Statins in Coronary Bypass Surgery: Rationale and Clinical Use

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Statins produce angiographic and clinical benefits in patients undergoing coronary bypass surgery. We review the present knowledge about the effects of statins on this pathologic condition and the evidence supporting an early treatment initiation.


Coronary artery bypass graft (CABG) surgery relieves debilitating myocardial ischemia and in some patients, it prolongs life [1]. The intervention, however, is palliative as a consequence of accelerated arteriosclerosis in grafts and progression of disease in native vessels. Although arterial conduits are less prone to develop graft disease than saphenous vein grafts, these are usually necessary for multiple vessel revascularization, which is the typical indication for CABG. Therefore, prevention of early graft occlusion, chronic graft disease, and recurrence of symptomatic coronary arteriosclerosis in native vessels continues at the forefront of clinical research. Clinical studies have clearly demonstrated that reduction of plasma cholesterol, particularly cholesterol transported in low-density lipoproteins (LDL), lowers the risk of cardiovascular events for both primary and secondary prevention. Significant cholesterol reductions may be produced by the 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors, commonly named statins. It is implicit that the beneficial effect of statins on coronary events is related to their hypocholesterolemic properties. However the immediate product of HMG-CoA reductase, mevalonic acid, is not only the substrate for cholesterol synthesis but also the precursor of isoprenoids and other metabolites involved in different cellular pathways of atherogenesis and thrombosis [2]. As a consequence, statins have the potential to result in pleiotropic effects, which are independent of cholesterol reduction and may explain many of the direct antiatherosclerotic and anti-thrombotic properties of these compounds [2–7]. These mechanisms of action of statins are depicted in Figure 1. The pathogenesis of and general measures to prevent graft disease have been extensively reviewed elsewhere [8]. In this article, we focus on the accumulated and recent experimental and clinical data supporting the role of statins in patients undergoing CABG.

Statins and Prevention of Graft Disease
The biology of the vascular conduits obtained for grafting is strongly altered during harvesting, surgical manipulation, and the subsequent exposure to hemodynamic stress [8]. These stimuli elicit a series of changes in the graft that may lead, in certain conditions, to early thrombotic occlusion or to progressive thrombatherosclerotic disease. In addition, the marked systemic changes produced by cardiopulmonary bypass and surgical trauma on inflammation and hemostasis, in addition to the metabolic status of the host (namely hyperglycemia and dyslipidemia), may affect graft evolution [9]. A series of studies listed in Table 1 and described below in further detail reveals that various of these phenomena may be prevented by statin therapy. Although the relative clinical significance of the LDL-lowering effect rather than the direct actions of statins on the arterial wall is hard to establish, probably both play a role to prevent early or delayed phenomena leading to recurrence of disease after CABG.

Early Changes After CABG and Effects of Statins
Endothelial damage occurs in surgically prepared vascular segments [10] and early occlusions after CABG may depend on thrombosis associated with focal endothelial loss [8]. Even though careful vessel harvesting and surgical handling may reduce deendothelialization, critical cell functions are extremely sensitive to injury due to hypoxia, manipulation, or hemodynamic shear stress. Platelet adherence, fibrin deposition, and attachment of
neutrophils are enhanced in the graft, and the extrinsic coagulation cascade is activated by tissue factor (TF) expressed in the exposed subendothelium [11]. Several antithrombotic endothelial properties are attenuated such as the release of tissue plasminogen activator (tPA), prostacyclin, and nitric oxide (NO) [12]. In addition, postoperative thrombocytosis occurs in a significant number of the patients undergoing CABG with cardiopulmonary bypass [13]. Some of these early changes may be favorably affected by statins.

Statins and Platelets
Preoperative control of hypercholesterolemia with simvastatin seems to significantly reduce the incidence of postoperative thrombocytosis [17]. Unfortunately these intriguing data are not still corroborated by subsequent investigations. Studies on the effects of statins on platelet function provided contrasting results. Fluvastatin was reported to modestly reduce platelet aggregation, but pravastatin was ineffective [18, 19]. In some studies [20, 21], but not in others [22], simvastatin reduced platelet aggregation as well as urinary excretion of 11-dehydrothromboxane B2, a marker of in vivo platelet thromboxane A2 biosynthesis. Moreover, diverse experimental conditions were used to evaluate platelet function. For instance, although pravastatin failed to influence platelet reactivity induced by exogenous agonists and platelet eicosanoid synthesis, platelet thrombus formation evaluated by exposing porcine aortic media to the patient’s venous blood was significantly inhibited by
pravastatin [23, 24] but not by simvastatin [24]. The magnitude of vessel injury may determine the ability of a statin to prevent the formation of platelet thrombus in vivo. In fact, Badimon and colleagues [25] found that atorvastatin significantly diminishes platelet deposition on a mildly damaged but not on a severely injured vessel wall. These data suggest that statins may prevent platelet attachment to eroded vessels, reducing the thrombotic risk associated with erosions of the luminal surface. The implications of these findings on CABG patients are evident, at least on a theoretical basis.

Statins and Local Fibrinolysis

In vitro culture studies of smooth muscle and endothelial cells, and ex vivo studies in rat aortas show that a short-term exposure to different statins induces tPA and

Table 1. Effects of Statins on Pathophysiologic Pathways of Coronary Artery Bypass Graft Disease Beyond Low-Density Lipoprotein-Lowering

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EC = endothelial cell; eNOS = endothelial nitric oxide synthase; HUVEC = human umbilical vein endothelial cells; IL = interleukin; MMP = matrix metalloproteinase; SMC = smooth muscle cell; TF = tissue factor.

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Statins and Vasoactive Factors

The propensity of the graft to vasoconstriction may not only reduce lumen diameter and relative blood supply to the myocardium but also determine acute flow changes leading to thrombotic phenomena. Statins may potentially counterbalance this perturbation. In cultured bovine aortic ECs, atorvastatin and simvastatin inhibit preproendothelin-1 mRNA expression and reduce immunoreactive endothelin-1 levels. In addition, these compounds prevent the inhibitory action of ox-LDL on endothelial NO synthase (eNOS) mRNA and protein levels [33]. A series of in vitro and in vivo studies demonstrate that up-regulation of eNOS expression is a common pharmacodynamic action of statins [34–36], which is independent, at least in part, from changes in serum cholesterol levels [37]. Importantly, eNOS expression declines rapidly after statin withdrawal [38], suggesting that a continuous administration of the compound is required to preserve endothelial function.

Statins and Tissue Factor

Tissue factor expression in different cell types is modulated by statins. Colli and colleagues [39] first demonstrated that fluvastatin and simvastatin, but not pravastatin, decreased TF activity, protein, and mRNA in monocyte-derived human macrophages in culture. Inhibition of TF was shown to be independent on the inhibition of cholesterol biosynthesis as it was observed in the presence of exogenously added cholesterol. Rather geranylgeraniol prevented the effect of the statin on TF biosynthesis. This observation suggests that at least in vitro the effect of statins on TF is not dependent on cholesterol lowering.

Inhibition of TF expression concomitant with cholesterol reduction has been shown in rabbits fed a high cholesterol diet [40]. Moreover macrophage accumulation and TF content was reduced by statins in rabbit carotid neointimal lesions even in the absence of changes in blood cholesterol [41]. Finally evidence for an in vivo effect of statins on TF expression in human vessels was recently provided by the Atorvastatin and Thrombogenicity of the Carotid Atherosclerotic Plaque (ATROCAP) study [42] in patients undergoing bilateral carotid endarterectomy with an average interval time between the first and second carotid endarterectomy of 4 to 6 months. Atorvastatin significantly reduced TF protein and activity as well as macrophage infiltration in atherectomy specimens. These data strongly suggest that lipophilic statins by reducing cell-mediated generation of thrombin are capable of attenuating atherosclerotic plaque thrombogenicity.

Statins and Fibrinogen

We have previously reported that fibrinogen augments perioperatively in CABG patients [43]. Data indicate that some of the statins may mildly augment fibrinogen levels [44] in hypercholesterolemic patients by mechanisms not clearly established. Whether this undesirable effect of statins may in part offset the antithrombotic properties of these compounds is unknown.

Statins and Inflammation

In some aspects, arteriosclerosis may be regarded as a rather stereotyped response of the vessel to a diversity of stimuli, with an inflammatory component that includes early leukocyte infiltration [45] and local release of different chemoattractants and cytokines [46, 47]. Statins display antiinflammatory properties that may be of relevance during the early stages of neointima formation, beyond the postulated antiinflammatory actions that presumably lead to the stabilization of advanced lesions [48]. In this regard, several studies indicate that statins reduce C-reactive protein (CRP), an inflammatory biomarker and an accepted prognostic index of coronary instability [47].

Clinical data about acute antiinflammatory actions of statins in patients submitted to first elective CABG with cardiopulmonary bypass were reported. In a cohort study, Brull and colleagues [49] compared immediate postoperative variations in plasma interleukin-6 (IL-6) levels between CABG patients who were receiving chronic therapy with statins at the time of surgery and in a group who were not. Although peak IL-6 levels increased many fold after the intervention in both groups, levels were significantly lower in patients receiving statins, a finding that suggests that these drugs may ameliorate acute inflammatory phenomena occurring perioperatively. In contrast, Florens and colleagues [50] reported that acute perioperative administration of atorvastatin (40 mg the evening before and 40 mg the morning of surgery) failed to attenuate the increase in several inflammatory markers after cardiopulmonary bypass. Although longer statin treatment before surgery might be necessary to inhibit the acute response, further studies are warranted to define whether statins exert antiinflammatory effects perioperatively in CABG patients.

Late Changes After CABG and Effects of Statins

After the first month and throughout the first postoperative year, intimal hyperplasia represents the major histologic change in the graft. A combination of conditions promote smooth muscle cell (SMC) proliferation. These include (1) transient attenuation of endothelial antiproliferative signals (NO, transforming growth factor-β, prostacyclin, adenosine); (2) release of growth factors from adhering platelets and nonocclusive thrombi (platelet-derived growth factor); and (3) up-regulation of vein

reduce plasminogen activator inhibitor 1 (PAI-1) [26–29], potentially offsetting the fibrinolytic imbalance that characterizes vascular grafts. Moreover, in the in vivo situation, the effects of statins on fibrinolysis may be potentiated by their LDL-cholesterol lowering action. In fact, oxidized LDL (ox-LDL) stimulates PAI-1 release and inhibits tPA release by cultured ECs [30] and LDL reduction induced by statins may diminish lipoprotein availability for oxidation, which may add up to the direct antioxidant action of some members of this class of drugs [31, 32].
graft receptors for growth factors (basic fibroblast growth factor) [8]. A prerequisite for SMC proliferation and migration in vivo is degradation of the basement membrane, achieved by activation of matrix metalloproteinases, mostly the matrix-degrading gelatinases matrix metalloproteinas-2 (MMP-2) and MMP-9 [51]. In this hyperplastic period and thereafter, lipoprotein-derived cholesterol esters accumulate in the vessel wall. Lipid accretion occurs initially into smooth muscle and macrophage-derived foam cells and then extracellularly, progressively developing a mature atheromatous plaque, indistinguishable from the typical lesions found in native arteries. Statins may influence various of the steps involved in this process.

**Statins and SMC Migration and Proliferation**

Some studies indicate that statins affect MMP-9 secretion from unstimulated monocytes (cerivastatin) [52] and mouse macrophages or human monocyte-derived macrophages (fluvastatin and simvastatin) [53]. Moreover, recent studies using organ-cultured human saphenous veins show that simvastatin reduces neointima formation as a result of a combined inhibition of SMC proliferation and migration, the latter associated with a reduction of MMP-9 activity [54]. Conversely, the antiproliferative action of statins has been reported consistently on SMC from different species (including humans), both in vitro [4, 54, 55] and in vivo [56], and with different members of the statin family [4, 56]. The antiproliferative action of statins has been ascribed to inhibition of the farnesyltransferase activity [4, 7, 57].

**Statins and Atheroma Progression**

The association between hyperlipidemia and aggravation of graft vessel disease has been recognized [58]. In denuded vessels, high levels of circulating atherogenic lipoproteins enhance neointima formation, at least in part by increasing the number of SMC- and macrophage-derived foam cells [59]. Conversely, lipid lowering by itself ameliorates the rate and extent of this change [60]. Although the potent hypcholesterolemic effect of statins may explain the inhibitory effect of these drugs on lipid accretion some statins also show antioxidant properties [31, 32], which may reduce LDL oxidation. Therefore, statins may reduce atheroma development by affecting lipoproteins not only quantitatively but also qualitatively.

**Do Statins Actually Prevent Graft Disease and Occlusion?**

The Cholesterol Lowering Arteriosclerosis Study (CLAS) has shown that aggressive cholesterol reduction with a resin plus niacin in hypercholesterolemic subjects (mean LDL-C reduction −43%) for a period of 2 to 4 years significantly reduces new lesion formation in native vessels and bypass grafts [61]. It is worth noting, however, that both resins and nicotinic acid are not well tolerated in practice by most patients, particularly at the high doses used in the CLAS, making this treatment program highly unfeasible.

The Post-Coronary Artery Bypass Graft (Post-CABG) trial evaluated the effects of a statin/low-dose cholestyramine regimen in CABG patients [62]. In this study, angiographic changes were assessed in CABG patients with moderate hypercholesterolemia receiving lovastatin at high or low doses for an average of 4.3 years. Titration of the statin (2.5 to 5 mg/d in moderate and 40 to 80 mg/d in aggressive treatment) and addition of 8 g cholestyramine, if necessary, reduced mean LDL-C levels to 136 and 93 mg/dL in patients assigned to moderate or aggressive treatment, respectively. The percentage per patient of vein grafts with progression (27% versus 39%), new vein graft occlusions (10% versus 21%), or new vein graft lesions (10% versus 16%) were all significantly lower in the latter group.

Coronary benefits obtained in the Post-CABG trial with aggressive treatment do not restrict to the venous grafts but also affect native coronary arteries. Indeed, a recent subanalysis of changes in the native left main coronary artery in a sample of 402 Post-CABG trial participants showed a significantly reduced lesion progression with aggressive statin treatment as compared with moderate treatment (in 24.1% versus 13.8% of the patients, respectively) [63]. Thus, both venous grafts and native arteries benefit angiographically from a program of intensive postoperative intervention with statins.

**Do Statins Actually Reduce Clinical Events in CABG Patients?**

Beyond any favorable change in intermediate variables (either humoral or angiographic), the relevant issue is the effect of the intervention on a patient’s cardiovascular and global health. Lovastatin, pravastatin, or simvastatin were the compounds administered in the large studies performed so far addressing the efficacy of statins to reduce “hard outcomes” in secondary prevention. Yet, there is a general opinion and there are reasonable bases to support a drug class effect. Short- and long-term clinical benefits were reported in CABG patients treated with statins.

**Short- and Medium-Term Clinical Trials**

In a retrospective analysis, Dotani and colleagues [64] addressed the efficacy of statins administered preoperatively. In this study, “hard” short-term outcomes after elective CABG were compared between patients who were receiving or were not receiving statins at the time of the surgical intervention. Use of statins was associated with a reduced incidence of clinical events (death, acute myocardial infarction [AMI], unstable angina, or arrhythmias) both at 60 days and 1 year after CABG. It should be recognized, however, that differences in sex distribution, prevalence of hypertension, and presence or severity of dyslipidemia, as well as other unmeasured traits, may have introduced relevant biases in this nonrandomized study. Moreover, Christenson [65] reported the short-term effects of preoperative statins on angiographic and
clinical outcomes in hypercholesterolemic subjects. In particular, a preoperative 4-week simvastatin treatment not only reduced the occurrence of graft lesions and graft occlusions but also the incidence of AMI during the first year after CABG (7 of 37 untreated versus 0 of 40 statin treated; \( p = 0.03 \)). The study, however, was not placebo controlled and data are far from conclusive.

Although the results of these reports are encouraging, further investigations with proper design are mandatory to define the efficacy of statins in preventing early clinical events in CABG patients.

**Long-Term Clinical Trials**

In the Cholesterol and Recurrent Events (CARE) trial [66], patients of both sexes with a documented AMI and an average total and LDL-C levels were treated with either pravastatin or placebo for a mean period of 5 years. Pravastatin produced a statistically significant reduction (24%) in the relative risk of a composite endpoint of fatal coronary event or nonfatal AMI and significant reductions in the need of coronary revascularization or in the incidence of stroke. The CARE trial included 1,091 patients (527 allocated to pravastatin and 564 allocated to placebo) who had previously undergone CABG surgery. An analysis of treatment effect in this subgroup of patients [67] revealed that pravastatin significantly reduced by 33\% the incidence of the composite primary endpoint of coronary heart disease (CHD) death or nonfatal AMI (absolute risk 9.1\% versus 12.9\% in the placebo group), by 41\% the incidence of coronary death (4.6\% versus 7.8\%), and by 35\% total mortality (8\% versus 12.4\%).

In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, patients of both sexes with a history of AMI or hospitalization for unstable angina and a broad range of cholesterol levels were treated with either pravastatin or placebo for a mean period of 6.1 years [68]. In the entire treated population, pravastatin produced a significant 24\% relative reduction in the primary study outcome of mortality from coronary heart disease and also reduced by 24\% the combined incidence of CHD death or nonfatal AMI. The LIPID study included a 27\% of patients with a history of CABG (n = 2,436 patients; 1,217 and 1,219 allocated to pravastatin or placebo, respectively). Unfortunately, this was not a predefined subgroup and published data do not allow subgroup analyses.

The results of long-term follow-up of the patients included in the Post-CABG trial were recently published [69]. Follow-up during the main trial averaged 4.3 years whereas the extended follow-up added another 3 years. At this time, the aggressive hypocholesterolemic approach was associated with 30\% reduction in revascularization procedures and 24\% reduction in a composite clinical endpoint (death from cardiovascular or unknown causes, nonfatal AMI, stroke, CABG, or percutaneous coronary angioplasty) compared with patients assigned to moderate strategy, both differences statistically significant. Yet, the occurrence of the primary endpoint (cardiovascular death or nonfatal AMI) was 15.1\% in the aggressive strategy group and 20.3\% in the moderate strategy group, a 26\% reduction that was not significantly different by study criteria. At least two considerations may be of help in explaining these results. The first is that moderate treatment is not “placebo” and favorable effects may have occurred in the comparative group even at low statin doses. The second is that an unknown number of patients in the moderate approach may have been shifted to an aggressive approach during the period of extended follow-up.

Further support for the use of statins in a variety of high coronary risk conditions emerge from the favorable results of the recently published Heart Protection Study (HPS), which addressed the clinical long-term effect of simvastatin in high-risk patients with a wide range of cholesterol levels [70, 71]. In the HPS, patients with coronary disease (including a nonspecified number of subjects with previous CABG surgery), other occlusive arterial disease, or diabetes were randomly allocated to receive simvastatin or matching placebo. After a mean 5-year follow-up, simvastatin significantly reduced total mortality (13\%), vascular mortality (17\%), and the incidence of major coronary events (27\%) and strokes (25\%), as well as the need for coronary or extracoronary revascularizations (24\%). These effects in the whole treated population are highly encouraging, and information about the specific treatment effect in the subgroup of patients with previous CABG is eagerly awaited.

**When Should Statins Be Started in CABG Patients According to Present Data?**

In the Post-CABG trial, lipid-lowering therapy was started long after the bypass procedure. In fact, saphenous vein grafts had been placed 1 to 11 years before study entry. Similarly, a minimum of 3 months between CABG and enrollment was required in CARE and LIPID, and the period that elapsed between a previous bypass and randomization was not specified in HPS. Consequently, the gap between surgical intervention and statin initiation prevents any assessment of potential treatment effects on early changes occurring after CABG. This aspect is not unimportant inasmuch as early phenomena account for as many as 15\% to 25\% of venous graft occlusions during the first postoperative year and probably explain a much higher number of grafts with nonocclusive disease.

Although the term “preoperative” was explicit in the titles of the studies from Dotani and colleagues [64] and Christenson [17], these studies did not rigorously assess whether preoperative initiation of the statin provided any incremental benefit above a postoperative start. Indeed, to answer this relevant question both groups should have been treated similarly postoperatively, which was not the case. Therefore, more robust and properly designed clinical studies are necessary to obtain rigorous evidence about the efficacy, safety, and cost/benefit ratio of preoperative initiation of statins. Yet, statins generally show a very good safety profile and, therefore, unless the use of these compounds is formally contraindicated (patients with active liver disease or...
primary myopathy) or whenever caution is generally recommended (elderly women, hypothyroidism, renal insufficiency, concomitant use of interacting drugs), the potential benefits associated with an early start of statins might warrant their empirical preoperative use. Indeed, the reported favorable effects of statins on endothelial recovery, postoperative inflammatory phenomena, and postoperative thrombocytosis (see above) may be further potential advantages to justify the initiation of statin treatment preoperatively. More conservatively and according to current expert recommendations [72], patients undergoing CABG with a preoperative LDL-C level of 130 mg/dL or higher (or 100 to 129 mg/dL based on clinical judgment) should be administered a statin—and have a follow-up plan—as a part of their hospital discharge indications, unless contraindicated. Indeed, prescription of statins at the time of discharge as a part of hospital programs for risk factor management has been shown useful for substantially reducing morbidity and mortality [73].

**Should We Still Take Into Account LDL-C Level for Statin Prescription in CABG Subjects?**

Clinical evidence is starting to emerge suggesting that the current recommendations and goals in secondary prevention may not be aggressive enough. The Post-CABG study shows that the angiographic benefits in grafts and native arteries are associated with an aggressive statin treatment capable of achieving and maintaining LDL-C levels lower than 100 mg/dL. An even lower goal is suggested by the HPS results, demonstrating that statin treatment significantly and safely reduces the risk of major coronary events in subjects with a high coronary risk, even among those presenting with LDL-C below 100 mg/dL [71]. Indeed, the optimal LDL-C goal in coronary patients has not been definitely determined and results from ongoing studies (SEARCH, TNT) might provide an answer. In addition, the direct antithrombotic and antiatherosclerotic actions of statins may have a protective role against graft disease independently of starting and resulting LDL-C levels. One may anticipate that these and further upcoming data will support the conception of renewed guidelines, with the proposal of an earlier and more aggressive use of statins for patients with CABG as well as for other high-risk patients.

**Comment**

Native artery arteriosclerosis and graft vessel disease are complex processes with many pathophysiologic overlappings. Statins favorably modulate the expression of molecules involved in atherothrombotic properties of blood and vascular cells, either by reducing the levels of plasma cholesterol or through lipid-independent mechanisms. More importantly, statins started postoperatively exert benefits that can be documented angiographically, both in native vessels and in grafts, and may reduce morbidity and mortality among patients with previous CABG. Inasmuch as the thrombotic and inflammatory components dominate the early stages of graft disease, additional information on the nonhypolipidemic effects of the statins, including those on the prothrombotic and fibrinolytic systems, may provide an additional rationale for the preoperative initiation of these drugs.

**References**


