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REVIEW ARTICLE

# A peri-operative statin update for non-cardiac surgery. Part I: The effects of statin therapy on atherosclerotic disease and lessons learnt from statin therapy in medical (non-surgical) patients

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## Summary

The utility of peri-operative statin therapy is currently considered to be inconclusive. To provide a platform for more meaningful peri-operative statin literature in the future, this is the first of two review articles evaluating peri-operative statin therapy. This review examines the predictors of cardiovascular outcome and therapeutic targets which are established in medical (non-surgical) patients. In patients with stable coronary artery disease at least 4–6 weeks of standard statin therapy are required to realise most of the beneficial cellular and metabolic effects of statin therapy. Low-density lipoprotein-cholesterol reduction is associated with improved survival in these patients. In comparison, patients who sustain an acute coronary event require high-dose statin therapy probably initiated within 24 h with a therapeutic target of C-reactive protein reduction. Withdrawal of statin therapy results in a rapid return to endothelial dysfunction and amplification of the inflammatory process, which may increase cardiovascular risk.

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The role of statin therapy in the management of cardiovascular disease has evolved rapidly as a result of the potential benefits statins offer to a wide range of cardiovascular patients. A MEDLINE search (8 May 2007) revealed almost 4900 new publications from the beginning of 2005. Yet, in anaesthesia there remains one small randomised controlled trial in non-cardiac surgery [1]. The two systematic reviews considering peri-operative statin therapy suggest that as the majority of the data are observational, further prospective studies are needed [2, 3].

To avoid a similar scenario developing with peri-operative statin therapy to that which now bedevils peri-operative beta-blockade, where initial enthusiasm [4] has been tempered by inconclusive reviews [5, 6], it is important at this early stage of peri-operative statin therapy to identify appropriate surgical patients, therapeutic strategies and possible confounders (such as therapy withdrawal) that should be considered in all peri-operative statin research.

Adopting a standardised approach to possible statin studies, which report similar endpoints in publication, may help in preventing the 'beta-blocker scenario'. The peri-operative beta-blockade literature has highlighted factors that may have contributed to the confusion regarding the cardioprotection of acute peri-operative beta-blockade, including dosage [7], duration of therapy [8, 9], the risk profile of the patient group [9, 10], and the role of chronic therapy [11].

To make appropriate recommendations, this, the first of two review articles, focuses on recent developments in our understanding of cellular and metabolic responses to statin therapy, in particular with respect to time to clinical effect in both stable and unstable coronary artery disease

(CAD), as well as recent publications concerning meta-analyses of the efficacy of statins in various patient groups. The second review article considers the role inflammation plays in peri-operative cardiac events, and the utility and safety of statin therapy in vascular surgical patients with comorbidities that traditionally have been considered contra-indications to statin therapy. Recommendations for peri-operative statin therapeutic strategies, prospective study design and appropriate retrospective reporting are suggested.

## The pathophysiology of atherosclerosis

Atherosclerosis is a well-defined inflammatory process [12]. Endothelial dysfunction results from various factors, including haemodynamic disturbances such as turbulence or shear stress, classical cardiovascular risk factors, changes in coagulation status and oxidation of low-density lipoprotein-cholesterol (LDL-C) [12–17]. Increased endothelial gene expression of the atherothrombogenic cell surface protein CD40/CD40L and the nuclear transcription factor kappa B (NFκB) follows [15]. Endothelial cells secrete chemoattractant molecules to recruit mononuclear phagocytes, of which vascular cell adhesion molecule-1 (VCAM-1) appears to be particularly important [14]. Monocytes pass into the intima down a chemoattractant gradient partly generated by monocyte chemoattractant protein-1, where the monocyte is transformed into a tissue macrophage [14]. Lipid accumulates in the intima, which is scavenged by macrophages that become lipid-laden foam cells. They further amplify the inflammatory process by secreting inflammatory cytokines and mediators, increasing leucocytes in the intima. This early atherosclerotic lesion consisting of foam cells and activated T-lymphocyte cells is known as a 'fatty streak' [12]. ICAM-1, P-selectin and E-selectin secretion further increases leucocyte recruitment [13].

Exposure to oxidised LDL and heat shock proteins results in T cells secreting other cytokines. This in turn results in the macrophages increasing the expression of the procoagulant tissue factor and extracellular matrix-degrading proteinases (matrix metalloproteinases, MMP), which weaken the fibrous cap. Release of pro-inflammatory cytokines (such as interferon (IFN)-γ) further limit synthesis of collagen [14]. Interleukins, NFκB and MMP also stimulate smooth muscle migration [18], which is necessary to isolate the atherosclerotic lesion from the vessel lumen [12]. Release of these mediators results in pro-inflammatory polarisation of helper T-cell secretion ($T_H1$) as opposed to anti-inflammatory cytokine release ($T_H2$) [14]. Plaque formation progresses with continued recruitment of inflammatory cells and lipid accumulation in the intima, which expands abluminally [14]. Neovascularisation of the atherosclerotic lesion further amplifies the inflammatory response [13].

Plaque rupture is a function of intrinsic and extrinsic factors acting on the plaque [19]. Intrinsic factors are related to the plaque morphology. Vulnerable plaque has a thin fibrous cap, with a large necrotic lipid pool, characterised by neovascularisation and many inflammatory cells [13, 19]. In contrast, a stable plaque has a thick fibrous cap, with a small lipid pool and a preserved vascular lumen [14]. Intrinsic factors associated with fibrous cap rupture include endothelial erosion secondary to MMPs, which degrade the extracellular matrix, and IFN-γ, which induces smooth muscle cell apoptosis and decreases collagen synthesis [15].

The extrinsic factors that may be associated with plaque rupture include circumferential stress, haemodynamic shear stress, vasospasm, plaque fatigue and coagulation factors [13]. Plaque rupture results in thrombosis secondary to exposure to macrophage-derived tissue factor and collagen [20]. Rupture with thrombosis formation results in unstable coronary syndromes [12]. Thrombin further stimulates smooth muscle proliferation, platelet-derived growth factor (TDGF) stimulates smooth muscle migration, and transforming growth factor-β (TGF-β) released from activated platelets stimulates interstitial collagen production [14]. This results in an increase in the extracellular matrix and subsequent encroachment on the lumen [14]. If it is non-occlusive, it may be re-absorbed, with resultant fibrous or calcified cap formation [16]. It is these lesions that lead to significant stenosis and stable angina [16].

## The documented beneficial effect of statins on atherosclerosis

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase and thus decrease cholesterol synthesis. A second effect of HMG CoA reductase inhibition is decreased L-mevalonic acid synthesis, which inhibits synthesis of isoprenoid intermediates such as farnesyl pyrophosphate and geranylgeranylpyrophosphate [21]. These intermediates are necessary for post-translation modification of various proteins essential for cellular signalling and intracellular trafficking [21]. These pleiotropic effects can be anti-inflammatory, vasodilatory and antithrombogenic [21].

The reported times for these beneficial effects to appear following statin initiation in stable CAD, following unstable coronary syndromes and the time to reversal of

effects following withdrawal of statin therapy are shown in Table 1.

The following important trends need to be considered to determine an appropriate duration of statin therapy for peri-operative protocols. The time to documentation of beneficial effects as listed in Table 1 is generally longer in hypercholesterolaemic patients than in normocholesterolaemic patients. This is probably because oxidised lipoproteins are potent inducers of inflammation [14]. Furthermore, early immunomodulation with statin therapy is quicker following acute coronary syndromes in comparison with the time in patients with stable CAD. This may be a result of the important role inflammation plays in unstable coronary syndromes [22] as opposed to stable CAD.

Withdrawal of statin therapy results in a shorter time to reversal of beneficial pleiotropic effects, in comparison with the time taken to exert significant immunomodulation following acute coronary syndromes. In particular, cell signalling and endothelial permeability and dysfunction may be very rapidly reversed, whereas there may be a prolonged period of protection from the detrimental matrix metalloproteinase activity.

*Implications for anaesthetists*

In patients with stable CAD presenting for surgery in whom peri-operative statin therapy is considered desirable, at least 4–6 weeks of statin therapy would be required pre-operatively potentially to realise most of the beneficial cellular and metabolic effects of statin therapy. In patients who are hypercholesterolaemic, this run-in period should be longer.

Patients who sustain an acute coronary event may have rapid reversal of inflammatory markers following initiation of statin therapy, although endothelial dysfunction is prolonged. The clinical importance of this observation is discussed later.

Finally, following withdrawal of statin therapy there is a rapid return to endothelial dysfunction and amplification of the inflammatory process, which may increase cardiovascular risk.

## Mechanisms of statin-associated survival in medical patients

The cardioprotective mechanisms of statin-associated survival differ following acute coronary syndromes (ACS) and in stable CAD. In addition, analysis of percutaneous coronary interventions (PCI) may provide information on statin-mediated cardioprotection prior to a coronary insult. An understanding of these mechanisms is essential for ensuring an appropriate peri-operative therapeutic strategy.

### Stable coronary artery disease

Statin therapy has been shown to be cardioprotective in patients with hypercholesterolaemia, stable CAD, cardiovascular disease equivalents and patients at risk of cardiovascular disease [50–56]. LDL-C lowering is probably the most important mechanism by which statins improve long-term cardiovascular outcomes [57]. A recent meta-analysis showed a proportional reduction of 12% in all-cause mortality per $mmol.l^{-1}$ reduction in LDL-C (relative risk (RR) 0.88, 95% CI 0.84–0.91, $p < 0.0001$) [58]. This was attributed to the significant decrease in coronary heart disease deaths (RR 0.81, 95% CI 0.76–0.85, $p < 0.0001$). All other deaths (secondary to stroke, other vascular causes and non-vascular causes) were non-significantly decreased [58].

A recent meta-regression analysis could not differentiate statin trials from other modalities of LDL-C reduction (such as diet, bile acid sequestrants and ileal bypass surgery) when the effect of the achieved LDL-C in the identified studies was compared to late coronary heart disease death and fatal and non-fatal stroke [59]. It appears that the relative-risk reduction of cardiac death and non-fatal myocardial infarction is directly proportional to the percentage LDL-C reduction [59]. Others have suggested that this is not necessarily true, as some of the non-statin trials were conducted over a longer period of time to achieve the same clinical benefit [21]; however, the duration of therapy was controlled in this meta-regression analysis and thus the argument that LDL-C reduction is of primary importance still holds true [59]. The implication of this study is that the pleiotropic effects of statins offer little or no additional late cardiovascular protection over and above the degree of LDL-C reduction.

The duration of statin therapy is important. Whereas the majority of cellular and metabolic benefits of statins require 1–2 months of therapy in stable CAD (Table 1), this only translates into a survival benefit after about a year of therapy [55]. Further statin therapy may also result in atherosclerotic regression after 18–24 months of statin therapy. Independent predictors of coronary atherosclerosis regression exceeding 5% are a decrease in LDL-C to a mean $< 87.5$ $mg.dl^{-1}$ ($2.3$ $mmol.l^{-1}$) and increase in HDL-C $> 45.1$ $mg.dl^{-1}$ ($1.2$ $mmol.l^{-1}$) [60].

The efficacy of high-dose (intensive) statin therapy for patients with stable coronary artery disease is controversial. Atorvastatin 80 mg daily with LDL-C of approximately 2 $mmol.l^{-1}$ possibly offers cardiovascular protection (a composite of cardiac death, non-fatal myocardial infarction, non-fatal cardiovascular accident (CVA) and non-fatal cardiac arrest) to patients with stable CAD [61, 62]. This is, however, associated with a significantly increased incidence of raised aminotransferases (1–1.2% vs 0.1–0.2%) [61, 62].

**Table 1** The shortest reported times to a significant change in lipid lowering and anti-inflammatory actions of statins in humans.

| Pathophysiology of atherosclerosis | Marker studied | Reported times to a significant change in | | |
|---|---|---|---|---|
| | | Stable CAD | Unstable CAD | Withdrawal in CAD-reversal of beneficial effect |
| ↑ Cholesterol | Total cholesterol | 6 weeks* [23]<br>8 weeks† [24] | 1 month [28] | No change 7 days* [23] |
| | LDL-C | 1 week*‡ [25]<br>1 week* [26]<br>4 weeks [27]<br>6 weeks* [23]<br>16 weeks† [24] | 1 month [28]<br>1 month† [29] | No change 7 days* [23] |
| ↑ Oxidised LDL | Antibodies against oxidised LDL | 16 weeks† [24] | | 14 days [30] |
| ↑ Reactive oxygen species | TBARS, FRAP | 6 weeks [31] | | 6 weeks [31] |
| Activation of CD-40, NFκB pathways | Soluble CD40 ligand | 3 months* [32] | | |
| Endothelial dysfunction: | Nitroglycerin-mediated dilation | | 4 months [33] | |
| ↓ nitric oxide, ↑ endothelin 1 | Nitric oxide synthetase | 4 weeks [27] | | |
| | Flow-mediated dilation | 6 weeks* [34]<br>1 week*‡ [25] | 10 days (only UAP) [35]<br>4 months [33] | 36 h*‡ [25] |
| | Acetylcholine-mediated coronary vasoconstriction | 24 h [36] | | |
| Adhesion molecules: | ICAM, E-selectin | 12 weeks* [37] | 7 days (after PCI) [39] | |
| ↑ ICAM, VCAM, E-selectin, P-selectin | VCAM | No change at 3 months* [38]<br>No change at 16 weeks† [24] | | 2 days* [37] |
| ↑ interleukins | IL-6 | 6 weeks [40],<br>6 weeks* [23] | | 3 days* [23] |
| Chemotaxis:<br>↑ Monocyte chemoattractant protein-1 | | | 4 weeks† [41] | |
| ↑ Inflammatory cytokines | TNF-α, IFN-γ | | 72 h [42] | |
| ↑ Acute phase proteins | C-reactive protein | 2 weeks* [26]<br>4 weeks [43]<br>No change 16 weeks† [24] | 5 days† [44] | 3 days* [23]<br>6 weeks [31] |
| | Serum amyloid A | | 5 days [44] | |
| ↑ growth factors:<br>↑ Platelet-derived growth factor, fibroblast growth factor, transforming growth factor-β | | | | |
| ↑ Matrix metalloproteinases, ↓ tissue inhibitors of MMP | MMP-1 | 6 weeks [40]<br>No change 3 months* [38] | | |
| | MMP-2 | 3 months* [38] | | No change 120 days* [45] |
| | MMP-3 | No difference at 6 weeks [40] | | Reduced 120 days* (beneficial effect) [45] |
| | MMP-8 | 6 weeks [40] | | |
| | MMP-9 | No difference at 3 months* [38] | | No change 120 days* [45] |
| ↑ Pro-inflammatory helper T cells | $T_H1$ | No difference after 3 months* [32] | 72 h [42] | |
| Neutrophil activation | Serum myeloperoxidase | | 7 days [46] | |
| Hypercoagulability: | Platelet aggregation | | | 14 days [30] |
| ↓ TF, ↑ thrombomodulin, ↑ PAI, ↓ tPA, ↑ vWF | Soluble endothelial protein C receptor, free TF pathway inhibitor | | 6 h [48] | |
| | tPA | 12 weeks* [37] | | 3 days* [37] |
| | vWF | 60 days* [47] | 180 days [49] | No change 90 days [49] |
| | | No difference at 16 weeks† [24] | | |
| ↓ Fibrinolysis: Platelet-derived factors and endothelial-derived factors | Platelet-dependent thrombin generation | 2 weeks* [47] | | |
| | PAI-1 | 3 weeks* [47] | | |

**Table 1** (*Continued*).

| Pathophysiology of atherosclerosis | Marker studied | Reported times to a significant change in | | |
|---|---|---|---|---|
| | | Stable CAD | Unstable CAD | Withdrawal in CAD-reversal of beneficial effect |
| ↑ Inflammatory cells | Leucocytes<br>Lymphocytes | No difference after 3 months* [32] | | |

*Hypercholesterolaemic patients. †Intensive vs standard statin therapy. ‡Intensive statin therapy vs placebo.
LDL-C, low-density lipoprotein-cholesterol; CAD, coronary artery disease; TBARS, thiobarbituric acid reactive substance; FRAP, ferric-reducing ability of plasma; NFκB, nuclear transcription factor kappa B; UAP, unstable angina pectoris; ICAM, intercellular adhesion molecule; VCAM, vascular adhesion molecule; IL-6, interleukin-6; TNF-α, tumour necrosis factor α; IFN-γ, interferon γ; MMP, matrix metalloproteinase; $T_H$, T-helper cells; TF, tissue factor; PAI, plasminogen activator inhibitor; tPA, tissue plasminogen activator; vWF, von Willebrand factor

The role of intensive statin therapy in decreasing inflammatory markers, such as highly selective C-reactive protein (hsCRP), for primary cardiovascular protection is currently being investigated in patients with stable CAD [63].

Importantly, withdrawal of statin therapy for up to 6 weeks in patients with stable CAD does not result in an increased number of acute coronary events [64].

*Implications for anaesthetists*

Although 4–6 weeks of pre-operative statin therapy is desirable based on cellular and metabolic responses, in patients with stable CAD it is possible that a longer duration of therapy is necessary to realise survival benefits. In addition, LDL-C reduction should be considered important prior to surgery, as it is this response to statin therapy that is associated with improved survival in patients with stable CAD.

## Acute coronary syndromes (ACS)

The fundamental difference between ACS and stable CAD is the number of recurrent coronary events within the first 6 months following an ACS in comparison with stable CAD [57]. Whereas death and recurrent myocardial infarction may exceed 12% in patients following ACS, the same outcome may be less than 2% in patients with stable CAD [57].

The amount of plaque and the degree of inflammation have been associated with ACS. Acute coronary syndromes are associated with vulnerable atherosclerotic plaques [20]. The amount of plaque (or plaque burden) is a predictor of ACS [65]. hsCRP, the marker of inflammation, has been associated with adverse cardiovascular outcomes [21]. Importantly, there is a correlation between systemic inflammation and local coronary inflammation in acute coronary syndromes [66]. Thus the pleiotropic effects associated with statins may be relatively more important following ACS [57] and assessment of the LDL-C in isolation would be inappropriate.

Analysis of the efficacy of statins following acute coronary events is essential if one is to identify appropriate management protocols for patients who sustain an acute coronary event following surgery. Indeed, the efficacy of statin therapy following ACS is surprisingly poor when compared to the efficacy shown in long-term trials of stable medical patients. Whereas the relative-risk reduction in a composite endpoint of death, non-fatal myocardial infarction and non-fatal stroke at 4 months following an acute coronary event is 7.4% [67], in stable CAD the relative-risk reduction for coronary events alone is 14% for the first year and then 20–30% per subsequent year per $mmol.l^{-1}$ reduction in LDL-C [58]. The relative-risk reduction for all-cause mortality is 12% and 19% for coronary heart disease mortality in long-term secondary and primary prevention studies, respectively [58]. At 2 years, the relative-risk reduction for a composite of cardiovascular outcomes is only approximately 20% following ACS [68].

Analysis of the prospective studies of ACS [28, 29, 69] have identified the following therapeutic principles for statin therapy:

- it should start early;
- it should be high-dose (intensive) therapy, guided by inflammatory markers;
- it should not be withdrawn;
- it should continue for the long-term.

## Statin therapy should be initiated as early as possible following an acute coronary event

*Prospective studies*

A meta-analysis of the prospective randomised trials that started statins within 14 days of an acute coronary event showed no improvement in short-term composite outcome of death, non-fatal myocardial infarction and non-fatal stroke at 1 and 4 months (RR 0.93, 95% CI 0.80–1.09, p = 0.39) and (RR 0.93, 95% CI 0.81–1.07, p = 0.3), respectively [67]. A further meta-analysis showed that survival and cardiovascular events only begin

to separate at 4 months and only achieve statistical significance for a composite of any cardiovascular event at 6 months [68]. Over 2 years of follow-up, statin therapy decreased death and cardiovascular events (hazard ratio (HR) 0.81, 95% CI 0.77–0.87, $p < 0.001$), with a relative-risk reduction of approximately 20% [68].

The studies included in this meta-analysis however, randomly assigned patients to statin therapy as late as a mean of 14 days after the acute coronary event [67, 68]. As inflammation is central to the pathophysiology of the acute coronary event, it may be argued that randomisation after 14 days may be too late to realise any short-term clinical benefits secondary to the profound amplification of the inflammatory response over a 2-week period. It is possible that statin therapy should administered close to the acute coronary event to improve early cardiac outcomes, secondary to earlier immunomodulation. However, no significant improvement in 30-day outcome was shown in an analysis of the studies that randomly assigned all patients within a mean of the first 3 days following an ACS using RevMan (version 4.2.8 for Windows; The Nordic Cochrane Centre, Copenhagen, Denmark) with random effects meta-analysis and analysis of a combined endpoint of death, non-fatal myocardial infarction and non-fatal stroke (Table 2, Figs 1–3). The heterogeneity between these studies is, however, large, with an $I^2$ statistic exceeding 25% in all the analyses.

**Table 2** ACS and 30-day composite endpoint of death, non-fatal myocardial infarction and non-fatal stroke in prospective randomised trials.

| Randomisation following ACS | RR | 95% CI | p | $I^2$ |
|---|---|---|---|---|
| Mean day 1 [70, 71] | 0.60 | 0.22–1.64 | 0.31 | 71.9% |
| Mean days 1 and 2 [70–73] | 0.73 | 0.37–1.41 | 0.35 | 37.7% |
| Means days 1–3 [69–73] | 0.90 | 0.66–1.23 | 0.50 | 35.9% |
| Mean up to 12 days [67] | 0.93 | 0.80–1.09 | 0.39 | |

RR, relative risk; ACS, acute coronary syndrome.

Interestingly, the time to a significant improvement in cardiac outcome following ACS tracks the time to improvement of endothelial function following initiation of statin therapy after ACS, which is 4 months [33], despite the rapid improvement in inflammatory markers within a week of statin therapy (Table 1).

*Retrospective studies*

Retrospective data that are covariate-adjusted suggest that statin therapy initiated within 24 h of admission for an acute coronary event may be beneficial (Table 3), significantly decreasing in-hospital death (RR 0.62, 95% CI 0.57–0.67, $p < 0.001$) [74]. There is also a suggestion that statin initiation within 24 h of admission is preferable to administration after 24 h, with a significant decrease in the composite endpoint for in-hospital death, re-infarction and non-fatal stroke (odds ratio (OR) 0.62, 95% CI 0.39–1.00, $p < 0.5$) [75].

When interpreting the retrospective studies regarding statin administration (and withdrawal) following acute coronary events (Table 3), one needs to consider the following. Firstly, patients on chronic statin therapy should be distinguished from patients who have statins administered for the first time after an acute coronary event, as these two groups may have different outcomes [74]. Secondly, studies must control for other cardiac medications. Patients on outpatient statin therapy are more likely to be on other cardiac medication [74]. Thirdly, it is important to ensure that studies reporting a 'no statin group' ensure that this group does not include patients who have had statins withdrawn prior to recruitment [76], as withdrawal of statin therapy is often associated with withdrawal of other cardiac medications such as beta-blockers. For example, the study of Fonarow

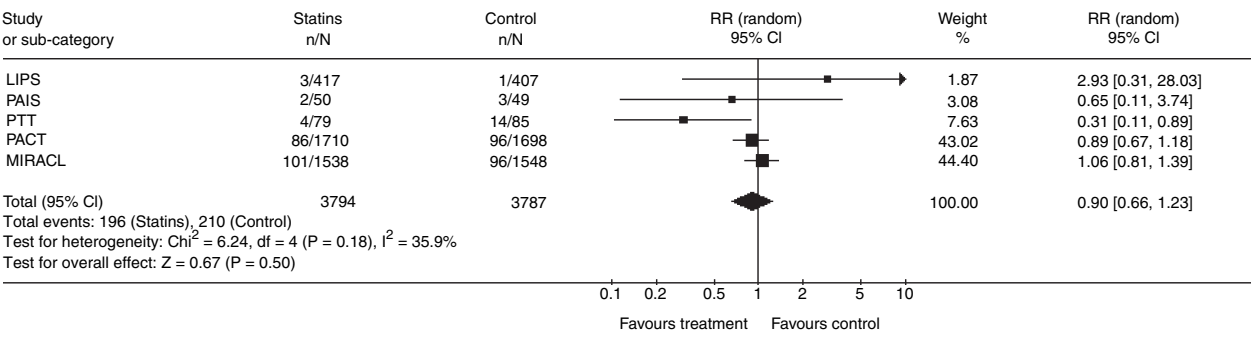


**Figure 1** Thirty-day composite endpoint of death, non-fatal myocardial infarction and non-fatal stroke in the prospective studies of statin therapy following acute coronary syndromes which randomly allocated patients within a mean period of 3 days of the acute coronary event.

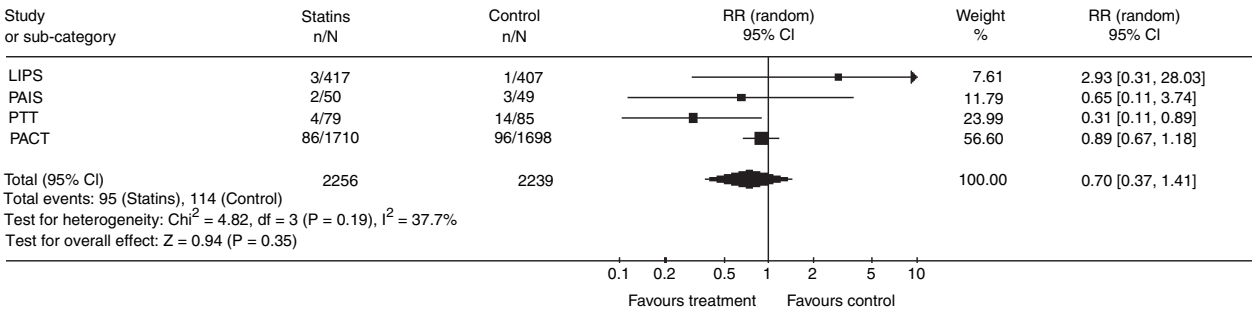


**Figure 2** Thirty-day composite endpoint of death, non-fatal myocardial infarction and non-fatal stroke in the prospective studies of statin therapy following acute coronary syndromes which randomly allocated patients within a mean period of 2 days of the acute coronary event.

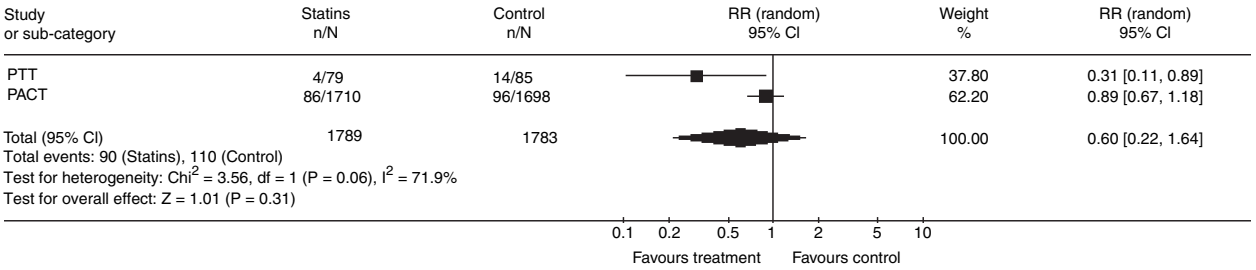


**Figure 3** Thirty-day composite endpoint of death, non-fatal myocardial infarction and non-fatal stroke in the prospective studies of statin therapy following acute coronary syndromes which randomly allocated patients within a mean period of first day of the acute coronary event.

**Table 3** Characteristics of retrospective statin studies following acute coronary syndromes.

| Study | Time of statin initiation after admission | ''Chronic statin therapy included in 'statin group''' | '''No statin group' includes chronic statin withdrawal'' | Covariate-adjusted | Statin therapy (before and after ACS) | | |
|---|---|---|---|---|---|---|---|
| | | | | | NY vs NN (statin with no chronic therapy) | YY vs NY (chronic vs acute therapy) | YN vs NN (withdrawal) |
| Fonarow et al. [74] | < 24 h | No | No | Yes | Adjusted OR 0.62 (0.57–0.67)* | Unadjusted OR 1.34 (1.22–1.48)* | Adjusted OR 1.12 (1.05–1.20)* |
| Lenderink et al. [79] | < 24 h | No | No | Yes, but not for pre-admission medication | Adjusted HR 0.34 (0.15–0.79)† | Not studied | Not studied |
| Wright et al. [76] | < 24 h | Possible | Possible | No | Impossible to assess | Impossible to assess | Impossible to assess |
| Saab et al. [75] | < 24 h | No | No | Yes | Adjusted OR 0.62 (0.39–1.00) p < 0.05§ | Not studied | Not studied |
| Spencer et al. [80] | < 24 h | No | No | Yes, except chronic beta-blockade | Not studied | Unadjusted OR 1.00 (0.75–1.33)* | Adjusted HR 1.03 (0.93–1.15)* |
| Heeschen et al. [81, 82] | Not specified | No | No | Yes | Not studied | Not studied | Adjusted HR 1.50 (0.7–3.19)‡ |

Y, yes; N, no. ACS, acute coronary syndrome.
*In-hospital mortality; †7-day mortality; ‡30-day death or non-fatal myocardial infarction; §in-hospital death, re-infarction and non-fatal stroke.

and colleagues [74] showed that the group that had statin withdrawal had the lowest rate of beta-blocker administration within the first 24 h (57%) compared to the groups that had statins continued (74.5%) or initiated (80.9%) within the first 24 h. The withdrawal of chronic beta-blockade is an independent predictor of in-hospital

mortality in surgical patients [77], although this has not been shown in medical patients following acute myocardial infarction [78]. Withdrawal of beta-blockade does, however, increase subsequent myocardial ischaemia [78]. Covariate adjustment that does not include pre-admission medications cannot therefore control for withdrawal of cardiac medications. Caution is therefore advised in interpreting the results of Wright et al. [76] and Lederink et al. [79] in Table 3. Studies that do not control for these covariates (timing of beta-blocker and statin administration and/or withdrawal) show an increased risk for adverse cardiac outcomes in the non-statin group [76].

Surprisingly, there appear to be no studies comparing chronic statin therapy to acute statin administration following acute coronary syndromes. However, data are available in two retrospective studies (Table 3), although unadjusted for covariates [74, 80]. One of these studies showed an increased risk of in-hospital mortality in the group of patients on chronic statin therapy; however, these patients had significantly more diabetes, renal dysfunction, previous myocardial infarction, hypertension and congestive heart failure [74]. It is therefore impossible to assess the relative beneficial effect of chronic statin therapy compared to acute statin therapy following acute coronary syndromes.

*Implications for anaesthetists*

It is highly probable that early cardioprotection following ACS will only be realised if statins are started before or very early (within 24 h) after an acute coronary event. Thus it is probably more important for anaesthetists to identify correctly patients at risk of peri-operative coronary events and institute statins pre-operatively in these patients, as opposed to initiating statin therapy after an established coronary event.

## Statin therapy should be intensive following acute coronary syndromes

Intensive statin therapy may result in earlier cardioprotection (before 4 months) following ACS. A recent meta-analysis has defined intensive statin therapy as atorvastatin 80 $mg.day^{-1}$, simvastatin 80 $mg.day^{-1}$ or rosuvastatin 20–40 $mg.day^{-1}$ [83]. In the PROVE-IT study, 80 mg atorvastatin daily decreased the composite endpoint of death, myocardial infarction and recurrent ACS significantly by 30 days (HR 0.72, $p = 0.048$) [29, 57], despite the relatively late median time to randomisation of 7 days after the acute coronary event. Early intensive therapy improves the combined endpoint within 30 days of an ACS and continues to provide superior cardioprotection at 4 months [28] and 6 months [29]. Importantly, as inflammatory modification is necessary following ACS, intensive therapy should be initiated irrespective of LDL-C level [29]. Intensive statin therapy also decreases all-cause mortality from 4.6% to 3.5% (relative-risk reduction 24%) at 2 years following acute coronary syndromes (OR 0.75, 95% CI 0.61–0.93, $p = 0.01$) [83].

This is in contrast to stable coronary heart disease, where intensive therapy decreases major adverse cardiac events (MACE) (OR 0.82, 95% CI 0.75–0.91, $p < 0.0001$) and hospitalisations for heart failure (OR 0.77, 95% CI 0.64–0.92, $p = 0.003$), but not all-cause mortality over 4.7 years [83]. It appears that intensive statin therapy does not offer further anti-inflammatory advantages in comparison with standard statin therapy in patients with stable cardiovascular disease [24]. Intensive therapy is cost-effective in ACS, whereas in patients with stable CAD it is controversial [84]. These observations are important as intensive statin therapy significantly increased the incidence of elevated hepatic transaminases $>3$ times the upper limit of normal (ULN) (OR 3.72, 95% CI 2.10–6.57, $p < 0.00001$) [83].

*Implications for anaesthetists*

Although intensive statin therapy decreases MACE in patients with stable CAD, it is not cost-effective and is associated with significantly increased transaminase levels. It would be appropriate to consider standard therapy preferable in all patients except those who sustain an acute coronary event.

## The utility of inflammatory markers to guide statin therapy in acute coronary syndromes

In the PROVE-IT trial, CRP was significantly reduced at 4 weeks, and it was independent of the LDL-C [85]. Importantly, both CRP and LDL-C were independent predictors of an adverse outcome [43]. An elevated CRP at the time of hospital admission for unstable angina is associated with a poorer outcome [22]. Intensive statin therapy results in lower CRP levels following ACS [85–87]. Although LDL-C is probably more important for long-term outcome, CRP reduction is probably more important for earlier outcomes [87]. At 1 month, PROVE-IT found significantly lower CRP between treatment groups in comparison to the A–Z study. In the PROVE-IT study, patients with lower hsCRP had a significantly better outcome independent of LDL-C levels [43, 85, 86]. hsCRP also has a positive correlation with multiple plaque rupture following myocardial infarction [88]. The therapeutic target associated with the most significant decrease in cardiac death and recurrent myocardial infarction following an acute coronary syndrome was a combined target of LDL-C $< 70$ $mg.dl^{-1}$ (1.8 $mmol.l^{-1}$) and an hsCRP $< 2$ $mg.l^{-1}$ [85].

*Implications for anaesthetists*

C-reactive protein should be used as a therapeutic target in all patients who have had an acute coronary event.

## Early withdrawal of statin therapy following acute coronary syndromes

It is currently controversial whether statin therapy withdrawal following an acute coronary event increases the risk of major cardiac morbidity and mortality. Covariate-adjusted retrospective studies have shown both an increased in-hospital mortality [74] and no difference in in-hospital mortality [80] or in-hospital mortality and recurrent myocardial infarction [82] when statins were withdrawn within the first 24 h following an acute coronary event, in comparison with patients who have never received statin therapy (Table 3). Importantly, however, these studies show a trend towards increased major cardiac mortality or morbidity associated with withdrawal of statins following acute coronary syndromes.

If statin withdrawal is detrimental, then what is the pathophysiology of increased coronary events? Table 1 suggests that the beneficial effects of improved flow-mediated dilation of arteries and decreased inflammatory mediators such as adhesion molecules and cytokines are rapidly reversed following statin withdrawal (most within the first 3 days). The implications are that flow may increase in coronary arteries within the first 24 h, which may increase shear stress on the plaque. An increased heart rate is an independent predictor of plaque rupture [89]. Inflammation is probably integral to further plaque rupture in these patients.

## Percutaneous coronary syndromes

An analysis of statin initiation prior to elective PCI may give anaesthetists an idea of the degree of cardioprotection afforded by starting statin therapy shortly before a possible acute coronary event (similar to starting statins electively in the pre-operative period in high-risk non-cardiac surgical patients). Two studies have administered standard dose statin therapy for 7 days [90] and $17 \pm 8$ days [91] prior to PCI, with associated improved cardiovascular outcomes. In the first study, atorvastatin 40 mg daily was used in a study which excluded patients with unstable coronary syndromes or myocardial infarction within the preceding 3 months and patients with a previous history of statin therapy [90]. In the second study, the dose of statins was not controlled. However, the mean dosage administered was consistent with standard statin therapy [91]. The patients in these two studies could be considered similar to statin naïve patients presenting for elective non-cardiac surgery, with no obvious unstable coronary conditions. Both these studies showed significantly decreased markers of myocardial damage (creatine kinase-MB, troponin I and myoglobin) in the statin group [90, 91], and significantly decreased myocardial infarction in the statin group (5% vs 18%, $p = 0.025$) [90].

In comparison with placebo, 7 days of atorvastatin 40 mg daily decreases ICAM-1 24 h after the percutaneous procedure. E-selectin was significantly lower at 8 h after the procedure and the difference between the groups continued to increase over the following 16 h. Vascular cell adhesion molecule-1 was not different at any point between the two groups. Thus an alteration of the endothelial inflammatory response may be responsible for the early cardiac protection [39].

Whether intensive statin therapy is beneficial in the patients with stable coronary artery disease prior to elective PCI is controversial. The randomised studies showing improved cardiovascular outcomes associated with intensive statin therapy have recruited patients with both stable and unstable coronary syndromes for PCI, recruited either after PCI [72] or with both stable and unstable coronary syndromes recruited before PCI [92]. Similarly, the retrospective study associated with improved cardiovascular outcomes with statin administration prior to PCI recruited patients with both stable and unstable angina [93].

A summary of therapeutic targets in medical patients is shown in Table 4.

In conclusion, the ideal peri-operative therapeutic strategy for elective surgery would be to attempt to emulate standard statin therapy for patients with stable

**Table 4** Established therapeutic targets for various presentations of coronary artery disease in medical patients.

| | Stable CAD | ACS | Elective PCI |
|---|---|---|---|
| LDL-C reduction | Decrease all-cause mortality† [58] | Decrease all-cause mortality† [68] | Decreased myocardial infarction [91] |
| Intensive therapy | Beneficial for MACE [83] | Decrease all-cause mortality*† [83] | Controversial |
| CRP reduction | Study in progress [63] | Beneficial for MACE [85] | Unknown |

*2 years. †cost-effective.

CAD, coronary artery disease; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein-C; CRP, C-reactive protein; MACE, major adverse cardiovascular events.

CAD with a long run-in time and associated LDL-cholesterol reduction, which is known to be associated with improved survival in medical patients.

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