LEADING ARTICLE

The Controversy of Peri-operative ß-blockade: What Should I Do?

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A recently published meta-analysis evaluating the role of perioperative beta-blockade is alarming the medical community and has reignited the debate regarding whether patients undergoing non-cardiac surgery benefit from perioperative beta-blockade.[1]

This meta-analysis included nine randomized, controlled trials of beta-blockers initiated before non-cardiac surgery in 10,529 patients. However, the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) I[2] and IV studies[3] were excluded from the meta-analysis following the dismissal of Professor Don Poldermans by Erasmus University in Rotterdam in 2011 following alleged scientific misconduct. He had been the principal investigator of the DECREASE studies.

The meta-analysis reported a 27% increased risk in all-cause mortality, a 73% increase in non-fatal stroke and a 72% decrease in non-fatal myocardial infarction associated with perioperative beta-blocker therapy (Table 1). Based on these findings and an extrapolation of operations performed in the United Kingdom (UK), the authors proposed that ignoring the European Society of Cardiology's (ESC) recommendations on perioperative beta-blocker therapy[4] could prevent up to 10,000 peri-operative deaths each year in the UK.

The current ESC recommendations include a Class I recommendation that peri-operative beta-blockade is indicated in patients with known ischaemic heart disease or myocardial ischaemia according to preoperative stress testing, or in those undergoing high risk surgery (emergency or major vascular surgery). The ESC guideline also includes a class IIa recommendation that peri-operative beta-blockade be considered in patients undergoing intermediate risk non-cardiac surgery. The authors of the latest meta-analysis[1] now demand an immediate retraction of current guidelines on perioperative beta-blocker therapy by the ESC,[4] as well as the American College of Cardiology (ACC) and the American Heart Association (AHA).[5]

On what data do the authors base their conclusions and demands?

In a 2008 meta-analysis by Bangalore et al.,[6] there were almost identical results and conclusions. For the purpose of assessing the effect of bias on reported outcomes, the authors separately analysed studies with a low or high risk of bias (indicating high and low scientific quality respectively) as defined by the Cochrane Collaboration.[7] The DECREASE I study[2] was categorized as a high risk of bias trial. A meta-analysis of all 33 included trials found no increase in overall mortality and an 81% decrease in the risk of non-fatal myocardial infarction (MI) associated with perioperative beta-blocker therapy. A separate meta-analysis of the 13 low risk of bias trials (which did not include the DECREASE I study) showed a 28% increased risk in overall mortality and only a 28% decrease in the risk of non-fatal MI (Table 1). As there was a major overlap in analyzed trials and because the large POISE trial[8] dominated both meta-analyses, it was entirely to be expected that the magnitude of associations between perioperative beta-blocker therapy and mortality and non-fatal MI in the low risk of bias and "secure" trials were identical in both studies (Table 1). Surprisingly, however, whereas Bangalore[6] found a strong association between perioperative beta-blocker therapy and stroke, the latest meta-analysis by Bouri[1] did not (Table 1). This discrepancy remains difficult to explain and demonstrates the risk of accepting the results of meta-analyses as ultimate evidence.

Based on the findings of their 2008 meta-analysis, Bangalore et al.[6] concluded that *"because evidence does not support the use of ß-blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery … ß-blockers should not be routinely used for perioperative treatment of patients undergoing non-cardiac surgery unless patients are already taking them for a clinically indicated reason (heart failure, coronary artery disease, previous myocardial infarction)."* They appealed to the ACC/AHA guideline committee to *"soften their stance on perioperative ß blockade until definitive evidence shows clear benefit."* They felt that *"the use of perioperative ß blockade as a performance measure, when there is no robust evidence for improved outcome, was inappropriate."* Five years later, Bouri et al.[1] have arrived at basically the same conclusion. Accordingly; the new meta-analysis actually does not provide truly novel information.

There are several limitations to Bouri's 2013 meta-analysis which limit uncritical application into routine clinical practice. First; the value of 1.01 for the lower limit of the 95% confidence interval (CI) reflects borderline statistical significance; i.e. questioning the clinical relevance of the observed statistically significant increase in mortality risk. Second; this meta-analysis (as with all recent meta-analyses on this topic) is dominated by the large POISE study[8] (Table 1). If the results of the POISE study were excluded, unequivocal evidence for or against perioperative beta-blockade would be lacking. The authors acknowledge that *"if the appropriateness of the POISE protocol is doubted, then the remaining secure data are not sufficient*

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Table 1. Associations between perioperative beta-blocker therapy and outcomes.

	n	RR	95% CI	*p* Value	Weight of POISE study
Mortality					
Lancet, 2008	7	1.27	1.01—1.61	0.044	75.2%
Heart, 2013	9	1.27	1.01—1.60	0.04	33.5%
Non-fatal MI					
Lancet, 2008	6	0.72	0.59—0.87	0.001	82.3%
Heart, 2013	5	0.73	0.61—0.88	0.001	47.2%
Non-fatal stroke					
Lancet, 2008	5	2.16	1.27—3.68	0.004	74.7%
Heart, 2013	5	1.73	1.00—2.99	0.05	64.0%

n, number of low-bias or secure trials; RR, risk ratio; CI, confidence interval.MI, myocardial infarction; *Lancet, 2008* (ref. [6]); *Heart, 2013* (ref. [1]); POISE study, (ref. [8]).

to guide physicians either way". There are, actually, valid reasons for such doubt to exist. Beta-blockade was started shortly before surgery, the dose was not titrated to effect, fixed doses were administered, cardiac and surgical risk varied between patients and the selected beta-blocker was exclusively metoprolol. All of these factors might *per se* modify outcome (see below).

Third; while everyone would agree that the findings of the DECREASE studies[2,3] can no longer be trusted, judgement on the scientific value and clinical impact of each of the nine trials currently termed "secure" is not so straightforward. The term "secure" merely designates a study as not belonging to the group of DECREASE trials. It does not automatically indicate studies of impeccable scientific quality. For example; whereas the POBBLE trial[9] was categorized in Bangalore's 2008 meta-analysis as being a 'high risk of bias' trial, it was considered to be a secure study in Bouri's 2013 meta-analysis.

Fourth; the claim by Bouri et al. that up to 10,000 lives per year could be saved in the UK is likely to be an exaggeration. There is already evidence that adherence to the ESC and ACC/AHA's recommendations on perioperative beta-blocker therapy has declined over the past couple of years, possibly related to the logistic difficulties in implementing efficient beta-blockade in the perioperative period and to the findings of the POISE trial.[10,11]

Finally, and perhaps most importantly, the 2013 meta-analysis (like all previous ones) included studies with considerable differences in practice regarding perioperative beta-blockade. Studies varied in; (i) the choice of beta-blocker (bisoprolol ($n = 3$), metoprolol ($n = 5$) and atenolol ($n = 2$)); (ii) the timing of preoperative initiation of beta-blockade (between 37 days and 30 min); (iii) the duration of postoperative administration (between 5 and 30 days), and (iv) the surgical risk (high, intermediate and low risk). Information on acute anaemia and blood transfusion was also lacking. Each (all) of these variables could modify the effectiveness of perioperative beta-blocker therapy.

The most commonly used beta-blockers differ in their $ß_1/ß_2$ selectivity ratios (metoprolol, 2.3; atenolol, 4.7; bisoprolol, 13.5).[12] There is experimental evidence that beta-blockade might predispose to stroke by attenuating $ß_2$-adrenoceptor-mediated cerebral vasodilation.[13—15] In agreement with animal data, in humans the more $ß_1$-selective antagonist bisoprolol was associated with a considerably lower stroke incidence compared with the less $ß_1$-selective antagonists metoprolol and atenolol.[16] Likewise, atenolol was associated with a considerably lower stroke incidence when compared to metoprolol.[11,17] To my knowledge, there is only one study (involving 140 cardiac surgery patients) where beta-blockade was not associated with a trend for an increased risk of stroke.[18] In this study, the ultra-short acting beta-blocker landiolol was used and its very high $ß_1/ß_2$-selectivity ratio of 250 might have contributed to this finding. As a lower incidence of stroke was also associated with a lower incidence of other severe adverse events,[16] highly $ß_1$-selective beta-blockers may *per se* decrease the risk of overall adverse outcomes.

Metoprolol undergoes selective (70—80%) metabolism by the CYP2D6 isoenzyme of cytochrome P-450. Atenolol and bisoprolol do not.[19,20] In the presence of genetic variations of the CYP2D6 isoenzyme, variations in elimination half-lives and plasma concentrations and, in turn, in cardiovascular effects must be expected to be greater with metoprolol than with atenolol and bisoprolol. Whereas peak and trough plasma concentrations of bisoprolol were unaffected by polymorphisms of the CYP2D6*10 allele, peak and trough plasma concentrations of metoprolol were twice as high in patients homozygous for the CYP2D6*10 allele (reflecting poor metabolism of metoprolol), compared to those without or who were heterozygous for the CYP2D6*10 allele.[21] As a consequence of the higher plasma concentrations in the poor metabolizers, the increases in heart rate in response to low and high doses of isoproterenol were significantly blunted. Similarly, polymorphisms of the CYP2D6*4 allele affected the heart rate of patients taking metoprolol, but not in those taking atenolol.[19] At identical daily doses, mean plasma concentrations of metoprolol were five times higher in poor metabolizers compared to normal metabolizers.[22] This was associated with lower heart rates and lower mean and diastolic blood pressures. These findings clearly show that the degree of beta-blockade is far less predictable with metoprolol than with atenolol or bisoprolol. This would be of particular clinical relevance when fixed-dose beta-blocker therapy was started shortly before surgery (as in the POISE trial). The risk of exaggerated perioperative hypotension and bradycardia will then be enhanced if the chosen beta-blocker is metoprolol.

The timing and titration of beta-blockade do not appear to crucially affect cardioprotection. However, they might affect all-cause mortality and the risk of stroke, because acute initiation of fixed-dose beta-blockers may more often lead to hypotension and bradycardia, both of which are independent predictors of those outcome variables.[8] There is evidence suggesting that beta-blocker treatment for longer than one week before surgery is associated with better outcome than beta-blockade initiated less than one week preoperatively.[23,24] By contrast, a recent analysis

failed to confirm an association between duration of preoperative beta-blocker exposure and outcome.[11] However, this analysis included only a small number of patients receiving beta-blockers within 7 days of surgery. Nevertheless, considering the varying and unpredictable metabolism of beta-blockers and individual patient responsiveness, it seems advisable to initiate beta-blocker therapy well ahead of planned surgery, if such a therapy is medically indicated.

The type of surgery and underlying cardiac risk may also influence the effectiveness of perioperative beta-blockade. Patients undergoing emergency surgery might not benefit as much as those undergoing elective surgery. This might be related to a higher incidence of bleeding and hypotension which were identified in the POISE study[8] as being predictors of adverse outcome. The risk factors associated with emergency surgery may be accentuated by the reduction in cardiac output reserve caused by beta-blockers. In a large retrospective cohort analysis (using a propensity model), perioperative beta-blockade was associated with a lower 30-day mortality and morbidity following major non-cardiac surgery, but not following vascular surgery.[11] In non-vascular surgery, the extent of underlying cardiac risk influenced mortality, but not morbidity. Whereas patients with none or only one revised cardiac risk index factor did not benefit from beta-blockade, mortality progressively decreased as the number of risk factors increased.[11] It is difficult to explain the lack of association between beta-blockade and outcome in vascular surgery patients who are considered to be at highest risk of adverse cardiovascular outcome. There has been speculation that a relative small sample size and the possibilities of medication and higher level of care not being captured by the database may explain this somewhat unexpected finding.

The cardioprotective effect of beta-blockers seems to be affected by acute surgical anaemia. Overall, major cardiac events occurred twice as often in patients being treated with beta-blockers compared to beta-blocker naïve patients.[25] However, this difference was limited to patients who experienced a 35% decrease in haemoglobin concentration from their baseline value. With increasing amounts of bleeding during vascular surgery, the cardioprotective effect of beta-blockade was lost and the risk of death and/or multi-organ dysfunction syndrome increased.[26] The probability of postoperative stroke associated with metoprolol, atenolol and bisoprolol increased with decreasing postoperative haemoglobin concentrations.[16] The threshold postoperative haemoglobin concentration below which the probability of stroke started to increase significantly was about 9 g/dL for all beta-blockers. This is consistent with findings in humans where the compensatory cardiac output response to acute anaemia becomes predominantly heart rate dependent at haemoglobin concentrations below 9—10 g/dL.[27]

All beta-blockers will blunt the cardiac output response to acute anaemia by comparable blockade of $ß_1$-receptors. However, highly $ß_1$-selective beta-blockers may partly counteract this cardiodepressant effect by facilitating organ perfusion through preserved $ß_2$-mediated systemic and regional vasodilation. During low plasma concentrations of the highly $ß_1$-selective beta-blocker nebivolol, the acute increase in regional cerebral blood flow in response to experimentally induced acute haemodilution was preserved and cerebral tissue oxygenation was not further impaired. By contrast, higher plasma concentrations blunted the increase in cerebral blood flow and worsened cerebral oxygenation.[15] A possible explanation for the concentration-dependent differential effects on cerebral perfusion and oxygenation (despite concentration-independent comparable depressant effects on cardiac output and heart rate) may be the increasing affinity of nebivolol for the vascular $ß_2$-adrenoceptor at the high plasma concentration, interfering with $ß_2$-mediated cerebral vasodilation. In corroboration, beta-blockers administered to anaemic animals at doses that occupy $ß_2$-adrenoceptors impair cerebral oxygenation.[13,14,28] Less $ß_1$-selective beta-blockers may blunt $ß_2$-mediated cerebral vasodilation even independent of the haemoglobin concentration. In the experimental animal, metoprolol increases systemic vascular resistance and impairs cerebral oxygenation even at normal haemoglobin concentrations.[14] In humans, stroke risk was higher during metoprolol than during bisoprolol at nadir postoperative haemoglobin concentrations greater than 9 g/dL.[16]

In the POISE study,[8] bleeding was associated with an increased risk of stroke. The association between experimentally impaired cerebral perfusion and oxygenation and an increased risk of perioperative stroke on one hand, and anaemia and beta-blockade on the other, suggests that higher than usually accepted haemoglobin concentrations and transfusion trigger might benefit beta-blocked patients.

So where do we stand in 2014? The meta-analysis by Bouri et al.[1] does not provide sufficient evidence to justify a general ban on perioperative beta-blockade in general and on preoperative initiation of beta-blocker therapy in particular. The question of which patients might benefit from perioperative beta-blockade remains unanswered. If the medical indication for institution of beta-blockade arises preoperatively, it should be started well before surgery and the dose should be titrated to effect. Initiation of fixed dose beta-blockade shortly before surgery must be avoided. The various experimental and human data suggest that beta-blockers other than metoprolol should be considered.

Perioperative titration of beta-blockers solely on the basis of heart rate is potentially dangerous because it may disguise non-myocardial ischaemic causes of tachycardia and blunts/suppresses cardiovascular compensatory mechanisms. Thus, before administration of beta-blockers, all non-myocardial ischaemic causes of tachycardia must be ruled out (e.g., insufficient analgesia, latent hypovolaemia/hypervolaemia, hypo-/hyperthermia, latent heart failure and anaemia).

The ESC, ACC and AHA have now reacted to Bouri's 2013 meta-analysis. On 01 Aug 2013 the ESC issued the following press release:[29] *"Further to the publication of a 'Meta-analysis of secure randomised controlled trials of ß-blockade to prevent perioperative death in non-cardiac surgery'[1],*

which refers to the ESC Clinical Practice Guidelines on Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery, the ESC would like to state the following: (i) the ESC is currently revising these guidelines as announced in a previous statement in March 2013, taking into account this very complex scientific issue; (ii) the ESC Board is taking these new findings very seriously, keeping patients' best interests at heart; (iii) the ESC has convened an urgent task force to decide whether further actions are required and (iv) the ESC, AHA and ACCF are collaborating."

This was followed by a Joint Statement issued by the ACC, AHA and the ESC on 05 Aug 2013 stating:[30] *"The American College of Cardiology, American Heart Association and the European Society of Cardiology are all in the process of completing updated versions of our Guidelines for Perioperative Care. Our respective writing committees are undertaking a careful analysis of all relevant validated studies and always incorporate appropriate new trials and meta-analyses into our evidence review. In the interim, our current joint position is that the initiation of beta blockers in patients who will undergo non-cardiac surgery should not be considered routine, but should be considered carefully by each patient's treating physician on a case-by-case basis."*

This is where we stand at the beginning of 2014.

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