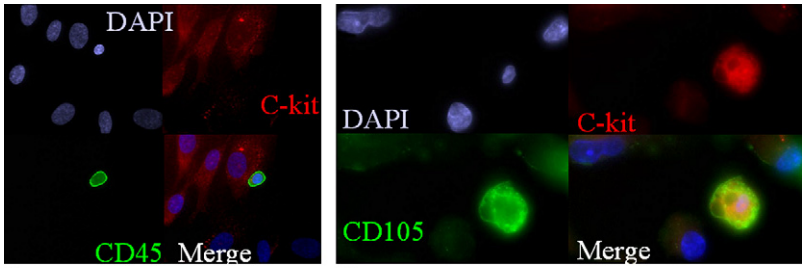

Figure 1. Immunofluorescent staining on cells grown out of cardiac tissue. Cells incubated with CD45-FITC (A, *lower left*) and C-kit-phycoerythrin (A, *upper right*). 4,6-diamino-2-phenylindole (A and B, *upper left*) was used to stain nuclei. A, Outgrown c-kit$^+$ cells do not coexpress CD45 and c-kit. B, Cells are incubated with CD105-FITC (*lower left*) and c-kit-phycoerythrin (*upper right*); 95% of the cells do express CD105 and a subpopulation coexpresses c-kit. *DAPI,* 4,6-diamino-2-phenylindole.

outgrowth. So the difference in the expression profile between our c-kit$^+$ cells and that detected by Pouly and colleagues[1] cannot be the result of cell processing.

Our findings indicate that c-kit$^+$ cells, present in right atrial appendages, coexpress CD105 but are CD45$^-$. It is therefore unlikely that these cells are mast cells because our data indicate that they are probably cardiac progenitor cells.

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Reply to the Editor:

We thank Koninckx and colleagues for their comments. As stated in our article, data were obtained from both endomyocardial biopsies and atrial appendages, and these 2 sampling sites yielded concordant data. However, the major difference is that we performed in situ detection and characterization of cells, whereas Koninckx and colleagues cultured cells for 2 weeks before immunostainings. Such a time interval can change the cell phenotype and delete some cell populations that do not survive under these conditions. The latter phenomenon could explain why Koninckx and colleagues did not find any mast cell in their myocardial tissue cultures, whereas it is well established that the myocardium does contain such cells. Because a minor component of the c-kit-positive cells could have represented a subset of cells different from mast cells, we also tested them for other markers of stemness (CD105, islet-1, and MDR1). However, in our hands, these markers remained negative. The data of Koninckx and colleagues suggest that after a period of culture, c-kit-positive cardiac "stem" cells can be identified, but it would be clinically relevant that they provide a quantitative estimate of these cells to assess whether this number allows one to reasonably envision their use for therapeutic purposes.

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Aprotinin; An economy of truth?

To the Editor:

I write to comment on the editorials by Drs Sundt[1] (April 2008) and Westaby[2] (March 2008). Dr Sundt is perceptive but fails to consider that the observational studies suggesting a danger with aprotinin may have had bias in the analysis.

At the advisory committee meeting of the Food and Drug Administration (FDA) held on September 12, 2007, Dr Mangano allowed the FDA access to the McSPI (Multicenter Study of Perioperative Ischemia) data set. Whereas Mangano and colleagues[3] used a propensity score that was based on likelihood of bleeding, the FDA reanalysis of these data used stratification according to risk of adverse outcome. The FDA analysis showed no increases in relative risks (RRs) for death (RR 0.91, 95% confidence interval [CI] 0.54–1.53), heart failure (RR 1.05, 95% CI 0.75–1.47), myocardial infarction (RR 1.10, 95% CI 0.88—1.39), or renal dysfunction (RR 1.26, 95% CI 0.76–2.11) when data from 1222 aprotinin-treated patients were compared with those of 1307 patients who did not receive the drug.[4]

At the same FDA meeting, Dr Karkouti, who used matching of pairs of data, showed that the inclusion into the model of cardiopulmonary bypass variables (time and circulatory arrest) and transfusion (>4 units of red blood cells and fresh-frozen plasma) removed the statistical effects of aprotinin on renal function.[4] The Toronto data have never shown any other mortality or morbidity risk. Dr Funary also presented the North West Consortium analysis, which showed that any apparent effect of aprotinin on adverse outcome is lost when red blood cell transfusion numbers are included as a confounding variable.[5]

In the article from Shaw and colleagues[6] of the Duke University Medical Center, the populations of patients receiving aprotinin or ϵ-aminocaproic acid (EACA) were hugely different. No matter how clever the statistical modeling, clinicians will recognize that there must be differences in management and outcome between a patient with isolated myocardial ischemia undergoing primary, elective revascularization (given EACA) and one undergoing a nonelective reoperation for heart failure associated with valve pathology (who would likely receive aprotinin in about 70%-80% of cases worldwide). Despite this, Shaw and colleagues[6]

concluded that aprotinin use was the factor associated with mortality when comparing data from 1343 aprotinin-treated patients with those from 6776 given EACA and 2029 given neither therapy.

Two aspects may lead the interested reader to question this conclusion. First, the propensity analysis did not include red blood cell transfusion numbers as a factor (transfusion was graded as either yes or no). More worrisome is that a matched-pairs analysis was relegated to the supplementary data available online from the *New England Journal of Medicine*. In this analysis, which included 1992 patients with comparable risks, aprotinin showed no effects on 30-day ($P = .58$) and 1-year mortalities ($P = .36$) relative to EACA.

Thus if propensity scoring is achieved by linear regression, and confounding variables known to be associated with adverse outcomes are excluded, then observational studies show aprotinin to be a dangerous drug. Aprotinin is not seen to be dangerous, however, when the analysis is performed with matching or stratification of risk and known confounders are included.

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doi:10.1016/j.jtcvs.2008.05.023

Reply to the Editor:

I appreciate Dr Royston's kind comment regarding my editorial. I am quite certain that he agrees with me that we are "worse off without [aprotinin] in our arsenal." Indeed, I feel this sentiment particularly this evening, as I wait for a call from the operating room to start repair of an acute dissection in an 80-year-old patient who is receiving warfarin 5 years after coronary bypass and aortic valve replacement. I am also sure that he agrees that, in the best of all possible worlds, the risks and benefits determining the use of a drug should pertain to the welfare of the patient as judged by physicians and not to the litigation risks of a pharmaceutical company as judged by lawyers.

I also appreciate Dr Royston's comments regarding bias. The biases of which he speaks have not (entirely) escaped me; all studies have biases. Randomized studies are of necessity biased at entry. Rigid eligibility criteria are necessary to define a population with sufficient precision to permit analysis, and the demands of equipoise encourage inclusion of low-risk patients for whom harm is the least likely–but so is benefit. Consequently, few such studies truly reflect the spectrum of disease that we face in clinical practice. The populations included in observational studies are more representative of practice; however, the bias introduced by the clinical judgments made in the application of a therapy or administration of a drug impose considerable challenges to balanced interpretation, as so beautifully demonstrated in Dr Royston's letter. I could not agree more. As noted in his comments, understanding the appropriate application and interpretation of propensity analysis demands a learned understanding of the methods as well as the aims of the matching. Unfortunately, few of us (certainly not I) are so statistically sophisticated. I know that in this regard Dr Royston can run circles around me. No contest.

In the end, where we differ, it would appear, is regarding just where the rest of the medical community is struggling. What are the real risks associated with aprotinin? Is it "a potentially harmful drug"? If so, what is the magnitude of that risk? Personally, I remain amazed that today (May 23, 2008), with more than 7100 citations now retrievable on a PubMed search for *aprotinin,* there is still room for debate.

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Notice of Correction

Re: A near-fatal presentation of a bronchogenic cyst compressing the left main coronary artery. *J Thorac Cardiovasc Surg*. 2008;135:1395-6.

In the above-noted article, Dr Malcom Finlay should have been listed as the second author on the article. Dr Finlay was the admitting physician in the case. He supplied the angiographic image of the left main stem (LMS) compression (acting as operator) and transoesophageal echo (TOE) image, and he also obtained the patient's consent for publication.