Beta-blockers and Non-cardiac Operations What will change after the POISE Study?

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In 2007 alone, there were as much as 3 million surgery admissions in Brazil. As the world population ages, elderly patients with multiple diseases, thus presenting greater risk, are being operated[1]. The occurrence of perioperative myocardial infarction (MI) prolongs hospital stay, increasing costs and mortality[2]. Therefore, strategies to reduce postoperative cardiac complications are called for.

Beta-blockers have been used in the past decade to provide cardiac perioperative protection has surged in the past decade. It is recommended to patients with coronary artery disease and high-risk patients, according to the American College of Physicians, and the I Guideline on Perioperative Evaluation of the Brazilian Cardiology Society (SBC)[3]. Nevertheless, for minor risk patients, this benefit is not yet defined. In May 2008, the POISE Study was published on *The Lancet,* suggesting that beta-blockers could be harmful in the perioperative period due to an increase of stroke in patients who received beta-blockers, although some of them have presented a decrease in the number of AMI[4]. This study were controversial among physicians, patients and journalists.

The mechanism through which the beta-blocker reduces cardiac events is not fully clarified. It is known that it improves the ratio between myocardial oxygen supply and consumption by decreasing the heart rate; prevents ischemia; increases filling of coronary arteries in the diastole; reduces the AMI area; stabilizes coronary artery plaques; and increases the threshold for ventricular fibrillation upon a myocardial ischemia condition.

Back in the 90s, Mangano et al[5] published the first randomized, double blind, placebo-controlled, prospective study, which included 200 patients with coronary artery disease (CAD) or with two or more CAD risk factors (aged ≥ 65, systemic arterial hypertension, smokers, total cholesterol ≥ 240 mg/dl or diabetes), who would be submitted to non-cardiac surgery procedures. The patients were administered atenolol or placebo upon induction of anesthesia until the 7 postoperative stage and were monitored for two years. After this period, the patients who received atenolol managed to survive for longer periods (90% in the atenolol group and 79% in the placebo group; p = 0,019) and, these patients had a smaller number of events (AMI, unstable angina, heart failure and the need for myocardial revascularization): 16 in the atenolol group and 32 in the placebo group (p = 0,008), establishing the benefit of using beta-blockers in these patients. Later, Poldermans et al[6] established the benefit of beta-blockers in a high-risk population that would be submitted to vascular surgeries. One hundred and twelve patients with positive findings on dobutamine ecocardiography and one of the following: age over 70 years, previous AMI, history of heart failure, diabetes or ventricular arrhythmia were randomized to receive bisoprolol, from the previous week until one month after the surgery or conventional treatment. This study had to be early stopped due to a greater mortality of the group without beta-blocker (17% x 3.4%; p = 0,02) and a greater number of AMI (7% x 0%; p < 0.01).

However, one doubt remained: patients presenting smaller surgery risks would benefit from the use beta-blockers? In 2005, Lindenauer et al[7] conducted a major study of retrospective cohort with 663 635 patients submitted to non-cardiac interventions. Patients were divided into two groups (with x without beta-blocker) and separated by Lee's Revised Cardiac Risk Index. The RCRI is a cardiovascular risk assessment score in which each of the following variables represents one point: presence of CAD, heart failure history, cerebrovascular disease history, diabetes with use of insulin, creatinine greater than 2,0 mg/dl and high risk surgery. For patients with RCRI with 2, 3 or more than 4 points, the beta-blocker reduced mortality levels (number needed to treat 227, 62 and 33, respectively). For patients with RCRI = 1, no benefits were found, but a potential harm to patients with RCRI = 0. It is worth underlining that the study was retrospective, thus restricted to the period of admission, providing timely assessments as to whether the patient received beta-blockers at any time during hospital stay. Because of that, smaller-risk patients may have received beta-blockers for therapy purposes due to some event, but not to prevent perioperative events. Establishing the benefit of beta-blockers in smaller risk patients is very difficult, once this population presents small rates of events, being necessary a large number of patients who should be monitored for a long time until any benefit is found.

The POISE Study was designed to solve definitely the role of beta-blockers in the perioperative period of non-cardiac surgeries. Approximately 8,000 individuals were randomized to receive metoprolol or placebo. Worth of note is the fact that only elective surgery interventions were analyzed and patients who have already been using beta-blockers, for other reasons,

Key words

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were not included in this study. As far as cardiovascular outcomes are concerned, the POISE study revealed similar outcomes as previous studies: the group receiving metoprolol presented deaths due to cardiac causes and non-fatal infarction significantly smaller than the control group. On the other hand, investigators were startled with the result of the analysis of secondary outcomes: death due to all causes and stroke, which was higher in the metoprolol group. According to the authors, hypotension and bradycardia, more frequent in the metoprolol group, could be responsible for the higher number of complications, especially stroke. The interpretation of these data led POISE investigators to conclude that the use of metoprolol in the perioperative environment is capable of reducing the likelihood of cardiovascular complications, but at a high cost: increase of death or stroke chances. The authors also stated that recommendations related to the use of beta-blockers set out in the guidelines of perioperative treatment should be redesigned.

Nevertheless, many investigators did not agree on the conclusions found, which did not allow that this study represented the final word on the use of beta-blockers in the perioperative environment. The editorial accompanying the article recommended caution. The authors pointed out problems relating to the choice of metoprolol dose adopted by the POISE Study – 100 mg in the first dose, reaching 200 mg a day; that is, 50% of the maximum dose allowed for this therapy. According to the editorial, this dose is much higher than the one prescribed in previous studies, which could explain hypotension and bradycardia[8]. Additionally, the initial dose is not used in the clinical practice, mainly in patients with ventricular dysfunction or with history of cerebrovascular disease. The analysis of POISE data, including the additional material offered by the authors, available on the website of the magazine, reveals that 625 patients (15%) presented hypotension and 277 (6,6%) presented bradycardia in the metoprolol group. The POISE authors did not explain why only 555 patients had their therapy discontinued. By analyzing these data, we noticed that at least 70 patients continued receiving metoprolol, despite a formal indication of discontinuation, and we do not know the effect on these patients in the secondary outcome (general mortality and stroke)[9]. Although hypotension and bradycardia may represent potentially severe complications, when promptly recognized and treated by discontinuing the beta-blocker and following procedures to increase heart rate and blood pressure, these conditions are not associated to significant increases of complications.

How to deal with the POISE information, apparently contradictory concerning in-rooted concepts conflicting with the physiopathology of perioperative cardiovascular complications? Once again, with caution. We suggest that the class I recommendations for the use of beta-blockers as set out by the I Guideline on Perioperative Evaluation of the Brazilian Cardiology Society be kept[3]. Beta-blocker must be started before the surgery, at low doses, adjusting this dose according to the patient's heart rate and blood pressure. For patients who have already been treated with beta-blockers, the medication must not be discontinued in the perioperative period. For low and intermediate risk patients, who do not have coronary artery disease and are not using beta-blockers, such therapy must not be prescribed.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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