One-Year Clinical Outcomes, Midterm Survival, and Predictors of Mortality After Carotid Stenting in Elderly Patients

Paul T.L. Chiam, MBBS, MRCP; Gary S. Roubin, MD, PhD; Georgia Panagopoulos, PhD; Sriram S. Iyer, MD; Richard M. Green, MD; Christina Brennan, MD; Jiri J. Vitek, MD, PhD

Background—It has been demonstrated recently that carotid stenting can be performed safely in patients ≥80 years of age. However, it is uncertain whether these patients will derive benefit because longevity after revascularization is an important consideration. This study was conducted to determine survival and predictors of mortality of selected elderly patients after stenting.

Methods and Results—One hundred forty-two consecutive elderly patients who were non–high risk for stenting underwent 153 procedures. Patients had either symptomatic stenosis ≥50% or asymptomatic stenosis ≥70%. Demographics and in-hospital outcomes were entered into a database; subsequent outcomes and mortality data were obtained retrospectively. Mean ± SD age was 83.3 ± 3.1 years. Symptomatic patients accounted for 28%. Overall survival at 3 years was 76% (85% at 2 years). At 1 year, 1 fatal stroke had occurred, with 97% of survivors (n = 114) free of neurological events (neurological status was undetermined in the remaining 3%). Predictors of mortality were remote (≥6 months) transient ischemic attack or cerebrovascular accident, smoking history, and creatinine clearance (hemoglobin level showed a strong trend toward achieving significance); for the asymptomatic subgroup, predictors of mortality were smoking history, previous carotid endarterectomy, hemoglobin level, and increasing age. In particular, symptom status and sex were not independent predictors of mortality.

Conclusions—This study demonstrates that in selected elderly patients, a high proportion (85%) survived 2 years and 75% survived 3 years after stenting. Carotid stenting may be considered a revascularization option in such patients. Better selection of patients using the predictors of mortality may help to reduce unwarranted procedures and to optimize survival likelihood. (Circulation. 2009;119:2343-2348.)

Key Words: angioplasty ■ carotid arteries ■ revascularization ■ stenosis ■ stents ■ stroke ■ survival

Carotid stenting (CS) is increasingly performed as a method of carotid revascularization. Previous randomized trials demonstrate that revascularization with carotid endarterectomy (CEA) reduces stroke risk in both symptomatic and asymptomatic patients.1–4 Stenting has been shown to be noninferior compared with CEA in high–surgical-risk patients.5 Stenting has been shown to be noninferior compared with CEA in high–surgical-risk patients.5 with clinical equipoise maintained at 3 years.6

Editorial see p 2302 Clinical Perspective on p 2348

Several studies have demonstrated that increasing age is an important predictor of complications associated with CS. The Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) lead-in phase showed that octogenarians had a markedly elevated 30-day periprocedural stroke or death rate of 12.1% versus 3.2% in nonoctogenarians, which was not influenced by symptom status, lesion severity, or use of distal embolic protection devices.7 A large German registry showed that the in-hospital event rate in octogenarians was 5.5% compared with 3.2% in younger patients (P = 0.03).8 Other single-center studies and postmarketing registries have also reported increased risk of adverse events in this group of patients.9–12

More recent reports suggest that CS can be performed in octogenarians with low complication rates between 2.1% and 3.4%.13–15 In 1 single-center registry, CS performed by experienced operators in carefully selected patients resulted in low periprocedural event rates.15 The outcomes were within the American Heart Association guidelines for stroke prevention through carotid revascularization for both symptomatic and asymptomatic patients.16,17

Low periprocedural event rates notwithstanding, it remains uncertain whether elderly patients, particularly those with asymptomatic disease, will benefit from CS. In addition to...
periprocedural risks, longevity after revascularization is an important consideration. Symptomatic patients derive benefit from carotid revascularization within 2 years, with those ≥75 years of age having the greatest risk reduction.\textsuperscript{1,18} In the Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST), a lifespan of 5 years was required to derive benefit in asymptomatic patients.\textsuperscript{2,4} With an aging population,\textsuperscript{19} it is likely that the proportion of elderly patients considered for revascularization will rise.\textsuperscript{20} Data from the US National Vital Statistics Report show that the average 80- and 90-year-olds have life expectancies of 9.1 and 5.0 years, respectively.\textsuperscript{21} Elderly patients undergoing CS, however, may not represent the “average” elderly patient. No data on survival after CS in elderly patients are available.

The aims of this study were to assess the survival of selected elderly (≥80 years of age) patients after CS and to determine whether certain clinical variables could predict mortality, thus enabling better selection of these patients for CS.

### Methods

#### Patient Population

From July 2003 through October 2007, 142 consecutive patients ≥80 years of age who underwent CS (153 procedures) were included. Patients were considered candidates for revascularization if they had symptomatic ≥50% diameter stenosis or asymptomatic stenosis ≥70%. Criteria for case selection have been published elsewhere.\textsuperscript{15,22} In brief, patients with any one of the following were excluded: reduced cerebral reserve, excessive vascular tortuosity, and heavy concentric lesion calcification. The definitions of reduced cerebral reserve, excessive vascular tortuosity, and heavy concentric lesion calcification and the CS protocol and procedural technique have been detailed previously.\textsuperscript{15}

#### Data Collection

All demographic and in-hospital outcome data were collected prospectively into a database. Subsequent outcome and mortality data were obtained from reviews of hospital records, outside records, telephone surveys, and the Social Security database. The majority (128 procedures) were part of carotid stent investigational device exemption studies for high or normal CEA risk or Food and Drug Administration–approved postmarket surveillance studies. The remainder (25 procedures) were performed outside of trials. All procedures were performed at least 6 months previously (range, 6 to 57 months).

#### Definitions

Major stroke was defined as new neurological deficit that persisted at 30 days and that changed the National Institutes of Health Stroke Scale by ≥4. Minor stroke was defined as new neurological deficit that either resolved completely within 30 days or increased the National Institutes of Health Stroke Scale by ≤3. Present and poststenotic carotid artery stenoses were determined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.\textsuperscript{1} Fatal stroke was defined as death resulting from either ischemic or hemorrhagic stroke.

#### Ethics Approval

The study was approved by our hospital’s institutional review board.

#### Statistical Analysis

Categorical variables were compared by use of $\chi^2$ or Fischer’s exact test. Continuous variables were reported as mean±SD. The Kaplan-Meier survival analysis was used to estimate the unadjusted survival rate. The 3-year survival rate is presented because the number of patients at 4 years was small. Cox proportional-hazards regression analysis was used to model the time to death data to identify possible predictors of mortality. The first step was selection of the variables using univariate analysis. $P≤0.1$ was used as a cutoff value for variable selection so that no potentially important predictors would be missed. The final fitted model was constructed using backward stepwise Cox regression. Statistical significance remained the conventionally defined $P≤0.05$ in the univariate and multivariate models.

Variables examined were age (as a continuous variable), sex, symptom status, presence of diabetes mellitus, hypertension or dyslipidemia, presence of coronary artery disease, previous percutaneous coronary intervention, previous coronary artery bypass graft surgery, smoking history, previous remote (≥6 months) neurological (stroke or transient ischemic attack) history, previous CEA, calculated creatinine clearance level, and hemoglobin level. For the 11 patients who had bilateral procedures, the index procedure was used to construct the Kaplan-Meier survival graph and to perform Cox regression analysis. Statistical analyses were performed with SPSS version 16.0.2 (SPSS, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

#### Results

One hundred forty-two patients ≥80 years of age underwent 153 CS procedures. Of the 142 patients, 39 (28%) had symptomatic stenoses, and 103 (72%) were asymptomatic. The mean age was 83.3±3.1 years. The clinical characteristics are shown in Table 1. Survival data were available for all patients, and the mean survival duration was 29.3±15.1 months. Neurological outcomes were complete at 6 months in 98.6%. At 1 year, 129 patients were available for analysis (at least 1 year of postprocedure follow-up), with neurological outcomes available in 93.8%.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Age, mean (range), y</th>
<th>Procedures (n=153)</th>
<th>Patients (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 60–84 y, n (%)</td>
<td>111 (72.5)</td>
<td>102 (71.8)</td>
</tr>
<tr>
<td>Age 85–99 y, n (%)</td>
<td>36 (23.5)</td>
<td>34 (24)</td>
</tr>
<tr>
<td>Symptomatic, n (%)</td>
<td>39 (25.5)</td>
<td>39 (27.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>96 (62.7)</td>
<td>87 (61.3)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>38 (24.8)</td>
<td>32 (22.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>134 (87.6)</td>
<td>123 (86.6)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>130 (85)</td>
<td>120 (84.5)</td>
</tr>
<tr>
<td>Current/ex-smoker, n (%)</td>
<td>77 (50.3)</td>
<td>72 (51.7)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>100 (65.4)</td>
<td>90 (63.4)</td>
</tr>
<tr>
<td>CAGB, n (%)</td>
<td>41 (26.8)</td>
<td>37 (26.1)</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>31 (20.3)</td>
<td>27 (19)</td>
</tr>
<tr>
<td>Remote history of TIA/CVA, n (%)</td>
<td>22 (14.4)</td>
<td>22 (15.5)</td>
</tr>
<tr>
<td>Prior ipsilateral CEA, n (%)</td>
<td>13 (8.5)</td>
<td>13 (9.1)</td>
</tr>
<tr>
<td>Any prior CEA, n (%)</td>
<td>...</td>
<td>18 (12.7)</td>
</tr>
<tr>
<td>Contralateral ICA occlusion, n (%)</td>
<td>9 (6)</td>
<td>9 (6.3)</td>
</tr>
<tr>
<td>Creatinine ≥1.4 mg/dL, n (%)</td>
<td>47 (30.7)</td>
<td>42 (29.6)</td>
</tr>
</tbody>
</table>

CAGB indicates coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; CVA, cerebrovascular accident; and ICA, internal carotid artery.
Table 2. Clinical Outcomes: 30-Day Event Rates

<table>
<thead>
<tr>
<th></th>
<th>All (n=153 Procedures), n (%)</th>
<th>Symptomatic (n=39), n (%)</th>
<th>Asymptomatic (n=114), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.7)</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>2 (1.3)</td>
<td>0</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Minor stroke or death</td>
<td>3 (2.0)</td>
<td>0</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Any stroke or death</td>
<td>5 (3.3)</td>
<td>2 (5.1)</td>
<td>3 (2.6)</td>
</tr>
</tbody>
</table>

Periprocedural Outcomes

Among the 153 procedures, 5 events (1 death, 2 major strokes, 2 minor strokes) occurred, resulting in an overall 30-day stroke or death rate of 3.3% (5.1% in the symptomatic group, 2.6% in asymptomatic patients). No patient suffered a myocardial infarction or intracranial hemorrhage. The 30-day major stroke or death rate was 2% (Table 2).15

Clinical Outcomes at 6 Months and 1 Year

At 6 months, 134 of 142 patients (94.4%) were alive, including the 4 patients who experienced periprocedural strokes. Eight deaths had occurred (5.6%), including the single periprocedural death. Among the 134 patients who were alive, 133 (99.2%) did not suffer any additional stroke; the neurological status of the remaining patient could not be determined. Four of the deaths (50%) were due to cardiac causes; 1 was caused by malignancy; 1 was a “nonstroke” death; and the cause could not be determined for 1 (Table 3).

At 1 year, the Kaplan-Meier estimate of survival was 90% (including the 4 patients who experienced periprocedural strokes). Among the 129 patients with at least 1 year of postprocedure follow-up, 15 deaths occurred, including the periprocedural death. Of the 114 surviving patients, 110 (96.5%) were free from any stroke; the neurological status of the remaining 4 could not be determined. Six of the deaths (40%) were due to cardiac causes; 1 resulted from stroke; 1 was caused by malignancy; 2 were nonstroke deaths; and the cause could not be determined for 4 (Table 3).

Survival Analyses

Throughout the study period, 31 patients died, 23 and 8 in the asymptomatic and symptomatic groups, respectively (P=1.0). The causes of death were available for 18. Seven deaths were due to cardiac causes; 5 were the result of malignancy; 4 were nonstroke deaths; and 2 were fatal strokes (including the periprocedural fatal stroke). Cause of death could not be determined in the remaining 13 patients.

For the entire cohort, survival at 36 months was estimated to be 76% (85% at 2 years) (the Figure). Thus, the average mortality rate in the overall cohort was 8.7% per year.

Predictors of Mortality

Using Cox regression analysis, we identified 3 significant clinical variables as independent predictors of mortality in these elderly patients after CS (Table 4). The variables were previous remote (≥6 months) stroke or transient ischemic attack (TIA; hazard ratio [HR], 2.99; P=0.004; 95% confidence interval [CI], 1.42 to 6.29), smoking status (current or ex-smoker; HR, 2.61; P=0.014; 95% CI, 1.21 to 5.59), and preprocedural creatinine clearance (per 1-mL/min increase; HR, 0.97; P=0.026; 95% CI, 0.95 to 0.99). The mean preprocedural creatinine clearance was 49±16 mL/min for men and 40±16 mL/min for women. Preprocedural hemoglobin level showed a strong trend toward significance (per 1-g/dL increase; HR, 0.75; P=0.053; 95% CI, 0.56 to 1.00).

The mean hemoglobin was 12.7±1.4 g/dL for men and 11.9±1.2 g/dL for women. Importantly, symptom status and sex were not independent predictors of mortality.

In a separate analysis of the symptomatic patients, previous remote stroke and TIA (P=0.441) and creatinine clearance (P=0.085) and were no longer significant. Smoking status (HR, 4.63; P=0.005; 95% CI, 1.59 to 13.40), hemoglobin (per 1-g/dL increase; HR, 0.72; P=0.043; 95% CI, 0.52 to 0.99), previous CEA (ipsilateral or contralateral) (HR, 3.69; P=0.005; 95% CI, 1.48 to 9.18), and age (per 1-year increase; HR, 1.19; P=0.007; 95% CI, 1.05 to 1.35; mean age of this subgroup, 83.2±2.9 years) were found to be independent predictors in this subgroup (Table 4). Separate Cox regression analysis was not performed for the asymptomatic group because of the small sample size.

Discussion

Previous studies have documented a significantly increased rate of adverse events during CS in octogenarians.7–10,23 Recent reports have suggested, however, that in selected patients ≥80 years of age, CS can be performed with periprocedural event rates within the American Heart Association guidelines.14,15

The question remains whether these elderly patients will benefit from carotid revascularization because of the possibility that survival may not be of sufficient duration, especially in asymptomatic patients. The NASCET trial initially excluded patients ≥80 years of age,1,18 and the ACST trial concluded that patients ≥75 years of age were unlikely to derive benefit because mortality was 50% within 5 years.4 Despite these findings, CS is increasingly performed in this group of patients as a result of an aging population without clear data on survival after CS.

This study shows a 3-year survival estimate of 76%. The average mortality rate of ≈8%/y is similar to the recently reported long-term results of the Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial6 and a study examining long-term outcomes of CEA in patients ≥75 years of age.24 One CEA study

*Neurological status was unknown in 1; cause of death was undetermined in 1.
†Fatal stroke. Neurological status was unknown in 4; cause of death was undetermined in 4.
showed, however, that elderly patients had an 81% survival at 4 years, similar to that of younger patients.\textsuperscript{20} This difference may be related to referral patterns for CEA (those deemed unfit were less likely to have been referred by their primary care physicians for CEA) and appropriate patient selection on the surgeons’ part.

This study shows that CS can be considered in most elderly patients because a high proportion of elderly patients survived 2 and 3 years (85% and 76%, respectively). However, greater caution should perhaps be exercised in asymptomatic elderly patients because previous studies demonstrate that a longer postprocedure survival duration is required to achieve benefit.\textsuperscript{2,4} This result differs from the ACST trial, which concluded that no benefit was achieved in those \textasciitilde 75 years of age because of the 50% mortality within 5 years.\textsuperscript{4} Combined with the possibility that the timing of benefit for both symptomatic and asymptomatic patients \textasciitilde 80 years of age may be shorter because it is known that stroke rates increase with age\textsuperscript{25,26} and the fact that the ACAS trial showed significant reduction in ipsilateral stroke and perioperative stroke or death even at 3 years (although of lesser magnitude),\textsuperscript{2} the benefit-to-risk ratio may now favor carotid revascularization. Extreme caution is imperative, however, if CS is to be considered in the asymptomatic elderly subgroup.

It must be emphasized that these statements hold true only if the periprocedural event rates are within American Heart Association guidelines. Any benefit may be completely eliminated if the periprocedural event rates are higher. Thus, centers or operators who choose to perform CS in this population must first demonstrate an ability to meet or exceed the guideline standards. Only when that is achieved can the focus shift to selecting such patients to optimize likelihood of survival to accrue the greatest benefit.

Cox regression analysis identified 3 clinical variables that were predictors of mortality for the entire group. Previous remote stroke or TIA and smoking status (current or ex-smoker) were the strongest predictors, with HRs of 2.99 and 2.6, respectively. Patients with remote (\textasciitilde 6 months) stroke or TIA have more advanced vascular disease, and smoking is a known cause of increased mortality even in the general population. That remote stroke or TIA is a predictor of mortality is a new and interesting finding that requires further study because these patients may also be the ones who may benefit from carotid revascularization. The only laboratory parameter found to predict mortality was the periprocedural creatinine clearance level (each 1-ml/min decrease increasing the risk of mortality by 3%), with a strong trend toward significance for periprocedural hemoglobin level (each 1-g/dL decrease increasing the risk of mortality by 25%). Creatinine
clearance closely reflects renal function, which is well known to affect mortality.

When the asymptomatic patients were considered separately, 4 clinical predictors were found. Smoking status remained significant, and hemoglobin level achieved significance. Most likely, hemoglobin level is a sensitive marker of underlying chronic disease, including occult malignancy and chronic heart disease, which is likely to contribute to increased mortality in these patients. In addition, previous CEA (ipsilateral or bilateral) and age were found to be significant predictors in this subgroup, with previous CEA increasing mortality risk by 3.6-fold and each increasing year of age increasing mortality risk by 19%. Previous CEA may be a marker for both advanced vascular disease and previous neurological symptoms.

Considering both analyses, the single most consistent variable was smoking. Future decisions on whether to perform CS in these elderly patients should consider not only case selection to optimize periprocedural outcome but also patient selection using these variables to maximize likelihood of survival.

Although not the primary aim of this study, the 6-month and 1-year data provide some information on short-term neurological outcomes. Ninety-five percent of patients were alive at 6 months, with 99% free of any intervening neurological events (neurological status was unavailable in the remaining 1 patient). At 1 year, freedom from stroke was 97% in those who were alive (neurological status was unavailable in the remaining 4 patients); 1 fatal stroke had occurred at 1 year, along with 4 undetermined causes of death. These data suggest that after the periprocedural period, these elderly patients experience high rates of freedom from stroke. These findings are concordant with a previous large registry that demonstrated 99% freedom from all fatal and nonfatal ipsilateral stroke at 3 years in those who survived the initial periprocedural period.

Just as the major CEA trials carefully selected low-surgical-risk patients treated by experienced surgeons, this same should now be applied to CS. Patients selected should be at low stent risk; elderly patients should also be at low risk of short-term mortality.

Because this study is a retrospective, single-center registry of highly selected elderly patients undergoing CS, the results may not be generalizable to elderly patients who were not initially selected with the clinical and anatomic criteria used to exclude those at high stent risk. Another limitation of this study is that 72% of patients were asymptomatic; the need for revascularization in asymptomatic elderly patients is still being debated. However, this study was not performed to assess the benefit of CS in this group, and the proportion of asymptomatic patients is similar to those in the SAPPHIRE and the Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH) trials and to current practice patterns of CEA.

The relatively small number of patients limited the accuracy and ability to analyze subgroups. This study also could not provide midterm clinical outcome data because clinical follow-up beyond 1 year was limited. Future studies with larger numbers of patients ≥80 years of age with longer periods of follow-up are required to determine survival after CS more conclusively, to validate the predictors of mortality found in this study, and to further identify variables that will predict mortality. In addition, mortality data were obtained through hospital records, outside records, telephone surveys, and the Social Security database. These data are accurate but do not provide cause of death in many patients.

This study cannot advocate the long-term advantage of CS in these elderly patients because no comparative group exists with medical therapy or CEA. It only demonstrates that with appropriate selection, the majority of elderly patients experience sufficient survival duration to derive potential benefit from the procedure. In particular, these data cannot address the long-term outcomes or prevention of stroke in asymptomatic carotid stenosis. This will have to await data of ongoing randomized trials such as CREST.

Conclusions

This study demonstrates that in this population of elderly patients selected for CS, a high proportion (85%) survived for 2 years and >75% survived for 3 years after the procedure. Thus, CS may be considered a revascularization option in most elderly patients. Better selection of patients using the predictors of mortality identified may help to reduce unwarranted procedures and to optimize the likelihood of survival. Prospective randomized trials comparing stenting with endarterectomy and medical therapy are required to validate the role of CS in the elderly.

Acknowledgments

We would like to thank Isaac Opoku Asare, MD, and Arielle Black for their assistance with data collection and Lay-Wai Khin, MBBS, MSc, for her assistance with the statistical analyses.

Disclosures

Dr Roubin is a consultant to Abbott Vascular and receives royalties from Cook Inc. Dr Iyer is a speaker for Abbott Vascular and Boston Scientific, receives royalties from Abbott Vascular and Boston Scientific, and has ownership interest in Boston Scientific. Dr Green is a consultant to Abbott Vascular and Cohera, receives honoraria from Abbott Vascular and Gore, and has ownership interest in Vascular Innovations. Dr Brennan is a consultant to Abbott Vascular. The other authors report no conflicts.

References

Carotid stenting (CS) is increasingly performed as a method of carotid revascularization. CS has been shown to be noninferior compared with carotid endarterectomy in high–surgical-risk patients. The Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) lead-in phase showed that octogenarians had a markedly elevated 30-day noninferior compared with carotid endarterectomy in high–surgical-risk patients. The Carotid Revascularization Endarterectomy in elderly patients: importance of case selection. Catheter Cardiovasc Interv. 2008;72:318–324.


One-Year Clinical Outcomes, Midterm Survival, and Predictors of Mortality After Carotid Stenting in Elderly Patients
Paul T.L. Chiam, Gary S. Roubin, Georgia Panagopoulos, Sriram S. Iyer, Richard M. Green, Christina Brennan and Jiri J. Vitek

*Circulation.* 2009;119:2343-2348; originally published online April 20, 2009;
doi: 10.1161/CIRCULATIONAHA.108.805465
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/119/17/2343

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/