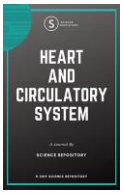

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Research Article

Perioperative Statin Reloading in Cardiac Surgery: A Review

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ABSTRACT

Introduction: There is good evidence that perioperative statin therapy is cardioprotective and reduces postoperative complications after cardiac surgery in statin-naive patients. However, most cardiac surgical patients will already be established on chronic statin therapy. Clinical and experimental evidence suggests that additional doses of statin treatment in this setting may be able to provide further benefit.

Methods: MEDLINE using the OVID interface was searched to December 2019 for randomised controlled trials of statin reloading in cardiac surgery.

Results: 932 papers were identified of which 5 met eligibility criteria. No study demonstrated a significant difference in clinical endpoints. One study found a 7.3% absolute risk reduction in the odds of postoperative atrial fibrillation which did not reach significance. Two further studies reported a reduction in proinflammatory cytokines. One of these also demonstrated decreased markers of cardiac and renal injury.

Discussion: Although statin reloading is cardioprotective in animal models, there is little translational evidence in humans. Current evidence suggests a protective effect of perioperative statin therapy for atrial fibrillation. However, this was not replicated by any of the reloading trials. Furthermore, studies were small trials with significant heterogeneity in both baseline and intervention statin regimens. We conclude that the current evidence base does not support additional statin therapy in patients on chronic statin treatment scheduled for cardiac surgery.

Background

Statins exert a lipid-lowering effect mediated by the reversible and competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme responsible for the rate limiting step in cholesterol biosynthesis. This leads to upregulation of hepatic low-density lipoprotein (LDL) receptors and increased clearance of LDL-cholesterol. Statins also reduce serum triglycerides and raise high-density lipoprotein (HDL) cholesterol levels [1]. The maximum therapeutic effect is seen after 4-6 weeks of starting treatment [2]. Beyond their role in the primary and secondary prevention of cardiovascular disease, statins exert a host of beneficial cholesterol-independent pleiotropic effects. These include vasodilatation, attenuation of inflammation and oxidative stress, platelet inhibition, anticoagulation and promotion of endothelial function [1, 3]. Many of these effects occur within 24 hours of statin initiation and before any significant reduction in serum cholesterol levels. These may act to oppose sympathetically mediated surgical stress and myocardial injury from the ischaemia reperfusion sequence.

A systematic review of 11 randomised controlled trials (RCTs) of preoperative statin therapy in cardiac surgery demonstrated a reduced incidence of postoperative atrial fibrillation (AF) (OR 0.54, 95% CI 0.43 to 0.67; $p < 0.01$) [4]. Statin therapy was also associated with a shorter length of intensive care unit (ICU) and hospital stay, although significant heterogeneity was observed. Studies included different proportions of participants taking different durations of pre-existing statin medication prior to study enrolment and subgroup analysis was not performed. A prospective observational study in elective coronary artery bypass graft surgery (CABG) of 5,436 patients found a significant reduction in early cardiac death with preoperative statin treatment [5]. In addition, meta-

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analysis of statin treatment in statin-naive patients undergoing both cardiac and non-cardiac surgery has shown a decreased perioperative incidence of mortality and myocardial infarction [6]. Meta-analysis of high-dose statin pre-treatment in patients undergoing percutaneous coronary intervention has also demonstrated a cardioprotective effect [7].

There is a growing body of clinical and experimental evidence that suggests additional preoperative statin doses can recapture this benefit which normally wanes with time in patients on chronic statin treatment [8]. Statins are thought to confer cardio protection and limit myocardial infarct size through activation of the reperfusion injury salvage kinase (RISK) pathway [9]. Animal studies have shown that atorvastatin reload before ischaemia reperfusion significantly reduced infarct size and rosuvastatin reload enhanced myocardial and coronary function after cardiac surgery with cardiopulmonary bypass (CPB) [10, 11]. In addition, patients receiving atorvastatin reload before percutaneous coronary intervention had a significant reduction in major adverse cardiac events at 30 days from 9.4% in placebo to 3.7% in the reload group [12]. This was primarily driven by a 59% reduction in periprocedural myocardial infarction. Biochemical markers of cardiac injury were also significantly lower in the statin reload group.

Most cardiac surgical patients will already be on statin treatment in line with current clinical guidelines. As a result, initiation of statin therapy has limited applicability in day-to-day clinical practice. The aim of this paper is to investigate whether additional preoperative doses of statin medication in patients already established on chronic statin treatment can reduce postoperative complications in cardiac surgery.

Methods

MEDLINE to December 2019 was searched using the OVID interface: (Statin*.mp OR Hydroxymethylglutaryl-coa reductase inhibitors/ OR (Simvastatin OR Rosuvastatin OR Fluvastatin OR Cerivastatin OR Lovastatin OR Pravastatin OR Atorvastatin).af) AND (Cardiac Surgery.mp OR Heart Surgery.mp OR Cardiac Surgical Procedures/ OR Coronary Artery Bypass/ OR Heart Valve Prosthesis Implantation/)

The titles and abstracts of studies were reviewed, and RCTs of patients undergoing cardiac surgical procedures were assessed for eligibility. Studies were included if they met the following criteria: prospective, patients already on long-term statin treatment or subgroup analysis performed for statin use prior to study entry and postoperative clinical or biochemical outcomes reported. Studies were excluded if they were not written in English or performed on animals.

Table 1: Overview of the studies.

Author, date, journal and country **Study type (level of evidence)**	**Patient group**	**Outcomes**	**Key results**	**Comments/weaknesses**
Kourliouros et al. (2011), *J Thorac Cardiovasc Surg*, United Kingdom [13] Single-centre prospective randomised trial (level 1b)	Patients on routine statin treatment. Atorvastatin given for 7 days before and 14 days after surgery, or until discharge. Atorvastatin 10 mg: n = 53 Atorvastatin 80 mg: n = 49	Atrial fibrillation (AF)	AF occurred in 19 of 53 (36%) in the 10 mg group vs 14 of 49 (29%) in the 80 mg group (p = 0.43)	Single-blinded Elective first-time coronary artery bypass graft (CABG) or aortic valve replacement (AVR) by a single surgeon Usual statin dose: atorvastatin 10 or 20 mg; simvastatin 10, 20 or 40 mg Usual statin discontinued during intervention period
Ludman et al. (2011), *Basic Res Cardiol*, United Kingdom [14] Single-centre prospective randomised trial (level 1b)	Patients on >4 weeks statin treatment. Study 1: Atorvastatin 160 mg 2 hours prior to surgery and 24 hours after: n = 23 Control (standard chronic statin therapy): n = 22	Myocardial injury (Troponin T (TnT) and creatine kinase (CK) prior to surgery and at 6, 12, 24, 48 and 72 hours) AF Duration of intensive care unit (ICU) stay Hours on mechanical ventilation	No significant difference between groups in all outcomes	Single-blinded Elective on-pump CABG Usual statin therapy continued in both groups Not adequately powered for clinical endpoints

	Study 2: Atorvastatin 160 mg 12 hours prior to surgery and 24 hours after: n = 30 Control (standard chronic statin therapy): n = 26	Need for re-operation		
Castaño et al. (2015), *J Cardiovasc Surg (Torino)*, Spain [15] Single-centre prospective randomised trial (level 1b)	Patients with dyslipidaemia on >15 days statin treatment. 2 hours prior to induction of anaesthesia: Pravastatin 80 mg: n = 10 Pravastatin 40 mg: n = 10 Placebo control: n = 10	AF Mortality (30 day) Duration of hospital stay Duration of ICU stay Myocardial injury (Troponin I (TnI) and CK-MB on ICU admission and 4, 8, 16, 24, 32, 40, 48, 96 hours and at 30 days) CK, AST, ALT and creatinine at the same time points Proinflammatory cytokines TNF-α and IFN-γ at baseline, 30 minutes after cross-clamp removal and at 24 hours and 5 days after surgery	No significant difference between groups in clinical outcomes or markers of myocardial, renal and hepatic injury Statin reloading reduced postoperative serum concentrations of proinflammatory cytokines: At 24 hours TNF-α and IFN-γ was lower in 80 mg pravastatin group compared with 40 mg and placebo groups ($p < 0.05$) After 5 days both 40 mg and 80 mg pravastatin groups had lower TNF-α and IFN-γ than placebo control ($p < 0.05$)	Double-blinded placebo-controlled Elective on-pump CABG under aortic cross-clamping Usual statin dose omitted night before surgery Usual statin dose: atorvastatin 20, 40 or 80 mg; simvastatin 20 or 40 mg; fluvastatin 40 or 80 mg
Billings et al. (2016), *JAMA*, USA [16] Single-centre prospective randomised trial (level 1b)	Patients on routine statin treatment Atorvastatin 80 mg given on the morning of surgery and 40 mg the morning after Intervention: n = 206 Placebo control: n = 210	Acute kidney injury (AKI) Creatinine peak at 48 hours Delirium Myocardial injury (Day 1 CK-MB) AF Stroke Pneumonia Time to extubation Duration of ICU stay Hospital mortality	No significant difference between groups in all outcomes	Double-blinded placebo-controlled Elective CABG, valve surgery or ascending aorta repair Usual statin was discontinued on day of surgery and resumed on postoperative day 2 AKI defined as an increase of 0.3 mg dL^{-1} in serum creatinine within 48 hours of surgery
Chee et al. (2017), *J Cardiothorac*	Patients on routine simvastatin or atorvastatin treatment with dose ≤40 mg	Serum IL-8 and MMP-9 levels at baseline, 5 minutes and 4 hours after cross-clamp removal	No significant difference between groups in clinical end points or MMP-9 levels at all time points	Study not blinded Elective on-pump cardiac surgery (including CABG,

Surg, Ireland [17] Single-centre prospective randomised trial (level 1b)	Atorvastatin 80 mg for 2 weeks before surgery Intervention: n = 15 Control: n = 15	High sensitivity TnI at baseline and 4 hours after cross-clamp removal Urine neutrophil gelatinase-associated lipocalin (NGAL) at 4 hours after cross-clamp removal Creatinine on admission and daily to postoperative day 5 Duration of ICU stay Duration of hospital stay Transient ischaemic attack Hours on mechanical ventilation	Trend towards lower creatinine in the treatment group which did not reach significance Urine NGAL 75.9 ± 35.9 ng ml^{-1} in control vs 48.4 ± 102.8 ng ml^{-1} in treatment (p = 0.002) Serum IL-8 was 8.6 ± 1.0 pg ml^{-1} at baseline in control vs 11.2 ± 1.8 pg ml^{-1} in treatment (p = 0.036). No significant difference at 5 minutes. At 4 hours, 28.3 ± 4.3 pg ml^{-1} vs 44.3 ± 8.5 pg ml^{-1} (p = 0.035). High sensitivity TnI similar at baseline. At 4 hours, 3516.1 ± 465.2 pg ml^{-1} in control vs 6380.6 ± 1672.5 pg ml^{-1} in treatment (p = 0.002).	valve and combined surgery) Study was not powered to detect a difference in clinical end points

Results

932 papers were found using the reported search. In total, 5 RCTs were identified that met eligibility criteria. Included studies ranged in size from 30 to 416 patients and evaluated a range of different statin medications and regimens in elective cardiac surgery. These are presented in (Table 1).

Kourliouros et al. compared 10 mg (n = 53) vs 80 mg (n = 49) atorvastatin daily for 1 week before and 2 weeks after elective CABG or AVR by a single surgeon [13]. High dose 80 mg atorvastatin was associated with a 7.3% absolute risk reduction in the odds of postoperative AF which was not statistically significant (p = 0.43). The study was underpowered due to an unexpected number of dropouts. In addition, a significantly higher rate of β-blocker usage in the low dose atorvastatin group (75% vs 53%, p = 0.002) may have attenuated any protective effect of higher dose atorvastatin. Discontinuation of usual statin therapy during the intervention period also represented a statin dose decrease for many patients in the 10 mg atorvastatin group, which may have had an adverse effect in this group.

Ludman et al. compared two atorvastatin reloading protocols (160 mg at 2 hours (n = 23) or 12 hours (n = 30) before, and 24 hours after elective on-pump CABG) against standard chronic statin therapy (n = 22 and 26 respectively) [14]. Usual statin therapy was continued in both groups. Despite high doses of atorvastatin, no biochemical or clinical side effects were seen. No benefit was found in relation to incidence of AF, duration of ICU stay and biochemical markers of myocardial injury at 6, 12, 24, 48 and 72 hours after surgery. However, surgery was confined to lower risk CABG with relatively low aortic cross-clamp and cardiopulmonary bypass times which limited the power to detect a significant difference between groups.

Castaño et al. evaluated dyslipidaemic patients with >15 days chronic statin therapy scheduled for on-pump CABG [15]. Usual statin therapy was discontinued the night before surgery with patients randomised to receive 40 mg (n = 10) or 80 mg pravastatin (n = 10) or placebo control (n = 10) at 2 hours prior to induction of anaesthesia. No significant difference in clinical outcomes and biomarkers of myocardial injury were reported. Statin reloading significantly reduced postoperative serum concentrations of proinflammatory cytokines (IFN-γ, TNF-α) in a dose-dependent manner. At 24 hours after surgery, IFN-γ and TNF-α was lower in the 80 mg pravastatin group compared with 40 mg and placebo groups ($p < 0.05$). After 5 days, both 40 mg and 80 mg pravastatin groups had lower IFN-γ and TNF-α than placebo control ($p < 0.05$). However, chronic statin treatment included simvastatin, atorvastatin and fluvastatin in a range of doses. This included doses as high as 80 mg atorvastatin which is more potent than both 40 and 80 mg pravastatin. As a result, it was unclear whether patients were reloaded or substituted with a weaker statin regimen at a critical time point before surgery.

Billings et al. reloaded patients already taking a statin with 80 mg atorvastatin at least 3 hours before CABG, valve surgery or ascending aorta repair and 40 mg the morning after (n = 206) [16]. This was compared with a time-matched placebo regimen (n = 210). Usual statin therapy was discontinued on the day of surgery and restarted on postoperative day 2. Subsequent continuation was at the discretion of the treating physician. There was no significant difference in reported clinical or biochemical outcomes between high dose atorvastatin reload

or short-term statin withdrawal (Table 1). Limitations to this study were the short 2-day duration of treatment which may not have been enough for pleiotropic effects to establish and control group statin withdrawal in the short perioperative study period.

Chee et al. studied patients already taking atorvastatin or simvastatin at a dose ≤ 40 mg undergoing cardiac surgery with cardiopulmonary bypass [17]. Operations included CABG, valve surgery and a combination of both. Treatment with 80 mg atorvastatin for at least 2 weeks before surgery (n = 15) was compared with continuation of their usual statin therapy (n = 15). The study was not powered to detect a difference in clinical outcomes but instead to a significant difference in IL-8 and MMP-9. Biochemical markers of inflammation, myocardial and renal injury were measured at baseline and at sequential time points after surgery. Serum IL-8 at baseline was lower in the control group than the intervention group (8.6 ± 1.0 pg ml^{-1} vs 11.2 ± 1.8 pg ml^{-1}, p = 0.036). This difference persisted at 4 hours after cross clamp removal (28.3 ± 4.3 pg ml^{-1} vs 44.3 ± 8.5 pg ml^{-1}, p = 0.035) but is difficult to interpret in view of the pre-existing difference at baseline. There was no difference in MMP-9 production at any time point.

There was a trend towards lower serum creatinine at postoperative day 5 in the reload group which did not reach significance. Urine NGAL is a predictive biomarker which rises in a dose-dependent and proportional manner to the degree of acute kidney injury. NGAL at 4 hours after cross clamp removal was significantly higher in the control group than the intervention group (75.9 ± 35.9 ng ml^{-1} vs 48.4 ± 102.8 ng ml^{-1}, p = 0.002). However, studies in adults undergoing cardiac surgery have found limited sensitivity in using NGAL to predict changes in serum creatinine [18, 19]. High sensitivity TnI was similar at baseline between both groups but was significantly higher in the control group at 4 hours after cross clamp removal (3516.1 ± 465.2 pg ml^{-1} vs 6380.6 ± 1672.5 pg ml^{-1}, p = 0.016).

Discussion

All included studies were small randomised controlled trials consisting of low risk, elective patients. Many studies excluded higher risk patients such as concomitant valve surgery, redo surgery, increased cross-clamp time, high Euroscore and impaired left ventricular function. These patients would be at higher risk of postoperative complications which may provide greater power to demonstrate a positive result from statin reloading. Most studies were of poor quality and not adequately powered to allow meaningful interpretation of clinical endpoints. Kourliouros et al. found a trend towards a reduction in the odds of postoperative AF [13]. Chee et al. also demonstrated a reduction in postoperative biomarkers of myocardial and renal injury, although the study only recruited 30 patients [17]. No complications of statin therapy were reported including increased skeletal muscle or hepatic markers of toxicity. While statin reloading is safe, there is limited evidence at present that this approach can recapture additional cardio protection.

Studies have included statin regimens of varying potency and duration with a high degree of heterogeneity with baseline chronic statin therapy. In many cases, the control group represented withdrawal of established statin medication which may have had an adverse effect. There is evidence that even statin withdrawal on day of PCI increases myocardial injury compared with a regimen of high dose atorvastatin [8]. Furthermore, the intervention in many studies involved switching from one statin to another, which makes the effect of reloading difficult to quantify. In addition, findings were limited in a few studies by inadequate blinding which introduced potential bias. None of the studies performed sufficient follow up to assess the effect of treatment on myocardial and renal function over a longer time period.

Statins vary in their potency and effectiveness in lowering LDL cholesterol levels. Pravastatin, fluvastatin, lovastatin and simvastatin are considered less potent than atorvastatin and rosuvastatin [20]. In addition, statins also possess different potencies for extra-hepatic effects which have not yet been fully explored [2]. The hydrophilic statins rosuvastatin and pravastatin require activated carrier-mediated transport to cross cell membranes and are more selective for hepatic tissues than lipophilic statins. It is unclear whether and to what extent statin pleiotropy relates to their hepatic or non-hepatic effects and how this differs between different statin medications.

The available evidence suggests a protective effect of perioperative statin therapy on complications after cardiac surgery in statin-naive patients [4]. These favourable effects have been replicated in statin reloading prior to percutaneous coronary intervention with a significant reduction in major adverse cardiac events [12]. However, there is little published evidence on this topic in cardiac surgery despite this being a more pragmatic clinical approach. Although Kuhn et al. found that a statin reload prior to cardiopulmonary bypass enhanced myocardial and coronary function in porcine models, there is currently little translational evidence in humans [10]. A large multi-centre RCT of statin reloading in CABG is currently underway with the hope of clarifying the uncertainty surrounding this approach [21]. While statin-naive patients should be commenced on a statin prior to elective surgery, current best evidence does not support a strategy of reloading in the context of chronic therapy.

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