Preoperative β-Blockade in Coronary Artery Bypass Grafting Surgery

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In the current issue, Brinkman and colleagues1 use the Society of Thoracic Surgeons National Database (STS-ND) to study the effect of preoperative β-blockade on postoperative coronary artery bypass grafting (CABG) outcomes. Their results show no mortality advantage and a paradoxically increased incidence of atrial fibrillation (AF) in patients receiving preoperative β-blockers, findings that challenge the continuation of this practice and its use as a quality metric. I will examine the rationale for preoperative β-blockade, controversies regarding its use in noncardiac surgery, the value of β-blockade in CABG, and reasonable clinical recommendations based on the preponderance of current evidence.

β-Blockade and Cardiovascular Disease

β-Blockers have diverse, beneficial effects for cardiovascular patients, including diminished sympathetic nervous system activity, antiarrhythmic properties, and decreased heart rate, systolic blood pressure, and myocardial contractility. They reduce myocardial oxygen consumption, myocardial ischemia, infarction, and death. β-Blockers may blunt the perioperative inflammatory response, and they increase the threshold for ischemia-induced ventricular arrhythmias. The American College of Cardiology/American Heart Association (ACC/AHA) classifies β-blockade as “recommended” (class I) or “reasonable” (class II) treatment for many cardiovascular conditions, including stable ischemic heart disease, unstable angina, ST elevation myocardial infarction (STEMI) in hemodynamically stable patients without other contraindications to β-blockade, non-STEMI, heart failure, secondary prevention, and risk reduction.

β-Blockade in Noncardiac Surgery

For noncardiac surgery, preoperative β-blockade, titrated to heart rate and blood pressure, remains an ACC/AHA class I recommendation for patients previously receiving these medications and a class II recommendation for patients with known coronary disease, inducible ischemia, or multiple cardiac risk factors who undergo higher-risk procedures. These recommendations for selective, judicious use of perioperative β-blockade were informed by the findings of the Perioperative Ischemic Evaluation (POISE) trial,2 which demonstrated increased mortality, stroke, hypotension, and bradycardia in patients given metoprolol succinate. However, the POISE trial used a fixed, relatively high-dose, long-acting metoprolol formulation, started shortly before surgery, which many argue is not consistent with optimal current practice. Additional concerns regarding β-blockade3 have recently been raised by the discovery of scientific misconduct in the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) studies, which provided much of the original evidence base for prophylactic β-blockade in noncardiac surgery.

β-Blockade in Cardiac Surgery

Perioperative β-blockade in cardiac surgery has been recommended to reduce postoperative AF and cardiovascular ischemic events. The former occurs more frequently after cardiac surgery (about 25% of patients undergoing isolated CABG) vs noncardiac surgery (typically <5%). The increased frequency in cardiac surgery results from sympathetic nervous system activation, cardiopulmonary bypass, topical and systemic cooling and rewarming, direct manipulation of the heart, and the use of arrhythmogenic drugs. When postoperative AF occurs, it increases the risk for stroke and other thromboembolic complications and may produce hemodynamic compromise. Atrial fibrillation substantially increases length of stay, costs, and readmission and decreases long-term survival.4

In contrast to the present report, almost 30 randomized studies demonstrate the value of perioperative β-blockade in reducing the incidence of AF after cardiac surgery.5-7 For example, the meta-analysis by Wiesbauer and colleagues6 found that postoperative ventricular tachycardia/fibrillation (odds ratio, 0.28 [95% CI, 0.13-0.57]) and AF (0.37 [0.28-0.48]) were significantly less frequent with β-blockers, although the timing of administration varied (preoperative, intraoperative, or postoperative). However, given the hypothesized protective mechanisms of β-blockade in CABG patients, it would seem prudent to initiate therapy before the stresses of anesthesia induction, sternotomy, cannulation, and cardiopulmonary bypass.

In CABG patients without contraindications, preoperative β-blockade (≥24 hours before operation) is an ACC/AHA class I recommendation to reduce postoperative AF; therapy with these agents should be continued postoperatively and, if possible, at discharge. Preoperative β-blockade is also a class II (reasonable) therapy to improve hospital survival in patients with an ejection fraction of more than 30%.

The Current Study—More Questions Than Answers

How can the findings of Brinkman and colleagues1 be reconciled with the extensive evidence supporting preoperative β-blockade in cardiac surgery?

First, short-term CABG mortality rates, which have decreased to about 1%, may no longer be a sufficiently sensitive outcome to assess the value of perioperative β-blockade. The effect of β-blockade on longer-term survival8 or a composite of nonfatal outcomes may provide additional insights. Of the 6 complications studied by Brinkman and colleagues,1 only stroke and AF are likely affected by β-blockade, at least in the...
short term. Other outcomes such as the need for postoperative inotropic support, perioperative myocardial infarction (MI) (detected by electrocardiography, measurement of cardiac enzyme levels, or imaging), cardiac arrest, arrhythmias requiring an implanted cardioverter defibrillator or pacemaker, prolonged intensive care unit stay, and overall length of stay may be useful in future studies.

Second, this study excluded 28.00% of patients with isolated CABG because of an MI within 21 days before surgery, thus eliminating patients with STEMI and non-STEMI. Many patients with recent infarcts or more active ischemia may derive substantial benefit from perioperative β-blockade (in the absence of hemodynamic instability).

Third, critical variables necessary to address the efficacy of perioperative β-blockade are not present in the STS-ND versions used in this study. Examples include the specific β-blocker used, whether the patient was receiving long-term β-blocker therapy, and the exact timing and protocol for β-blocker administration. Amiodarone hydrochloride use is another potential unmeasured confounder, because it is now used by some programs as their preferred prophylactic antiarrhythmic agent (although it lacks other desirable effects of β-blockers). Because amiodarone provides highly effective AF prophylaxis, this could explain the idiosyncratic findings of the present study (ie, lower AF incidence in the non-β-blocker group because some of these patients received amiodarone).

Fourth, substantial differences were noted in the baseline characteristics of the β-blocker and non–β-blocker groups (see Brinkman et al,1 Table 2), the former having higher prevalences of many risk factors (eg, diabetes mellitus, hypertension, dialysis, congestive heart failure, previous MI, unstable angina, recent AF, prior CABG or percutaneous coronary intervention, prior cardiovascular operations, and urgent vs elective surgery). The authors used 1:1 propensity matching to account for these differences, with the final matched samples (eTable in the Supplement by Brinkman et al) including virtually all the original non–β-blocker patients but only one-sixth of the original β-blocker group. The propensity-matched patients from the β-blocker and non–β-blocker groups had similar clinical characteristics and risk (eTable in the Supplement by Brinkman et al). However, compared with the much larger, original cohort of patients who received β-blockers (see Table 2 in Brinkman et al), the propensity-matched subset of β-blocker patients has lower prevalences of many important clinical comorbidities and thus lower surgical risk. They are not representative of the broader population of β-blocker patients, and this difference may affect the generalizability of the study’s findings.

Finally, pharmacogenetic variation may affect the efficacy of perioperative β-blockade. Isoenzyme CYP2D6 is involved in the hepatic elimination of lipophilic β-blockers (especially metoprolol), whereas hydrophilic β-blockers like atenolol and sotalol hydrochloride are excreted by the kidneys largely unchanged. Kertai and colleagues9 found that perioperative non–CYP2D6-dependent β-blocker use, but not CYP2D6–dependent β-blocker use, was associated with decreased operative mortality. Future studies must include the specific agent used.

Conclusions
The study by Brinkman and colleagues1 is an important and hypothesis-generating observational analysis. However, owing to the limitations discussed above, continued adherence to current ACC/AHA guidelines regarding perioperative β-blockade in CABG surgery, together with good medical judgment, is advisable. Important considerations include perioperative continuation of β-blockade in patients receiving long-term therapy and administration and titration of β-blockers to optimal heart rate and blood pressure in β-blocker-naïve patients, initiated as long before surgery as possible (preferably weeks before in elective patients). Additional randomized and observational studies, including new variables in STS-ND version 2.8, might shed further light on this issue.

ARTICLE INFORMATION
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