

Perioperative β -Blockade May Raise Stroke Risk

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Perioperative β -blockers may reduce the risk of myocardial infarction after noncardiac surgery, but they confer a doubling in the risk of disabling strokes, especially among lower-risk patients, according to a meta-analysis of 33 randomized controlled trials.

In light of these findings, the guideline committee of the American College of Cardiology, which recommends the drugs for patients undergoing noncardiac surgery, "should soften their stance on perioperative β -blockade until definitive evidence shows clear benefit," Dr. Sripal Bangalore wrote in an article published online in *The Lancet* (doi:10.1016/S0140-6736(08)61560-3). " β -Blockers should not be routinely used for perioperative treatment ... unless patients are already taking them for clinically indicated reasons."

Trials including high-risk patients drove the beneficial effects of β -blockers, while trials with low- or intermediate-risk patients drove the risks.

The risks associated with β -blockers were most apparent in trials that included low- to intermediate-risk patients, particularly the recent Perioperative Ischemic Evaluation (POISE) trial, which is considered a landmark study (*Lancet* 2008;371:1839-47). POISE, which included more than 8,300 patients randomized to extended-release metoprolol succinate or placebo before surgery, found a doubling in the risk of stroke among those in the active group.

The drugs also were associated with significant increases in other cardiac problems, wrote Dr. Bangalore of Brigham and Women's Hospital, Boston, and his colleagues. "For the overall cohort, we estimate that treatment of 1,000 patients with β -blockers results in 16 fewer nonfatal myocardial infarctions in survivors, but at the expense of three disabling strokes, 45 patients with clinically significant perioperative bradycardia, 59 with hypotension, and potentially increased mortality."

The 33 trials included in the meta-analysis comprised 12,300 patients: 6,300 randomly assigned to β -blockers and 6,000 given placebo. The trials varied with regard to the drug used, the dosage, and the timing and duration of administration.

Overall, β -blockers did not result in any significant decrease in the risk of all-cause mortality, cardiovascular mortality, or heart failure. There was a 35% decreased risk of nonfatal heart attack (number needed to treat [NNT]: 63), and a 64% decreased risk of myocardial ischemia (NNT: 16). But the investigators also found a 116% increased risk of nonfatal stroke (number needed to harm [NNH]: 275), based on trials with low- or intermediate-risk patients.

β -Blockade also resulted in a tripling of the risk of perioperative bradycardia (NNH: 8), as well as a 70% increased risk

of perioperative hypotension (NNH: 17).

When the researchers examined outcomes according to the risk level of patients in each trial, trials including high-risk patients drove the beneficial effects of β -blockers, while trials with low- or intermediate-risk patients drove the risks.

In high-risk trials, the investigators found no increased risk of all-cause mortality, an 81% decreased risk of nonfatal MI (NNT: 15), and a 69% decreased risk of MI (NNT: 9), although there were no signifi-

cant benefits for cardiovascular mortality or heart failure.

Trials conducted using low- or intermediate-risk patients found a 28% increased risk of all-cause mortality (NNH: 164), and a 116% increased risk of nonfatal stroke (NNH: 275), with a 28% decreased risk of nonfatal MI (NNT: 80), a 59% decreased risk of myocardial ischemia (NNT: 23), and no reduction in rates of cardiovascular mortality or heart failure.

The POISE trial carried the most sta-

tistical weight among lower-risk trials, while a 1999 study drove the findings among high-risk trials. That study randomized 59 high-risk patients to perioperative bisoprolol or standard care. Nine patients in the standard-care group and two in the bisoprolol group died of cardiac causes during the perioperative period (*N. Eng. J. Med.* 1999;341:1789-94).

This study had no sponsors, noted the authors, none of whom declared any financial conflicts of interest. ■

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The Office of the Surgeon General's Call to Action Against Deep Vein Thrombosis and Pulmonary Embolism

The high incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), has a devastating effect on patients and their families. The Surgeon General has announced a Call to Action to raise awareness about the risk factors and prevention of VTE.

"DVT/PE are major national health problems that have a dramatic, negative impact on the lives of hundreds of thousands of Americans each year."¹

Rear Admiral Steven K. Galson, MD, MPH, US Public Health Service, Acting Surgeon General

According to the Surgeon General's Call to Action, VTE is a major cause of morbidity and mortality among hospitalized patients.^{1,2} It is the third leading cause of cardiovascular death in the United States, following myocardial infarction and stroke.²

- There are up to 600,000 cases of DVT and PE annually, resulting in at least 100,000 deaths per year¹
- More annual deaths are attributed to VTE than breast cancer and AIDS combined³
- Many patients with VTE do not have any clinical signs or symptoms, with 25% of patients presenting with sudden death⁴

Even when accurately diagnosed, complications due to VTE can be long-standing and reduce quality of life, despite adequate treatment. The first step in reducing the incidence of DVT is to increase awareness among the public as well as health care providers about risk factors that may lead to DVT. By understanding patient risk factors, appropriate prophylaxis may be initiated.

"The majority of DVT/PE events are related to specific, identifiable triggering events..."¹

Partial list of risk factors associated with DVT and PE^{5,6}

- Restricted mobility
- Age >40 years
- ICU admission
- Obesity
- Surgery
- Varicose veins
- Prior history of VTE (DVT and/or PE)
- Chronic lung disease
- Inflammatory bowel disease
- Smoking

Table 1. Partial list of risk factors. Clinicians are advised to consider other risk factors or conditions that may predispose to DVT/PE.

"Much is known today about how to prevent DVT/PE, and how to minimize the impact for those patients who suffer from these conditions. If this knowledge were applied consistently, the burden could be reduced substantially."¹

Advancing DVT Awareness

According to the American Public Health Association Deep-Vein Thrombosis Omnibus Survey, 74% of adults had very little or no awareness of DVT.⁷ Even among those mindful of DVT, 57% did not know of any risk factors associated with DVT. Surprisingly, 95% of respondents said their physician had never discussed the importance of DVT with them.⁷

Both patients and physicians must educate themselves about the dangers of DVT. It is important for health care providers to routinely assess DVT risk in hospitalized patients as well as screen high-risk patients more thoroughly. All hospitalized patients are at risk of developing DVT. Patients not receiving prophylaxis and undergoing certain general, urologic, gynecologic, or surgical procedures have a 15% to 40% risk of developing DVT.⁵ For hospitalized acutely ill medical patients, the risk is 10% to 20%. Patients having hip or knee arthroplasty are at even higher risk, 40% to 60% without prophylaxis.⁵ Given the high prevalence of DVT in hospitalized patients, all patients should periodically be risk assessed for DVT.

"Individuals, families, and their communities need to understand DVT and PE, the risk factors for these diseases, and how to reduce these risks."¹

DVT Prophylaxis Reduces the Incidence of DVT, Which May Lead to PE

The use of anticoagulation therapy has been shown to significantly reduce the risk of VTE by as much as 52%⁸; however, implementation and lack of appropriate prophylaxis in at-risk medical patients continue to be problematic,⁹ despite evidence-based DVT/PE guidelines (Table 2).

Please see a brief summary of prescribing information, including boxed WARNING, at the end of the article.