Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: A systematic review and meta-analysis of randomized clinical trials

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Objective: Despite proven blood transfusion benefits, aprotinin may be underused in coronary artery bypass grafting. Reluctance to use aprotinin may stem from safety concerns. The current objective was to evaluate clinical outcomes (mortality, myocardial infarction, renal failure, stroke, atrial fibrillation) in patients undergoing coronary artery bypass grafting who receive aprotinin by performing a quantitative overview of published, randomized, controlled trials.

Methods: MEDLINE, EMBASE, and PHARMLINE (1988-2001) and reference lists of relevant articles were searched for coronary artery bypass grafting studies. Criteria for data inclusion were as follows: (1) random allocation of study treatments, (2) placebo control, (3) enrollment only of patients undergoing coronary artery bypass grafting, (4) no combination with another experimental medication or device, and (5) prophylactic and continuous intraoperative use.

Results: Data from 35 coronary artery bypass grafting trials (n = 3879) confirm that aprotinin reduces transfusion requirements (relative risk 0.61, 95% confidence interval 0.58-0.66) relative to placebo, with a 39% risk reduction. Aprotinin therapy was not associated with increased or decreased mortality (relative risk 0.96, 95% confidence interval 0.65-1.40), myocardial infarction (relative risk 0.85, 95% confidence interval 0.63-1.14), or renal failure (relative risk 1.01, 95% confidence interval 0.55-1.83) risk, but it was associated with a reduced risk of stroke (relative risk 0.53, 95% confidence interval 0.31-0.90) and a trend toward reduced atrial fibrillation (relative risk 0.90, 95% confidence interval 0.78-1.03).

Conclusions: Aprotinin reduces transfusion requirements. Concerns that aprotinin therapy is associated with increased mortality, myocardial infarction, or renal failure risk is not supported by data from published, randomized, placebo-controlled clinical trials. Evidence for a reduced risk of stroke and a tendency toward reduction of atrial fibrillation occurrence was observed in patients who received aprotinin.

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protinin (Trasylol) is the only pharmacologic treatment approved by the US Food and Drug Administration to reduce blood transfusion in coronary artery bypass grafting (CABG). The use of aprotinin in CABG has been associated with more than 45% reduction in blood transfusion relative to placebo in many large multicenter trials.¹⁻³ Growing literature relating blood transfusion to adverse outcomes and associated costs heightens the need to use strategies to reduce transfusion.

A reluctance by surgeons to use aprotinin routinely may result from concerns about the risk of a possible procoagulable state, including such adverse outcomes as myocardial infarction (MI), stroke, and atrial fibrillation, induced by an agent that reduces blood loss. Although some side effects (MI and renal failure) have been

reported in the literature,⁴ evidence supporting these associations is limited and primarily based on case series.⁵ A recent prospective, uncontrolled, observational study reported that therapy with antifibrinolytic agents including aprotinin was associated with increased mortality,⁶ whereas a previous literature review analysis⁷ showed aprotinin use to be associated with decreased mortality. The latter study addressed safety and efficacy of aprotinin use in cardiac surgery by analyzing a mixture of cardiac surgical procedures; the study,⁷ however, did not address important clinical end points reported in more recent studies, such as stroke⁸ and atrial fibrillation.⁹ In addition, numeric discrepancies in the evaluation⁷ led to the criticism that a more rigorous analysis was required.¹⁰

This investigation analyzed the association of aprotinin with mortality, myocardial infarction, renal failure, stroke, and atrial fibrillation by performing a rigorous quantitative overview of all randomized, controlled trials of aprotinin in CABG. As a secondary end point, the relationship of aprotinin administration to the reduced risk of blood transfusion was calculated. The impact of preoperative aspirin use on these clinical outcomes was also evaluated.

Methods

Selection of Trials

Only trials enrolling patients undergoing CABG were included, because that is the only indication approved by the US Food and Drug Administration for aprotinin use in cardiac surgery. Randomized clinical trials of aprotinin use in CABG were identified by searching the MEDLINE, EMBASE, and PHARMLINE databases (1988-2001 through MEDLINE) with the key words *aprotinin* or *trasyol* in combination with *coronary-artery-bypass**, *Me*, *coronary and bypass*, *myocardial revascularization*, *aortocoronary and bypass*, *aortocoronary and shunt*, *aortocoronary and anastomosis*, *coronary and graft*, and *coronary and surgery*. A standard filter designed by the Cochrane Collaboration for identifying randomized clinical trials was used for MEDLINE and EMBASE (adopted from Scottish Intercollegiate Guideline Network [<http://www.sign.ac.uk/methodology/filters.html>]). In addition, reference lists of published trials of aprotinin were searched for additional studies. The initial widest search produced 112 English-language and 3 non-English language articles. Then criteria for study inclusion in the overview were applied, which were as follows: (1) random allocation of study treatments, (2) placebo control, (3) enrollment of only patients undergoing CABG, (4) no combination with another experimental medication or device, and (5) preoperative and continuous intraoperative use (studies with only pump prime use or only postoperative use of aprotinin were excluded). After initial screening of abstracts, 72 studies appeared to conform to the inclusion criteria. After evaluating full reports of all 72 studies, 9 studies were excluded because of only pump prime use of aprotinin (aprotinin used as a single bolus in the cardiopulmonary pump with no continuous infusion; see Appendix Figure 1, 1-9, available online). Another 8 studies were excluded because of enrollment of both patients undergoing CABG and those undergoing valve operation (see Appendix Figure 1, 10-17, available

online). Thorough analysis of the remaining reports found 2 studies in which patients were not randomly assigned to placebo and active treatment groups (see Appendix Figure 1, 18,19, available online), another study that was a subgroup analysis (see Appendix Figure 1, 20, available online), and another study in which recombinant aprotinin was used (see Appendix Figure 1, 21, available online). Fifty-one studies remained. Contact with all 51 corresponding authors was attempted by e-mail or facsimile transmission to clarify and gain additional data not published in the report. Current contact information of corresponding authors was gleaned from recent publications cited in MEDLINE and the World Wide Web. Data were used only from articles that reported adverse event information of interest, and those adequately supplemented by personal communication with the primary investigator; therefore a final 16 studies were not included (see Appendix Figure 1, 22-37, available online). The remaining 35 trials (45 published articles) reported information on any outcomes of interest (mortality, MI, renal failure, stroke, and atrial fibrillation) and met predefined criteria to be selected for the overview (see Appendix Figure 1, 38-82, available online).

Data Collection

For each trial, abstracted data included the frequencies of the events in the aprotinin (full-dose, low-dose, or other) and placebo groups, as well as the numbers of patients randomly allocated to the treatment groups. Information on methodologic quality of the included studies, such as method of randomization, blinding and its methodology, group comparability, and information on similar treatment and follow-up after randomization was also collected. Additional abstracted data included surgical history of the patients (primary CABG trials versus mixed [including both primary and reoperative CABG] trials or only reoperative CABG trials), preoperative (within 7 days) aspirin use, mean age, gender, race, left ventricular ejection fraction, and the publication date. One of the authors (A.S.) abstracted the data, and another author (J.A.E.) participated in adjudication of any discrepancies.

Mortality reported in all trials included only in-hospital deaths. The criterion for defining MI was "definite MI" report according to Minnesota coding classification,¹¹ or in the absence of such coding information, the reports of "new Q-wave MI." The criterion for defining renal failure was the report of this event as clinical diagnosis. Most of the trials that reported renal failure did not report assessment method. However, trials funded by a pharmaceutical company reported a definition of renal failure as any of the following diagnoses: "anuria," "kidney failure," "acute kidney failure," "kidney tubular necrosis," and "uremia." The criteria for the evaluation of stroke frequency were clinical diagnosis of "stroke" and "severe neurologic deficit." In addition, such diagnoses as "cerebrovascular accident," "cerebral embolism," "cerebral hemorrhage," "cerebral infarct," and "cerebral ischemia" were considered. The definition of atrial fibrillation was based on clinical diagnosis of that event.

Although the methods of ascertainment of the events were not standardized among the trials, within each trial they were applied equally to the treatment groups. Reports and descriptions such as "no major complications were observed in the study" were *not* considered to represent 0 events. Only explicit description of the absence of any outcome event was considered as 0 events.

Figure 1. Reported outcomes and blood transfusion requirements in the aprotinin and placebo groups. Data detailing numbers of events and patients randomized are cumulative for all trials; RRs were calculated according to methods described in Statistical Analysis section.

Quality of the Studies

Methodologic quality of included studies was evaluated according to Jadad and coworkers' criteria,¹² which are based on following:

1. "Randomized" study description
2. Description of correct randomization procedure
3. "Double-blinding" study description
4. Description of correct double-blinding
5. Dropouts and adequate description of the end points of interest

Statistical Analysis

The risk estimates for mortality, MI, renal failure, stroke, and atrial fibrillation in the aprotinin and placebo groups were assessed separately. Information from the trials was combined with the general inverse variance-based method,¹³ which incorporates a fixed-effect model and assumes that studies under examination share a common true effect size, that the sampling distribution of these effects is normal, and that all the variability is due to sampling error (homogeneity assumption). In this model, the weights of individual studies correspond to the inverse of the total variance for each study. Numbers-needed-to-treat and their confidence intervals (CIs) were also calculated using risk difference (RD) analysis. RD statistics were particularly important in the trials with 0 events, in which relative risk (RR) was not estimable. In these instances RD statistics still provided an estimate of uncertainty around 0. On the basis of number-needed-to-treat statistics, number of events averted or induced were calculated per 1000 patients undergoing CABG.

The assumption of homogeneity was tested with the χ^2 statistic, formed by summing the weighted difference between each individual estimate and the pooled estimate. This assumption was rejected in only instance of blood transfusion analysis. To account for this, a random effect model was applied to estimate the variance component associated with between-study variation.¹⁴ According to this method, the variance for each individual study in the overview is the sum of within- and between-study components of the variance. However, the estimate from this model was not different from a fixed-effect model; thus rejection of homogeneity

did not influence the results of the blood transfusion analysis. Only fixed-effect model results are reported in this article.

Sensitivity analyses were performed to evaluate the importance of methodologic quality. This factor was not found to have substantial influence on the results. RevMan 4.1 (Cochrane Collaboration, <http://www.cc-ims.net/RevMan>) was used for all statistical analyses.

Results

A total of 35 trials were included in the overview, involving more than 3887 patients (see Appendix Table 1, available online). Most of the studies were double-blind. Age (mean 60.9 years) was reported in 32 randomized trials. Gender was reported in 28 trials, and on average only 16% of study participants were female. Patient race was reported in only 3 randomized trials. In 3 other trials, patient race was determinable from the study country of origin.¹⁵⁻¹⁷ Reoperative CABG was performed in 13.7% of participants as reported in 29 trials.

Full-dose aprotinin was used in 29 trials, whereas low-dose or some other dose was used in 12 trials. Both full-dose and low-dose or other dose aprotinin were used in 6 trials. Aspirin use within a 7-day preoperative period was reported in 27 trials. In 14 of these trials, patients receiving aspirin within the 7-day preoperative period were excluded by the investigators, whereas in the other 13 trials, patients were not excluded on the basis of this criterion.

Mortality

Mortality was assessed in 32 randomized trials including 3779 patients (Figure 1; Appendix Table 2, available online). The overall occurrences of death were similar in combined (full-dose, low-dose) aprotinin (2.47%) and placebo (2.40%) groups, and no significant increased risk of mortality was associated with use of aprotinin (RR 0.96,

95% CI 0.65-1.40). RD statistics showed a 0 mortality difference between the groups per 1000 patients undergoing CABG (95% CI -10 to 10).

MI

MI was assessed in 28 trials including 3555 patients (Figure 1; Appendix Table 2, available online). The occurrence of MI was moderately high in both aprotinin (4.74%) and placebo (5.03%) groups. A tendency toward reduction of the risk of MI in the aprotinin group was relative to placebo (RR 0.85, 95% CI 0.63-1.14); however, it did not reach statistical significance at the 5% level. RD statistics calculated for 1000 patients determined a similar tendency (RD -10, 95% CI -20 to 10). Sensitivity analyses with exclusion of an early study of aprotinin⁴ (in which increased risk of MI was reported and monitoring of anticoagulation not fully appropriate) or the largest study¹ (favoring aprotinin despite concerns related to graft closure) showed no substantial influence on the estimate of RR (range 0.79-0.87).

Renal Failure

Renal failure data were available in 17 trials including 3003 patients (Figure 1; Appendix Table 2, available online). Renal failure incidence also did not vary by study group (aprotinin 1.48%, placebo 1.28%). Meta-analytic estimate for renal failure also did not show increased risk associated with aprotinin therapy (RR 1.01, 95% CI 0.55-1.83). Similarly, RD statistics showed 0 events averted or induced per 1000 patients undergoing CABG when aprotinin was compared with placebo (95% CI -10 to 10).

Stroke

Stroke was reported in 18 trials and evaluated in 2976 patients (Figure 1; Appendix Table 2, available online). Aprotinin use was associated with consistently fewer strokes in most of the individual trials. Stroke occurred in 1.10% of aprotinin and 2.22% of placebo groups. Aprotinin use was associated with a 47% RR reduction (RR 0.53, 95% CI 0.31-0.90) relative to placebo. The exclusion of a trial in which the quality of diagnosis of cerebrovascular accident was questionable and not confirmed in personal communication¹⁷ had little influence on the magnitude of the association (RR 0.49). RD statistics showed a 10-event reduction per 1000 patients undergoing CABG treated with aprotinin (95% CI -20, 0) relative to placebo.

Atrial Fibrillation

Only 11 studies (Figure 1; Appendix Table 2, available online) involving 2460 patients reported information on atrial fibrillation. The occurrences of atrial fibrillation reported in individual trials were substantial in both aprotinin (22.72%) and placebo (25.00%) groups. A tendency toward risk reduction associated with aprotinin use was observed (RR 0.90, 95% CI 0.78-1.04). RD statistics also showed a

tendency toward a more than 30 event reduction (per 1000 CABGs) associated with the use of aprotinin (95% CI -60 to 10).

Blood Transfusion

The number of patients who required any blood transfusion was evaluated in 25 trials involving 3430 patients (Figure 1; Appendix Table 2, available online). The use of aprotinin was consistently associated with fewer patients requiring any blood transfusion. Total numbers of patients requiring any blood transfusion were 40.33% in aprotinin and 63.34% in placebo groups. Accordingly, a 39% risk reduction of blood transfusion was associated with use of aprotinin (RR 0.61, 95% CI 0.58-0.66). RD statistics determined that RR of this magnitude corresponded to more than 250 patients prevented from receiving any blood transfusion per 1000 CABG procedures (95% CI -280 to -220).

Events by Subgroups of Preoperative Aspirin Use

Subgroup analyses stratified by aspirin use were evaluated in fewer trials (Figure 2). In addition, sufficient numbers of events were available regarding only three outcomes (mortality, MI, and blood transfusion). Presence or absence of aspirin use had no impact on mortality as related to aprotinin therapy. The stratified analysis shows that in trials where aspirin users within 5 to 7 days before surgery were excluded, aprotinin use was associated with statistically significant risk reduction in the occurrence of MI (RR 0.40, 95% CI 0.17-0.92). In trials where aspirin users were not excluded, no difference between aprotinin and placebo groups was observed regarding the occurrence of MI (RR 1.00, 95% CI 0.71-1.40). In addition, fewer patients required blood transfusion in trials where aspirin users were excluded (RR 0.53, 95% CI 0.47-0.60) than in trials where aspirin users were not excluded (RR 0.67, 95% CI 0.61-0.72).

Discussion

Our quantitative systematic overview of clinical endpoints indicates that aprotinin therapy is not associated with increased risks of mortality, MI, or renal failure. In contrast, a tendency toward a reduction of MI was observed among patients treated with aprotinin relative to placebo. Moreover, use of aprotinin was associated with a 47% reduction in stroke and tended to be associated with a reduced risk of atrial fibrillation. Aprotinin therapy was also associated with a 39% reduction in the number of patients requiring blood transfusion.

Concerns about MI (graft closure) and renal failure may contribute to relative underuse of this medication in CABG. The contention that aprotinin might be associated with MI and renal failure originated when Cosgrove and colleagues⁴ reported overall 14 MI events among 113 patients treated

Figure 2. Reported outcomes and blood transfusion requirements in the aprotinin and placebo groups stratified by aspirin users (upper panel) and nonusers (lower panel). Study participants were considered preoperative aspirin users if investigators did not exclude patients taking aspirin 7 days before surgery. Data detailing numbers of events and patients randomized are cumulative for all trials; RRs were calculated according to methods described in Statistical Analysis section.

with aprotinin versus 4 among 56 treated with placebo. Although substantial increase in creatinine was also reported in aprotinin-treated patients, occurrence of renal failure itself was not different between the groups (8 of 133 vs 4 of 56 in the clinical study report). Although a similar trend was reported in another well-known clinical trial,¹⁸ evidence linking aprotinin to these side events was limited. Further studies on coagulation monitoring have shown that aprotinin increases the activated clotting time in the Celite-based measurement,¹⁹ which could potentially lead to underheparinization and contribute to the observed findings in studies conducted earlier. Although increased or decreased risks of MI and renal failure cannot be definitely excluded (because of wide confidence intervals), our findings should alleviate concerns that aprotinin causes increases in the occurrence of these adverse events.

One previous study attempting to address systematically the issue of mortality and MI found aprotinin to be associated with reduced mortality and slightly higher risk of MI.⁷ However, the analysis included a mixture of cardiac surgical procedures (mitral valve, aortic valve, coronary bypass, etc). In addition, others have indicated concerns about inaccuracies in patient numbers, discrepancies in odds ratios extracted from individual studies, and inappropriate appli-

cation of inclusion criteria, casting doubt on conclusions drawn from this previous systematic analysis.¹⁰ A recent report suggested that antifibrinolytic therapy, including aprotinin, increased mortality among patients undergoing CABG.⁶ The study used data from studies in which treatment group assignment was not described as randomized or controlled; thus treatment bias or use of antifibrinolytics as rescue therapy, instead of as prophylaxis for bleeding, could well explain the data in this observational study. In our analysis of aprotinin therapy, no decrease or increase in mortality was confirmed; the data showed aprotinin therapy to be associated with a mortality risk ratio of 0.96 (95% CI 0.65, 1.40). In addition, no tendency toward an increased occurrence of MI in aprotinin treated patients was shown, and in fact the opposite tendency was observed.

To our knowledge, this is the first systematic analysis study to report that substantial stroke reduction benefits could theoretically be associated with aprotinin use, supporting an observation originally published by Levy et al.² The current analysis indicates that approximately 10 cerebrovascular accidents can be averted per 1000 patients undergoing CABG when aprotinin is used. A number of theories describing the effect of aprotinin on risk of stroke have been discussed. As early as 1994, Murkin and associ-

ates²⁰ reported that serine protease inhibitors such as aprotinin may have cerebroprotective effects and proposed that aprotinin could prevent or ameliorate the initial endothelial response in the presence of ischemic cerebral injury and could improve the outcome after cerebral ischemia. Later, Smith and Muhlbaier⁵ also reported a tendency toward stroke reduction in a combined analysis of US aprotinin trials. In a review study, Royston²¹ also reported that anti-inflammatory actions and modifications in vascular tone associated with aprotinin therapy may be related to improved outcome by reducing the occurrence of permanent neurologic deficit or stroke after heart operations. A recent retrospective analysis of a cardiac surgery population at high risk for stroke⁸ observed a significant decrease in the occurrence of stroke among patients administered full-dose aprotinin relative to the placebo group. Our investigation provides additional data describing the cerebrovascular effect of aprotinin. The tendency toward a reduction in atrial fibrillation associated with aprotinin, supporting clinical data published previously,^{9,22} provides another possible mechanism. Atrial fibrillation is associated with a higher risk of cerebrovascular accidents, particularly in the early postoperative period, so the tendency toward prevention of approximately 30 atrial fibrillations per 1000 patients undergoing CABG could potentially contribute to the observation of fewer strokes associated with aprotinin.

In our study, the number of patients averted from receiving any blood transfusion when treated with aprotinin was accurately quantified. Although blood transfusion benefits associated with aprotinin have been reported at length,¹⁻⁴ a summary estimate with the large population (n = 3430) generated in this study has not been reported previously in the literature. These data demonstrate that relative to placebo approximately 250 of 1000 patients undergoing CABG could theoretically be prevented from any blood transfusion if treated with aprotinin.

Subgroup analysis of patients enrolled in the trials in which aspirin users were excluded showed aprotinin therapy to have no influence on mortality; however, a reduction in the occurrence of MI was observed. The reduction in MI is likely to result from some aspect of aprotinin action other than its ability to reduce blood transfusion requirements. However, these findings should be interpreted with caution, because fewer patients were enrolled in these trials. Similarly, we found that neither full-dose regimen nor low-dose regimen was associated with more frequent adverse events relative to placebo (data not included). Although full-dose aprotinin seemed to be associated with a higher reduction in the transfusion requirements (RR 0.59, 95% CI 0.55-0.64) than low-dose aprotinin (RR 0.65, 95% CI 0.59-0.72), comparison of these two regimens is a question of its own, and these results need to be confirmed in a more specific meta-

analyses that also include trials without a placebo arm that directly compare these regimens.

Conclusions

Aprotinin substantially decreases transfusion requirements in patients undergoing CABG. The concern that aprotinin therapy is associated with increased risk of mortality, MI, or renal failure is not supported by data from published, randomized, placebo-controlled clinical trials. For stroke, evidence of a reduced risk associated with aprotinin therapy was shown. A tendency toward reduction in atrial fibrillation occurrence associated with aprotinin use was observed. The balance of effects is positive with aprotinin use.

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