Perioperative Statin Therapy for Patients Undergoing Coronary Artery Bypass Grafting

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Coronary artery bypass grafting is associated with an intense systemic inflammatory response, which is linked to postoperative complications. Beyond lipid lowering, statins exert a constellation of beneficial actions, including an antiinflammatory role, known as pleiotropic effects. There is increasing evidence that perioperative statin therapy improves outcomes in patients undergoing coronary artery bypass grafting. Statins are underused in the coronary artery bypass grafting population, because perioperative discontinuation remains a common practice. This article provides an extensive review of the available literature on the effect of perioperative statin therapy on post–coronary artery bypass grafting outcomes and weighs the evidence for the concerns about increased incidence of statin-related adverse effects in this setting.

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Hydroxymethylglutaryl-CoA reductase inhibitors, well known as statins, are recommended by both the American College of Cardiology and the American Heart Association for treatment of patients with coronary artery disease [1]. Beyond their primary lipid-lowering role, they exert a group of other beneficial effects, including an antiinflammatory action, commonly referred to as pleiotropic effects [2]. Coronary artery bypass grafting (CABG) is known to be associated with an intense systemic inflammatory response (SIR), particularly when cardiopulmonary bypass is used [3, 4]. Such a state of postoperative SIR has been implicated in increased morbidity and mortality in patients undergoing CABG [5].

Despite evidence suggesting that preoperative statin therapy (PST) showed a beneficial role in the attenuation of postoperative SIR [6, 7], the common practice of discontinuation of statins before CABG remains unchanged because of concerns about adverse effects that could be precipitated by the stress of surgery [8]. In this review, we shed light on the current evidence behind the role of PST and its effect on postoperative outcomes in CABG patients.

REVIEW

Methods

For the purpose of this review, a systematic search of the Medline database from inception until July 2015 was conducted using the key words "statins" and "coronary artery bypass graft" for articles related to statin therapy in patients undergoing CABG. To ensure that no potentially important studies were missed, the reference lists from these articles were also checked.

Pathophysiology of Statins Benefit in Coronary Artery Bypass Grafting

Major operations, especially those associated with prolonged anesthesia, are known to create a state of postoperative SIR [9]. In CABG, this response is exaggerated by the use of cardiopulmonary bypass. The exposure of blood to artificial surfaces that lack endothelium, nonphysiologic changes in intravascular pressures and blood gas composition, major fluid shifts, paradoxical effects on the coagulation system, and ischemia–reperfusion injury are among a wide spectrum of alterations in homeostatic mechanisms that amplify this SIR, leading to major organ dysfunction [4]. At the level of the coronary arteries, this state of inflammation along with enhanced blood thrombogenicity is similar to the pathophysiologic changes described in acute coronary syndrome [10]. The reintroduction of off-pump CABG in the early 1990s has helped to some extent in reducing this state of whole-body inflammation. Yet, even without cardiopulmonary bypass, a significant amount of proinflammatory cytokines and cytotoxic enzymes are released into the circulation after off-pump CABG [11].

Stemming from a strong belief that less inflammation is potentially linked to improved outcomes, many pharmacologic and nonpharmacologic interventions aimed at controlling the inflammatory response in the postoperative period have been continuously studied during the past several years [12, 13].

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Abbreviations and Acronyms

AF = atrial fibrillation
AKI = acute kidney injury
CABG = coronary artery bypass grafting
CI = confidence interval
LDL = low-density lipoprotein
OR = odds ratio
PST = preoperative statin therapy
RCTs = randomized controlled trials
RRT = renal replacement therapy
SIR = systemic inflammatory response

Pleiotropic Effects of Statins in Patients Undergoing Coronary Artery Bypass Grafting

The lipid-lowering effect of statins is mediated by their reversible and competitive inhibition of the hydroxymethylglutaryl-CoA reductase enzyme that normally catalyzes the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, the rate-limiting step in the pathway of cholesterol synthesis. The inhibition of cholesterol synthesis results in upregulation of hepatic low-density lipoprotein (LDL) receptors, which increases the uptake of circulating LDL and LDL precursors, leading to a reduction in their plasma levels [14, 15]. Beneficial effects of statins that are independent of LDL reduction are commonly referred to as pleiotropic effects [2]. This pleotropic effect was first suggested in 1998 in a post-hoc analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) that showed improved outcomes in patients treated with pravastatin versus placebo, independent of the serum LDL levels [16].

The main pleiotropic effect of statins is the antiinflammatory role that was demonstrated in clinical trials by a significant reduction in serum levels of C-reactive protein, usually within 14 days of initiation of statin therapy, independent of serum LDL levels [17, 18]. This reduction was proven to be associated with delayed progression of atherosclerosis and improved cardiovascular outcomes [19, 20]. Statins also promote endothelial function by correcting the imbalance between nitric oxide, a vasodilator, and endothelin-1, a potent vasoconstrictor [21, 22]. The upregulation of nitric oxide, coupled with decreased production of thromboxane A_2 and increased production of prostacyclin, is thought to be the basis of the antithrombotic effects of statins [23, 24]. Besides, higher nitric oxide levels inhibit smooth muscle proliferation and partly explain the potential effect of statins in reducing the incidence of in-stent restenosis [25]. Statins also decrease atherosclerotic plaque neovascularization and macrophage content, leading to plaque stabilization and a reduction in the risk of plaque rupture [26]. Furthermore, statins demonstrated an antioxidant role through a reduction in LDL oxidation and its deleterious effects on vascular endothelial function [27]. Figure 1 illustrates the pleiotropic effects of statins.

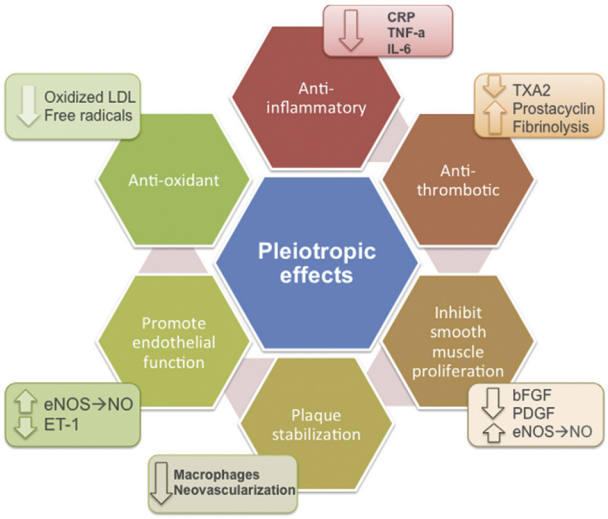

Fig 1. Pleiotropic effects of statins. (bFGF = basic fibroblast growth factor; CRP = C-reactive protein; eNOS = endothelial NO synthase; ET-1 = endothelin-1; IL-6 = interleukin 6; LDL = low-density lipoprotein; NO = nitric oxide; PDGF = platelet-derived growth factor; TNF-α = tumor necrosis factor alpha; TXA2 = thromboxane A_2.)

Nakamura and colleagues [28] randomly assigned 31 patients undergoing CABG to either aspirin alone or combined aspirin and atorvastatin therapy started on the day after surgery. On postoperative day 14, patients on combined therapy showed better inhibition of platelet activation and lower levels of thromboxane A_2, thrombin–antithrombin III complex, cytokine, cytokine receptor, and C-reactive protein compared with aspirin alone, demonstrating a favorable effect on the inflammatory response, endothelial cell function, and blood coagulation cascade in those patients. Another randomized trial by Radaelli and associates [29] showed that combined perioperative use of high-dose statins (either simvastatin 80 mg or atorvastatin 40 mg) with angiotensin-converting enzyme inhibitors (either ramipril 10 mg or enalapril 20 mg) resulted in significant attenuation in postoperative levels of interleukin 6 and tumor necrosis factor alpha with almost complete prevention of the intense SIR associated with on-pump CABG. Medications were started preoperatively (mean preoperative treatment duration was 21.9 ± 2.7 days) and were continued in the postoperative period. Similar effects were not reproducible with lower doses of statins [29]. Since then, multiple studies confirmed the positive effects of PST in the attenuation of SIR after CABG, using different inflammatory markers, such as C-reactive protein and interleukin 6 [6, 7].

Interestingly, recent studies showed that reloading patients who are on chronic statin therapy with higher doses of pravastatin preoperatively has an additional benefit in reducing SIR [30]. This novel therapeutic approach is currently under investigation in the ongoing Statin Recapture Therapy before Coronary Artery Bypass Grafting (StaRT-CABG) trial, to assess its effect on