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Editorial

Recommendations on perioperative β-blockers: differing guidelines: so what should the clinician do?

Two new guidelines concerned with B-blockade in the perioperative period have been published recently. The first was the European Society of Cardiology (ESC) guideline, endorsed by the European Society of Anaesthesiology, which was published in August 2009.¹ It addressed all the issues of the management of patients with heart disease, especially coronary heart disease presenting for non-cardiac surgery, and included a section on perioperative β-blockade. The second was the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) focused update on perioperative β -blockade, published in November 2009,² and included in the subsequently published guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery.³ These guidelines include definitions of the classification of recommendations and the accompanying level of evidence.²

An updating of existing guidelines was needed because of the results of the PeriOperative Ischemia Study Evaluation Trial (POISE) which showed that perioperative β -blockade decreased cardiac risks but increased all-cause mortality and the risk of disabling stroke.⁴ As POISE was the largest randomized controlled trial (RCT) ever undertaken in perioperative medicine, the findings called for a thorough review of previous guidelines and accepted practice.⁵ Several editorials and comments followed the publication of POISE and expressed diverse views as to the indications for β -blockade.^{6–8}

Both sets of guidelines take into consideration the results of POISE, but differ in their definition of which groups of patients may benefit or, conversely, be exposed to harm by the introduction of β -blockade before non-cardiac surgery (Table 1). Both sets of guidelines advocate the careful assessment of patient- and surgery-specific risk factors in determining who should receive therapy.

There are only three recommendations that are common to both guidelines. The first is that patients on chronic treatment with β -blockers should be maintained on this medication throughout the perioperative period (Class I C recommendation). The second is that perioperative high-dose β -blockers without titration is either not recommended (Class III A; ESC guideline) or labelled as 'not useful and maybe harmful' (Class III B, ACCF/AHA guideline). Both guidelines stress that β -blockers should be titrated to heart rate and arterial pressure stipulated as 60-70 beats min⁻¹ and more than 100 mm Hg, respectively (ESC), or 60-80 beats min⁻¹ in the absence of hypotension (undefined) (ACCF/AHA).

All other recommendations are <u>different</u> either in terms of groups of patients considered or in terms of classification of the evidence to support the recommendation. The results of the POISE study cannot be interpreted as supporting Class I recommendation for β -blockers either for patients with known ischaemic heart disease or presenting for high-risk surgery.

The ESC guideline states that β -blockers are recommended in patients who have known ischaemic heart disease or myocardial ischaemia according to preoperative testing (Class I B) without stipulation of the type of surgery. In contrast, the ACCF/AHA recommendation is only for such patients undergoing vascular surgery (Class IIa B).

The ESC guideline recommends β -blockers in patients undergoing <u>high-risk</u> surgery (I B) <u>without</u> reference to the <u>severity</u> of <u>cardiac</u> risk. The ACCF/AHA recommendation that most closely matches this is for high-risk patients undergoing <u>vascular</u> surgery (considered as high risk), with Class IIa recommendation with level of evidence C; and as such is a much <u>more restrictive approach</u>.

Both the ESC and ACCF/AHA guidelines consider that patients undergoing <u>intermediate-risk</u> surgery should be <u>considered</u> for β -blockade (ESC Class IIa recommendation, level of evidence B). Again, the ACCF/AHA guideline is more restrictive as it requires the presence of

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Table 1 Summary of recommendations on perioperative β -blockers. Both guidelines recommend to start treatment with β -blockers early [optimally 30 days or at least 1 week before surgery (ESC), or days to weeks before surgery (ACCF/AHA)] and to titrate β -blockade to heart rate of 60–70 beats min⁻¹ (ESC) or 60–80 beats min⁻¹ (ACCF/AHA). β -Blocker should be omitted if systolic arterial pressure is not >100 mm Hg (ESC), or if there is hypotension (level not defined; ACCF/AHA)

ESC guideline August 2009	ACCF/AHA guideline November 2009
 Class I β-Blockers recommended in patients With known ischaemic heart disease or myocardial ischaemia on preoperative testing (I B) Undergoing high-risk surgery (I B) Who were previously treated with β-blockers because of IHD, arrhythmias, or hypertension (I C) 	Class I β -Blockers recommended in patients Who are receiving β -blockers for treatment of conditions with ACC/AHA Class I indication for the drug (I C)
Class II	Class II
β -Blockers should be considered in patients	β -Blockers are probably recommended in patients
Undergoing intermediate-risk surgery (IIa B)	Undergoing vascular surgery who suffer from coronary artery disease or show ischaemia on preoperative testing (IIa B)
Previously treated with β-blockers because of chronic heart failure with systolic dysfunction (IIa C) Scheduled for low-risk surgery with risk factor(s) (IIb B)	In the presence of coronary artery disease or high cardiac risk (more than one risk factor) who are undergoing intermediate-risk surgery (IIa B) Where preoperative assessment for vascular surgery identifies high cardiac risk (more than one risk factor; IIa C)
	The usefulness of β -blockers is uncertain in patients
	Undergoing vascular surgery with no risk factors who are not currently taking β-blockers (IIb B)
	Undergoing either intermediate-risk procedures or vascular surgery with a single clinical risk factor in the absence of coronary artery disease (IIb C)
Class III	Class III
β -Blockers not recommended	β -Blockers not to be given
Perioperative high-dose β -blockers without titration (III A)	High-dose β-blockers without titration are not useful and may be harmful to patients not currently taking β-blockers who are undergoing surgery (III B)
Patients undergoing low-risk surgery without risk factors (III B)	Patients undergoing surgery who have an absolute contraindication to β -blockade (III C)

coronary artery disease or high cardiac risk (more than one risk factor) (Class IIa B). It also states that in the presence of a single clinical risk factor, the usefulness of β -blockers is uncertain for patients undergoing intermediate-risk procedures or vascular surgery (Class IIb C).

Although the <u>ESC</u> guideline suggests that patients undergoing <u>low-risk</u> surgery with risk factor(s) should be <u>considered</u> for β -blockade (yet, there is only limited evidence cited), there is no such recommendation in the ACCF/AHA guideline.

Why does one guideline recommend β -blockers to a much larger extent than the other? The reason is that the results of POISE have created considerable <u>controversy</u>. Yet, as it is the largest study of perioperative β -blockade ever undertaken, it carries a lot of weight and different experts consider it, and all the other RCTs, in a different light, hence the differences.

Some experts argue that the dose of <u>metoprolol</u> in the POISE trial was too high.⁸ Certainly, POISE has revealed risks that were, hitherto, unrecognized because the numbers needed to harm are, respectively, 130 for all-cause death and 190 for strokes. Previous studies did not include a large enough number of patients to reveal these major complications as statistically significant, though systematic reviews of non-POISE RCTs have identified the risk of stroke.⁹

The recommendation to start β -blockers <u>30</u> days or at <u>least 1 week before</u> surgery is supported <u>exclusively</u> by the protective effects reported by <u>Poldermans</u> and colleagues¹⁰

in <u>DECREASE</u>, and Dunkelgrun and colleagues¹¹ in the <u>DECREASE IV</u> trial. Most of the other studies, including <u>POISE</u>, started β -blockers on the <u>day of surgery</u>.

What are the take home messages?

- (i) The balance of risks and benefits needs to be evaluated in all individual patients for whom β -blockade is considered because of the increased risk of stroke and all-cause death shown by POISE.
- (ii) High cardiac risk patients undergoing high-risk surgery, particularly vascular surgery, are more likely to benefit than lower risk patients undergoing intermediate- or low-risk surgery. The latter group may be harmed.¹²
- (iii) There is agreement that β -blockade should be continued in patients on chronic treatment.^{13 14}
- (iv) There is agreement that β-blockers, should they be indicated perioperatively, should be <u>started between 30 days</u> and 1 week before surgery¹ or days to weeks before surgery;² but this is based on limited evidence.^{10 11}
- (v) There is agreement that <u>titration to heart rate</u> and arterial pressure is necessary in order to minimize or reduce the risk of hypotension bearing in mind that β -blockers can lead to the development of hypotension <u>irrespec-</u> tive of the level of reduction in heart rate. This is important as hypotension has been shown in POISE to be a major contributor to the risk of all-cause death and disabling strokes in the first 30 days post-surgery. The

suggested levels of heart rate are 60–80 and 60–70 beats min⁻¹, respectively, in ACCF/AHA and ESC guidelines. Only ESC defines the level of systolic arterial pressure (>100 mm Hg) for administration of the next dose of β -blocker. The ACCF/AHA stipulates 'in the absence of hypotension'. For patients with arterial hypertension, 100 mm Hg may be considered too low. It is our view that these protocols should be adapted and include a higher threshold for the next dose of β -blocker in hypertensive patients.

What are the implications of these sets of guidelines?

- (i) The need for titration over a period of between at least 1 week and 30 days will impose a considerable constraint on the initiation of perioperative β-blockade as it may require several visits to clinics over the preoperative period to satisfy the conditions as defined under section (v) above.
- (ii) Rather than abandoning perioperative β -blockade because of this important constraint, it is imperative to consider further the need for strengthening assessment clinics, so that preoperative treatment could be initiated safely with the appropriate follow-up.
- (iii) For patients on chronic β -blocker medication, there is probably an equal need for perioperative β -blockade <u>titration</u> in order for β -blockade to be protective and not harmful. However, as this will be under conditions of hospital care, it should be achievable.

Overall, these two sets of guidelines aim to facilitate the clinician in his care of high- and intermediate-risk patients undergoing non-cardiac surgery. Although administration of β -blockers to obtund perioperative increases in heart rate may be useful, particularly in the patients with cardiovascular disease, it is widely accepted not to be without the need to balance the risks and benefits of such treatment.^{15 16} Before using these drugs, other reasons for increases in heart rate such as pain, hypo- or hypervolaemia, latent congestive cardiac failure, and anaemia should always be excluded.

Declaration of interest

J.W.S. and P.F. are POISE investigators and Consultants for Baxter.

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References

- I Poldermans D, Bax JJ, Boersma E, et al. Guidelines for preoperative 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
- 2 Fleischmann KE, Beckman JA, Buller CE, et al. ACCF/AHA focused update on perioperative beta blockade. J Am Coll Cardiol 2009; 54: 2102–28
- 3 Fleisher LA, Beckman JA, Brown KA, et al. ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/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: e169–276
- 4 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
- 5 Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH. Perioperative beta blockers in patients having noncardiac surgery: a meta-analysis. *Lancet* 2008; 372: 1962–76
- 6 Sear JW, Foex P. Perioperative beta-blockade in non-cardiac surgical patients. Br / Surg 2008; 95: 1077–8
- 7 London MJ. Quo vadis, perioperative beta blockade? Are you 'POISE'd' on the brink? Anesth Analg 2008; 106: 1025-30
- 8 Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? *Lancet* 2008; 371: 1813-4
- 9 Poldermans D, Schouten O, van Lier F, et al. Perioperative strokes and beta-blockade. Anesthesiology 2009; 111: 940–5
- 10 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
- 11 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
- 12 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
- 13 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
- 14 Hoeks SE, Scholte Op Reimer WJ, van Urk H, et al. Increase of I-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients. Eur J Vasc Endovasc Surg 2007; 33: 13–9
- 15 Howell SJ, Sear JW, Foex P. Perioperative beta-blockade: a useful treatment that should be greeted with cautious enthusiasm. Br J Anaesth 2001; 86: 161–4
- 16 Sear JW, Giles JW, Howard-Alpe G, Foex P. Perioperative betablockade, 2008: what does POISE tell us, and was our earlier caution justified? Br J Anaesth 2008; 101: 135–8