Title: Perioperative statins

In this issue of the journal Saasouh et al1 evaluate whether statins influenced postoperative pain and opioid consumption after hip surgery.

Using a large and long established Cleveland Clinic database a group of patients already taking statins were matched with otherwise similar patients who were not. The authors conclude that there was no significant relationship between statin taking and post-operative pain and opioid consumption during the initial 72 hours after hip surgery.

Statins are amongst the most widely prescribed drugs. 16% of men and 12% of women in the UK are prescribed a statin by their primary care physician (GP).2 International guidelines recommend statins for high risk patients with atherosclerotic cardiovascular disease.3 Table 1. Lower-risk patients are also thought to benefit from the robust cholesterol reduction provided by statins. 3 A recent Lancet review evidences the efficacy of statins for both secondary and primary prevention of heart attacks and strokes.4

Clearly, a significant number of people presenting for surgery will be on long-term statin therapy. If we consider the mechanism of action of statins, it is important to understand how they might impact on pain.

How do statins work?

Statins reduce cholesterol synthesis and increase its clearance whilst decreasing triglycerides. They also reduce inflammatory mediators with beneficial effects on vasomotor tone, platelets, oxidation status, coagulation and inflammation.5 These characteristics also appear to stabilise plaques of atheroma. These animal and human studies demonstrate that statins can also reduce neuropathic pain.6 The effects on inflammatory pathways may be particularly relevant in situations where there is tissue injury, such as occurs with surgery. To date, there has been very limited clinical study of the effects of statins on pain in the peri-operative period.

Why might statins influence pain after surgery?

The anti-inflammatory effects of statins, seen in preclinical studies are associated with reductions in C-Reactive Protein (CRP) and pro-inflammatory cytokines. Animal neuropathy models demonstrate that statins can also reduce neuropathic pain.7 A number of animal studies have reported analgesic effects with high dose statins (5-300mg/kg), although these are much larger doses than those routinely used in clinical practice. Table 1. Animal models employed include carrageenan, formaldehyde, acetic acid- and formalin-induced pain in both rats and mice.8

How statins might exert their effect on pain processing is likely to be influenced by a number of factors, including dynamic changes in somatosensory processing during the peri-operative period, and dose (and possibly duration) of statin treatment, all of which may alter susceptibility to pro- or anti-nociceptive effects.

Limitations of the current report
Patients in the Cleveland Clinic database were taking statins to reduce cardiovascular risk and to improve lipid profile. The standard clinical doses used in these indications may be lower than those believed to support analgesia in preclinical models, and may have been suboptimal for that purpose. Total hip replacement is an uncomfortable procedure but not as painful as knee replacement or some other operations. It is possible that statins might have been efficacious against a greater painful stimulus.

Was the methodology appropriate?

This study is not a prospective randomised controlled trial (RCT) but a retrospective review of data from a cohort. The analyses may appear daunting, convoluted and unfamiliar to non-statisticians. In an attempt to address the lack of randomization in these retrospective data, the authors use a Propensity Score Matching (PSM) technique called the Inverse Probability Of Treatment Weighting (IPTW) method. IPTW is a ‘greedy’ algorithm that retains all patients in the analysis in order to maintain statistical power. Unlike other less greedy approaches, some compromises may be required. As a simple example in Table 1 in the paper, it appears that a proportion of patients underwent gender or ethnicity reassignment to balance the groups! This serves to remind us that these outcomes from PSM are only modelled effects. PSM methods do not compensate for known and unknown potential confounders for which there are no data. Only large RCTs can address this issue.

The authors use a “Joint Hypothesis Framework” and a two-sided non-inferiority approach. The logic of the joint-hypothesis is to test simultaneously the related outcomes of pain scores together with opioid consumption before accepting non-inferiority or concluding any superiority with statins. The problem with a retrospective review is that the investigator can only join hypotheses for testing for which data are available. For example, patients may elect to tolerate some pain and avoid opioids rather than suffer Postoperative Nausea And Vomiting (PONV). Clearly such patients may have a different idea of what should constitute non-inferiority or superiority. Unfortunately, no PONV data were available.

The authors found some signals of statin-associated analgesia within the raw observed, not modelled, data. There are statistically significant reductions in pain scores and opioid consumption with statin use. However, these effects are not apparent in the modelled data. How are we to interpret this? The authors show that they could not identify evidence for any independent beneficial analgesic effects for statins using PSM with IPTW and the potential confounders that were entered. However, it appears that such patients already on statins, whatever the mechanism, have lower pain scores and opioid requirements for reasons that cannot, as yet, be identified. As such, the observed and modelled results from these retrospective data can only really serve as hypothesis generators to justify a large RCT.

Why do eligible patients not take statins?

Scepticism about clinical benefit and fear of side effects are plausible explanations for failure of physicians to prescribe statins to patients who might benefit from them. Poor compliance with statin therapy is an issue – up to one fifth of patients opt to discontinue their statin therapy long-term. Patient-reported intolerance is primarily
due to Statin Associated Muscle Symptoms (SAMS). SAMS is a clinical spectrum of signs, symptoms and biochemical results, ranging from mild myalgia, the most frequent clinical picture, to more severe myositis, and, rarely, fatal rhabdomyolysis. Despite this, the consensus from the evidence to date is that the beneficial cardiovascular effects outweigh risks of musculoskeletal pain, neuropathy or SAMS.

Statin induced myopathy is a rare complication, where 10,000 patients would need to be treated with statins for 5 years for 5 cases of myopathy to develop, 50-100 patients may suffer from muscle pain or weakness. A recent systematic review found no increased risk of myalgia, but evidence of reduced cardiovascular risk, with current advice being that this risk reduction outweighs any potential muscle related problems.

The association between statin treatment and myalgia is controversial and the adverse events profile of statins may have been overplayed, perhaps as a result of over-reliance on observational studies. A recent analysis suggests that statins do not increase the risk of muscle pains. Gupta et al. reviewed data from the Lipid-Lowering Arm of the Anglo-Scandinavian CardiacOutcomes Trial (ASCOT-LLA). They compared rates of Adverse Events (AEs) during blinded randomised atorvastatin therapy, when atorvastatin 10mg was compared with placebo and, in a separate non-randomised non-blinded phase, users of statins were compared with non-users. An identical follow-up procedure and AE ascertainment process was used in the same population. An excess of muscle-related AEs was found only in the non-blinded phase of the trial when patients were aware they taking statins – the so-called nocebo effect.

This absolution of statins from alleged poor tolerability offers a rational basis to encourage statin prescribing by physicians and uptake by patients.

**Do statins provide perioperative cardioprotection?**

Recent evidence from the VISION (Vascular Events In Non-Cardiac Surgery Patients Cohort Study Evaluation) study would suggest they do. VISION was a large (>40,000 patients) international prospective cohort study evaluating perioperative events. The pre-operative use of statins was associated with a 17% reduction of the primary outcome, a composite of all-cause mortality, myocardial injury after non-cardiac surgery (MINS), or stroke at 30 days. Statins were also associated with a significant lower risk of all-cause mortality, cardiovascular mortality and MINS.

However, there are limitations to the VISION data. Despite adjustment for covariates, the use of statins in an observational data set may represent a surrogate marker for unmeasured confounding variables which relate to prognosis. Even after matching, standard deviations were >10% in 5 pre-operative variables. Further, contraindications to statins were not recorded. Therefore, some control patients may have presented a contraindication to statins – a potential source of bias. Finally, the VISION analysis assumes that any patient treated pre-op with a statin continued it afterwards.

There are a number of observational and small RCTs which suggest that statins may reduce the risk of CV events in patients having non-cardiac surgery. However, there remains a need for a large RCT to evaluate perioperative statins.
Timing is probably important

Curtis et al reviewed data from >3000 patients undergoing CABG to determine the optimal preoperative timing and dose of statins. They found the incidence of 30day mortality was 1.7% in those who had taken a statin 24h or less preoperatively, compared with 24-72h (2.9%), more than 72h, or no dose (3.8%). They also reported that a preoperative statin dose of 20mg or more was associated with lower 30-day all cause mortality. London et al, retrospectively analysed >180,000 patients undergoing non-cardiac surgery. Those exposed to a statin on the day of or day after surgery had reduced mortality and complications.

There is also evidence showing the beneficial effects of restarting statins post-operatively. Amongst 300,000 patients who had been taking statins before non-cardiac surgery, 30-day mortality was 40% greater (2.6%) in those patients who failed to restart their statin within 48h postoperatively, compared with those who quickly resumed or never stopped taking their statin.

It seems that timing of peri-operative statin therapy is crucial. There is an increased risk to surgical patients if regular statin therapy is interrupted.

How can anaesthetists contribute?

There are excellent reasons for those patients who meet evidence based criteria to have statins prescribed and then to take them. The preoperative anaesthetist consultation is necessarily brief and focused. However, surgery is common and the preoperative consultation provides an opportunity for brief interventions in healthcare and lifestyle. Recently an anaesthetist administered brief smoking-cessation intervention was associated with 26% new abstinence at 6 months. Perhaps anaesthetists should be promoting uptake of guideline advised statin treatment.

What further evidence do we need?

Although the current evidence is compelling it is not comprehensive. A large RCT is needed. Berwanger randomised 648 statin-naïve patients booked for non-cardiac surgery to a loading dose of 80mg atorvastatin or placebo followed by a maintenance dose of 40mg (or placebo) for 7 days. Despite not demonstrating a reduction in major CV complications between the two groups, the point estimates for the main study outcomes are suggestive of a possible beneficial effect of moderate size. Larger controlled trials are feasible and justified but will need to be large. Berwanger et al, found that the potential effects of statins are at best moderate. Even coupling this with a high control group event rate at 30 days (18.7%), a future trial would need to enrol >7000 patients to detect a relative risk reduction of 15% on the outcome of death, MINS or stroke at 30 days. Important considerations for this potential RCT are the duration of statin therapy and timing for assessment of primary outcome. From the literature, it would seem that a two week (minimum) course of therapeutic statin dose (20-80mg) should be used. Some data suggest that statins have the potential to cause AKI, however, metanalysis suggests that the evidence is inconclusive. There have also been reports linking statins with low mood and suicide, but the evidence of this is ambiguous.
How long a “run in” is appropriate?

In acute coronary syndrome/MI treatment, 30 days of statin therapy is suggested as the time to produce benefit. Long term benefits appear to be due to the reduction in LDL-C. However, the more immediate pleiotropic effects of statins produce plaque stability and attenuation of local inflammation shortly after oral administration and may explain their benefit in the perioperative period. In their post hoc VISION analysis Berwanger et al. found that the treatment effect of statin on outcome appears to be noted 2 days after initiation of therapy. However, they found no significant beneficial effect from 1 week of post-op statin therapy. Trials showing a reduction in post-op CV complications have utilised a 2-week perioperative statin course. This supports the introduction of statin therapy by the anaesthetist in the preoperative anaesthesia clinic, without the need for referral back to primary care.

References
10 Mascha EJ, Turan A. Joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. Anesthes Analg 2012; 114: 1304-17
### Primary Prevention

<table>
<thead>
<tr>
<th>10-Year Risk of developing CVD &gt;10%:</th>
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### Secondary Prevention

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<td>If non-HDL-C decreases to &lt;40%: consider higher dose</td>
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Table 1: 2014 UK National Institute For Health and Clinical Excellence (NICE) Guidelines on Lipid Modification