Thrombolysis in Patients With Unstable Angina Improves the Angiographic but Not the Clinical Outcome

Results of UNASEM, A Multicenter, Randomized, Placebo-Controlled, Clinical Trial With Anistreplase

F.W. Bär, MD; F.W. Verheugt, MD; J. Col, MD; P. Materne, MD; J.P. Monassier, MD; P.G. Geslin, MD; J. Metzger, MD; P. Raynaud, MD; J. Foucault, MD; C. de Zwaan, MD; and F. Vermeer, MD

**Background.** The value of thrombolytic therapy in unstable angina is unclear.

**Methods and Results.** To study this problem, 159 patients were studied in a double-blind, placebo-controlled multicenter trial. Patients without a previous myocardial infarction, with a typical history of unstable angina, and ECG abnormalities indicative of ischemia were included. After baseline angiography, study medication (anistreplase or placebo) was given. Angiography was repeated after 12–28 hours. A significant decrease occurred in diameter stenosis between the first and second angiogram in the anistreplase group compared with the placebo group (11% versus 3%, p=0.008). This difference was caused by reopening of occluded vessels in the thrombolytic group. However, no beneficial clinical effects of thrombolytic treatment were found. Bleeding complications were significantly higher in patients who received thrombolytic therapy (21 versus seven patients, p=0.001).

**Conclusions.** Thus, angiographic but no clinical improvement after thrombolytic treatment with anistreplase was found in patients with unstable angina with an excess of bleeding complications. Therefore, thrombolytic treatment cannot be recommended in patients diagnosed as having unstable angina until proven otherwise. (*Circulation* 1992;86:131–137)

**Key Words** • thrombolysis • unstable angina • angiography

Thrombolytic therapy in early stages of a myocardial infarction reduces mortality, limits infarct size, and improves left ventricular function.1–4 Although the high incidence of coronary thrombosis in unstable angina is well recognized,5–20 the value of thrombolytic therapy in patients is less clear. Outcomes of several studies21,11,21–27 indicated that coronary anatomy can be improved by thrombolytic therapy, but most did not demonstrate a significant effect on clinical outcome.21–24,27,28 The limitations of these studies include a small sample size; in most, a lack of a control group; and absence of criteria that well define the patient population or angiographic findings.29

---

**Methods**

Our study reports the outcome of thrombolytic therapy with anistreplase (eminase or APSAC) in patients with unstable angina.

The Unstable Angina Study using Eminase (UNASEM) was a double-blind, placebo-controlled, randomized, multicenter trial in nine European hospitals. To be enrolled, patients had to fulfill rigid clinical, ECG, and angiographic criteria. After informed consent, a telephone service was used for randomization of patients before the first catheterization. At that point, enzymes were not available. Trial medication was given after this investigation. Repeat catheterization was performed early, at 12–28 hours after study medication, to collect optimal knowledge on the effect of the thrombolytic treatment. This window was taken because myocardial infarction studies with anistreplase showed best angiographic results within this time frame. In total, 159 patients were included in the study, of which 126 received study medication. There was a 1-year follow-up planned. Only the clinical and coronary angiographic outcomes during hospital stay will be reported.

**Inclusion Criteria**

Typical history of unstable angina included angina pectoris at rest or with minimal exercise (class IV
Patients with chest pain prior to admission

ECG after pain

ST segment depression
≥ 0.1 mV in at least 2 extremity leads or 3 precordial leads

Patients with chest pain in hospital

ECG during pain

ST segment depression
≥ 0.1 mV in at least 2 extremity leads or 3 precordial leads

Terminal negative T wave
> 0.2 mV in at least 2 extremity or precordial leads and ST segment elevation < 0.2 mV in all leads

ECG after pain

ST segment elevation
≥ 0.1 mV in at least 2 extremity leads or 3 precordial leads

ST segment elevation
< 0.1 mV in all leads

Normal ST segment or ST segment elevation

(Terminal) negative T wave
> 0.2 mV in at least 2 extremity or precordial leads and ST segment elevation < 0.2 mV in all leads

FIGURE 1. ECG inclusion criteria for the UNASEM.

according to the criteria of the Canadian Cardiovascular Society, angina of recent onset (less than 4 weeks) or of the crescendo type, and with the last episode of chest pain either in hospital or maximally 12 hours before admission.

The ECG abnormalities had to be indicative for the presence of ischemia and not for acute myocardial infarction (Figure 1).

Criteria for patients with chest pain before hospital admission included ST segment depression in two or more inferior leads, or in three or more precordial leads (leads V2-V6), of at least 0.1 mV; or terminal negative T waves with a minimal depth of 0.2 mV in two or more leads (inferior leads: II, III, aVF; anterior leads: V2-V6) with or without slight ST segment elevation (maximally 0.2 mV in the same leads) present on admission or developing within 3 hours after admission to the hospital.

Criteria for patients having chest pain in hospital included chest pain disappearing or diminishing mark-
edly either spontaneously or within 30 minutes after sublingual or intravenous nitroglycerin.

Furthermore, ECG changes that had to be present were ST segment depression or elevation in two extremity leads or three precordial leads of at least 0.1 mV during chest pain. ST segment depression should regress with at least 0.1 mV within 30 minutes. ST segment elevation should diminish to less than 0.1 mV within 30 minutes. As an alternative, (pseudo) normal ST segments had to be present during chest pain, developing to terminal negative T waves after relief of pain. These negative T waves should have a minimal depth of 0.2 mV in two or more leads (inferior: leads II, III, aVF; anterior: leads V2-V6) with or without slight ST segment elevation (maximally 0.2 mV in the same leads) and develop within 3 hours after the onset of the attack of chest pain.

Exclusion Criteria

Criteria include age <30 years or >70 years; previous myocardial infarction, percutaneous transluminal coronary angioplasty, or any cardiac surgery; abnormal initial activation of the QRS complex (left bundle branch block, Wolff-Parkinson-White) or ECG signs of left ventricular hypertrophy; abnormal ST-T segments due to the use of digitalis; cardiac pacemaker with or without pacemaker rhythm; resting heart rate of <50 beats per minute or >100 beats per minute; 1 hour after admission in absence of chest pain; arrhythmia-induced angina or arrhythmia-induced ST-T changes; anemia (hemoglobin <6.0 mmol/l); known hypertension (190 mm Hg systolic or 110 mm Hg diastolic blood pressure) less than 6 months before admission; known renal insufficiency; severe valvular heart disease, heart failure (New York Heart Association functional class III or IV), cardiomyopathy (congestive or hypertrophic), or any severe concomitant disease; treatment with streptokinase or anistreplase within 1 year of admission; aspirin in a dosage of ≥1,000 mg/day; oral anticoagulant therapy or intravenous infusion of heparin; contraindication for thrombolytic therapy specified as recent major surgery, gastrointestinal ulcer bleeding or genitourinary tract bleeding less than 3 months before admission, any cerebrovascular accident (thrombotic, embolic, or hemorrhagic), recent trauma or cardiac resuscitation, intramuscular injection given within the past 72 hours, bleeding diathesis, diabetic retinopathy, pregnancy, or menstruation; technical or organizational problems to be anticipated with regard to both cardiac catheterizations; and no informed consent.

Cardiac Catheterization

If the patient met the inclusion criteria, randomization to study medication was performed. Then, baseline cardiac catheterization was done within 3 hours, including coronary and left ventricular angiography. Thereafter, study medication was started if no angiographic or other contraindications were present. Medication was withheld in case of left main stenosis of ≥70%, normal coronary arteries or nonsignificant stenosis (<50%) in the coronary arteries, development of acute myocardial infarction after randomization but before the start of the study medication, complications such as severe bleeding in the groin, and inability to perform cardiac
catheterization. Angiography was repeated after 12–28 hours.

Coronary angiography was assessed qualitatively by an angiography committee and separately measured by the CAAS system for computerized quantification of the lesions. Both assessments were performed blinded for treatment allocation and sequence of the angiograms. In case of multivessel disease, the culprit lesion was identified by using wall motion abnormalities, ECG changes, and differences in coronary anatomy between the two angiograms. The flow chart (Figure 2) indicates the steps taken during the study.

**Trial Medication**

Trial medication consisted of either an intravenous injection of 30 units anistreplase or placebo given over 5 minutes after the first cardiac catheterization.

**Comedication**

Intravenous nitroglycerin was started before the first catheterization. A heparin bolus of 5,000 IU was injected at the start of the first catheterization followed by a heparin infusion (1,000 IU/hr). Further titration was done according to APTT levels to maintain optimal and constant values (1.5–2.5×control values). Heparin therapy was continued at least to completion of the second cardiac catheterization. β-Blocking agents (e.g., 75–200 mg/day metoprolol) or calcium blockers (e.g., 180 mg/day diltiazem) were given routinely according to the local protocol. Aspirin (300 mg/day) was started after completion of the second angiogram.

**Myocardial Infarction**

The patients who suffered from myocardial infarction during admission were divided into two groups: small myocardial infarction if the maximal ASAT level was less or equal to trice the upper limit of the normal value and larger myocardial infarction if the maximal ASAT level was higher.

**Other Interventions**

Percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery was recommended only if recurrent angina was present despite medical treatment. The procedure was performed after the second angiography unless the clinical condition of the patient did not allow delay. In significant left main disease (≥70%), study medication was withheld, and the patient was scheduled for bypass graft surgery.

**Statistical Analysis**

The calculation of the number of patients required in the trial was based on an assumed angiographic difference in the decrease in the degree of diameter stenosis in the angiina-related coronary artery between patients treated with anistreplase and the placebo group. Assuming a mean decrease in the diameter stenosis of 15% (±15%) in the anistreplase group and of 5% (±15%) in the placebo group, 120 analyzable patients had to be enrolled to give 95% power of detecting a statistically significant difference (p<0.05 by two-tailed t test). Assuming a 25% dropout rate, 160 patients had to be included.

If applicable, Fisher’s exact test or Student’s t test was performed. Two-sided p values are reported.

**Results**

Baseline characteristics of the 159 patients included in the study are presented in Table 1. The ECG data are shown in Table 2. Angiographic data of the baseline and follow-up catheterizations are presented in Tables 1 and 3. Distribution of the baseline and ECG characteristics was similar for both groups. By chance, seven patients of the placebo group had significant (≥70%) main stem disease compared with none of the patients randomized to thrombolysis.

In total, 33 of 159 patients did not receive study medication. Reasons included significant main stem stenosis (seven patients), nonsignificant coronary artery disease (17), bleeding in groin (two), myocardial infarction before study medication (four), cardiogenic shock (one), and no angiography due to technical problems (two).

Of the 126 patients receiving study medication, 65 patients were randomized to thrombolysis, and 61 patients received placebo. (Assessment of the angiography committee indicated that two placebo patients incorrectly received study medication. Both had nonsignificant coronary artery disease.) Three patients had no second angiogram (one patient had myocardial infarction and cardiogenic shock, one patient had angioplasty 2 hours after baseline angiography, and one patient had logistic problems). In these three patients, clinical outcome was assessed, but they could not be used for angiographic analysis. Median time frames for the first and second catheterizations were identical for both study groups.

**Angiographic Results**

Comparison between the two coronary angiograms before and after treatment is presented in Table 3. Compared with placebo, a significant decrease in severity of the lesion (p=0.002) was found in the anistreplase group (qualitative assessment by the angiography committee).
These data were in accordance with the quantitative CAAS analysis: Diameter stenosis decreased significantly \((p=0.008)\) in the anistreplase patients and remained nearly unchanged in placebo patients. Seventeen thrombolitics and 11 placebo patients had an occluded artery at baseline angiography; in all, collaterals provided blood supply to the ischemic area. The difference in degree of stenosis before and after study medication was the result of reopening of 12 of 17 occluded arteries after thrombolytic therapy. In contrast, none of the 11 placebo patients showed reopening of the occluded vessel. Decrease in diameter stenosis of open arteries between the first and second angiographic procedures of the thrombolysis group was 5% compared with 3% of the placebo group \((p=NS)\).

**Clinical Results**

Clinical outcome during admission did not differ markedly between the groups (Table 4). Median duration of hospitalization was identical for the groups. Cardiac events, i.e., mortality, myocardial infarction, recurrence of angina, angioplasty and bypass surgery, occurred in the majority of the patients. Angioplasty was performed only in patients with recurrent angina despite antianginal medication. Only one of the 56 angioplasty patients had this procedure performed before the second angiogram. Six of the seven patients with significant main stem disease had bypass graft surgery. In addition, 16 other patients underwent surgery after the second angiogram because of recurrent anginal complaints. Average time delay between inclusion in the study and angioplasty was 3 days (range, 0–33 days), and the delay between inclusion and graft surgery was 6 days (range, 0–20 days).

The incidence of cardiac events was not significantly different between treatment groups. Recurrence of angina was higher in the patients receiving a thrombolytic agent. The high incidence of coronary bypass surgery in the group randomized to placebo (16 versus six in anistreplase group) can be explained by the seven patients with significant main stem disease because in patients receiving study medication, there was no significant difference between groups in the number of coronary bypass surgery patients. A significantly higher number of patients from the thrombolytic group developed bleeding (21 patients versus seven placebo patients), of whom seven had major bleeds requiring blood transfusion (six thrombolysis and one placebo).

No difference in time of occurrence of myocardial infarction and infarct size was found between the two groups (Table 5). In most patients, myocardial damage occurred within the first 24 hours.

Usually, as indicated by the enzyme pattern, necrosis had developed before admission, although the admission ECG did not show a typical infarct pattern. In 15 patients, myocardial infarction developed after more than 24 hours. Thrombolytic therapy did not protect against the development of myocardial infarction during admission, nor did it reduce infarct size. There was no relation between the presence of an occluded artery at the first angiogram and occurrence of early myocardial infarction.

**Relation Between Angiographic and Clinical Results**

Clinical outcome was independent of angiographic results. The incidence of cardiac events was similar
TABLE 4. Clinical Outcome During Admission

<table>
<thead>
<tr>
<th></th>
<th>Anistreplase</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>80 (15)</td>
<td>79 (18)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (1)</td>
<td>1 (0)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>29 (3)</td>
<td>21 (3)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>6 (0)</td>
<td>16 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angioplasty</td>
<td>30 (3)</td>
<td>26 (0)</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>27 (5)</td>
<td>12 (0)</td>
<td>0.06</td>
</tr>
<tr>
<td>One or more cardiac events</td>
<td>55 (6)</td>
<td>51 (9)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>21 (1)</td>
<td>7 (2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Numbers within parentheses indicate the patients who did not receive study medication.

between patients having improvement (74%) and no improvement in coronary anatomy (77%).

Discussion

Patients with unstable angina are at high risk: Myocardial infarction rates vary from 10% to 30% and mortality rates vary from 1% to 10% within the first 3 weeks after onset of symptoms.33-35 It is recognized that coronary thrombosis plays an important role in unstable angina. This is proven by angiography, angioscopy, and autopsy and indirectly by biochemical examinations.5-20 Presence of thrombosis is reported to be dependent on delay between onset of complaints and cardiac catheterization. The incidence of thrombosis is considerable (52-85%) when patients undergo cardiac catheterization within 2 weeks after onset of instability.10,14,15

Benefits of thrombolytic therapy should at least outweigh the risks. For the current study, anistreplase was chosen as the thrombolytic agent because of its ease of administration and its good performance in acute myocardial infarction in terms of mortality reduction,26 its high recanalization rate, and its low incidence of early reocclusion.37,38

Because of the small sample size of most previous studies, we decided to evaluate angiographic effects of thrombolytic therapy in a larger group of patients with unstable angina. The present study demonstrates an overall decrease of coronary stenosis after thrombolytics, especially occluded arteries. The angiographic findings contrast with the absence of beneficial clinical effects.

Furthermore, the price of bleeding complications is paid in this angiographic study of a selected group of patients with unstable angina.

It should be stated that the majority of bleeds were perivascular and would not have occurred if angiography had not been performed.

The reasons for the lack of improvement in clinical outcome after thrombolytic therapy are unknown. It could be explained in part by nonthrombotic lesions in the coronary arteries not reacting to antithrombotic medication. Furthermore, it is well known from myocardial infarction studies that thrombolytic therapy, even when combined with heparin and aspirin, does not fully protect from reocclusion.

Several smaller studies suggested angiographic improvement after thrombolytic treatment in patients with unstable angina.10,11,21-25,27 Usually, no improvement of symptoms, even after apparent angiographically successful thrombolysis with disappearance of thrombus or a lower degree of stenosis, could be demonstrated.22-24,26-28 Very recently, the TIMI III-A trial (consisting of more than 300 patients) also demonstrated an angiographic improvement, especially in those who had non-Q wave myocardial infarction (unpublished data).

Only Gold et al.,21 Beigbeder et al.,25 and Ardissino et al.39 were able to show better clinical outcomes in small groups of patients. However, patients in the Beigbeder et al study were randomized to thrombolysis combined with either aspirin or placebo. Therefore, aspirin might have been responsible for the better outcome in the streptokinase/aspirin group. Ardissino et al.39 randomized only patients with persistent instability after 48 hours.

Importantly, in our study, 19 patients (12%) had no or only slight abnormalities in their coronary arteries despite a typical history of unstable angina and ECG abnormalities. Eighteen of these patients had an uncomplicated clinical outcome; one patient suffered from acute myocardial infarction 4 days after inclusion in the study. This 12% incidence illustrates that a considerable group of patients fulfilling strict criteria of unstable angina have no or minimal coronary artery abnormalities. We could not determine a certain pattern in their ECG abnormalities or in the presence or absence of chest pain in or outside the hospital. It underlines the difficulty in decision making as to which patients with the clinical history of unstable angina have coronary artery disease or thrombus formation as the cause of symptoms and ECG findings.

Although the ECGs were not diagnostic, 35 patients presented with myocardial infarction on admission or within the first 24 hours as indicated by an early enzyme increase. Four patients did not receive study medication because myocardial infarction appeared just before administration of study medication. In addition, 15 patients developed myocardial infarction during hospital admission. De Zwaan et al.22 postulated that thrombolytic therapy may lead to temporary improvement of the clinical condition, allowing the physician to select appropriate intervention for longer-lasting treatment. (That opinion is not confirmed by the outcome of the present study.) The occurrence of myocardial infarction after study medication in 15 patients did not significantly differ in the anistreplase and placebo groups.

TABLE 5. Time of Occurrence and Size of Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Anistreplase</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>80 (15)</td>
<td>79 (18)</td>
</tr>
<tr>
<td>Larger MI ≤ 24 hours</td>
<td>6 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Small MI ≤ 24 hours</td>
<td>13</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Larger MI &gt;24 hours</td>
<td>9 (1)</td>
<td>4</td>
</tr>
<tr>
<td>Small MI &gt;24 hours</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

MI, myocardial infarction.

Numbers within parentheses indicate the patients who did not receive study medication. Small MI, maximal ASAT, threefold or less the upper limit of the normal value; larger MI, maximal ASAT more than threefold the upper limit of the normal value.
A second hypothesis from the same authors\textsuperscript{22} that thrombolysis limits infarct size also could not be confirmed. On the contrary, the number of large myocardial infarctions was even higher in the group receiving thrombolytic therapy.

It has been suggested that angioplasty in unstable angina patients is safer after thrombolysis.\textsuperscript{27} In the present study, angioplasty was equally successful in both groups: In 25 of 30 thrombolysis and 23 of 26 placebo patients, residual stenosis after the procedure was <50%. The angioplastical procedures did not influence the angiographic findings, whereas all except one patient had this intervention after the second angiogram. The number of patients (56) who underwent such procedure clearly is very high. The protocol stated that such procedure was allowed only in patients with recurrent angina. The first explanation of this high rate of angioplasty is that due to the strict inclusion criteria, a highly selective sick group of patients was collected. In addition, in case of repeated anginal complaints, it is likely that the threshold to perform the intervention is lower when the coronary anatomy is known.

The advantage of the current study is the number of patients, its prospective placebo-controlled randomized nature, and the evaluation of both anatomic and clinical outcome. Furthermore, the inclusion criteria were defined strictly, and the time interval between onset of unstable angina and angiography was very short. Also, attention was given to the identification of the culprit lesion in patients with multivessel disease by using the ECG, left ventricular wall motion, and a comparison of the two angiograms. We feel that the careful approach described above underlines the conclusion that at the present time thrombolytic treatment cannot be recommended in patients with unstable angina.

This trial was designed as an angiographic study, and a clinical trial with a much larger sample size was planned. However, the outcome of the present investigation indicated that positive clinical results were unlikely. Therefore, it was decided not to proceed to the new trial. We hope that the large TIMI III-B trial investigating the clinical effects of thrombolytics in unstable angina will provide definite answers.

Acknowledgments

Many people participated in the research presented in this article. We gratefully acknowledge the help of the members of the Centre Hospitalier Universitaire, Trouseau, Tours (Prof. Dr. Brochier, Prof. Dr. Raynaud, Dr. Lang, Dr. Pacouret); Centre Hospitalier Universitaire, Angers (Prof. Dr. Geslin); Clinique Saint Joseph, Colmar (Dr. Monassier, Dr. Hansen); Centre Hospitalier Universitaire, Necker-Enfants-Malades, Paris (Prof. Dr. Vacheron, Prof. Dr. Metzger, Dr. Le Feuvre); Centre Hospitalier Universitaire et Regional, Caen (Prof. Dr. Foucault); Hospital Universitaire St. Luc, Brussels (Prof. Dr. Col, Dr. Renkin); Hopital de la Citadelle, Liège (Dr. Boland, Dr. Materne); Academic Hospital of the Free University of Amsterdam (Prof. Dr. Verheugt, Dr. Werter); and Academic Hospital of Maastricht (Prof. Dr. Wellens, Dr. Bär, Dr. de Zwaan, Dr. Vermeer, Dr. Janssen, Dr. Gorgels). Furthermore, we would like to thank Mr. Höppner for his statistical work and Mrs. Lejeune for typing the manuscript.

References

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI): Long-term effects of intravenous thromboly-
7. Feldman RL: Coronary thrombosis, coronary spasm and speculation on the link between unstable angina and acute myocardial infarction. \textit{Am J Cardiol} 1987;59:1187–1190


35. Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group: Early treatment of unstable angina in the coronary care unit: A randomised, double blind, placebo-controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. Br Heart J 1986;56:400-413


38. Anderson JL: Reperfusion, patency and reocclusion with anistreplase (APSAC) in acute myocardial infarction. Am J Cardiol 1989;64:12A-17A

Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome. Results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase.
F W Bär, F W Verheugt, J Col, P Materne, J P Monassier, P G Geslin, J Metzger, P Raynaud, J Foucault and C de Zwaan

Circulation. 1992;86:131-137
doi: 10.1161/01.CIR.86.1.131

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 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/86/1/131

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/