Statins and other drugs that make a difference

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ABSTRACT
The aetiology of perioperative cardiac morbidity and mortality is multifactorial. With the many and diverse aetiological factors involved, it is highly unlikely that one single intervention will successfully improve cardiac outcome following noncardiac surgery. Based on increasing knowledge of the nature of atherosclerotic coronary artery disease, and in view of the poor positive predictive value of the non-invasive cardiac stress tests and the considerable risk of coronary angiography and coronary revascularisation in high-risk patients, the paradigm is shifting from an emphasis on extensive non-invasive preoperative risk stratification to an emphasis on a combination of selective non-invasive testing and aggressive pharmacological perioperative therapy. Perioperative plaque stabilisation by pharmacological means may well be one of the most important cardioprotective interventions.

Introduction

Overall evidence suggests that optimal cardiac medication is as effective as coronary revascularisation in patients with stable coronary artery disease (CAD).[1,2] Existing clinical practice guidelines acknowledge the effectiveness of intensive medical therapy and, accordingly, state that even in patients with symptomatic, extensive, multivessel CAD, percutaneous coronary intervention (PCI) can be safely deferred if optimal medical therapy is provided in patients with stable CAD.[3,4] Consistent with the results of the COURAGE trial,[2] a lack of benefit from preoperative coronary revascularisation may partly be explained by the long-term aggressive medical therapy in revascularised as well as non-revascularised patients in both of these studies.[5,6]

All of this provides further evidence for the potential benefit of aggressive perioperative medical therapy in patients with stable CAD. Accordingly, the following will provide a brief review of existing evidence for a perioperative cardioprotective effect of perioperative therapy with statins, beta-adrenoceptor antagonists (ß-blockers) and alpha-2 adrenoceptor agonists. In this context, the classifications of the recommendations are defined as follows: *class I:* conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective; *class II:* conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; *class IIa:* weight of evidence/opinion is in favour of usefulness/efficacy; and *class IIb:* usefulness/efficacy is less well established by evidence/opinion. The levels of evidence for the recommendations are defined as follows: *grade A:* data are derived from multiple randomised clinical trials or meta-analyses; *grade B:* data are derived from a single randomised trial, or non-randomised studies; *grade C:* only consensus opinion of experts, case studies, or standard of care.

Statins

Mechanisms of action

Statins have numerous 'pleiotropic' effects that are entirely independent of their lipid-lowering activity. Statins exert anti-inflammatory,[7,8] anti-thrombotic[9] and anti-arrhythmic activity.[10]. They decrease platelet aggregation,[11,12] reverse endothelial dysfunction,[13] stabilise atheromatous plaque,[13] reverse atherosclerosis,[14] and limit infarct size by stimulating ischaemic preconditioning.[15] The ischaemic preconditioning effect may be related to the activation of several pro-survival kinase pathways[15] within minutes of administration,[16] and to the activation of both endothelial nitric oxide (NO) synthase (eNOS) and inducible NOS (iNOS).[17,18,19]

The anti-arrhythmic activity of statins appears to be independent of the lipid-lowering activity, but to correlate with the various pleiotropic actions of statins (i.e. anti-inflammatory, anti-proliferative, antioxidant and plaque-stabilising properties; atherosclerotic plaque regression; regulation of NO-dependent coronary arterial endothelial function; decrease in ischaemia-induced cardiomyocyte hypertrophy; activation of injured myocardium, attenuation of atrial remodelling; regulation of ventricular repolarisation heterogeneity; changes in transmembrane ion channel properties; regulation of autonomous nervous system activity; increase in parasympathetic tone; and down-regulation of the renin-angiotensin system).[10] The anti-arrhythmic property may partly account for the statin-associated decrease in cardiovascular events in the non-operative setting.[20,21,22]

Accordingly, the guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) for the management of ventricular arrhythmias[23] and atrial fibrillation[24] suggest a possibly protective role of statin therapy against ventricular arrhythmias and atrial fibrillation.

Perioperative use of statins

The findings of numerous clinical studies suggest that perioperative statin therapy is associated with improved cardiac outcome during noncardiac surgery,[22,25-41] endovascular interventions,[39,42] as well as during cardiac surgery,[22,36,37,43,44] including protection against arrhythmias.[45,46] Much, if not all, of the beneficial effects of statins on cardiovascular outcome are likely due to their pleiotropic actions, rather than their lipid-lowering actions.

In a retrospective analysis, the withdrawal of statins after major vascular surgery was associated with an increased risk for postoperative myocardial cell injury, whereas early resumption of statin therapy was associated with cardioprotection.[40] In another non-randomised observational cohort study, multivariate and propensity score analyses showed an association between statin discontinuation and increased 30-day postoperative risk of myocardial cell injury and combined myocardial infarction and cardiovascular death.[47] Extended-release fluvastatin was associated with better cardiac outcome than atorvastatin, simvastatin

and pravastatin. The findings suggest that acute preoperative discontinuation of statins may result in adverse perioperative cardiac outcome, and that extended-release statins may be of benefit. The findings of these two studies suggest a deleterious effect of acute preoperative withdrawal of statin therapy in patients taking statins for secondary prevention, and strongly suggest the continuation of statin therapy in this patient population.[48,49]

Two recent meta-analyses of studies on the effect of perioperative statin therapy on postoperative outcome showed a reduction in mortality associated with perioperative statin use.[36,37] However, with very few exceptions, the evidence for a beneficial effect of perioperative statin therapy is largely based on retrospective observational studies with poor control of, or lack of information on, time of initiation and duration of statin therapy, statin dose, indications for statin use, and low-density lipoprotein concentration. At present, there is insufficient evidence to recommend routine perioperative statin therapy for perioperative cardiovascular risk reduction.[50] The results of a large, randomised trial are necessary to provide an ultimate answer on the effectiveness of perioperative statin therapy.

Based on the available evidence, the recently revised guidelines for perioperative cardiac care for noncardiac surgery published by the ACC and AHA recommend that (i) patients currently taking statins and scheduled for noncardiac surgery should be continued on statins (class I, level of evidence: B); (ii) statin use is reasonable in patients undergoing vascular surgery with or without clinical risk factors (class IIa, level of evidence: B), and (iii) that statins may be considered in patients with at least one clinical risk factor who are undergoing intermediate-risk procedures (class IIb, level of evidence: C).[51,52]

ß-Blockers

Numerous cardiovascular and other effects (anti-arrhythmic, anti-inflammatory, altered gene expression and receptor activity, protection against apoptosis) of ß-blockers may account for their possible cardioprotective effect in the operative and non-operative setting.[53]

The benefit of perioperative atenolol in patients with or at risk for CAD undergoing major noncardiac surgery under general anaesthesia was examined in a randomised, double-blind, placebo-controlled study.[54] Over the two-year follow-up period, the overall mortality after hospital discharge was significantly lower in the atenolol (10%) than in the placebo group (21%, p=0.019). The combined cardiovascular outcomes were similarly reduced in the atenolol group. This study has been criticised on numerous grounds. Most importantly, in-hospital cardiac morbidity and mortality were not included in the analysis. If this is done, the difference in outcome between the groups is no longer statistically significant.

A subsequent randomised, placebo-controlled, non-blinded study looked at the benefit of perioperative bisoprolol in patients with documented CAD (diagnosed by new wall-motion abnormalities on dobutamine stress echocardiography) undergoing major vascular surgery.[55] The outcome parameters included cardiac death and non-fatal myocardial infarction during the first 30 days following surgery. In the bisoprolol group, perioperative cardiac events were tenfold lower compared to the 'standard care' group (3.4% vs 34%; p=0.001). This investigation also has several limitations. Most importantly, the study was terminated before the *a priori* calculated number of patients was reached, no aspect of the study was blinded, and a 90% relative reduction in 30-day adverse outcome by ß-blockers is entirely unrealistic. In view of the small sample size, it is highly likely that the results occurred by chance alone.

A non-randomised, non-blinded observational cohort study in 272 vascular surgery patients with documented CAD investigated the effect of different dosages of various ß-blockers, and of tight perioperative heart rate control on the incidence of perioperative myocardial ischaemia and myocardial cell injury.[56] The patients were non-randomly allocated to three study groups: no ß-blockers (n=97), low-dose ß-blockers (1–25% of maximum recommended therapeutic dose, MRTD; n=97), and high-dose ß-blockers (> 25% of MRTD; n=78). High-dose perioperative ß-blocker therapy and tight perioperative heart rate control were associated with a reduced incidence of myocardial ischaemic episodes, reduced release of cardiac troponin T, and improved long-term outcome.

Although the findings seem impressive at first sight, the study has numerous limitations. Most importantly, it was not randomised. Numerous adjustments by multivariate analysis were made for age, sex, numerous cardiac risk factors, dobutamine-stress-echocardiography test results, and for statin and angiotensin-converting enzyme-inhibitor medication. No exact information is provided for individual groups on type and duration of surgery, type of anaesthesia, type of primary endpoint, and follow-up time.

Despite suggestive evidence for a cardioprotective effect of perioperative ß-blocker therapy, a recent meta-analysis failed to provide convincing evidence for a reliable cardioprotective effect of perioperative ß-blocker therapy.[57] In addition, three subsequently published double-blind, randomised, placebo-controlled trials also failed to demonstrate a cardioprotective effect of perioperative ß-blocker therapy.[58,59,60] Thus, the repeated recommendations for perioperative ß-blockade in patients with suspected or documented CAD are mainly based on the findings of two prospective, randomised controlled trials of highly questionable methodology and data analysis in a little over 300 patients,[54,55] and on a non-randomised observational cohort study.[56]

Although the available evidence supports the recommendation to consider perioperative ß-blocker therapy in selected patients at high cardiac risk, a large trial is essential to document the effectiveness and safety of perioperative ß-blockade before widespread use. Such a trial, the POISE (PeriOperative ISchemic Evaluation) study, funded by the Canadian Institute of Health Research, was started in 2002.[61] The goal of this randomised, double-blind trial is to compare the effectiveness of perioperative ß -blocker therapy with metoprolol with that of a placebo on major cardiovascular events in patients undergoing noncardiac surgery. Based on an *a priori* power calculation, the targeted number of patients was 10 000. Patients were to receive metoprolol 100 mg controlled release (CR) or a placebo two to four hours before surgery, and metoprolol 200 mg CR or a placebo daily for 30 days postoperatively. The primary endpoint is combined cardiovascular death, myocardial infarction and cardiac arrest. Secondary endpoints are need for coronary revascularisation, atrial fibrillation, total mortality, hypotension, and bradycardia.

Patient entry into the trial was closed in mid-2007. Thus far, the preliminary results are available in abstract form only.[62] A total of 4 174 patients were randomised to the metoprolol group, and 4 177 to the placebo group. Underlying cardiovascular morbidity includes coronary artery disease (43%), peripheral vascular disease (41%) and prior stroke (15%). The types of surgery were vascular (42%), intraperitoneal (22%), orthopaedic (21%), and others (15%).

During the first 30 postoperative days, the primary endpoint (combined cardiovascular death, myocardial infarction and cardiac arrest) was significantly less in the ß-blocker group (incidence 5.8% vs. 6.9%; hazard ratio [HR] 0.83; 95% confidence interval [CI] 0.70-0.99; p=0.04). This was primarily due to a marked reduction in the incidence of non-fatal myocardial infarctions in the ß-blocker group (incidence 3.6% vs. 5.1%; HR 0.70; p=0.0007). The need for revascularisation (0.3% vs. 0.6%; p=0.01) and the incidence of atrial fibrillation (2.2% vs. 2.9%; p=0.04) were also significantly lower in the group of patients who had received ß-blockers.

However, in the ß-blocker group, total mortality (3.1% vs. 2.3%; HR 1.33; p=0.03), and the incidences of stroke (1.0% vs. 0.5%; HR 2.17; p=0.005), significant hypotension (15.0% vs. 9.7%; p< 0.0001) and significant bradycardia (6.6% vs. 2.4%; p< 0.0001) were higher, negating the beneficial effects of perioperative ß-blocker therapy on the primary endpoint. An adequate analysis and interpretation of the data will only be possible after the complete results have become available. Until such time, it seems fair to conclude that, at the time of this writing (December 2007), the evidence for a reliable and consistent cardioprotective effect of perioperative ß-blocker therapy is weak at best.[50,63]

Based on the available evidence, the recent updates of the ACC/AHA guidelines on perioperative cardiovascular evaluation list several class I indications for perioperative ß-blocker therapy: (i) continuation of ß-blockers in patients receiving ß-blockers to treat angina, symptomatic arrhythmias, hypertension or other ACC/AHA class I guideline indications (level of evidence: C); and (ii) patients undergoing vascular surgery at high cardiac risk owing to the finding of myocardial ischaemia on perioperative testing (all level of evidence: B).[51,52,64]

Perioperative ß-blocker therapy is *probably* recommended (class IIa recommendations, level of evidence: B) for patients undergoing vascular surgery in whom preoperative assessment identifies CAD; in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than one clinical risk factor; and in whom preoperative assessment identifies CAD or high cardiac risk, as defined by the presence of more than one clinical risk factor, who are undergoing intermediate-risk or vascular surgery.

These recommendations should be applied with caution to patients with decompensated heart failure, non-ischaemic cardiomyopathy, or severe valvular heart disease in the absence of congenital heart disease. In patients at lower perioperative cardiac risk, perioperative ß -blocker therapy may actually worsen the outcome.[65]

Alpha-2 agonists

Alpha-2 adrenoceptor agonists improve cardiovascular morbidity and mortality following noncardiac and cardiac surgery.[66–71] In two randomised, placebo-controlled studies, premedication with clonidine in vascular[72] and general surgery patients[73] was associated with a reduced incidence of perioperative myocardial ischaemia. A meta-analysis of 23 studies up to the year 2002 including 3 395 patients showed reduced mortality and incidence of myocardial infarction in vascular surgery patients who had received alpha-2 agonists.[66] Perioperative administration of clonidine orally and by patch reduced perioperative myocardial ischaemia and overall mortality at two years postoperatively.[67]

The mechanism of the protective effect of alpha-2 agonists is likely to be manifold. Alpha-2 adrenoceptor agonists attenuate perioperative haemodynamic instability,[69] inhibit central sympathetic discharge,[74] reduce peripheral norepinephrine release,[73] and dilate post-stenotic coronary vessels.[75] As in the case of perioperative ß-blocker therapy, a large trial on perioperative alpha-2-agonist therapy is needed to provide convincing evidence of a perioperative cardioprotective effect of such therapy.

Based on the available evidence, the recently updated guidelines for perioperative cardiac care for noncardiac surgery recommend that alpha-2 agonists may be considered for patients with known CAD or at least one clinical risk factor who are undergoing surgery (class IIb, level of evidence: B).[51,52]

Conclusion

The aetiology of perioperative cardiac morbidity and mortality is multifactorial.[76] With the many and diverse aetiological factors involved, it is highly unlikely that one single intervention will successfully improve cardiac outcome following noncardiac surgery. A multifactorial, step-wise approach is indicated.[77,78] Based on increasing knowledge of the nature of atherosclerotic coronary artery disease, and in view of the poor positive predictive value of the non-invasive cardiac stress tests and the considerable risk of coronary angiography and coronary revascularisation in high-risk patients,[79] the paradigm is shifting from an emphasis on extensive non-invasive preoperative risk stratification to an emphasis on a combination of selective non-invasive testing (to reliably identify those patients who truly benefit from preoperative intervention, such as cancellation of surgery, preoperative coronary revascularisation, initiation or optimisation of cardioprotective medication), and aggressive pharmacological perioperative therapy.[80–83]

On the basis of increasing knowledge of the nature of atherosclerotic coronary artery disease, perioperative plaque stabilisation by pharmacological means (statins, ß-blockers, aspirin) may be as important in the prevention of perioperative myocardial infarction as is an increase in myocardial oxygen supply (by coronary revascularisation) or a reduction in myocardial oxygen demand (by ß-blockers or α_2-agonists). Aggressive perioperative medical therapy may well be one of the most important, if not *the* most important, cardioprotective intervention.

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