Pharmacodynamics and Pharmacokinetics of Higher-Dose, Double-Bolus Eptifibatide in Percutaneous Coronary Intervention

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Background—Pharmacodynamics of eptifibatide, a cyclic heptapeptide antagonist of platelet glycoprotein IIb/IIIa, are substantially altered by anticoagulants that chelate calcium, resulting in overestimation ex vivo of the in vivo effects of this agent. We conducted a dose-ranging study to characterize the pharmacodynamics and pharmacokinetics of eptifibatide under physiological conditions.

Methods and Results—Patients (n = 39) undergoing elective percutaneous coronary intervention were randomly assigned to an eptifibatide bolus followed by an infusion (180-μg/kg bolus followed by 2 μg/kg per minute or 250-μg/kg bolus followed by 3 μg/kg per minute) for 18 to 24 hours. In a 2:1 ratio, these patients received either a second bolus of eptifibatide (90 μg/kg or 125 μg/kg for the initial 180-μg/kg or 250-μg/kg groups, respectively) or placebo 30 minutes after the initial bolus. Bleeding times, ex vivo platelet aggregation, receptor occupancy, and plasma eptifibatide levels at baseline and at 1, 2, 3, 4, 6, and 8 hours were evaluated. Platelet inhibition was dose dependent and >80% in all groups by steady state. The single-bolus regimens had a transient loss of inhibition at 1 hour, consistent with rapid distribution and drug elimination. Pharmacokinetic modeling suggested that optimal dosing of eptifibatide would be obtained with a 180-μg/kg bolus and a 2-μg/kg per minute infusion followed by a second 180-μg/kg bolus 10 minutes later.

Conclusions—A novel higher-dose, double-bolus regimen of eptifibatide in coronary intervention attains and maintains >90% inhibition of platelet aggregation in >90% of patients, providing the pharmacodynamic construct for the design of the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial of adjunctive eptifibatide in coronary stent implantation. (Circulation. 2001;104:406-411.)

Key Words: glycoproteins ♦ stents ♦ pharmacokinetics

Treatment with platelet glycoprotein (GP) IIb/IIIa antagonists has consistently improved clinical outcomes of patients with acute coronary syndromes and in those undergoing percutaneous coronary intervention (PCI).1-3 Eptifibatide (Integrilin, COR Therapeutics, Inc, and Schering-Plough, Inc), a cyclic heptapeptide antagonist of the GP IIb/IIIa integrin receptor, is an intravenous antagonist with rapid onset of action and short half-life. In the IMPACT-II (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II) study of eptifibatide as an adjunct to PCI, eptifibatide was given as a single 135-μg/kg bolus before PCI followed by either a 0.5- or 0.75-μg/kg per minute infusion for 20 to 24 hours.3 Subsequently, Phillips et al4 reported that the pharmacodynamics of these doses of eptifibatide were substantially overestimated by the use of the conventional ex vivo assay methodologies as the result of chelation of calcium by the anticoagulant sodium citrate. Specifically, only 50% of maximal GP IIb/IIIa receptor blockade was achieved with the doses studied in IMPACT-II.

As a prelude to the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, we conducted a dose-escalation, dose-confirmation study termed the PRIDE (Platelet aggregation and Receptor occupancy with Integrilin—a Dynamic Evaluation) trial. The purpose of PRIDE was to characterize the pharmacodynamics and pharmacokinetics of higher-dose eptifibatide in PCI. This report details the pharmacodynamic profiles of the higher-dose eptifibatide regimens observed in the
dose-confirmation phase of the PRIDE trial and articulates the modeling that identified the specific double-bolus, higher-dose eptifibatide regimen subsequently tested in the PCI indication.

**Methods**

**Clinical Protocol**

The PRIDE trial was a phase II, randomized, open-label, dose-escalation and dose-confirmation evaluation of the pharmacodynamics and pharmacokinetics of 5 dosing regimens of eptifibatide as an adjunct to PCI. The confirmation phase of the trial reported herein evaluated 4 different dosing regimens in 39 patients at 6 sites in the United States. Institutional review board approval was obtained at each participating institution. Inclusion criteria included age <75 years, indication for PCI, aspirin (81 to 325 mg) 24 hours before PCI, and informed consent. Exclusion criteria included current or anticipated GP IIb/IIIa inhibitor therapy, aspirin contraindication, history of hemorrhagic stroke, other stroke of any cause within 2 years, $200/110\text{ mm Hg}$, major surgery within 6 weeks, history of prothrombin time exceeding 1.2 times control, international normalized ratio >2.0, platelet count <100 000 cells/mm$^3$, or hematocrit <30%.

The dose-escalation portion of the PRIDE trial studied only single-bolus eptifibatide dosing regimens. Details have been previously described. The present dose-confirmation portion of the PRIDE study compared single-bolus versus double-bolus eptifibatide regimens. The first 20 patients received an initial bolus of 180 $\mu$g/kg bolus followed by an infusion of 2.0 $\mu$g/kg per minute. In a 2:1 ratio, these patients were randomly assigned to receive either a second 90 $\mu$g/kg bolus of eptifibatide or placebo 30 minutes after the first bolus. The next group of 19 patients received eptifibatide as an initial bolus of 250 $\mu$g/kg followed by an infusion of 3.0 $\mu$g/kg per minute. Again, in a 2:1 ratio, these patients were randomly assigned to receive either a second bolus of 125 $\mu$g/kg of eptifibatide or placebo 30 minutes after the first bolus.

All patients received aspirin, and heparin was administered to achieve an activated clotting time of 200 to 300 seconds before the initiation of the PCI procedure. PCI was performed per local standards with stent implantation encouraged. The first study drug bolus was given immediately before activation of the first angioplasty treatment device. The infusion was started immediately after the first study drug bolus. Absent contraindication, study drug infusion was continued for 18 to 24 hours. Baseline clinical, procedural, and outcome variables were obtained prospectively.

**Pharmacodynamic and Pharmacokinetic Analyses**

Blood samples were drawn at baseline (30 minutes before the study drug bolus) and during the study drug infusion at 1, 2, 3, 4, 6, and 8 hours after the first study drug bolus. These samples were assayed for platelet aggregation, GP IIb/IIIa receptor occupancy, and eptifibatide plasma concentration. Simplate bleeding times were also performed at baseline, at study drug termination, and at 2 hours and 4 hours after infusion discontinuation.

The platelet aggregation studies were performed at each investigational site and analyzed by the platelet core laboratory at the University of Tennessee, Memphis. Blood samples were anticoagulated in $\alpha$-phenylalanly-l-prolyl-l-arginine chloromethyl ketone (PPACK). Platelet aggregation was measured by light transmission aggregometry in response to 5 $\mu$mol/L thrombin receptor agonist peptide (TRAP) or 20 $\mu$mol/L ADP per previously described methods. Blood samples (anticoagulated with PPACK) were shipped to the platelet core laboratory for receptor occupancy determination by measuring D3-antibody binding with eptifibatide. For eptifibatide concentration assays, blood was collected into chilled tubes containing EDTA. Analysis was performed with the use of solid-phase extraction/high-performance liquid chromatography.

**Statistical and Data Analyses**

Baseline clinical and procedural characteristics were tabulated by simple descriptive statistics. Means were expressed followed by standard deviations and medians (25th, 75th quartiles). Platelet aggregation, receptor occupancy, and Simplate bleeding time results were summarized by plotting medians. Because of the limited data, individual patient pharmacokinetic parameters could not be determined. Therefore, plasma concentration-time data from all subjects at each dosing regimen were analyzed by means of the population pharmacokinetic approach. Because concentration-time data were not available during either the initial time points when the intravenous bolus doses were administered nor after discontinuation of the infusion, the modeling of the composite concentration-time data relied heavily on the parameter estimates previously generated from the dose-escalation portion of the PRIDE study. Eptifibatide plasma concentration-time data from the present PRIDE study were fitted to a biexponential equation with a weighing factor of 1/$C^2$ for both the single-bolus and double-bolus groups, with the use of WinNonlin.
The volume of distribution in the central compartment, \( V_c \), was calculated from the ratio of dose to steady-state levels for each dosing group. Total body clearance, \( CL \), was calculated from the ratio of dose to AUC (medication half-life) over time from baseline to 8 hours into eptifibatide infusion for 4 treatment groups. 2 Pharmacokinetic model graphics were superimposed over the baseline to 8 hours into eptifibatide infusion for 4 treatment groups. Abbreviations as in Figure 1.

Inhibition of platelet aggregation in response to 20 \( \mu \)mol/L ADP (Figure 1A) and 5 \( \mu \)mol/L TRAP (Figure 1B) shows the expected dose-dependent inhibition aggregation. At steady state, >80% inhibition after ADP stimulation was seen in all groups. However, at the 1-hour sampling point, the single-bolus patients showed less inhibition of platelet aggregation than observed either immediately after the bolus or at steady state. Inhibition to TRAP stimulation was less than ADP stimulation but paralleled the ADP observations.

Figure 2 depicts receptor occupancy results by dosing group. Greater occupancy was achieved in a dose-dependent fashion. Steady-state occupancy of the GP IIb/IIIa integrin was maintained at >80% in all groups. The decrement in inhibition of aggregation seen at 1 hour with the single bolus was also reflected in a slight drop in receptor occupancy at 1 hour.

Figure 3 illustrates the clinical effect of dosing on the Simplate bleeding time. Bleeding times were not measured beyond 30 minutes. At the termination of eptifibatide infusion median bleeding times were >30 minutes in all groups. No clinically important differences were observed among the dosing regimens.

Table 2 shows the eptifibatide plasma concentrations for the treatment groups at each time point. Predicted plasma concentrations and pharmacokinetics of eptifibatide in single-bolus patients were similar to those in the dose-escalation substudy of PRIDE. Plasma concentration followed first-order kinetics, with a calculated volume of distribution range of 0.203 to 0.229 L/kg, distribution half-life of 0.22 to 0.52 hours, and terminal elimination half-life of 2.57 to 2.71 hours. For the 2.0–\( \mu \)g/kg per minute infusion, the model-estimated 8-hour plasma eptifibatide concentration of 1619 ng/mL compares favorably with the measured concentration of 1645 ng/mL. The model estimated steady-state eptifibatide concentration at 1710 ng/mL, similar to plasma concentrations achieved 6 to 8 hours into the infusion (Figure 4). Clearance of eptifibatide ranged from 1.0 to 1.2 mL/min per kilogram. Derived pharmacokinetic parameters for each group, based on the population approach, are summarized in Table 3. The double-bolus approach minimized the initial decline in eptifibatide concentrations seen early after the first bolus (Table 2). The second bolus resulted in a higher steady-state drug concentration regardless of the infusion rate (Figure 4).
Discussion

Our study indicates that higher doses of eptifibatide, along with the addition of a double-bolus initiation, maintained more adequate platelet blockade than in the single-bolus regimens evaluated in IMPACT-II and PURSUIT. Definition of this “adequate blockade” of the GP IIb/IIIa receptor was initially based on several observations. First, patients with Glanzmann thrombasthenia born with defective or absent GP IIb/IIIa receptors provided a critical insight. In the heterozygous form, no significant hemorrhagic morbidity occurs when 50% of the receptors are absent. However, in the homozygous form, a 1% per annum incidence of significant bleeding is observed.9,10

Second, work with other GP IIb/IIIa inhibitors (particularly abciximab) in animals suggested that 80% platelet inhibition prevented platelet-induced thrombosis in stenotic coronary arteries and similar models.11,12 Whereas >80% platelet inhibition nearly eliminated platelet aggregation, the bleeding times only became prolonged to 15 to 30 minutes when receptor blockade was >90%.13,14

The first dose-finding studies of eptifibatide were designed to identify doses that also achieved >80% inhibition of platelet aggregation.15,16 Results of these studies provided the rationale for the single-bolus regimens of IMPACT-II (135-mg/kg bolus with either a 0.5– or 0.75–mg/kg per minute infusion). Although a treatment effect was observed in IMPACT-II, relative and absolute clinical efficacy appeared to be approximately half that seen in abciximab studies.

The dose-escalation phase of the PRIDE trial confirmed the role of calcium chelation in the overestimation of the pharmacodynamic effects of eptifibatide5,17,18 that led to the relative underdosing in IMPACT II. Furthermore, modeling from the dose-escalation phase also confirmed some initial observations in healthy volunteers19 that there is a strong relation between plasma eptifibatide concentrations and ex vivo platelet aggregation as well as GP IIb-IIIa receptor occupancy.17 Closer evaluation of the dose-escalation data suggested a new observation. In the first hour after the initiation of eptifibatide, a relative nadir in platelet inhibition developed, suggesting a rapid distribution phase that might expose patients with PCI to less-than-maximal inhibition during the critical first hour after PCI.20 These observations from the dose-escalation phase of PRIDE, coupled with the results of a clinical pharmacology study in which the effects of various bolus doses of eptifibatide were evaluated,17,21 led to the realization that a double-bolus approach would optimize eptifibatide therapy. The double-bolus approach was therefore incorporated into this dose-confirmation portion of PRIDE.

The present dose-confirmation study documents that a second bolus of eptifibatide given 30 minutes after the first bolus eliminates this transient loss of platelet inhibition. The addition of the second bolus produced plasma eptifibatide concentrations in the first few hours comparable to those seen at steady state. Mean eptifibatide concentrations achieved by the second bolus exceed 1700 ng/mL during the first hour of treatment initiation, and concentrations greater than ≈1600 ng/mL are maintained during the first 4 hours of the infusion (Figure 4). With continued infusion of 2.0 μg/kg per minute eptifibatide, plasma concentrations again rise above the 1700-ng/mL level at 4 hours until they reach concentrations of ≈1900 ng/mL at steady state (ie, 12 to 24 hours after the initiation of the infusion). Plasma eptifibatide concentrations of ≈1700 ng/mL have been shown to produce ≈80% platelet GP IIb-IIIa receptor occupancy and >90% inhibition of ex vivo platelet aggregation in patients undergoing PCI.17 Because eptifibatide has a relatively short t1/2, steady-state plasma concentrations (and therefore maximum platelet inhibition for a given infusion dose) are not expected until 6 to 8 hours.
The double-bolus regimen obviates this pharmacodynamic issue, maintaining maximal inhibition of aggregation during the first critical hours of therapy.

With the use of the pharmacokinetic parameters derived from the PRIDE study, the effects of altering the timing of the second bolus administration were modeled (Figure 5). This suggested that the best timing for the second bolus dose to cover the transient reduction of platelet inhibition that occurs 15 to 60 minutes after single-bolus therapy is at 10 minutes after the initial bolus. Specifically, the optimal predicted eptifibatide dosing regimen to achieve and maintain 80% inhibition of platelet aggregation was a double-bolus regimen consisting of a 180-\(\mu\)g/kg bolus repeat after 10 minutes and a 2.0 – 3.0  \(\mu\)g/kg per minute infusion.

These calculations served as the underpinnings for the double-bolus approach that was evaluated in the ESPRIT trial. This placebo-controlled study of double-bolus eptifibatide during elective coronary stent implantation was discontinued prematurely because of a compelling benefit in the eptifibatide group. The primary composite end point of death, myocardial infarction, urgent target vessel revascularization, or crossover to open-label GP IIb/IIIa eptifibatide treatment was significantly reduced from 10.5% to 6.6%, a relative risk reduction of 37% (\(P=0.0015\)). The ESPRIT trial results thus confirm the conclusions of the present study. Taken together, these data suggest that maximizing the inhibition of platelet aggregation with the platelet GP IIb/IIIa integrin antagonists remains the key to optimal outcomes in PCI.

### TABLE 2. Eptifibatide Concentrations* Over Time for Treatment Groups

<table>
<thead>
<tr>
<th>Hours After Initial Bolus</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>180/2.0 (n=7)</td>
</tr>
<tr>
<td>1</td>
<td>1223 (327)</td>
</tr>
<tr>
<td>2</td>
<td>1404 (172)</td>
</tr>
<tr>
<td>3</td>
<td>1330 (97)</td>
</tr>
<tr>
<td>4</td>
<td>1458 (120)</td>
</tr>
<tr>
<td>6</td>
<td>1432 (35)</td>
</tr>
<tr>
<td>8</td>
<td>1645 (250)</td>
</tr>
</tbody>
</table>

*Mean eptifibatide levels (ng/mL) and standard deviations (in parentheses) of mean.
†Median, 2085 ng/mL.
180/2.0 indicates initial 180-\(\mu\)g/kg bolus plus 2.0 – 3.0  \(\mu\)g/kg per minute infusion of eptifibatide; 180/90/2.0, initial 180-\(\mu\)g/kg bolus and 90-\(\mu\)g/kg bolus at 30 minutes plus 2.0 – 3.0  \(\mu\)g/kg per minute infusion; 250/3.0, initial 250-\(\mu\)g/kg bolus plus 3.0 – 3.0  \(\mu\)g/kg per minute infusion of eptifibatide; and 250/125/3.0, initial 250-\(\mu\)g/kg bolus and 125-\(\mu\)g/kg bolus at 30 minutes plus 3.0 – 3.0  \(\mu\)g/kg per minute infusion.

### TABLE 3. Estimated Eptifibatide Pharmacokinetic Parameters in Population of Patients Undergoing Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Estimate</th>
<th>SE</th>
<th>Estimate</th>
<th>SE</th>
<th>Estimate</th>
<th>SE</th>
<th>Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ng/mL</td>
<td>18 326</td>
<td>25 060</td>
<td>21 828</td>
<td>54 095</td>
<td>33 458</td>
<td>42 799</td>
<td>32 998</td>
<td>130 412</td>
</tr>
<tr>
<td>B</td>
<td>ng/mL</td>
<td>7666</td>
<td>14 972</td>
<td>10 794</td>
<td>3833</td>
<td>13 799</td>
<td>61 959</td>
<td>13 792</td>
<td>6955</td>
</tr>
<tr>
<td>(\alpha)</td>
<td>1/h</td>
<td>1.34</td>
<td>3.96</td>
<td>2.42</td>
<td>5.16</td>
<td>3.06</td>
<td>0.70</td>
<td>2.41</td>
<td>7.86</td>
</tr>
<tr>
<td>(\beta)</td>
<td>1/h</td>
<td>0.256</td>
<td>0.36</td>
<td>0.256</td>
<td>0.10</td>
<td>0.270</td>
<td>0.672</td>
<td>0.263</td>
<td>0.143</td>
</tr>
<tr>
<td>%(\alpha)</td>
<td></td>
<td>31 *</td>
<td>18 *</td>
<td>18 *</td>
<td>20 *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%(\beta)</td>
<td></td>
<td>69 *</td>
<td>82 *</td>
<td>82 *</td>
<td>80 *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C_o)</td>
<td>ng/mL</td>
<td>1529</td>
<td>1864</td>
<td>2585</td>
<td>2492</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C_{ss})</td>
<td>ng/mL</td>
<td>1710</td>
<td>1946</td>
<td>2441</td>
<td>2560</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC ($)</td>
<td>mg*h⁻¹/mL⁻¹</td>
<td>43 652</td>
<td>10 159</td>
<td>51 109</td>
<td>6250</td>
<td>62 025</td>
<td>23 335</td>
<td>66 826</td>
<td>10 820</td>
</tr>
<tr>
<td>(T_{1/2a})</td>
<td>h</td>
<td>0.52</td>
<td>1.53</td>
<td>0.29</td>
<td>0.61</td>
<td>0.22</td>
<td>14.79</td>
<td>0.29</td>
<td>0.94</td>
</tr>
<tr>
<td>(T_{1/2b})</td>
<td>h</td>
<td>2.71</td>
<td>3.84</td>
<td>2.70</td>
<td>1.07</td>
<td>2.57</td>
<td>6.39</td>
<td>2.67</td>
<td>1.46</td>
</tr>
<tr>
<td>(V_c)</td>
<td>L/kg</td>
<td>0.118</td>
<td>0.164</td>
<td>0.097</td>
<td>0.031</td>
<td>0.097</td>
<td>1.60</td>
<td>0.100</td>
<td>0.277</td>
</tr>
<tr>
<td>(V_{ss})</td>
<td>L/kg</td>
<td>0.204</td>
<td>0.073</td>
<td>0.203</td>
<td>0.070</td>
<td>0.229</td>
<td>0.090</td>
<td>0.216</td>
<td>0.143</td>
</tr>
<tr>
<td>CL</td>
<td>mL/min⁻¹·kg⁻¹</td>
<td>1.17</td>
<td>0.027</td>
<td>1.03</td>
<td>0.126</td>
<td>1.23</td>
<td>0.47</td>
<td>1.17</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Not calculated.
%\(\alpha\) indicates percent contribution of \(\alpha\) to area under the curve; %\(\beta\), percent contribution of \(\beta\) to area under the curve; A, coefficient of exponential term \(\alpha\); \(\alpha\), distribution rate constant (\(\alpha\)); AUC ($), area under predicted concentration-time curve from time zero to infinity; B, coefficient of exponential term \(\beta\); \(\beta\), elimination rate constant (\(\beta\)); \(C_o\), calculated initial plasma concentration; \(C_{ss}\), maximum observed plasma concentration at end of dosing interval; SE, standard error; \(T_{1/2a}\), distribution phase half-life; \(T_{1/2b}\), elimination phase half-life; \(V_c\), volume of distribution in central compartment; and \(V_{ss}\), volume of distribution at steady state. Other abbreviations as in Tables 1 and 2.
Formulas for fitting the plasma concentration-time data to biexponential equations are given.

Single-bolus groups:

\[ C(t) = C(t)_{\text{Initial Bolus}} + C(t)_{\text{Infusion}} \]

\[ C(t)_{\text{Initial Bolus}} = A(e^{-\alpha t}) + B(e^{-\beta t}) \]

Double-bolus groups:

\[ C(t) = C(t)_{\text{Initial Bolus}} + C(t)_{\text{Second Bolus}} + C(t)_{\text{Infusion}} \]

\[ C(t)_{\text{Initial Bolus}} = A(e^{-\alpha t}) + B(e^{-\beta t}) \]

\[ C(t)_{\text{Infusion}} = \frac{A(e^{-\alpha t} - e^{-\alpha TSTAR})}{A(e^{-\alpha t} - e^{-\alpha TBOL})} + B(e^{-\beta t} - e^{-\beta TBOL}) \]

where TSTAR = t - ti for t > ti and TSTAR = 0 for t ≤ ti; TBOL = t - 0.5 for t > 0.5 hours, and TBOL = 0 for t < 0.5 hours; t and ti are the sampling time and time of infusion, α and β are the distribution and elimination phase constants, and A and B are the coefficients of the exponential terms for α and β.

Appendix

Sites, Principal Investigators, and Study Coordinators

Baylor College of Medicine and Ben Taub Hospital: Neal S. Kleinman, MD, Principal Investigator; Kelly Marsh, RN, Study Coordinator; University of Arkansas for Medical Science and John McClellan Memorial Veterans Hospital: David Talley, MD, Principal Investigator; Sheri Ashcraft, RN, Study Coordinator; Saint Louis University Hospital: Frank Aguirre, MD, Principal Investigator; Amy Devereux, RN, Study Coordinator; Pennsylvania State University: Ian C. Gilchrist, MD, Principal Investigator; Helen Zimmerman, RN, Study Coordinator; Northwestern University: Charles Davidson, MD, Principal Investigator; Andi Schaechter, RN, Study Coordinator; Christ Hospital: John Runyon, MD, Principal Investigator; Linda Martin, RN, MBA, Study Coordinator.

Platelet Core Laboratory

Lisa K. Jennings, PhD, Shila Cholera, and Melanie M. White.

References

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_Circulation_. 2001;104:406-411
doi: 10.1161/hc2901.093504
_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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