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Editorials

Beta-blockade and other perioperative pharmacological protectors: what is now available and efficacious?

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Publication, in 2008, of the results of POISE, the largest randomized controlled trial (RCT) of perioperative beta-blockade, confirmed previous studies that had shown beta-blockade to offer cardiac protection in patients with, or at risk for, coronary heart disease.[1] However, this protection was associated with significantly increased all-cause mortality, particularly in patients who became septic or hypotensive, and significantly increased disabling strokes, contributed to by hypotension. Indeed, as might be expected, hypotension and bradycardia were much more frequent in the beta-blocked patients than in the placebo group. There was also controversy surrounding the dose of the slow-release metoprolol preparation used in the trial. It was regarded by some as too high; also the initiation of beta-blockade the day of surgery precluded titration.[2] A meta-analysis of RCTs including POISE data showed that some subgroups of patients could benefit from perioperative beta-blockade: those at high risk and those in whom beta-blockade was strictly titrated.[3]

However some of the RCTs that were most supportive of beta-blockade[4 5] arise from researches reported by the group led by Professor Poldermans. As Professor Poldermans was dismissed by Erasmus Medical Centre for academic misconduct in 2011, these trials are now regarded as 'insecure'.[6] Thus the case for initiating beta-blockade before surgery was weakened. From the position advocated by previous guidelines, where there was support for the initiation of beta-blockade in ALL patients at risk for, or with, coronary disease,[7] the 2009 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommended their introduction in patients at high risk,[8] while the European Society of Cardiology (ESC) guideline recommended them also in patients at more moderate risk (ESC).[9] After highly critical comments in respect of the 2009 guidelines in the discussion of a meta-analysis that excluded the 'insecure' trials,[6] the ACCF/AHA and ESC published a joint interim statement in 2013 to the effect that beta-blockade should not be initiated routinely but only after careful evaluation of risks and benefits in individual patients.[10]

Updated guidelines from the ACC/AHA[11] and ESC/ESA,[12] published in August 2014 now clarify the issue of perioperative beta-blockade (Table 1). Both sets of guidelines recommend to maintain long-term treatment with beta-blockers (recommendation Class **I,** level of evidence **B**). As far as initiation of perioperative beta-blockade, there are no Class **I**, or Class **IIa** recommendations. There are only relatively weak class **IIb** recommendations. Essentially the new guidelines recommend to consider starting beta-lockers in patients with known ischaemic heart disease or myocardial ischaemia, and in patients with multiple cardiac risk factors, two in the ESC/ESA guideline, and three in the ACC/AHA guideline. The ACC/AHA guideline suggests that initiating beta-blockers in patients with a compelling indication for beta-blockers but with NO OTHER cardiac risk factor is of uncertain benefit. Both sets of guidelines recommend starting beta-blocker therapy well in advance of surgery, preferably more than one day before surgery (ACC/AHA) or between 30 and 2 days before surgery (ESC/ESA). The possibility of harm is emphasized. The ACC/AHA guideline considers starting beta-blockers the day of surgery as potentially harmful (recommendation **III B**), a view endorsed by the ESC/ESA guideline with another caveat against initiation of beta-blockers in patients undergoing low-risk surgery (recommendation **III B**). Interestingly, the ESC/ESA guideline recommends to use atenolol or bisoprolol as first choice (recommendation **IIb B**). While the 2009 sets of guidelines indicated targets for heart rate, only the ESC/ESA 2014 guideline

Table 1 Comparison of recommendations made by ACCF/AHA (2009) and current ACC/AHA guidelines (2014)

2009 ACCF/AHA guideline Recommendations	2014 ACC/AHA guideline Recommendations
Class I Beta blockers should be continued in patients undergoing surgery who are receiving beta-blockers for treatment of conditions with ACCF/AHA Class I guideline indications for the drugs I C	**Class I** Beta blockers should be continued in patients undergoing surgery who have been on beta blockers chronically I B
Class IIa Beta blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischaemia on preoperative testing IIa B	**Class IIa** It is reasonable for the management of beta blockers after surgery to be guided by clinical circumstances, independent of when the agent was started IIa B
Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than 1 clinical risk factor IIa C	**Class IIb** In patients with intermediate- or high-risk myocardial ischaemia noted in preoperative risk stratification tests, it may be reasonable to begin perioperative beta blockers IIb C
Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of more than 1 clinical risk factor, who are undergoing intermediate-risk surgery IIa B	In patients with 3 or more RCRI risk factors (e.g. diabetes mellitus, HF, CAD, renal insufficiency, cerebrovascular accident), it may be reasonable to begin beta blockers before surgery IIb B
Class IIb The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor in the absence of coronary artery disease IIb C	In patients with a compelling long-term indication for beta-blocker therapy but no other RCRI risk factors, initiating beta blockers in the perioperative setting as an approach to reduce perioperative risk is of uncertain benefit IIb B
The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors* who are not currently taking beta blockers IIb B	In patients in whom beta-blocker therapy is initiated, it may be reasonable to begin perioperative beta blockers long enough in advance to assess safety and tolerability, preferably more than 1 day before surgery IIb B
Class III Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta-blockade III B	**Class III** Beta-blocker therapy should not be started on the day of surgery III B
Routine administration of high-dose beta- blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta blockers who are undergoing noncardiac surgery III B	

comments on the need to titrate to resting heart rate 60–70 beats min $^{-1}$ and systolic blood pressure >100 mm Hg. The ACC/AHA view is that there insufficient evidence in respect of titration.

Although the use of RCTs represent the 'gold standard' for the development of guidelines, examination of outcomes in observational studies may also be helpful. This is the case with the recent meta-analysis from Wan and colleagues[13] Depending upon the individual outcomes considered, the number of patients included was between 52 300 and 470 000. While perioperative beta-blockade was not associated with increased mortality (RR 0.88 [CI 0.75–1.04]), 3 studies with 4101 patients showed that mortality was increased in patients taking beta-blocker on the day of surgery (RR 1.91 [CI 1.01–3.62]). The messages of observational studies are very similar to those of 'secure' RCTs; however at variance with RCTs, there was no reduction in the risk of myocardial infarction (107 974 patients, RR 1.3 [0.76–2.23]). Similarly there was only a non-significant increase in the risk of stroke (106 320 patients, RR 1.17 [CI 0.53–2.57]). Thus, for beta-blockade, results from observational studies do not suggest that the current guidelines, urging caution, are not partly representative of 'real life'.

As sympathetic over-activity is detrimental to patients with coronary artery disease, an alternative to beta-adrenoceptor blockade could be the perioperative use of an alpha$_2$-adrenoceptor agonist. Previous RCTs had shown beneficial effects of alpha$_2$-adrenoceptor agonists (mivazerol, dexmetedomidine, clonidine) in cardiac and in non-cardiac surgery;[14–16] while a meta-analysis including all RCTs using clonidine, dexmetedomidine and mivazerol showed significant reductions of major cardiac events in cardiac and non-cardiac surgery.[17] Thus clonidine could be expected to confer protection, even though the number of patients in clonidine RCTs was small. POISE 2 was designed as a 2×2 RCT with clonidine and aspirin and appropriate placebos.[18 19] The study enrolled just over 10000 patients. Clonidine did not reduce the risk of perioperative cardiac events. Though the dose was low (2 mg orally just before surgery and a 2 mg patch left for three days [or removed in case of hypotension]) it caused clinically important hypotension and bradycardia in a large proportion of patients.[16] However, at variance with POISE, the clonidine-induced hypotension did not increase all-cause deaths or the risk of stroke. Thus, after the much more cautious recommendations for beta-blockers, an attractive alternative, low-dose clonidine, is clearly not conferring cardiac protection. There was even a significant increase in non-fatal cardiac arrest, and, though not reaching statistical significance, small increases in death from

vascular causes, myocardial infarctions, and need for cardiac revascularisation. The 2014 ACC/AHA guidelines are quite clear that alpha$_2$-receptor agonists for the prevention of cardiac events are not recommended (recommendation **III B**). The ESC/ESA make no specific recommendation but states: therefore, alpha$_2$-receptor agonists should not be administered to patients undergoing non-cardiac surgery, an equivalent to a Class III recommendation.

Based also on limited evidence, another candidate for perioperative protection is aspirin. It has been shown to confer protection after cardiac surgery,[20] and its continuation appears to be beneficial in non-cardiac surgery.[21] It is generally accepted that aspirin should not be discontinued before surgery[22] as this increases the risk of adverse cardiac events. Of course there is risk of increased bleeding but this is not usually life-threatening. POISE2 randomly allocated patients to aspirin whether or not they were previously on aspirin, thus in some patients aspirin was withdrawn after randomisation if they were to receive the aspirin-placebo medication. The results of the aspirin arm of the trial showed no cardiac protection and confirmed the risk of increased major bleeding.[17] Thus another potential candidate for perioperative cardiac protection was found to be ineffective and with significant risks.

Unsurprisingly, the ACC/AHA guideline states that initiation or continuation of aspirin is ***not*** beneficial in patients undergoing elective non-cardiac, non-carotid, surgery who have not had previous coronary stenting, unless the risk of ischaemic events outweighs the risk of surgical bleeding (recommendation **III C**). The ESC/ESA guideline states that continuation of aspirin, in patients previously thus treated, may be considered in the perioperative period, and should be based on an individual decision that depends on the perioperative bleeding risk, weighed against the risk of thrombotic complications (recommendation **IIb B**). Thus, with aspirin, the decision about initiating or continuing its administration needs to be informed by the risk of thrombotic events and the risk of excessive bleeding.

Why are there discrepancies between previous RCTs that indicated benefits of alpha$_2$-agonists and aspirin and the results of POISE2, and, maybe also, of POISE in respect of beta-blockade?

One possible explanation is the change of 'context'. Many of the studies that showed benefits of pharmacological interventions recruited patients up to 20 years ago or more. Over the past two decades many aspects of perioperative management have changed and also the management of co-morbidities. Arterial hypertension is controlled much more effectively than 20 or even 10 years ago. Over the past five years, the treatment of acute coronary syndromes has been revolutionised by primary percutaneous interventions. Anaesthetic techniques have changed and perioperative monitoring is now much more comprehensive. These changes over time have contributed to the safety of anaesthesia. Thus, current advances in perioperative medicine may reduce the scope for perioperative pharmacological protection, such that previously effective treatments are no longer beneficial. It also likely that in large RCTs, risks that were present in much smaller trials but never reached statistical significance were ignored, as the small studies were not powered for relatively rare events. By relying too much on the lack of statistical significance, and ignoring trends, we may have allowed serious complications to be disregarded, imperilling our patients.

Today only statins have been shown consistently to afford cardiac protection but almost exclusively in observational studies, some very large.[23] Initiating statin treatment before surgery has been studied in RCTs in cardiac and non-cardiac surgery. A meta-analysis of these trials has shown that statins reduce the risk of myocardial infarction and atrial fibrillation.[24] In non-cardiac surgery the largest studies are those from Professor Poldermans' group[5 25] if they are considered 'insecure', the number of patients in statins RCTs is reduced from 1186 to 156 and firm conclusions cannot be drawn. However, the evidence from observational studies showing protection in patients on long-term statin medication, suggests that initiating statins ahead of surgery could be beneficial.[23] Indeed, there are limited recommendations for the initiation of statins before surgery in the 2009 ACCF/AHA[8] and in the ESC guidelines.[9] While an increasing number of patients at risk for cardiovascular disease take statins, only 32% of patients recruited into POISE[1] and 37% into POISE2[26] were receiving statins at the time of surgery. Thus there may be scope for improving protection by introducing statins preoperatively in patients at risk who should be on statins for medical reasons alone. The new ACC/AHA guidelines recommend to continue statins perioperatively(recommendation **I B**), with the interesting comment in the ESA/ESC guidelines that continuation of statins should favour statins with long half-life or extended-release (recommendation **I C**). This is in order to maintain some of statins' effects at a time oral administration may be impossible. In both guidelines, perioperative initiation of statins is recommended in patients undergoing vascular surgery (**IIa B**). The ACC/AHA suggests that statins may be considered in patients who have a medical indication and undergo elevated-risk surgery. What then can be done to protect the heart? First of all, it is recommended to maintain chronic beta-blocker and statin therapy. It is also probably reasonable to continue low dose aspirin therapy, unless surgery is associated with a significant risk of excessive bleeding. In selected high-risk patients undergoing high risk surgery beta-blockade initiated as early as possible (at the very least a week before surgery) should be considered for individual patients. Initiating statin therapy in patients who should be on statins for medical reasons alone is also indicated before major surgery. However, initiating clonidine or aspirin for cardiac protection is not supported by evidence.

Against the background of the lack of efficacy of pharmacological prophylaxis, maybe a change of strategy is called for. Myocardial injury after non-cardiac surgery (MINS) is associated with significant short- and long-term morbidity and mortality.[18 27] Currently there is no agreement on the best way of managing patients with raised troponin concentrations after non-cardiac surgery. Many drugs are used in the management of perioperative ischaemic cardiac events. Beta-blockers, anticoagulants, antiplatelet agents, non-dihydropyridine calcium channel blockers, and statins have all been used, but for most interventions, strong scientific evidence is still lacking. However the reduced risk of adverse outcome in patients with MINS who received aspirin or statins,[28] suggests that more prospective studies of interventions could are needed and may prove very valuable.

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