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Widely Used Cardiac Surgery Drug Now Shown to Increase Risk of Death

**Aprotinin—Shown to Cause Kidney Failure One Year Ago—
Now Shown to Cause More Than 2,000 Deaths per Year
In Today's *Journal of the American Medical Association***

SAN BRUNO, CA— Aprotinin—a drug approved by the FDA, marketed internationally for the last 13 years, and given to more than 4 million patients—has now been proven to increase a patient's risk of dying during the first 5 years after cardiac surgery. These results—published in this week's *Journal of the American Medical Association*—are based on an independent (non-commercial), long-term observational study conducted by the **Ischemia Research and Education Foundation (IREF)**, in association with the *McSPI* Research Consortium—both nonprofit biomedical research organizations dedicated to saving and extending lives.

The new 5-year follow-up mortality study, led by IREF and *McSPI* founder and principal scientist, **Dennis T. Mangano, Ph.D., M.D.**, provides further compelling evidence of aprotinin's serious risks, and suggests discontinuation of use and replacement with either of the two alternative generic—and far less costly—medications proven safe in this study. The study, "**Mortality Associated with Aprotinin During 5 Years Following Coronary Artery Bypass Graft Surgery**," is published nearly one year to the day after Mangano's group's first study (*NEJM*, January 2006) in which they found that Aprotinin caused acute kidney failure. Despite the 2006 warnings, several hundreds of thousands of patients per year continue to receive Aprotinin. Had Aprotinin been replaced with either of the two safer generic drugs, even for one year, as many as **2,000 deaths per year over the 5 subsequent years** (or 10,000 deaths overall) could have been avoided, with savings of at least **\$1 billion** in healthcare costs, and at least **\$250 million** in drug costs.

Approximately one million patients worldwide undergo surgical treatment following a heart attack, with the majority of these patients receiving one of three antifibrinolytic agents to limit blood loss during surgery: aprotinin (Bayer Healthcare Pharmaceuticals, Inc.), ε-aminocaproic acid (generic), or tranexamic acid (generic). The two generic drugs have proven safe in limiting blood loss, and do not have the harmful effects of aprotinin. Aprotinin is at least ten times more expensive than its generic competitors. Patients scheduled for cardiac surgery should consult their physicians and avoid this risk.

Aprotinin was approved by the U.S. Food and Drug Administration in 1993 and is manufactured by Bayer under the brand name Trasylo1. Over the past 20 years, more than 4 million patients worldwide have received Trasylo1, and in the United States approximately 246,000 had received it in 2005.

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The study is the first comprehensive, observational, non-industry sponsored analysis of aprotinin’s long-term safety. Its findings are based on a systematic sampling scheme at 69 of the world’s leading cardiac centers and institutions in North and South America, Europe, the Middle East and Asia. Approximately **7,500 data fields** were collected from 4,374 patients by independent *McSPI* investigators, and of these **3,876 patients** from **62 centers** completed the 5-year study.

The observational research model for assessment of drug safety is in contrast to randomized clinical trials, which seeks to confirm the immediate safety and efficacy of a drug without examining how the drug interacts with a multitude of other variables. The observational approach allows researchers to collect a depth of information about a particular behavior and to look at the association and interaction of a particular drug with thousands of other variables in specific groups of people - at risk populations, people over 65, or people already sick—groups likely to be excluded in clinical trials prior to approval.

The nonprofit Ischemia Research and Education Foundation provided all of the funding for the study, totaling more than \$35 million for the in-hospital study and \$20 million for the long term study, including site grants, central analysis and data disposition and manuscript grants. The good will of the 69 participating *McSPI* cardiac centers in the U.S. and worldwide contributed similar in kind support through reduced research and data collection fees. Two of the authors with *McSPI* had received prior financial support from the manufacturer of aprotinin; no investigator associated with IREF had received pharmaceutical company support.

The current finding is the fifth major cost-saving therapeutic discovery by Dr. Mangano and IREF-*McSPI* colleagues over the past decade. In 1996, this team found that generic beta-blockers reduced death after major surgery, saving 250,000 lives a year at a cost of \$15 per patient (*New England Journal of Medicine*). In 2002, Dr. Mangano reported that giving heart patients aspirin immediately following surgery reduced the threat of thrombosis (*New England Journal of Medicine*). This is now standard practice and saves over 25,000 lives a year at a cost of pennies per patient. In 2003, IREF-*McSPI* reported for the first time that the COX-2 inhibitor, Bextra (valdecoxib, parecoxib), was associated with stroke and impaired wound healing, eventually leading to its recall (*J Thoracic and Cardiovascular Surgery*). In 2006, the group reported that replacement of aprotinin (\$500 to \$1,500 per use) with a generic antifibrinolytic (\$10 to \$50 per use) could save 10,000 patients from dialysis each year (*New England Journal of Medicine*). The current finding addressing long-term drug safety (*Journal of the American Medical Association*) is IREF’s latest biomedical breakthrough using large-scale, counterintuitive research design and implementation to uncover ways to save and extend lives.

The full article is available at <http://jama-archives.org/> or at <http://www.iref.org/>.

About IREF and McSPI

IREF is a California-based, independent, nonprofit biomedical research organization founded in 1987 and dedicated to performing quality medical and scientific research that saves and extends lives. The Multicenter Study of Perioperative Ischemia (*McSPI*) Research Group, founded in 1988 by Dr. Mangano, over the years has included 246 research centers around the world. Since their inception, IREF and *McSPI* have conducted large-scale, complex multi-center studies addressing myocardial ischemia, infarction, stroke, and renal failure in high-risk patients undergoing both cardiac and non-cardiac surgery.

The IREF/*McSPI* collaboration provides a cohesive matured system for the accumulation of large-scale databases, as well as the rapid commencement, conduction, and completion of complex U.S. and global clinical trials. Find more information at <http://http://www.iref.org/>.

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