Drug Safety 2008; 31 (7): 557-560
0114-5916/08/0007-0557/$48.00/0

Perioperative Safety of Aprotinin in Coronary Artery Bypass Graft Surgery

Is there Life After BART?

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The safety profile of perioperative aprotinin in coronary artery bypass grafting (CABG) has been intensely scrutinized since the publication in 2006 of the controversial article by Mangano and colleagues[1] in which they evaluated the outcome risk associated with aprotinin for CABG. In this landmark study, propensity-adjusted multivariate analysis demonstrated that the adverse outcomes after CABG were not only significantly associated with aprotinin exposure but also that they were dependent on the aprotinin dose. Even though low-dose aprotinin was associated with a lower outcome risk than high-dose aprotinin, it was still a significant perioperative risk factor for renal dysfunction ($p < 0.001$) and composite adverse outcome ($p = 0.003$).[1]

Since this paper was published in January 2006, there has been a flood of discussion about the perioperative safety of aprotinin.[2] Recent high-quality meta-analysis has demonstrated that low-dose aprotinin reduces blood loss and transfusion, but is not associated with any adverse end-organ injury, including renal dysfunction.[3,4] These meta-analyses focused attention on the clinical priority for phase IV randomized trials adequately powered to compare not only efficacy but also safety of the common antifibrinolytic agents for CABG, namely aprotinin, aminocaproic acid and tranexamic acid.[3,4] Furthermore, recent meta-analyses also highlighted the significant redundancy of efficacy clinical trials of aprotinin, which as a result has obscured the evaluation of its perioperative safety.[5,6]

As a result of these concerns about the perioperative safety of aprotinin, the manufacturer significantly modified the package insert for aprotinin to address clinical adverse events such as allergic reactions and renal dysfunction.[2,7] Recently, the manufacturer has also suspended worldwide marketing of aprotinin due to disturbing data from BART (Blood Conservation using Anti-Fibrinolytics: A Randomized Trial),[8] a Canadian multicentre randomized trial of aprotinin, aminocaproic acid and tranexamic acid in high-risk cardiac surgery (further details of this are available at the manufacturer's website).[7]

The BART trial was recently halted after planned interim data analysis by the data monitoring and safety board demonstrated an increase in all-cause mortality associated with aprotinin exposure as compared with aminocaproic acid or tranexamic acid. It is important to remember that the aprotinin regimen selected for the BART trial was high-dose (i.e. 2 million units bolus; 2 million units in cardiopulmonary bypass pump prime; 2 million units via infusion over 4 hours). Thus, the main contemporary phase IV randomized trial powered and designed to examine perioperative safety of aprotinin in cardiac surgery does not address the safety profile of low-dose aprotinin.

The findings of the BART trial (total n = 2331: 761 aprotinin; 770 tranexamic acid; 780 aminocaproic acid, 2002–7) were very recently published in the *New England Journal of Medicine*

(29 May 2008).[8] Indeed, in high-risk cardiac surgery, aprotinin was associated with increased mortality (relative risk [RR] 1.5; 95% CI 1.06, 2.22), with a modest reduction in massive bleeding (RR 0.79; 95% CI 0.59, 1.05). The BART investigators conclude that aprotinin, as compared to the lysine analogues aminocaproic acid and tranexamic acid, should not be utilized in high-risk cardiac surgery. The accompanying editorial questions whether there is life for aprotinin in cardiac surgery after the BART trial.[9]

There are, however, important limitations with the BART trial. Firstly, the study population was exclusively undergoing high-risk cardiac surgery, defined as repeat cardiac surgery, isolated mitral valve replacement, combined valve and CABG surgery, multiple valve replacement/repair, and/or surgery of the ascending aorta or aortic arch. Secondly, only 11.1% (259/2331) of the entire cohort underwent isolated CABG. Thirdly, as mentioned earlier, it only tested high-dose aprotinin. Taken together, these limitations make it impossible to assess the efficacy and safety of low-dose aprotinin in CABG surgery.

Therefore, the article by Dr Kluth and colleagues[10] about low-dose aprotinin after CABG in this issue of *Drug Safety* is most timely. In this paper, the investigators analyse with multivariate logistic regression the relationship between low-dose aprotinin (2 million units in cardiopulmonary bypass pump prime only) and outcome after CABG (n = 2436: 1162 low-dose aprotinin; 1274 no antifibrinolytic) at their institution, Ruhr University, Germany from August 2005 to July 2006.

The main findings of this retrospective investigation are summarized as follows:

- In the total cohort (n = 2436), low-dose aprotinin decreased perioperative blood loss and red blood cell transfusion, with no difference in major clinical outcomes such as survival and major organ injury (brain, heart or kidney). The aprotinin subjects were significantly younger, taller, had better preoperative renal function and were less likely to have preoperative angiotensin blockade. However, the aprotinin subgroup also had a higher prevalence of previous cardiac surgery (7.3% vs 4.1%; p = 0.001), reflecting a common clinical indication for perioperative aprotinin.
- In a cohort subgroup (n = 2049) of patients undergoing primary CABG with internal mammary artery grafting, low-dose aprotinin decreased perioperative blood loss and red blood cell transfusion, with no difference in major clinical outcomes such as survival and major organ injury (brain, heart or kidney).

These major findings from this large contemporary retrospective analysis are consistent with updated meta-analyses of low-dose aprotinin.[3,4] It is interesting to note institutional variation in aprotinin utilization after the release of the Mangano article in 2006.[1] In the study by Kluth et al.,[10] the utilization of low-dose aprotinin fell sharply; however, at an institution in the USA, the utilization of low-dose aprotinin increased significantly throughout 2006.[11]

Although the study by Dr Kluth and colleagues at Ruhr University was retrospective with no randomization of aprotinin exposure, it nevertheless has multiple strengths, as pointed out by the authors. It is, to date, the largest single-centre evaluation of low-dose aprotinin for CABG. The short period of patient recruitment has limited the impact of changes in perioperative care that typically occur over time and that typically introduce major bias in clinical trials. The two study groups stratified by aprotinin exposure (aprotinin, no aprotinin) were relatively clinically homogeneous so that propensity score adjusting was not required in statistical analysis.

The potential sources of bias in this study include the advanced age, better renal function and lower prevalence of angiotensin blockade in the aprotinin subgroup. These factors could combine to be nephroprotective since age and preoperative angiotensin blockade in the presence of aprotinin are known to be significantly nephrotoxic after CABG (odds ratio 2.9; 95% CI 1.4, 5.8; p < 0.0001).[12] However, Dr Kluth and colleagues have highlighted that these intergroup differences, although statistically significant, are hardly clinically significant and

that these small differences were controlled for in the statistical analysis.

How should the perioperative clinician interpret these findings in light of the most current literature, including the BART trial? Two massive studies of protinin and outcome after CABG were very recently published (February 2008) in the *New England Journal of Medicine*.[13,14] The Duke study by Dr Shaw and colleagues[13] analysed data for 10 275 CABG patients at Duke (13.2% aprotinin; 66.8% aminocaproic acid; 20% no antifibrinolytic therapy: 1996–2005). Although the dose of aprotinin was not specified in the paper, aprotinin exposure was associated with a significantly higher risk of mortality and renal dysfunction.[13] The Harvard study by Dr Schneeweiss and colleagues[14] analysed outcome data for 78 199 CABG patients (33 517 aprotinin; 44 682 aminocaproic acid). The aprotinin dose chosen for patient inclusion was a minimum of 2 million units. As a result, the Harvard trial does not discriminate between low-and high-dosage aprotinin regimens. Aprotinin exposure was treated as a categorical variable (yes/no) with disregard for differential effects due to dose. In the Harvard trial, aprotinin exposure was associated with a significantly higher mortality rate. Hence, these two recent highly-powered trials (cumulative n = 88 474) both demonstrate increased mortality risk with aprotinin after CABG, but they do not discriminate whether this mortality risk is dose-dependent or not.

In contrast, a very recent single-centre study from Birmingham, UK (published March 2008)[15] assessed perioperative outcome in 7836 cardiac surgical patients (445 aprotinin; 5403 isolated CABG; 1998–2006). The aprotinin regimen was high-dose. This Birmingham study demonstrated that aprotinin not only reduces bleeding but is also safe and does not affect postoperative survival. A major limitation of this study is the comparatively small size of the aprotinin group, which significantly limits the power of this study to detect adverse outcomes associated with aprotinin.

Where do we go from here: *quo vadis*, aprotinin? The road forward has largely been determined by the published results from the BART trial. Further clinical studies of aprotinin in cardiac surgery will be restricted, but possible.[16] Based on the current literature and aforementioned discussion, a case can be made for a prospective evaluation of the efficacy and safety of low-dose aprotinin compared with the lysine analogues in low-risk cardiac surgery such as CABG. Practically, patient enrolment for such a study may be difficult, given the overall widely publicized negative safety performance of high-dose aprotinin in cardiac surgery.

There is ongoing reflection about the plethora of important lessons learned from the aprotinin saga: the priority to avoid trial redundancy;[5,6] the importance of phase IV trials to investigate therapeutic index;[17,18] the mandate for trials to evaluate comparative efficacy and safety[19] and the clinical caution required with an effective drug.[20] Furthermore, the future of aprotinin may extend beyond safety to improve clinical outcomes both in non-cardiac surgery and cardiac surgery, e.g. haemostasis in general thoracic surgery with ultra-low dose regimens[21] and reduction in heart transplant rejection (note that heart transplantation was not studied in the BART trial).[22]

In summary, I congratulate Dr Kluth and colleagues for highlighting that perioperative aprotinin dose (i.e. the therapeutic window of aprotinin) may be a critical issue in its safety for CABG. Future clinical trials of aprotinin and related perioperative transfusion-sparing drugs must define not only the efficacy but also the safety of each agent as a function of drug dose.

Acknowledgements

Financial support was provided by the Department of Anesthesiology and Critical Care, Hospital of the University of Pennsylvania. The author has no conflicts of interest that are directly relevant to the content of this article.

References

1. Mangano DT, Tudor JC, Dietzel C. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation: the risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 354: 353-65
2. Augoustides J. Con: aprotinin should not be used in cardiac surgery with cardiopulmonary bypass. J Cardiothor Vasc Anesth 2007; 21: 302-4

3. Brown JR, Birkmeyer NJO, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation 2007; 115: 2801-13
4. Henry DA, Carless PA, Moxey AJ, et al. Antifibrinolytic use for minimizing perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2007; 4: CD001886
5. Fergusson D, Glass KC, Hutton B, et al. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? Clin Trials 2005; 2: 218-30
6. Augoustides JG, Fleisher LA. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? Clin Trials 2005; 2: 231-2
7. Bayer HealthCare Pharmaceuticals. Important trasylol safety information. November 5, 2007 [online]. Available from URL: http://www.trasylol.com [Accessed 2008 May 27]
8. Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008; 358: 2319-31
9. Ray WA, Stein CM. The aprotinin story: is BART the final chapter? N Engl J Med 2008; 358: 2398-400
10. Kluth M, Lueth JU, Zittermann A, et al. Low-dose aprotinin use is not associated with adverse effects on safety variables in coronary artery bypass graft surgery. Drug Saf 2008; 31 (7): 617-26
11. Strouch ZY, Chaney MA, Augoustides JG, et al. Case 1-2008: one institution's decreasing use of aprotinin during cardiac surgery in 2006. J Cardiothorac Vasc Anesth 2008; 22: 139-46
12. Kincaid EH, Ashburn DA, Hoyle JR, et al. Does the combination of aprotinin and angiotensin-converting enzyme inhibitor cause renal failure after cardiac surgery? Ann Thorac Surg 2005; 80: 1388-93
13. Shaw AD, Stafford-Smith M, White WD, et al. The effect of aprotinin on outcome after coronary-artery bypass grafting. N Engl J Med 2008; 358: 784-93
14. Schneeweiss S, Seeger JD, Landon J, et al. Aprotinin during coronary-artery bypass grafting and risk of death. N Engl J Med 2008; 358: 771-83
15. Pagano G, Howell NJ, Freemantle N, et al. Bleeding in cardiac surgery: the use of aprotinin does not affect survival. J Thorac Cardiovasc Surg 2008; 135: 495-502
16. US Food and Drug Administration. FDA clinical advisory on aprotinin [online]. Available from URL: http://www.fda.gov/cder/infopage/aprotinin/default.htm [Accessed 2008 May 27]
17. Dietrich W, Busley R, Kriner M. High-dose aprotinin in cardiac surgery: is high-dose enough? An analysis of 8281 cardiac surgical patients treated with aprotinin. Anesth Analg 2006; 103: 1074-81
18. Ferguson TB. Aprotinin: are there lessons learned. JAMA 297: 527-529
19. Ray WA. Learning from aprotinin-mandatory trials of comparative efficacy and safety needed. N Engl J Med 2008; 358: 840-2
20. Sundt TM. The demise of aprotinin: our share of the blame. J Thorac Cardiovasc Surg 2008; 135: 729-31
21. Apostolakis E, Panagopoulos H, Koletsis EN, et al. Influence of ultra-low dose aprotinin on thoracic surgical procedures: a prospective randomized trial. J Cardiothorac Surg 2008 Mar 24; 3: 14
22. Shuhaiber JH, Goldsmith K, Large SR, et al. Does perioperative use of aprotinin reduce the rejection rate in heart transplant recipients? Eur J Cardiothorac Surg 2008; 33 (5): 849-55

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