Perioperative use of beta-blockers
Hans-Joachim Priebe

Address: Department of Anesthesia and Critical Care Medicine, University Hospital Freiburg, Hugstetter Street 55, 79106 Freiburg, Germany
Email: priebe@ana1.ukl.uni-freiburg.de

F1000 Medicine Reports 2009, 1:77 (doi:10.3410/M1-77)

Abstract
Perioperative beta-blocker therapy has been considered a mainstay of perioperative cardioprotection in patients with or at risk of coronary artery diseases. However, current recommendations for perioperative beta blockade are based mainly on the findings of trials with inadequate methodology and data analysis. The recently published results of the first adequately powered large controlled randomized trial on the efficacy and safety of perioperative beta-blocker therapy confirmed the benefit of such therapy on the perioperative incidence of non-fatal myocardial infarctions. However, such a benefit occurred at the expense of increased total mortality and increased incidence of stroke, negating any beneficial effect. A subsequently published meta-analysis confirmed, in large part, these findings. Given these recent publications, most of the current recommendations for perioperative beta-blocker therapy are no longer supported by evidence, therefore respective revision is needed.

Introduction and context
Perioperative cardiovascular morbidity and mortality contribute greatly to overall perioperative morbidity and mortality. The perioperative period is frequently associated with a mismatch of myocardial oxygen supply and demand and may induce large, unpredictable, and unphysiological alterations in coronary plaque morphology, function, and progression. With many diverse factors involved, it is highly unlikely that a single intervention will successfully improve cardiac outcome following non-cardiac surgery. Based on the increasing knowledge of the nature of atherosclerotic coronary artery disease and of the benefits of aggressive cardiovascular medication in coronary artery disease in general, the paradigm is shifting from an emphasis on preoperative cardiac testing and coronary revascularization to aggressive pharmacological perioperative therapy. Perioperative beta-adrenoceptor antagonist (hereafter referred to as beta-blocker) therapy is one example of the latter. Numerous cardiovascular and other effects of beta-blockers may possibly contribute to perioperative cardioprotection [1].

Two randomized controlled trials seemed to support the effectiveness of perioperative beta blockade in improving cardiac outcome in patients with or at risk for coronary artery disease [2,3]. It had been suggested, mostly on the basis of these two studies, that beta-blockers should be administered to almost all patients with one or more cardiac risk factors [4]. However, both studies included just a little over 300 patients and had major flaws in study design and data analysis, which render the findings highly questionable. A meta-analysis performed in 2005 [5] and results of three subsequently published double-blind randomized placebo-controlled trials [6-8] failed to demonstrate a cardioprotective effect of perioperative beta-blocker therapy.

Recent advances
The POISE study
The investigation into perioperative beta-blocker therapy changed considerably after publication of the results of the POISE (PeriOperative ISchemic Evaluation) study [9]. This is the first adequately powered controlled randomized trial on the efficacy and safety of perioperative beta-blocker therapy. It was carried out in 190 hospitals in 23 countries. The goal of this trial was to compare the effectiveness of perioperative beta-blocker therapy with metoprolol with that of placebo on major
cardiovascular events during the first 30 postoperative days following non-cardiac surgery in patients with or at risk for atherosclerotic disease. Four thousand one hundred seventy-four patients were randomly assigned to the metoprolol group, and 4,177 to the placebo group. Underlying cardiovascular morbidity included coronary artery disease (43%), peripheral vascular disease (41%), and prior stroke (15%). Patients received metoprolol 100 mg controlled release (CR) or placebo 2-4 hours before surgery, and metoprolol 200 mg CR or placebo daily for 30 days postoperatively. The primary endpoints were combined cardiovascular death, non-fatal myocardial infarction, and cardiac arrest. Secondary endpoints were total mortality, cardiovascular mortality, need for coronary revascularization, atrial fibrillation, and clinically significant hypotension and bradycardia requiring therapy.

During the first 30 postoperative days, the primary endpoint was significantly less in the beta-blocker group compared with the placebo group (incidence 5.8% versus 6.9%, hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.70-0.99; \( P = 0.04 \)). This was due primarily to a marked reduction in the incidence of non-fatal myocardial infarctions in the beta-blocker group (incidence 3.6% versus 5.1%, HR 0.70, 95% CI 0.57-0.86; \( P = 0.0008 \)). The need for revascularization (0.3% versus 0.6%; \( P = 0.01 \)) and the incidence of atrial fibrillation (2.2% versus 2.9%; \( P = 0.04 \)) were also significantly lower in the group of patients that had received beta-blockers. However, in the beta-blocker group, total mortality (3.1% versus 2.3%, HR 1.33, 95% CI 1.03-1.74; \( P = 0.03 \)) and the incidences of stroke (1.0% versus 0.5%, HR 2.17, 95% CI 1.26-3.74; \( P = 0.005 \)), significant hypotension (15.0% versus 9.7%; \( P < 0.0001 \)), and significant bradycardia (6.6% versus 2.4%; \( P < 0.0001 \)) were higher, negating the beneficial effect of perioperative beta-blocker therapy on the primary endpoint. Incidences of intra- and postoperative clinically relevant hypotension were independent predictors of death and stroke. The higher incidence of hypotension in the metoprolol group might possibly explain the more frequent strokes.

As was to be expected, a multicenter study of this size will be prone to criticism on various grounds. Most criticism relates to (a) the dosage of metoprolol (considered by some to be too high), (b) the formulation (CR), (c) acute preoperative start of beta-blocker therapy without individual titration to effect, and (d) fixed dosages in the perioperative period during which cardiovascular physiology, pharmacokinetics, and pharmacodynamics may change within short periods of time. However, the dosage of metoprolol was compatible with recent recommendations [10]. The two studies on which the recommendations for perioperative beta-blocker therapy had largely been based had also used long-acting beta-blockers [2,3]. In addition, a large perioperative cohort study indicated that long-acting beta-blockers are more cardioprotective than short-acting ones [11]. Finally, dosage was adjusted (that is, medication was withheld if heart rate decreased to less than 45 beats per minute and systolic blood pressure to less than 100 mm Hg). Although the dosage in the POISE study was, indeed, eight times the equivalent of the dosage of bisoprolol used in the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) study [3], only 15% of patients treated with metoprolol in the POISE study developed hypotension. This is a lower incidence than reported in other studies [6]. A previous meta-analysis had shown that perioperative beta-blocker therapy is generally accompanied by an increased incidence of therapy-requiring hypotension (relative risk 1.27, 95% CI 1.04-1.56) [5]. The respective findings of the POISE study are comparable (relative risk 1.55, 95% CI 1.38-1.77). Finally, beta-blocker therapy had been started immediately prior to induction of anesthesia in one of the landmark studies [2]. Overall, the results of the POISE study can hardly be dismissed on the grounds of major flaws in study design [12, 13].

**Meta-analysis by Bangalore et al.**

A recently published meta-analysis (based on 33 randomized controlled trials that included a total of 12,036 patients) confirmed, in large part, the findings of the POISE study [14]. Perioperative beta-blocker therapy was associated with a 35% decreased risk for perioperative non-fatal myocardial infarction (odds ratio [OR] 0.65, 95% CI 0.54-0.79) (number needed to treat [NNT] = 63) at the expense of a doubling of the risk for non-fatal disabling strokes (OR 2.01, 95% CI 1.27-3.68) (number needed to harm [NNH] = 293) and for therapy-requiring hypotension (NNH = 17) and a tripling of the risk for therapy-requiring bradycardia (NNH = 22). Perioperative beta-blocker therapy was not associated with any significant risk reduction for all-cause mortality, cardiovascular mortality, or heart failure. This meta-analysis suggests that the perioperative treatment of 1,000 patients with beta-blockers can be expected to be associated with 16 fewer non-fatal myocardial infarctions in survivors at the expense of three non-fatal strokes, 45 patients with clinically relevant perioperative bradycardia, and 59 patients with clinically relevant perioperative hypotension and potentially increased mortality. This meta-analysis is methodologically sound and probably the most complete of all meta-analyses ever carried out in the area of perioperative beta-blocker therapy.
Relevance of heart rate control

The importance of strict heart rate control as a prerequisite for effectiveness of perioperative beta-blocker therapy has been emphasized repeatedly. A non-randomized non-blinded observational cohort study in 272 vascular surgery patients with documented coronary artery disease investigated the effect of different dosages of various beta-blockers and of tight perioperative heart rate control on the incidence of perioperative myocardial ischemia and myocardial cell injury [15]. High-dose perioperative beta-blocker therapy and tight perioperative heart rate control were associated with a reduced incidence of myocardial ischemic episodes, reduced release of cardiac troponin T, and improved long-term outcome.

Although the findings seem to underline the importance of heart rate control, the study has numerous limitations. Most importantly, it was not randomized. Numerous adjustments by multivariate analysis were made for age, gender, several cardiac risk factors, dobutamine stress echocardiography test results, and statin and angiotensin-converting enzyme inhibitor medication. No exact information was provided for individual groups on type and duration of surgery, type of anesethia, type of primary endpoint, and follow-up time.

A recently published meta-analysis of 10 trials showed that strict control of heart rate (maximum perioperative heart rate of 99 beats per minute) was associated with a decreased risk of perioperative myocardial infarction, but at the expense of an increased risk for heart failure and bradycardia [16]. However, this meta-analysis looked only at the risk of myocardial infarction, and four of the 10 analyzed trials were not blinded. Another meta-analysis could not confirm strict heart rate control to be an independent predictor of outcome during perioperative beta-blocker therapy [17]. Furthermore, a subgroup sensitivity analysis within the meta-analysis of Bangalore et al. [14] did not detect a significant interaction between mean maximum heart rate and efficacy of beta-blocker therapy.

A very recent randomized controlled trial investigated the effectiveness and safety of perioperative beta-blocker and statin therapy on 30-day postoperative cardiac outcome in intermediate-risk patients undergoing noncardiovascular surgery [18]. Bisoprolol was titrated to a perioperative heart rate of between 50 and 70 beats per minute. Patients receiving bisoprolol had a lower incidence of perioperative cardiac death and non-fatal myocardial infarction than control patients (2.1% versus 6.0%, HR 0.34, 95% CI 0.17-0.67; \( P = 0.002 \)). Although these findings suggest that tight perioperative heart rate control is an essential part of perioperative beta-blocker therapy, they remain inconclusive because the study was statistically underpowered. A priori power analysis indicated that 1,500 patients would be required. However, ultimately only 533 patients were included in the bisoprolol group.

In a retrospective cohort study that looked at 30-day postoperative cardiac outcome in intermediate- and low-risk patients receiving beta-blockers perioperatively, mean preoperative heart rate was significantly higher in patients who died within 30 days of surgery than in those who survived (86 versus 70 beats per minute; \( P = 0.03 \)) [19]. This finding points to a possible role of perioperative beta-blocker dose titration on the basis of heart rate response.

American College of Cardiology and American Heart Association guidelines

The strength of a particular recommendation for a treatment option can be judged by the class of recommendation and the level of evidence (LOE) on which the recommendation is based (Table 1). The updated guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) on perioperative cardiovascular evaluation [20,21] strongly recommend (class I recommendation) perioperative beta-blocker therapy in two situations: (a) continuation of beta-blockers in patients receiving them to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA class I guideline indications (LOE C) and (b) patients undergoing vascular surgery at

| Classes of recommendation | Levels of evidence (LOEs) |
|---------------------------|--------------------------|
| Class I                   | Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective |
| Class II                  | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure |
| Class IIa                 | Weight of evidence/opinion is in favor of usefulness/efficacy |
| Class IIb                 | Usefulness/efficacy is less well established by evidence/opinion |
| Class III                 | Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful |

LOE A: Data derived from multiple randomized clinical trials or meta-analyses
LOE B: Data derived from a single randomized clinical trial or large non-randomized studies
LOE C: Consensus of opinion of the experts and/or small studies, retrospective studies, or registries
high cardiac risk owing to the finding of myocardial ischemia on perioperative testing (LOE B). Perioperative beta-blocker therapy is probably recommended (class IIa recommendations, LOE B) for patients undergoing vascular surgery in whom preoperative assessment identifies coronary artery disease, in whom preoperative assessment for vascular surgery identifies high cardiac risk (as defined by the presence of more than one clinical risk factor), and in whom preoperative assessment identifies coronary artery disease or high cardiac risk (as defined by the presence of more than one clinical risk factor) prior to intermediate-risk or vascular surgery.

The just-published European Society of Cardiology guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery [22] list the following recommendations for perioperative beta-blocker therapy:

*Class I recommendations:* patients (a) having known coronary artery disease or myocardial ischemia according to preoperative stress testing (LOE B), (b) scheduled for high-risk surgery (LOE B), and (c) having previously been treated with beta-blockers because of coronary artery disease, arrhythmias, or hypertension (LOE C).

*Class IIa recommendations:* patients (a) scheduled for intermediate-risk surgery (LOE B) and (b) previously having been treated with beta-blockers because of chronic heart failure with systolic dysfunction (LOE C).

*Class IIb recommendation:* patients scheduled for low-risk surgery with risk factor(s) (LOE B).

*Class III recommendations:* (a) high-dose beta-blockers without titration (LOE A) and (b) patients scheduled for low-risk surgery without risk factor(s) (LOE B).

It is further stated that ‘treatment should be initiated optimally between 30 days and at least 1 week before surgery’ and targeted heart rate and systolic blood pressure should be 60-70 beats per minute and greater than 100 mm Hg, respectively. Interestingly, for this recommendation, the class of recommendation and LOE are not provided.

**Implications for clinical practice**

The POISE study [9] is the first perioperative beta-blocker study with an adequate number of patients (75 times the number of patients included in the non-blinded DECREASE study) and events. It documents, on the one hand, the beneficial effect of routine perioperative beta-blocker therapy as reflected by a decrease in the incidence of perioperative non-fatal myocardial infarctions. It equally documents that routine perioperative beta-blocker therapy may carry considerable problems by increasing the risks for death and stroke. The POISE study highlights (a) the importance and need for large randomized trials in the perioperative setting and (b) the risk of assuming that an effective treatment regimen can have substantial benefit without carrying the potential for substantial harm. Patients may be unwilling to accept the increased risks of disabling stroke associated with perioperative beta-blocker therapy but be willing to accept the increased risk of non-fatal myocardial infarction associated with the lack of perioperative beta-blocker therapy.

Surely, the results of the POISE study cannot be interpreted as a general *pro* or *con* for perioperative beta-blocker therapy. However, they clearly show that it is generally not justified to start a fixed beta-blocker protocol preoperatively, even in patients with cardiac risk factors undergoing surgery associated with increased cardiac risk. It needs to be emphasized that the findings apply only to newly started beta-blocker therapy. Chronic beta-blocker therapy for symptomatic cardiovascular disease or secondary cardiovascular prevention must not be interrupted in the perioperative period [13].

The importance of strict heart rate control in the context of perioperative beta-blocker therapy as an independent predictor of outcome remains open to debate. From a physiological and pathophysiological standpoint, it is difficult to imagine how strict heart rate control *per se* can be expected to be of predictable benefit in the perioperative setting. There are numerous reasons for the development of perioperative tachycardia apart from myocardial ischemia (for example, hypovolemia, anemia, hypothermia, inadequate pain relief, latent heart failure, and developing sepsis). Each of these requires markedly different therapeutic interventions, and in none of these conditions is administration of beta-blockers a first-choice therapy. A ‘one-therapy-fits-all approach’ (that is, uniform heart rate control by beta-blockers) will predictably harm a certain high percentage of patients. Heart rate control by beta-blockers blunts compensatory cardiovascular mechanisms that might, however, be vital in the perioperative period to satisfy the frequently increased perioperative cardiovascular demands. It is time to change the paradigm from routinely administering beta-blockers to all patients with risk factors for adverse perioperative cardiac outcome to one of administering beta-blockers only when the indication has been clearly established and the effects of therapy can be closely monitored [23].
Conclusions
Given the results of the POISE study [9] and the recent meta-analysis by Bangalore et al. [14], most of the recommendations for perioperative beta-blocker therapy are no longer supported by evidence and require revision. Only the recommendation to continue beta-blockers in patients taking them for symptomatic cardiovascular disease remains unchallenged. It remains to be seen whether there will be, after all, a subgroup of patients who may benefit from perioperative beta-blocker therapy. Controversy will continue until the issues regarding choice and dosage of beta-blocker, timing (start and duration), and monitoring of beta-blocker therapy are settled.

Abbreviations
ACC, American College of Cardiology; AHA, American Heart Association; CI, confidence interval; CR, controlled release; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; HR, hazard ratio; LOE, level of evidence; NNH, number needed to harm; NNT, number needed to treat; OR, odds ratio; POISE, PeriOperative ISchemic Evaluation.

Competing interests
The author declares that he has no competing interests.

References
1. London MJ, Zaugg M, Schaub MC, Spahn DR: Perioperative β-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: Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996, 335:1713-20 [Erratum: N Engl J Med 1997, 336:1039].
3. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yl Ho Ti, Trocino G, Vigna C, Roelandt JR, van Urk H: 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.
4. Kertai MD, Bax JJ, Klein J, Poldermans D: Is there any reason to withhold β blockers from high-risk patients with coronary artery disease during surgery? Anesthesiology 2004, 100:4-7.
5. Devereaux PJ, Beattie WS, Choi PT, Badner NH, Guyatt GH, Villar JC, Cina CS, Leslie K, Jacks MJ, Montori VM, Bhandari M, Avezzù A, Cavalcanti AB, Giles JW, Br J Anaesth 2008, 100:23-8.
6. POBBLE Trial Investigators: Perioperative β-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg 2005, 41:602-9.
7. Juul AB, Wetterslev J, Gluud C, Kofod-Enevoldsen A, Jensen G, Callesen T, Nergaard P, Frueugarda K, Bestle M, Vedelsdal R, Miran A, Jacobsen J, Roed J, Mortensen MB, Jørgensen L, Jørgensen J, Roising ML, Petersen PL, Pott F, Haas M, Albret R, Nielsen LL, Johansson G, Stjernholm P, Møggaard Y, Foss NB, Elkaer J, Dehlie B, Boysen K, Zaric D, et al.: Effect of perioperative β-blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. BMJ 2006, 332:1482.
8. Yang H, Raymer K, Butler R, Parlow J, Roberts R: The effect of perioperative β-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. Am Heart J 2006, 152:983-90.
9. 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.

Changes Clinical Practice
F1000 Factor 6.6 Must Read
Evaluated by Lee Fleisher 10 Aug 2006, Simon Howell 23 Aug 2006, Lena Napolitano 07 Sep 2006, Tukio Hayashi 06 Nov 2006
8. Yang H, Raymer K, Butler R, Parlow J, Roberts R: The effect of perioperative β-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. Am Heart J 2006, 152:983-90.
9. 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.

Changes Clinical Practice
F1000 Factor 7.2 Must Read
Evaluated by Johlan Coetzee 07 Aug 2006, Lee Fleisher 20 Aug 2008, Michael O’Connor 04 Sep 2008, Fred Weaver 05 Sep 2008, Greg McAunulty 11 Sep 2008, Philippa Newfield 22 Jan 2009
10. BNF55: British National Formulary March 2008. London: BMJ Publishing Group Ltd and RPS Publishing Group; 2008.
11. Redelmeier D, Scales D, Kopp A: Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. BMJ 2005, 331:932.
12. Sar JW, Giles JW, Howard-Alpe G, Fox E: Perioperative β-blockade, 2008: what does POISE tell us, and was our earlier caution justified? Br J Anaesth 2008, 101:135-8.
13. Yang H, Beattie WS: POISE results and perioperative β-blockade. Can J Anaesth 2008, 55:727-34.
14. Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH: Perioperative β blockers in patients having non-cardiac surgery: a meta-analysis. Lancet 2008, 372:1962-76.

Changes Clinical Practice
F1000 Factor 6.4 Must Read
Evaluated by Gregor Thielmeier 07 Jan 2009, Pamela Lipsitz 15 Apr 2009
15. Feringa HH, Bax JJ, Boersma E, Kertai MD, Meij SH, Galal W, Schouten O, Thomson IR, Kloohtwijk P, van Sambeek MR, Klein J, Poldermans D: High-dose β-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation 2006, 114:I-344-9.

Changes Clinical Practice
F1000 Factor 6.0 Must Read
Evaluated by Lee Fleisher 29 Sep 2006
16. 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.

F1000 Factor 6.4 Must Read
Evaluated by Michael Irwin 23 Apr 2008, Alex Sia 02 Jul 2008
17. Biccard BM, Sar JW, Fox E: Meta-analysis of the effect of heart rate achieved by perioperative beta-adrenergic blockade on cardiovascular outcomes. Br J Anaesth 2008, 100:23-8.
18. Dunkelgrun M, Boersma E, Schouten O, Koopman-van Gemert AW, van Poorten F, Bax JJ, Thomson IR, Poldermans D; Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group: Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing...
noncardiovascular surgery: a randomized controlled trial (DECREASE-IV). Ann Surg 2009, 249:921-6.

19. Kaafarani HM, Atluri PV, Thornby J, Itani KM. β-blockade in noncardiac surgery: outcome at all levels of cardiac risk. Arch Surg 2008, 143:940-4.

20. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fusster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B: ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative β-blocker therapy. J Am Coll Cardiol 2006, 47:2343-55.

21. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fusster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato JP, Page RL, Tarkin LG, et al.: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2007, 116:e418-99.

22. Poldermans D, Bax JJ, Boersma E, De Hert S, Eekhout E, Fowkes G, Gorenek B, Hennerici MG, Jung B, Kelm M, Kjeldsen KP, Kristensen SD, Lopez-Sendon J, Pelosi P, Philippe F, Pierard L, Ponikowski P, Schmid JP, Sellevold OF, Sicari R, Van den Berghe G, Vermaas F, Additional Contributors, Hoeks SE, Vanhorebeek I: ESC Committee for Practice Guidelines (CPG), Vahanian A, Auricchio A, Bax JJ, Ceconi C, et al.: Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). Eur Heart J 2009, [Epub ahead of print].

23. Oksanen T, Hynninen M: Perioperative β-blockade: time to change the paradigm? Acta Anaesthesiol Scand 2009, 53:553-5.