# Perioperative β-blockers: To Use or Not to Use?

*London MJ, Hur K, Schwartz GG, Henderson WG. Association of perioperative β-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. JAMA 2013;309:1704–13.*

## Study Overview

Objective. To determine the association of perioperative β-blocker use with 30-day postoperative mortality and cardiovascular morbidity following major noncardiac surgery.

Design. Retrospective cohort study.

Setting and participants. 136745 veterans in 104 VA hospitals who had noncardiac surgical procedures in 7 surgical subspecialties (vascular, general, neurosurgery, orthopedics, thoracic, urology, and otolaryngology) between 1 October 2005 and 30 September 2010 were included in the cohort, which was obtained from the VA Surgical Quality Improvement Program database. This database was linked with inpatient and outpatient pharmacy records containing data on the use of β-blockers and other cardiovascular medications. Data from discharge and treatment codes from outpatient visits and inpatient medical admissions within a year prior to surgery were included to allow for additional risk variables, which were used for propensity score analysis. Patients who were not admitted on the day of surgery or were not hospitalized after the day of surgery and those who died on either of those days were excluded from the sample. Mean (SD) age of the cohort was 64.4 (10.2) years; 96.3% were male and 66.4% were white.

Main outcome measure. All-cause mortality at 30 days after surgery. The secondary outcome was a composite of Q-wave myocardial infarction or nonfatal cardiac arrest also assessed at 30 days after surgery. In addition, the incidence of new cerebrovascular accident was examined. Statistical analysis. A propensity score matched analysis was performed using the initial cohort. A propensity score was estimated using logistic regression model including covariates of age, race, sex, body mass index, preoperative risk by American Society of Anesthesiologists physical status classification, cardiac risk index variables which included chronic cardiac and non-cardiac comorbidities, laboratory measurements, surgical type and other characteristics and preoperative medications, and a dummy variable for geographical region of VA facility where the surgery was performed. One-to-one matching was conducted using a greedy matching algorithm with a 0.2 standard deviation caliper width of the log odds of the estimated propensity score. After matching, the McNemar test was used to compare the frequency of the primary and secondary outcomes between the matched groups; relative risks and number needed to treat were calculated using standard methods. Association of long term β-blocker use and acute (new) β-blocker use with outcomes was examined, so was the association between withdrawal of β-blocker with outcomes.

Main results. Within the cohort, 33.2% had an active outpatient prescription of β-blockers within 7 days of surgery, and 40.3% were exposed to β-blocker on postoperative day 0 or day 1. Patients who were exposed to β-blockers were older and had a higher burden of cardiovascular and related comorbidities. Inpatient β-blocker use was more common among patients who underwent vascular vs. nonvascular surgery; rate of use was also higher with increasing number of Revised Cardiac Risk Index variables. Metoprolol tartrate was the most commonly prescribed preoperative outpatient β-blocker followed by atenolol.

Propensity score matching yielded 37,805 pairs for the primary outcome measure and 37,662 pairs for secondary cardiac morbidity analysis. Rate of mortality among those exposed to β-blocker was lower than the non-exposed group with a relative risk (RR) of 0.73 (95% confidence interval [CI], 0.65–0.83, $P < 0.001$) and the number needed to treat (NNT) to prevent 1 death was 241 (95% CI, 173–397). When stratified by number of Revised Cardiac Risk Index variables, exposure to β-blocker did not have an association with mortality among those with none or 1 factor, but had reduced mortality among those with 2, 3, 4 or more factors (NNT, 105, 41, and 18, respectively). For thee secondary outcome of cardiac morbidity, β-blocker use was associated with a lower rate of cardiovascular events (RR = 0.67, 95% CI, 0.57–0.79, $P < 0.001$, NNT = 339, 95% CI, 240–582), and the association was only present among patients with 2 or 3 factors of the Cardiac Risk Index in the stratified analysis. In the matched analysis, stroke incidence did not differ between those who were exposed to those who were not (0.35% vs. 0.32%; $P = 0.45$). Institution of β-blocker within 30 days of surgery was associated with similar outcomes as those with longer term use, but the effect of institution within 7 days of surgery was not determined due to limited sample size. Withdrawal of β-blocker was associated with a twofold increased risk of the primary outcome.

Conclusions. Perioperative β-blocker exposure was associated with a lower rate of all-cause mortality and cardiac morbidity; and the effect differs by number of risk factors on the Revised Cardiac Risk Index but not by whether patients underwent vascular surgery or not.

## Commentary

London et al reported on the potential benefits of perioperative β-blocker use with mortality and cardiac morbidity among a veteran population that underwent noncardiac surgery, highlighting that patients with different numbers of risk factors on the Revised Cardiac Risk Index may derive more or less benefit from perioperative β-blocker use. The strength of this study lies in its large number of patients, based on a large veteran population, with the VA databases providing detailed and comprehensive data that allowed for including multiple pre and perioperative factors. Although this is an observational study with its inherent biases and limitations, the propensity score–matched analysis also strengthens the conclusions by balancing observed patient characteristics to approximate a clinical trial. In contrast with randomized controlled trials conducted on this very subject, this analysis allowed for observation of patient outcomes in clinical rather than trial settings, avoided potential issue of placebo effects, allowed for inclusion of patients otherwise excluded in clinical trials, and allowed the exploration of factors that may modify the effect of perioperative β-blockade. The study results argue for using the Revised Cardiac Risk Index to stratify patients for β-blocker use, suggesting that 2 or more risk factors would be the threshold for yielding mortality benefit with β-blocker use. However, these results must be considered in the context of previous high-quality studies including multiple randomized controlled trials that have been conducted.

Conflicting reports of benefits and harms have generated significant controversy over whether, how, and in whom to use β-blockers in noncardiac surgery. The largest trial, POISE, enrolled 8351 patients and randomly assigned patients undergoing noncardiac surgery to fixed-dose metoprolol or placebo in the perioperative period. This study found that β-blocker use led to a reduction in cardiovascular events and death but increased total mortality and incidence of stroke. Critics of the study note that the metoprolol dose was high and of fixed dose and the initiation of β-blocker was 2 to 4 hours prior to surgery rather than days before [1]. Other smaller randomized controlled trials using bisoprolol or atenolol demonstrated that cardiovascular or overall mortality is reduced when used in perioperative settings [2,3]. A meta-analysis of 33 randomized controlled trials, although with the majority of patients in the meta-analysis included from the POISE trial, found that β-blocker use was not associated with better total mortality or cardiovascular mortality outcomes but may have a decrease in the rate of myocardial infarction and

an increase in the rate of stroke [4]. Considering these data, the American College of Cardiology and American Heart Association have recommended that those who were on β-blockers before should continue its use as its withdrawal has been associated with worse outcomes, and perioperative β-blockade could be initiated among those with cardiovascular risk factors or those undergoing vascular surgery, but its initiation should be days to weeks before surgery and should be carefully titrated [5].

## Applications for Clinical Practice

How does the current study fit in? This study by itself, because of limitations due to study design, should not change practice, particularly in view of all of the high-quality studies that have previously been conducted. Also, because of the data source, the study results may not pertain to female patients and those who are non-veterans. However, this study does identify a group of patients that may potentially benefit from β-blocker use—those with 2 Revised Cardiac Risk Index factors, a group that may not have been the focus of prior clinical trials, thereby suggesting that a future trial be conducted focusing on this intermediate-risk group of patients. This study also confirmed that in clinical practice settings β-blockers should not be withdrawn in the perioperative period as this practice is associated with increased mortality.

*—William Hung, MD, MPH*

## References

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