Quo Vadis, Perioperative Beta Blockade? Are You "POISE'd" on the Brink?

Martin J. London, MD

Over a decade has past since the seminal report of Mangano et al. on the efficacy of a hemodynamically targeted protocol of perioperative β-blockade with oral or IV atenolol on "intermediate term" postoperative outcome (6–24 mo) in a mixed cohort of vascular and nonvascular surgical patients (Atenolol study).[1] Shortly thereafter, Poldermans et al. reported a striking reduction in perioperative cardiac mortality in a small cohort of vascular patients with positive preoperative dobutamine stress echocardiographic findings (DECREASE study).[2] It had previously been appreciated from several smaller, less sophisticated, and considerably less well publicized studies of either unselected vascular surgery patients or poorly treated hypertensive patients undergoing surgery that administration of β-blockers at periods of "high stress" (particularly during tracheal intubation, on emergence from anesthesia, and in the early postoperative period) reduced hypertension, tachycardia, arrhythmias, and the incidence of ST segment depression.[3–6]

The Atenolol and DECREASE studies were embraced by clinicians, researchers, and administrators as breakthrough studies in the newly delineated specialty of perioperative medicine. Given their sophisticated design and longitudinal breadth, perioperative β-blockade of at-risk individuals was recommended as a strong candidate for best clinical practice guidelines, performance measures, and institutional benchmarking.[7] The coincident publication of the Institute of Medicine's controversial report on medical errors added to the enthusiastic adoption of this apparently low-risk, high-benefit perioperative intervention.[8] This also coincided with aggressive efforts by national subspecialty societies to increase use of β-blockers for secondary prevention after myocardial infarction (MI) and as first-line therapy for congestive heart failure (CHF).[9,10] These resulted in widespread enthusiasm for perioperative β-blockade and rapid institution of β-blocker protocols at many university and private institutions.

Not all clinicians were convinced of the safety and efficacy of aggressive perioperative β-blockade. Thus, a variety of small clinical studies were subsequently performed, some of which supported the beneficial effects of β-blockade on "surrogate" outcome measures.[11–13] Other investigators openly challenged the key findings of the Atenolol and DECREASE trials.[14,15] The criticisms most often put forth have been well summarized elsewhere, but the Atenolol study was criticized for its small sample size, a controversial statistical analysis that resulted in excluding in-hospital deaths from the long-term survival analysis, and the surprising lack of perioperative benefit. The DECREASE study has similarly been criticized for a small sample size, lack of a true placebo control, early termination of the trial, and a magnitude of efficacy nearly unprecedented in contemporary clinical trials.[16]

Given these objections, particularly the small cumulative number of patients studied, several groups proposed conducting larger multicenter studies.[17] However, the prevailing wisdom, particularly in the United States, was that perioperative β-blockade was potentially life-saving, and

From the University of California, San Francisco, California.

Accepted for publication December 21, 2007.

Address correspondence to Martin J. London, MD, Anesthesia (129), Veterans Affairs Medical Center, 4150 Clement St., San Francisco, CA 94121. Address e-mail to londonm@anesthesia.ucsf.edu.

DOI: 10.1213/ane.0b013e3181684af6

thus withholding it from at-risk individuals was unethical. Given this assumption, designing or conducting a larger double-blind, randomized, placebo controlled trial was nearly impossible to consider. However, without such a trial, millions of patients worldwide might be treated with perioperative β-blockers, based nearly exclusively on two cohorts: male veterans at a single medical center (the Atenolol trial) or vascular patients with easily inducible ischemia on dobutamine stress echocardiography (the DECREASE trial). Although one could argue that evaluating the safety of perioperative β-blockade in larger cohorts than the Atenolol study was necessary (an issue contentiously debated in the early 1970s in patients undergoing coronary artery bypass grafting, which was clearly settled in favor of continuation in patients with adequate ventricular function),[18] the aforementioned trends promoting aggressive use of β-blockers in patients with coronary artery disease (CAD) or CHF would have essentially required recruitment of patients with hypertension or other risk factors only (e.g., long-term Framingham predictors). This would make it cumbersome to recruit adequate numbers of patients. Perhaps most importantly, it was perceived that the commonly observed Hawthorne effect (e.g., "collateral" improvements inpatient care in the vicinity of an active study protocol) would contaminate any large scale study, as would the common practice of administering small doses of β-blockers in the operating room, postanesthesia recovery unit or intensive care unit to control overt hypertension or tachycardia (e.g., causing a "treatment crossover").

This author's attempts to mount a study in the Department of Veterans Affairs (DVA) supported with a planning grant by its Cooperative Studies Program in 2002 in the shadow of the Atenolol and DECREASE studies was stymied by these issues and the deeper philosophical question: "Just what is perioperative β-blockade?"[19] Is it simply suppression of the resting heart rate to the 50–60 bpm range (as most clinical cardiologists promote for CAD patients)? Is it suppression of heart response to stress or exercise independent of the resting heart rate (as most studies of efficacy in stable angina suggest)? Is it reduction of cardiac output at rest or in response to stress (as studies of its efficacy in chronic hypertension seem to suggest)? Is it protection of the myocyte from the toxic effects of elevated intra and extracellular catecholamines (as studies of its efficacy in CHF suggest)? Or are there other "pleiotropic" effects based on assorted laboratory studies suggesting antiinflammatory effects of β-blockers (a term usually reserved for statins but indirectly evoked by some authors to explain the unexplained improvement in intermediate-term outcome in the Atenolol study)?[20] The multidimensional matrix of β-blocker effects and outcomes, the complexities of dosing and safely titrating β-blockers pre-, intra-, and postoperatively in a large cohort of patients undergoing many different surgical procedures, and a required sample size estimated at well over 5000 patients, brought the DVA proposal to its knees. Thus, a hybrid trial of aggressive perioperative β-blockade with strict titration based on heart rate and arterial blood pressure measured at multiple time periods versus a standard care control group with a sample size of 10,000 patients was presented to the evaluation committee, nearly all of whom were experts in well controlled large simple trials of therapy versus placebo.[21] The evaluation committee ultimately felt the proposal was too complex for funding (or even further investigation).

However, in the preceding year, an effort had already been mounted by the Canadian-based POISE group to conduct a "proper" large, simple, placebo controlled trial. They were able to obtain funding from the Canadian Institute of Health Research and from the drug manufacturer Astra Zeneca (makers of extended release metoprolol). They also obtained permission from the responsible IRBs to include the high-risk CAD and CHF groups that were perceived to be not randomizable in the United States.[22] These investigators designed the study with key logistical issues in mind, quite differently from the DVA proposal that incorporated the recommendations of the newly released at the time 2002 American Heart Association Perioperative Evaluation guidelines advising preoperative titration of β-blockers to a low heart rate as was done in the DECREASE study. Such an approach was felt logistically feasible, given the DVA's well developed clinic system and robust systemwide computerized electronic medical record. The POISE investigators more closely followed the Atenolol study approach of acutely instituting aggressive perioperative β-blockade using a single oral dose of extended release metoprolol at what clearly appears to be a generous dose (100 mg) to avoid the logistical impediments of preoperative titration followed by 30 days of oral (200 mg) or IV therapy (15 mg metoprolol every 6 h). The POISE group also realized that pursuing their protocol in the United States would not be possible given the prevailing sentiment regarding randomization to placebo (and very limited funding)* but was ultimately quite successful in involving numerous countries outside Canada. After enrolling and analyzing data from 8351 patients, they presented their preliminary findings at the American Heart Association Annual meeting in November 2007.

The presented results of the POISE study (30 day outcomes), although not formally published at the time of this writing, are dramatic.† At first reading, they appear to pose a nearly impossible conundrum for clinicians (and patients). Statistically significant

*Personal communication, POISE Steering Committee and DVA CSP #534 Executive Committee Joint Conference Call, 2002.

†http://www.cardiosource.com/clinicaltrials/trial.asp?trialID=1629, http://scientificsessions.americanheart.org/portal/scientificsessions/ss/lbctnr13.2007, http://www.theheart.org/article/826435.do, last accessed December 15, 2007.

reductions in the important primary outcomes of cardiac death, nonfatal MI, and cardiac arrest (5.8% vs 6.9%; hazard ratio [HR]: 0.83; 95% CI: 0.70–0.99; $P = 0.04$) were essentially counterbalanced by an increase in death (3.1% vs 2.3%; HR: 1.33; $P = 0.03$) and stroke (1.0% vs 0.5%; HR: 2.17; $P = 0.005$). Other beneficial effects included a reduction in atrial fibrillation and the need for myocardial revascularization. A particularly troubling adverse effect was a doubling of the percentage of patients dying from sepsis. Bradycardia and significant hypotension were also more common although, of some assurance, there was no increase in the incidence of acute heart failure.

Early reaction to the POISE study results among perioperative clinicians appears similar to the "shock waves" caused by the initial report of the large scale COMMIT study (45,852 patients) (with formal publication more than a year later), which reevaluated, in one of its treatment arms, the well established, yet poorly validated, practice of aggressive early institution of β-blockade during acute MI (in contrast to the better validated efficacy of "delayed" secondary prevention).[23] This landmark study, coincidentally performed exclusively outside of the United States in China, reported that the benefits of reduced reinfarction with acute β-blockade were nearly counterbalanced by an increased incidence of early cardiogenic shock. The COMMIT study revealed that patients at greatest risk for this serious adverse outcome were already hemodynamically unstable, thus leaving the clinician latitude to treat stable lower risk patients more aggressively should they prefer to. It is important to note that the major result of the COMMIT study does not proscribe β-blocker use "peri acute MI," but does suggest that it should only be instituted orally in lower risk patients after the first 24 h (or later if at all in less stable patients). It is of particular importance to the issue of perioperative β-blockade that adverse safety implications of the COMMIT study regarding aggressive β-blockade are now prominently displayed as Class III Level of Evidence A recommendations in the recently released American College of Cardiology/American Heart Association Guidelines for Management of Patients with ST and Non-ST elevation Myocardial Infarction Practice Guidelines.[24,25]

The preliminary results of the POISE study suggest that delineation of patients at increased risk for adverse outcomes was not detected. This finding is very troublesome for the future of widespread treatment protocols and would likely preclude widespread perioperative β-blockade protocols from a Class 1 type recommendation in subsequent Practice Guidelines. Analysis the results of the POISE study results will clearly have to await publication of the final manuscript. Many issues will be debated: What were the heart rates and blood pressures at key time periods and what dose adjustments occurred? How were MIs detected? Are there center and country level effects with regards to the adverse outcomes that clearly have an established and rapidly growing scientific basis (but was not specifically addressed in the POISE protocol)? Were there genetic or racial effects?[26–29]

Until the full details are known, the discussions will center around the "surrogate outcomes" of arterial blood pressure and heart rate. The hypothesis that low blood pressure or cardiac output might worsen gut translocation and increase risk of sepsis may have been borne out by POISE. The increase in stroke may be related to critical cerebral hypoperfusion from low blood pressure. Critics of POISE will state that the patients were clearly overdosed, whereas its supporters will point out that cardiologists and others have been quite insistent that adequate β-blockade requires aggressive heart rate control as long as the systolic blood pressure is more than 100 mm Hg. It is equally likely that POISE would have been roundly criticized had the heart rates not been aggressively controlled and had found no positive treatment effect. The latest observational and secondary analysis of pilot randomized controlled trial (RCT) data from Dr. Polderman's group continues to strongly support aggressive heart rate control and notably, consideration of arterial blood pressure in these studies is limited solely to its use as a safety end-point only (dosing withheld for a systolic blood pressure <100 mm Hg).[30,31] The critics will propose cutting the existing doses in their protocols by half, or perhaps more, whereas POISE supporters will argue that safe titration is likely not possible, and thus widespread use of a drug that now appears to have a more narrow therapeutic index than previously appreciated should never be considered a standard therapy (nor used as a performance measure for quality of care). The arguments raised here may be similar to the aprotinin controversy, in which a supposedly well established drug, which appeared to have a very beneficial effect on a very important surrogate outcome (blood transfusion) may be less safe than thought, based on outcome results of a much larger clinical trial than previously conducted.[32,33]

Vexing clinical questions remain. POISE apparently enrolled patients who were naïve to β-blockers at the time of study enrollment, many of whom had known CAD. Are the results generalizable to those already receiving such therapy, which in the United States may approach or exceed half of all adult patients in some settings? Critics will point out that withdrawal of β-blockade is exceedingly hazardous, a finding widely, but not universally, supported[34] in the literature.[35–38] Perhaps the biggest issue is how should we manage heart rate and arterial blood pressure? It is in this context that the meta-analysis of Beattie et al. presented in this issue of the journal is of considerable interest.[39]

This meta-analysis examined 10 contemporary (but pre-POISE) RCTs (1997–2006) involving 2176 patients in which some heart rate data were presented, a decidedly controversial aspect of this analysis given lack of continuous longitudinal data in many of these reports.

Although, in aggregate, perioperative β-blockade was not associated with a reduction in perioperative MI (odds ratio, 0.76; 95% CI: 0.4–1.4), a significant reduction (odds ratio, 0.23; 95% CI: 0.08–0.65) was noted when perioperative β-blockade resulted in "aggressive" heart rate control, based on a somewhat arbitrarily defined threshold of 100 bpm derived from the data presented in the RCTs alone (which coincidentally corresponds to the commonly used clinical threshold promoted by older observational clinical studies of perioperative ischemia). However, hypotension and bradycardia were significantly more common with such control (as noted by POISE) with a weak suggestion of an increase in the incidence of CHF (not noted by POISE). The incidence of stroke in these RCTs was too small to be investigated, in contrast to the much larger POISE trial. Subanalysis of derived variables related to heart rate (e.g., mean, maximum, and variation in heart rate) all supported the statistical association of strong heart rate control with reduction in perioperative MI.

But perhaps apropos of what appears to be a continuously uncertain atmosphere surrounding perioperative β-blockade, a very recently published meta-analysis by Biccard et al. of the same RCTs (sans one study) reported no such relation.[40] When comparing the methodology of these meta-analyses, it appears that the upper hand with regards to statistical sophistication goes to that of Beattie et al. However, both groups note that the amount of hemodynamic data presented in the RCTs are quite limited. Given an increasing trend to substitute meta-analysis for large-scale clinical research, there is a definite suggestion in the recent literature that the limitations of meta-analysis should be carefully considered before they are used to guide clinical care.[41–43] Nonetheless, it is also clear that well done meta-analyses have shaped medical practice, and one need only look as far as the widespread promotion of β-blockers for secondary prevention post-MI in medical patients to observe this in action.[44]

So *quo vadis* perioperative β-blockade? After a decade have we established what perioperative β-blockade is? Is it simply prevention or attenuation of tachycardia? In this regard, the conflicting meta-analyses of Beattie et al. and Biccard et al. are disappointing.[39,40] Hopefully, the full results of POISE will shed light on this topic, although the constrained data collection (particularly of "surrogate outcomes" which includes hemodynamics) mandated by a "large simple trial" make this unlikely. Will we be able to delineate groups of patients in which efficacy and safety can be assured? Will the trends towards increased use of β-blockers in CAD be counterbalanced or even decrease in response to recent evidence and guideline recommendations against the use of β-blockers as first-line drugs for hypertension (in the absence of a strong suspicion for or documentation of underlying CAD) given evidence that they are inferior to diuretics and angiotensin receptor blockers with regards to stroke and adverse renal outcome reduction?[45,46] What of the increasing number of large observational studies suggesting strong efficacy of statins independent of β-blockers?[47] Do alpha2 agonists have superior efficacy or safety?[48] Will the eagerly awaited DECREASE-IV β-blocker-statin RCT reach supporting or confliction conclusions to POISE?[49] Conflicting meta-analyses aside, clinicians should jointly consider and manage both heart rate and arterial blood pressure (as well as cardiac output which is rarely measured directly), attempting to balance increased left ventricular diastolic perfusion time from a low heart rate while maintaining adequate coronary (and other organ) perfusion pressure. Perhaps, it is as simple as that . . . . but as the POISE study clearly points out, the devil is in the details.

REFERENCES

1. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. New Engl J Med 1996;335:1713–20
2. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H, Fioretti PM, Paelinck B. 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
3. Pasternack PF, Imparato AM, Baumann FG, Laub G, Riles TS, Lamparello PJ, Grossi EA, Berguson P, Becker G, Bear G. The hemodynamics of beta-blockade in patients undergoing abdominal aortic aneurysm repair. Circulation 1987;76:III1–7
4. Stone JG, Foëx P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Risk of myocardial ischaemia during anaesthesia in treated and untreated hypertensive patients. Br J Anaesth 1988;61:675–9
5. Stone JG, Foëx P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. Anesthesiology 1988;68:495–500
6. Pasternack PF, Grossi EA, Baumann FG, Riles TS, Lamparello PJ, Giangola G, Primis LK, Mintzer R, Imparato AM. Beta blockade to decrease silent myocardial ischemia during peripheral vascular surgery. Am J Surg 1989;158:113–6
7. Auerbach AD, Goldman L. beta-Blockers and reduction of cardiac events in noncardiac surgery: scientific review. JAMA 2002;287:1435–44
8. Leape LL, Berwick DM, Bates DW. What practices will most improve safety? Evidence-based medicine meets patient safety. JAMA 2002;288:501–7
9. Mehta RH, Montoye CK, Gallogly M, Baker P, Blount A, Faul J, Roychoudhury C, Borzak S, Fox S, Franklin M, Freundl M, Kline-Rogers E, LaLonde T, Orza M, Parrish R, Satwicz M, Smith MJ, Sobotka P, Winston S, Riba AA, Eagle KA. Improving quality of care for acute myocardial infarction: The Guidelines Applied in Practice (GAP) Initiative. JAMA 2002;287:1269–76
10. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldmanmd AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC, Jr.: ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. Circulation 2001;104:2996–3007

11. Raby KE, Brull SJ, Timimi F, Akhtar S, Rosenbaum S, Naimi C, Whittemore AD. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. Anesth Analg 1999;88:477–82
12. Zaugg M, Tagliente T, Lucchinetti E, Jacobs E, Krol M, Bodian C, Reich DL, Silverstein JH. Beneficial effects from beta-adrenergic blockade in elderly patients undergoing noncardiac surgery. Anesthesiology 1999;91:1674–86
13. Urban MK, Markowitz SM, Gordon MA, Urquhart BL, Kligfield P. Postoperative prophylactic administration of beta-adrenergic blockers in patients at risk for myocardial ischemia. Anesth Analg 2000;90:1257–61
14. Devereaux PJ, Yusuf S, Yang H, Choi PT, Guyatt GH. Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? CMAJ 2004;171:245–7
15. London MJ, Zaugg M, Schaub MC, Spahn DR. Perioperative beta-adrenergic receptor blockade: physiologic foundations and clinical controversies. Anesthesiology 2004;100:170–5
16. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. CMAJ 2005;173:779–88
17. London MJ, Itani KM, Perrino AC Jr, Guarino PD, Schwartz GG, Cunningham F, Gottlieb SS, Henderson WG. Perioperative beta-blockade: a survey of physician attitudes in the Department of Veterans Affairs. J Cardiothorac Vasc Anesth 2004;18:14–24
18. Ferguson TB Jr, Coombs LP, Peterson ED. Preoperative beta-blocker use and mortality and morbidity following CABG surgery in North America. JAMA 2002;287:2221–7
19. 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
20. 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
21. 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
22. Devereaux PJ, Yang H, Guyatt GH, Leslie K, Villar JC, Monteri VM, Choi P, Giles JW, Yusuf S. 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
23. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1622–32
24. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction-Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 2007;50:652–726
25. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith SC Jr. 2007 Focused update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2008;117:296–329
26. Lanfear DE, Jones PG, Marsh S, Cresci S, McLeod HL, Spertus JA. {beta}2-Adrenergic receptor genotype and survival among patients receiving {beta}-blocker therapy after an acute coronary syndrome. JAMA 2005;294:1526–33
27. Rochais F, Vilardaga JP, Nikolaev VO, Bunemann M, Lohse MJ, Englelhardt S. Real-time optical recording of beta1-adrenergic receptor activation reveals supersensitivity of the Arg389 variant to carvedilol. J Clin Invest 2007;117:229–35
28. Akhter SA, D'Souza KM, Petrashevskaya NN, Mialet-Perez J, Liggett SB. Myocardial beta1-adrenergic receptor polymorphisms affect functional recovery after ischemic injury. Am J Physiol Heart Circ Physiol 2006;290:H1427–32
29. Zaugg M, Bestmann L, Wacker J, Lucchinetti E, Boltres A, Schulz C, Hersberger M, Kalin G, Furrer L, Hofer C, Blumenthal S, Muller A, Zollinger A, Spahn DR, Borgeat A. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. Anesthesiology 2007;107:33–44
30. Feringa HH, Bax JJ, Boersma E, Kertai MD, Meij SH, Galal W, Schouten O, Thomson IR, Klootwijk P, van Sambeek MR, Klein J, Poldermans D. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation 2006;114:I344–9
31. Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, Feringa HH, Dunkelgrun M, de Jaegere P, Maat A, van Sambeek MR, Kertai MD, Boersma E. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. J Am Coll Cardiol 2007;49:1763–9
32. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006;354:353–65
33. Karkouti K, Beattie WS, Dattilo KM, McCluskey SA, Ghannam M, Hamdy A, Wijeysundera DN, Fedorko L, Yau TM. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion 2006;46:327–38
34. Croft CH, Rude RE, Gustafson N, Stone PH, Poole WK, Roberts R, Strauss HW, Raabe DS, Thomas LJ, Jaffe AS, Muller J, Hoagland P, Sobel BE, Passamani ER, Braunwald E, Willerson JT. Abrupt withdrawal of beta-blockade therapy in patients with myocardial infarction: effects on infarct size, left ventricular function, and hospital course. Circulation 1986;73:1281–90
35. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 1990; 263:1653–7
36. Morimoto S, Shimizu K, Yamada K, Hiramitsu S, Hishida H. Can beta-blocker therapy be withdrawn from patients with dilated cardiomyopathy? Am Heart J 1999;138:456–9
37. Shammash JB, Trost JC, Gold JM, Berlin JA, Golden MA, Kimmel SE. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. Am Heart J 2001;141:148–53
38. Hoeks SE, Scholte Op Reimer WJ, van Urk H, Jorning PJ, Boersma E, Simoons ML, Bax JJ, Poldermans D. Increase of 1-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients. Eur J Vasc Endovasc Surg 2007;33:13–9
39. Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G: Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomized trials. Anesth Analg 2008;106:1039–48
40. Biccard BM, Sear JW, Foex P. Meta-analysis of the effect of heart rate achieved by perioperative beta-adrenergic blockade on cardiovascular outcomes. Br J Anaesth 2008;100:23–8
41. Cleophas TJ, Zwinderman AH. Meta-analysis. Circulation 2007;115:2870–5
42. Gotzsche PC, Hrobjartsson A, Maric K, Tendal B. Data extraction errors in meta-analyses that use standardized mean differences. JAMA 2007;298:430–7
43. Pildal J, Hrobjartsson A, Jorgensen K, Hilden J, Altman D, Gotzsche P. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol 2007;36:847–57
44. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ (Clin Res Ed) 1999;318:1730–7

45. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: a critical review of the evidence. J Am Coll Cardiol 2007;50:563–72
46. Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL Jr, Kaplan NM, O'Connor CM, O'Gara PT, Oparil S. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the Am Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007;115:2761–88
47. Kapoor AS, Kanji H, Buckingham J, Devereaux PJ, McAlister FA. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. BMJ 2006;333:1149
48. London MJ. Beta blockers and alpha2 agonists for cardioprotection. Best Pract Res Clin Anaesthesiol 2008; (in press)
49. Schouten O, Poldermans D, Visser L, Kertai MD, Klein J, van Urk H, Simoons ML, van de Ven LL, Vermeulen M, Bax JJ, Lameris TW, Boersma E. 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