

**MUZAMMIL MUSHTAQ, MD**

Assistant Professor of Clinical Medicine,  
Interdisciplinary Stem Cell Institute, Division  
of Hospital Medicine, University of Miami  
Miller School of Medicine, Miami, FL

**STEVEN L. COHN, MD**

Medical Director, UHealth Preoperative Assess-  
ment Center; Director, UMH Medical Consulta-  
tion Service; Professor of Clinical Medicine,  
Division of Hospital Medicine, University of  
Miami Miller School of Medicine, Miami, FL

# Perioperative beta-blockers in noncardiac surgery: The evidence continues to evolve

## ABSTRACT

The effectiveness and safety of giving beta-blockers to patients undergoing noncardiac surgery remain controversial. The use of these drugs in this clinical scenario increased after the publication of two positive trials in the late 1990s and was encouraged by national organizations and clinical guidelines. However, when several subsequent studies failed to show a benefit, recommendations became more limited and use decreased. This paper reviews recent evidence for and against the perioperative use of beta-blockers.

## KEY POINTS

If patients have other indications for beta-blocker therapy, such as a history of heart failure, myocardial infarction in the past 3 years, or atrial fibrillation, they should be started on a beta-blocker before surgery if time permits.

Of the various beta-blockers, the cardioselective ones appear to be preferable in the perioperative setting.

Beta-blockers may need to be started at least 1 week before surgery, titrated to control the heart rate, and used only in patients at high risk (Revised Cardiac Risk Index score > 2 or 3) undergoing high-risk surgery.

Further clinical trials are necessary to clarify the ongoing controversy, particularly regarding the risk of stroke, which was increased in the large Perioperative Ischemic Evaluation (POISE) trial.

**P**ROPHYLACTIC USE of beta-blockers in the perioperative period is highly controversial. Initial studies in the 1990s were favorable, but evidence has been conflicting since then.

The pendulum swung away from routinely recommending beta-blockers after the publication of negative results from several studies, including the Perioperative Ischemic Evaluation (POISE) trial in 2008.<sup>1</sup> Highlighting this change in practice, a Canadian study<sup>2</sup> found that the use of perioperative beta-blockade increased between 1999 and 2005 but subsequently declined from 2005 to 2010. However, there was no appreciable change in this pattern after the POISE trial or after changes in the American College of Cardiology guidelines in 2002 and 2006.<sup>3</sup>

In 2008, Harte and Jaffer reviewed the perioperative use of beta-blockers in noncardiac surgery in this journal.<sup>4</sup> Since then, a number of meta-analyses and retrospective observational studies have reported variable findings related to specific beta-blockers and specific complications.

In this paper, we review the rationale and recent evidence for and against the perioperative use of beta-blockers as guidance for interventionalists and hospitalists.

## POTENTIAL CARDIOPROTECTIVE EFFECTS OF BETA-BLOCKERS

Myocardial infarction and unstable angina are the leading cardiovascular causes of death after surgery.<sup>5</sup> These events are multifactorial. Some are caused by the stress of surgery, which precipitates physiologic changes related to in-

**Beta-blockers do several things that may be beneficial in the perioperative setting**

flammatory mediators, sympathetic tone, and oxygen supply and demand; others are caused by acute plaque rupture, thrombosis, and occlusion.<sup>6</sup> Most perioperative infarcts are non-Q-wave events<sup>7</sup> and occur within the first 2 days after the procedure, when the effects of anesthetics, pain, fluid shifts, and physiologic changes are greatest. Because multiple causes may contribute to perioperative myocardial infarction, a single preventive strategy may not be sufficient.<sup>8,9</sup>

Beta-blockers do several things that may be beneficial in the perioperative setting. They reduce myocardial oxygen demand by decreasing the force of contraction and by slowing the heart rate, and slowing the heart rate increases diastolic perfusion time.<sup>10</sup> They suppress arrhythmias; they limit leukocyte recruitment, the production of free radicals, metalloproteinase activity, monocyte activation, release of growth factors, and inflammatory cytokine response; and they stabilize plaque.<sup>11</sup> Their long-term use may also alter intracellular signaling processes, thus improving cell survival by decreasing the expression of receptors for substances that induce apoptosis.<sup>12</sup>

## ■ INITIAL POSITIVE TRIALS

Mangano et al<sup>13</sup> began the beta-blocker trend in 1996 with a study in 200 patients known to have coronary artery disease or risk factors for it who were undergoing noncardiac surgery. Patients were randomized to receive either atenolol orally and intravenously, titrated to control the heart rate, or placebo in the immediate perioperative period.

The atenolol group had less perioperative ischemia but no difference in short-term rates of myocardial infarction and death. However, the death rate was lower in the atenolol group at 6 months after discharge and at 2 years, although patients who died in the immediate postoperative period were excluded from the analysis.

Although this finding did not appear to make sense physiologically, we now know that patients may experience myocardial injury without infarction after noncardiac surgery, a phenomenon associated with an increased risk of death in the short term and the long term.<sup>14</sup> Preventing these episodes may be the explanation for the improved outcome.

The DECREASE trial<sup>15</sup> (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) provided additional support for beta-blocker use. The patients were at high risk, had abnormal dobutamine stress echocardiograms, and were undergoing vascular surgery; 112 patients were randomized to receive either oral bisoprolol (started 1 month before surgery, titrated to control the heart rate, and continued for 1 month after surgery) or placebo.

The study was stopped early because the bisoprolol group reportedly had a 90% lower rate of myocardial infarction and cardiac death 1 month after surgery. However, the study was criticized because the total number of patients enrolled was small and the benefit was much greater than usual for any pharmacologic intervention, thus calling the results into question.

In a follow-up study,<sup>16</sup> survivors continued to be followed while receiving bisoprolol or usual care. The incidence of myocardial infarction or cardiac death at 2 years was significantly lower in the group receiving bisoprolol (12% vs 32%, odds ratio [OR] 0.30,  $P = .025$ ).

Boersma et al,<sup>17</sup> in an observational study, analyzed data from all 1,351 patients scheduled for major vascular surgery being considered for enrollment in the DECREASE trial. The DECREASE protocol required patients to undergo dobutamine stress echocardiography if they had one or more risk factors (age 70 or older, angina, prior myocardial infarction, congestive heart failure, treatment for ventricular arrhythmia, treatment for diabetes mellitus, or limited exercise capacity) or if their physician requested it. Twenty-seven percent received beta-blockers.

In multivariate analysis, clinical predictors of adverse outcome were age 70 or older; current or prior history of angina; and prior myocardial infarction, heart failure, or cerebrovascular accident.

In patients who had fewer than three clinical risk factors, beta-blocker use was associated with a lower rate of complications (0.8% vs 2.3%). Dobutamine stress echocardiography had minimal predictive value in this lower-risk group, suggesting that stress testing may not be necessary in this group if beta-blockers are used appropriately. However, in patients

who had three or more risk factors, this test did provide additional prognostic information; those without stress-induced ischemia had lower event rates than those with ischemia, and beta-blocker use further reduced those rates, except in patients with extensive ischemia (more than five left ventricular segments involved).

**The Revised Cardiac Risk Index.** Lee et al<sup>18</sup> devised an index to assist in preoperative cardiac risk stratification that was subsequently incorporated into the 2007 American College of Cardiology/American Heart Association preoperative risk guidelines. (It does not, however, address the beta-blocker issue.) It consists of six independent risk-predictors of major cardiac complications derived from 4,315 patients over age 50 undergoing non-cardiac surgery. The risk factors, each of which is given 1 point, are:

- Congestive heart failure based on history or examination
- Renal insufficiency (serum creatinine level > 2 mg/dL)
- Myocardial infarction, symptomatic ischemic heart disease, or a positive stress test
- History of transient ischemic attack or stroke
- Diabetes requiring insulin
- High-risk surgery (defined as intrathoracic, intra-abdominal, or suprainguinal vascular surgery).

Patients with 3 or more points are considered to be at high risk, and those with 1 or 2 points are considered to be at intermediate risk. The American College of Cardiology/American Heart Association preoperative cardiac risk algorithm subsequently included five of these six risk factors (the type of surgery was considered separately) and made recommendations concerning noninvasive stress testing and heart rate control.

On the basis of these studies, specialty societies, guideline committees, and hospitals enthusiastically recommended the prophylactic use of beta-blockers to decrease postoperative cardiac complications.

### ■ THREE NEGATIVE TRIALS OF METOPROLOL

In 2005 and 2006, two studies in vascular surgery patients and another in patients with diabetes cast doubt on the role of beta-blockers

when the results failed to show a benefit. The trials used metoprolol, started shortly before surgery, and with no titration to control the heart rate.

**The MaVS study<sup>19</sup>** (Metoprolol After Vascular Surgery) randomized 496 patients to receive metoprolol or placebo 2 hours before surgery and until hospital discharge or a maximum of 5 days after surgery. The metoprolol dose varied by weight: patients weighing 75 kg or more got 100 mg, those weighing between 40 and 75 kg got 50 mg, and those weighing less than 40 kg got 25 mg. Overall effects at 6 months were not significantly different, but intraoperative bradycardia and hypotension requiring intervention were more frequent in the metoprolol group.

**The POBBLE study<sup>20</sup>** (Perioperative Beta Blockade) randomized 103 patients who had no history of myocardial infarction to receive either metoprolol 50 mg twice daily or placebo from admission to 7 days after surgery. Myocardial ischemia was present in one-third of the patients after surgery. Metoprolol did not reduce the 30-day cardiac mortality rate, but it was associated with a shorter length of stay.

**The DIPOM trial<sup>21</sup>** (Diabetic Postoperative Mortality and Morbidity) randomized 921 diabetic patients to receive long-acting metoprolol succinate controlled-release/extended release (CR/XL) or placebo. Patients in the metoprolol group received a test dose of 50 mg the evening before surgery, another dose 2 hours before surgery (100 mg if the heart rate was more than 65 bpm, or 50 mg if between 55 and 65 bpm), and daily thereafter until discharge or a maximum of 8 days. The dose was not titrated to heart-rate control.

Metoprolol had no statistically significant effect on the composite primary outcome measures of time to death from any cause, acute myocardial infarction, unstable angina, or congestive heart failure or on the secondary outcome measures of time to death from any cause, death from a cardiac cause, and nonfatal cardiac morbidity.

### ■ ADDITIONAL POSITIVE STUDIES

Lindenauer et al<sup>22</sup> retrospectively evaluated the use of beta-blockers in the first 2 days after surgery in 782,969 patients undergoing non-cardiac surgery. Using propensity score match-

**After initial positive trials, prophylactic beta-blockers were recommended to decrease postoperative cardiac complications**

ing and Revised Cardiac Risk Index scores, they found a lower rate of postoperative mortality in patients with three or more risk factors who received a beta-blocker. There was no significant difference in the group with two risk factors, but in the lowest-risk group (with a score of 0 to 1), beta-blockers were not beneficial and may have been associated with harm as evidenced by a higher odds ratio for death, although this was probably artifactual and reflecting database limitations.

Feringa et al,<sup>23</sup> in an observational cohort study of 272 patients undergoing vascular surgery, reported that higher doses of beta-blockers and tight heart-rate control were associated with less perioperative myocardial ischemia, lower troponin T levels, and better long-term outcome.

### THE POISE TRIAL: MIXED RESULTS

The randomized POISE trial,<sup>1</sup> published in 2008, compared the effects of extended-release metoprolol succinate vs placebo on the 30-day risk of major cardiovascular events in 8,351 patients with or at risk of atherosclerotic disease who were undergoing noncardiac surgery. The metoprolol regimen was 100 mg 2 to 4 hours before surgery, another 100 mg by 6 hours after surgery, and then 200 mg 12 hours later and once daily for 30 days.

The incidence of the composite primary end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest at 30 days was lower in the metoprolol group than in the placebo group (5.8% vs 6.9%;  $P = .04$ ), primarily because of fewer nonfatal myocardial infarctions. However, more patients in the metoprolol group died of any cause (3.1% vs 2.3%  $P = .03$ ) or had a stroke (1.0% vs 0.5%  $P = .005$ ) than in the placebo group.

The metoprolol group had a higher incidence of clinically significant hypotension, bradycardia, and stroke, which could account for much of the increase in the mortality rate. Sepsis was the major cause of death in this group; hypotension may have increased the risk of infection, and beta-blockers may have potentiated hypotension in patients who were already septic. Also, the bradycardic and negative inotropic effects of the beta-blocker could have masked the physiologic response to systemic infection, thereby delaying recog-

nition and treatment or impeding the normal immune response.

One of the major criticisms of the POISE trial was its aggressive dosing regimen (200 to 400 mg within a 36-hour period) in patients who had not been on beta-blockers before then. Also, the drug was started only a few hours before surgery. In addition, these patients were at higher risk of death and stroke than those in other trials based on a high baseline rate of cerebrovascular disease, and inclusion of urgent and emergency surgical procedures.

### STUDIES SINCE POISE

The POISE trial results<sup>1</sup> prompted further questioning of the prophylactic perioperative use of beta-blockers. However, proponents of beta-blockers voiced serious criticisms of the trial, particularly the dosing regimen, and continued to believe that these drugs were beneficial if used appropriately.

**The DECREASE IV trial.** Dunkelgrun et al,<sup>24</sup> in a study using bisoprolol started approximately 1 month before surgery and titrated to control the heart rate, reported beneficial results in intermediate-risk patients. In their randomized open-label study with a  $2 \times 2$  factorial design, 1,066 patients at intermediate cardiac risk were assigned to receive bisoprolol, fluvastatin, combination treatment, or control therapy at least 34 days before surgery. Bisoprolol was started at 2.5 mg orally daily and slowly titrated up to a maximum dose of 10 mg to keep the heart rate between 50 and 70 beats per minute. The group of 533 patients randomized to receive bisoprolol had a lower incidence rate of cardiac death and nonfatal myocardial infarction than the control group (2.1% vs 6.0%, HR 0.34,  $P = .002$ ). A potential limitation of this study was its open-label design, which might have led to treatment bias.

**Updated guidelines.** Based on the results from POISE and DECREASE IV, the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines<sup>25</sup> published a focused update on beta-blockers in 2009 as an amendment to their 2007 guidelines on perioperative evaluation and care for noncardiac surgery. The European Society of Cardiology<sup>26</sup> released similar but somewhat more liberal guidelines (TABLE 1).

**POISE:**  
More patients  
on metoprolol  
died or had  
strokes than  
in the placebo  
group

TABLE 1

## Perioperative beta-blockade guidelines

Class of recommendation	2009 American College of Cardiology/ American Heart Association <sup>25</sup>	2010 European Society of Cardiology <sup>26</sup>
<b>Class I (treatment should be given)</b>	Beta-blockers should be continued if the patient is already receiving a beta-blocker (level of evidence C) <sup>a</sup>	Beta-blockers are recommended for those with known ischemic heart disease or ischemia on preoperative stress testing (level of evidence B)  Recommended for high-risk surgery (level of evidence B)  Continuation recommended if previously treated with beta-blockers for ischemic heart disease, arrhythmias, or hypertension (level of evidence C)
<b>Class IIa (treatment is reasonable)</b>	Beta-blockers titrated to heart rate and blood pressure are: Probably recommended for vascular surgery plus known coronary artery disease or ischemia on preoperative stress testing (level of evidence B) Reasonable for vascular surgery plus more than 1 clinical risk factor (level of evidence C) Reasonable for intermediate-risk surgery plus coronary artery disease or more than 1 clinical risk factor (level of evidence C)	Should be considered in intermediate-risk surgery  Consider continuation if previously treated with beta-blocker for congestive heart failure with systolic dysfunction (level of evidence C)
<b>Class IIb (treatment may be considered)</b>	Usefulness of beta-blockers is uncertain for patients undergoing: Intermediate-risk or vascular surgery with 1 clinical risk factor in the absence of coronary artery disease (level of evidence C) Vascular surgery with no clinical risk factors (level of evidence B)	Beta-blockers may be considered: low-risk surgery + risk factors
<b>Class III (treatment should not be given)</b>	Beta-blockers should not be given to patients with absolute contraindications to them (level of evidence C)  Routinely giving high-dose beta-blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta-blockers who are undergoing noncardiac surgery (level of evidence B)	Perioperative high-dose beta-blockers without titration are not recommended (level of evidence A)  Beta-blockers are not recommended in low-risk surgery without risk factors (level of evidence B)

<sup>a</sup> Levels of evidence: A = multiple populations evaluated, data derived from multiple randomized clinical trials or meta-analyses; B = limited populations evaluated, data derived from a single randomized trial or nonrandomized studies; C = very limited populations evaluated, only consensus opinion of experts, case studies, or standard of care

London et al,<sup>27</sup> in an observational study published in 2013, found a lower 30-day overall mortality rate with beta-blockers (relative risk [RR] 0.73, 95% confidence interval [CI] 0.65–0.83,  $P < .001$ , number needed to treat [NNT] 241), as well as a lower rate of cardiac morbidity (nonfatal myocardial infarction

and cardiac death), but only in nonvascular surgery patients who were on beta-blockers within 7 days of scheduled surgery. Moreover, similar to the findings of Lindenauer et al,<sup>22</sup> only patients with a Revised Cardiac Risk Index score of 2 or more benefited from beta-blocker use in terms of a lower risk of death,



TABLE 2

Beta-blocker meta-analyses before and after the POISE trial

Study (year)	No. of trials	No. of patients	Relative risk in beta-blocker groups				
			Ischemia	Periop- erative MI	Overall mortality	Periop- erative stroke	Composite (MI/death)
Before POISE							
Devereaux et al, <sup>43</sup> 2005	22	2,437		0.38	0.56	4.8	0.44 <sup>a</sup>
McGory et al, <sup>44</sup> 2005	6	632	0.47 <sup>a</sup>	0.14 <sup>a</sup>	0.52		
Schouten et al, <sup>45</sup> 2006	15	1,077	0.35 <sup>a</sup>	0.44 <sup>a</sup>	1.2		0.33 <sup>a</sup>
Wiesbauer et al, <sup>46</sup> 2007	24	3,567	0.38 <sup>a</sup>	0.59	0.78		
After POISE							
Bangalore et al, <sup>47</sup> 2008	33	12,306	0.36 <sup>a</sup>	0.65 <sup>a</sup>	1.20	2.16 <sup>a</sup>	
Bouri et al, <sup>29</sup> 2014	9 ("secure") <sup>b</sup> 2 (DECREASE)	10,529 1,178	NR	0.73 <sup>a</sup> 0.21 <sup>a</sup>	1.27 <sup>a</sup> 0.42 <sup>a</sup>	1.73 <sup>a</sup> 1.33	
Guay et al, <sup>30</sup> 2013	14 <sup>c</sup>	11,738	NR	0.65 <sup>a</sup>	0.91	2.18 <sup>a</sup>	
Dai et al, <sup>31</sup> 2014	8	11,180	NR	0.73 <sup>a</sup>	0.91	2.17 <sup>a</sup>	
Summary			Beneficial	Beneficial	No effect	Potentially harmful <sup>d</sup>	

<sup>a</sup>Statistically significant

<sup>b</sup>Not including the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) trials,<sup>15,16</sup> which have been discredited

<sup>c</sup>Noncardiac surgical trials only

<sup>d</sup>Including the POISE trial

MI = myocardial infarction; POISE = Perioperative Ischemic Evaluation trial<sup>1</sup>

whereas the lower-risk patients did not:

- Risk score of 0 or 1—no association
- Score of 2—RR 0.63, 95% CI 0.50–0.80,  $P < .001$ , NNT 105
- Score of 3—RR 0.54, 95% CI 0.39–0.73,  $P < .001$ , NNT 41
- Score of 4 or more—RR 0.40, 95% CI 0.24–0.73,  $P < .001$ , NNT 18).

Beta-blocker exposure was associated with a significantly lower rate of cardiac complications (RR 0.67, 95% CI 0.57–0.79,  $P < .001$ , NNT 339), also limited to nonvascular surgery patients with a risk score of 2 or 3.

**The Danish Nationwide Cohort Study**<sup>28</sup> examined the effect of beta-blockers on major adverse cardiac events (MACE, ie, myocardial infarction, cerebrovascular accident, and death) in 28,263 patients with ischemic heart

disease undergoing noncardiac surgery; 7,990 with heart failure and 20,273 without. Beta-blockers were used in 53% of patients with heart failure and 36% of those without heart failure. Outcomes for all of the beta-blocker recipients:

- MACE—HR 0.90, 95% CI 0.79–1.02
- All-cause mortality—HR 0.95, 95% CI 0.85–1.06.

Outcomes for patients with heart failure if they received beta-blockers:

- MACE—HR 0.75, 95% CI 0.70–0.87
- All-cause mortality—HR 0.80, 95% CI 0.70–0.92.

There was no significant benefit from beta-blockers in patients without heart failure. Outcomes for those patients if they received beta-blockers:

- MACE—HR 1.11, 95% CI 0.92–1.33
- All-cause mortality—HR 1.15, 95% CI 0.98–1.35.

However, in patients without heart failure but with a history of myocardial infarction within the past 2 years, beta-blockers were associated with a lower risk of MACE and all-cause mortality. In patients with neither heart failure nor a recent myocardial infarction, beta-blockers were associated with an increased risk of MACE and all-cause mortality.

This difference in efficacy depending on the presence and timing of a prior myocardial infarction is consistent with the 2012 American College of Cardiology/American Heart Association guidelines for secondary prevention, in which beta-blockers are given a class I recommendation only for patients with a myocardial infarction within the past 3 years.

### Meta-analyses and outcomes

A number of meta-analyses have been published over the past 10 years, with conflicting results (TABLE 2). The divergent findings are primarily due to the different studies included in the analyses as well as the strong influence of the POISE trial.<sup>1</sup> The studies varied in terms of the specific beta-blocker used, dose titration and heart rate control, time of initiation of beta-blocker use before surgery, type of surgery, patient characteristics, comorbidities, biomarkers and diagnosis of myocardial infarction, and clinical end points.

In general, these meta-analyses have found that prophylactic perioperative use of beta-blockers decreases ischemia and tends to reduce the risk of nonfatal myocardial infarction. They vary on whether the overall mortality risk is decreased. The meta-analyses that included POISE<sup>1</sup> found an increased incidence of stroke, whereas those that excluded POISE found no significant difference, although there appeared to be slightly more strokes in the beta-blocker groups.

The beta-blocker controversy increased even further when Dr. Don Poldermans was fired by Erasmus Medical Center in November 2011 for violations of academic integrity involving his research, including the DECREASE trials. The most recent meta-analysis, by Bouri et al,<sup>29</sup> included nine “secure trials” and excluded the DECREASE trials in

view of the controversy about their authenticity. The analysis showed an increase in overall mortality as well as stroke, primarily because it was heavily influenced by POISE.<sup>1</sup> In contrast, the DECREASE trials had reported a decreased risk of myocardial infarction and death, with no significant increase in stroke. The authors concluded that guideline bodies should “retract their recommendations based on the fictitious data without further delay.”<sup>29</sup>

Although the design of the DECREASE trials (in which beta-blockers were started well in advance of surgery and doses were titrated to achieve heart rate control) is physiologically more compelling than those of the negative trials, the results have been questioned in light of the integrity issue. However, to date, none of the published DECREASE trials have been retracted.

Two other meta-analyses,<sup>30,31</sup> published in 2013, also found a decreased risk of myocardial infarction and increased risk of stroke but no significant difference in short-term all-cause mortality.

### ■ ARE ALL BETA-BLOCKERS EQUIVALENT?

In various studies evaluating specific beta-blockers, the more cardioselective agents bisoprolol and atenolol were associated with better outcomes than metoprolol. The affinity ratios for beta-1/beta-2 receptors range from 13.5 for bisoprolol to 4.7 for atenolol and 2.3 for metoprolol.<sup>32</sup> Blocking beta-1 receptors blunts tachycardia, whereas blocking beta-2 receptors may block systemic or cerebral vasodilation.

In patients with anemia, beta-blockade in general may be harmful, but beta-2 blockade may be even worse. Beta-blockers were associated with an increased risk of MACE (6.5% vs 3.0%)<sup>33</sup> in patients with acute surgical anemia if the hemoglobin concentration decreased to less than 35% of baseline, and increased risks of hospital death (OR 6.65) and multiorgan dysfunction syndrome (OR 4.18) with severe bleeding during aortic surgery.<sup>34</sup>

In addition, the pathway by which the beta-blocker is metabolized may also affect outcome, with less benefit from beta-blockers metabolized by the CYP2D6 isoenzyme of the cytochrome P450 system. Individual variations in CYP2D6 activity related to genetics or drug interactions may result in insufficient or exces-

**To date,  
none of the  
DECREASE trials  
have been  
retracted**

TABLE 3

## Specific beta-blockers and rates of adverse perioperative outcomes

Study	Outcome	Atenolol	Bisoprolol	Metoprolol	No beta-blocker
Redelmeier et al, <sup>36</sup> 2005	Myocardial infarction or death	2.5%		3.2%	
Wallace et al, <sup>37</sup> 2011	30-day mortality 1-year mortality	1% 7%		3% 13%	
Ashes et al, <sup>39</sup> 2013	Stroke, myocardial infarction, or death	4.0%	6.2%	11.9%	2.2%
Dai et al, <sup>31</sup> 2014 (meta-analysis)	Mortality	Lowest	Intermediate <sup>a</sup>	Highest <sup>b</sup>	
London et al, <sup>27</sup> 2013	Mortality	0.6%		1.1%	1.5%

<sup>a</sup> Odds ratio 1.42 (95% confidence interval 0.27–7.48) compared with atenolol

<sup>b</sup> Odds ratio 2.66 (95% confidence interval 1.20–5.89) compared with atenolol

In patients with anemia, beta-blockade in general may be harmful, but beta-2 blockade may be even worse

sive beta-blockade. Because metoprolol is the most dependent on this system, patients using it may be more susceptible to bradycardia.<sup>35</sup>

Studies comparing atenolol and metoprolol found that the atenolol groups had fewer myocardial infarctions and deaths<sup>36</sup> and lower 30-day and 1-year mortality rates<sup>37</sup> than the groups on metoprolol. Studies comparing the three beta-blockers found better outcomes with atenolol and bisoprolol than with metoprolol—fewer strokes,<sup>38,39</sup> a lower mortality rate,<sup>31</sup> and a better composite outcome<sup>39</sup> (TABLE 3 and TABLE 4).

#### ■ START THE BETA-BLOCKER EARLY, TITRATE TO CONTROL THE HEART RATE

A number of studies suggest that how long the beta-blocker is given before surgery may influence the outcome (TABLE 5). The best results were achieved when beta-blockers were started approximately 1 month before surgery and titrated to control the heart rate.

Because this long lead-in time is not always practical, it is important to determine the shortest time before surgery in which starting beta-blockers may be beneficial and yet safe. Some evidence suggests that results are better when the beta-blocker is started more than 1 week preoperatively compared with less than 1 week, but it is unknown what the minimum or optimal time period should be.

If a beta-blocker is started well in advance of the scheduled surgery, there is adequate time for dose titration and tighter heart rate control. Most of the studies demonstrating beneficial effects of perioperative beta-blockers used dose titration and achieved lower heart rates in the treatment group than in the control group. A criticism of the MaVs,<sup>19</sup> POBBLE,<sup>20</sup> and DIPOM<sup>21</sup> trials was that the patients did not receive adequate beta-blockade. The POISE trial<sup>1</sup> used a much higher dose of metoprolol in an attempt to assure beta-blockade without dose titration, and although the regimen decreased nonfatal myocardial infarctions, it increased strokes and the overall mortality rate, probably related to excess bradycardia and hypotension. The target heart rate should probably be between 55 and 70 beats per minute.

#### ■ RISK OF STROKE

POISE<sup>1</sup> was the first trial to note a clinically and statistically significant increase in strokes with perioperative beta-blocker use. Although no other study has shown a similar increased risk, almost all reported a higher number of strokes in the beta-blocker groups, although the absolute numbers and differences were small and not statistically significant. This risk may also vary from one beta-blocker to another (TABLE 4).



TABLE 4

**Beta-blockers and incidence of perioperative stroke**

Study	Beta-blocker	Titrated to heart rate?	Started < 7 days before surgery?	Stroke rate (%)	
				Beta-blocker group	Placebo group
Mangano et al, <sup>13</sup> 1996	Atenolol	Yes	Yes	4%	1%
Brady et al, <sup>20</sup> 2005	Metoprolol	No	Yes	3.8%	0%
Yang et al, <sup>19</sup> 2006	Metoprolol	No	Yes	2.0%	1.6%
Juul et al, <sup>21</sup> 2006	Metoprolol	No	Yes	0.4%	0%
POISE, <sup>1</sup> 2008	Metoprolol	No <sup>a</sup>	Yes	1%	0.5%
van Lier et al, <sup>42</sup> 2010 <sup>b</sup>	Bisoprolol	Yes	No	0.5%	0.4%
London et al, <sup>27</sup> 2013	All beta-blockers			0.40%	0.3%
	Metoprolol			0.40%	
	Atenolol			0.23%	
Andersson et al, <sup>28</sup> 2013	Not specified			0.12%	0.2%
Mashour et al, <sup>38</sup> 2013	Metoprolol			0.34% <sup>c</sup>	0.1%
	Atenolol			0.07%	
	Bisoprolol			0%	
Ashes et al, <sup>39</sup> 2013	Metoprolol			0.62%	0.1%
	Atenolol			0.35%	
	Bisoprolol			0.16%	

<sup>a</sup> High dose used<sup>b</sup> Data from the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) I, II, and IV trials from 1999–2009<sup>c</sup> Odds ratio 4.2 for all perioperative strokes, 3.3 for intraoperative strokes

The usual incidence rate of postoperative stroke after noncardiac, noncarotid surgery is well under 1% in patients with no prior history of stroke but increases to approximately 3% in patients with a previous stroke.<sup>40</sup> An observational study from the Dutch group reported a very low incidence of stroke overall (0.02%) in 186,779 patients undergoing noncardiac surgery with no significant difference in those on chronic beta-blocker therapy.<sup>41</sup> The DECREASE trials, with a total of 3,884 patients, also found no statistically significant increase in stroke with beta-blocker use (0.46% overall vs 0.5% with a beta-blocker),<sup>42</sup> which in this case was bisoprolol started well in advance of surgery and titrated to control the heart rate. Although the DECREASE data are under sus-

picion, they seem reasonable and consistent with those of observational studies.

Proposed mechanisms by which beta-blockers may increase stroke risk include the side effects of hypotension and bradycardia, particularly in the setting of anemia. They may also cause cerebral ischemia by blocking cerebral vasodilation. This effect on cerebral blood flow may be more pronounced with the less cardioselective beta-blockers, which may explain the apparent increased stroke risk associated with metoprolol.

## ■ WHAT SHOULD WE DO NOW?

The evidence for the safety and efficacy of beta-blockers in the perioperative setting continues to evolve, and new clinical trials

**New trials are needed to resolve the controversy, particularly regarding the risk of stroke**

TABLE 5

Timing of beta-blocker initiation before surgery and outcomes

Study	Outcome	Start of beta-blocker before surgery			No beta-blocker
		< 1 week	1–4 weeks	> 4 weeks	
Mangano et al, <sup>13</sup> 1996	Myocardial infarction or death at 2 years	10%			21%
Poldermans et al, <sup>15</sup> 1999	Myocardial infarction or death at 28 days			3.4%	34%
Brady et al, <sup>20</sup> 2005	Cardiovascular events at 30 days Myocardial infarction, stroke, or death	32% 13%			34% 15%
Yang et al, <sup>19</sup> 2006	Cardiovascular events at 30 days	10.1%			12%
Juul et al, <sup>21</sup> 2006	Cardiovascular events in hospital	21%			20%
POISE, <sup>1</sup> 2008	Myocardial infarction Stroke Death	3.6% 1.0% 3.1%			5.1% 0.5% 2.3%
Dunkelgrun et al, <sup>24</sup> 2009	Myocardial infarction or death at 30 days			2.1%	6%
Flu et al, <sup>48</sup> 2010	Troponin elevation, stroke, death	27%	15%	16%	
London et al, <sup>27</sup> 2013	Death Myocardial infarction or cardiac arrest	1.3% 0.8%	1.2% 0.5%	1.0% 0.8%	2.3% 2.1%
Wijeyesundera et al, <sup>49</sup> 2014	Myocardial infarction Stroke Death (30 days) Death (1 year)	4.1% 0.7% 2.9% <sup>a</sup> 7.8%	2.8% 0.5% 1.6% 5.9%	3.3% 0.6% 1.8% 6.4%	
Dai et al, <sup>31</sup> 2014	Myocardial infarction Stroke Death	1.60 <sup>b</sup> 1.36 <sup>b</sup> 2.75 <sup>b</sup>			

<sup>a</sup> Statistically significant difference between < 1 week and > 4 weeks (odds ratio 1.49,  $P = .03$ )

<sup>b</sup> Relative risk comparing start of the beta-blocker < 1 week vs > 1 week before surgery

are needed to clarify the ongoing controversy, particularly regarding the risk of stroke.

If patients have other indications for beta-blocker therapy, such as history of heart failure, myocardial infarction in the past 3 years, or atrial fibrillation for rate control, they should be receiving them if time permits.

If prophylactic beta-blockers are to be effective in minimizing perioperative complications, it appears that they may need to be more cardioselective, started at least 1 week

before surgery, titrated to control heart rate, and used in high-risk patients (Revised Cardiac Risk Index score > 2 or 3) undergoing high-risk surgery.

Ideally, a large randomized controlled trial using a cardioselective beta-blocker started in advance of surgery in patients with a Revised Cardiac Risk Index score greater than 2, undergoing intermediate or high-risk procedures, is needed to fully answer the questions raised by the current data. ■

## REFERENCES

1. POISE Study Group; 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; 371:1839–1847.
2. Wijeyesundera DN, Mamdani M, Laupacis A, et al. Clinical evidence, practice guidelines, and  $\beta$ -blocker utilization before major noncardiac surgery. *Circ Cardiovasc Qual Outcomes* 2012; 5:558–565.
3. American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery); 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; Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative  $\beta$ -blocker therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update 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, and Society for Vascular Medicine and Biology. *J Am Coll Cardiol* 2006; 47:2343–2355.
4. Harte B, Jaffer AK. Perioperative  $\beta$ -blockers in noncardiac surgery: evolution of the evidence. *Cleve Clin J Med* 2008; 75:513–519.
5. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990; 72:153–184.
6. London MJ, Zaugg M, Schaub MC, Spahn DR. Perioperative  $\beta$ -adrenergic receptor blockade: physiologic foundations and clinical controversies. *Anesthesiology* 2004; 100:170–175.
7. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW. Myocardial infarction after noncardiac surgery. *Anesthesiology* 1998; 88:572–578.
8. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. *Br J Anaesth* 2004; 93:9–20.
9. Zaugg M, Schaub MC, Foëx P. Myocardial injury and its prevention in the perioperative setting. *Br J Anaesth* 2004; 93:21–33.
10. Zaugg M, Schaub MC, Pasch T, Spahn DR. Modulation of  $\beta$ -adrenergic receptor subtype activities in perioperative medicine: mechanisms and sites of action. *Br J Anaesth* 2002; 88:101–123.
11. Landesberg G. The pathophysiology of perioperative myocardial infarction: facts and perspectives. *J Cardiothorac Vasc Anesth* 2003; 17:90–100.
12. Yeager MP, Fillinger MP, Hettelman BD, Hartman GS. Perioperative  $\beta$ -blockade and late cardiac outcomes: a complementary hypothesis. *J Cardiothorac Vasc Anesth* 2005; 19:237–241.
13. 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; 335:1713–1720.
14. Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; 120:564–578.
15. 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; 341:1789–1794.
16. Poldermans D, Boersma E, Bax JJ, et al; Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. *Eur Heart J* 2001; 22:1353–1358.
17. Boersma E, Poldermans D, Bax JJ, et al; DECREASE Study Group (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography). Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and  $\beta$ -blocker therapy. *JAMA* 2001; 285:1865–1873.
18. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; 100:1043–1049.
19. 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; 152:983–990.
20. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR; POBBLE trial investigators. Perioperative  $\beta$ -blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg* 2005; 41:602–609.
21. Juul AB, Wetterslev J, Gluud C, et al; DIPOM Trial Group. Effect of perioperative  $\beta$ -blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *BMJ* 2006; 332:1482.
22. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative  $\beta$ -blocker therapy and mortality after major non-cardiac surgery. *N Engl J Med* 2005; 353:349–361.
23. Feringa HH, Bax JJ, Boersma E, et al. High-dose  $\beta$ -blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. *Circulation* 2006; 114(suppl 1):1344–1349.
24. Dunkelgrun M, Boersma E, Schouten O, et al; 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; 249:921–926.
25. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; 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; Society for Vascular Surgery; Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative  $\beta$ -blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol* 2009; 54:e13–e118.
26. Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery; European Society of Cardiology (ESC); Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J* 2009; 30:2769–2812.
27. London MJ, Hur K, Schwartz GG, Henderson WG. Association of perioperative  $\beta$ -blockade with mortality and cardiovascular morbidity following major noncardiac surgery. *JAMA* 2013; 309:1704–1713.
28. Andersson C, Mérie C, Jørgensen M, et al. Association of  $\beta$ -blocker therapy with risks of adverse cardiovascular events and deaths in patients with ischemic heart disease undergoing noncardiac surgery: a Danish nationwide cohort study. *JAMA Intern Med* 2014; 174:336–344.
29. Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of  $\beta$ -blockade to prevent perioperative death in non-cardiac surgery. *Heart* 2014; 100:456–464.
30. Guay J, Ochroch EA.  $\beta$ -blocking agents for surgery: influence on mortality and major outcomes. A meta-analysis. *J Cardiothorac Vasc Anesth* 2013; 27:834–844.
31. Dai N, Xu D, Zhang J, et al. Different  $\beta$ -blockers and initiation time in patients undergoing noncardiac surgery: a meta-analysis. *Am J Med Sci* 2014; 347:235–244.
32. Baker JG. The selectivity of  $\beta$ -adrenoceptor antagonists at the human  $\beta$ 1,  $\beta$ 2 and  $\beta$ 3 adrenoceptors. *Br J Pharmacol* 2005; 144:317–322.
33. 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.
34. 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; 117:1203–1211.
35. Badgett RG, Lawrence VA, Cohn SL. Variations in pharmacology of  $\beta$ -

- blockers may contribute to heterogeneous results in trials of perioperative beta-blockade. *Anesthesiology* 2010; 113:585–592.
36. **Redelmeier D, Scales D, Kopp A.** Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. *BMJ* 2005; 331:932.
  37. **Wallace AW, Au S, Cason BA.** Perioperative beta-blockade: atenolol is associated with reduced mortality when compared to metoprolol. *Anesthesiology* 2011; 114:824–836.
  38. **Mashour GA, Sharifpour M, Freundlich RE, et al.** Perioperative metoprolol and risk of stroke after noncardiac surgery. *Anesthesiology* 2013; 119:1340–1346.
  39. **Ashes C, Judelman S, Wijeyesundera DN, et al.** Selective beta1-antagonism with bisoprolol is associated with fewer postoperative strokes than atenolol or metoprolol: a single-center cohort study of 44,092 consecutive patients. *Anesthesiology* 2013; 119:777–787.
  40. **Selim M.** Perioperative stroke. *N Engl J Med* 2007; 356:706–713.
  41. **van Lier F, Schouten O, van Domburg RT, et al.** Effect of chronic beta-blocker use on stroke after noncardiac surgery. *Am J Cardiol* 2009; 104:429–433.
  42. **van Lier F, Schouten O, Hoeks SE, et al.** Impact of prophylactic beta-blocker therapy to prevent stroke after noncardiac surgery. *Am J Cardiol* 2010; 105:43–47.
  43. **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. *BMJ* 2005; 331:313–321.
  44. **McGory ML, Maggard MA, Ko CY.** A meta-analysis of perioperative beta blockade: what is the actual risk reduction? *Surgery* 2005; 138:171–179.
  45. **Schouten O, Shaw LJ, Boersma E, et al.** A meta-analysis of safety and effectiveness of perioperative beta-blocker use for the prevention of cardiac events in different types of noncardiac surgery. *Coron Artery Dis* 2006; 17:173–179.
  46. **Wiesbauer F, Schlager O, Domanovits H, et al.** Perioperative beta-blockers for preventing surgery-related mortality and morbidity: a systematic review and meta-analysis. *Anesth Analg* 2007; 104:27–41.
  47. **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; 372:1962–1976.
  48. **Flu WJ, van Kuijk JP, Chonchol M, et al.** Timing of pre-operative beta-blocker treatment in vascular surgery patients: influence on post-operative outcome. *J Am Coll Cardiol* 2010; 56:1922–1929.
  49. **Wijeyesundera DN, Beattie WS, Wijeyesundera HC, Yun L, Austin PC, Ko DT.** Duration of preoperative beta-blockade and outcomes after major elective noncardiac surgery. *Can J Cardiol* 2014; 30:217–223.

.....  
**ADDRESS:** Steven L. Cohn, MD, University of Miami Miller School of Medicine, 1120 NW 14th St., CRB-1140, Miami, FL 33136;  
 e-mail: [scohn@med.miami.edu](mailto:scohn@med.miami.edu)