

EDITORIAL

 β -Blockers and cardiac protection: 5 yr on from POISE

P. Foex and J. W. Sear*

Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

* E-mail: john.sear@gtc.ox.ac.uk

For many years, β -blockers have been regarded as the best drugs to protect patients with, or at risk for, coronary heart disease, from perioperative major adverse cardiac events (MACE). This was based on observational studies, randomized controlled trials (RCTs), experts' opinions, and guidelines. The strongest support was expressed in the 1997 guidelines of the American College of Physicians,¹ after very encouraging results after administration of atenolol before non-cardiac surgery by Mangano and colleagues.² The guideline advocated the administration of atenolol to all patients with, or at risk for, coronary disease undergoing surgery. In the USA, initiation of perioperative β -blockade was regarded as having the greatest strength of evidence in its favour.³ However, a less supportive view was expressed in the American College of Cardiology/American Heart Association (ACC/AHA) guideline 2007.⁴ β -Blockers were considered to protect against myocardial ischaemia (as we had found in an RCT 20 yr earlier),⁵ they may reduce the risk of myocardial infarction and cardiac death in patients with known coronary artery disease. This followed the realization that some RCTs did not show statistically significant cardiac protection. Indeed, several studies did not show a statistically significant reduction in cardiac mortality,⁶⁻¹⁰ or non-fatal myocardial infarction.¹¹⁻¹⁵

A meta-analysis by Devereaux and colleagues¹⁶ of all RCTs of perioperative β -blockade failed to show statistically significant protection. These data were the justification for the POISE trial.

In 2008, the POISE study,¹⁷ the largest RCT in perioperative medicine ever undertaken, showed statistically and clinically significant cardiac protection but revealed an increase in all-cause mortality, disabling strokes, and hypotension. Because of the much smaller size of all previous RCTs, these risks may have been present but had never reached statistical significance. Subsequent meta-analysis confirmed both cardiac protection and significant risks associated with the initiation of β -blockade shortly before surgery.¹⁸ The result of POISE was criticized, especially the potential for high doses of metoprolol to be administered, and the choice of slow-release metoprolol.¹⁹

In 2009, new guidelines on the management of patients with heart disease undergoing non-cardiac surgery were published on both sides of the Atlantic by the ACCF/AHA²⁰ and the European Society of Cardiology (ESC) endorsed by the

European Society of Anaesthesiology (ESA),²¹ respectively. Both sets of guidelines recommended to continue long-term treatment with β -blockers, to avoid high-dose β -blockade, and to consider the introduction of β -blockers in patients with known coronary artery disease, patients with reversible ischaemia on stress test, and in those at risk for coronary artery disease undergoing high-risk surgery, especially vascular surgery.²⁰ The European guideline regarded the above recommendations as Class I (as opposed to Class IIa for the American guidelines) and was more liberal suggesting that β -blockade could be initiated in patients undergoing intermediate-risk surgery (Class IIa).²¹ Both groups of experts advocated titration of β -blockade to slow heart rates (ESC 60–70 beats min^{-1} ; ACCF/AHA 60–80 beats min^{-1}) with the limit of at least 100 mm Hg systolic arterial pressure before administration of the next dose of β -blocker (ESC), or no hypotension (ACCF/AHA). Both advocated starting β -blockade at least 7 days, preferably 30 days before surgery. However, there is only limited supporting evidence for this approach.

In respect of the recommendation to continue chronic β -blockade perioperatively, there is good evidence from observational studies²²⁻²⁴ and one RCT²⁵ to support the continuing of chronic β -blockade during anaesthesia and surgery. The case for discontinuing therapy was first put forward by Crandell²⁶ who stated that 'antihypertensive drugs interfered with haemodynamic adjustments and could cause profound cardiovascular collapse in patients subjected to the stress of anaesthesia and surgery'. This approach was extended to β -blockers.²⁷ However, more recent studies have shown that discontinuing therapy is associated with significant increases in perioperative morbidity and mortality.²²⁻²⁴ Indeed, maintaining chronic therapy has been shown by Wallace and colleagues²⁴ to be associated with a similarly improved outcome when compared with patients receiving acute perioperative β -blockade. In contrast, Ellenberger and colleagues²⁸ found that chronic therapy was superior to the introduction of β -blockers within the first 2 days of surgery.

We are now in 2013. The interpretation of existing data, coupled with new research, needs to be reconsidered. First, there is the problem of the alleged intellectual misconduct relating to the studies from Poldermans and colleagues at the Erasmus Medical Center. However, the correspondence

between Poldermans and the Editor of the *American Journal of Medicine*²⁹ in response to the commentary by Chopra and Eagle³⁰ does nothing to throw a clearer light on the overall picture.

New meta-analysis

The second new development is the publication of a new meta-analysis by Bouri and colleagues³¹ which excludes what they regard as 'insecure' studies—namely, DECREASE³² and DECREASE IV³³ trials from the Erasmus Medical Center. Based on data from nine other clinical trials (10 529 patients), the investigators report that the treatment of patients undergoing non-cardiac surgery and receiving β -blockers according to the existing recommendations of the AACC/AHA or ESC guidelines was subject to a significant 27% increase in the all-cause mortality risk. Translated into figures relevant to the UK, this would imply that the drugs could have resulted in >10 000 surgical deaths per year had guidelines been strictly followed! In addition, their use may be associated with a 73% increase in the incidence of non-fatal stroke, and 51% increased incidence of hypotension. On the benefit side, there was a 27% reduction in non-fatal myocardial infarction. If we return to the analysis of Bangalore and colleagues,¹⁸ they show similar outcomes, where any benefit of β -blockade is driven by trials with a high intrinsic risk for bias—namely, DECREASE and DECREASE IV.

When should we start β -blockers

In respect of the early start of β -blockade advocated by the current guidelines,^{20 21} only four studies have used this approach,^{8 13 32 33} and in two of them, β -blockade was not shown to be beneficial. In contrast, in two studies from Poldermans' group, early administration (at least 7 days before surgery) was beneficial. All the other RCTs started β -blockade the day of surgery. While an early start is logical, new data do not support this. Wallace and colleagues²⁴ collated observation in more than 37 000 non-cardiac operations. A protocol for perioperative β -blockade was available in their institution but was not mandatory. Patients were followed for 1 yr. Survival was best for those who had been given a β -blocker at the time of surgery, followed by those who had been maintained on β -blockade. Poorer survival was noted for those not on a β -blocker; worst outcome (unsurprisingly) was in those in whom β -blockade had been withdrawn. Thus, in the groups of patients in whom β -blockade is supported by the current guidelines, late start, if early start was not possible should not preclude the introduction of β -blockade.

Another indication for perioperative β -blockade may be to obtund the adrenergic responses to noxious stimuli or to reduce myocardial ischaemia. Our analysis of 14 studies ($n=1298$ patients) shows this single-dose treatment to be effective in reducing perioperative myocardial infarction [odds ratio (OR) 0.17 (0.044–0.203), seven studies] and myocardial ischaemia [0.22 (0.135–0.353), eight studies]. These treatments were not associated with significant hypotension or bradycardia.

β -Blocker formulation

There has been controversy in respect of the choice of slow-release metoprolol in POISE. A large observational study by Wallace and colleagues³⁴ has shown in 3789 patients on continuing β -blockade that atenolol was associated with better protection in terms of 30 day and 1 yr mortality than metoprolol. Today, bisoprolol is used increasingly frequently and may also prove to be more protective than metoprolol.

Existing guidelines

Guidelines^{20 21} underline that initiating β -blockade perioperatively should be limited to high-risk patients. This was largely based on the data from a very large cohort study by Lindenauer and colleagues.³⁵ The revised cardiac risk index (RCRI) was used to categorize cardiac risk. As the data concerned the years 2000 and 2001 and the management of patients with coronary artery disease have changed with the introduction of coronary stenting, especially in patients with acute coronary syndromes, it is interesting to see that observational data collected between 2005 and 2010 by London and colleagues³⁶ confirm that the benefits of β -blockade are only significant in patients with an RCRI of more than 1. The ACCF/AHA guideline²⁰ recommended perioperative β -blockade in patients undergoing high-risk surgery, especially vascular surgery. However, the observational study of London and colleagues³⁶ did not confirm benefits of exposure to β -blockade in vascular surgical patients irrespective of the RCRI. This is surprising and more research is needed in this group of patients.

β -Blocker titration

The recommendation of close titration of β -blockade with the goal of a heart rate of 60–70 beats min^{-1} is in principle desirable because of the need to maintain a long diastolic period to maximize flow in narrowed coronary arteries. However, there is the risk of severe bradycardia and cardiac failure as observed in a meta-analysis by Beattie and colleagues.³⁷ As hypotension was found in POISE to be an important contributor to perioperative strokes, the suggestion that 100 mm Hg systolic arterial pressure is sufficient before giving the next dose of the β -blocker is at least questionable. The current recommendation of the ACCF/AHA to withhold the β -blocker if there is hypotension (undefined) seems more logical as even moderately hypertensive patients presenting for surgery may suffer complications if their arterial pressure decreases to and remains at 100 mm Hg for a prolonged period.

Anaemia and β -blockade

An observational study by Beattie and colleagues³⁸ has shown that as the nadir of haemoglobin decreases, the risk of MACE increases as the reduction reaches 60% of control and is much higher in β -blocked than in non- β -blocked patients. Similarly, Le Manach and colleagues³⁹ found that perioperative β -blockade was associated with an overall reduction in post-operative cardiac events. Hence, while cardiac protection was observed in those patients with low perioperative bleeding,

patients receiving β -blockers who experienced severe bleeding had higher mortality and an increased frequency of multiorgan dysfunction syndrome. These important observations require confirmation in future studies because they may indicate a need to revise the threshold for blood transfusion in patients on β -blockers.

What for the future?

On August 5, 2013, a joint statement by the ACCF/AHA and ESC⁴⁰ stated: 'Our respective committees are undertaking a careful analysis of all relevant *validated* studies and always incorporate new trials and meta-analyses into our evidence review. In the interim, our current joint position is that the initiation of beta-blockers in patients who will undergo non-cardiac surgery should not be considered routine, but should be considered carefully by each patient's treating physician on a case-by-case basis'.

Before new guidelines are published, what may be a reasonable approach to perioperative β -blockade?

- Current β -blockade should be maintained, with the previously mentioned caveat of a potential risk in patients developing severe perioperative anaemia.
- Initiating β -blockade should be limited to high-risk patients undergoing high-risk surgery, especially in those who would be given β -blockade for co-existing medical reasons, that is, known coronary artery disease, reversible ischaemia on stress test.
- High-dose β -blockade should be avoided.
- Titration is recommended, but the ACCF/AHA guideline for heart rate (60–80 beats min^{-1}) is probably more appropriate owing to the risk of bradycardia with higher doses of β -blockade that can occur with the lower limit (60–70 beats min^{-1}) advocated by the ESC guideline.
- Titration should include clear instruction for each patient as to the level of arterial pressure required before the next dose of the β -blocker is given, as a function of pre-operative arterial pressure, as avoidance of hypotension is important.
- Starting β -blockade and titrating its effects over at least 7 days is logical. However, starting β -blockade on the day of surgery may still be legitimate where there is a clear indication, such as the administration of a single premedicant dose to prevent exaggerated haemodynamic responses to laryngoscopy and intubation; or provide anxiolysis by reducing adrenergic responses; or prevent perioperative myocardial ischaemia.
- Metoprolol appears to be inferior to atenolol and in the future, bisoprolol is likely to become the drug of choice once more research has been carried out.
- As anaemia has been shown to markedly increase the risk of adverse cardiac events and mortality in the face of β -blockade, consideration should be given to increase the threshold for blood transfusion in these patients.

Declaration of interest

None declared.

References

- 1 Palda VA, Detsky AS. Perioperative assessment and management of risk from coronary artery disease. *Ann Intern Med* 1997; **127**: 313–28
- 2 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multi-center Study of Perioperative Ischemia Research Group. *N Engl J Med* 1996; **335**: 1713–20
- 3 Making Health Care Safer: A Critical Analysis of Patient Safety Practices. *Evidence Report/Technology Assessment*. Number 43. Chapter 57. Practices rated by strength of evidence, Table 57.1, 622. Rockville, MD: Agency for Healthcare Research and Quality. U.S. Department of Health and Human Services. Available from <http://archive.ahrq.gov/clinic/ptsafety/pdf/ptsafety.pdf> (accessed 22 August 2013)
- 4 Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: 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 on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation* 2007; **116**: 1971–96
- 5 Stone JG, Foex 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
- 6 Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR. 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
- 7 Zaugg M, Bestmann L, Wacker J, et al. 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
- 8 Bayliff CD, Massel DR, Incullet RI, et al. Propranolol for the prevention of postoperative arrhythmias in general thoracic surgery. *Ann Thorac Surg* 1999; **67**: 182–6
- 9 Juul AB, Wetterslev J, Kofoed Enevoldsen A, Callesen T, Jensen G, Gluud C. The Diabetic Postoperative Mortality and Morbidity (DIPOM) trial: Rationale and design of a multicenter, randomized, placebo-controlled, clinical trial of metoprolol for patients with diabetes mellitus who are undergoing major noncardiac surgery. *Am Heart J* 2004; **147**: 677–83
- 10 Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J* 2006; **152**: 983–90
- 11 Lai RC, Xu MX, Huang WQ, Wang XD, Zeng WA, Lin WQ. Beneficial effects of metoprolol on perioperative cardiac function of elderly esophageal cancer patients. *Ai Zheng* 2006; **25**: 609–13
- 12 Liu Y, Huang CL, He M, Zhang LN, Cai HW, Guo QL. Influences of perioperative metoprolol on hemodynamics and myocardial ischaemia in elderly patients undergoing noncardiac surgery. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2006; **31**: 249–53

- 13 Magnusson J, Thulin T, Werner O, Jarhult J, Thomson D. Haemodynamic effects of pretreatment with metoprolol in hypertensive patients undergoing surgery. *Br J Anaesth* 1986; **58**: 251–60
- 14 Urban MK, Markowitz SM, Gordon MA, Urquhart BL, Kligfield P. Post-operative prophylactic administration of beta-adrenergic blockers in patients at risk for myocardial ischemia. *Anesth Analg* 2000; **90**: 1257–61
- 15 Jakobsen CJ, Blom L. Effect of pre-operative metoprolol on cardiovascular and catecholamine response and bleeding during hysterectomy. *Eur J Anaesthesiol* 1992; **9**: 209–15
- 16 Devereaux PJ, Beattie WS, Choi PT, et al. How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *Br Med J* 2005; **331**: 313–21
- 17 Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371**: 1839–47
- 18 Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH. Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet* 2008; **372**: 1962–76
- 19 Poldermans D, Devereaux PJ. The experts debate: perioperative beta-blockade for noncardiac surgery—proven safe or not? *Clev Clin J Med* 2009; **76**: S84–92
- 20 Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACCF/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *Circulation* 2009; **120**(Suppl. 4): e169–276
- 21 Poldermans D, Bax JJ, Boersma E, 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; **30**: 2769–812
- 22 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
- 23 Hoeks SE, Scholte Op, Reimer WJ, van Urk H, et al. 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
- 24 Wallace AW, Au S, Cason BA. Association of the pattern of use of perioperative beta-blockade and postoperative mortality. *Anesthesiology* 2010; **113**: 794–805
- 25 Ponten J, Biber B, Bjuro T, Henriksson BA, Hjalmarson A. Beta-receptor blocker withdrawal. A preoperative problem in general surgery? *Acta Anaesthesiol Scand Suppl* 1982; **76**: 32–7
- 26 Crandell DL. The anesthetic hazards in patients on antihypertensive therapy. *J Am Med Assoc* 1962; **179**: 495–500
- 27 Viljoen JF, Estafanous FG, Kellner GA. Propranolol and cardiac surgery. *J Thorac Cardiovasc Surg* 1972; **64**: 826–30
- 28 Ellenberger C, Tait G, Beattie WS. Chronic beta blockade is associated with a better outcome after elective noncardiac surgery than acute beta blockade: a single-center propensity-matched cohort study. *Anesthesiology* 2011; **114**: 817–23
- 29 Poldermans D. Scientific fraud or a rush to judgment? *Am J Med* 2013; **126**: e5–6
- 30 Chopra V, Eagle KA. Perioperative mischief: the price of academic misconduct. *Am J Med* 2012; **125**: 953–5
- 31 Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of β -blockade to prevent perioperative death in non-cardiac surgery. *Heart Online* 2013 Advance Access published on 31 July 2013, doi: 10.1136/heartjnl-2013-304262
- 32 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
- 33 Dunkelgrun M, Boersma E, Schouten O, et al. 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
- 34 Wallace AW, Au S, Cason BA. Perioperative beta-blockade: atenolol is associated with reduced mortality when compared to metoprolol. *Anesthesiology* 2011; **114**: 824–36
- 35 Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005; **353**: 349–61
- 36 London MJ, Hur K, Schwartz GG, Henderson WG. Association of perioperative beta-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. *J Am Med Assoc* 2013; **309**: 1704–13
- 37 Beattie WS, Wijeyesundera 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
- 38 Beattie WS, Wijeyesundera DN, Karkouti K, et al. Acute surgical anemia influences the cardioprotective effects of beta-blockade: a single-center, propensity-matched cohort study. *Anesthesiology* 2010; **112**: 25–33
- 39 Le Manach Y, Collins GS, Ibanez C, et al. Impact of perioperative bleeding on the protective effect of beta-blockers during infrarenal aortic reconstruction. *Anesthesiology* 2012; **117**: 1203–11
- 40 ACCF/AHA, ESC. Joint Statement: issued by the American College of Cardiology, American Heart Association and the European Society of Cardiology. 2013. Available from www.esccardio.org/about/press/press-releases/pr-13/Pages/joint-statement-perioperative-guidelines.aspx (accessed 10 August 2013)