A recent article and accompanying editorials in the New England journal of Medicine have questioned the safety of using aprotinin in patients having heart surgery. This review will focus on this article in relation to previously published data and experience.

Efficacy

There are over 30 publications from randomized placebo-controlled studies of the use of high dose aprotinin, as described in 1987, in a variety of heart surgeries. These studies, together with two meta-analyses have also shown that aprotinin is effective in not only reducing bleeding but also transfusions and the rates of return to the operating theatre to control bleeding after surgery. Aprotinin is the only drug with this Class A Level 1 evidence for efficacy.

Randomized placebo-controlled studies have also shown the efficacy of aprotinin to reduce transfusion burden in hepatic transplantation and major orthopaedic surgery.

Safety

Studies conducted for regulatory approval

Because aprotinin had no license for use in North America and the Food and Drug Administration required certain pivotal studies to determine both efficacy and safety. These studies included eligible data from patients. The results of those studies have been published separately and as grouped data. These data showed no increased incidence of myocardial infarction or renal impairment and a reduction in the incidence of stroke. Also published is an analysis of pooled data (n = 2283) from all sponsored US clinical trials in patients undergoing primary or repeat coronary revascularization and valvular surgery. This demonstrated a significant reduction in the incidence of stroke in patients receiving full-dose aprotinin compared to placebo, 1.0% vs 2.4% (p = 0.027).

The data for renal function in the pivotal regulatory studies do however show that the plasma creatinine tends to be higher in aprotinin treated patients from about day 4 post operatively and this rise tends to be more protracted in duration. However the rise is not usually to outside the normal range and the incidence of a rise of more than 44 µ mol/L was 18.5% of patients with aprotinin and 15% in the placebo patients. The incidence of an abnormal rise in creatinine was slightly higher in patients having repeat surgery through a prior sternotomy and again the duration of this rise tended to be more prolonged. However this rise was again not statistically significant and in one study was associated with a non-significant RISE in creatinine clearance.

Meta-analysis of data

The Cochrane Collaboration has published an evidence-based review of randomized controlled trials in adults scheduled for non-urgent surgery conducted to assess the effects of aprotinin, aminocaproic acid, and tranexamic acid on perioperative red blood cell (RBC) transfusion. Other outcomes measured included re-operation due to bleeding, mortality, and post-operative complications (non-fatal myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, any thrombosis, renal failure). Of the 89 trials that met inclusion criteria, 61 evaluated aprotinin, of which 55 were in patients undergoing cardiac surgery with 3814 patients randomized to receive aprotinin and 2755 patients randomized to a control group. Relative risk of transfusion was reduced by 30% (RR 0.71; 95% CI 0.66-0.77 p < 0.0001). In 27 studies evaluated of 1758 patients were returned to theatre for re-exploration for bleeding in aprotinin treated patients compared with 58 of 1152 patients included in the control arms of these studies (relative risk 0.40; 95%CI 0.25-0.66: p = 0.0003).

In 28 studies that reported data on mortality, there was a non-significant relative risk reduction of 13% (RR=0.87: 95%CI: 0.63 to 1.19) in those participants treated with aprotinin (N = 2828) compared to control (N = 2085).
In 20 trials that reported data on non-fatal myocardial infarction (MI), the pooled relative risk of sustaining a non-fatal myocardial infarction in those participants treated with aprotinin (N = 1871) compared to control (N = 1117) was 0.97 (95% CI: 0.69 to 1.36).

In 8 trials that reported data on stroke, the pooled relative risk of developing a stroke in those participants treated with aprotinin (N = 605) compared to control (N = 373) was 0.43 (95% CI: 0.16 to 1.19). Aprotinin therapy was therefore associated with a 57% reduction in relative risk of stroke but this did not reach statistical significance.

Of the 13 trials that reported data on renal failure / renal dysfunction, the risk of developing renal failure / renal dysfunction in those participants treated with aprotinin (N = 2210) compared to control (N = 1566) was significantly elevated (RR=1.19: 95% CI: 0.79 to 1.79).

Sedrakyan and colleagues performed a meta-analysis of 35 published, prospective, randomized controlled trials (N = 3,879) that evaluated clinical outcomes (transfusion, mortality, myocardial infarction, renal failure, stroke, atrial fibrillation) in CABG patients administered aprotinin. Aprotinin reduced transfusion requirements by about 40% (RR, 0.61; 95% CI, 0.58-0.66) compared to placebo.

The analysis showed no increased risk of myocardial infarction (28 trials, N = 3555) in which 96/2024 aprotinin treated patients developed an MI vs 77/1531 with placebo (relative risk 0.96, 95% CI 0.65-1.40).

Of note, in aspirin non-users (9 trials, N = 776), patients developed an MI in 6/440 aprotinin-treated and 13/336 placebo-treated patients (relative risk 0.40, 95% CI 0.17-0.92; p< 0.05).

Stroke was evaluated in 18 trials (n = 2,976). Aprotinin therapy was associated with a 47% reduction in relative risk of stroke (RR, 0.53; 95% CI, 0.31-0.90; p<0.05). In the 17 trials that evaluated renal failure/dysfunction included in this analysis aprotinin therapy was not associated with increased or decreased risks of renal failure (RR, 1.01; 95% CI, 0.55-1.83).

The interpretation of the data presented in these meta-analyses was that high dose aprotinin therapy significantly reduced transfusion burden and need for re-exploration, had no significant effect on mortality, myocardial infarction of renal function and may be associated with a statistically significant reduction in the incidence of stroke.

**Multicenter Studies of Perioperative Ischemia (McSPI) Research Group and the Ischemia Research and Education Foundation (IREF) publications.**

This group has collected two large data sets. The McSPI epidemiology 1 dataset collected data from 2417 patients having surgical myocardial revascularization in 24 centers in the USA. These data were collected between 1991 and 1996. The epidemiology 2 database collected data between 1996 and 2000 from patients having myocardial revascularisation in 70 centres in 17 countries. The database captured data from 5436 patients. Of these 5065 patients data were included in the final dataset. These data have been analysed and published in a number of articles 14-19. The one that has caused most attention is the most recent article published in the New England Journal of Medicine (NEJM)15 and, in strident tones, purports to show that the use of aprotinin therapy is associated with a significantly increased risk of myocardial infarction and heart failure, stroke and encephalopathy in patients having primary isolated coronary revascularisation. In addition the article claims to show a doubling of the risk for renal dysfunction and need for dialysis in those patient having primary low risk surgery and also in those having complex surgery. The abstract of the article received massive publicity in the media in the USA and has excited the interest of large numbers of malpractice groups hoping to make vast amounts of money in the courts by ‘helping’ those patients who have been ‘damaged’ by aprotinin therapy. A more careful reading of the article and analysis of the data suggests that, based on published evidence, they may fail in this endeavor.

Re-examination of medical practice in light of any new scientific development is prudent and appropriate. However, scientific examination needs to be in depth, unbiased, based upon prior knowledge and not fraught with emotion and/or panic. One single study in a literature containing well over 1500 articles does not by itself trump all other literature no matter how many patients it contains.

The NEJM article acknowledges that the patients who received aprotinin were considerably more ill and at higher risk for worse outcomes. Table 1 of that article lists and compares 27 different pre-operative characteristics. Notably some very important factors are missing such as patient age and times of cardiopulmonary bypass, use of anti-aggregatory therapy and the influence of country and centre. This is more surprising given that these data have been published by the same authors elsewhere and have been separately shown by this group to have a highly significant impact on risks for renal failure 19, all of the ischemic events discussed in the current article 14 and mortality, heart failure and myocardial infarction separately 18.
Illustrative data from this publication is shown in the table below.

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
<th>Death</th>
<th>Death, MI, Cardiac Failure</th>
<th>Aprotinin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>834</td>
<td>3.8%</td>
<td>18.5%</td>
<td>69%</td>
</tr>
<tr>
<td>USA</td>
<td>1283</td>
<td>2.7%</td>
<td>13.6%</td>
<td>20%</td>
</tr>
<tr>
<td>Canada</td>
<td>444</td>
<td>2.0%</td>
<td>12.4%</td>
<td>6%</td>
</tr>
<tr>
<td>UK</td>
<td>619</td>
<td>1.5%</td>
<td>9.2%</td>
<td>23%</td>
</tr>
<tr>
<td>p</td>
<td>0.034</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Other parts of the article are difficult to interpret due to missing or excluded data. The 2006 NEJM article reports on the data from 4374 of the 5065 eligible patients. In an earlier article using the same dataset, death was reported in 164 patients however multiplying the mortality rates shown in the new article figure 2B by the numbers of patients in each group in figure 1 gives \( \approx 114 \) deaths. This means that the death rate in the 691 excluded patients (7.2%) was about 3 fold higher than the reported patients. This goes without comment but would surely have been apparent to a group of experienced statisticians and experts in data analysis. There are other anomalies and differences between reported numbers of events between the various publications from the same database particularly in relation to myocardial infarction and encephalopathy. Finally Figure 3 of the article shows a statistically significant dose-dependent effect of aprotinin therapy on renal and cardiovascular outcome. These data were from 596 patients given aprotinin therapy. The figure does not differentiate between primary and complex surgery. It is left to the reader to speculate if this neat relationship would still be apparent if the data from the other 699 patients who received aprotinin had been included.

Notwithstanding the problems of interpreting how the data was analysed the fundamental message (to the lawyers and others that have only read the abstract) is that aprotinin is nephrotoxic. Let us examine these data and the conclusions drawn from those data. Studies have been reported from various countries that have investigated the relationship between postoperative renal impairment and preoperative risk. These articles can be used to show the likely proportion of patient who have postoperative renal impairment based on a large rise in plasma creatinine or a rise above an absolute value. Data presented from Italy\(^{14}\) (\( N=2009, \) criteria = creatinine > 177\( \mu \)mol/L) Finland\(^{21}\) (\( N=815, \) criteria = 2-fold rise or > 100 \( \mu \)mol/L rise), Duke University Medical Center in the USA (\( N=2672, \) criteria = rise of > 88 \( \mu \)mol/L) and the original McSPI epidemiology 1 dataset that reported on 2222 patients using the same criteria as in the current article of either a rise of > 62 mmol/L or an absolute value of > 177 \( \mu \)mol/L. If the data from these studies are now plotted together with the data shown in Figure 2A for non-risk adjusted renal dysfunction rates then the following is produced.

Instead of trying to explain why the reported 2-3 fold increased risk of renal dysfunction with aprotinin is not due to an increase with aprotinin but a decrease in the no drug group when compared to current literature the authors dredge out studies in rats from the 1960’s to the 1980’s. These papers were prior to when aprotinin had undergone prospective randomized FDA trials. Cellular effects of aprotinin upon renal cells in rats tested without cardiopulmonary bypass or anticoagulation in the 1960-1980’s may have little relevance to the contemporary argument at hand. Many commentators have noted that the NEJM article does not quote from a study reported from Stanford University in 853 patients having a period of deep hypothermic circulatory arrest. The article\(^{23}\) (whose lead authors was Mrs. Mangano) failed to show an association between renal failure and the use of aprotinin in this setting.

So, what should the members of the caring team conclude or do in light of this recent publication? This prospective data based association study should be digested into the overall 1500 plus papers on cardiac surgery and aprotinin. Everyone should read it carefully and in light of what data is present and what is missing ask him/herself whether he/she agrees or supports the conclusions. The FDA as well as others will review the data and perhaps the methods involved. That may well take time but it is probably certain that some reanalysis will show whether the study is groundbreaking or flawed. It is recognised that the risks of perioperative infection, respiratory and renal failure, length of stay and death all worsen with more transfusion. No transfusion data are presented in the NEJM paper. If the NEJM is incorrect and patients suffer increased transfusions, pneumonias, strokes and death what debt is owed to the public, that is our patients for such information?


