Extended Mortality Benefit of Early Postinfarction Reperfusion

Allan M. Ross, MD; Karin S. Coyne, RN, MPH; Eduardo Moreyra, MD; Jonathan S. Reiner, MD; Samuel W. Greenhouse, PhD; Pamela L. Walker, RN; Maarten L. Simoons, MD; Yasmine C. Draoui, MS; Robert M. Califf, MD; Eric J. Topol, MD; Frans Van de Werf, MD; Conor F. Lundergan, MD; for the GUSTO-I Angiographic Investigators

Background—Reperfusion therapy for myocardial infarction, understood to reduce mortality by preserving left ventricular function, was initially expected to provide increasing benefits over time. Surprisingly, large controlled thrombolysis trials demonstrated maximum benefit at 4 to 6 weeks with no subsequent increased treatment advantage. Such studies, however, compared groups by assigned treatment, not physiological effectiveness.

Methods and Results—We calculated 2-year survival differences among 2431 myocardial infarction patients according to early infarct artery patency and outcome left ventricular ejection fraction using Kaplan-Meier curves. Hazard ratios for significant survival determinants were derived from Cox regression models. Two-year vital status (minimum, 688 days) was determined in 2375 patients (97.7%). A substantial mortality advantage for early complete reperfusion (Thrombolysis in Myocardial Infarction [TIMI] grade 3) and for preserved ejection fraction occurred beyond 30 days. The unadjusted hazard ratio for the TIMI 3 group compared with lesser grades at 30 days was 0.57 (95% confidence interval [CI], 0.35 to 0.94) and 30 days to ≥688 days was 0.39 (95% CI, 0.22 to 0.69). Consequently, early TIMI 3 flow was associated with approximately a 3 patient per 100 mortality reduction the first month with an additional 5 lives per 100 from 30 days to 2 years. For ejection fraction >40% compared with ≤40%, the unadjusted hazard ratio was 0.25 (95% CI, 0.16 to 0.37) at 30 days and 0.22 (95% CI, 0.15 to 0.33) after 30 days through 2 years (lives saved, ~9 and 11 per 100, respectively).

Conclusions—Successful reperfusion and myocardial salvage produce significant mortality benefits that are amplified beyond the initial 30 days. (Circulation. 1998;97:1549-1556.)

Key Words: myocardial infarction • thrombolysis • reperfusion • follow-up studies • mortality

The generally accepted view of the benefits of restoration of normal infarct related artery flow (Thrombolysis in Myocardial Infarction [TIMI] grade 3 flow) in acute myocardial infarction is that early complete reperfusion preserves left ventricular function, which in turn increases the likelihood of survival. Extension of this model would lead to an expectation that patients with successful early reperfusion and improved ejection fraction would exhibit not only increased early survival but also a further increase in survival benefit with the progression of time. Such an outcome would be consistent with observations from the prethrombolytic era demonstrating a strong correlation between late ejection fraction after myocardial infarction and long-term risk of mortality. Surprisingly, however, large clinical trials in the thrombolytic era have shown that patients assigned to reperfusion therapy demonstrate a maximum survival advantage at 4 to 6 weeks after infarction compared with a control group. Thereafter, the survival curves remain parallel over variable periods of long-term follow-up. A similar pattern has been observed in follow-up of a year or more comparing patients assigned to different active therapy groups. In The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial (GUSTO-I), for example, the 30-day survival advantage of alteplase over streptokinase is maintained but not amplified 12 months after infarction. Because a significant number of treated patients fail to achieve normal (TIMI 3) flow in response to therapy, previously developed models that purport to detail independent determinants of long-term survival but that use variables that only indirectly relate to reperfusion (eg, assignment to active treatment) rather than actual achieved early TIMI 3 flow may underestimate the true long-term advantage of successful reperfusion. The purpose of this analysis was to describe the effect of early and complete reperfusion of the infarct artery and the resultant preservation of left ventricular function on long-term (2-year) survival.
TABLE 1. Baseline Characteristics and Cardiac Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>TIMI 0, 1, 2 (n=553)</th>
<th>TIMI 3 (n=519)</th>
<th>P</th>
<th>EF ≤40 (n=242)</th>
<th>EF &gt;40 (n=1701)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.0</td>
<td>59.3</td>
<td>.02</td>
<td>62.1</td>
<td>59.8</td>
<td>.004</td>
</tr>
<tr>
<td>Male, %</td>
<td>77.4</td>
<td>78.0</td>
<td>NS</td>
<td>79.3</td>
<td>78.3</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>14.1</td>
<td>12.8</td>
<td>NS</td>
<td>28.6</td>
<td>10.8</td>
<td>.001</td>
</tr>
<tr>
<td>Previous CAGB, %</td>
<td>4.2</td>
<td>3.9</td>
<td>NS</td>
<td>8.7</td>
<td>3.5</td>
<td>.001</td>
</tr>
<tr>
<td>Killip class &gt;2, %</td>
<td>1.8</td>
<td>1.4</td>
<td>NS</td>
<td>5.0</td>
<td>0.8</td>
<td>.001</td>
</tr>
<tr>
<td>Time to treatment, h</td>
<td>3.1</td>
<td>3.1</td>
<td>NS</td>
<td>3.2</td>
<td>3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Entry heart rate, bpm</td>
<td>75.9</td>
<td>73.5</td>
<td>.03</td>
<td>81.3</td>
<td>73.2</td>
<td>.0001</td>
</tr>
<tr>
<td>Previous angina, %</td>
<td>32.4</td>
<td>34.8</td>
<td>NS</td>
<td>49.8</td>
<td>32.8</td>
<td>.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>12.3</td>
<td>14.1</td>
<td>NS</td>
<td>13.6</td>
<td>11.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>37.0</td>
<td>36.8</td>
<td>NS</td>
<td>32.8</td>
<td>35.4</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.8</td>
<td>26.8</td>
<td>NS</td>
<td>26.3</td>
<td>26.8</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior MI, %</td>
<td>43.8</td>
<td>32.5</td>
<td>.001</td>
<td>70.0</td>
<td>33.1</td>
<td>.001</td>
</tr>
<tr>
<td>No. of diseased vessels, %</td>
<td>68.8</td>
<td>63.7</td>
<td>NS</td>
<td>48.3</td>
<td>67.0</td>
<td>.001</td>
</tr>
<tr>
<td>1</td>
<td>59.9</td>
<td>63.7</td>
<td>NS</td>
<td>48.3</td>
<td>67.0</td>
<td>.001</td>
</tr>
<tr>
<td>2</td>
<td>26.0</td>
<td>25.7</td>
<td>NS</td>
<td>23.8</td>
<td>23.4</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>14.1</td>
<td>10.6</td>
<td>NS</td>
<td>27.9</td>
<td>9.0</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>45.5</td>
<td>47.3</td>
<td>NS</td>
<td>40.9</td>
<td>47.1</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130.0</td>
<td>127.2</td>
<td>.04</td>
<td>124.4</td>
<td>128.8</td>
<td>.005</td>
</tr>
</tbody>
</table>

TIMI indicates Thrombolysis in Myocardial Infarction; MI, myocardial infarction; CAGB, coronary artery bypass graft; and BP, blood pressure.

Methods

Study Patients

The GUSTO-1 angiographic study has been described in detail previously. Briefly, in the angiographic study, 2431 patients who met the following enrollment criteria were enrolled: chest pain lasting <6 hours and elevation of the ST segment in at least two contiguous leads. Patients were randomized to one of four thrombolytic regimens and to one of four times (90 minutes, 180 minutes, 24 hours, or 5 to 7 days) for initial coronary angiography and ventriculography after the start of thrombolytic therapy. Patients randomized to angiography at 90 minutes also had follow-up angiography at 5 to 7 days. For the purposes of this analysis, we used the final TIMI flow grade determined from an initial angiogram obtained 90±45 minutes after the start of lytic therapy. Correlations between left ventricular function and survival used data from the last available contrast ventriculogram obtained during the index hospitalization period for all patients.

Core Angiographic Laboratory Procedures and Cineangiographic Analysis

All films were interpreted by an experienced angiographer (A.M.R., C.F.L., and J.S.R.) who had no knowledge of treatment allocation or time of angiography. Patency of the infarct-related artery, as measured by TIMI flow grade, was assessed according to standard methods. Ventriculographic silhouettes were acquired digitally at end systole and end diastole, and the borders were defined by the core laboratory angiographer.

Follow-up Methods

Two-year patient follow-up was conducted by telephone contact by personnel at individual clinical sites. Additional efforts at patient contact were made by investigators at central facilities in Washington, DC; Leuven, Belgium; and Rotterdam, the Netherlands. If a patient could not be contacted by telephone, inquiries were addressed to the next of kin and primary care physicians. Other efforts included searches of hospital medical records, clinic records, and public death records. The follow-up study protocol was reviewed and either approved or exempted by the Institutional Review Boards of all participating hospitals. All interviewed patients provided verbal consent; next of kin provided written consent for death certificate/medical record information.

Statistical Analysis

Estimated survival curves for patients with and without early complete (TIMI 3) flow in the infarct-related artery and for those with ejection fractions either <40% or >40% were determined to 688 days by the Kaplan-Meier method. Comparing Kaplan-Meier survival curves according to TIMI flow grades revealed that the survival function for TIMI 2 was not statistically different from TIMI 0, 1 for any time period (0 to 30, 30 to 688, or 0 to 688). Therefore, the TIMI 2 and 0, 1 groups were combined for all subsequent analyses. The log rank test was used to test the hypothesis that survival rates were the same for the two groups. After verifying assumptions of proportionality, we constructed univariable and multivariable Cox proportional hazards models to determine the relationship between TIMI flow grade or ejection fraction and survival time. We computed unadjusted and adjusted hazard ratios for statistically significant explanatory variables (with 95% confidence limits) using the regression coefficient of the Cox proportional hazard models. Clinical variables tested were chosen on the basis of their previously reported independent effect on 30-day mortality after myocardial infarction, which included age, sex, diabetes, history of hypertension, time to treatment, Killip class at study entry, body weight, history of coronary artery bypass surgery, smoking status, history of hypercholesterolemia, height, in-hospital percutaneous transluminal coronary angiography, in-hospital coronary artery bypass surgery, history of angina, site of infarction, and history of infarction. Patients with incomplete data were excluded from multivariable modeling. TIMI flow grade was entered into the model as a dichotomous variable: TIMI grade 3 versus grades 2, 1, or 0 combined. Ejection fraction was entered as a dichotomous variable: TIMI grade 3 versus grades 2, 1, or 0 entered as a continuous variable. The x2 test (two sided) was used to determine whether the proportions of the two groups were different. A value of P<.05 defined statistical significance.
Figure 1. Two-year survival curves for all enrolled patients with 90-minute Thrombolysis in Myocardial Infarction (TIMI) flow: A, TIMI 3 vs TIMI 2 vs TIMI 0,1 flow; B, TIMI 3 vs TIMI 0,1,2; C, TIMI 3 vs TIMI 0,1,2 for patients who survived to 30 days. Vertical lines denote censored cases. MI indicates myocardial infarction.
Results

Vital status ascertained at least 688 days after infarction was confirmed in 2375 of 2431 patients (97.7%) and will, for convenience, be referred to as 2-year survival. Analysis of early patency was performed on 1072 patients assigned to the earliest first postlytic angiogram group. Analysis according to left ventricular function is based on 1943 patients for whom adequate left ventriculography and 2-year survival data were available. Baseline characteristics are displayed by TIMI flow grade and ejection fraction in Table 1.

Survival by early infarct flow grade is displayed as Kaplan-Meier curves for the entire 2-year period in Fig 1A. Because there were no significant differences in long-term outcome between patients with TIMI 2 versus 0 or 1, the categories have been subsequently combined (Fig 1B). Patients with early complete reperfusion had a 30-day mortality rate of 4.6% compared with 8.0% for those with lesser flow grades, which is an approximate advantage of 3 lives per 100 (unadjusted hazard ratio, 0.57; 95% confidence interval [CI], 0.35 to 0.94). For the entire 2-year period, the cumulative mortality was 7.9% for those patients with TIMI 3 flow and 15.7% in patients with lesser flow grades (unadjusted hazard ratio, 0.48; 95% CI, 0.33 to 0.70). Recalculated curves, beginning with survivors at 30 days, emphasize a second divergence such that after 30 days through 2 years there was an additional 3.3% mortality in the TIMI 3 group and a further 8.3% mortality in the TIMI 0 to 2 group (unadjusted hazard ratio, 0.39; 95% CI, 0.22 to 0.69; Fig 1C). The approximate gain during this period is an additional 5 lives per 100.

Ejection fraction was measured from contrast ventriculograms at a mean time of 90.9 hours after treatment (25th percentile was 3.3 hours; the 50th percentile, 114.6 hours; and the 75th percentile, 153.6 hours). Two-year survival curves for the patients stratified by last in-hospital left ventricular ejection fraction demonstrated that 30-day deaths occurred in 3.1% of those whose ejection fraction was >40% and 12% for those with more severely depressed function (unadjusted hazard ratio, 0.25; 95% CI, 0.16 to 0.37; Fig 2A). The overall 2-year mortality in patients with ejection fractions >40% was
72% versus 26.6% in those with ejection fractions ≤40% (unadjusted hazard ratio, 0.23; 95% CI, 0.17 to 0.31). Between 30 days and 2 years after myocardial infarction, the corresponding mortality rates were 4.3% and 16.4%, respectively (unadjusted hazard ratio, 0.22; 95% CI, 0.15 to 0.33; Fig 2B). Thus, the survival advantage for the preserved ventricular function group (ejection fraction >40%) was ~20 patients per 100 at the end of 2 years.

The effect of ejection fraction was also analyzed as a continuous variable. The probability of death was determined by logistic regression for the early, late, and combined time periods (Fig 3) which confirmed the relationships based on the dichotomy (>40% versus ≤40%). This relationship also remained significant in multivariable models.

Figs 4 and 5 display the hazard ratios for mortality according to the final TIMI flow grade assessed at the 90-minute angiogram and the last recorded ejection fraction, after adjustment for the clinical variables and for each other. Hazard ratios were calculated with 30-day nonsurvivors included in the analysis (Figs 4A and 5A) and without them (Figs 4B and 5B). Normalization of flow in the infarct-related artery within 90 minutes of thrombolytic treatment and relative preservation of left ventricular function were each significant determinants of long-term survival after adjustment for multiple clinical variables. Only patient age was more strongly related to 2-year mortality than either TIMI flow grade or ejection fraction, and diabetes was more strongly related to 2-year mortality than TIMI flow grade (Table 2).

Discussion

The primary finding of this analysis is that restoration of early and normal (TIMI 3) flow in the infarct related artery and early preservation of left ventricular function each provide a significant survival advantage well beyond the 30 days immediately after infarction. These effects appear to be independent and persist after adjustment for multiple patient-related variables.

Previous large-scale trials in patients with acute myocardial infarction have shown that intravenous thrombolytic therapy reduces in-hospital or 30- to 35-day mortality compared with placebo or conservative management, but beyond 30 days, the survival curves have been consistently parallel for the following 1 to 5 years, indicating no further treatment advantage. Similar findings have been observed in comparative trials of different thrombolytic agents, and provided that a patient is alive at 30 days, no additional separation in survival rates over time has been evident.

To explain these previous observations, it has been hypothesized that survival curves do not widen after 1 month, in part because reperfusion therapy saves mostly high-risk patients, leaving a paradoxically vulnerable subgroup in the cohort alive at 30 days. In actuality, there has not been a high rate of late fatalities in any group followed years beyond the index infarct. The risk of post-myocardial infarction death (in this data set) is highest in the first 24 hours and declines steeply thereafter, reaching a nadir after about 200 days. The relative paucity of late deaths is, in fact, a likely contributor to the previous difficulty in showing late divergence of survival curves. It should also be appreciated that when two groups start with equal numbers, parallel survival curves after initial separation may seem to imply the same absolute number of patients deceased over a period of time, but in actuality, a lower relative mortality rate is present in the upper curves of such analyses because of a larger residual denominator.
intracoronary streptokinase have reported significantly lower 1-year mortality in patients with complete reperfusion compared with patients with partial or no reperfusion. Simoons et al.\(^6\) reported on 533 patients randomized to either intracoronary streptokinase or conventional therapy. Ejection fraction assessed between days 10 and 40 was the best predictor of long-term survival in both patient groups, and the beneficial effect of better systolic function increased over time. This is consistent with our findings in a much larger population, one treated with intravenous thrombolysis and characterized by angiography at early and uniform times after treatment.

A potential limitation of this study is that the groups forming these analyses are defined by an outcome (TIMI flow grade, ejection fraction) which is then related to a second outcome, mortality. However, the rigorous conditions of this clinical trial design lead to valid and generalizable inferences because there was no self-selection into the defined groups and the investigation of the relationships between the outcomes was prospectively planned. Nonetheless, it remains possible that common patient baseline characteristics predispose specifically to both the angiographic and the clinical outcome. In an attempt to compensate for these circumstances, we adjusted for the coexistence of mortality influencing baseline variables by entering them into multivariable analysis. TIMI flow grade and ejection fraction retained their outcome. In an attempt to compensate for these circumstances, we adjusted for the coexistence of mortality influencing baseline variables by entering them into multivariable analysis. TIMI flow grade and ejection fraction retained their 2-year is about the same or better than it is at 30 days in each of the four independent treatment groups, so within this data set, there are four replications of the beneficial late effect of early reperfusion on survival.

Longer-term survival may also be favorably influenced by certain pharmacological treatments, specifically \(\beta\)-blockers, ACE inhibitors, and lipid-lowering agents, and by percutaneous coronary revascularization procedures. Our data collection is not complete concerning all medical and mechanical therapies over the entire 2-year period, but we have details concerning some of these therapies during the index hospitalization, including discharge medications. Patients with TIMI 3 flow at 90 minutes had fewer angioplasties (1.5% versus 25.2%, \(P = .008\)) during their initial angiogram and were less likely to have been discharged on an ACE inhibitor (15.6% versus 21.9%, \(P = .008\)) than those with lesser TIMI flow grades. When patients were stratified by ejection fraction, \(\beta\)-blockers were more often prescribed (67.6% versus 47.5%, \(P = .001\)) for patients with preserved ventricular function, while the reverse is true for ACE inhibitors (14.6% versus 35.0%, \(P = .001\)).
versus 44.6%, \( P = .001 \). The differences tend to conform to advised patterns of practice, eg, ACE inhibitors for poor left ventricular function and rescue percutaneous transluminal coronary angioplasty for closed arteries.

In summary, this study has provided intriguing evidence that successful early reperfusion and myocardial salvage correlate with a survival advantage that continues to increase well beyond the first month after myocardial infarction. These observations, although hypothesis generating, further underscore the need to develop more effective reperfusion strategies. Although cost analysis was not a component of this study, the substantial additional late benefits should be taken into account in considerations of the cost-effectiveness of aggressive infarct treatment strategies.

Appendix

The following centers and investigators collaborated on the GUSTO Two-Year Survival Study.

**Study Chair:** Allan M. Ross. **Coordinating Center:** George Washington University, Washington, DC. **Co-investigators:** C. Lundergan, J. Reiner, K. Coyne, and P. Walker; **Coordinators:** D. Bashford and Y. Draoui; **Data Management:** D. Boyle; **Data Analysis:** S. Greenhouse; **Research Assistant:** C. Fink; **Administrator:** A. Bhatt.


**Participating Centers (Ordered by Patient Recruitment)**

**United States (n=1117):** St. Mary’s Hospital, Rochester, Minn: S. Kopecky and M. Peterson; George Washington University Hospital, Washington, DC: A. Ross, K. Coyne, P. Walker, and D. Bashford; Tulsa (Okla) Regional Medical Center: E. Pickering, P. Coatham, and J. Gaber; McKay-Dee Hospital, Ogden, Utah: D. Rigby; St Vincent’s Medical Center, Jacksonville, Fla: G. Pilcher, P. Zaenger, and P. j Gaber; McKay-Dee Hospital, Ogden, Utah: D. Rigby; St Agnes Medical Center, Philadelphia, Pa: D. McCormick.

**Australia (n=101):** Flinders Medical Center, S.A. Adelaide, P. Ayliward, and B. Krieg; Royal North Shore Hospital, St Leonards Mass: D. Gossman and G. Woodhead; University of Michigan Hospital, Ann Arbor: E. Bates and T. Alexandris; Mother Frances Hospital, Tyler, Tex: N. Israel and L. Oyer L; St Mark’s Hospital, Tottenham, Fla: J. Smith and L. Harrah; Humana Medical City, Jacksonville, Fla: G. Pilcher, P. Zaenger, and P. j Gaber; McKay-Dee Hospital, Ogden, Utah: D. Rigby; St Agnes Medical Center, Philadelphia, Pa: D. McCormick.

**Europe (n=197):** Medisch Spectrum, Enschede: G. Molhoek and R. Lalissang; Spaarne, Ziekenhuis Heemstede: E. Miiller; Dijkzigt, Rotterdam: M. Simoons, M. van de Brand, T. Baardman, P. Kint, and D. van Berkel.

**Canada (n=177):** University of Alberta Hospital, Edmonton: J. Burton and C. Kee; Victoria General Hospital, Halifax, NS: C. Kells and T. Fawcett; Vancouver (BC) General Hospital: A. Fung and C. Davies; St Paul’s Hospital, Vancouver, BC: C. Thompson, D. Heinrich, and B. Mercier.

**Switzerland (n=46):** University Clinics, Basel: M. Pfisterer and R. Hämmerli.

**Germany (n=42):** Krankenhaus am Urban, Berlin: W. Dissmann and H. Topp; Medizinische Universität zu Lübeck, Lübeck: H. Djonlagic, V. Kurowski, and A. Sheikhzadeh; and H. Topp; Medizinische Universität zu Liibeck, Lubeck: H. Hammerli.

**Denmark (n=118):** Hvidovre Hospital, Copenhagen: M. Voss; Northern Michigan Hospital, Petoskey: W. Meengs and B. Stone; Hackensack (NJ) Medical Center: J. Zimmerman and J. Francesco; VA Lakeside Medical Center, Chicago III: A. Hsieh and B. McDermott.


**Argentina (n=177):** University of Alberta Hospital, Edmonton: J. Burton and C. Kee; Victoria General Hospital, Halifax, NS: C. Kells and T. Fawcett; Vancouver (BC) General Hospital: A. Fung and C. Davies; St Paul’s Hospital, Vancouver, BC: C. Thompson, D. Heinrich, and B. Mercier.

**Ireland (n=26):** St James’s Hospital, Dublin: M. Walsh, N. Walsh, and U. White; Mater Hospital, Dublin: D. Sugrue and A. Hennyesy.

Acknowledgments

This study was supported by a combined grant from Bayer (New York City, NY), Ciba-Corning (Medfield, Mass), Genentech (South San Francisco, Calif), ICI Pharmaceutical (Wilmington, Del), and Sanoﬁ Pharmaceutical (Paris, France).

References


Extended Mortality Benefit of Early Postinfarction Reperfusion
for the GUSTO-I Angiographic Investigators

Circulation. 1998;97:1549-1556
doi: 10.1161/01.CIR.97.16.1549
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/16/1549

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/