

Bayer Responds to study and commentary published in *Journal of American Medical Association (JAMA)*

February 2007 West Haven, CT, USA. Bayer has conducted a preliminary review of the observational study entitled “Mortality Associated with Aprotinin During 5 Years Following Coronary Artery Bypass Graft Surgery” by Mangano et al. as well as the editorial by T. Bruce Ferguson, Jr., MD from the East Carolina University, Greenville, NC, scheduled for publication on February 7, 2007 in the *Journal of the American Medical Association (JAMA)* regarding long-term mortality rates in coronary artery bypass graft surgery patients including those treated with aprotinin.

The study published in JAMA is a follow-on to a previous observational study from the Ischemia Research and Education Foundation published in January 2006 on which Dr. Mangano was also the lead author. Bayer believes the methodological and analytical approaches used in the earlier study were not reliable and do not support the authors’ reported conclusions. This newest paper reports on a subset of the same patient population and uses methodology and analytical approaches similar to those used in the earlier publication.

One of the limitations of both of these studies is that doctors chose whether to administer aprotinin or another treatment based on the patient’s condition. Generally, sicker patients who were already at greater risk for mortality were treated with aprotinin. As noted in the editorial by Dr. Ferguson, “Aprotinin use in cardiac surgery has never been uniformly standardized, but generally has been reserved for patients in whom the surgical team anticipated a higher risk for intraoperative blood loss. This anticipation was driven by the surgical team’s perception of increased technical complexity, increased risk of adverse outcome, or both for the patient in question.” The statistical methodologies as applied by Mangano et al. in the JAMA paper did not adequately address this bias.

In addition, and applicable to both studies, major differences in clinical practice among the contributing countries have been reported in the literature. These differences have also been reported to influence outcomes. Both studies involved more than 60 sites from all over the world and these differences in clinical practice may have affected the reported findings.

Pointing out differences in the percent of patients in the different treatment groups who underwent complex surgical procedures, Dr. Ferguson comments, “Importantly, these biases, at the level of the surgical team, were not captured in the extensive patient level data collection process nor in the analysis.” Dr. Ferguson concludes, “The mechanism for this late mortality difference is not clear and causality [to aprotinin] cannot be inferred from this data set analysis.”

Patient safety is always Bayer’s highest priority. Based on this initial review, Bayer believes that the results of this study should not serve as a basis for affecting the use of aprotinin in clinical practice. Bayer will work with regulatory agencies and external experts in the field to further evaluate the findings.

About Trasylol

Trasylol® is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood transfusion. The effects of Trasylol use in CPB involve a reduction in systemic inflammatory response to surgery, which translates into a decreased need for allogeneic (blood donated from another individual) blood transfusions reduced bleeding and decreased mediastinal re-exploration for bleeding.

Trasylol® administration may cause fatal anaphylactic or anaphylactoid reactions. Fatal reactions have occurred with an initial (test) dose as well as with any of the components of the dose regimen. Fatal reactions have also occurred in situations where the initial (test) dose was tolerated. The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure and a history of any prior aprotinin exposure must be sought prior to Trasylol® administration. The risk for a fatal reaction appears to be greater upon re-exposure within 12 months of the most recent prior aprotinin exposure. Trasylol® should be administered only in operative settings where cardio-pulmonary bypass can be rapidly initiated. The benefit of Trasylol® to patients undergoing primary CABG surgery should be weighed against the risk of anaphylaxis associated with any subsequent exposure to aprotinin. (See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS in the prescribing information.)

Safety Considerations

Trasylol is contraindicated in patients with a known or suspected aprotinin exposure during the last 12 months. Aprotinin may also be a component of some fibrin sealant products.

- In clinical studies, hypersensitivity and anaphylactic reactions were rare (<0.1%) in patients with no prior exposure to Trasylol.

Trasylol administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period.

- This risk may be increased for patients with pre-existing renal impairment or those who receive aminoglycosides or drugs that alter renal function.
- The incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was statistically higher in the high-dose aprotinin group (9.0%) compared with placebo (6.6%).

In clinical trials Trasylol did not increase the risk of the following perioperative events: myocardial infarction, hepatic dysfunction and mortality.

About Bayer HealthCare

Bayer HealthCare, a subsidiary of Bayer AG, is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Diabetes Care, and Pharmaceuticals divisions. The Pharmaceuticals division comprises the following business units: Women's Healthcare, Diagnostic Imaging, Specialized Therapeutics, Hematology/Cardiology, Primary Care, and Oncology. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. The products enhance well-being and quality of life by diagnosing, preventing and treating diseases.

Forward-Looking Statements

This news release contains forward-looking statements based on current assumptions and forecasts made by Bayer Group management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in our public reports file with the Frankfurt Stock Exchange and with the U.S. Securities and Exchange Commission (including our Form 20-F). The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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