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Widely Used Cardiac Surgery Drug Doubles Risk Of Kidney Failure

**Aprotinin Proven Unsafe 13 Years After Approval
In Today's *New England Journal of Medicine***

SAN BRUNO, CA— Aprotinin—a drug approved by the FDA, marketed internationally for the last 13 years, and given to an estimated one million surgery patients to limit bleeding—has now been proven to double a patient's risk of kidney failure, and increase the risk of heart attack, heart failure, and stroke. These results—published in this week's *New England Journal of Medicine*—are based on an independent (non-commercial), observational study conducted by **The Ischemia Research and Education Foundation (IREF)**, in association with the *McSPI* Research Group—nonprofit biomedical research organizations dedicated to saving and extending lives.

“Our study provides compelling evidence of aprotinin's serious risks, and strongly suggests discontinuation of use and replacement with either of the two alternative generic and far less costly medications proven safe in this study.” said IREF and *McSPI* founder and principal scientist, **Dennis T. Mangano, Ph.D., M.D.** “Certainly, our findings—coming on the heels of the Vioxx experience—indicate that the problem of drug safety is not only ubiquitous, but also much more elusive than previously thought. In fact, our findings raise even more troubling concerns, for: (1) aprotinin has been on the market for three times as long as Vioxx, yet few comprehensive safety studies have been conducted since approval; (2) the life-threatening complications with aprotinin found here occurred far more frequently than those with Vioxx; and (3) far less expensive generic alternatives to aprotinin which are equally effective in limiting bleeding have been available, but have been underused.”

The article, “**The Risk of Aprotinin in Cardiac Surgery**,” states that replacing aprotinin with one of two safe generic drugs would *annually* prevent as many as **11,050 dialysis complications**, save at least **\$1 billion** in healthcare (dialysis) costs, and reduce drug costs by at least **\$250 million**. Each year 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. 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 three years, Trasylo1 sales have accelerated, with 2006 sales projected in excess of **\$US 600 million**.

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“We estimate that as many as 10,000 patients may be unnecessarily on dialysis today due to aprotinin use. This serious impact on human lives underscores once again the necessity for meticulous, post-approval surveillance, as well as ongoing, unbiased analysis of drug safety—all conducted by entirely independent entities,” said Dr. Mangano. “This is easier said than done, however, for the economic forces are—and will continue to be—substantial, with little corporate incentive to identify safety problems once drugs are approved and marketed.”

The *New England Journal of Medicine* article documents how aprotinin use was associated with a two-fold increase in renal failure requiring dialysis in patients undergoing both complex coronary artery surgery and primary surgery (excluding prior cardiac and current valve surgery.) Among primary surgery patients, Dr. Mangano and colleagues found that aprotinin use also increased risk of myocardial infarction (**48 percent**), heart failure (**109 percent**), and stroke (**181 percent**). Neither of aprotinin’s generic competitors, ε-aminocaproic acid and tranexamic acid, was associated with increased renal, cardiac or cerebral events. Aprotinin is at least ten times more expensive than its generic competitors.

The study is the first comprehensive, observational, non-industry sponsored analysis of aprotinin’s 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.

The observational research model for assessment of drug safety is in contrast to randomized clinical trials, which seek 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. Regarding this, Mangano stated that “Perhaps as important as the research findings themselves is the approach taken here to assess safety. We believe that the independent observational approach is likely the only method practical for unbiased assessment of drug safety in high-risk populations once a drug is marketed and practice is imbedded. Unfortunately, comprehensive observational studies also are very costly, and given that there truly is no mandate or incentive for the pharmaceutical industry to aggressively find safety problems once a drug is marketed, it is up to society to find creative ways to independently assess safety. Otherwise, the Vioxx—and now Aprotinin—sagas will only be but the first of a series of public health drug-safety failures.”

The 4,374 patients examined in the study either received no antifibrinolytic agent, or one of the three agents (aprotinin, ε-aminocaproic acid or tranexamic acid). The control group, which received no antifibrinolytic, numbered **1,374**. **1,295** patients received aprotinin, **883** patients received ε-aminocaproic acid, and **822** patients received tranexamic acid.

The nonprofit Ischemia Research and Education Foundation provided all of the funding for the study, totaling more than \$35 million, 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. None of the authors received direct or indirect support from any of the manufacturers of these three drugs.

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The current finding is the fourth 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*). The current finding around aprotinin 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://content.nejm.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 1989 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 www.iref.org

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