Hypertension is a highly prevalent disorder that affects the vast majority of adults in the United States during their lifetimes. It is an established risk factor for myocardial infarction, stroke, and peripheral vascular disease, and it constitutes a major source of cardiovascular morbidity and mortality. Nevertheless, our understanding of the mechanisms that contribute to the most common form of hypertension, essential hypertension, is relatively limited, as is our ability to identify individuals at highest risk of developing hypertension in the short and medium term who could be targeted for nonpharmacological interventions.

Experimental and physiological studies support a fundamental role for the kidneys in the pathogenesis of essential hypertension. In animal models of hypertension, one of the earliest findings is a defect in renal sodium excretion at normal perfusion pressures (abnormal pressure natriuresis). Elevated glomerular pressures are required to excrete a sodium load, which, over time, leads to glomerular scarring and endothelial dysfunction (hyperfiltration injury). Glomerular hyperfiltration initiates a cycle of progressive increases in intraglomerular pressure and repetitive renal injury.4,5

In contrast to the wealth of experimental evidence, clinical data investigating whether glomerular hyperfiltration and endothelial dysfunction contribute to hypertension in humans are limited. Hyperfiltration injury is observed in diabetic nephropathy; an early finding in these patients is microalbuminuria, usually defined as a urinary albumin excretion 30 to 300 mg/d. The "classic" microalbuminuria (as defined above) is uncommon in nondiabetic individuals, but lesser degrees of urinary albumin excretion (0 to 30 mg/d) frequently may be found.7

Prior cross-sectional studies indicate that microalbuminuria may be a feature of hypertension and a marker of
target-organ damage.6–10 We hypothesized that elevated urinary albumin excretion may predict the development of hypertension, a hypothesis that has not been tested prospectively in humans. Accordingly, we examined the relations of urinary albumin excretion with the incidence of hypertension and blood pressure progression in a large community-based sample of nondiabetic individuals.

Methods

Study Sample

In 1971, 5124 offspring (and their spouses) of the original Framingham Heart Study participants were enrolled in a longitudinal cohort study known as the Framingham Offspring Study.11 Participants have attended examinations in the Framingham Heart Study clinic approximately every 4 years. Individuals attending the sixth examination cycle (1995 to 1998, hereafter referred to as the baseline examination) were eligible for this investigation. The seventh examination (1998–2001) will be referred to as the follow-up examination.

Of 3532 attendees at the baseline examination, 2033 were excluded from the present investigation for the following reasons: prevalent hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications; n = 1468 at the baseline examination),12 diabetes mellitus (fasting glucose ≥126 mg/dL or use of insulin or hypoglycemic medications; n = 111),13 history of heart failure or myocardial infarction (n = 42), serum creatinine >2.0 mg/dL (n = 1), missing urinary albumin or creatinine data (n = 278), urine albumin-creatinine ratio (UACR) >300 mg/g (n = 4), missing covariates (n = 8), nonattendance or missing blood pressure information at the follow-up examination (n = 113), weight loss >100 lb between the baseline and follow-up examination (n = 1), and incident heart failure or myocardial infarction related to baseline and follow-up examination (n = 7). Participants with diabetes were excluded because UACR is already routinely measured for the early detection of diabetic nephropathy. We excluded those with myocardial infarction or heart failure, because these disorders may lead to changes in urinary albumin excretion or blood pressure that are independent of the mechanisms we intended to study. After the above exclusions, 1499 attendees (58% women) remained eligible.

Clinical Evaluation and Blood Pressure Measurement

At all examinations, participants underwent a routine medical history, anthropometry (including measurement of height and weight), a physical examination, and laboratory assessment of cardiovascular disease risk factors. Participants were classified as current cigarette smokers if they smoked cigarettes regularly during the previous year.

Blood pressures were measured by physician investigators using a mercury column sphygmomanometer and a cuff of appropriate size. A standardized protocol was followed, in which systolic and diastolic blood pressures were measured in the left arm after participants had been seated for at least 5 minutes. Quality control measures related to blood pressure measurement at the Framingham Heart Study include yearly recertification of all physician examiners and quarterly assessment of adjusted-mean blood pressure readings and digit preference across examiners. The average of 2 systolic and diastolic blood pressure measurements was used for the analyses.

Urinary Albumin Excretion

A single void morning urine sample at the baseline examination was used to measure the UACR (in mg/g). Urinary albumin concentration was determined by immunoturbidimetry (Tina-quant Albumin assay; Roche Diagnostics), and urinary creatinine concentration was measured by a modified Jaffe method. Coefficients of variation were 7.2% and 2.3%, respectively, for the urine albumin and urine creatinine assays.14 UACR measured in a spot urine sample is highly correlated with 24-hour urine albumin excretion.15,16

Blood Pressure Outcomes on Follow-Up

We examined the relations of UACR to 2 blood pressure outcomes on follow-up: (1) hypertension, defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications12,17,18; (2) blood pressure progression, defined as an increase in blood pressure category on follow-up. For this purpose, participants without hypertension were assigned to 1 of 3 blood pressure categories at baseline: systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg; systolic blood pressure 120 to 129 mm Hg or diastolic blood pressure 80 to 84 mm Hg; or systolic blood pressure 130 to 139 mm Hg or diastolic blood pressure 85 to 89 mm Hg.17,18

Statistical Analyses

We used multivariable logistic regression analysis to examine the association of UACR and the risks of incident hypertension and blood pressure progression.19 We analyzed UACR as both a continuous and a categorical variable in separate analyses. Continuous UACR was log-transformed to normalize its skewed distribution. In the categorical analyses, we used gender-specific quartiles of UACR, to account for gender-related differences in urine creatinine excretion.20 Logistic regression models were adjusted for the following covariates, on the basis of their use in prior studies:21 age, gender, baseline systolic and diastolic blood pressure, baseline blood pressure category, current smoking, body mass index, serum creatinine (all defined at baseline), and percent weight change on follow-up. Separate analyses were performed for each of the blood pressure outcomes.

Because albuminuria may reflect antecedent elevations in blood pressure that produce subclinical target-organ damage, we repeated the above analyses with additional adjustment for antecedent blood pressure variables. These variables were the average of all available systolic and diastolic blood pressure readings and any use of cardioactive medications (including vasodilators, diuretics, calcium channel blockers, or β-blockers) during the 5 Framingham examinations that preceded the baseline examination (covering ≥20 years). All participants attended at least 1 prior examination, and a majority (n = 1406, 94%) attended at least 4 examinations.

In secondary analyses, we further adjusted for impaired fasting glucose, defined as a fasting glucose ≥110 mg/dL but <126 mg/dL. This adjustment was performed to ensure that our findings were not confounded by a potential association between albuminuria and preclinical diabetes. We also examined multivariable-adjusted models that included interactions terms for UACR with age, gender, or body mass index to examine whether the association between UACR and incident hypertension and blood pressure progression varied according to these factors. Additionally, given the importance of "prehypertension," as defined in the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), we repeated the analyses of hypertension incidence restricted to participants with a systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg.12

An additional analysis was performed with the following covariates to compare the effect sizes of urinary albumin excretion and clinical risk factors: age >65 years (versus ≤65 years), female gender, baseline blood pressure category (optimal as referent), baseline body mass index category, elevated weight gain (percent weight gain above versus below gender-specific median), elevated serum creatinine (above versus below gender-specific median), current cigarette smoking, and UACR quartile.

All analyses were performed with SAS software, version 6.12 (SAS Institute). Two-sided probability values <0.05 were considered statistically significant.

Results

Baseline characteristics of the study sample are shown in Table 1. Quartile ranges for UACR were as follows: in men, 0.02 to 1.66, 1.66 to 3.84, 3.84 to 6.65, and 6.67 to 190.75 mg/g; in women, 0.02 to 3.34, 3.35 to 7.49, 7.49 to 15.23, and
15.24 to 297.20 mg/g. Only 2.6% of men and 8.8% of women had UACR values >30 mg/g.

**Risk of Incident Hypertension**

The follow-up examination occurred a mean of 2.9 years after the baseline examination. Over this period, 230 participants (15%) developed hypertension. Participants in the second to fourth quartiles of UACR were more likely to develop hypertension than those in the lowest quartile of UACR (Table 2). Results of multivariable logistic regression analyses that examined the risk of incident hypertension are shown in Table 3. After multivariable adjustment, a 1-SD increment in log UACR was associated with an adjusted OR for hypertension of 1.20 (95% CI 1.01 to 1.44, \(P=0.04\)). The odds of developing hypertension were higher in the second through fourth quartiles of UACR compared with the first quartile (Table 3). Participants with UACR values in the highest quartile had a 2-fold risk of hypertension compared with participants in the lowest quartile (adjusted OR 1.93, 95% CI 1.21 to 3.09, \(P=0.006\)).

**Blood Pressure Progression**

During the follow-up period, 499 participants (33%) progressed by at least 1 blood pressure category. The proportion of participants with blood pressure progression increased across quartiles of UACR (Table 2). After multivariable adjustment, a 1-SD increment in log UACR was associated with a modest increase in the odds of blood pressure progression that did not attain statistical significance (adjusted OR 1.09, 95% CI 0.96 to 1.23); however, the association between UACR and blood pressure was statistically significant in the categorical analyses, with an adjusted OR of 1.14 per quartile increase in UACR (95% CI 1.03 to 1.26, \(P=0.01\); Table 3). Participants in the highest quartile of UACR had a 30% increased risk of blood pressure progression compared with participants in the lowest quartile (adjusted OR 1.45, 95% CI 1.04 to 2.00, \(P=0.03\)).
TABLE 3. Multivariable-Adjusted ORs for Blood Pressure Outcomes

<table>
<thead>
<tr>
<th>UACR Quartile</th>
<th>Incident Hypertension</th>
<th>Blood Pressure Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Models adjusting for baseline blood pressure variables*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.71 (1.06–2.75)</td>
<td>1.08 (0.78–1.50)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.33 (0.82–2.16)</td>
<td>1.32 (0.95–1.82)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.93 (1.21–3.09)</td>
<td>1.45 (1.04–2.00)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>II. Models adjusting for baseline and antecedent blood pressure variables†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.90 (1.17–3.11)</td>
<td>1.16 (0.83–1.63)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.37 (0.84–2.24)</td>
<td>1.33 (0.95–1.85)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.91 (1.18–3.10)</td>
<td>1.45 (1.04–2.03)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.04</td>
<td>0.02</td>
</tr>
</tbody>
</table>

UACR quartiles are gender specific.

*Models are adjusted for age, gender, baseline systolic and diastolic blood pressure, baseline blood pressure category, baseline serum creatinine, cigarette smoking, baseline body mass index, and percent weight change from baseline to follow-up.

†Models are adjusted for above covariates in addition to average systolic blood pressure at prior examinations, average diastolic blood pressure at prior examinations, and use of cardiovascular medications at prior examinations.

Adjustment for Antecedent Blood Pressure

In models that adjusted for antecedent blood pressure variables in addition to current blood pressure variables, UACR remained significantly associated with blood pressure outcomes (Table 3). Individuals in the highest quartile of UACR had adjusted ORs of 1.91 (95% CI 1.18 to 3.10, P=0.008) for hypertension and 1.45 (95% CI 1.04 to 2.03, P=0.03) for blood pressure progression.

Secondary Analyses

There was no statistically significant effect modification of the association between UACR and hypertension in analyses that included interaction terms for age group (above versus below 55 years), gender, or body mass index (above versus below 30 kg/m²); the probability value for all interaction terms exceeded 0.25. The association between UACR and blood pressure outcomes persisted on adjustment for the presence or absence of impaired fasting glucose. In addition, results were unchanged in multivariable models that adjusted for systolic and diastolic blood pressure rather than for both blood pressure values and blood pressure category.

We estimated an additional multivariable model to compare the effect sizes of elevated UACR and clinical risk factors for hypertension. The strongest predictor of incident hypertension was baseline blood pressure category (adjusted OR 3.22 [95% CI 2.03 to 5.10] for “normal” and 13.86 [95% CI 9.01 to 21.31] for “high normal,” as defined by JNC 6). Elevated urinary albumin excretion (UACR in the highest quartile) was associated with the next highest OR (1.98 [95% CI 1.25 to 3.15]) and had an effect size comparable to or greater than that of obesity (1.66 [95% CI 1.08 to 2.57]), weight gain (1.96 [95% CI 1.42 to 2.70] for values above median), and advanced age (1.68 [95% CI 1.14 to 2.48] for age >65 years). None of the other variables were significantly associated with an elevated risk of hypertension.

Among 769 participants with prehypertension, 198 (26%) developed hypertension during follow-up. Each quartile increment in UACR was associated with an adjusted OR for hypertension of 1.22 (95% CI 1.04 to 1.43, P=0.02). Those in the highest quartile of UACR had an adjusted odds for hypertension of 2.05 (95% CI 1.23 to 3.42, P=0.006).

Discussion

The present study suggests that elevated urinary albumin excretion is associated with the development of hypertension in nondiabetic individuals who are not currently hypertensive. The increased risk of hypertension was evident at UACR values well below the conventional threshold for microalbuminuria. UACR values in the highest quartile conferred a doubling of hypertension risk, even after accounting for clinical risk factors, including baseline blood pressure, body mass index, and serum creatinine. These findings were further corroborated by an association of UACR with blood pressure progression.

Possible Mechanisms

The present data lend support to the hypothesis that glomerular endothelial dysfunction, as indicated by microalbuminuria, is a potentially important precursor of essential hypertension. Several lines of evidence suggest that renal dysfunction itself may be an underlying abnormality that leads to hypertension. Experimental studies indicate that the hypertensive phenotype can be transferred from hypertensive mice to normotensive mice by cross-transplantation of kidneys.3 Brenner and colleagues4 have proposed that a congenital reduction in the number of nephrons plays an etiologic role in hypertension, via elevation of glomerular filtration rates in the residual nephrons followed by a deleterious cycle of elevated intraglomerular pressures and glomerular injury. A recent autopsy study suggests that young, hypertensive individuals may in fact have fewer nephrons than normoten-

sive individuals.22 Lastly, it has been observed that normoten-

tive children of hypertensive parents have increased urina-

ry albumin excretion, which may further support the premise that microalbuminuria is an early finding in individuals with a predisposition to hypertension.23

Although the aforementioned studies underscore an important role for the kidneys, the etiology of essential hypertension is almost certainly multifactorial. Accordingly, microalbuminuria may reflect additional processes that may contribute to both renal dysfunction and the pathogenesis of hypertension. In particular, microalbuminuria has been viewed as a marker of vascular dysfunction in both the kidneys and systemic vasculature.24 Studies in both diabetic25,26 and nondiabetic27,28 individuals indicate that elevated urinary albumin excretion is associated with abnormalities in tests of endothelial function. Whether such abnormalities may contribute to hypertension is unknown, although hypertension...
is one component of the metabolic or insulin resistance syndrome in which endothelial dysfunction is thought to play a prominent role.29,30

An alternative explanation for the present findings deserves mention. Elevated urinary albumin excretion may reflect prior exposure of glomeruli and kidneys to elevated blood pressure. Prior cross-sectional studies have shown that microalbuminuria is more common in individuals with elevations in blood pressure within the normal range.31 Thus, the amount of urinary albumin excretion may predict future hypertension because it is an index of antecedent blood pressure rather than a cause of blood pressure progression. Antecedent blood pressure may provide a more stable estimate of one’s true blood pressure than a single measurement and may be less prone to misclassification.32 Additionally, the mate of one’s true blood pressure than a single measurement and may be less prone to misclassification.32

The prevention of hypertension is a major focus of the most recent JNC report, which emphasizes that individuals with a systolic blood pressure ≥120 mm Hg or diastolic blood pressure ≥80 mm Hg are at risk of progressing to overt hypertension.12 Nonetheless, rates of progression within any blood pressure subgroup are characterized by considerable interindividual variability.21 Given that the prehypertension category encompasses a sizable range of blood pressures, it would be useful for clinicians to have biochemical tests that could aid in the identification of individuals most likely to develop hypertension within the next several years, thus allowing for more targeted nonpharmacological interventions and follow-up.

The present data suggest that UACR, which is already widely measured in patients with diabetes, is a candidate for such a biomarker. Given the rates of progression shown in Table 2, we estimate that values of UACR in the upper quartile would have a sensitivity of 31% and specificity of 76% for detecting the development of hypertension over the next 3 years. Although this sensitivity is modest, it has been argued that high specificity is the important feature of tests being considered for screening in low-risk populations.33 The positive predictive value of UACR using the top quartile cutoff is 19% among all individuals (negative predictive value 86%) and 44% among those with high-normal blood pressure (JNC 6). These values compare favorably with those of other biomarkers such as C-reactive protein assessed for the prediction of cardiovascular events in healthy populations.34

Nonetheless, further studies are required to assess the performance characteristics of UACR testing in a prospective manner. Additionally, data are needed on the cost-effectiveness of measuring UACR in nondiabetic individuals. Boulware and colleagues35 found that proteinuria screening was not cost-effective in low-risk populations, although the outcome they focused on was chronic kidney disease. Estimation of the costs and benefits of screening may differ when viewed from the perspective of a more common condition such as hypertension.

Other biomarkers have been associated with the development of hypertension.36–38 A report from the Women’s Health Study cohort indicates that elevated C-reactive protein levels may be associated with the development of hypertension (adjusted relative risk 1.52, 95% CI 1.36 to 1.69 for the highest versus the lowest quintile).36 Prior data from the Framingham Study suggest that elevated plasma aldosterone levels may also predict incident hypertension (adjusted relative risk 1.61, 95% CI 1.05 to 2.46 for the highest versus the lowest quartile).38 Although the relative risk for hypertension associated with elevated UACR appears higher than these previously reported relative risks, comparison of multiple biomarkers was beyond the scope of the present investigation. Future studies are warranted to evaluate the joint and comparative value of biomarkers for predicting the risk of developing hypertension.

The present data also confirm that very low degrees of urinary albumin excretion, below the conventional threshold for microalbuminuria (UACR of 30 mg/g), may be clinically important. UACR values as low as 1.7 to 3.8 mg/g for men and 3.4 to 7.5 mg/g for women (corresponding to the second quartile) were associated with a 71% increase in the risk for developing hypertension compared with lower values. Low-grade urinary albumin excretion has also been associated with the risk for cardiovascular events in both diabetic and nondiabetic individuals,7,39 which lends support to the notion that the conventional threshold for microalbuminuria may be higher than the cutpoint at which substantial risk for adverse outcomes begins to be detectable.20 Although the risk of blood pressure progression increased monotonically across quartiles of UACR, the risk of incident hypertension appeared to increase between the first 2 quartiles and plateau thereafter. We did not conduct post hoc analyses to test whether thresholds of UACR differed among end points.

Strengths and Limitations

Strengths of this investigation include the large, community-based sample of individuals without hypertension or diabetes, standardized ascertainment of blood pressure over several decades, and the ability to adjust for multiple conventional risk factors associated with hypertension. Several limitations of the present study should be acknowledged. Although we did not observe any effect modification by age, gender, or body mass index, we had limited statistical power to detect moderate degrees of effect modification. Similarly, we had limited statistical power to determine whether the risk of hypertension rose in a linear fashion with UACR (as models with log UACR might suggest) or observed a threshold (as the quartile-based analyses suggest). The risk of hypertension may also be affected by one’s parental history; we did not adjust for this risk factor because parental history data were not available in approximately half of the present study sample.
Urinary albumin was assessed on a single morning urine specimen rather than multiple specimens or a timed collection. Although urinary albumin levels may exhibit intra-individual variability, national practice guidelines recommend the use of spot specimens for UACR because this test is easily done in the office and the results correlate well with those of 24-hour collections. We submit that any measurement error would bias the present study toward an underestimation of the risk for hypertension associated with albuminuria. Additional studies would be needed to address whether multiple determinations of urinary albumin provide better discrimination of hypertension risk.

Similarly, blood pressure was measured only at the Framingham Study clinic examination. There is evidence that ambulatory blood pressures may correlate more strongly than conventional blood pressures with cardiovascular disease risk. The pattern of diurnal variation in blood pressure may affect urinary albumin excretion. A small proportion of individuals (~4%) reported use of cardiac medications before but not at the baseline examination. In keeping with prior reports, we did not attempt to exclude such individuals from the analyses, because ascertainment of whether a medication was being taken for hypertension, peripheral edema, or other indications was not uniform at earlier examinations. Furthermore, physicians are most likely to base clinical decisions using contemporary information on a patient’s medication use and blood pressure.

Although the follow-up period was relatively short, this time frame may be of greater clinical relevance than longer follow-up periods. We have previously shown that individuals in this age group have a high rate of progression to hypertension over the short term. The incidence of hypertension reported in the present study is also consistent with that seen in other cohorts. Although misclassification of hypertension over the short term, the incidence of hypertension reported in the present study is also consistent with that seen in other cohorts. We did not attempt to exclude such individuals from the analyses, because ascertainment of whether a medication was being taken for hypertension, peripheral edema, or other indications was not uniform at earlier examinations. Furthermore, physicians are most likely to base clinical decisions using contemporary information on a patient’s medication use and blood pressure.

Although the follow-up period was relatively short, this time frame may be of greater clinical relevance than longer follow-up periods. We have previously shown that individuals in this age group have a high rate of progression to hypertension over the short term.

Although the follow-up period was relatively short, this time frame may be of greater clinical relevance than longer follow-up periods. We have previously shown that individuals in this age group have a high rate of progression to hypertension over the short term.

Although the follow-up period was relatively short, this time frame may be of greater clinical relevance than longer follow-up periods. We have previously shown that individuals in this age group have a high rate of progression to hypertension over the short term.

Although the follow-up period was relatively short, this time frame may be of greater clinical relevance than longer follow-up periods. We have previously shown that individuals in this age group have a high rate of progression to hypertension over the short term.

Although the follow-up period was relatively short, this time frame may be of greater clinical relevance than longer follow-up periods. We have previously shown that individuals in this age group have a high rate of progression to hypertension over the short term.

Although the follow-up period was relatively short, this time frame may be of greater clinical relevance than longer follow-up periods. We have previously shown that individuals in this age group have a high rate of progression to hypertension over the short term.


Boyko EJ. Ruling out or ruling in disease with the most sensitive or specific diagnostic test: short cut or wrong turn? *Med Decis Making.* 1994;14:175–179.


Low-Grade Albuminuria and the Risks of Hypertension and Blood Pressure Progression
Thomas J. Wang, Jane C. Evans, James B. Meigs, Nader Rifai, Caroline S. Fox, Ralph B. D'Agostino, Daniel Levy and Ramachandran S. Vasan

_Circulation._ 2005;111:1370-1376; originally published online February 28, 2005; doi: 10.1161/01.CIR.0000158434.69180.2D

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 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/111/11/1370

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/