Clinical Investigation and Reports

Improved Arterial Compliance by a Novel Advanced Glycation End-Product Crosslink Breaker

David A. Kass, MD; Edward P. Shapiro, MD; Miho Kawaguchi, MD; Anne R. Capriotti; Angelo Scuteri, MD, PhD; Robert C. deGroof, PhD; Edward G. Lakatta, MD

Background—Arterial stiffening with increased pulse pressure is a leading risk factor for cardiovascular disease in the elderly. We tested whether ALT-711, a novel nonenzymatic breaker of advanced glycation end-product crosslinks, selectively improves arterial compliance and lowers pulse pressure in older individuals with vascular stiffening.

Methods and Results—Nine US centers recruited and randomly assigned subjects with resting arterial pulse pressures >60 mm Hg and systolic pressures >140 mm Hg to once-daily ALT-711 (210 mg; n=62) or placebo (n=31) for 56 days. Preexisting antihypertensive treatment (90% of subjects) was continued during the study. Morning upright blood pressure, stroke volume, cardiac output, systemic vascular resistance, total arterial compliance, carotid-femoral pulse wave velocity, and drug tolerability were assessed. ALT-711 netted a greater decline in pulse pressures than placebo (−5.3 versus −0.6 mm Hg at day 56; P=0.034 for treatment effect by repeated-measures ANOVA). Systolic pressure declined in both groups, but diastolic pressure fell less with ALT-711 (P=0.056). Mean pressure declined similarly in both groups (−4 mm Hg; P<0.01 for each group, P=0.34 for treatment effect). Total arterial compliance rose 15% in ALT-711–treated subjects versus no change with placebo (P=0.015 versus ALT-711), an effect that did not depend on reduced mean pressure. Pulse wave velocity declined 8% with ALT-711 (P<0.05 at day 56, P=0.08 for treatment effect). Systemic arterial resistance, cardiac output, and heart rate did not significantly change in either group.

Conclusions—ALT-711 improves total arterial compliance in aged humans with vascular stiffening, and it may provide a novel therapeutic approach for this abnormality, which occurs with aging, diabetes, and isolated systolic hypertension.

(Circulation. 2001;104:1464-1470.)

Key Words: ALT-711 ■ arteries ■ compliance ■ aging ■ glycosylation end products, advanced ■ hypertension

Arterial wall stiffening often occurs with aging and is exacerbated by diabetes and hypertension.1–3 It is the major cause of reduced total arterial compliance (C a) and increased central pulse-wave velocity, changes that both widen the pulse and disproportionately increase systolic pressure. A growing recognition that vascular stiffening and increased pulse pressure (PP) are dominant risk factors for cardiovascular disease,4–8 particularly among the elderly,9–12 is driving the search for novel agents that can specifically enhance C a and reduce pressure pulsatility.13,14

Artery compliance is determined by ambient mean pressure, endothelial function, vessel tone, and artery structure and composition. Current antihypertensive therapies focus on the first 3 factors,13,15 yet this can run the risk of reducing diastolic pressure while inadequately lowering PP.13,15–17 Treatments targeting structural factors remain largely unexplored. Among the latter are alterations in matrix proteins within the vessel wall from nonenzymatic crosslinks between glucose (or other reducing sugars) and amino groups that generate advanced glycation end-products (AGE).18,19 AGE accumulate slowly on long-lived proteins such as collagen and elastin to stiffen both arteries and the heart, and decreasing these crosslinks can enhance vessel and cardiac compliance in experimental animals.20–23

The new thiazolium derivative, ALT-711 (3-phenacyl-4,5-dimethylthiazolium chloride), which catalytically breaks established AGE crosslinks between proteins,24 reduces arterial stiffening, slows pulse-wave velocity, enhances cardiac output, and improves LV diastolic distensibility in experimental animals.20,22,23 The present study tested whether ALT-
11 improves $C_A$ and lowers PP in older human subjects with baseline vascular stiffening.

Methods

Patients

A total of 93 individuals aged $\geq 50$ years, with evidence of vascular stiffening (PP $\geq 60$ mm Hg, systolic blood pressure $\geq 140$ mm Hg, and large artery compliance $\leq 1.25$ mL/mm Hg) were entered into the study. Concomitant antihypertensive treatment was permitted as long as it started at least 4 weeks before screening and was expected to continue unchanged throughout the study. Patients were excluded if they had a history of coronary angina, myocardial infarction, bypass surgery, coronary angioplasty, cerebrovascular accident, valvular disease, malignant hypertension, type 1 or unstable type 2 diabetes mellitus, documented autonomic neuropathy, chronic active hepatitis B.

Patients underwent noninvasive cardiovascular testing and safety evaluations at a screening visit (which occurred $\leq 21$ days before first dosing), at baseline (day 1), and over the subsequent 8-week study period. Physiological evaluations consisted of resting arm-cuff blood pressure, radial arterial tonometry, and echo-Doppler ultrasonography to assess vascular compliance, cardiac output, stroke volume (SV), peripheral resistance, and carotid-femoral pulse wave velocity. Full cardiovascular assessments (echo-Doppler and pressure/tomometry) were obtained at baseline, day 28, and day 56. Pressure-only data and clinical assessments were also obtained on day 3, and biweekly. Smoking and caffeine and alcohol consumption were prohibited 8 hours before and during testing.

Arm-cuff blood pressures were recorded in triplicate in an upright/semirecumbent position, after an overnight fast and before taking study medication. The average of the 2 latter recordings was used. Duplicate supine radial pulse waveforms and cuff pressures (CR-2000, HDI) were averaged. Pulse-Doppler waveforms (HP Sonos 5500 or equivalent) from the aortic root, right carotid, and femoral artery, with simultaneous ECG and 2D aorta annulus area images were obtained.

Vital signs, 12-lead ECG, clinical laboratory testing, and full physical examination were obtained at each visit. Adverse events were monitored by patient interview and/or observed adverse experiences.

Data Analysis

Mean arterial pressure (MAP) was estimated using the following equation: $[\text{systolic blood pressure} - (2 \times \text{diastolic blood pressure})]/3$. Demographic data are provided as percent of subject group; other data are mean $\pm$ SD. ARB indicates angiotensin II receptor blocker.

*P $\leq 0.06$; all other comparisons are P $>0.35$.

### Table 1. Demographic, Clinical, and Baseline Hemodynamic Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALT-711 (n=62)</th>
<th>Placebo (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>42</td>
<td>61.3</td>
</tr>
<tr>
<td>White, %</td>
<td>59.7</td>
<td>74.2</td>
</tr>
<tr>
<td>Age, y</td>
<td>66.8 $\pm$ 8.9</td>
<td>67.5 $\pm$ 6.6</td>
</tr>
<tr>
<td>Weight, lbs</td>
<td>189.8 $\pm$ 39.2</td>
<td>190.0 $\pm$ 34.9</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>24.2</td>
<td>22.6</td>
</tr>
<tr>
<td>Concurrent pharmacological treatment, %</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>Ca$^{2+}$-channel blocker</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>$\beta$-Blocker</td>
<td>44</td>
<td>58</td>
</tr>
<tr>
<td>Other (Diuretics)</td>
<td>31</td>
<td>58</td>
</tr>
<tr>
<td>$\geq$2 Agents</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

#### Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALT-711 (n=62)</th>
<th>Placebo (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>158.8 $\pm$ 12.1</td>
<td>159.3 $\pm$ 13.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>84.0 $\pm$ 9.4</td>
<td>88.2 $\pm$ 1.3*</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>74.9 $\pm$ 9.5</td>
<td>71.1 $\pm$ 8.2*</td>
</tr>
<tr>
<td>$Ca$, mL/mm Hg</td>
<td>0.93 $\pm$ 0.27</td>
<td>0.988 $\pm$ 0.37</td>
</tr>
<tr>
<td>PWV, cm/s</td>
<td>872 $\pm$ 257</td>
<td>914 $\pm$ 287</td>
</tr>
<tr>
<td>SV/PP, mL/mm Hg</td>
<td>1.31 $\pm$ 0.41</td>
<td>1.37 $\pm$ 0.41</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.6 $\pm$ 1.0</td>
<td>4.6 $\pm$ 1.1</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes $\cdot$ sec$^{-1}$ $\cdot$ cm$^{-2}$</td>
<td>1979 $\pm$ 458</td>
<td>2040 $\pm$ 534</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66.8 $\pm$ 11.2</td>
<td>67.0 $\pm$ 9.8</td>
</tr>
</tbody>
</table>

Demographic data are provided as percent of subject group; other data are mean $\pm$ SD. ARB indicates angiotensin II receptor blocker.

70 mg of ALT-711 or placebo of identical appearance were dispensed with instructions to take 3 tablets once a day at $\approx$8 hours after an overnight fast. Both sponsor and investigators were blinded to treatment assignments during the study.

Patients underwent noninvasive cardiovascular testing and safety evaluations at a screening visit (which occurred $\leq 21$ days before first dosing), at baseline (day 1), and over the subsequent 8-week study period. Physiological evaluations consisted of resting arm-cuff blood pressure, radial arterial tonometry, and echo-Doppler ultrasonography to assess vascular compliance, cardiac output, stroke volume (SV), peripheral resistance, and carotid-femoral pulse wave velocity. Full cardiovascular assessments (echo-Doppler and pressure/tomometry) were obtained at baseline, day 28, and day 56. Pressure-only data and clinical assessments were also obtained on day 3, and biweekly. Smoking and caffeine and alcohol consumption were prohibited 8 hours before and during testing.

Arm-cuff blood pressures were recorded in triplicate in an upright/semi-recumbent position, after an overnight fast and before taking study medication. The average of the 2 latter recordings was used. Duplicate supine radial pulse waveforms and cuff pressures (CR-2000, HDI) were averaged. Pulse-Doppler waveforms (HP Sonos 5500 or equivalent) from the aortic root, right carotid, and femoral artery, with simultaneous ECG and 2D aorta annulus area images were obtained.

Vital signs, 12-lead ECG, clinical laboratory testing, and full physical examination were obtained at each visit. Adverse events were monitored by patient interview and/or observed adverse experiences.
Radial tracings from 30-second recordings were de-trended and calibrated to match mean and diastolic brachial pressures, on the basis of the similarity of these values to invasive measurements. Individual waveforms outside the 95% confidence interval of the mean were excluded, and remaining beats (typically >10) were processed by a 10-term autoregression-exogenous filter to synthesize central pressures. C_A was determined by the area method and indirectly evaluated from the quotient of SV to resynthesized central complex to the foot of each flow wave.

Influence of ALT-711 on Blood Pressure

In Figure 1, PP declined in the ALT-711 group (P<0.0001 for within-group RMANOVA), but this effect was not observed in placebo (P=0.46). The net drug interaction was significant (P=0.033 for RMANOVA; Table 1A), with a -5.3±9.9 mm Hg decline with ALT-711 at day 56 versus -0.6±8.2 mm Hg decline with placebo (P=0.02 between groups).

The disproportionate decline in PP was not due to differences in mean pressure, which fell similarly by 3 to 5 mm Hg in both groups (P<0.015 in placebo, P=0.001 in ALT-711), with no significant treatment interaction. Systolic pressure declined similarly in both groups (P=0.034 for treatment-interaction), but significantly more than placebo, significantly less in both groups, and although ALT-711 responses tended to be somewhat greater, this did not reach statistical significance. D, Diastolic pressures declined slightly less with ALT-711 than placebo, and this interaction effect achieved borderline significance.

ALT-711 Effects on C_A and PWV

ALT-711 increased C_A at day 28 nearly 15% (Figure 2A; P<0.005), and it remained significantly elevated at day 56 (P<0.05). C_A was not altered with placebo (P=0.01 for treatment interaction). PWV (Figure 2B) was not significantly altered at day 28 (P>0.25 in both groups); however, it declined at day 56 in the ALT-711 group (~7%; P<0.05 versus baseline) while remaining unchanged in placebo (P=0.08 for treatment-time interaction, P=0.041 by analysis based on paired changes-versus-baseline). This is consistent with an early decline in PP in both groups but a subsequent disappearance of this change in placebo only. The SV/PP ratio (Figure 2C) strongly correlated with C_A (r=0.95, 0.001). Other correlations are shown in Figure 2D.

Results

Clinical characteristics and baseline hemodynamics are provided in Table 1. Type II diabetes was present in 25% of each group. Nearly 90% of subjects received at least one antihypertensive agent, usually an ACE inhibitor or angiotensin II receptor blocker. There were no significant differences in C_A, PWV, SV/PP, systemic vascular resistance, cardiac output, or heart rate. Pulse and diastolic pressures were borderline different between groups (P=0.06 for both).
ALT-711 Effects on C_A Are Independent of Mean Pressure

Figure 3A displays the absolute change in C_A versus the corresponding change in MAP in the same subject. To enhance display clarity, data from days 28 and 56 were bin-averaged over incremental ΔMAP ranges. Covariance analysis of these relations was based on the raw (nonaveraged) data for combined and individual study day results. There was a significant negative correlation between the parameters in both study groups (P<0.0005 for placebo; P<0.05 for ALT-711) as expected, because vascular stiffness increases at higher MAPs. However, ALT-711 treatment shifted this data upward (P<0.001), demonstrating a greater rise in C_A for any given change in MAP. This drug-interaction effect was significant at day 28 (P<0.001) and at day 56 (P<0.05), as well as for the combined analysis shown in Figure 3A.

The ALT-711 effect on C_A was particularly notable in those individuals in who ΔMAP declined modestly (<3 mm Hg), was unchanged, or rose (Figure 3A; region noted by bracket). Compared with baseline, C_A declined at day 28 and day 56 in placebo group, but increased with ALT-711. This occurred despite similar net increases in MAP for both groups (Figure 3B). The C_A response difference was also not associated with differential responses in PP (P>0.4 at both time points).

Tolerability and Safety

ALT-711 was well tolerated, with a similar proportion of patients reporting an adverse experience in ALT-711 (n=34; 54.8%) and placebo (n=19; 61.3%) groups. Adverse experiences reported by at least 5% of patients are provided in Table 2. More serious events included 2 instances of atrial fibrillation, and one each of noncardiac chest pain, dizziness, uncontrolled hypertension, and lung neoplasm (the latter two
occurred in placebo group). There was a modest increase in serum triglyceride levels in the ALT-711 (mean change, increase of 33.5 mg/dL at day 56 versus increase of 3.5 mg/dL in placebo group). There were no changes in any other laboratory parameters or ECGs during the study, including glycosylated hemoglobin.

Discussion
Pharmacological Profile of ALT-711
This randomized, double-blind, placebo-controlled study shows that ALT-711 favorably impacts measures of vascular stiffening in older human subjects. The pharmacological profile of ALT-711 is fairly unique in that CA, PWV, and PP all changed without an apparent disproportionate decline in mean pressure, systemic resistance, cardiac output, or heart rate. The ALT-711 effect on CA was particularly striking (directionally opposite placebo) in individuals in whom mean pressure declined little or rose, again despite a lack of corresponding disparities in mean pressure.

The rapid onset of PP decline with ALT-711 was somewhat surprising, although it should be noted that differences between ALT-711 and placebo groups did not reach statistical significance until day 42. Experimental data do support AGE-crosslink breaker activity as early as 1 week, and unpublished in vitro results show substantial ALT-711 effects within hours. The apparent early decline in PP should also be considered in light of concomitant reductions in pulse and mean pressure in the placebo group. Such responses are common in hypertension trials and may relate to familiarization with the clinical environment. The early fall in PP with ALT-711 also likely included this effect, making the true drug-related time course more gradual.

These data are the first to suggest that AGE-crosslinks contribute to arterial stiffening in humans, supporting experimental studies performed in diabetic and nondiabetic models. These animal studies have also reported declines in systemic arterial resistance with ALT-711 (ranging from 25% to 40%), resulting in elevated cardiac output, and this change was not observed in the present study. Although a modest decline in systemic vascular resistance may have occurred yet been undetected due to measurement noise, it is highly unlikely that changes of the magnitude observed in animals were missed in error because our sample size provided more than adequate power to detect even 10% changes. Other potential causes for the disparity in systemic vascular resistance response may have been greater large-vessel stiffening in humans and the lack of anesthesia, which can influence baroreflexes. Finally, none of subjects had symptomatic ventricular hypertrophy or diastolic dysfunc-

TABLE 2. Tolerability Profile of ALT-711

<table>
<thead>
<tr>
<th></th>
<th>ALT-711 (n=62)</th>
<th>Placebo (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting adverse events, %</td>
<td>54.8</td>
<td>61.3</td>
</tr>
<tr>
<td>Patients reporting drug-related adverse events, %</td>
<td>14.5</td>
<td>22.6</td>
</tr>
<tr>
<td>Patients with serious adverse events, %</td>
<td>6.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Common adverse experiences (&lt;5% incidence), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>11.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Headache</td>
<td>8.1</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8.1</td>
<td>9.7</td>
</tr>
<tr>
<td>Pain</td>
<td>13</td>
<td>9.7</td>
</tr>
<tr>
<td>Asthenia/dizziness</td>
<td>13</td>
<td>16.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>9.7</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Values are provided as percent of subject group.
tion, so whether ALT-711 enhances cardiac chamber distensibility in humans, as reported in several animal studies, remains unknown.

Methodological Limitations
We used an oscillometric device to assess arm cuff pressure. This commonly used method displays somewhat higher reproducibility than other approaches, which is an important consideration for our study. However, data also suggest that vascular stiffening can lead to overestimated systolic and diastolic pressures with the technique, particularly when compared with zero-reference sphygmonanometry. With lowered stiffening, one might observe a greater apparent decline in both blood pressures and a slight rise in PP. However, we found the opposite, with PP declining more and diastolic pressure falling less than with placebo.

We did not assess regional vascular distensibility (i.e., pressure-dimension analysis) and although the parameters obtained are certainly influenced by central conduit stiffness, they are also sensitive to changes in small vessel capacitance and resistance. Clarification of the site(s) of ALT-711 effects awaits further study. Importantly, the parameters obtained provide important markers of cardiovascular risk. PWV was obtained using image-based noninvasive analysis, which reflected practical concessions for this multicenter study. However, this likely contributed to increased signal noise.

Carotid tonometry was not performed because few centers had experience with the method, but this limited the analysis of wave reflections. Reconstructed central pressures cannot be used for this purpose, because there is insufficient high-frequency detail after band-pass filtering. We used radial (as opposed to brachial) tonometry to enhance signal reliability and standardization among centers. One drawback is that waveform calibration becomes indirect, requiring an assumed fixed weighting of systole/diastole to estimate mean pressure from arm cuff data. Real changes in wave-shape can alter this weighting, and assuming it constant might result in underestimation of MAP decline or overestimation of CA rise. However, for this to have contributed to a directional bias between groups requires an undetected, greater decline in systemic vascular resistance with ALT-711. As noted, our study was adequately powered to detect modest changes in systemic vascular resistance, so a substantial yet undetected disparity was unlikely. Finally, although the HDI radial-pulse waveforms seem similar to those obtained by applanation tonometry, they have not been directly compared with intra-arterial recordings.

The 2:1 randomization to ALT-711 provided additional safety/tolerance data, and it also enhanced the statistical power for revealing within-subject changes in the larger group. However, it did not necessarily favor revealing between-group treatment effects, which was our major focus. Because most subjects were concomitantly treated with various antihypertension therapies, the subset without treatment was too small to test the impact of therapy per se on the ALT-711 response. The study was also not powered to test the effect of diabetes mellitus on the ALT-711 response. Furthermore, inclusion of diabetes as an additional categorical variable did not alter the significance of drug treatment on any of the affected parameters. Only one dose of ALT-711 was studied, and short- and long-term safety data and identification of the full range of side effects awaits further study. Finally, ALT-711 may have sustained effects that could ultimately influence optimal dosing for humans, and this too remains to be determined.

Clinical Implications and Future Directions
ALT-711 seems to target larger compliance arteries by interacting with the structural molecules in the vessel wall. Its ability to reduce age-associated vascular stiffening without lowering systemic resistance, even in subjects with no change or an increase in mean pressure, suggests it may offer a novel therapeutic option to reduce PP. Nearly half of individuals older than 60 years have systolic pressures >160 mm Hg and diastolic pressures <90 to 95 mm Hg. In such patients, increased arterial stiffness interacts with even modest changes in systemic resistance to elevate systolic pressure and PP. Current treatment often focuses on lowering vascular volume or reducing smooth muscle tone, which can reduce both systolic and diastolic pressures, resulting in less fall in PP and suboptimal therapeutic benefit. Nitrites can selectively affect systolic pressures, although hysteresis and other factors have limited their use. ACE inhibitors, calcium-channel blockers, and nonpharmacological interventions such as exercise also improve large vessel compliance; however, the independence of these effects from mean pressure is less certain. The present data show that ALT-711 can be effective, even in the presence of concomitant use of an ACE inhibitor/angiotensin II receptor blocker or calcium channel blocker. Thus, ALT-711 exerts additive effects by a presumably different mechanism.

Conclusion
In summary, ALT-711, an agent that reverses AGE crosslinking, improves C\textsubscript{a} and reduces arterial PP in older individuals with a stiffened vasculature. The likely ability of ALT-711 to target large vessel stiffness represents a novel hemodynamic profile and offers a promising new approach to reduce vascular stiffening and PP.

Appendix
Study Investigators
David Kass, Baltimore, Md, Principal Investigator; George Bakris, Chicago, Ill; Alan Bank, St Paul, Minn; Deanna Cheung, Long Beach, Calif; Stephen Glasser, Minneapolis, Minn; Edward Lakatta, Baltimore, Md; Joel Neutel, Orange, Calif; Leopoldo Rajt, Minneapolis, Minn; Elijah Saunders, Baltimore, Md; and Edward Shapiro, Baltimore, Md.

Acknowledgments
This study was supported by a National Institute on Aging Intramural Research Program and a grant from Alteon Inc. The authors acknowledge the assistance of John Egan and Jan Lessin in developing the study protocol, Margaret Douglas for data analysis, and Patricia Fitzgerald for clinical coordination.
References


Improved Arterial Compliance by a Novel Advanced Glycation End-Product Crosslink Breaker
David A. Kass, Edward P. Shapiro, Miho Kawaguchi, Anne R. Capriotti, Angelo Scuteri, Robert C. deGroof and Edward G. Lakatta

Circulation. 2001;104:1464-1470; originally published online September 4, 2001;
doi: 10.1161/hc3801.097806

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 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/104/13/1464

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/