CAGS AND ACS EVIDENCE BASED REVIEWS IN SURGERY. 34

Effects of β-blockers in patients undergoing noncardiac surgery

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The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."[1] The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) and is supported by an educational grant from ETHICON and ETHICON ENDO-SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson and ETHICON Inc. and ETHICON ENDO-SURGERY Inc., divisions of Johnson & Johnson Inc. The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

Reference

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

SELECTED ARTICLE

POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;371:1839-47

ABSTRACT

Question: Do β-blockers have an effect on the 30-day risk of major cardiovascular events in patients with or at risk of atherosclerotic disease undergoing noncardiac surgery? **Design:** Randomized controlled trial. **Setting:** Multicentre trial in 190 hospitals in 23 countries. **Patients:** In total, 8351 patients with or at risk of atherosclerotic disease undergoing noncardiac surgery. **Intervention:** Patients were randomly assigned by a computerized 24-hour phone service to receive extended-release metoprolol succinate 200 mg (n = 4174) or placebo (n = 4177). Treatment was started 2–4 hours before surgery and continued for 30 days. **Main outcome:** Cardiovascular death, nonfatal myocardial infarction (MI) and nonfatal cardiac arrest. **Results:** Of those randomized, 8331 (99.8%) patients completed the 30-day follow-up. Fewer patients in the metoprolol group than in the placebo group had an MI (176 [4.2%] v. 239 [5.7%] patients; hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.60–0.089, p = 0.0017). However, there were more deaths in the metoprolol group than in the placebo group (129 [3.1%] v. 97 [2.3%] patients; HR 1.33, 95% CI 1.03–1.74, p = 0.0317). More patients in the metoprolol group than in the placebo group had a stroke (41 [1.0%] v. 19 [0.5%] patients; HR 2.17, 95% CI 1.26–3.74, p = 0.0053). **Conclusion:** A perioperative β-blocker regimen results in fewer MIs but is associated with an increased risk of stroke and perioperative death in patients with or at risk for atherosclerotic disease undergoing noncardiac surgery. Patients are unlikely to accept the risks associated with perioperative extended-release metoprolol use.

COMMENTARY

Noncardiac surgery in adults accounts for most of the estimated 200 million surgical procedures performed worldwide annually.[1] Major cardiovascular complications occur in 1–2 million patients undergoing surgical procedures every year.[2] The POISE trial[3] is the largest and most recent trial comparing β-blockers with placebo in patients undergoing noncardiac surgery; the aim of this trial was to assess the effect of β-blockade on outcomes such as myocardial infarction (MI), stroke and cardiovascular-related death. The results are generalizable because of the large number of participants, the multiple centres involved and the heterogeneity of the surgical populations included in the study.

This was a well-designed and conducted randomized controlled trial that met its goals of investigating the effectiveness of β-blockade in perioperative noncardiac surgery patients. Specifically, the auditing and monitoring process gives confidence about the quality of the data presented. This trial has shed light on the impact of the use of β-blockers around the time of surgery on postoperative outcomes, which was only possible because it was a large randomized controlled trial.

The results of the POISE study show that the use of β-blockers in the perioperative period reduces the risk of the composite outcome of cardiovascular death, nonfatal MI and nonfatal cardiac arrest at 30 days after randomization. The marked reduction in nonfatal MIs afforded by the addition of β-blockers to the clinical regimen had a large impact on the benefits seen with this composite outcome, but it was at the expense of an increase in bradycardic and hypotensive events in patients receiving β-blockers, resulting in an increase in deaths and strokes. Thus, the POISE trial presents a challenging dichotomy for clinicians to interpret: refining the indications for β-blockade in the perioperative period to provide the proven myocardial protection against ischemic events while monitoring and tempering dosages to ensure that adverse events do not thwart the benefit.

This trial is often criticized for the dosages of β-blocker used. In fact, the dose of extended-release metoprolol chosen has been found to have a better impact on exercise heart rate compared with 100 mg atenolol and to have superior antianginal effects compared with 100 mg metoprolol twice daily.[3,4] The POISE trialists chose these dosages based on the COMMIT trial, recognizing that lower doses are ineffective in reducing cardiac complications.[5,6] The challenge of large, simple, randomized controlled trials is the need to protocolize dosages of interventional drugs for all patients. It could be argued that a more personalized or individualized approach for each patient receiving a β-blocker may have decreased the number of adverse events that occurred. However, from a methodologic point of view, this would have created a statistical challenge in determining the final effect.

The POISE trial has provided some very important information about the risk profile of β-blockers in the perioperative period. Clinicians are now sensitized to the importance of avoiding bradycardia and hypotension because there is evidence that they may decrease the effectiveness of β-blockade by increasing the risk of nonfatal stroke. These data were not apparent in the smaller trials predating POISE, and this serves as an example of the important need for large randomized controlled trials to determine both risks and benefits of a treatment. The standard of care will inevitably change as a result to temper the enthusiasm for universal use of β-blockers in patients undergoing noncardiac surgery.

Ultimately, the POISE trial did not provide overwhelming support for the use of β-blockers in the perioperative period. It did, however, inform clinicians of the risks and benefits of their use. It is up to us, as clinicians, to

interpret how the result of this trial will translate to individual patients.

Competing interests: None declared.

References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery a modeling strategy bases on available data. *Lancet* 2008;372:139-44.
2. Deveraux PJ, Goldman L, Cook DJ, et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005;173:627-34.
3. POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;371:1839-47.
4. Auerbach AD. Changing the practice of perioperative cardioprotection: perioperative beta-blockers after POISE (PeriOperative ISchemic Evaluation). *Circ Cardiovasc Qual Outcomes* 2008;1:58-61.
5. Blomqvist I, Westergren G, Sandberg A, et al. Pharmacokinetics and pharmacodynamics of controlled-release metoprolol: a comparison with atenolol. *Eur J Clin Pharmacol* 1988;33(Suppl):S19-24.
6. Egstrup K, Gundersen T, Harkonen R, et al. The antianginal efficacy and tolerability of controlled-release metoprolol once daily: a comparison with conventional metoprolol tablets twice daily. *Eur J Clin Pharmacol* 1988;33(Suppl):S45-9.

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