Drug fails to curb heart bypass complications, but surgery gets safer

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A drug designed to shield the heart from injury during bypass surgery failed to reduce deaths, strokes and other serious events among patients at high risk of complications, according to a large, prospective study lead by researchers at Duke University Medical Center.

But the international study also produced a surprising silver lining. As reported in the July 11 issue of the Journal of the American Medical Association, the researchers discovered that complications among bypass surgery patients were far less frequent than previously reported.

"We expected about 10 percent of patients were at high risk for complication following coronary artery bypass grafting," said Mark F. Newman, M.D., chairman of the Department of Anesthesiology at Duke and lead author of the study. "But the actual risk was 5 percent. What that means is cardiac surgery has gotten much safer, even for high-risk patients."

Newman said surgical management of patients undergoing coronary artery bypass grafting (CABG) has improved worldwide in the past decade.

The study, which began in 2009, tested a drug called acadesine in a Phase III trial that was one of the largest involving a surgical procedure. The primary objective was to determine whether acadesine would cut the rate of complications from CABG – the most common type of open heart surgery in the United States. The procedure is highly successful in

restoring blood flow to the heart caused by blockages, but strokes, ventricular damage and death can result even after successful surgery.

One cause of complications is called ischemia reperfusion injury, which stems from changes that occur to tissue starved of oxygen during the surgery, when blood vessels are clamped to establish the grafts. This period of oxygen deprivation triggers inflammation and cell death once blood flow is restored.

Earlier evidence from smaller studies suggested acadesine, given before, during and after surgery, could offer protection by easing some of the inflammatory responses that kill cells. Most of those studies occurred before 1997, however, when the rate of serious complications was 10 percent or greater.

Newman and colleagues at 300 sites in seven countries randomly assigned patients to receive the trial drug or a harmless placebo, and provided followup for a month. The group found that the drug was no better than placebo at protecting people from complications, with five percent of patients having a severe event within that month regardless of taking acadesine or a mock treatment. The study, funded by the manufacturer Merck, was halted early based on a prespecified interim analysis after 3,080 patients were enrolled.

Still, the 5 percent complication rate was good news, Newman said. It is likely the result of improved surgical methods in recent years, including better anesthesia and advances in surgical and heart-lung machine management.

"A lot of things have played a part in the gradual improvement of outcomes over the years," Newman said. "We wish we had a drug that could help with ischemia/reperfusion injury – and that remains something that would benefit patients tremendously -- but we have made

strides in other areas. As a result, older, sicker patients are now undergoing cardiac surgery with very good results."

Newman also said that support for publication of a negative study by the sponsor, Merck, and by the publisher *JAMA*, is an important step in defining the appropriate therapy for heart surgery patients going forward.

Provided by Duke University Medical Center