Perioperative β-Blockade: How Best to Translate Evidence into Practice

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During the 1980s, preoperative testing to identify patients with significant coronary artery disease and coronary revascularization was the mainstay of therapy to reduce the cardiac risk of noncardiac surgery (1). Beginning in the mid-1990s, several groups began to focus on postoperative monitoring and therapy, including the perioperative administration of β-adrenergic blocking drugs (or β-blockers) as a more effective approach (2,3). In 2002, Shojania et al. (4) published an evidence-based review funded by the Agency for Healthcare Research and Quality which identified perioperative β-blockade for noncardiac surgery as a practice with the strongest basis in the literature. This followed a review of the literature on the use of perioperative β-blockers that included clinical recommendations (5,6). These articles were followed by the establishment of perioperative quality of care measures by groups such as Leapfrog and the National Quality Forum which included perioperative β-blockade. This in turn has led many groups of perioperative caregivers, including surgeons, anesthesiologists, cardiologists, and medical physicians, to debate the best protocols to accomplish this goal. In this issue of *Anesthesia & Analgesia*, the editors have chosen to publish a series of articles to help frame this debate, and better inform the clinician. By publishing the Guidelines from the American Heart Association/American College of Cardiology (ACC/AHA), a new meta-analysis, and a pro–con debate from leaders in the field, they hope to provide the individual practitioner with sufficient information to make his or her own informed decision and define the best protocol for their own interventions (7–10).

In trying to translate evidence into clinical practice, it is important to understand the different forms of evidence that frame this debate and how best to apply them (11). As all the articles published this month indicate, the strongest evidence for perioperative β blockade comes from prospective randomized trials. Although several small randomized trials demonstrated a strong beneficial effect, others did not (12). Randomized trials offer the advantage of providing the strongest internal validity, but their external validity (i.e., ability to generalize the results) is less robust. In contrast, large cohort studies [e.g., administrative datasets used in the article by Lindenauer et al. (13)] offer insights into the efficacy of an intervention in routine clinical practice (i.e., external validity), but have much less internal validity. It is within this framework that the four articles are discussed.

The meta-analysis by Wiesbauer et al. (10) adds to a growing number of such analyses on this topic (12,14,15). The authors of the current meta-analysis focused on randomized controlled trials and included both published manuscripts and abstracts. By analytically combining these trials, the authors were unable to demonstrate an effect of β-blockers on the hard end points of perioperative myocardial infarction or mortality. The clinician could therefore assume that either 1) β-blockers are not effective, or 2) the studies included in the meta-analysis should not have been

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Accepted for publication October 5, 2006.

Conflict of Interest: Dr. Fleisher is currently Chair, American College of Cardiology/American Heart Association Task Force Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery).

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DOI: 10.1213/01.ane.0000250367.56805.b0

combined in the manner performed in the analysis because the populations or protocols used are different. If the latter is true, then the clinician should exert caution in specifics with regard to implementation of the protocols.

The pro–con debate (7,8) nicely illustrates this last point by outlining the issues related to interpretation of the data and how two groups of experts in this area choose to approach their own practice. On the pro side, the Dutch group led by Dr. Poldermans (8) clearly believes that many of the other trials did not control heart rate as tightly or provide perioperative β-blockade for as long a duration as in their own studies. The importance of these comments is highlighted by two articles published by the group (16,17), after the editorial was accepted, which further demonstrate the beneficial effect of β-blocker dosage and heart rate control on outcome. In contrast, Dr. London (7) presents a less expansive view with regard to the use of perioperative β-blockade. He argues that the evidence is insufficient to generalize beyond the known literature, and outlines some of the deficiencies in both the evidence and the theoretical underpinnings of widespread treatment. As he notes in his conclusion, given the evidence, it is important to separate the mandatory use of β-blockers as a quality assurance measure from their judicious use in the armamentarium to manage high risk patients.

It is in the context of this debate that the ACC/AHA produced a Focused Update on Perioperative Beta Blockade (9). Specifically, the American Medical Association Physician Consortium on Performance Improvement and the Surgical Care Improvement Project had both begun to evaluate the class and level of evidence to determine the appropriateness of developing performance measures based on continuation and initiation of perioperative β-blockade in noncardiac surgery. It became increasingly important that the appropriate specialty societies weigh in and develop evidence-based guidelines upon which performance measures can be developed. As outlined in the introduction to the Guidelines, the American College of Cardiology has issued a formal position statement indicating that performance measures should be limited to Class I or Class III recommendations—those recommendations in which patients should or should not have the form of therapy—and that they should not include Class IIa or IIb recommendations, in which the evidence is less strong and for which opinion dictates the class of indications. The ACC/AHA mandates that only published trials be included in defining recommendations, and therefore, some of the literature discussed in the meta-analysis could not be included. Importantly, in developing Table 1 (see Ref. 9), we attempted to review the published literature and develop a schemata whereby recommendations for individual cohorts of patients can be easily changed to reflect new evidence.

So, how would I put it all together? Clearly, Class I recommendations should be followed, and therefore, patients receiving β-blockers should be continued on β-blockers, and patients with a positive stress test undergoing vascular surgery should be started on β-blockers. There are large groups of patients currently not taking β-blockers but who have Class I indications for β-blockers independent of noncardiac surgery. For example, β-blockers should be started and continued indefinitely in all patients who have myocardial infarction, acute coronary syndrome, or left ventricular dysfunction, with or without heart failure symptoms, unless contraindicated (18). As shown in multiple studies, many patients who are not taking β-blockers present to vascular surgery with a history of a myocardial infarction (19,20). Therefore, there are patients who should be taking β-blockers for long-term benefits, but for whom there is no evidence to demonstrate that acute administration in the perioperative period will impact outcome. For this reason, we considered such instances as Class IIa indications in the new guidelines, suggesting that they are likely beneficial but that this indication lacks evidence to mandate inclusion as a quality of care measure. In patients who do not have the above indications for β-blockers independent of noncardiac surgery, there are now several trials and the meta-analysis that demonstrate no effect. The use of perioperative β-blockers in the latter group thus represents a Class IIb indication. Finally, Lindenauer et al. (13) suggest harm in subpopulations of surgical patients without any coronary artery disease risk factors. If this harmful effect is shown in randomized trials, then this would qualify as a Class III indication.

The question remains regarding the best protocol to initiate perioperative β-blockade. Ideally, these drugs should be started a week before surgery similar to the protocol by Poldermans et al. and titrated to heart rate-decreasing effect, but this is not always practical. Given emerging data suggesting that inadequate β-blockade and heart rate control may be associated with worse outcomes, it is important to ensure that any protocol will yield the desired effect and not cause harm. Given the lack of data regarding the efficacy of starting β-blockade the morning of surgery versus intraoperatively, the Surgical Care Improvement Project recently defined "appropriate" β-blockade for patients who have not received this therapy before arrival at the operating room as initiating treatment before arriving in the postanesthesia care unit. This allows the caregivers to individualize therapy. In my opinion, further data are needed to understand the risks and benefits of starting β-blockers in this group of patients, and that the results of the Perioperative Ischemic Evaluation (POISE) trial (21), a randomized controlled trial of metoprolol versus placebo in 10,000 patients undergoing noncardiac surgery, are eagerly awaited. The information and opinions in these four articles should allow clinicians to develop their own

best approach to perioperative β-blocker therapy in specific patient populations.

REFERENCES

1. Eagle K, Brundage B, Chaitman B, et al. Guidelines for perioperative cardiovascular evaluation of the noncardiac surgery. A report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. Circulation 1996;93: 1278–317.
2. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996;335:1713–20.
3. Rosenfeld BA, Breslow MJ, Dorman T. Postoperative management strategies may obviate the need for most preoperative cardiac testing. Anesthesiology 1996;84:1266–8.
4. Shojania KG, Duncan BW, McDonald KM, Wachter RM. Safe but sound: patient safety meets evidence-based medicine. JAMA 2002;288:508–13.
5. Auerbach AD, Goldman L. β-Blockers and reduction of cardiac events in noncardiac surgery: scientific review. JAMA 2002; 287:1435–44.
6. Auerbach AD, Goldman L. β-Blockers and reduction of cardiac events in noncardiac surgery: clinical applications. JAMA 2002;287:1445–7.
7. London MJ. Con: β-blockers are indicated for all adults at increased risk undergoing non-cardiac surgery. Anesth Analg 2007;104:11–4.
8. Schouten O, Bax J, Dunkelgrün M, et al. Pro: β-blockers are indicated for patients at risk for cardiac complications undergoing non-cardiac surgery. Anesth Analg 2007;104:8–10.
9. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative β-blocker therapy—a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Anesth Analg 2007;104:15–26.
10. Wiesbauer F, Schlager O, Domanovits H, et al. Peri-operative β-blockers for preventing surgery related mortality and morbidity—a systematic review and meta-analysis. Anesth Analg 2007;104:27–41.
11. Fleisher LA, Mantha S, Roizen MF. Medical technology assessment: an overview. Anesth Analg 1998;87:1271–82.
12. Devereaux PJ, Beattie WS, Choi PT, et al. How strong is the evidence for the use of perioperative β blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. BMJ 2005;331:313–21.
13. Lindenauer PK, Pekow P, Wang K, et al. Perioperative β-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005;353:349–61.
14. McGory ML, Maggard MA, Ko CY. A meta-analysis of perioperative β blockade: what is the actual risk reduction? Surgery 2005;138:171–9.
15. Stevens RD, Burri H, Tramer MR. Pharmacologic myocardial protection in patients undergoing noncardiac surgery: a quantitative systematic review. Anesth Analg 2003;97:623–33.
16. Feringa HH, Bax JJ, Boersma E, et al. High-dose β-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation 2006;114:I344–9.
17. Poldermans D, Bax JJ, Schouten O, et al. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving β-blocker therapy with tight heart rate control? J Am Coll Cardiol 2006;48:964–9.
18. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update—endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113:2363–72.
19. Mukherjee D, Lingam P, Chetcuti S, et al. Missed opportunities to treat atherosclerosis in patients undergoing peripheral vascular interventions: insights from the University of Michigan Peripheral Vascular Disease Quality Improvement Initiative (PVD-QI2). Circulation 2002;106:1909–12.
20. Nass CM, Allen JK, Jermyn RM, Fleisher LA. Secondary prevention of coronary artery disease in patients undergoing elective surgery for peripheral arterial disease. Vasc Med 2001;6:35–41.
21. Devereaux PJ, Yang H, Guyatt GH, et al. Rationale, design, and organization of the perioperative ischemic evaluation (POISE) trial: a randomized controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery. Am Heart J 2006;152:223–30.

Con: Beta-Blockers Are Indicated for All Adults at Increased Risk Undergoing Noncardiac Surgery

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Although anesthesiologists have long recognized the value of using β-adrenergic receptor blocking drugs perioperatively to attenuate adrenergic "stressors," it is only recently that other specialties have rallied around "perioperative β-blockade" (PBB) (1). This enthusiasm is linked to the publication of two seminal but controversial reports in the *New England Journal of Medicine* (2–3) and the tentative recommendation for PBB by the American College of Physicians in 1997 (4). Interest in PBB has grown to a "fevered pitch" with its designation as a top tier "safety practice" by the Agency for Healthcare Research and Quality's report (5) and has become "highly desirable" in the eyes of clinicians interested in optimizing patient outcome, hospital administrators eager to enhance their hospitals status as a provider of "safe care," and, more recently, by administrative organizations developing performance measures for benchmarking care and reducing costs. From the onset, however, there was skepticism about PBB by clinicians and researchers trained in classical epidemiologic techniques for evaluating efficacy (e.g., results in a highly controlled setting such as the randomized clinical trial with strict inclusion and exclusion criteria) and effectiveness (e.g., results in the larger universe of clinical practice) (6).

Although efficacy (either perioperative or long-term) has been challenged by a few outspoken critics (supported in part by 2 meta-analyses), (7–10) this debate focuses on the evidence that PBB should be routinely administered to all "at-risk patients" and excludes patients already receiving β-blockers or those with clear-cut indications for this therapy regardless of surgery (11). "At-risk" patients are usually considered to belong to either of 2 categories: 1) those undergoing high-risk vascular surgery with no evidence of coronary artery disease (CAD) or with stable CAD but without easily inducible ischemia, and 2) those undergoing nonvascular procedures with comorbidities predictive of CAD identified with traditional risk factors (advanced age, high total and HDL cholesterol, elevated blood pressure, cigarette smoking, family history of premature CAD, and diabetes mellitus). Although vascular surgery is recognized as producing the greatest percentage of perioperative adverse cardiac events, the latter group of patients undergoing noncardiac surgery is numerically much larger and thus, in many respects, of greatest interest.

Central to this debate are several linked questions: Just how large a problem is cardiac morbidity and mortality in patients without overt CAD (and in what types of surgery)? Do risk factors (or even overt CAD) influence short-term or longer-term (e.g., 1–2 yr) "intermediate" outcome after surgery? What does the current literature of PBB report?

With regards to the magnitude of the problem, the literature on the epidemiology of perioperative myocardial infarction (PMI) is derived primarily from investigations of patients with known prior MI and those undergoing vascular surgery (12). Both groups are recognized to have substantially higher risk over the general surgical population. Definitive reports of increased risk for PMI in patients with risk factors alone undergoing nonvascular surgery are lacking. Although accumulating evidence suggests that even low-grade postoperative "troponin leakage" has adverse implications for outcome for up to a year

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Accepted for publication May 23, 2006.

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DOI: 10.1213/01.ane.0000231830.13665.05

after surgery, even less data are available with regard to patients with CAD risk factors only (13).

Using classic Framingham predictors for CAD to risk stratify patients for PMI is problematic. Although predictive for CAD events over a timeframe measured in decades, these clinical markers are not intended for risk prediction over a period of weeks to months (14). To further confuse matters, the National Cholesterol Education Program-III considers diabetes or peripheral vascular disease as CAD equivalents (based on a 10-yr risk of a CAD event of ≥20%) (14). These epidemiologic complexities have contributed to the favored use by consultants of the "revised Cardiac Risk Index"(RCRI), which has identified stronger risk factors such as overt CAD, congestive heart failure, and highest risk surgery as most predictive of adverse perioperative outcomes (15). Although the RCRI has significant limitations, a recent report suggests its predictive ability can be enhanced by incorporating age and additional surgical details (16).

This discussion of the potential efficacy of PBB is complicated not only by the issue of risk factors alone versus overt CAD but also by purported effects of PBB on longer-term outcome after surgery (e.g., 1 to 2 yr). Although anesthesiologists have traditionally focused on perioperative outcomes, extending attention to long-term events entails the probability that one is evaluating the "natural history" of the patient's surgical indication (e.g., malignancy) or comorbidities (peripheral vascular disease, renal disease, diabetes) along with the impact of other important unmeasured factors (e.g., surgeon skill and outpatient medical care). There is currently no well-defined hypothesis as to why a short course of PBB might influence long-term outcomes leading to poorly substantiated speculation regarding perioperative inflammation and plaque stability as potential mechanisms (17).

Regardless, the existing literature of PBB centers primarily on two well-publicized studies. Mangano et al. (2) evaluated a short perioperative course (immediately before induction to up to 7 days after surgery or the time of hospital discharge) of atenolol versus placebo titrated to heart rate in 200 male veterans selected based on a history of known CAD or the presence of CAD risk factors. Although perioperative outcomes were not different between treatment groups, risk for adverse cardiac events was reduced approximately 65% the first year after surgery. In the other study, Poldermans et al. (3) reported a striking reduction (90%) in perioperative risk in a small study of 112 high-risk patients (easily inducible ischemia on preoperative dobutamine stress echo), recommending a prolonged period of preoperative and postoperative PBB.

It is important to consider the direct precursor for the atenolol trial of Mangano et al. (2), a National Institutes of Health-funded observational study of the predictors of perioperative cardiac morbidity. In this study, 454 male veterans (of which approximately 40% underwent vascular surgery and 50% had known CAD) were evaluated using perioperative Holter monitoring (2 days preoperatively, intraoperatively, and 2 days postoperatively). Postoperative myocardial ischemia occurred in 40% of patients and it imparted a ninefold increased risk of combined cardiac death, nonfatal MI, or unstable angina (18). The latter end-points occurred in only 3.2% of patients. In a subsequent 2-yr follow-up report of this cohort, 11% of patients developed major cardiovascular complications (19). Independent predictors of longer-term adverse cardiac events were known vascular disease, history of congestive heart failure (CHF), known CAD, and perioperative cardiac events that included PMI, unstable stable angina, and Holter-detected myocardial ischemia (hazards ratio, 2.2; $P = 0.03$) (19). Curiously, the hypotheses and sample size estimations for the subsequent atenolol study (performed at the same center) were presented as dual goals to simultaneously evaluate reduction of in-hospital "surrogate" events (hemodynamic changes, dysrhythmias, and Holter-detected myocardial ischemia) and longer-term outcome, rather than the 3.2% perioperative cardiac event rate (fatal/nonfatal MI or unstable angina) of more interest to clinicians and with the most direct physiologic rationale. However, a properly performed power analysis suggests that the latter hypothesis would require 6,000–10,000 patients. Thus, the rationale for PBB in at-risk patients (particularly the large group of nonvascular surgery patients) was never really supported by existing data, which suggested that known CAD, CHF, and vascular surgery were the major risk factors.

Regardless, in the multivariate analysis of the atenolol trial, diabetes was identified as the major risk factor for adverse long-term outcome (hazard ratio, 2.8; $P = 0.01$), and atenolol use was actually not a significant protective factor in this model (with a 95% confidence interval of 0.2–1.1; P value of 0.06). This finding is of interest given the preliminary report of a large (more than 900 patients) randomized trial of diabetic patients (DIPOM) that reported that PBB did not influence either perioperative or intermediate adverse cardiac outcomes in this group of patients (20). Furthermore, although Holter-detected myocardial ischemia was reduced by approximately 50% by atenolol in the trial of Mangano et al. (2), it is unclear why this reduction did not influence perioperative outcome given its role as a major prognostic factor in the original "predictors" study (21). This failure is most consistent with the well accepted truism that myocardial ischemia alone is a relatively nonspecific "surrogate outcome."

The recent large-scale retrospective observational analysis of Lindenauer et al (22) of in-hospital mortality in over 780,000 patients at 329 United States hospitals (predominantly nonteaching facilities) in 2000 and 2001, using data obtained from a large proprietary administrative database, has generated considerable attention with regard to the findings of neutral or even adverse associations of PBB in low and at-risk only patients (22). Of the 85% of patients without contraindications to β-blockers, 18% received them (tracked only during the first 2 hospital days), increasing from 14% in those with

no RCRI risk factors (50% of patients) to 44% in those with ≥4 risk factors (which notably were present in only <1% of patients). PBB was associated with lower mortality only in patients with 3 or more risk factors (3% of the total cohort). The most controversial findings were that in the lowest-risk patients PBB actually increased mortality. As speculated by the authors, the increased mortality may reflect the use of β-blockers to treat complications, rather than as prophylaxis. Despite its large size, this study has numerous important caveats and limitations, the most important of which is its nonrandomized design. Other preliminary data by Yang et al. (23) in more than 400 patients (MAVS trial) and a recently reported peer-reviewed small (103 patients) randomized controlled trial (POBBLE) (24) found no differences in perioperative outcomes in lower-risk vascular patients with PBB. The peer reviewed results of the MAVS trial are eagerly awaited. A large ongoing multinational randomized trial (POISE) is likely to provide the most definitive data within the next few years regarding the benefits versus risk of PBB, particularly for low-risk patients (10).

To summarize, there is little evidence demonstrating that patients not already identified as having CAD or CHF and not undergoing major vascular surgery (particularly aortic or lower extremity revascularization) are at substantially increased risk for PMI. Further, there has been little effort to document a rational mechanism for the purported long-term protection afforded by a short-term course of PBB. The focus on long-term outcomes in vascular patients is driven by the observation that, in the absence of medical therapy and lifestyle modifications, these patients have a high mortality over time as a result of their underlying cardiovascular disease (25,26). In contrast to the documented benefits of β-adrenergic blockers on secondary prevention in post-MI patients (e.g., prevention of a subsequent recurrent MI with enhanced long-term survival) (27) and their long-term benefits in patients with CHF (28), there is minimal, if any, evidence for primary preventive effects of β-blockers alone, either on development of overt CAD or MI, in patients with risk factors only (particularly in large cohorts of patients treated for hypertension). These medical observations may be analogous to the perioperative setting. There is no debate that β-blockers are a great option that can be offered to any at-risk patient undergoing major surgery. As Devereaux and Yusuf (29) emphasize, evidence-based decision-making should equally use research evidence, the clinical state, the patient's preference, and the clinician's expertise. Some patients will clearly be interested in therapy and others will refuse it. The skillful perioperative use of β-adrenergic blockers to control hemodynamic stress is rapidly approaching, if not already established as, standard of care for all patients. Their mandatory use, especially when used as a measure of quality of care, is still a hypothesis awaiting adequate supporting data.

REFERENCES

1. London MJ, Zaugg M, Schaub MC, Spahn DR. Perioperative beta-adrenergic receptor blockade: physiologic foundations and clinical controversies. Anesthesiology 2004;100:170–5.
2. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 1996;335:1713–20.
3. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. N Engl J Med 1999;341:1789–94.
4. Palda VA, Detsky AS. Perioperative assessment and management of risk from coronary artery disease. Ann Intern Med 1997;127:313–28.
5. Shojania K, Duncan B, McDonald K, Wachter R. Making health care safer: a critical analysis of patient safety practices. Rockville, MD: Agency for Healthcare Research and Quality, 2001.
6. Mukherjee D, Eagle KA. Improving quality of care in the real world: efficacy versus effectiveness? Am Heart J 2003;146:946–7.
7. Devereaux PJ, Yusuf S, Yang H, et al. Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? CMAJ 2004;171:245–7.
8. London MJ, Zaugg M, Schaub MC, Spahn DR. A large trial is vital to prove perioperative beta-blockade effectiveness and safety before widespread use. Anesthesiology 2004;101:804–5.
9. Stevens RD, Burri H, Tramer MR. Pharmacologic myocardial protection in patients undergoing noncardiac surgery: a quantitative systematic review. Anesth Analg 2003;97:623–33.
10. Devereaux PJ, Beattie WS, Choi PT, et al. How strong is the evidence for the use of perioperative beta blockers in noncardiac surgery? Systematic review and meta-analysis of randomised controlled trials. BMJ 2005;331:313–21.
11. Lopez-Sendon J, Swedberg K, McMurray J, et al. Expert consensus document on beta-adrenergic receptor blockers. Eur Heart J 2004;25:1341–62.
12. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2002;105:1257–67.
13. Oscarsson A, Eintrei C, Anskar S, et al. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. Acta Anaesthesiol Scand 2004;48:1071–9.
14. Ford ES, Giles WH, Mokdad AH. The distribution of 10-year risk for coronary heart disease among US adults: findings from the National Health and Nutrition Examination Survey III. J Am Coll Cardiol 2004;43:1791–6.
15. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043–9.
16. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. Am J Med 2005;118:1134–41.
17. Yeager MP, Fillinger MP, Hettleman BD, Hartman GS. Perioperative beta-blockade and late cardiac outcomes: a complementary hypothesis. J Cardiothorac Vasc Anesth 2005;19:237–41.
18. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990;323:1781–8.
19. Mangano DT, Browner WS, Hollenberg M, et al. Long-term cardiac prognosis following noncardiac surgery. JAMA 1992;268:233–9.
20. Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, Norgaard P, Fruergaard K, Bestle M, Vedelsdal R, Miran A, Jacobsen J, Roed J, Mortensen MB, Jorgensen L, Jorgensen J, Rovsing ML, Petersen PL, Pott F, Haas M, Albret R, Nielsen LL, Johansson G, Stjernholm P, Molgaard Y, Foss NB, Elkjaer J, Dehlie B, Boysen K, Zaric D, Munksgaard A, Madsen JB, Oberg B, Khanykin B, Blemmer T, Yndgaard S, Perko G, Wang LP, Winkel P, Hilden J, Jensen P, Salas N; DIPOM Trial Group. Effect of perioperative beta blockade in patients with diabetes undergoing majornon-cardiac surgery: randomised

placebo controlled, blinded multicentre trial. BMJ 2006; 332:1482.
21. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. Anesthesiology 1998;88:7–17.
22. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005;353:349–61.
23. Yang H, Raymer K, Butler R, et al. Metoprolol after vascular surgery (MaVS). Can J Anaesth 2004;51 (Suppl 1):A7.
24. Brady AR, Gibbs JS, Greenhalgh RM, et al. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg 2005;41:602–9.
25. Mukherjee D, Lingam P, Chetcuti S et al. Missed opportunities to treat atherosclerosis in patients undergoing peripheral vascular interventions: insights from the University of Michigan Peripheral Vascular Disease Quality Improvement Initiative (PVD-QI2). Circulation 2002;106:1909-12.
26. Conte MS, Bandyk DF, Clowes AW, et al. Risk factors, medical therapies and perioperative events in limb salvage surgery: observations from the PREVENT III multicenter trial. J Vasc Surg 2005;42:456–64.
27. Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318:1730-7.
28. Dulin BR, Haas SJ, Abraham WT, Krum H. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. Am J Cardiol 2005;95:896–8.
29. Devereaux PJ, Yusuf S. The evolution of the randomized controlled trial and its role in evidence-based decision making. J Intern Med 2003;254:105–13.

ERRATUM

In the April 2006 issue, in the article by Anta et al., "Accidental Epidural Administration of Succinylcholine" (Anesth Analg 2006;102:1139–40), on page 1139, the names of the authors are transposed in the authors' byline.

The corrected names should be: Anta Sofianou, MD, PhD, Athanasios Chatzieleftheriou, MD, Panorea Mavrommati, MD, PhD, and Kyriaki Velmachou, MD, PhD.

The authors apologize for the error.

Editorial

Pro: Beta-Blockers Are Indicated for Patients at Risk for Cardiac Complications Undergoing Noncardiac Surgery

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Of the estimated 100 million adults undergoing noncardiac surgery annually, approximately 500,000 patients (0.5%) will experience cardiac death perioperatively (1). Lee et al. (2) reported an overall risk for myocardial infarction (MI) after noncardiac surgery to be 1.1%, translating into about 1.1 million MIs annually worldwide. Although the pathophysiology of perioperative MI is not entirely clear, coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is implicated, similar to MI in the nonoperative setting (3). The incidence of plaque rupture is possibly increased by the stress response to major surgery. This response includes sympathetic activation promoting sheer stress on arterial plaques, enhanced vascular reactivity conducive to the development of vasospasm, reduced fibrinolytic activity, platelet activation, and hypercoagulability (4). Heightened sympathetic tone further increases myocardial oxygen demand (e.g., tachycardia and increased contractility), leading to myocardial oxygen supply/demand mismatch that, when sustained, might lead to MI (4,5). At least two studies evaluating the pathophysiology of perioperative MI using noninvasive tests, coronary angiography, and autopsy have shown that coronary plaque rupture and thrombus formation occurred in 50% of all fatal MIs, whereas a sustained oxygen supply/demand mismatch was responsible for the remaining 50% (3,6).

MECHANISM OF THE PROTECTIVE EFFECT OF BETA-BLOCKERS

Because of the role of sympathetic activation in adverse perioperative cardiac outcomes, β-adrenergic receptor blocking drugs have been proposed as a means for providing cardioprotection. Potential cardioprotective mechanisms of β-blockers include a) reduced heart rate and contractility and subsequently lower myocardial oxygen demand; b) a shift in energy metabolism from free fatty acids to the more energy efficient glucose; c) antiarrhythmic effects; d) anti-renin/angiotensin properties; and e) antiinflammatory effects possibly promoting plaque stability (7–9). The effects on heart rate, contractility, and energy substrate shift occur almost instantly, whereas the antiinflammatory effects may be observed only after prolonged use of β-blockers.

CLINICAL EVIDENCE FOR THE EFFECTIVENESS OF PERIOPERATIVE BETA-BLOCKER THERAPY

Although widely prescribed as a means for reducing perioperative cardiac events, the evidence supporting this indication for β-blockers is based mainly on two small, prospectively randomized clinical trials and several observational studies. In the first study, Mangano et al. (10) randomized 200 patients

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Accepted for publication May 26, 2006.

Dr. O. Schouten is supported by an unrestricted research grant from The Netherlands Organization for Health Research and Development (ZonMw), The Hague, the Netherlands and an unrestricted research grant from "Lijf & Leven" Foundation, Rotterdam, the Netherlands. Dr. M. Dunkelgrun is supported by an unrestricted research grant (#2003B143) from the Netherland Heart Foundation, The Hague, the Netherlands.

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DOI: 10.1213/01.ane.0000231636.50782.d6

with either known or suspected coronary artery disease undergoing high-risk noncardiac surgery to receive atenolol (50 mg or 100 mg) or placebo. Atenolol therapy was not associated with an improved in-hospital outcome (cardiac death or MI); however, it was associated with a 50% reduction in electrocardiogram evidence of myocardial ischemia detected with continuous 3-lead Holter monitoring during the first 48 h after surgery. Interestingly, patients receiving perioperative atenolol had a reduced rate of cardiac events 6 to 8 mo after surgery compared with the placebo group, suggesting a delayed beneficial response. In the second trial, the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study)-I trial (11), of 112 vascular surgery patients with evidence of myocardial ischemia on preoperative dobutamine stress-echocardiography, Poldermans et al. showed a 10-fold reduction in the incidence of perioperative cardiac death and MI with perioperative bisoprolol use compared with placebo (3.4% versus 34%; $P < 0.001$). The high incidence of perioperative cardiac events was explained by the selection of high-risk patients for study. From a population of 1351 patients, only 112 met entrance criteria of inducible myocardial ischemia.

These promising results supporting perioperative β-blocker use as a means for improving cardiac outcomes are not supported by two more recent trials. In the POBBLE (PeriOperative Beta-BLockadE) trial (12), only low-risk patients (history of ischemic heart disease was an exclusion) scheduled for vascular surgery were studied. This low-risk population was randomized to receive either metoprolol 25 mg or 50 mg ($n = 55$) or placebo ($n = 48$) starting the day before surgery and continued during the first 7 days after surgery. There was no difference in the incidence of perioperative cardiovascular events between the placebo and metoprolol groups (34% versus 32%). The duration of hospitalization though was shorter for those patients receiving metoprolol versus placebo (10 days versus 12 days).

In the DIPOM (Diabetic Postoperative Mortality and Morbidity) study (20) the cardioprotective effect of 100 mg metoprolol started the evening before major noncardiac surgery was compared with placebo in 921 diabetic patients. In that study, there were no difference in 30-day morbidity and mortality (21% versus 20%; $P = 0.66$). A limitation of the DIPOM study was that it was only powered to detect a 10% difference in mortality after 1 yr of follow-up.

EXPLAINING THE CONFLICTING RESULTS OF PERIOPERATIVE BETA-BLOCKER TRIALS

There are several explanations for the divergent findings from randomized trials of perioperative β-blockers, including the use of a fixed versus individualized dose titrated to the patients heart rate.

In a study of 150 patients, Raby et al. (13) assessed the heart rate threshold for myocardial ischemia before surgery using Holter monitoring. Patients with myocardial ischemia ($n = 26$) were then randomized to receive a) IV esmolol titrated to aiming at tight heart rate 20% less than the ischemic threshold but >60 bpm or b) placebo. Of the 15 patients receiving esmolol, 9 had mean heart rates below the ischemic threshold and none experienced postoperative ischemia. Four of 11 patients receiving placebo had a mean heart rate below the ischemic threshold, and 3 of the 4 had no postoperative ischemia. Together, of the 13 patients with heart rates below the ischemic threshold, 1 (7.7%) had postoperative electrocardiogram myocardial ischemia versus 12 of 13 (92%) patients with heart rates exceeding the ischemic threshold. Feringa et al. (14) found similar results in a study of 272 patients receiving β-blocker therapy and undergoing vascular surgery. In that study it was shown that higher doses of β-blockers and lower heart rate (HR) were associated with reduced Holter monitoring-detected perioperative myocardial ischemia (HR, 2.49; 95% confidence interval [CI], 1.79-3.48) and troponin T release (HR, 1.53; 95% CI, 1.16-2.03) increased. These data suggest that monitoring of the heart rate and consequent β-blocker dose adjustment is of critical importance.

The conflicting results of perioperative β-blocker trials might be further explained by varying durations of therapy. As mentioned, although the sympathicoinhibitory effects of β-blockers occur almost instantly, the antiinflammatory effects may be observed only after prolonged treatment. As mentioned, in the Mangano et al. study (10), the major benefits of atenolol were observed in the months after surgery. In both the DIPOM and POBBLE trials, β-blocker therapy was initiated on the day before surgery. The DECREASE-I trial showed the largest effect of perioperative β-blocker therapy. The time between β-blocker therapy initiation and surgery was 37 days in this trial (11). Further, withdrawal of β-blocker therapy shortly before surgery, or in the immediate postoperative period, might contribute to adverse myocardial effects resulting from a "rebound" effect resulting in increased arterial blood pressure, HR, and plasma noradrenalin concentrations (15). Redelmeier et al. (16) have recently shown that the long-acting agent atenolol was superior to the short-acting drug, metoprolol, when given perioperatively, probably as the result of acute withdrawal effects from missed doses of short-acting β-blockers.

Finally, recent data from Lanfear et al. (17) suggest that gene polymorphisms might modulate the response to β-blockers. They found that survival for patients receiving β-blocker therapy after an acute coronary syndrome was lower for patients with the 70C and 46A ADRB2 genotypes. In the future, perhaps, identifying patients most likely to benefit from perioperative β-blocker therapy might be possible by genotyping patients before surgery.

SHOULD ALL PATIENTS AT INCREASED CARDIAC RISK RECEIVE PERIOPERATIVE BETA-BLOCKER THERAPY?

The central question asked in these editorials is whether, based on existing evidence, all high-risk patients should receive a β-blocker perioperatively. A simple answer would be "yes." Perhaps a more critical question involves identifying which patients are at increased risk for perioperative cardiac complications. In a recent cohort study of 663,635 patients, Lindenauer et al. (18) reported that, in patients at intermediate or high risk (i.e., ≥2 risk factors according to the Revised Cardiac Risk Index (2), undergoing major noncardiac surgery, β-blocker use was associated with a reduced incidence of in-hospital mortality. On the other hand, patients at low risk for cardiac complications were found to have no benefit from perioperative β-blocker therapy and in fact experienced a higher incidence of in-hospital mortality. This finding indicates that perioperative β-blocker therapy is effective for selected patients, based on their risk for cardiac complications.

CONCLUSION

In high-risk patients, the existing data suggest that perioperative β-blocker use is effective for reducing the frequency of adverse cardiac events when administered in a dose titrated to a heart rate below the ischemic threshold typically between 60 and 65 bpm. Beta-blocker therapy should be started before surgery to achieve the optimal protective effect and most likely it should be continued after surgery, and possibly the treatment should be life-long. For patients at intermediate risk and for diabetics, the benefits of β-blockers are less clear. The results of randomized trials in patients at intermediate risk conducted so far (i.e., DIPOM and POBBLE) cannot be considered conclusive because poor heart rate control and the short interval between initiation and surgery may have seriously influenced the outcome of these two studies. The results of two large ongoing trials might help better define β-blocker use in these populations. In the POISE (PeriOperative ISchemic Evaluation) trial, a fixed dose of β-blockers is compared with placebo in patients at low or intermediate risk for cardiac complications. The DECREASE IV trial will evaluate the effect of β-blockers (aiming at a heart rate between 60 and 65 bpm), statins, or a combination of both in patients at intermediate cardiac risk undergoing major noncardiac surgery (19). These trials may help to determine the effectiveness of perioperative β-blocker use in patients at intermediate risk.

REFERENCES

1. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. Am J Med 2005;118:1134–41.
2. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043–9.
3. Poldermans D, Boersma E, Bax JJ, et al. Correlation of location of acute myocardial infarct after noncardiac vascular surgery with preoperative dobutamine echocardiographic findings. Am J Cardiol 2001;88:1413–4, A6.
4. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990;72:153–84.
5. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999;8:133–9.
6. Dawood MM, Gutpa DK, Southern J, et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57:37–44.
7. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischaemic conditions. Potential for pharmacological interventions. Cardiovasc Res 1997;33:243–57.
8. Cruickshank JM. Beta-blockers continue to surprise us. Eur Heart J 2000;21:354–64.
9. Yeager MP, Fillinger MP, Hettleman BD, Hartman GS. Perioperative beta-blockade and late cardiac outcomes: a complementary hypothesis. J Cardiothorac Vasc Anesth 2005;19:237–41.
10. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996;335:1713–20.
11. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999;341:1789–94.
12. Brady AR, Gibbs JS, Greenhalgh RM, et al. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg 2005;41:602–9.
13. Raby KE, Brull SJ, Timimi F, et al. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. Anesth Analg 1999;88:477–82.
14. Feringa HHH, Bax JJ, Boersma E, et al. High dose b-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation 2006;114(1 Suppl): I344-9.
15. Maling TJ, Dollery CT. Changes in blood pressure, heart rate, and plasma noradrenaline concentration after sudden withdrawal of propranolol. BMJ 1979;2:366–7.
16. Redelmeier D, Scales D, Kopp A. Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. BMJ 2005;331:932–939.
17. Lanfear DE, Jones PG, Marsh S, et al. Beta2-adrenergic receptor genotype and survival among patients receiving beta-blocker therapy after an acute coronary syndrome. J Am Med Assoc 2005;294:1526–33.
18. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005;353:349–61.
19. Schouten O, Poldermans D, Visser L, et al. Fluvastatin and bisoprolol for the reduction of perioperative cardiac mortality and morbidity in high-risk patients undergoing non-cardiac surgery: rationale and design of the DECREASE-IV study. Am Heart J 2004;148:1047–52.
20. Juul AB, Wetterslev J, Kofoed-Enevoldsen A, et al. Randomized, blinded trial on perioperative metoprolol versus placebo for diabetic patients undergoing non-cardiac surgery [abstract]. Circulation 2005;111:1725.