Aprotinin But Not $\epsilon$-Aminocaproic Acid Decreases Interleukin-10 After Cardiac Surgery With Extracorporeal Circulation

Randomized, Double-Blind, Placebo-Controlled Study in Patients Receiving Aprotinin and $\epsilon$-Aminocaproic Acid

Philip E. Greilich, MD; Kuniyuki Okada, MD; Paige Latham, MD; Ramaswamy Ravi Kumar, MD; Michael E. Jessen, MD

Background—Extracorporeal circulation induces a systemic inflammatory response, which may adversely affect organ function. One manifestation of this response is increased fibrinolysis. Antifibrinolytic drugs such as aprotinin and $\epsilon$-aminocaproic acid have been effective in reducing fibrinolysis and blood loss after extracorporeal circulation; however, the effects of antifibrinolytic drugs on proinflammatory and anti-inflammatory mediators are not known. This study examined the effects of aprotinin and $\epsilon$-aminocaproic acid on plasma levels of proinflammatory [interleukin-6 (IL-6)] and anti-inflammatory [interleukin-10 (IL-10)] cytokines during and after extracorporeal circulation.

Methods and Results—Seventy-two patients undergoing coronary artery bypass grafting with extracorporeal circulation were randomly assigned in a double-blind study to receive high-dose aprotinin, $\epsilon$-aminocaproic acid, or saline placebo. Plasma levels of IL-6 and IL-10 were measured at 5 time points before, during, and after extracorporeal circulation. In all 3 groups, both IL-6 and IL-10 rose significantly after institution of extracorporeal circulation and remained elevated through the first postoperative day. Compared with saline, aprotinin significantly reduced IL-10 ($P = 0.02$) and peak IL-6 ($P = 0.02$) after extracorporeal circulation. In contrast, none of the reductions in IL-6 and IL-10 by $\epsilon$-aminocaproic acid achieved statistical significance. Both aprotinin and $\epsilon$-aminocaproic acid decreased blood loss compared with saline, but there was no significant difference in the number of patients receiving blood products among the treatment groups.

Conclusions—These data suggest that aprotinin and $\epsilon$-aminocaproic acid differ in their effects on the inflammatory response to extracorporeal circulation. Aprotinin but not $\epsilon$-aminocaproic acid appears to attenuate the rise in the proinflammatory and anti-inflammatory cytokines IL-6 and IL-10. Further studies will be required to determine if these cytokine alterations translate to changes in clinical outcomes.

Key Words: interleukins $\bullet$ antifibrinolytic agents $\bullet$ aprotinin $\bullet$ extracorporeal circulation $\bullet$ surgery

Patients undergoing cardiac surgery with extracorporeal circulation have a pronounced systemic inflammatory response, which leads to significant increases in both the proinflammatory cytokine interleukin (IL)-6 and the anti-inflammatory cytokine IL-10. Kawamura et al demonstrated that both IL-6 and IL-10 increase dramatically during extracorporeal circulation, peaking approximately 60 minutes after declamping of the aorta.

Aprotinin, a serine protease inhibitor, decreases the inflammatory response associated with extracorporeal circulation. Aprotinin inhibits plasmin-mediated fibrinolysis and many of the enzymatic intermediaries that contribute to the generalized extracorporeal circulation inflammatory response. Some but not all studies have shown that aprotinin effectively reduces the production of IL-6. The effect of aprotinin on IL-10, however, is not clear. Hill et al demonstrated that IL-10 levels were lower at 1 hour but higher at 24 hours after extracorporeal circulation in patients who received aprotinin (compared with saline placebo).

$\epsilon$-Aminocaproic acid is commonly used in heart surgery to inhibit fibrinolysis and reduce blood loss after extracorporeal circulation. $\epsilon$-Aminocaproic acid is a lysine analog that blocks binding of plasminogen and tissue plasminogen activator to fibrinogen, yet has no known effect on the systemic inflammation response. More specifically, the effects of $\epsilon$-aminocaproic acid on IL-6 and IL-10 following extracorporeal circulation have not been reported. Our study is a randomized, double-blind, placebo-controlled study that was designed to evaluate the effect of both aprotinin and $\epsilon$-aminocaproic acid on cytokines IL-6 and IL-10 and to test...
the hypothesis that inhibition of extracorporeal circulation–
induced hyperfibrinolysis with aprotinin and e-aminocaproic
acid will decrease the production of the both the proinflam-
atory and anti-inflammatory cytokines after extracorporeal
circulation.

Methods

Patient Selection

After institutional review board approval and written informed
consent was given, 72 patients scheduled for elective, primary
corony artery bypass with extracorporeal circulation were
enrolled in the study. Patients were randomly assigned to receive (1)
full-dose aprotinin (2×10^6 KIU [load], 2×10^6 KIU [pump prime],
5×10^3 KIU/h [infusion]); (2) e-aminocaproic acid (100 mg/kg
[load], 5 g [pump prime], 30 mg/kg per hour [infusion]); or (3) saline
(200 mL [load], 200 mL [pump prime], 50 mL/h [infusion]) in a
double-blinded fashion. Patients were excluded if they received
corticosteroids, dipyridamole, or anticoagulants or had documented
platelet or coagulation abnormalities or had treatment with
thrombolytic therapy within 5 days of surgery. Other exclusion
criteria included a creatinine level >2.0 mg/dL, ejection fraction
<30%, and a history of adverse reaction to aprotinin or
e-aminocaproic acid. Patients were not excluded from the study if
they were receiving salicylates, nonsteroidal anti-inflammatory
drugs, or heparin before surgery.

Technique of Operation

Preoperative medications, including β-blockers, nitrates, and antiarrhythmic
agents, were continued until surgery. After sedation with 2
to 5 mg midazolam, intravenous access, a radial arterial cannula, and
routine monitors were placed. After induction with 0.3 mg/kg
etomidate, 5 to 10 μg/kg fentanyl, and 1 mg/kg rocuronium, a
pulmonary arterial catheter was inserted through the right internal
jugular vein. Anesthesia was maintained with inhaled isoflurane (0.2
to 1.0%) and fentanyl (25 to 50 μg/kg). A propofol infusion, 25 to 50
μg/kg per minute, was started at the beginning of rewarming during
cardiopulmonary bypass and continued into the postoperative period
for sedation. The following parameters were measured: heart rate,
mean arterial blood pressure, peripheral arterial saturation, central
venous pressure, mean pulmonary arterial pressure, pulmonary
artery pressure, mean arterial blood pressure, peripheral arterial saturation,
cardiac output (all measurements made in triplicate with the thermodynamical technique), and continuous ST-
segment analysis in ECG leads II and V_5.

In the intensive care unit, sedation was provided as needed with 10
to 50 μg/kg per minute propofol and 2 mg IV morphine sulfate until
the following extubation criteria were met: awake and alert, arterial
P_o2>80 mm Hg on ≤40% O_2, arterial P_CO2<50 mm Hg on
10 mm Hg pressure support, tidal volume ≥7 mL/kg, temperature
>36.0°C, hemodynamically stable on minimal inotropic support,
>0.5 mL/h urine output, and ≤50 mL/h chest tube output.

All the procedures were performed by 1 of 3 surgeons using a
standardized technique for coronary revascularization and myocardial
protection. Extracorporeal circulation was performed with the use of a
membrane oxygenator (Gish) with nonpulsatile flow with a
centrifugal pump (Biomedicus). The extracorporeal circulation
was primed with 2 L of lactated Ringers solution, 100 mL of
25% albumin, 44.6 meq of sodium bicarbonate, and 50g of mannitol.
Perfusion was done at moderate systemic hypothermia (28° to 32°C),
and myocardial protection was achieved with antegrade and retro-
grade sanguineous (4:1, blood:cardioplegia) cardioplegia adminis-
tered every 20 minutes. Perfusion flow rates were maintained at 2
L/min per m² during hypothermia and at 2.5 L/min per m² during
normothermia.

Anticoagulation was achieved with bovine heparin and monitored
to achieve target kaolin activated clotting time levels of 480 seconds.
Temperature was monitored with a bladder probe, and separation of
bypass was initiated at 36.5°C. Reversal and the presence of residual
heparin were monitored with a protamine titration protocol.

Blood was collected from the surgical field by pump suctions
during full anticoagulation and returned to the patient during surgery.
Mediastinal chest drainage was not reinfused. Packed red blood cells
were transfused when the hemoglobin level fell below 8.0 g/dL, and
platelet concentrates were given for platelet counts <70 000/μL in
patients with clinical evidence of microvascular bleeding.

Interleukin Measurements

Arterial blood samples (5 mL) were collected at (1) baseline (before
induction); (2) 10 minutes of extracorporeal circulation; (3) 30
minutes after extracorporeal circulation (after heparin reversal), (4) 3
hours after extracorporeal circulation; and (5) 18 hours after extra-
corporeal circulation. Blood was drawn from an arterial line directly
into a polypropylene syringe and was transferred into a 3.2% sodium
citrate–buffered Becton Dickinson brand Vacutainer. The concen-
trations of IL-6 and IL-10 in plasma were determined with a
sandwich-type ELISA kit (R&D Systems). All standards and samples
were assayed in duplicate.

Postoperative Physiological Variables

Hemoglobin, hematocrit, platelet counts, fibrinogen concentration,
and white blood counts were measured at all data points. Mediastinal
chest tube drainage and blood product administration was recorded for
the first 24 hours after surgery. Postoperative physiological variables
(body temperature, cardiac index, and systemic vascular resistance) were measured immediately after induction of anesthesia
and 30 minutes after extracorporeal circulation. The duration of
postoperative mechanical ventilation, the duration of inotropic sup-
port, and the length of the intensive care unit stay were recorded.

Statistical Analysis

A power analysis was performed to estimate the number of patients
required for this study. On the basis of preliminary data, it was
assumed that a change in interleukin levels of 15% would occur in
the aprotinin group compared with the other groups. Assuming a
2-sided test with a probability of a type I error of 0.05 and a
statistical power of 80%, it was calculated that each group would
require at least 20 patients.

Statistical analysis was performed with SAS statistical software
(SAS Institute). Differences in dichotomous variables between
groups were evaluated by Fisher’s exact test, and differences in
continuous variables were analyzed by a 1-way ANOVA for norm-
dally distributed data and a nonparametric 1-way ANOVA when
applicable. The behavior of each of the 3 treatment groups over time
was analyzed by repeated-measures ANOVA. The treatment effect at a
given time point was compared with the pre-CPB value (baseline) and
the post-CPB value (either 30 minutes or 3 hours after extracor-
poreal circulation). For the analysis of continuous variables (body
temperature, cardiac index, and systemic vascular resistance) were measured immediately after induction of anesthesia
and 30 minutes after extracorporeal circulation. The duration of
postoperative mechanical ventilation, the duration of inotropic sup-
port, and the length of the intensive care unit stay were recorded.

Results

A total of 72 patients were randomly assigned to either the
aprotinin (n=24), e-aminocaproic acid (n=23), or saline
(n=25) group. The patient and surgical demographics are data
outlined in Tables 1 and 2, respectively. There were no
significant differences between the patient and surgical de-
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TABLE 1. Patient Demographics

<table>
<thead>
<tr>
<th>Medications, n (%)</th>
<th>Saline</th>
<th>EACA</th>
<th>Aprotinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin therapy</td>
<td>23 (79)</td>
<td>19 (90)</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Intraavenous heparin</td>
<td>7 (24)</td>
<td>5 (24)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>24 (83)</td>
<td>17 (81)</td>
<td>20 (83)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>20 (69)</td>
<td>14 (67)</td>
<td>19 (79)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>17 (59)</td>
<td>17 (81)</td>
<td>17 (71)</td>
</tr>
<tr>
<td>H/o smoking</td>
<td>24 (83)</td>
<td>14 (67)</td>
<td>17 (71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (66)</td>
<td>16 (76)</td>
<td>19 (79)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (48)</td>
<td>10 (48)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2 (7)</td>
<td>4 (19)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>H/o myocardial infarction</td>
<td>16 (55)</td>
<td>11 (52)</td>
<td>11 (46)</td>
</tr>
<tr>
<td>H/o congestive heart failure</td>
<td>7 (24)</td>
<td>4 (17)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>2.1±0.2</td>
<td>2.1±0.2</td>
<td>2.1±0.3</td>
</tr>
<tr>
<td>Systolic</td>
<td>128±7</td>
<td>126±7</td>
<td>125±10</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>55.3±15</td>
<td>58.2±15</td>
<td>55.5±13</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.1±0.2</td>
<td>2.1±0.2</td>
<td>2.1±0.3</td>
</tr>
<tr>
<td>Age, y</td>
<td>62±7</td>
<td>63±8</td>
<td>64±9</td>
</tr>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| Values are mean±SD or n (%). EACA indicates ε-aminocaproic acid; BSA, body surface area; and H/o, history of.  

4-hour blood loss. Patients in the aprotinin and ε-aminocaproic acid groups had significantly less blood loss compared with the saline group (P<0.05). There was no significant difference in blood loss noted between patients in the aprotinin and ε-aminocaproic acid groups.

The influence of extracorporeal circulation on IL-10 for each treatment group (aprotinin, ε-aminocaproic acid, saline) is illustrated in the Figure. There were no significant differences in the baseline IL-10 between groups. Administration of aprotinin resulted in a significant overall treatment effect compared with saline (P=0.02), whereas ε-aminocaproic acid did not (P=0.51). In addition, no significant differences were noted between the aprotinin and ε-aminocaproic acid groups (P=0.10). IL-10 levels at 18 hours after extracorporeal circulation were significantly elevated compared with preinduction (P<0.05) yet did not differ between treatment groups.

Compared with saline, peak IL-6 was significantly lower in the aprotinin (P=0.024) but not the ε-aminocaproic acid (P=0.46) group in the early postbypass period (30 minutes to 3 hours). IL-6 levels at 18 hours after extracorporeal circulation were also significantly increased in all treatment groups compared with preinduction levels (P<0.01).

The influence of aortic cross-clamp time, total extracorporeal circulation time, and blood transfusions on peak IL-6 and IL-10 were analyzed overall and within each treatment group. We found no correlation between peak IL-6 or IL-10 and aortic cross-clamp time or total extracorporeal circulation times. When analyzed by treatment group, there was a weak correlation between peak IL-6 and aortic clamp (r=0.550) and total extracorporeal circulation (r=0.555) times in the ε-aminocaproic acid group only. There were no significant differences in the overall and peak IL-6 and IL-10 levels between those receiving blood products (before drawing these samples) and those who did not receive blood products. The percentage of subjects receiving blood products during surgery and the early after the bypass period did not differ between treatment groups, nor did their peak levels of IL-6 or IL-10 within each group (Table 2).

Table 3 lists postoperative physiological and clinical milestones for each of the 3 treatment groups. The complete blood counts were not significantly different, with the exception of the white blood cell count between patients in the ε-aminocaproic acid and saline groups (P<0.05).

Discussion

Although multiple studies have demonstrated that heart surgery with extracorporeal circulation significantly increases proinflammatory and anti-inflammatory cytokines, the effect of aprotinin and ε-aminocaproic acid on the cytokine synthesis inhibitory factor (CSIF) IL-10 remains unclear.3,8,11 The findings from this study indicate that high-dose aprotinin significantly attenuates increases in IL-10 seen in patients after extracorporeal circulation. The decreased IL-10 response in the aprotinin group was also associated with a reduction in peak IL-6 levels. A significant effect of ε-aminocaproic acid on the IL-10 and IL-6 response was not identified.

The significant increase and time course of peak IL-10 levels in our study was consistent with previously reported data in patients undergoing cardiac surgery with extracorporeal circulation.6,13 The effect of high-dose aprotinin on the IL-10 response after extracorporeal circulation is less clear. Hill and colleagues1 showed a minor reduction in IL-10 levels with aprotinin in the period immediately after extracorporeal circulation, but paradoxically reported a significant increase in IL-10 levels in the aprotinin group 24 hours after surgery (compared with a saline control group). Some investigators have suggested that the anti-inflammatory effects of aprotinin are similar to steroids,14 yet only steroids have consistently increased IL-10 levels after extracorporeal circulation in well-controlled trials.4,15 These data suggest that the mechanism by which aprotinin and steroids influence the balance of proinflammatory and anti-inflammatory cytokines may differ.
The response of IL-6 levels to the stimulus of extracorporeal circulation seen in this study was qualitatively similar to that observed for IL-10. A significant reduction in peak IL-6 levels after extracorporeal circulation was identified with aprotinin but not e-aminocaproic acid. These findings are consistent with studies reported elsewhere, although other investigators have failed to identify any modulating effect using lower doses of this drug.

Increases in IL-10 after heart surgery are believed to represent an endogenous reaction aimed at suppressing the inflammatory response, with its major putative effect directed toward inhibition of clot-bound plasmin activity. The reasons for the decrease in the IL-10 response with aprotinin found in the present study are not known. If IL-10 levels represent a response to the proinflammatory cytokines (such as IL-6) that are invoked by extracorporeal circulation, then reduction in proinflammatory molecules by aprotinin may be the primary event. Alternatively, aprotinin may directly affect the production and/or release of IL-10 by monocytes and T-cells. Additional studies will be required to identify the mechanism of this observation. e-Aminocaproic acid did not significantly reduce the response of either IL-6 levels and show signs of improved respiratory and hemodynamic function after extracorporeal circulation surgery. In contrast, elevations in IL-10 have also been associated with an increased mortality in patient with febrile disease and morbidity (infection and so forth) in selected groups of patient undergoing extracorporeal circulation.

The clinical relevance of elevated anti-inflammatory cytokines, such as IL-10, after extracorporeal circulation surgery is not clear. Multiple studies have demonstrated that steroids increase IL-10 and decrease the proinflammatory cytokines (IL-6 and IL-8). Patients receiving steroids achieve higher IL-10 levels and show signs of improved respiratory and hemodynamic function after extracorporeal circulation surgery. Like all clinical investigations, there are significant limitations to the conduct of the study and interpretation of the data. Blood samples are collected at time points determined by the progress of the operation (in relation to extracorporeal circulation, protamine administration, or temperature) but not at fixed times after skin incision because of variability in the length of the surgical procedures. Studies that use additional time points have shown that IL-6 levels sharply peak then rapidly fall over the first 6 hours after extracorporeal circulation. Furthermore, patients in the present study were subjected on average to a longer period of extracorporeal circulation than that reported in other studies. Because longer duration of extracorporeal support appears to represent a

### TABLE 2. Surgical Demographics

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>EACA</th>
<th>Aprotinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of distal anastomoses</td>
<td>3.3±1.0</td>
<td>3.4±0.6</td>
<td>3.3±0.9</td>
</tr>
<tr>
<td>Aortic cross-clamp time, min</td>
<td>74±23</td>
<td>72±19</td>
<td>76±26</td>
</tr>
<tr>
<td>ECC time, min</td>
<td>123±36</td>
<td>128±39</td>
<td>126±33</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin, units×100</td>
<td>477±141</td>
<td>438±101</td>
<td>464±102</td>
</tr>
<tr>
<td>Protamine, mg</td>
<td>338±110</td>
<td>317±98</td>
<td>332±90</td>
</tr>
<tr>
<td>Blood loss/transfusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-h blood loss, median (25th, 75th)</td>
<td>372 (200, 405)</td>
<td>192* (100, 366)</td>
<td>100* (95, 215)</td>
</tr>
<tr>
<td>Excessive early blood loss, n (%)</td>
<td>5 (25)</td>
<td>3 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Transfused intraoperatively and early post-ECC, n (%)</td>
<td>6 (24)</td>
<td>6 (26)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Transfused before discharge, n (%)</td>
<td>13 (45)</td>
<td>5 (24)</td>
<td>7 (29)</td>
</tr>
</tbody>
</table>

Values are mean±SD unless otherwise indicated.
EACA indicates e-aminocaproic acid; ECC, extracorporeal circulation; and excessive blood loss, >600 mL of mediastinal chest tube drainage in the first 4 hours after placement.

### TABLE 3. Postoperative Physiological Variables and Clinical Milestones

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>EACA</th>
<th>Aprotinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>36.7±0.1</td>
<td>36.7±0.2</td>
<td>36.8±0.1</td>
</tr>
<tr>
<td>White blood cell count, 10^3/μL</td>
<td>10.9±1.3*</td>
<td>7.1±0.6</td>
<td>9.1±1.2</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.0±0.4</td>
<td>2.2±0.4</td>
<td>2.1±0.3</td>
</tr>
<tr>
<td>SVRI, dyne · s · cm⁻²/m²</td>
<td>440±90</td>
<td>404±78</td>
<td>466±58</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-a gradient, mm Hg</td>
<td>306±30</td>
<td>314±36</td>
<td>250±18</td>
</tr>
<tr>
<td>Clinical milestones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionsotropic and pressor support, h</td>
<td>39±8</td>
<td>40±7</td>
<td>35±6</td>
</tr>
<tr>
<td>Mechanical ventilation, h</td>
<td>24±5</td>
<td>26±6</td>
<td>21±3</td>
</tr>
<tr>
<td>ICU length of stay, d</td>
<td>4.3±1.8</td>
<td>4.6±2.1</td>
<td>4.4±2.0</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
EACA indicates e-aminocaproic acid; SVRI, systemic vascular resistance index; A-a gradient, alveolar-arterial oxygen gradient; and ICU, intensive care unit.
P<0.05 compared with e-aminocaproic acid.
greater stimulus to the inflammatory response, this may in part explain why other investigators have not identified an effect of aprotinin on IL-10 levels.

The use of blood products, especially platelet concentrates, can increase circulating IL-6 levels. The subset of our patient population receiving blood products before the peak of IL-6 and IL-10 was small (≈25%), and subgroup analysis of patients not receiving blood products did not alter our findings. Finally, the ultimate effect of modulation of the inflammatory response on clinical outcomes such as infection, respiratory failure, or survival cannot be determined in a study of this size.

**Acknowledgments**

This study was funded by the Department of Veterans Affairs (VSN 17 New Investigator Award) and by Research Starter Grants from the Society of Cardiovascular Anesthesiologists and Bayer Corporation. The authors would like to express appreciation to all of the members of the Cardiothoracic Research Team (anesthesiologists, surgeons, perfusionists, and nurse coordinators) for their outstanding work in completing this trial.

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_Circulation_. 2001;104:I-265-I-269
doi: 10.1161/hc37t1.094781

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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