Administration of regulating agent prior to CABG surgery does not appear to improve outcomes

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Among intermediate- to high-risk patients undergoing coronary artery bypass graft surgery, administration of the agent acadesine to regulate adenosine (a naturally occurring chemical that dilates blood flow and can improve coronary blood flow and perfusion) did not reduce all-cause death, nonfatal stroke, or need for mechanical support for ventricular dysfunction, for approximately a month after surgery, according to a study in the July 11 issue of *JAMA*.

"Despite improvements in myocardial protection and perioperative care, the risk of death is still substantial in the first month after coronary artery bypass graft (CABG) surgery, averaging 3 percent to 6 percent, and can be even higher in patients with poor left ventricular function. Up to 50 percent of these deaths have been attributed to a cardiac cause, and this percentage has remained fairly constant over time," according to background information in the article. "In a meta-analysis of randomized controlled trials, perioperative and postoperative infusion of acadesine, a first-in-class adenosine-regulating agent, was associated with a reduction in early cardiac death, myocardial infarction, and combined adverse cardiac outcomes in participants undergoing on-pump CABG surgery." The authors add that the administration of adenosine during CABG surgery is difficult to regulate and led to the development of adenosine-regulating agents, of which acadesine is the first to be tested in large-scale clinical trials.

Mark F. Newman, M.D., of Duke University Medical Center, Durham, N.C., and colleagues conducted a study designed to more definitely test whether acadesine could reduce the composite of all-cause mortality, nonfatal stroke, or need for mechanical support for severe left ventricular dysfunction (SLVD) occurring during and after CABG surgery through postoperative day 28. The Reduction in Cardiovascular Events by Acadesine in Patients Undergoing CABG (RED-CABG) trial, a randomized, placebo-controlled study included intermediate- to high-risk patients (median [midpoint] age, 66 years) undergoing nonemergency, on-pump CABG surgery at 300 sites in 7 countries. The majority of participants were white men with a history of hyperlipidemia, diabetes, family history of cardiovascular disease, and previous percutaneous coronary intervention (procedures such as balloon angioplasty or stent placement used to open narrowed coronary arteries). Enrollment occurred from May 2009 to July 2010. Eligible participants were randomized to receive acadesine or placebo beginning just before anesthesia induction.

The trial was stopped after 3,080 of the originally projected 7,500 study participants were randomized because early analysis indicated a very low likelihood of a statistically significant efficacious outcome. The final sample size consisted of 2,986 patients in the intention to treat analysis. The researchers found that the primary efficacy outcome (composite of all-cause mortality, nonfatal stroke, or need for mechanical support for SLVD) was observed in 5 percent of participants overall. There was no significant difference between the placebo and acadesine groups, with incidence rates of 5.0 percent and 5.1 percent, respectively.

Additional exploratory efficacy end points, including length of mechanical ventilation, intensive care unit and hospital stay, and quality of life, did not reach statistical significance.

"These findings illustrate inherent risks of using promising meta-analysis

results to plan 'confirmatory' clinical trials. There are several potential explanations for the negative results we observed. One consideration is the decision around study eligibility criteria and the overall primary end point of the trial," the authors write. They add that the lack of benefit of acadesine may be related to the dosing regimen used.

The researchers conclude that the incidence of the primary composite end point of 5 percent indicates the need for continued investigation into therapies to reduce perioperative morbidity and mortality. "However, effective therapies remain elusive."

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