for all antifibrinolytic agents. Our analysis supports the recent recommendations from Health Canada and the European Medicine Agency.

References

1. Bridgewater B, Keogh B. Sixth National Adult Cardiac Surgical Database report, demonstrating quality. Henley-on-Thames, UK: Dendrite Clinical Systems; 2009.
2. Vivacqua A, Koch CG, Yousuf AM, Nowicki ER, Houghtaling PL, Blackstone EH, et al. Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? *Ann Thorac Surg*. 2011;91:1780-90.
3. Karthik S, Grayson AD, McCarron EE, Pullan DM, Desmond MJ. Reexploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay. *Ann Thorac Surg*. 2004;78:527-34; discussion 34.
4. Scott BH, Seifert FC, Grimson R. Blood transfusion is associated with increased resource utilisation, morbidity and mortality in cardiac surgery. *Ann Card Anaesth*. 2008;11:15-9.
5. Kuduvali M, Oo AY, Newall N, Grayson AD, Jackson M, Desmond MJ, et al. Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. *Eur J Cardiothorac Surg*. 2005;27:592-8.
6. NHS Blood and Transplant. *Annual review: saving and improving lives*. Walford, UK: National Health Service Blood Transfusion Review Board; 2009/2010.
7. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev*. 2011;3:CD001886.
8. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med*. 2008;358:2319-31.
9. European Medicines Agency [Internet]. London: The Agency; c1995–c2012 [updated 2012 Feb 17; cited 2012 May 2]. European Medicines Agency recommends lifting suspension of aprotinin. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001447.jsp&mid=WC0b01ac058004d5c1&jsenabled=true.
10. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23:3105-24.
11. Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJ, Briët E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet*. 1999;354:1940-7.
12. Henry DA, Moxey AJ, Carless PA, O'Connell D, McClelland B, Henderson KM, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev*. 2001;1:CD001886.
13. Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg*. 2004;128:442-8.
14. Rosén M. The aprotinin saga and the risks of conducting meta-analyses on small randomised controlled trials—a critique of a Cochrane review. *BMC Health Serv Res*. 2009;9:34.
15. Young C, Horton R. Putting clinical trials into context. *Lancet*. 2005;366:107-8.
16. Health Canada [Internet]. Ottawa: Health Canada; c2012 [updated 2011 Sep 21; cited 2011 Oct 10]. Health Canada decision on Trasylol (aprotinin). Available from: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_124-eng.php.
17. Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med*. 2008;358:771-83.
18. Pagano D, Howell NJ, Freemantle N, Cunningham D, Bonser RS, Graham TR, et al. Bleeding in cardiac surgery: the use of aprotinin does not affect survival. *J Thorac Cardiovasc Surg*. 2008;135:495-502.
19. Gagne JJ, Griesdale DE, Schneeweiss S. Aprotinin and the risk of death and renal dysfunction in patients undergoing cardiac surgery: a meta-analysis of epidemiologic studies. *Pharmacoevid Drug Saf*. 2009;18:259-68.
20. Hall TS, Brevetti GR, Skoultchi AJ, Sines JC, Gregory P, Spotnitz AJ. Re-exploration for hemorrhage following open heart surgery differentiation on the causes of bleeding and the impact on patient outcomes. *Ann Thorac Cardiovasc Surg*. 2001;7:352-7.
21. DeSantis SM, Toole JM, Kratz JM, Uber WE, Wheat MJ, Stroud MR, et al. Early postoperative outcomes and blood product utilization in adult cardiac surgery: the post-aprotinin era. *Circulation*. 2011;124(11 Suppl):S62-9.

COMMENTARY

Facts, opinions, and conclusions: Aprotinin brings out all of these

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In general, an opinion is a subjective belief, and is the result of emotion or interpretation of facts. An opinion may be

supported by an argument, although people draw opposing opinions from the same set of facts. Almost all cardiac surgeons have an opinion about the use of aprotinin. These opinions range from strong support for drug use to adamant insistence that the drug causes harm. The facts that the supporters and detractors use to form their opinions are the same. Only conclusions differ.

WHAT ARE THE FACTS?

Fact 1: Aprotinin Reduces Bleeding, Blood Transfusion, and Reoperation for Bleeding in Patients Having a Variety of Cardiac Operations

There can be little doubt of this fact. In developing practice guidelines about blood conservation for the Society of

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Thoracic Surgeons, we identified >500 published articles that addressed the use of aprotinin for limiting bleeding and blood transfusion after cardiac operations.¹ This volume of literature represented the most studied facet of blood conservation by a huge margin. In fact, the next closest blood conservation intervention had <50 citations in the literature. Later on, it was even criticized that too many redundant trials addressed efficacy questions already answered definitively by previous studies.² Given the volume of published literature, it is not surprising that multiple meta-analyses exist to address the efficacy of aprotinin in reducing bleeding end points. The manuscript by Howell and coworkers³ is another example of one such meta-analysis that shows the benefit of aprotinin in limiting reoperation resulting from bleeding. If cardiac surgeons believe in randomized trials and published observational data, they should believe that aprotinin reduces bleeding and blood transfusion.

Fact 2: The Means of Controlling or Evaluating the Safety and Clinical Efficacy of a Drug After Its Regulatory Approval Are Ineffective

It is clear from the aprotinin story that randomized, controlled studies, which are the prerequisite for regulatory approval, do not reflect necessarily the real world of medical practice. More important, rare or uncommon complications are often lost in the relatively uniform populations found in randomized trials. Large clinical databases are valuable adjuncts to the discovery of adverse events related to drug or device therapy. For example, it seems apparent that a relationship exists between aprotinin and perioperative renal dysfunction. Whether this means that aprotinin causes this renal dysfunction or is simply associated with this complication remains debatable. Furnary and coauthors⁴ examined their large database to investigate the effect of aprotinin on renal function. They found significant association between postoperative renal dysfunction and blood transfusion, but not with use of aprotinin.⁴ Others found opposite results after examining large databases.⁵

Because of safety concerns about aprotinin, the Canadian Institutes of Health Research and the Ontario Ministry of Health sponsored a randomized trial comparing aprotinin with tranexamic acid in high-risk cardiac operations (the Blood Conservation Using Antifibrinolytics in a Randomized [BART] trial).⁶ Early discontinuation of the BART trial because of supposed excess mortality in the aprotinin group signaled the death knell of aprotinin in the United States. Since publication of this study, Health Canada reexamined the BART trial data and concluded “that the benefits of Trasylol outweigh the risks when Trasylol is used as authorized by Health Canada. Trasylol is authorized for patients undergoing coronary artery bypass graft (CABG) surgery. The evidence does not suggest an increased risk of death in this use. As a result of this assessment, the manufacturer, Bayer

Inc, can resume the marketing of Trasylol in Canada.”² For various reasons, possibly related to medical malpractice litigation, Bayer Pharmaceuticals, the manufacturer of aprotinin (Trasylol) will not reintroduce aprotinin into the U.S. market (personal communication, Bayer representative, June 2012). This drug is now available in Canada and other countries.

The European Medicines Agency is a European Union agency for the evaluation of medicinal products. Roughly parallel to the U.S. Food and Drug Administration, but without Food and Drug Administration–style centralization, the European Medicines Agency recommended temporary withdrawal of Trasylol in 2007 after publication of the BART trial suggested increased risk of complications or death. Ultimately, Bayer suspended Trasylol sales in May 2008. In February 2012, the European Medicines Agency scientific committee reversed its previous standpoint regarding aprotinin, and recommended that the suspension be lifted and that aprotinin be used as previously indicated. The shifting back and forth of the regulatory bodies as they approve or disapprove use of aprotinin highlights the ineffective postapproval surveillance that exists both in the United States and abroad.

WHAT ARE THE OPINIONS?

Opinion 1: Lysine Analogs Are Not Safer Than Aprotinin

Because of the widespread use of aprotinin in cardiac operations, large clinical databases discovered a relationship between aprotinin and certain adverse outcomes. The safety of aprotinin data was called into question. Examination of the Multicenter Study of Perioperative Ischemia Epidemiology II database conveyed early concerns about renal toxicity and mortality risk associated with aprotinin.⁵ These safety concerns caused authors to recommend lysine analogs (tranexamic acid and epsilon amino caproic acid) as a safer substitute for aprotinin.⁷ Much less safety data exist for the lysine analogs compared with the vast clinical experience reported for aprotinin. With the absence of aprotinin in the cardiac armamentarium, both tranexamic acid and epsilon-aminocaproic acid use increased. With this increase in use of other antifibrinolytic agents, some safety concerns arose. For example, most regulatory agencies in Europe have not approved Amicar for use in cardiac operations because of concerns about thrombosis. Seizure risk seems to be increased with use of high-dose tranexamic acid.⁸ It may be that wider use of lysine analogs will uncover safety issues not recognized in randomized trials. There is insufficient evidence to suggest that lysine analogs are safer than aprotinin.

Opinion 2: Perioperative Blood Transfusion Causes Death or Serious Morbidity

In most, but not all, studies that evaluate complications associated with aprotinin use, there is no difference in

mortality or nonbleeding serious morbidity between those treated with aprotinin and those treated with either placebo or other antifibrinolytic agents. This finding is reinforced in the manuscript by Howell and coworkers,³ who found no difference in mortality between aprotinin-treated patients and either placebo-treated patients or lysine analog-treated patients. This observation leads some surgeons to question whether postoperative bleeding is an important outcome. The fact that aprotinin decreases bleeding but does not alter significantly operative mortality or serious morbidity diminishes the importance of bleeding in some surgeons' eyes. By logical extension, some surgeons suggest that blood transfusion does not cause serious morbidity or death, but is simply associated with these outcomes. Sicker patients are likely to have worse outcomes and are more likely to require blood transfusion than less sick patients. This association may occur because of prolonged operations in older patients who are more likely to be anemic and to have more comorbidities. Transfusion is likely in these high-risk patients, but the transfusion itself may not cause adverse outcomes; it is simply associated with them. Advocates of the cause/effect relationship between blood transfusion and adverse outcomes cite evidence from randomized trials like those tested in an intensive care unit setting.⁹ Others admit that there is no really strong evidence to support this relationship, and suggest that a restrictive transfusion strategy needs to be tested in large clinical trials.¹⁰ I suspect there will never be a truly randomized trial to test the cause-and-effect relationship between blood transfusion and adverse nonbleeding surgical outcomes. Surgeons are not willing to assign transfusion or no transfusion randomly in high-risk patient groups. We are left with observational studies and large database studies to form an opinion about the cause-and-effect relationship between blood transfusion and adverse outcomes. There is increasing evidence that blood transfusion is the culprit—not the innocent bystander—in all types of operative procedures.¹¹⁻¹⁵ Opinions vary about this subject, but I bet that blood transfusion is an active contributor to serious morbidity and operative mortality in patients having cardiac operations.

WHAT ARE THE CONCLUSIONS?

Aprotinin reduces perioperative blood loss, blood transfusion, and reexploration for bleeding in cardiac operations. Experience with this drug is extensive and most of the safety concerns have been uncovered. The same cannot be said for lysine analogs. The aprotinin story points out the need for

drug surveillance following regulatory approval. Reforms are badly needed in this area.

Blood transfusion and perioperative bleeding are likely offenders in development of serious postoperative complications and operative mortality. Synthesis of facts and opinions points to the need to minimize blood transfusion to improve surgical outcomes. Too bad aprotinin is not here to help U.S. surgeons with this problem.

References

1. Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, Royston BD, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg.* 2007;83:S27-86.
2. Health Canada decision on Trasylol (aprotinin). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_124-eng.php. Accessed July 6, 2012.
3. Howell NJ, Senanayake EL, Freemantle N, Pagano D. Putting the record straight: aprotinin is safe and effective: results from a mixed treatment meta-analysis of trials of aprotinin including the BART study. *J Thorac Cardiovasc Surg.* 2013; 145:234-40.
4. Furnary AP, Wu Y, Hiratzka LF, Grunkemeier GL, Page US III. Aprotinin does not increase the risk of renal failure in cardiac surgery patients. *Circulation.* 2007;116:1127-33.
5. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. *N Engl J Med.* 2006;354:353-65.
6. Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med.* 2008;358:2319-31.
7. Mangano DT, Miao Y, Vuylsteke A, Tudor IC, Juneja R, Filipescu D, et al. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA.* 2007;297:471-9.
8. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. *Ann Thorac Surg.* 2012;93:148-54.
9. Hebert PC, Wells G, Tweeddale M, Martin C, Marshall J, Pham B, et al. Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) investigators and the Canadian Critical Care Trials group. *Am J Respir Crit Care Med.* 1997;155:1618-23.
10. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst. Rev (Online).* 2012;4:CD002042.
11. Ferraris VA, Davenport DL, Saha SP, Austin PC, Zwischenberger JB. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. *Arch Surg.* 2012;147:49-55.
12. Scott BH, Seifert FC, Grimson R. Blood transfusion is associated with increased resource utilisation, morbidity and mortality in cardiac surgery. *Ann Card Anaesth.* 2008;11:15-9.
13. Kuduvalli M, Oo AY, Newall N, Grayson AD, Jackson M, Desmond MJ, et al. Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. *Eur J Cardiothorac Surg.* 2005;27:592-8.
14. Ferraris VA, Davenport DL, Saha SP, Bernard A, Austin PC, Zwischenberger JB. Intraoperative transfusion of small amounts of blood heralds worse postoperative outcome in patients having noncardiac thoracic operations. *Ann Thorac Surg.* 2011;91:1674-80; Discussion 1680.
15. LaPar DJ, Crosby IK, Spiess BD, Rich JB, Kasirajan V, Fonner E Jr, et al. Blood product conservation is associated with improved outcomes and reduced costs following cardiac surgery. Presented at: the 92nd Annual Meeting of The American Association for Thoracic Surgery; April 28-May 2, 2012; San Francisco, CA.