BJA

British Journal of Anaesthesia, ■ (■): 1–10 (2018)

doi: 10.1016/j.bja.2018.02.004
Advance Access Publication Date: xxx
Special Article

SPECIAL ARTICLE

Beta-blockers in non-cardiac surgery: Did observational studies put us back on safe ground?

M. E. Jørgensen[1,*], C. Andersson[1], S. Venkatesan[2] and R. D. Sanders[3]

[1]The Cardiovascular Research Center, Herlev-Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark, [2]Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK and [3]Anesthesiology & Critical Care Trials & Interdisciplinary Outcome Network, Department of Anesthesiology, University of Wisconsin, Madison, WI, USA

*Corresponding author. E-mail: Mads.Emil.Joergensen@regionh.dk.

Abstract

Based on landmark trials, international guidelines had for years promoted the use of beta-blockers in the setting of non-cardiac surgery. In 2011, concerns were raised regarding the integrity of some of the landmark trials, as the Dutch Erasmus Medical Center found some of them to be scientifically incorrect. Based on the remaining studies that were to be trusted, investigations showed that, in contrast to prior beliefs, the widespread use of perioperative beta-blockers might be harmful. A call for further investigations into the matter ushered in several observational studies evaluating the safety of perioperative beta-blocker therapy in specific patient subgroups. Within this review, we discuss important aspects for making these decisions, and compare the major observational studies and specific estimates of risk in subgroups of interest. We conclude that patients at high risk with heavy co-morbidities, such as heart failure, may benefit from beta-blocker therapy, whereas low-risk patients, such as patients with uncomplicated hypertension, may be at increased risk with beta-blocker therapy. We provide a critical review of current perioperative guidelines in view of the new observational data, suggesting that the recommended schematics, such as the Revised Cardiac Risk Index, for risk stratification of patients in this setting may be suboptimal. Further, we provide discussions of other aspects, including risk of sepsis, type of beta-blocker, and the potential of perioperative beta-blocker withdrawal, which may be important in guiding future studies. Summarising the current evidence, we argue that, after a precarious decade, we may just now, be back on safe ground.

Keywords: adrenergic beta-antagonists; general surgery; perioperative care

Editorial decision: February 07, 2018; **Accepted:** February 7, 2018

Editor's key points

- The authors critically review the evidence base for a survival benefit granted by perioperative beta-blockade.
- They argue that, whilst recent work has helped to clarify the situation, it remains unclear whether any meaningful survival benefit exists, and that hazards (including worsened outcome) are likely in some contexts.

Since 2008, and thus, for almost a decade, there has been controversy regarding the use of beta-blockers in the setting of non-cardiac surgery. This issue of beta-blockers in a surgical setting is important, as it affects millions of patients undergoing non-cardiac surgery every year. The issue took off when realising that the findings of a few randomised clinical trials seemed too impressive,[1,2] with an investigation revealing scientific misconduct,[3,4] and the subsequent subtle response by major scientific journals and medical societies to the situation.[5] Ten years later, sparse new evidence has been added to the topic; but, is it enough to put us back on safe ground, or are clinicians and patients continuously left to wonder?

Issue in short

Important events and publications regarding the use of perioperative beta-blockers within the past 20 yr are outlined in Table 1. The first recommendations on the use of beta-blockers in the setting of non-cardiac surgery are found in the American College of Cardiology/American Heart Association (ACC/AHA) perioperative guidelines from 1996, advocating the continued use of beta-blockers in the perioperative period to reduce myocardial ischaemia.[6] As more evidence became available, the ACC/AHA perioperative guidelines from 2002 included a Class IIa recommendation (i.e. it is reasonable) for the use of beta-blockers when 'preoperative assessment identifies untreated hypertension, known coronary disease, or major risk factors for coronary disease'.[7] In addition, the need for dose titration and further research in the field was noted. The scientific basis for these recommendations was limited and included the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) I trial, which suggested a remarkable 91% lower risk of cardiovascular death and non-fatal myocardial infarction (MI) with bisoprolol administration.[1]

After several years, in 2008, the results from the Perioperative Ischemic Evaluation (POISE) trial[8] and a meta-analysis by Bangalore and colleagues[9] were published, both in the *Lancet*. The POISE trial was the first, and remains the only, large-scale trial randomising 8351 patients to metoprolol or placebo (extended release metoprolol 100 mg before surgery, followed by 200 mg daily for up to 30 days). The study found that all-cause death was significantly higher in the metoprolol group, compared with placebo (hazard ratio 1.33; confidence interval [CI] 1.03–1.74).[8] Also of interest, as part of the paper reporting the main findings of the trial, the POISE investigators included a meta-analysis with the notion that, if excluding the findings of extreme benefits with beta-blockers from the 1999 DECREASE I trial, the overall effect of beta-blockers on mortality was unfavourable, with a relative risk of 1.29 (CI 1.02–1.62), compared with placebo.[8] Six months later, a comprehensive meta-analysis by Bangalore and colleagues[9] confirmed these results with a net-zero effect analysing all studies, and a 28% increased risk of mortality if several studies with a high risk of bias (including DECREASE I) were excluded.

A few years later, in 2011, a report was published by the Erasmus Medical Center criticising the principal investigator of the DECREASE studies, with a specific focus on the DECREASE VI trial, which was found to be fraudulent and based on fictitious data.[3] The studies relevant to perioperative beta-blocker therapy (i.e. the DECREASE I and DECREASE IV trials) by this principal investigator were reviewed in a follow-up report published by the same institution in 2012.[4] DECREASE I was not thoroughly investigated, as the trial was conducted more than 10 yr before the Erasmus investigation, whilst the DECREASE IV trial was found to be, to quote, 'negligent and scientifically incorrect'.

After these revelations, the current European Society of Cardiology (ESC) and ACC/AHA perioperative guidelines were debated for their endorsement of beta-blocker use in the perioperative non-cardiac-surgery setting.[10–13] Several meta-analyses followed, amongst others was one reconfirming the 27% increased risk of all-cause death with perioperative beta-blockers, calling out both the ESC, ACC/AHA, and responsible journals for their lack of attention and willingness to respond to the issue and adjust current guidelines.[5] Discussions even reached mainstream media where rough calculations, based on a paper in the *European Heart Journal*, which was almost immediately retracted, suggested that guideline adherence could have led to the death of 800 000 people in Europe during a 5 yr period.[14]

The question of who should take the initiative to address the discrepancies was not easily resolved, as the 2012 report from the Erasmus Medical Center had not been able to provide proof that other trials than DECREASE VI were, in fact, fraudulent. Therefore, the journals publishing the trial results were hesitant to retract the papers and decided to leave them be with an editorial comment referring to the 2012 report from the Erasmus Medical Center.[15] Finally, the ESC and ACC/AHA put out the argument that, as the papers remained online, they were part of the scientific evidence, and decided to discuss the papers in future guidelines, but not to include them in the final guideline recommendation, which remains the situation as of today. Thus, it remained unclear which patients, if any, would benefit from perioperative beta-blocker therapy, with a subsequent need for further studies (Table 1).

One size does not fit all: to treat or not to treat

As mentioned, the 2002 ACC/AHA guidelines advocated for the use of beta-blockers where preoperative assessment had revealed coronary disease or major risk factors for coronary disease, suggesting its use in a wide variety of patients.[7] Over the years, recommendations have become increasingly narrow, as described in detail by Neuman and colleagues.[16] The most recent guidelines advocated to continue beta-blockers in patients chronically treated, and consider beta-blocker initiation in intermediate- to high-risk patients [i.e. ≥2 clinical risk factors, ASA status ≥III, or ≥3 factors from the revised cardiac risk index (RCRI)] (Table 2).[17,18] These newer recommendations suggest that the higher the risk, the more benefit from perioperative beta-blocker treatment, but major trials have been underpowered for analyses stratified by specific risk factors contributing to the ASA and RCRI score.

Several parameters need to be considered when evaluating the associations between beta-blocker therapy and