Arch Neurosci. 2017 October; 4(4):e57718. doi: 10.5812/archneurosci.57718.

Published online 2017 October 25. **Review Article**

# Benefits and Harms of Beta Blockers in the Perioperative Period of Non-Cardiac Surgery: A Narrative Review

Alborz Sherafati,[1] and Reza Mollazadeh[2,*]

[1]Assistant Professor of Cardiology, Cardiology Department, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]Associate Professor of Cardiac Electrophysiology and Pacemaker, Cardiology Department, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

[*]*Corresponding author*: Reza Mollazadeh, Cardiology Department, Imam Khomeini Hospital, Keshavarz Blv., Tehran, Iran. Tel: +98-9127334136, Fax: +98-2166939537, E-mail: mollazar@yahoo.com

**Received** 2017 July 07; **Accepted** 2017 October 04.

**Abstract**

Several trials have evaluated the role of treatment with beta-blockers in patients undergoing non-cardiac surgery. Debates are when and which agent and dosage to initiate and when and how to continue or discontinue. In addition, effects on perioperative arrhythmia, myocardial infarction, stroke, and mortality were studied. Herein we have tried to review the most common guidelines and large trials on the aforementioned issues.

*Keywords:* Beta-Blocker, Non-Cardiac Surgery, Myocardial Infarction, Death

## 1. Introduction

Cardiovascular complications are one of the most common causes of mortality and disability after non-cardiac surgery. It is estimated that 0.5% of the patients undergoing these operations die of cardiovascular causes and another 2% suffer from other cardiovascular complications, including myocardial infarction (MI) (1). The rates are even higher in patients with known cardiac diseases or risk factors. In fact, the mortality rate due to cardiac causes is 2% - 3% and the rate of MI is 4% - 6% in this high-risk population (2).

Unstable atherosclerotic plaque rupture leading to thrombus formation and stress induced ischemia due to mismatch between the myocardial oxygen supply and demand during intubation or intraoperative tachycardia (due to hypotension or bleeding) are the main mechanisms of perioperative cardiac complications (1, 3).

Beta-blockers are a class of drugs with negative chronotropic properties, resulting in a lower myocardial oxygen demand. They also have antiarrhythmic and anti-inflammatory effects and can affect energy metabolism (1). Thus, considering the mechanisms of myocardial ischemia and the properties of beta-blockers, several studies have been performed to assess the probable beneficial effects of perioperative beta-blocker therapy in non-cardiac surgery.

Despite initial positive reports encouraging the use of beta-blockers, there are concerns about the risk of side effects like hypotension and stroke in more recent studies. Furthermore, various results do not strongly support the beneficial effects of beta-blockers on mortality (4). Therefore, there is no definite agreement about the timing of initiation of beta-blocker therapy and the populations that will benefit more. In this review, we will discuss the probable benefits and harms of perioperative beta-blocker therapy in patients undergoing non-cardiac surgery.

## 2. Chronic Consumption

A subgroup of patients consumes beta-blockers chronically due to non-surgical indications like hypertension, coronary artery disease, heart failure, and arrhythmia. The last guideline of the American college of cardiology/American heart association (ACC/AHA) (4) on perioperative evaluation and management of non-cardiac surgery and the guideline of the European society of cardiology (ESC) (5) on non-cardiac surgery, both published in 2014, indicate that beta blockers should be continued in the perioperative period in patients who use them chronically. This is the only class I recommendation in both guidelines.

The ACC/AHA's rationale for this recommendation is based on the evidence in non-surgical settings suggesting that interrupting long-term beta-blocker use is harmful (4). The ESC guideline specifies that if a beta-blocker is used for treatment of hypertension, it is not recommended

to switch the drug class because other antihypertensive drugs lack perioperative protective effects (5).

The 2017 canadian cardiovascular society (CCS) guideline (6) states that there is a chance of increase in mortality when chronic beta-blocker therapy is interrupted in the perioperative period and thus, it recommends continuation of beta-blockers in chronic consumers. However, the guideline suggests dose reduction or holding beta-blocker consumption if the systolic blood pressure is low before surgery (6).

## 3. Time of Initiation

The 2014 ACC/AHA guideline is clearly against initiation of beta-blockers on the surgery day (class III recommendation) (4). According to the perioperative ischemic evaluation (POISE) study (7), starting extended-release metoprolol succinate 2 - 4 hours prior to surgery leads to increased mortality (7). On the other hand, the guideline has a class IIb recommendation for initiating beta-blockers more than 1 day (2 - 7 days) before surgery to evaluate their safety and tolerance (4). The authors of the ESC guideline believe that beta-blockers should be initiated preferably more than one day before surgery. They suggest that beta-blockers should be started at least 1 week but not more than 30 days before surgery (5).

London et al. conducted a retrospective cohort to assess the initiation of beta-blockers on the day of or one day after non-cardiac surgery. The rate of 30-day mortality and Q-wave MI were lower in patients treated with beta-blockers if the revised cardiac risk index (RCRI) was equal or more than 2 and the patient had nonvascular surgery. No significant difference was observed in vascular surgery. The overall rate of stroke was higher in the beta-blocker group (8).

Other than the Dutch echocardiographic cardiac risk evaluation (DECREASE) (9) trial, beta-blockers were started within 24 hours of surgery in all other trials. In a post hoc analysis of these trials, despite a decrease in the risk of MI, the risk of death, stroke, hypotension, and bradycardia increased if beta-blockers were initiated within 24 hours before surgery (10). Based on this systematic review, the 2017 CCS guideline recommends against the initiation of beta-blockers in the last 24 hours before surgery. The guideline has no specific recommendation about when to start the drug (6).

In 2014, Wijeysundera et al. conducted a cohort study on old patients undergoing non-cardiac surgery. The time since preoperative beta-blocker initiation to surgery was classified as 1 - 7 days, 8 - 30 days, and 31 days or more. The 30-day mortality was significantly higher in the "1 - 7 day" group but did not differ between "8 - 30" and "31 or more" groups. The 30-day MI, 30-day ischemic stroke, and 1-year mortality were similar in the three groups (11).

## 4. Titration and Duration

The ESC guideline suggests low dose initiation of beta-blockers and slow up-titration to achieve a resting heart rate of 60 - 70 beats per minute before surgery. This guideline still has a class III recommendation against high fix regimens of beta-blockers without titration (5). Due to these recommendations, the guideline suggests initiation of beta-blockers at least 1 week up to 30 days before surgery (5).

The CCS guideline mentions that most patients are visited in preoperative clinics within days before surgery that makes beta-blocker titration a challenging task. It also warns that the tolerated beta-blocker dose before surgery is not necessarily safe because hypotension is common during or after surgery (6). The guideline has no specific recommendation about titration.

The POISE trial used a high fixed dose of long-acting metoprolol succinate, resulting in higher rates of mortality and stoke but lower rates of MI compared to the control group (7). In contrast, the DECREASE IV study used low-dose bisoprolol and titrated the dose to reach a resting heart rate of 60 - 70 beats per minute. The rates of cardiac deaths and MI were significantly lower in the bisoprolol group, but the rate of stroke did not differ significantly (9). However, other than titration versus fixed dose regimens, the type of beta-blocker and time of initiation (median time of initiation was 34 days before surgery in DECREASE IV) were different in these trials, all of which may affect the results.

There is no specific recommendation about the duration of beta-blocker consumption after surgery. The ACC/AHA guideline has a class IIa recommendation that decision on continuing beta blockers is made based on clinical circumstances (4). The ESC guideline mentions that randomized clinical trials (RCTs) are silent about the duration and suggest that because of the risk of delayed cardiac events, it is better to continue the beta blocker for several months. If the preoperative stress test is abnormal, long-term beta-blocker therapy is suggested (5).

## 5. Effect on Myocardial Infarction

The first trials did not show any association between beta-blockers and decreased MI. The perioperative beta blocker (POBBLE) trial was conducted in 2005 in patients undergoing infrarenal vascular surgery. Metoprolol 50 mg twice daily was given for up to 7 days after surgery. The 30-day cardiovascular events including unstable angina and

MI did not differ when compared to the control group (12). In 2006, the diabetes postoperative mortality and morbidity (DIPOM) trial was conducted. Extended released metoprolol at a dose of 100 mg was administrated from 1 day before surgery to 8 days after the operation in diabetic patients. Although the mean heart rate significantly decreased in metoprolol groups, no significant difference was detected in cardiac morbidities including unstable angina, MI, or heart failure in 18 months (13). The metoprolol after vascular surgery (MaVS) trial was the next study conducted in 2006. A fixed dose of metoprolol was initiated 2 hours before abdominal aortic surgery and continued for 5 days. There was no difference in the incidence of unstable angina, MI, and heart failure at 1 and 6 months (14). In the Swiss beta blocker in spinal anesthesia (BBSA) trial in 2007, a fixed dose of bisoprolol was administered at least 3 hours before surgery with spinal block that was continued for a mean of 5 days. The 1-year rates of unstable angina, MI, or heart failure were not significantly different despite a significant reduction in the mean heart rate (15).

In another study in 2008, Kaafarani et al. noted that although patients who received beta-blockers had lower perioperative heart rates, the rate of 30-day MI was higher in the beta-blocker group (16). On the other hand, in a meta-analysis published by Rajeev et al. in 2009, myocardial ischemia significantly reduced in patients receiving beta-blockers before surgery or postoperatively (17). In another meta-analysis published in 2009, Talati et al. showed that postoperative MI reduced if a beta-blocker was administered preoperatively (18). A meta-analysis by Bouri et al. in 2014 showed that perioperative beta-blocker administration was associated with a significant decrease in MI (19).

In 2014, a Danish nationwide cohort study was published, evaluating patients with known ischemic heart disease undergoing non-cardiac surgery. The risk of MI and major adverse cardiac events (MACE) significantly decreased in the beta-blocker group, only in patients with heart failure or recent MI (less than 2 years before surgery) (20). In a meta-analysis conducted by Wijeysundera in 2014, a moderate reduction was detected in the rate of MI (10). Blessberger et al. showed similar results in their systematic review (21). By contrast, Jorgensen et al. reported that beta-blocker administration was associated with a significant increase in the 30-day MACE, including MI, in hypertensive patients. Combination of beta-blockers with other antihypertensive drugs led to even a higher MACE rate, compared to a renin-angiotensin inhibitor plus thiazide diuretic (22).

## 6. Effect on Mortality

There was no significant difference in all-cause mortality in the beta-blocker group in POBBLE (12) and DIPOM trials. The PMaVS trial (14) and BBSA trial (15) evaluated 30-day and 1-year cardiac mortality, respectively, and found no significant difference. In the POISE trial, the composite endpoint of cardiovascular mortality, MI, and non-fatal arrest was lower in the metoprolol group, mainly due to a reduction in MI, but the rate of cardiovascular death was significantly higher in the metoprolol group (7). In contrast, the 30-day cardiac mortality rate decreased significantly in the bisoprolol group in the DECREASE IV trial (9).

In 2015, Friedell et al. proposed a 4-point calculator for prediction of mortality. The items were renal failure, diabetes mellitus, coronary artery disease, and surgery in a major body cavity. They found that beta-blockers significantly decreased the mortality rate in score 3 or 4, had no association in score 1 or 2, and increased the mortality rate in score 0. They concluded that beta-blockers were beneficial in high-risk patients but could be hazardous in low-risk patients (23).

## 7. Effect on Stroke

In POBBLE (12), BBSA (15), and DECREASE IV (9) trials, the rate of stroke was not different in the beta-blocker group. However, in the POISE trial, the rate of stroke increased significantly upon beta-blocker administration (7). In a review study by Talati, the odds of stroke increased significantly following the use of beta-blockers. The risk was higher in patients with a lower baseline risk of stroke (18).

In 2009, Van Lier et al. evaluated the risk of stroke in chronic (more than 1 month before surgery) beta-blocker users undergoing non-cardiac surgery. They found that the risk of perioperative stroke did not differ significantly in chronic users (24). In 2010, Van Lier et al. had a pooled analysis on DECREASE trials and found no association between bisoprolol and postoperative stroke. They noted that patients with a previous history of stroke were at higher risk, regardless of beta-blocker therapy (25).

## 8. Effect on Blood Pressure and Heart Rate

MaVS (14), Talati (18), Bouri (19), Wijeysundera (10), and Blessberger (21) trials showed that intraoperative hypotension and intraoperative bradycardia were significantly more frequent in the beta-blocker group. However, the DECREASE IV trial showed no difference in clinically significant hypotension and bradycardia (9).

Although Beattie et al. published a meta-analysis indicating that beta-blockers have a cardio protective effect in

non-cardiac surgery if the patient's maximum heart rate is below 100 beats per minute, and the largest beneficial effect of the reduced heart rate is decreased risk of perioperative MI, the ACC/AHA guideline mentions that the evidence supporting tight heart rate control is weak and therefore does not have any specific recommendations in this regard (4); hence, the consensus is that tight rate control raises concerns about increased risk of intraoperative hypotension and bradycardia.

## 9. Effect on Arrhythmia

In the POBBLE trial, beta-blockers had no effect on perioperative ventricular arrhythmia (12). Similar results were obtained in the MaVS trial, and it was added that beta-blockers also had no effect on atrial arrhythmia (14). No association was found between beta-blockers and ventricular arrhythmia in an analysis conducted by Blessberger, but the rate of supraventricular tachycardia (SVT) decreased significantly (21).

## 10. Type of Beta-Blocker

In 2015, Patorno et al. assessed the pattern of beta-blocker administration. They found that beta-blocker consumption was relatively high in patients undergoing vascular surgery as well as in patients with an RCRI more than or equal to 2. Metoprolol was the most common prescribed beta-blocker (55%), followed by atenolol (31%) and carvedilol (6%) (26).

In a retrospective cohort in 2013, London et al. compared metoprolol and atenolol. Metoprolol was more frequently prescribed but the mortality rate was significantly higher in the metoprolol group compared to the atenolol group. The rate of stroke was also significantly higher in the metoprolol group (8). In 2016, Cohn noted that more cardioselective beta-blockers (atenolol or bisoprolol) had more beneficial effects than metoprolol did, and metoprolol had no beneficial effects in diabetic patients and in vascular surgery (27).

In 2013, Ashes et al. conducted a study to compare bisoprolol with metoprolol and atenolol. Bisoprolol treatment was associated with a lower rate of perioperative stroke. It was mentioned that in animal studies, attenuation in beta-2 mediated vasodilation in cerebral vessels might be the mechanism of beta-blocker related stroke. In rat models, less beta-1 selective blockers like metoprolol could decrease the cerebral tissue oxygen content, which was not seen in highly selective beta-1 blockers like nebivolol (28).

Based on the above data, the ESC guideline has a class IIb recommendation that use of atenolol or bisoprolol is preferred over metoprolol or other beta-blockers if the beta-blocker is initiated before non-cardiac surgery (5). The ACC/AHA guideline has no specific recommendation about the type of the beta-blocker.

Some studies have evaluated the role of esmolol in non-cardiac surgery. It is noted that esmolol can reduce myocardial ischemia and arrhythmia in cardiac surgery (29). In 2011, Yu et al. assessed esmolol in non-cardiac surgery, and found a significant decrease in the rate of myocardial ischemia. No significant bradycardia occurred in the esmolol group. They also reported that hypotension was dose-dependent (uncommon in bolus doses less than 500 mcg/kg), and more common in bolus regimens than continuous infusion (30).

## 11. Guideline Recommendations on New Initiation of Beta-Blockers

Due to concerns about the risk of stroke, hypotension, and bradycardia, and also different and sometimes contradictory reports about the risk of all-cause and cardiovascular mortality, there is no class I or IIa recommendation for new initiation of beta-blockers in order to reduce the risk of myocardial injury in non-cardiac surgery in ACC/AHA and ESC guidelines. However, there is a class IIb recommendation, indicating that the supporting evidence is still weak.

In the 2014 ACC/AHA guideline, there are three class IIb recommendations on initiating beta-blockers (4): 1) patients with evidence of intermediate or high risk of myocardial ischemia on preoperative stress tests, 2) patients with RCRI equal to or more than three, and 3) patients with indication of long-term beta-blocker therapy who did not initiate treatment before.

The 2014 ESC guideline has two class IIb recommendations for initiating beta blockers (5): 1) patients with known ischemic heart disease or myocardial ischemia and, 2) patients undergoing high risk surgery who have at least two clinical risk factors or American Society of Anesthesiologists (ASA) status 3 or more. The ESC guideline also has a class III recommendation that beta-blockers should not be initiated in low-risk operations (5).

## 12. Conclusion

There are still unanswered questions about the role of beta-blockers in non-cardiac surgery. Most of the previous studies initiated beta-blockers on the day of surgery, and most of them used metoprolol. Highly selective beta-1 blockers may decrease the risk of stroke. Moreover, it is suggested that hypotension and bradycardia are dose-dependent. Furthermore, the duration of beta-blocker

therapy and the effect of beta-blockers on perioperative arrhythmia have not been completely evaluated in previous studies, warranting further research.

It cannot be denied that beta-blockers have some benefits in non-cardiac surgery, especially in patients with ischemic heart disease and clinical cardiac risk factors. However, definite indications for initiating beta-blockers in the perioperative period await the results of upcoming RCTs.

## References


1. Daumerie G, Fleisher LA. Perioperative beta-blocker and statin therapy. *Curr Opin Anaesthesiol.* 2008;**21**(1):60–5. doi: 10.1097/ACO.0b013e3282f35ea5. [PubMed: 18195612].
2. White CM, Talati R, Phung OJ, Baker WL, Reinhart K, Sedrakyan A, et al. Benefits and risks associated with beta-blocker prophylaxis in noncardiac surgery. *Am J Health Syst Pharm.* 2010;**67**(7):523–30. doi: 10.2146/ajhp090088. [PubMed: 20237379].
3. Devereaux PJ, Sessler DI. Cardiac Complications in Patients Undergoing Major Noncardiac Surgery. *N Engl J Med.* 2015;**373**(23):2258–69. doi: 10.1056/NEJMra1502824. [PubMed: 26630144].
4. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol.* 2014;**64**(22):77–137. doi: 10.1016/j.jacc.2014.07.944. [PubMed: 25091544].
5. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert SD, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2014;**35**(35):2383–431. doi: 10.1093/eurheartj/ehu282. [PubMed: 25086026].
6. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. *Can J Cardiol.* 2017;**33**(1):17–32. doi: 10.1016/j.cjca.2016.09.008. [PubMed: 27865641].
7. Poise Study Group , Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008;**371**(9627):1839–47. doi: 10.1016/S0140-6736(08)60601-7. [PubMed: 18479744].
8. 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**(16):1704–13. doi: 10.1001/jama.2013.4135. [PubMed: 23613075].
9. Dunkelgrun M, Boersma E, Schouten O, Koopman-van Gemert AW, van Poorten F, Bax JJ, et al. Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: a randomized controlled trial (DECREASE-IV). *Ann Surg.* 2009;**249**(6):921–6. doi: 10.1097/SLA.0b013e3181a77d00. [PubMed: 19474688].
10. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;**130**(24):2246–64. [PubMed: 25085964].
11. Wijeysundera DN, Beattie WS, Wijeysundera HC, Yun L, Austin PC, Ko DT. Duration of preoperative beta-blockade and outcomes after major elective noncardiac surgery. *Can J Cardiol.* 2014;**30**(2):217–23. doi: 10.1016/j.cjca.2013.10.011. [PubMed: 24373755].
12. 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**(4):602–9. doi: 10.1016/j.jvs.2005.01.048. [PubMed: 15874923].
13. Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *BMJ.* 2006;**332**(7556):1482. doi: 10.1136/bmj.332.7556.1482. [PubMed: 16793810].
14. 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**(5):983–90. doi: 10.1016/j.ahj.2006.07.024. [PubMed: 17070177].
15. Zaugg M, Bestmann L, Wacker J, Lucchinetti E, Boltres A, Schulz C, et al. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *Anesthesiology.* 2007;**107**(1):33–44. doi: 10.1097/01.anes.0000267530.62344.a4. [PubMed: 17585213].
16. Kaafarani HM, Atluri PV, Thornby J, Itani KM. Beta-Blockade in noncardiac surgery: outcome at all levels of cardiac risk. *Arch Surg.* 2008;**143**(10):940–4.
17. Rajeev S, Wong DT. Effect of beta-blockers on perioperative myocardial ischemia in patients undergoing noncardiac surgery. *Curr Drug Targets.* 2009;**10**(9):833–41. [PubMed: 19799537].
18. Talati R, Reinhart KM, White CM, Phung OJ, Sedrakyan A, Kluger J, et al. Outcomes of perioperative beta-blockade in patients undergoing noncardiac surgery: a meta-analysis. *Ann Pharmacother.* 2009;**43**(7):1181–8. doi: 10.1345/aph.1L706. [PubMed: 19531697].
19. 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**(6):456–64. doi: 10.1136/heartjnl-2013-304262. [PubMed: 23904357].
20. Andersson C, Merie C, Jorgensen M, Gislason GH, Torp-Pedersen C, Overgaard C, 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**(3):336–44. doi: 10.1001/jamainternmed.2013.11349. [PubMed: 24247428].
21. Blessberger H, Kammler J, Steinwender C. Perioperative use of beta-blockers in cardiac and noncardiac surgery. *JAMA.* 2015;**313**(20):2070–1. doi: 10.1001/jama.2015.1883. [PubMed: 26010637].
22. Jorgensen ME, Hlatky MA, Kober L, Sanders RD, Torp-Pedersen C, Gislason GH, et al. beta-Blocker-Associated Risks in Patients With Uncomplicated Hypertension Undergoing Noncardiac Surgery. *JAMA Intern Med.* 2015;**175**(12):1923–31. doi: 10.1001/jamainternmed.2015.5346. [PubMed: 26436291].
23. Friedell ML, Van Way C3, Freyberg RW, Almenoff PL. beta-Blockade and Operative Mortality in Noncardiac Surgery: Harmful or Helpful? *JAMA Surg.* 2015;**150**(7):658–63. doi: 10.1001/jamasurg.2015.86. [PubMed: 26017188].
24. van Lier F, Schouten O, van Domburg RT, van der Geest PJ, Boersma E, Fleisher LA, et al. Effect of chronic beta-blocker use on stroke after noncardiac surgery. *Am J Cardiol.* 2009;**104**(3):429–33. doi: 10.1016/j.amjcard.2009.03.062. [PubMed: 19616679].
25. van Lier F, Schouten O, Hoeks SE, van de Ven L, Stolker RJ, Bax JJ, et al. Impact of prophylactic beta-blocker therapy to prevent

stroke after noncardiac surgery. *Am J Cardiol.* 2010;**105**(1):43–7. doi: 10.1016/j.amjcard.2009.08.646. [PubMed: 20102888].

26. Patorno E, Wang SV, Schneeweiss S, Liu J, Bateman BT. Patterns of beta-blocker initiation in patients undergoing intermediate to high-risk noncardiac surgery. *Am Heart J.* 2015;**170**(4):812–820 e6. doi: 10.1016/j.ahj.2015.06.028. [PubMed: 26386806].
27. Cohn SL. Preoperative Evaluation for Noncardiac Surgery. *Ann Intern Med.* 2016;**165**(11):ITC81–96. doi: 10.7326/AITC201612060. [PubMed: 27919097].
28. Ashes C, Judelman S, Wijeysundera DN, Tait G, Mazer CD, Hare GM, 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**(4):777–87. doi: 10.1097/ALN.0b013e3182a17f12. [PubMed: 23820187].
29. Zangrillo A, Turi S, Crescenzi G, Oriani A, Distaso F, Monaco F, et al. Esmolol reduces perioperative ischemia in cardiac surgery: a meta-analysis of randomized controlled studies. *J Cardiothorac Vasc Anesth.* 2009;**23**(5):625–32. doi: 10.1053/j.jvca.2009.01.003. [PubMed: 19297196].
30. Yu SK, Tait G, Karkouti K, Wijeysundera D, McCluskey S, Beattie WS. The safety of perioperative esmolol: a systematic review and meta-analysis of randomized controlled trials. *Anesth Analg.* 2011;**112**(2):267–81. doi: 10.1213/ANE.0b013e3182025af7. [PubMed: 21127279].