Cholesterol Reduction With Atorvastatin Improves Walking Distance in Patients With Peripheral Arterial Disease

Emile R. Mohler III, MD; William R. Hiatt, MD; Mark A. Creager, MD; for the Study Investigators

Background—Cholesterol modification reduces cardiovascular events in patients with atherosclerosis, including those with peripheral arterial disease. The purpose of this study was to determine whether cholesterol lowering with atorvastatin improves walking performance in patients with intermittent claudication.

Methods and Results—This randomized, double-blind, parallel-design study included 354 persons with claudication attributable to peripheral arterial disease. Patients were treated with placebo, atorvastatin (10 mg per day), or atorvastatin (80 mg per day) for 12 months. The outcome measures included change in treadmill exercise time and patient-reported measures of physical activity and quality of life based on questionnaires. Maximal walking time after 12 months of treatment with atorvastatin did not change significantly. However, there was improvement in pain-free walking time after 12 months of treatment for the 80-mg \( P=0.025 \) group compared with placebo. A physical activity questionnaire demonstrated improvement in ambulatory ability for the 10- and 80-mg groups \( P=0.011 \), whereas 2 quality of life instruments, the Walking Impairment Questionnaire and Short Form 36 Questionnaire, did not show significant change.

Conclusions—Atorvastatin improves pain-free walking distance and community-based physical activity in patients with intermittent claudication. When treated with atorvastatin, patients with peripheral arterial disease may experience improvement in symptoms to complement the anticipated reduction in cardiovascular events reported in other studies of statins. (Circulation. 2003;108:1481-1486.)

Key Words: claudication ■ lipids ■ peripheral vascular disease ■ statins ■ hypercholesterolemia

Peripheral arterial disease (PAD) is a clinical manifestation of atherosclerosis that is prevalent in industrialized societies. The cardinal symptom of PAD is intermittent claudication, which is classically described as pain or discomfort in the affected extremity on exertion that resolves with rest. \(^1\,^2\) It is estimated that intermittent claudication occurs in approximately 5\% of individuals older than 60 years of age. \(^3\) The prevalence increases among persons with atherosclerotic risk factors such as cigarette smoking, diabetes, hypertension, and hypercholesterolemia. \(^4\,^5\,^6\)

Lipid modification with statins has been advocated in the treatment of patients with PAD, largely because of data from clinical trials in coronary artery disease demonstrating reduction in cardiovascular events. \(^7\) Recently, the Heart Protection Study confirmed that statin treatment reduces the risk of death and adverse cardiovascular events in patients with coronary and noncoronary atherosclerosis, including patients with PAD who had not had a prior cardiovascular event. \(^8\) A drug that not only improves claudication symptoms but also reduces cardiovascular events would be a particularly useful therapy for patients with PAD. Accordingly, we tested the hypothesis that atorvastatin improves treadmill performance and physical activity levels in patients with claudication.

Methods

Trial Design

This was a multicenter double-blind, placebo-controlled, parallel-group, randomized study evaluating the efficacy of atorvastatin on treadmill walking distance in patients with PAD. The protocol was approved by the institutional review boards of the respective institutions participating in this study, and each patient gave written informed consent. Site monitoring, data collection, and data analysis were performed by Pfizer, Inc. The manuscript was prepared by the authors and reviewed by the advisory committee and the sponsor.

Screening and Patient Selection

The study comprised 3 phases: screening, baseline, and double-blind treatment. For at least 1 month before screening, patients received dietary counseling and were instructed to follow the National Cholesterol Education Program step 1 diet. \(^7\) All patients underwent a full medical history, as well as evaluation of atherosclerotic risk factors. This was followed by a clinical examination, which included...
a physical examination, 12-lead ECG, laboratory tests, and measurement of the ankle brachial index (ABI). Patients eligible for the study had to be older than 25 years of age with stable, intermittent claudication for longer than 6 months and able to complete a screening treadmill test. Evidence of PAD was confirmed if the patient’s resting ABI was ≥0.90. Patients then underwent an initial screening treadmill test whereupon the pain-free walking time (PFWT) and maximal walking time (MWT) were recorded. A graded treadmill protocol was chosen (Gardner Protocol) with a constant speed of 2 miles per hour, increasing by 2% grade every 2 minutes. The ABI 1 minute after completion of a screening treadmill test had to be at least 20% lower than the resting ABI in the index leg. Inclusion criteria also included a LDL cholesterol value of ≥160 mg/dL (4.14 mmol/L).

Patients were excluded from the study if they had the following: myocardial infarction or coronary revascularization, peripheral vascular surgery or percutaneous intervention procedure within 6 months, unstable angina within the previous 3 months, stroke or transient ischemic attack within 6 months, or deep venous thrombosis within the previous 3 months before randomization. Patients were advised not to take lipid-modifying drugs not prescribed in the protocol, including other statin drugs, or any other drugs prescribed solely for the treatment of PAD. All patients were advised to take aspirin at a dose recommended by the investigator. Patients were encouraged to continue their usual level of activity, including exercise. However, individuals actively participating in an exercise rehabilitation program were not eligible for enrollment in this study.

Baseline Phase
To qualify for the double-blind period of the study, patients were required to undergo at least 2 exercise treadmill studies on different days (in addition to the screening treadmill test) and meet 1 of the 2 following criteria: (1) MWT of between 1 and 5 minutes in the first qualifying exercise test and MWT in the second (consecutive) test within 60 seconds of the preceding test (both must be greater than 1 minute) or (2) a MWT of between 5 and 12 minutes in the first qualifying exercise test and a MWT in the second or sequential test within 20% of the first (but less than 12 minutes). The baseline was defined as the mean of 2 qualifying treadmill visits.

Additional baseline procedures included the measurement of the ABI and administration of physical activity and quality of life questionnaires. The Low Level Physical Activity Recall (LOPAR) questionnaire provides a global measure of physical activity, by assessing the total energy expenditure of the patient at work and during home and leisure-time activities for the preceding week. The SF-36 is a well-validated questionnaire that assesses overall health and includes 36 items measuring limitations in physical activity, mental activity, social activity, vitality, and general health perception. The Walking Impairment Questionnaire (WIQ) measures 4 domains of function, including walking distance, walking speed, severity of claudication pain, and ability to climb stairs. Also, blood was collected for chemistry studies, complete blood count, and lipoprotein profile.

Double-Blind Treatment Phase
At the randomization visit, patients were assigned to take either atorvastatin 10 mg/d, atorvastatin 80 mg/d, or placebo for 12 months. Thereafter, blood tests and clinic visits occurred at 3-month intervals. At each visit, the patient was counseled to continue a National Cholesterol Education Program step 1 diet. Subjects underwent exercise treadmill studies at 3 and 6 months after randomization. At 12 months, the subject had 2 treadmill tests performed 1 week apart, and the mean of the tests was used for analysis. At 3, 6, and 12 months, the ABI was measured, lifestyle questionnaires were administered, and blood was collected for analysis.

Outcome Measures
The primary efficacy parameter of the trial was change in MWT at 12 months. The change from baseline in PFWT was a secondary efficacy parameter. Additional secondary efficacy end points included the change from baseline in community-based functional status after randomization assessed by the SF-36, WIQ, and LOPAR, ABI, and the incidence of peripheral vascular and critical cardiovascular events, as defined below.

Peripheral vascular events were defined as having 1 of the following: worsening symptoms of claudication, development of rest ischemia, peripheral revascularization procedure, or limb amputation. Only 1 vascular event per patient was counted. All of the vascular events were adjudicated by an independent committee. Critical cardiovascular events included myocardial infarction, stroke, and vascular death.

Statistical Analysis
The primary analysis was performed using data from all randomized patients having at least 1 treadmill test during the treatment phase. The last observation while on treatment was carried forward for those patients who did not complete the study. Patients with diabetes and patients who smoked were stratified across treatment groups for the analysis.

The primary and secondary efficacy parameter were analyzed using ANCOVA with treatment and center as effects and baseline level of the parameter as a covariate. There was no adjustment made for multiple comparisons. Pairwise comparisons of each atorvastatin dose to placebo were used to determine differences. Additional models were run to examine the interaction of treatment with center and baseline covariate to help determine the consistency of results. Data are depicted as the mean and SE.

Results
By November 2000, 601 patients were screened for the study. Of these, 364 were eligible and randomized to receive either atorvastatin 10 mg/d, atorvastatin 80 mg/d, or placebo for 1 year. Although 364 patients were randomized into the study, the data describes only 354 of these. The data from 1 site that had randomized 10 patients were excluded because of premature closure of the site and failure to satisfactorily recover the data.

The demographic data of the patients are listed by treatment group in Table 1. Atherosclerotic risk factors such as smoking, dyslipidemia, hypertension, and diabetes mellitus did not significantly differ among the 3 groups. Also, the use of concomitant medications such as antiplatelet, anticoagulant, antihypertensive, or vasodilator drugs did not differ between the 2 groups.

The change in effect of treatment on the lipid profile levels is depicted in Figure 1. There was a significant reduction in

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Characteristics of Patients</th>
<th>Atorvastatin 10 mg</th>
<th>Atorvastatin 80 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (%)</td>
<td>90 (75)/30 (25)</td>
<td>95 (79)/25 (21)</td>
<td>88 (77)/26 (23)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173</td>
<td>173</td>
<td>171</td>
</tr>
<tr>
<td>Age, y</td>
<td>69</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>113 (94)</td>
<td>114 (95)</td>
<td>104 (91)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (4)</td>
<td>4 (3)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>23 (19)</td>
<td>22 (18)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>49 (41)</td>
<td>42 (35)</td>
<td>52 (46)</td>
</tr>
</tbody>
</table>
the total cholesterol, LDL cholesterol, and triglyceride levels for both the 10- and 80-mg doses compared with placebo ($P<0.001$) and a significant increase in HDL levels compared with placebo ($P=0.03$). There was no difference in lipid measurements between the 10- and 80-mg atorvastatin groups.

**Treadmill Results**

The baseline MWTs were $266\pm16$, $174\pm18$, and $243\pm17$ seconds in the atorvastatin 10-mg, 80-mg, and placebo groups, respectively ($P=NS$), and the baseline PFWTs were $137\pm10$, $132\pm9$, and $121\pm9$ seconds, respectively ($P=NS$). When evaluated on an intent-to-treat basis, there was no significance between the change in MWT from baseline at 12 months in the 2 atorvastatin-treated groups ($90\pm18$ and $90\pm18$ seconds, respectively) compared with the placebo-treatment group ($50\pm12$ seconds, $P=0.37$) (Figure 2). However, mean PFWT improved by 63% ($81\pm15$ seconds) in the atorvastatin 80-mg treatment group compared with 38% ($39\pm8$ seconds, $P=0.025$) in the placebo group (Figure 3). There was no significant difference in PFWT ($74\pm14$ seconds) in the 10-mg group compared with placebo ($P=0.130$). When the 80- and 10-mg groups were combined and then compared with placebo, there was a significant improvement in the PFWT ($78\pm10$ seconds) compared with placebo ($P=0.047$) but not in MWT ($P=0.16$).

Post-hoc analyses were performed to determine if selected baseline characteristics influenced the response to atorvastatin. These analyses included adjustments for smoking status and LDL cholesterol concentration and the interaction of those terms by treatment. Neither smoking status nor LDL cholesterol concentration had any significant effect on the change in MWT or PFWT in response to atorvastatin. However, there was a numerical trend toward greater improvement in patients whose baseline LDL cholesterol level was above the median of 123 mg/dL.
Ankle-Brachial Index
The ABI was 0.62±0.02, 0.62±0.01, and 0.59±0.01 at baseline and 0.64±0.02, 0.64±0.02, and 0.63±0.01 at 12 months for the 10-mg, 80-mg, and placebo groups, respectively, and without significant change across all groups (P=0.57). No significant interaction of the ABI was noted on the primary or secondary end points with variables such as smoking, diabetes, and hypertension.

Quality of Life Measures
There was a significant change in the results of the LOPAR questionnaire. The 80-mg group (P=0.020), 10-mg group (P=0.032), and combined 80- and 10-mg groups (P=0.011) showed an improvement in physical activity compared with placebo. There was no significant difference in the quality of life questionnaires, SF-36, and WIQ.

Adverse Events and Discontinuations
There were 6 deaths during this study, 4 in the atorvastatin 10-mg group (cancer, stroke, myocardial infarction, and respiratory failure), 1 in the atorvastatin 80-mg group (coronary artery disease), and 1 in the placebo group (myocardial infarction). The number of major cardiovascular events included 4 myocardial infarctions and 1 stroke in the atorvastatin 10-mg group, 2 myocardial infarctions, 1 death characterized as worsening coronary artery disease, and 1 stroke in the atorvastatin 80-mg group, and 3 myocardial infarctions in the placebo group. The proportion of subjects discontinuing from the study was similar among the treatment groups (Table 2).

Vascular Events
The peripheral vascular events were predefined and adjudicated blindly to study group and are listed in Table 3. Most vascular events occurred in the placebo group (9 of 12 events, 75%). Only 1 peripheral vascular event occurred in the 10-mg atorvastatin group, and 2 occurred in the 80-mg atorvastatin group. The incidence of peripheral vascular events was significantly higher in the placebo group than in the combined atorvastatin groups (P=0.003).

Discussion
This prospective study evaluated whether atorvastatin improves claudication symptoms in patients with PAD. Al-

<table>
<thead>
<tr>
<th>TABLE 2. Discontinuations From Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10 mg (N=120)</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Total discontinued (%)</td>
</tr>
<tr>
<td>Discontinuation related to study drug (%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Discontinuation not related to study drug (%)</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Subject defaulted (%)</td>
</tr>
<tr>
<td>Subject withdrew consent (%)</td>
</tr>
<tr>
<td>Lost to follow-up (%)</td>
</tr>
</tbody>
</table>

Figure 3. Graph with PFWT for 10 and 80 mg atorvastatin and placebo over the course of treatment. When analyzed on intent-to-treat basis, PFWT improved significantly in the atorvastatin 80-mg group (*P=0.025).
though MWT did not change significantly, PFWT improved after 12 months of treatment with atorvastatin. The change in PFWT is comparable to that achieved with other currently approved pharmacotherapies. The improvement in the LO-PAR questionnaire was consistent with the improvement in PWFT. The current study was not designed or powered to evaluate vascular events; however, most peripheral vascular events occurred in the placebo group.

Comparison With Other Studies

Other studies with lipid-modifying therapies have demonstrated favorable effects in patients with PAD. In the Cholesterol-Lowering Atherosclerosis Study, colestipol and niacin treatment prevented progression of femoral atherosclerosis. In the Program on the Surgical Control of Hyperlipidemias, the incidence of new cases of claudication was less in patients who underwent ileal bypass surgery to lower LDL cholesterol. A post-hoc analysis of the Scandinavian Simvastatin Survival Study data found that new or worsening claudication was reduced in the group that received the statin. A contemporaneous study found that simvastatin improves walking time in patients with claudication.

Potential Mechanisms of Action

Claudication occurs when blood flow to the extremity fails to meet the metabolic demands of the skeletal muscle during walking exercise. Therefore, several possible mechanisms might be considered on how modification of the lipid profile with a statin drug improves symptoms of claudication. One such mechanism may be reduction in plaque size, thereby improving blood flow in the large arteries of the lower extremities. Angiographic studies evaluating the effects of statin drugs on atherosclerotic plaque burden have found statistically significant, but very mild, increases in lumen size that would not impart any favorable effect on the hemodynamic profile through a stenotic segment. Thus, it is unlikely that the increase in PFWT in this study was attributable to improved hemodynamics in the conduit vessels of the lower extremities, especially given the lack of significant improvement in the ABI.

Another mechanism to be considered is statin-induced improvement of vasomotor regulation of blood flow, particularly in the microcirculation. Blood flow is primarily regulated at the arteriolar and capillary level by sympathetic nervous system activity and modulated by local vasoactive factors such as nitric oxide, prostacyclin, and adenosine. Cardiovascular risk factors, notably elevated LDL cholesterol, decreased HDL cholesterol, and elevated triglycerides are associated with endothelial dysfunction and reduced bioavailability of nitric oxide, leading to secondary perturbations in local vasomotor tone. Modification of the lipid profile with statins has been shown to increase endothelium-dependent vasodilation. Theoretically, this could reduce vascular resistance and improve blood flow through collateral vessels of the lower extremity. Moreover, the determinants of PWFT and MWT are likely to differ, and it is conceivable that nitric oxide contributes more to the former than the latter.

Lipid-lowering therapy with a statin may also affect new blood vessel formation. Data derived from animal studies indicate that hypercholesterolemia inhibits angiogenesis. Conceptually, a reduction in cholesterol may remove this inhibition and allow for new blood vessel development, which would result in improvement in symptoms of claudication. Statin drugs may also promote a proangiogenic response independent of cholesterol reduction. It was beyond the scope of this study to determine if any of these mechanisms are relevant to the improvement in PWFT realized after 1 year of treatment with atorvastatin.

Vascular Events

It is notable that in this study, only 3 of 240 (1.3%) patients receiving atorvastatin experienced adverse peripheral vascular events such as worsening symptoms of claudication or development of ischemic pain at rest or underwent a noncoronary revascularization procedure compared with 9 of 114 (7.9%) patients receiving placebo. This trial was not designed nor powered to assess the effect of atorvastatin on vascular events in patients with PAD. Nonetheless, the findings are congruous with the reduction in cardiovascular events that have been reported consistently in the secondary prevention trials of statins in patients with coronary artery disease.

Clinical Implications

The improvement in PWFT in this study can be considered in context to the 2 medications, pentoxifylline and cilostazol, approved by the Food and Drug Administration for treatment of intermittent claudication. Cilostazol is considered to be more efficacious than pentoxifylline, and this is supported by 1 clinical study. The improvement in PWFT in the present study is similar to that seen with studies of trials with cilostazol. In a recent meta-analysis of 6 trials, cilostazol 100 mg twice daily improved pain-free walking distance by 36% and maximal walking distance by 38%. The timing of clinical improvement for atorvastatin seems to be longer compared with cilostazol, and thus patients with claudication symptoms should not expect symptomatic improvement in PWFT after weeks but more likely after months of treatment.

### TABLE 3. Vascular Events

<table>
<thead>
<tr>
<th>Vascular Events</th>
<th>Atorvastatin 10 mg</th>
<th>Atorvastatin 80 mg</th>
<th>Placebo</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening symptoms of claudication</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Development of rest ischemia</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral revascularization</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Other (carotid endarterectomy)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>
We acknowledge that atorvastatin did not improve MWT, the primary outcome in this study. The decision to choose MWT rather than PFWT was based more on recent convention than on any particular scientific principle. Yet daily activities in patients with PAD are typically governed by the onset of symptoms and not maximally tolerated discomfort. Indeed, the improvement in the physical activity recall scores reflects this contention. Therefore, the important findings of this prospective study should not be diminished by the designation of PFWT as a secondary outcome measure.

Conclusions
The results from this study indicate that PFWT improves in patients taking atorvastatin. These data suggest that patients with claudication may not only benefit in a reduction of vascular events with atorvastatin but also have improvement in lifestyle with treatment.

Appendix: Principal Investigators
Canada
Pierre Auger, MD, PRCPC, Clinique de Cardiologie de Levis, Levis, Quebec; J. David Spence, MD, Stroke Prevention and Atherosclerosis Research Center, London, Ontario; and Paul Tanser, MD, St Joseph’s Hospital, Hamilton, Ontario.

United States
Mark A. Creager, MD, Brigham and Women’s Hospital, Boston, Mass; R. Scott Daarad, MD, Boulder Clinical Research, Boulder, Colo; Michael Davidson, MD, Chicago Center for Clinical Research, Chicago, Ill; Theodore Feldman, MD, Coral Gables, Fla (satellite); Gregory Geyar, MD, Pacific Northwest Clinical Research Center, Portland, Ore; William R. Hiatt, MD, Colorado Prevention Center, Denver, Colo; Donald Hunninghake, MD, and Alan T. Hirsch, MD, University of Minnesota Hospital and Clinics, Minneapolis, Minn; Jonathan Isaacochn, MD, and Evan Stein, MD, Metabolic and Atherosclerosis Research Center, Cincinnati, Ohio; Michael J. Koen, MD, Jacksonville Cardiovascular Clinic, South Jacksonville, Fla; Daniel Lips, MD, Mid-America Cardiology, Kansas City, Mo; James M. McKenzie, PharmD, Richard Memorial Hospital, National Clinical Research, Richmond, Va; Emile R. Mohler, III, MD, University of Pennsylvania School of Medicine, Philadelphia, Pa; Mohammed Mouri, MD, and Frederick Faas, MD, John L. McClellan VA Hospital, little Rock, Ark; Matthew Neubaur, MD, Jacksonville Heart Center, Jacksonville Beach, Fla (satellite); Jeffrey W. Olin, DO, and Dennis Sprecher, MD, The Cleveland Clinic Foundation, Preventive Cardiology, Cleveland, Ohio; Dennis Riff, MD, Advanced Clinical Research Institute, Raleigh, N.C.; Robert Samuels, MD, and Associated Internists, Phoenix, Ariz; and Laurence G. Yellen, MD, Cardiology Associates Medical Group, San Diego, Calif.

Acknowledgments
This study was funded by Pfizer, Inc. Dr Creager is the Simon C. Fireman Scholar in Cardiovascular Medicine at Brigham and Women’s Hospital; Dr Hiatt is the Novartis Foundation Professor of Cardiovascular Research at the University of Colorado Health Sciences Center. The authors gratefully acknowledge the members of the advisory committee, Scott Kinlay, and Henrick Sillesen for their review and advice regarding the manuscript and also Sally J. Leslie, PhD, Study Director, Kathleen McCann, Study Manager, and Jonathan Ma, Statistician.

References
Cholesterol Reduction With Atorvastatin Improves Walking Distance in Patients With Peripheral Arterial Disease
Emile R. Mohler III, William R. Hiatt and Mark A. Creager
for the Study Investigators

_Circulation_. published online September 2, 2003;
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 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/early/2003/09/02/01.CIR.0000090686.57897.F5.citation

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/