

## CARDIOVASCULAR

# β-Blockade in the perioperative management of the patient with cardiac disease undergoing non-cardiac surgery

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### Editor's key points

- β-Blockade in patients with ischaemic heart disease has been used for cardioprotection strategy for decades.
- Recent trials and meta-analyses show increased all-cause morbidity and mortality or no benefit despite cardioprotection.
- Despite controversy, recent guidelines downgrade recommendations for use of β-blockers perioperatively.

**Summary.** The cardiology literature has suggested for decades that β-blockade protects patients with ischaemic heart disease. Extending this concept to perioperative patients initially produced promising results, with reductions in perioperative myocardial ischaemia and longer-term cardiovascular complications observed in several small randomized trials. However, subsequent larger trials have either shown no benefit or greater morbidity (especially stroke), despite reductions in cardiovascular events. Retrospective database analyses have confirmed or disputed these findings. Speciality societies, most importantly, the American Heart Association/American College of Cardiology Foundation, have promulgated guidelines for perioperative β-blockade, which have been revised, as the evidence has changed. While the European guidelines continue to emphasize perioperative β-blockade in high-risk patients, the American guidelines have reduced the strength and breadth of recommendations, focusing on haemodynamic titration. Future work will need to focus on identifying populations most likely to benefit or to be harmed, including pharmacogenetic analyses and distinctions between individual β-blockers.

**Keywords:** adrenergic β-antagonists; brain, ischaemia; cardiovascular anaesthesia; cardiovascular diseases; heart, blood flow, myocardial; heart, coronary occlusion; heart, ischaemia; perioperative care; treatment outcome

Major adverse cardiac events (MACE) are a major cause of morbidity after non-cardiac surgery, accounting for 10–40% of perioperative mortality.<sup>1</sup> Patients who experience post-operative myocardial infarction (MI) have increased hospital and 30 day mortality (11%)<sup>2</sup> and increased risk for cardiovascular death and non-fatal MI for 6 months after surgery.<sup>3</sup>

Despite decades of research and intense debate regarding how best to decrease the incidence of MACE after non-cardiac surgery, the ideal strategy has remained elusive. Coronary revascularization has been shown to be of limited benefit as a prophylactic therapy<sup>4</sup> and also in the highest risk patients.<sup>5</sup> While enthusiasm for statin therapy has grown recently, perioperative β-blockers have been and remain at the forefront of intensive medical therapy for the reduction of MACE.

### β-Blockers and the non-surgical evidence

Except for a few observational studies regarding perioperative β-blockers,<sup>6–7</sup> the first significant randomized trial of

β-blockers in the operative setting did not appear until 1996.<sup>8</sup> The Multicenter Study of Perioperative Ischemia (McSPI) and later the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group) study<sup>9</sup> in 1999 extended nearly 50 yr of research in cardiology documenting the cardioprotective effects of β-blockers.<sup>10</sup>

The first American College of Cardiology/American Heart Association (ACC/AHA) guideline for the management of patients with acute MI (AMI) was published in 1996<sup>11</sup> and subsequently revised.<sup>12–14</sup> While initially these guidelines strongly recommended the use of β-blockers in patients suffering from unstable angina or MI, their use was not mentioned in more recent 2009 or 2011 updates.<sup>15–16</sup>

Studies before and after the availability of percutaneous coronary intervention (PCI) showed trends towards mortality improvement with β-blockade after AMI and acute coronary syndrome (ACS).<sup>17–20</sup> More recently, concern has grown about the early use of i.v. β-blockade after AMI. While

re-infarction and ventricular fibrillation were reduced in the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction) trial, early  $\beta$ -blocker therapy was also associated with a 30% increase in cardiogenic shock.<sup>21</sup> The ACC/AHA AMI guidelines therefore recommend only oral therapy within the first 24 h after MI; early i.v. therapy is reserved for those with significant hypertension (HTN) (Class IIa indication).<sup>19</sup>

$\beta$ -Blockers currently are less likely to be used for primary prevention based upon a 14% higher incidence of coronary events and 23% higher incidence of stroke when atenolol was used compared with amlodipine.<sup>22</sup> In recent meta-analyses,  $\beta$ -blockers showed no benefit for all-cause mortality, cardiovascular mortality, or MI when compared with other anti-hypertensives<sup>23</sup> or with placebo.<sup>23</sup> The incidence of stroke has consistently been shown to be higher with  $\beta$ -blockers when compared with other therapies.<sup>23–26</sup> Therefore, in the most recent American College of Cardiology Foundation (ACCF)/AHA guideline for the management of HTN in the elderly,  $\beta$ -blockers are no longer considered first-line therapy in uncomplicated HTN, although still are recommended in those with heart failure, aortic aneurysm, diabetes mellitus, or coronary artery disease (CAD).<sup>27</sup> Indeed, in some older studies<sup>28</sup> and newer trials,<sup>29</sup> no advantage to  $\beta$ -blockers compared with calcium-channel blockers was seen. These results are important, given side-effects of  $\beta$ -blockade such as insulin resistance, decreased exercise endurance, depression, lethargy, and peripheral vascular and pulmonary effects.<sup>23</sup> Multiple meta-analyses have consistently shown, however, a substantial benefit to  $\beta$ -blockers in the setting of chronic heart failure.<sup>30–32</sup>

## Pathophysiology of perioperative MI

The aetiology of perioperative MI (PMI) is multifactorial. PMI has traditionally been ascribed to prolonged stress-induced ischaemia in the setting of a fixed coronary stenosis. Plaque rupture has been found in only 7–46% of fatal PMIs. Most PMIs are preceded by prolonged tachycardia with ST-depression-type ischaemia and develop into non-Q-wave infarctions with the resting ECG subsequently returning to baseline.<sup>33–35</sup> Thus, the role for  $\beta$ -blockers in preventing PMI has been considered to improve myocardial oxygen balance by slowing heart rate (HR), reducing contractility, and improving diastolic coronary filling, thereby decreasing myocardial oxygen consumption. However, perioperative plaque instability, inflammation, and hypercoagulability likely also contribute to the development of PMI.<sup>36</sup> Rupture or fissuring of the intimal surface of the vulnerable plaque is promoted by haemodynamic stress;  $\beta$ -blockers can improve coronary plaque stability by decreasing shear forces during perioperative sympathetic nervous activation.<sup>10</sup> Perioperative stress can also promote thrombosis by increasing platelet activity and decreasing fibrinolysis. Perioperative inflammation of the endothelium can be prothrombotic, cause endothelial vasoconstriction, and be plaque-destabilizing.<sup>37</sup> This more complex nature of

PMI explains why stress testing has a low positive predictive value (20–30%) and a negative predictive value of 95–100%;<sup>38</sup> why perioperative ischaemia does not consistently lead to PMI,<sup>39</sup> and why  $\beta$ -blockers do not affect the incidence of PMI or perioperative mortality while reducing perioperative ischaemia.<sup>40</sup>

## Review of major randomized controlled trials of perioperative $\beta$ -blockade

### Mangano and colleagues<sup>8</sup>

The McSPI group trial<sup>8</sup> included Veterans Affairs (VA) patients with, or at risk for, CAD undergoing non-cardiac surgery. Atenolol was used as the study drug. The primary outcome was all-cause mortality at 6 months and 1 and 2 yr with a secondary outcome of combined MI, unstable angina, congestive heart failure (CHF), myocardial revascularization, and/or death. The study showed significant benefits in both the primary and secondary endpoints. At 2 yr follow-up, mortality was significantly lower in the atenolol group (10% vs 21% in the placebo group) with a reduction in the incidence of postoperative cardiac events.

However, there were important limitations to this trial. Patients were not excluded if they were on a  $\beta$ -blocker. Patients receiving a  $\beta$ -blocker could therefore have been randomized into the placebo arm and had the medication abruptly stopped. Abrupt withdrawal of  $\beta$ -blockade can increase HR, increase myocardial oxygen demand, and predispose to myocardial ischaemia.<sup>41</sup> Another possible mechanism is increased platelet aggregability upon withdrawal.<sup>41</sup>

Only patients who survived to hospital discharge were examined; it was not an intention-to-treat analysis. If all patients enrolled in the trial who died in hospital were included, the actual 2 yr mortality would not have been significantly different ( $P=0.1$ ). Additionally, the two groups were not comparable at baseline, with a greater weight of cardiovascular risk in the control group.

### Wallace and colleagues<sup>40</sup>

This second publication from the McSPI group was a subset analysis of data from Mangano and colleagues<sup>8</sup> and reported a significant reduction in the incidence of postoperative ischaemia from 34% to 17%. Despite the improvement in 2 yr mortality which was attributed to this reduction, no difference in perioperative cardiac endpoints was found.

### DECREASE I trial<sup>9</sup>

The first DECREASE trial examined patients with positive results on dobutamine stress echocardiography undergoing major vascular surgery. Patients were randomized to either standard perioperative treatment or bisoprolol. Patients were excluded if they were already on a  $\beta$ -blocker or if there were extensive wall motion abnormalities. Bisoprolol was started at least 1 week before surgery (average 37 days before) and continued for 30 days after operation. The initial dose of bisoprolol of 5 mg orally daily was titrated to a target HR of 51–79 beats  $\text{min}^{-1}$  (maximum 10 mg daily).

If the perioperative HR was  $>80$  beats  $\text{min}^{-1}$ , i.v. metoprolol was administered.

The study showed a significant reduction in its primary endpoint of composite death from cardiac causes or non-fatal MI within 30 days after operation (34% in the standard care group vs 3.4% in the bisoprolol group). The trial was stopped early because of a clear reduction in cardiac morbidity and mortality, despite only enrolling 112 patients and having 20 events. Critics of this study question the reduction in cardiac events by 90%, which is greater than expected. The trial was not double-blinded. A major difference between the DECREASE trial and the McSPI trials is the inclusion of only high-risk patients in DECREASE, whom some clinicians assert should have already been on a β-blocker or had cardiac catheterization, coronary revascularization, or both before surgery.

### POBBLE trial<sup>42</sup>

The POBBLE (Perioperative β-Blockade) trial was a randomized double-blinded placebo-controlled trial of metoprolol in patients without CAD undergoing infrarenal vascular surgery under general anaesthesia. Patients already on a β-blocker were excluded. Oral metoprolol (or placebo), dosed depending on patient weight, was initiated at hospital admission, usually the day before surgery, and was continued for 7 days after surgery. Outcome variables were 30 day cardiovascular morbidity and mortality and length of hospital stay. Cardiovascular event rate within 30 days was not statistically different (34% of the placebo group and 32% of the metoprolol group). Hospital stay was shorter in the metoprolol arm (10 compared with 12 days;  $P<0.02$ ). More patients in the metoprolol group required intraoperative inotropic support.

Critiques of the trial include the weight-based dosing of metoprolol in lieu of targeting HR parameters as in the DECREASE trial. The high cardiovascular event rate might not be representative.

### DIPOM trial<sup>43</sup>

In 2006, two negative trials were published. The first was a double-blinded randomized placebo-controlled study, DIPOM (DIabetic POstoperative Mortality and Morbidity). It investigated diabetic surgical patients. With 921 patients, DIPOM is the second largest double-blinded randomized placebo-controlled trial in the field. In DIPOM, diabetic patients undergoing major non-cardiac surgery received sustained-release metoprolol 100 mg per day or placebo starting the day before surgery, continuing after operation to a maximum of 8 days. The mean duration of postoperative metoprolol or placebo intervention was 4.6 and 4.9 days, respectively. The primary outcome was composite of all-cause mortality, AMI, unstable angina, or CHF.

The DIPOM investigators found no effect on cardiac morbidity and mortality throughout a mean follow-up period of 18 months. However, they did find a significant increase in

hypotension and bradycardia in the treatment group. One criticism of the DIPOM trial concerns the short duration of postoperative β-blockade.

### MaVS trial<sup>44</sup>

Metoprolol after Vascular Surgery (MaVS) was a double-blinded randomized placebo-controlled trial. Patients were administered a weight-based dose of oral or i.v. metoprolol 2 h before surgery and 2 h after surgery. Metoprolol was continued until hospital discharge, or for a maximum of five postoperative days. The primary outcome was a composite of cardiovascular complications, including cardiac death at 30 days.

This trial also failed to show a difference in the primary outcome. Cardiovascular events occurred in 10% of the metoprolol group and 12% of the placebo group. However, intraoperative bradycardia and hypotension requiring treatment were both significantly more frequent with metoprolol. At 6 months, there were no significant differences in cardiovascular events.

The MaVS trial did not show any clear benefit to perioperative β-blockade in vascular surgery patients, who were previously presumed to benefit from this therapy. By 2006, between the MaVS and DIPOM trials, 1417 patients had been investigated without outcome benefits in two groups of patients believed to be best candidates to benefit from perioperative β-blockade. In fact, there was a trend towards worse outcomes in the β-blocker recipients. It should be noted, however, that the cohort in both trials represented relatively low-risk vascular patients without a significant incidence of definitive CAD.

### BBSA<sup>45</sup>

The Swiss Beta Blocker in Spinal Anaesthesia (BBSA) study was a double-blinded placebo-controlled multicentre trial evaluating the cardiovascular protective effects of 10 days of oral bisoprolol in patients having spinal anaesthesia.<sup>46</sup> The primary outcome was composite cardiovascular mortality, non-fatal MI, unstable angina, CHF, and cerebrovascular event at 1 yr in high-risk patients who had CAD. Patients received the first dose of bisoprolol 3 h before spinal block placement. Oral bisoprolol 5–10 mg was administered depending on systolic arterial pressure (SAP) and HR parameters.

During 1 yr follow-up, there was no benefit to the addition of bisoprolol to spinal anaesthesia; the primary endpoint was reached in 22% of patients in each arm. The investigators also identified a variant genotype that contained at least one mutant allele of the β<sub>1</sub>-adrenergic receptor to be significantly associated with a higher number of adverse events.

### The POISE Study<sup>47</sup>

By 2008, clinicians were unsettled about the benefits of perioperative blockade in non-cardiac surgery.<sup>48</sup> Hence, the Canadian-based POISE (PeriOperative ISschemic Evaluation)

Study Group undertook a study with funding provided by the manufacturer of metoprolol (Astra-Zeneca).<sup>48</sup>

POISE included 8351 patients with or at risk of atherosclerotic disease randomized to placebo or metoprolol succinate extended release (ER) 100 mg orally. The therapy was initiated 2–4 h before operation and continued for 30 days. The study drug was held for HR <50 beats min<sup>-1</sup> or SAP <100 mm Hg. Within 6 h after operation, a second dose of 100 mg metoprolol ER was administered if HR >80 beats min<sup>-1</sup> and SAP >100 mm Hg. Twelve hours later, metoprolol ER 200 mg was given pending the same HR and SAP parameters and continued daily for 30 days. If the patient could not receive oral medication, 15 mg i.v. metoprolol every 6 h was given. Study drug was held for HR <45 beats min<sup>-1</sup> or SAP <100 mm Hg.

The primary endpoint of the POISE trial mirrored other trials with a composite of cardiovascular death, non-fatal MI, and non-fatal cardiac arrest at 30 days. Metoprolol reduced the primary endpoint (5.8% compared with 6.9%;  $P=0.04$ ). A significant decrease in MI (4.2% compared with 5.7%;  $P=0.0017$ ) was largely responsible for the overall reduction in the primary endpoint. However, there was a significant increase in total mortality in the metoprolol group (3.1% with the metoprolol group compared with 2.3%;  $P=0.0317$ ). Stroke incidence was 1% with metoprolol compared with 0.5% ( $P=0.0053$ ).

The higher incidence of stroke in the POISE trial might be due to more hypotension in the metoprolol group. The dosing differed from common practice, in that patients could receive as much as 400 mg metoprolol ER on the day of surgery. Large trials in non-operative settings used the same dose of metoprolol ER without an increase in stroke incidence.<sup>49</sup> However, other trials in non-operative patients have also shown an association between  $\beta$ -blockers and stroke.<sup>22 50 51</sup> POISE outcomes might have been due to differences between types of  $\beta$ -blocker, in that metoprolol could have more stroke events or worse cardiac protection than bisoprolol.

Sepsis or infection as a cause of death was significantly more common in the metoprolol group ( $n=53$ , 0.63%). Hypotheses on the aetiology implicate hypotension as a predisposing condition. Perhaps hypotensive patients are unable to mount a haemodynamic response to maintain gut integrity or deliver antibiotics or oxygen to tissues. Prevention of tachycardia by  $\beta$ -blockade could delay the recognition and treatment of sepsis.

### DECREASE IV<sup>52</sup>

In the DECREASE IV study, 1066 intermediate-risk patients [Revised Cardiac Risk Index (RCRI) 1 or 2] undergoing non-cardiac surgery were randomized to either bisoprolol, fluvastatin, a combination of bisoprolol plus fluvastatin, or a double placebo starting 30 days before surgery; bisoprolol was titrated to a HR of 50–70 beats min<sup>-1</sup>. Patients who received bisoprolol, with or without fluvastatin, had significantly reduced cardiac death and MI at 30 days after

operation. There was no difference in the incidence of stroke between the groups. Thus, the authors concluded that the increased incidence of stroke in the POISE trial was due to choice of drug, dosage, timing of initiation, or all three.<sup>53</sup> Importantly, the only major trials that have not shown a significant or non-significant trend for increased perioperative strokes in the  $\beta$ -blocker groups were DECREASE I and IV.

There are limitations to the DECREASE IV trial. Similar to DECREASE I, it was not blinded. DECREASE IV was terminated before target sample size was achieved due to slow patient recruitment; 78% of patients approached were already on a  $\beta$ -blocker or statin, instead of the anticipated 20%.

Table 1 provides a comparison of the studies including number of patients, drug and dosage, timing of administration, target HR, inclusion criteria, and study endpoint.

## Major meta-analyses and database queries of perioperative $\beta$ -blockade

### Lindenauer and colleagues<sup>54</sup>

By the early 2000s, momentum had been growing for the use of perioperative  $\beta$ -blockade. However, results of a massive retrospective database cohort study by Lindenauer and colleagues raised a red flag. The study used propensity score matching to adjust for differences in patients who received perioperative  $\beta$ -blockade and those who did not. The primary outcome was in-hospital mortality. This study utilized the RCRI (published in 1999 by Lee and colleagues),<sup>55</sup> which remains a standard in cardiovascular risk assessment in surgical patients. In patients with an RCRI score of 0 or 1,  $\beta$ -blocker treatment was associated with no benefit and possible harm. However, in patients with an RCRI of  $\geq 2$ , perioperative  $\beta$ -blockade was associated with a decreased risk of death.

### Bangalore and colleagues<sup>56</sup>

This meta-analysis of perioperative  $\beta$ -blockade in non-cardiac surgery analysed 33 randomized controlled trials (RCTs), including POISE. The study by Mangano and colleagues<sup>8</sup> was excluded due to lack of 30 day outcome reporting. The investigators did not find an association with  $\beta$ -blocker therapy and reduction in all-cause mortality, cardiovascular mortality, or heart failure. For the entire cohort, perioperative  $\beta$ -blockade was associated with a 35% decreased risk of non-fatal MI [number needed to treat (NNT) 63] and a 64% decreased risk of myocardial ischaemia (NNT 16) at the expense of a 116% increased risk of non-fatal strokes (number needed to harm 293).

## Other meta-analyses

A meta-analysis published in 2007, before POISE, examined multiple small RCTs ( $n=69$ ) of perioperative  $\beta$ -blockers.<sup>57</sup> Many of these studies only reported intermediate

**Table 1** Summary of randomized placebo-controlled and retrospective cohort trials of perioperative β-blockade. HR, heart rate; VA, Veterans Affairs Medical Center; MI, myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure; DBA, dobutamine; RCRI, Revised Cardiac Risk Index

Trial	No. of patients	Study drug and dose	Timing of β-blockade	Target HR	Inclusion criteria	Primary endpoint
Mangano and colleagues <sup>8</sup>	200 (1 hospital)	Atenolol 5–10 mg i.v. before surgery, immediately after surgery, and then 50–100 mg oral daily	30 min before surgery, after surgery, then orally throughout hospitalization (up to 7 days)	55 < HR < 65	VA patients with, or at risk for CAD	All-cause mortality at 6 months, 1, and 2 yr
Wallace and colleagues <sup>40</sup>	200 (1 hospital)	Atenolol 5–10 mg i.v. before surgery, immediately after surgery, and then 50–100 mg oral daily	30 min before surgery, after surgery, then orally throughout hospitalization (up to 7 days)	55 < HR < 65	VA patients with, or at risk for CAD	Postoperative MI within first 7 days
DECREASE I <sup>9</sup>	112 (7 hospitals)	Bisoprolol 5–10 mg oral daily titrated to HR 51–79 beats min <sup>-1</sup> . If unable to take oral, i.v. metoprolol to keep HR < 80	Started 7–89 (average 37) days before surgery; continued 30 days after operation	50 < HR < 80	High-risk vascular surgery patients (positive DBA stress test required)	Composite of death from cardiac causes or non-fatal MI within 30 days
POBBLE <sup>42</sup>	103 (4 hospitals)	Metoprolol 50 mg if >55 kg or 25 mg if <55 kg twice daily orally; or 2–4 mg metoprolol i.v. if unable to take oral	At admission (usually 1 day before surgery) until 7 days after operation	HR > 50	Patients without, or at risk for, CAD undergoing infrarenal vascular surgery	30 day cardiovascular morbidity or mortality
DIPOM <sup>43</sup>	921 (9 hospitals)	Sustained-release metoprolol 100 mg	Day before surgery until maximum 8 days after operation (mean duration 4–5 days)	HR > 55	Patients with DM type II undergoing major non-cardiac surgery	Short- and long-term composite of all-cause mortality, acute MI, unstable angina, or CHF
MaVS <sup>44</sup>	496 (3 hospitals)	Metoprolol 25, 50, or 100 mg orally based on weight. If unable to take oral, metoprolol 1 mg i.v. given	Two hours before surgery and 2 h after surgery. Continued oral metoprolol 50 or 100 mg twice daily for hospital stay (maximum 5 postoperative days)	50 < HR < 80	Vascular surgery patients undergoing abdominal aortic surgery and infrainguinal or axillofemoral revascularizations	30 day composite incidence of non-fatal myocardial infarction, unstable angina, new CHF, new atrial or ventricular dysrhythmia requiring treatment, or cardiac death
BBSA <sup>45</sup>	119 (4 hospitals)	Bisoprolol 10 mg orally for SAP > 120 mm Hg and HR > 65 beats min <sup>-1</sup> ; 5 mg for SAP 101–119 mm Hg and HR 51–64; withheld study drug if SAP < 100 mm Hg or HR < 50 beats min <sup>-1</sup>	Three hours before spinal and 6 h after surgery. Then daily for maximum 10 days (mean duration ~5 days)	50 < HR < 80	High-risk patients undergoing surgery with spinal anaesthetic	Time to composite of cardiovascular mortality, non-fatal MI, unstable angina, CHF, and cerebrovascular insult

Continued

Table 1 Continued

Trial	No. of patients	Study drug and dose	Timing of $\beta$ -blockade	Target HR	Inclusion criteria	Primary endpoint
POISE <sup>47</sup>	8351 (190 hospitals; 23 countries)	Metoprolol ER 100 mg before operation titrated to goal of 200 mg daily	100 mg 2–4 h before surgery and repeated 6 h post-surgery depending on AP and HR. Then 200 mg daily for 30 days	50 < HR < 80	Patients with, or at risk of, CAD	Cardiovascular death, non-fatal MI, non-fatal arrest
DECREASE IV <sup>52</sup>	1066 (? hospitals)	Bisoprolol 2.5 mg titrated to HR 50–70 beats min <sup>-1</sup>	Started median 34 days before operation	50 < HR < 70	Intermediate-risk (RCRI 1–2) patients undergoing non-cardiac surgery	Composite of non-fatal MI and cardiac death at 30 days
Trial	Secondary outcome	Results	Perioperative MI	Incidence of stroke	Notes	
Mangano and colleagues <sup>8</sup>	Combined MI, unstable angina, CHF, coronary revascularization, and/or death	Reduced mortality and cardiac events at 6 months, 1, and 2 yr	50% decrease in MI	Non-significant increase in stroke (4% vs 1%)	Not an intention-to-treat analysis No reduction in the risk of cardiac death during hospitalization	
Wallace and colleagues <sup>40</sup>	Death at 2 yr	Reduced MI in the postoperative period associated with reduced risk of death at 2 yr	Decreased from 34% to 17% in the atenolol group	Non-significant increase in strokes in the atenolol group (4 vs 1)	Subset analysis of Mangano and colleagues database	
DECREASE I <sup>9</sup>		90% reduction in cardiac events	9 patients in the standard therapy group vs 0 in the bisoprolol group had perioperative MI	No association with perioperative stroke and $\beta$ -blocker	Stopped at first interim analysis due to 'clear benefit' Not double-blinded May not reflect optimal practice of high-risk patients Metoprolol i.v. was used for HR > 80	
POBBLE <sup>42</sup>	Hospital length of stay	No difference in cardiovascular event rate. Significant reduction in length of hospital stay in the metoprolol group	No difference	Non-significant increase in strokes the in metoprolol arm (2 vs 0)	High cardiovascular event rate in both arms (nearly one-third of study population) Small trial More intraoperative inotropic support used in the metoprolol group	
DIPOM <sup>43</sup>	All-cause mortality, cardiac mortality, and non-fatal cardiac morbidity	No difference in primary or secondary outcome during mean follow-up period of 18 months	No difference	Non-significant increase in strokes the in metoprolol arm (2 vs 0)	Large trial Short duration of perioperative $\beta$ -blockade	
MaVS <sup>44</sup>	6 month composite outcomes	No difference in primary outcome at 30 days or 6 months	No difference (4 in the placebo arm, 5 in the metoprolol arm)	Non-significant increase in stroke incidence in the metoprolol arm (2% vs 1.6% in controls)	Short duration of perioperative $\beta$ -blockade Intraoperative bradycardia and hypotension more common in the treatment group	

Continued

Table 1 Continued

Trial	Secondary outcome	Results	Perioperative MI	Incidence of stroke	Notes
BBSA <sup>45</sup>	Evaluation of adrenergic receptor polymorphisms	No difference in primary outcome at 1 yr (22% in each arm). One β-receptor polymorphism was associated with increased risk	No difference in MI incidence during 1 yr follow-up	No difference in incidence of stroke (2 patients in each arm)	Bisoprolol group had 10 beats min <sup>-1</sup> lower HR Inherently less invasive surgery Genotyping of β-receptors added new information
POISE <sup>47</sup>	Total mortality, stroke, coronary revascularization, atrial fibrillation, CHF, hypotension, and bradycardia	Reduction in total MI, need for coronary revascularization, and atrial fibrillation. Increased all-cause mortality. Increased risk of stroke, hypotension, and bradycardia	Significantly reduced by 30%	Significantly increased risk of stroke by 33% in the metoprolol arm (1.0% vs 0.5% in controls)	Timing and dosing of study drug questioned Only 2 of 3 planned interim safety analyses performed Sepsis more common in the metoprolol arm
DECREASE IV <sup>52</sup>		67% reduction in primary endpoint in patients receiving bisoprolol	Significant reduction in MI	No association with stroke (0.8% incidence in β-blocker arm compared with 0.6% control)	Bisoprolol was associated with a decrease in primary endpoint Fluvastatin showed only trend towards a decrease in primary endpoint Small trial Not blinded Trial stopped early

intraoperative outcomes (e.g. myocardial ischaemia upon tracheal intubation). They concluded that ‘β-Blockers reduced perioperative arrhythmias and myocardial ischemia, but they had no effect on myocardial infarction, mortality, or length of hospitalization’. Stroke was evaluated in only five of the trials; while the odds ratio was 2.29 for stroke in the β-blocker group, the 95% confidence interval was 0.86–6.13.

Meta-analyses can also be used to discern specific patterns in outcomes.<sup>58</sup> Badgett and colleagues,<sup>59</sup> cardiologists, performed a meta-analysis to examine whether differences in β<sub>1</sub> receptor selectivity or dependence upon the cytochrome P450 for metabolism could explain differences in outcomes between different trials. Their meta-analysis suggests that acute administration of metoprolol, given its more variable metabolism by cytochrome P450, might result in inadequate or excessive β-blockade. However, β<sub>1</sub>/β<sub>2</sub> selectivity was not found to affect results. Beattie and colleagues<sup>60</sup> performed a meta-analysis that suggested that trials with superior HR control (estimated maximal HR <100 beats min<sup>-1</sup>) were associated with less PMI.

Database reviews have strengths and weaknesses. Strengths include large numbers, low costs, and generalizability to practice. Weaknesses include questionable clinical

validity of administrative data, lack of correlation to clinical variables of interest (e.g. haemodynamics), and difficulty in discerning confounding variables.<sup>61</sup> Statistical modelling with propensity analysis can improve retrospective analyses,<sup>62</sup> which are needed, given the falling rate of perioperative mortality.<sup>63</sup>

The group at the San Francisco VA Medical Center instituted a perioperative β-blocker protocol in 1998 after the McSPI study. They recently published two papers that retrospectively review data over 12 yr. The first examined mortality differences in patients in whom perioperative β-blockade was initiated, maintained, or discontinued.<sup>63</sup> They concluded that continuing or starting β-blockade was associated with lower mortality at 30 days and 1 yr, but that discontinuation had the opposite effect. Similar results were found in a cohort of joint replacement patients in Ottawa.<sup>64</sup>

In a second study, the San Francisco VA group<sup>65</sup> evaluated the choice of β-blocker. In almost 25 000 in-patient procedures, 3787 patients received perioperative β-blockade; 1011 with atenolol and 2776 with metoprolol. Thirty day mortality and 1 yr mortality were lower when patients received atenolol rather than metoprolol. Potential mechanisms that could produce worse outcomes in metoprolol-treated patients include its shorter half-life (thereby possibly

producing withdrawal), greater variability in metabolism, and poorer  $\beta$  adrenergic blockade.<sup>66</sup> Studies in the cardiology literature have also documented greater mortality in patients chronically treated with metoprolol compared with atenolol.<sup>67</sup>

Initiation of  $\beta$ -blockade in advance of surgery was supported by a retrospective database study with propensity matching showing that acute  $\beta$ -blockade was associated with worse outcome (composite of MI, non-fatal cardiac arrest, and perioperative mortality) than chronic  $\beta$ -blockade.<sup>68</sup> This lends credence to the DECREASE trials, which have informed the European Society of Cardiologists Perioperative guidelines—that starting  $\beta$ -blockade 30 days before surgery improves outcomes.

## Societal guidelines

The first societal guideline recommendation regarding perioperative  $\beta$ -blockers came from the American College of Physicians (ACP) in 1997.<sup>69</sup> The recommendation was that all patients with CAD or with risk factors for CAD should receive perioperative atenolol. The ACP has made no subsequent statements on the subject.

The first formal recommendation regarding perioperative  $\beta$ -blockers from ACC/AHA came in their 2002 update of the 1996 guideline for perioperative cardiovascular evaluation for noncardiac surgery,<sup>70</sup> based mostly on the McSPI group's work and the DECREASE trial. Class I indications included anyone who had required  $\beta$ -blockers in the past to control symptoms of HTN, angina, or arrhythmia, or those with CAD on testing before vascular surgery. All patients in whom the preoperative assessment revealed untreated HTN, known CAD, or major risk factors for CAD were defined as having Class IIa indications for perioperative  $\beta$ -blockade. Given the subsequent mixed evidence discussed above regarding perioperative  $\beta$ -blockers, the 2006 update represented a substantial downgrade.<sup>71</sup> Following the results of the POISE trial, the recommendations were further downgraded in the most recent 2009 update.<sup>72</sup> In this document, the only Class I indication for perioperative  $\beta$ -blockers was that they be continued during the perioperative period in patients taking chronic  $\beta$ -blockers before operation for Class I out-patient indications. Their use in patients undergoing vascular surgery with ischaemia identified on preoperative testing, a former Class I indication, was downgraded to a Class IIa indication. The use of perioperative  $\beta$ -blockers was defined as 'reasonable' (IIa recommendation) in those patients with CAD or those with more than one major clinical risk factor undergoing vascular or intermediate-risk surgery. Additionally, in those patients with defined IIa indications, it was recommended that some form of perioperative titration occur. Finally, in those with one or fewer clinical risk factors undergoing vascular or intermediate-risk surgery, the benefits of perioperative  $\beta$ -blockade were considered uncertain.

It appears that the overall mixed findings of the to-date perioperative  $\beta$ -blocker literature, in which mostly fixed

dosing regimes have been used, coupled with the strongly positive results of the few titrated studies in surgical patients<sup>9 73</sup> and in the cardiology literature,<sup>21 74</sup> formed the predominant basis for their recommendation. The relatively large fixed dosing regime in the POISE trial was associated with a significant incidence of bradycardia and hypotension, while in two recent meta-analyses, the benefit of targeted HR control in affecting cardiac outcome was found to be equivocal.<sup>60 75</sup> The 2009 ACC/AHA focused update on perioperative  $\beta$ -blockade practice guidelines stated: 'In light of the POISE results, routine administration of perioperative beta blockers, particularly in higher fixed-dose regimens begun on the day of surgery, cannot be advocated'.

While the most recent ACCF/AHA guidelines have significantly cut back their recommendations for perioperative  $\beta$ -blockade, the European Society of Cardiology produced guidelines in 2009 (endorsed by the European Society of Anesthesiology) that much more strongly recommend perioperative  $\beta$ -blockade.<sup>76 77</sup> Notably, the first author of the European guidelines (Poldermans) is the lead investigator of the DECREASE trials,<sup>9 52</sup> which have consistently shown a benefit for bisoprolol started a month before surgery without risk of increased stroke.<sup>78</sup>

A 2011 review<sup>79</sup> opined: 'The 2009 American and the European guidelines for perioperative  $\beta$ -blockade in vascular surgery disagree on the available evidence but do recommend  $\beta$ -blockade for several indications... Perioperative  $\beta$ -blockade reduces cardiac events, but at the expense of increased risk for mortality and stroke. The guidelines seem to be eager to follow positive outcome studies, without considering the effects of  $\beta$ -blockade on other organ systems'.

The differences between the most recent American and European guidelines have been summarized by London<sup>80</sup> and by Sear and Foex<sup>81</sup> in Table 2.

## SCIP guidelines

As part of a collaborative effort under the direction of the US Centers for Medicare and Medicaid Services and the Centers for Disease Control and Prevention, the prevention of adverse cardiac events during surgery was identified as one of the goals of the Surgical Care Improvement Project (SCIP). The SCIP-Card 2 measure seeks to prevent cardiac complications related to inappropriate perioperative discontinuation of chronically used  $\beta$ -blockers. The measure states that those on  $\beta$ -blockers coming for surgery must receive a  $\beta$ -blocker within 24 h of the perioperative period, with this period defined as from surgical incision to up to the first 6 h of recovery. This recommendation mirrors the 2009 ACC/AHA focused update that defines continuation of  $\beta$ -blockers perioperatively as a Class I indication.<sup>72</sup> These recommendations, however, are based mostly on a few retrospective studies with a limited number of events and also on some non-surgical data.<sup>82–85</sup>

**Table 2** 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 HR of 60–70 beats min<sup>-1</sup> (ESC) or 60–80 beats min<sup>-1</sup> (ACCF/AHA). β-Blocker should be omitted if SAP is not >100 mm Hg (ESC), or if there is hypotension (level not defined; ACCF/AHA). Table reproduced from Sear and Foex<sup>81</sup> with permission

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

### Comorbidities, future research agenda, and conclusions

Hypoperfusion, heart failure, and bronchial constriction are potential side-effects of β-blockade that concern anaesthetologists during surgery. While numerous randomized trials have therefore excluded patients with comorbidities such as heart failure and chronic obstructive pulmonary disease (Table 1), more recent trials have generally been more liberal in their inclusion. Indeed, β-blockade has become standard therapy for patients with ischaemic and non-ischaemic heart failure. Fortunately, studies of β<sub>1</sub> selective β-blockers suggest little increase in bronchial tone (based on spirometry) in cardiovascular patients.<sup>86 87</sup>

Concern has recently arisen that anaemia might complicate perioperative β-blockade, by further limiting oxygen delivery. A retrospective analysis found that β-blockade was associated with worse outcome (MACE composite) when haemoglobin levels decreased by >35%.<sup>88</sup> An animal study found that while cerebral oxygenation is maintained during haemodilution, further addition of metoprolol reduced

cerebral oxygenation.<sup>89</sup> Given potential abnormalities in macro- and microcirculation in elderly patients, this is a potential mechanism for the increased stroke rate found in the POISE trial and warrants further study.

Gender differences exist; a retrospective study showed that men benefited from β-blockade with reduced MI, but women suffered from clinically significant increases in CHF.<sup>90</sup>

We conclude that β-blockade might protect against perioperative cardiovascular complications, particularly in those at highest risk. However, acute administration, especially in fixed doses, may cause harm, especially if anaemia exists or hypotension occurs. The relatively recent association with major complications has further highlighted the need to determine how best to risk-stratify those patients not already on β-blockers and in whom prophylactic therapy will be beneficial. Evidence for pharmacogenetic variation in metabolism suggests that metoprolol might not be the best choice of β-blocker in the perioperative period. The role of early initiation of therapy with careful titration requires further study but appears promising, as the debate over perioperative β-blockers continues to evolve.

## Conflict of interest

J.E.E. is a member of the speaker's bureau for and consultant to Baxter Pharmaceutical, maker of the  $\beta$ -blocker esmolol. He has also been a member of the speaker's bureau for The Medicine Company, which makes the calcium-channel blocker clevidipine. Neither drug is specifically mentioned in the text, though one citation is a study using esmolol. Additionally, J.E.E. produces continuing medical education (CME) programmes through his corporation destination CME LLC.

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