult with cardiology and internal medicine colleagues regarding statin dosages and to communicate this information to local referring physicians. The beneficial pleiotropic effects of endothelial preservation and decreased inflammation and thrombosis are immediately instituted. Even more importantly, this strategy brings practices into compliance with the new ACC/AHA Acute Coronary Syndrome Guidelines, the National Cholesterol Education Program (NCEP), and the Adult Treatment Panel (ATP) III Guidelines, which recommend the initiation of lipid-lowering medications before discharge of in-hospital patients with atherosclerotic vascular disease [65, 66].

Statins have been well tolerated in CABG patients. In the Post-CABG trial, not one patient had to have their statin therapy discontinued. No incidence of rhabdomyolysis was noted in either the Post-CABG or CARE trials involving CABG patients. Statins have been studied in various trials for approximately 20 years and are one of
the safest classes of drugs developed [67]. Nevertheless, statins are associated with skeletal muscle symptoms, which include myositis, myalgia, and rhabdomyolysis [68]. The mechanism for statin-induced muscle injury is unknown but may be related to decreasing the cholesterol content of skeletal muscle cell membranes, making them unstable and reducing the level of isoprenoids and regulatory proteins responsible for muscle injury [69]. Rhabdomyolysis is the most serious skeletal muscle complication and can be fatal. Death results from hyperkalemia, cardiac arrhythmias, renal failure, and disseminated intravascular coagulation [70]. Creatinine kinase (CK) levels are usually 10 times the upper limit of normal. The risk for rhabdomyolysis, as with other statin-related musculoskeletal symptoms, increases in patients with renal and hepatic insufficiency, diabetes, or hypothyroidism, and in elderly females. Medications that inhibit the cytochrome P-450 3A4 system such as fibrates, erythromycin, itraconazole, cyclosporine, Coumadin, and digoxin will also increase the serum concentration of statins and may increase the risk for rhabdomyolysis [71]. All statins can cause rhabdomyolysis, but the incidence was 16 to 18 times higher with cerivastatin, which was withdrawn from the market in August 2001. In a recent review, the mortality associated with rhabdomyolysis was noted to be 7.8% [68]. Fortunately, the incidence of fatal rhabdomyolysis is extremely rare and is estimated at only 0.15 deaths per 1 million prescriptions [72]. This finding is supported by a recent review showing the incidence of rhabdomyolysis in numerous clinical trials to be only 7 patients out of 42,323 with no deaths [68].

Most statin-related complications involve myalgias, which are muscle complaints without serum CK elevations. In the HPS study, no difference was noted in the incidence of myalgias between patients receiving statins and those receiving a placebo. The rate of myalgia has been reported to be between 1% and 5% for statin drugs [68]. A recent retrospective study documented only a single (0.9%) abnormal CK measurement, which was unrelated to statin use [73]. A 1.0% incidence of significant elevation of liver enzymes was also noted. Statin-induced CK elevations should not be misinterpreted as cardiac ischemia during the early postoperative period, because the myocardial CK-MB fraction is rarely elevated [74]. A recent review assessed the safety of atorvastatin in the 10- to 80-mg dose range using pooled data from 44 trials comprising 9,416 patients [75]. Persistent elevation of liver enzymes occurred in 0.5% of atorvastatin patients. A persistent elevation of creatine phosphokinase was seen in only 1 patient. The incidence of myalgia was 1.9% and was not related to the atorvastatin dose. No cases of rhabdomyolysis or myopathy were noted.

Recent guidelines for the management of statin-related muscular symptoms include starting with the lowest dose that will achieve the therapeutic goal of lowering LDL, and discontinuing the medication if muscle pain or weakness or discoloration of urine is observed [76]. There is no contraindication to using a statin when a patient is receiving an agent that may increase the risk of myopathy such as Coumadin, digoxin, or cyclosporine, because the benefits are far likely to outweigh the risks. Routine measurement of CK levels in asymptomatic patients is not required, although a baseline CK may help to facilitate the evaluation of subsequent muscle complaints. There is also no need to discontinue statin therapy in asymptomatic patients in whom CK levels are elevated, but are not more than 10 times above the upper level of normal.

The new NCEP and ACC/AHA guidelines recommend achieving an LDL-C level of less than 100 mg/dL in all patients with coronary arteriosclerosis. This level should be the goal for all CABG patients. But what is the best method to achieve this goal? All CABG patients should receive a statin before and the day after their surgery. A list of statin agents, their dosages, interactions, and side effects is found in Table 1. In my own practice, I start with a low dose of atorvastatin, usually 10 mg. If a patient is already taking another statin or a higher dose of atorvastatin, then I will resume that statin at the preoperative dose. I do not obtain a lipid profile after surgery, since the acute-phase response triggered by the stress of surgery, or a recent episode of unstable angina or an MI, can substantially decrease the total cholesterol and LDL-C levels [77]. On discharge, patients are warned about the potential side effects of statins and to contact a physician should these symptoms occur. In the discharge letter, the referring physician is informed of the status of the patient’s statin therapy and asked to obtain a lipid panel, CK, and set of liver function studies in 6 weeks and to make the necessary adjustment in dosages to achieve an LDL-C level of less than 100 mg/dL. Patients are also discharged with an aspirin, β-blocker, and whenever possible, an ACE inhibitor.

Conclusions and Recommendations

Experimental studies have shown that statins, independent of their lipid-lowering effects, improve endothelial function, decrease vasoconstriction, suppress the inflammatory response, and reduce thrombosis. Clinical trials in patients undergoing CABG procedures have shown that statins prevent the progression of atherosclerotic disease in vein grafts, decrease the incidence of angina and ischemia, reduce the need for repeat revascularization, and improve clinical outcomes by reducing MIs, strokes, and the need for rehospitalization in response to a cardiovascular event.

All CABG patients should receive statin therapy during the postoperative period and, if possible, before surgery. Attempts should be made to lower LDL-C to less than 100 mg/dL. Revascularization alone is not sufficient to prevent recurrent ischemic events. By initiating statin therapy in the CABG patient, we as surgeons can take a major step in giving our patients the most optimal cardiac protection from recurrent ischemic events.
<table>
<thead>
<tr>
<th>Statin (Dosage)</th>
<th>↓ TC</th>
<th>↓ LDL</th>
<th>↓ TG</th>
<th>↑ HDL</th>
<th>Drug Interactions</th>
<th>Adverse Events</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (10–80 mg)</td>
<td>29%–45%</td>
<td>39%–69%</td>
<td>19%–37%</td>
<td>5%–9%</td>
<td>No dose limits with fibrates, niacin, cyclosporine. No effect on INR with warfarin.</td>
<td>Constipation, flatulence, dyspepsia, abdominal pain.</td>
<td>Start at 10 or 20 mg once a day, any time of day. No dose adjustment for renal patients.</td>
</tr>
<tr>
<td>Simvastatin (5–80 mg)</td>
<td>19%–36%</td>
<td>26%–47%</td>
<td>15%–24%</td>
<td>8%–15%</td>
<td>Maximum dose is 10 mg when given with cyclosporine, fibrates, niacin. Avoid giving with verapamil. INR is increased in patients taking warfarin.</td>
<td>Constipation, flatulence, upper respiratory infection, Abdominal pain, dyspepsia, pruritus.</td>
<td>Start at 20 mg once a day in the evening. Start at 5 mg in patients with renal insufficiency.</td>
</tr>
<tr>
<td>Pravastatin (10–80 mg)</td>
<td>16%–33%</td>
<td>22%–40%</td>
<td>11%–24%</td>
<td>2%–12%</td>
<td>In patients taking cyclosporine, start at 10 mg and do no exceed 20 mg. No effect on INR in patients taking warfarin.</td>
<td>Diarrhea, heartburn, myalgia, headache, dizziness.</td>
<td>Start at 10, 20, or 40 mg any time of the day. Renal and hepatic patients should start at 10 mg.</td>
</tr>
<tr>
<td>Fluvastatin XL (20–80 mg)</td>
<td>16%–27%</td>
<td>22%–36%</td>
<td>12%–25%</td>
<td>3%–11%</td>
<td>No effect on INR in patients taking warfarin.</td>
<td>Sinusitis, bronchitis, dyspepsia, nausea, urinary tract infections.</td>
<td>Start at 40 or 80 mg in the evening. In hepatic insufficiency, start at 40 mg. In renal patients, use caution above 40 mg.</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglyceride.
References

37. Heart Protection Study Collaborative Group. MRC/PHF


