Relative Value of Inflammatory, Hemostatic, and Rheological Factors for Incident Myocardial Infarction and Stroke

The Edinburgh Artery Study

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Background—The aim of our present study was to compare the association of a wide range of 17 biomarkers of inflammation, hemostasis, and blood rheology with incident heart disease and stroke after accounting for an indicator of subclinical atherosclerotic disease and traditional risk factors and also to determine their incremental predictive ability.

Methods and Results—We used data from the Edinburgh Artery Study, a population cohort study started in 1987 that comprised 1592 men and women aged 55 to 74 years. Subjects were followed for a mean of 17 years, and 416 of them suffered at least 1 cardiovascular event. In analyses adjusted for cardiovascular risk factors and history of cardiovascular disease (CVD): C-reactive protein, interleukin-6, fibrinogen, fibrin D-dimer, tissue plasminogen activator (t-PA), leukocyte elastase, and lipoprotein(a) (all P<0.01), as well as von Willebrand factor and plasma viscosity (both P<0.05), had significant hazard ratios for incident CVD. Further adjustment for a measure of subclinical atherosclerosis (ankle brachial index) had little impact on these associations. The hazard ratios (95% CI) for incident CVD between top and bottom tertiles in the latter analysis were 1.78 (1.30 to 2.45) for C-reactive protein, 1.85 (1.33 to 2.58) for interleukin-6, and 1.76 (1.35 to 2.31) for fibrinogen. Single biomarkers provided little additional discrimination of incident CVD to that obtained from cardiovascular risk factors and the ankle brachial index. An incremental score of multiple markers [interleukin-6, t-PA, intercellular adhesion molecule 1, and lipoprotein(a)] provided some added discrimination.

Conclusions—Several “novel” risk factors predicted CVD after adjustments for conventional risk factors and also for a measure of asymptomatic disease. However, their incremental predictive ability was modest and their clinical utility remains uncertain. (Circulation. 2007;115:2119-2127.)

Key Words: coagulation ▪ epidemiology ▪ fibrinolysis ▪ follow-up studies ▪ inflammation ▪ myocardial infarction ▪ stroke

A s our understanding of the pathophysiology of atherosclerotic disease has evolved, a series of circulating biomarkers that reflect inflammation, coagulation, impaired fibrinolysis, and increased blood viscosity have been proposed as potential novel risk factors for the development of cardiovascular disease (CVD).1 Some of these biochemical markers have shown consistent associations with future coronary heart disease events in large observational studies and meta-analyses,2–3 whereas information on stroke events is limited.9,10 However, the causality of these associations with CVD events is open to doubt given their strong correlations with traditional cardiovascular risk factors and measures of atherosclerotic disease, and the possibility of “reverse causality.”11

In the Edinburgh Artery Study, a prospective cohort study of the general population, we aimed to directly compare the associations with incident major CVD of a wide range of circulating markers. We included in our analysis well-studied
inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), as well as the less studied adhesion molecules that facilitate the firm attachment of leukocytes into the arterial wall and might contribute to atherosclerotic progression. In addition, we have also analyzed, for the first time, plasma levels of leukocyte elastase, a marker of leukocyte activation, in relation to incident CVD. Finally, among the inflammatory markers we included lipoprotein(a) [Lp(a)], which was recently described as an acute-phase reactant.

A number of hemostatic variables that were also included in the analyses ranged from the well-studied fibrinogen, fibrin D-dimer, tissue plasminogen activator (t-PA), and von Willebrand factor (vWF), to less-studied markers of coagulation, namely factor VII, prothrombin fragment 1+2, and urinary fibrinopeptide A. Finally, to test the association of blood rheology with future CVD, we included in our analysis blood viscosity, plasma viscosity, and hematocrit.

For all markers, we investigated their associations with future myocardial infarction (MI) and stroke separately to examine whether they had the same relationship across both disease manifestations. Importantly, we sought to determine which biomarkers added to the prediction of CVD after accounting for conventional risk factors and for asymptomatic atherosclerosis as measured by the ankle brachial index (ABI) at baseline. Finally, the incremental benefit of testing for multiple biomarkers was also examined.

Methods

Study Population

The Edinburgh Artery Study began in 1987 as a cross-sectional survey of 809 men and 783 women aged 55 to 74 years. This population, which was almost exclusively of white origin, was selected at random, in 5-year age bands, from 11 general practices that served a range of socioeconomic and geographic areas throughout the city. Details of the study recruitment and examination process have been described.

Clinical Examination

Subjects were invited for a comprehensive clinical examination at baseline as previously described. Clinical measurements were conducted by trained research staff during each examination. Systolic and diastolic (phase V) blood pressures were recorded in the right arm only, after 10 minutes of rest in the supine position. Ankle systolic pressures were measured first in the right leg and then in the left leg at the posterior tibial artery, with a Sonicaid Doppler ultrasound probe and a random zero sphygmomanometer. The ABI was calculated by division of the ankle systolic pressure by the brachial systolic pressure. The lower of the 2 leg indices was used in the analysis as indicative of worse disease. In the current analyses, 3 subjects at baseline had values of ABI >1.50 and were excluded because of probable arterial rigidity.

Measurement of Biochemical Variables

At baseline, a fasting 20-mL sample of venous blood and a urine sample were taken for estimation of biochemical, inflammatory, and hemostatic factors as previously described. Tests for serum total cholesterol, high-density lipoprotein cholesterol, and blood glucose were performed on a Cobas Bio analyzer (Roche Products, Basel, Switzerland) with standard kits. Diabetic status of the subject was assessed in a number of ways as previously described.

CRP was measured immunologically with a high-sensitivity assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). Plasma levels of IL-6, intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1, E-selectin, vWF, D-dimer, t-PA, and Lp(a) were measured with high-sensitivity ELISA kits as previously described. Fibrinogen was measured in citrated plasma by a thrombin-clotting turbidometric method in a centrifugal analyser. Urinary fibrinopeptide A and plasma leukocyte elastase were measured by radioimmunoassay; plasma factor VII was measured by a functional antigenic assay; and plasma prothrombin fragment 1+2 was measured by ELISA (Dade Behring, Marburg, Germany). Finally, blood and plasma viscosity were measured in a Coulter-Harkness viscometer at 37°C. Hematocrit was measured with a Hawksley microcentrifuge and a reader. Quality control data are presented in the online-only Data Supplement. Missing values in these markers were caused by decreasing availability of plasma samples and were considered “data missing at random.”

Identification and Coding of Cardiovascular Events

Detailed information about the follow-up procedure is published elsewhere (see online-only Data Supplement). Criteria to define fatal and nonfatal MI or stroke were those adopted by the American Heart Association and were previously described in detail. Subjects who developed major CVD during the follow-up years were those who had experienced an event of fatal/nonfatal MI or stroke or who had a coronary artery bypass or coronary angioplasty.

Data Analysis

Detailed description of statistical analysis is presented in the online-only Data Supplement. Distributions of CRP, IL-6, ICAM-1, vascular adhesion molecule-1, E-selectin, leukocyte elastase, Lp(a), D-dimer, vWF, urinary fibrinopeptide A, and prothrombin fragment 1+2 were positively skewed and were logarithmically transformed to approach normality. Similarly, t-PA and factor VII and pack-years of smoking were square-root transformed. Correlation coefficients between transformed inflammatory, hemostatic, and rheological variables were calculated with the Pearson correlation coefficient. The independent sample t test and the χ² test was used to compare mean levels of CVD risk factors, inflammatory, hemostatic, or rheological variables at baseline in subjects who developed a cardiovascular event to those who did not.

Cox proportional hazards models were used to estimate cause-specific hazards of combined CVD, MI, or stroke. Hazard ratios (HRs) (95% CIs) between top and bottom tertiles of each marker were calculated and were subsequently adjusted for age and sex, for ABI, and for body mass index, diabetes, total/high-density lipoprotein cholesterol ratio, pack-years smoking, physical activity, and history of CVD disease. Alternative models with inflammatory, hemostatic, and rheological variables fitted as continuous (transformed variables) rather than 3 level categorical variables were performed. Cox regression with backward selection that used all inflammatory, hemostatic, and rheological variables (as continuous variables) was also performed. The proportional hazards assumption of invariant HR was tested and found to be satisfactory for all models constructed.

Logistic regression models were also performed with incident CVD as the outcome variable. Receiver-operating characteristic (ROC) curves were used to examine the additive predictive value of inflammatory, hemostatic, and rheological markers or of a score to a traditional risk factors model in discrimination of subjects into those who suffered or did not suffer from a CVD event during the follow-up. The ROC curves were compared with likelihood ratio tests (χ² difference) between nested models.

Throughout all analyses, a 2-sided P value ≤0.05 was considered to denote statistical significance. All analyses were performed with SPSS v13 for Windows (SPSS, Inc, Chicago, III).

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

A total of 1592 subjects were examined at baseline and during a mean (SD) follow-up period of 17.0 (0.3) years, and 702 participants (44.1%) of the baseline population died. A total of 1592 subjects were examined at baseline and 106 (17%) of the baseline population died. Table 1 shows that cardiovascular risk factors and history of CVD were greater in those who had incident CVD compared with those who did not.

Baseline concentrations of CRP, IL-6, leukocyte elastase, fibrinogen, D-dimer, t-PA, vWF, and plasma viscosity were consistently higher in people who developed CVD (P<0.01), MI (P<0.01), and stroke (P<0.01) compared with those who remained free of CVD disease (Table 2). Plasma levels of E-selectin (P=0.03) and ICAM-1 (P=0.03) were elevated only in the group who developed stroke (Table 2). Overall, levels of these plasma markers were highly significantly and positively correlated (see online-only Data Supplement). The highest correlations observed were those between fibrinogen, CRP, and IL-6, which all had correlation coefficients >0.50 (P<0.001).

Table 3 presents the HRs (95% CIs) for major CVD between the top and bottom tertiles of each inflammatory, hemostatic, or rheological marker. Adjustments for a measure of subclinical disease (ABI) lessened the associations between the biomarkers under study and the outcome variable. For example, fibrinogen showed a >12% reduction in its HR after accounting for ABI. It should be noted that ABI was significantly associated with incident CVD and its HR (95% CI) (per unit decrease) was 2.78 (1.59 to 4.76) (P<0.001) in the multivariable model. Finally, adjustments for conventional risk factors and history of CVD further diminished the associations.

Among the inflammatory markers, IL-6 had the strongest association in the multivariable model and its HR (95% CI) between top and bottom tertiles was 1.85 (1.33 to 2.58) (P<0.001). Among the hemostatic factors, t-PA had the strongest association with major CVD in the final model: its HR (95% CI) between top and bottom tertiles was 1.86 (1.36 to 2.55) (P<0.001). The cumulative probabilities for incident CVD for thirds of IL-6 and t-PA are shown in Figure 1. A sensitivity analysis was conducted that fit the markers as continuous rather than 3-level categorical (tertiles); however, this barely altered our results (see online-only Data Supplement). An additional analysis that excluded those 277 (17%) people with baseline CVD defined as MI, stroke, angina, or claudication was also performed (Table 3; online-only Data Supplement). As expected, as a result of the decrease in sample size, the estimated HRs were slightly changed, but the CIs between this and the aforementioned analysis overlapped greatly.

Results of Cox regression on events of MI or stroke separately are also presented in the online-only Data Supplement. IL-6, fibrinogen, D-dimer, and t-PA showed compara-
ble associations across different disease groups (CVD, MI, or stroke). CRP showed a higher HR (95% CI) in prediction of stroke events 2.18 (1.30 to 3.66) (P < 0.01) compared with the HR (95% CI) in prediction of MI (1.56 (1.05 to 2.32) (P = 0.05). Similarly, Lp(a), leukocyte elastase, and E-selectin showed considerable stronger associations with stroke after adjustments for conventional risk factors and ABI, but these markers were not significantly associated with MI events even in age- and sex-adjusted analysis.

A stepwise Cox regression model was also conducted. All cardiovascular risk factors, history of CVD, and ABI were forced into the model, whereas inflammatory, hemostatic, or rheological variables were selected with a backward selection process. In the final step, IL-6, ICAM-1, t-PA, and Lp(a) were included in the model. The HR (95% CI) for each of these variables (per 1 SD increase) was 1.33 (1.02 to 1.74), P = 0.03; 0.79 (0.61 to 1.04), P = 0.09; 1.26 (0.98 to 1.63), P = 0.07; 1.27 (1.01 to 1.59), P = 0.04. However, the sample size of this analysis was restricted to only 366 subjects who had measurements of all cardiovascular risk factors and inflammatory, hemostatic, and rheological markers; thus, the power of this model was restricted. To further test the importance of these 4 markers, the baseline population was divided into groups of people who had none (171 subjects), 1 (222 subjects), 2 (165 subjects), or ≥3 (88 subjects) of these variables at the top tertile. The risk of CVD increased with increasing numbers of elevated markers and individuals with ≥3 biomarkers in the top tertile had a HR 2.50 (95% CI, 1.58 to 3.97) increase in risk in the multivariable model compared with those with all biomarkers in the bottom tertile (Figure 2).

The incremental benefit of consideration of inflammatory, hemostatic, or rheological markers in addition to conventional risk factors and clinical and subclinical disease (ABI) to discriminate incident CVD cases was further investigated by calculation of the area under the ROC curve (Table 4). The area under the ROC curve for the core model was 71.2% and was significantly elevated to 74.3% when the 4 markers that were selected in stepwise regression were entered in the model. When subjects with CVD at baseline were excluded, the area under the ROC curve for the core model was 69.4%, which was significantly elevated to 71.8% when the 4 markers were added.

To evaluate the specificity of the examined markers for CVD, HRs for CVD mortality (281 events) and non-CVD mortality (408 events) were calculated (online-only Data Supplement). Although many biomarkers were significantly associated both with CVD and non-CVD mortality, the HRs of CRP, IL-6, and fibrinogen were much higher in CVD associated both with CVD and non-CVD mortality, the HRs of CRP, IL-6, and fibrinogen were much higher in CVD than in non-CVD mortality.

## Discussion

The principal findings of the present study are that elevated levels of several inflammatory, hemostatic, and rheological
variables were associated with future CVD even after accounting for conventional risk factors and for asymptomatic atherosclerosis as measured by the ABI. Notably, IL-6 showed the highest and most consistent associations between different analyses and different disease manifestations. However, these markers add only modest prognostic information to traditional risk factors and ABI, and they were not specific to CVD prediction.

**CRP, Fibrinogen, and IL-6**

CRP and fibrinogen have been widely studied in many epidemiological studies in relation to CVD, which shows both consistency and generalizability.13,21 The proinflammatory cytokine IL-6 is less studied but has recently received attention as a potential risk factor for CVD because it is thought to promote atherosclerotic progression through both inflammatory and hemostatic pathways.7,15,22–24 All 3 markers have also been associated with measures of early atherosclerotic disease,15,25,26 which may further induce their production. In the present study, we have shown that their associations with incident CVD were statistically significant after adjustment not only for conventional CVD risk factors but also for a measure of subclinical disease. In addition, all 3 markers presented comparable associations even when people with history of CVD were excluded from the analysis. Thus our data suggest, but do not prove, that elevated levels of these markers may not simply reflect an inflammatory and hemostatic response to risk factors and early atherosclerotic development.11

CRP also showed relative importance as a risk factor for stroke, a finding that supports a meta-analysis of studies with long follow-up (>8 years) that showed that the risk for stroke in healthy individuals with the highest quartile of CRP concentrations increased nearly 70% compared with those with the lowest quartile.27 However, despite previous observations by others of an association of CRP with stroke,28–31 recent evidence shows limited use in the assessment of CRP in individual stroke risk.32 Moreover, the relative importance of CRP in stroke prediction compared with myocardial infarction is controversial.33,34 The association between increased inflammatory markers with future stroke is of particular interest because it might provide an explanation for the beneficial role of statins in cerebrovascular disease despite the fact that low-density lipoprotein cholesterol is not a strong risk factor for stroke.35
As previously noted, these markers were associated both with CVD and non-CVD mortality.11 These findings support the hypothesis that these markers may be general markers of poor health associated with a wide range of diseases. However, the magnitude of the reported associations between these markers and CVD mortality was generally much higher than that for non-CVD mortality.

D-Dimer and t-PA
D-dimer and t-PA are markers of activated coagulation and fibrinolysis, which are also acute-phase reactant proteins and have been consistently associated with incident CVD.5,6 The associations between D-dimer and CVD were marginal and much smaller than that observed for fibrinogen, CRP, or IL-6. On the other hand, t-PA had a relatively high association with incident CVD in the multivariable model, but this decreased greatly when individuals with history of CVD were excluded from the analysis. Both markers also had associations of equal strength with CVD and non-CVD mortality.

Leukocyte Elastase
To our knowledge, the present study is the first to examine the association between leukocyte elastase and future CVD in the general population. Leukocyte (neutrophil) elastase is a marker of activated leukocytes with a proatherogenic role that results in high-density lipoprotein destruction, increased low-density lipoprotein uptake, and foam cell formation.36,37 Moreover, morphologically vulnerable atheromatous plaques, such as those with a thin fibrous cap, were shown to contain high levels of leukocyte elastase.38 Here we confirm our previous analysis on angina patients39 and report that people in the top tertile of leukocyte elastase in the general population are at increased risk of CVD development. Leukocyte elastase also showed strong associations with incident stroke. However, further studies need to replicate these results, especially as the association with CVD reported here was smaller than that reported for other markers, and in a sensitivity analysis that excluded people with history of CVD it failed to retain significance in the multivariable model.

Other Markers
Our results are in agreement with previous published meta-analyses3,4,8,40 that show that relative risks of coronary heart disease associated with increased blood viscosity or its major determinants (plasma viscosity and hematocrit), vWF, Lp(a), and adhesion molecules are relatively modest, and their relevance remains uncertain. Lp(a) and E-selectin showed a relatively stronger association with stroke. The role of Lp(a) is poorly understood,41 and as no previous reports on E-selectin and stroke have been published, our data need to be replicated. Also, our present results agree with previously published negative reports for factor VII, prothrombin fragment 1+2, and urinary fibrinopeptide A.19,42,43 However, results form urinary fibrinopeptide A require cautious inter-

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**Figure 1.** Tertiles of IL-6 (A) and t-PA (B) associated with incident CVD up to 17 years of follow-up. The number of people at risk were 1348 at 5 years, 1076 at 10 years, and 842 at 15 years. P value for log rank test was <0.001 for both variables.

**Figure 2.** Hazard ratio (95% CI) for CVD associated with increasing numbers of elevated (top tertile) markers (IL-6, fibrinogen, t-PA, or ICAM-1) adjusted for age, sex, body mass index, diabetes, pack-years of smoking, total/high-density lipoprotein cholesterol ratio, physical activity, history of CVD, and subclinical atherosclerosis at baseline. The y-axis is on a logarithmic scale. The hazard ratio of CVD was computed with subjects with baseline levels of IL-6, Lp(a), t-PA, and ICAM-1 at the bottom or middle tertile as the reference group.
Clinical Utility

There is limited data on the predictive value of the biomarkers under study beyond that of traditional risk factors in the literature, and existing reports conflict with one another.34,44 Our data showed that these biomarkers provided very little added information beyond that of traditional risk factors in the present study cohort we found an incremental CVD risk for people with IL-6, t-PA, Lp(a), or ICAM-1 in the top tertile.

A number of limitations of the present study need to be considered. The generalizability of our results to other ethnic groups and ages is unknown. Also, all the plasma markers measured were only once and therefore intra-individual variation could not be taken into account. However, this would tend to result in an underestimation of the true effect.47 Not all subjects had measurements of all the markers studied here, but missing data were considered as missing at random (as a result of attrition of stored plasma samples with repeated assays) and hence were unlikely to bias our results. Some differences in sample size between models may have slightly influenced the effect sizes and significance levels. Furthermore, we did not adjust our analysis for aspirin or statin use at baseline. However, at the time of baseline examination (1987 to 1988), very few of the Edinburgh population took aspirin for the prevention of CVD, and statins had not been introduced. Moreover, residual confounding cannot be ruled out and the reported associations need not indicate causal relations. Finally, although the ROC curve has many advantages in the characterization of the clinical utility of a diagnostic test, it also has received considerable criticism that need to be taken into consideration when our results are interpreted.48

In the present study, we have used the ABI as a measure of subclinical atherosclerotic disease. The ABI is a commonly used noninvasive diagnostic test and is considered to be an accurate and reliable marker of subclinical peripheral and generalized atherosclerosis in populations.49 However, adjustment of our analysis for multiple measures of subclinical

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<th>Table 4. Area Under the ROC Curve (95% CI)</th>
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<td><strong>All Subjects</strong></td>
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<td>Cardiovascular Risk Factors* Plus Each Marker</td>
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| Subjects Without History of CVD | 95% CI     | P  |
| Cardiovascular Risk Factors* Plus Each Marker | 95% CI     | P  |
| CRP            | 69.2 (65.3 to 73.1) | 70.0 (66.1 to 73.9) | 0.006 |
| IL-6           | 69.9 (66.2 to 73.6) | 70.5 (66.8 to 74.3) | 0.034 |
| Lp(a)          | 69.2 (65.3 to 73.2) | 69.9 (65.9 to 73.9) | 0.021 |
| Leukocyte elastase | 70.0 (66.7 to 73.3) | 70.5 (67.3 to 73.8) | 0.055 |
| ICAM-1         | 69.7 (66.2 to 73.2) | 70.0 (66.5 to 73.5) | 0.531 |
| VCAM-1         | 69.5 (66.0 to 73.1) | 69.7 (66.2 to 73.3) | 0.775 |
| E-selectin     | 69.6 (66.1 to 73.1) | 69.9 (66.4 to 63.4) | 0.560 |
| Fibrinogen     | 69.8 (66.5 to 73.1) | 69.6 (64.2 to 72.9) | 0.037 |
| d-dimer        | 69.6 (66.2 to 73.0) | 70.1 (66.7 to 73.5) | 0.226 |
| t-PA           | 69.7 (66.2 to 73.1) | 70.4 (66.9 to 73.8) | 0.003 |
| vWF            | 69.7 (66.3 to 73.0) | 69.7 (66.3 to 73.0) | 0.326 |
| Factor VII     | 68.3 (64.3 to 62.4) | 68.9 (64.9 to 73.0) | 0.186 |
| F1 + 2         | 69.7 (65.8 to 73.0) | 70.3 (66.4 to 74.3) | 0.648 |
| Urinary FpA    | 69.7 (66.5 to 72.9) | 69.7 (66.5 to 73.0) | 0.393 |
| Plasma viscosity| 69.1 (65.8 to 72.4) | 69.2 (65.9 to 72.5) | 0.125 |
| Blood viscosity| 68.9 (65.5 to 72.3) | 68.9 (65.5 to 72.4) | 0.772 |
| Hematocrit     | 69.2 (66.0 to 72.5) | 68.3 (66.1 to 72.6) | 0.713 |
| IL-6, ICAM-1, Lp(a), t-PA | 69.4 (64.5 to 74.3) | 71.8 (66.9 to 76.8) | 0.004 |

VCAM-1 indicates vascular adhesion molecule-1; urinary FpA, urinary fibrinopeptide A; and F1 + 2, prothrombin fragment 1 + 2.

*Age, sex, subclinical disease, pack-years smoking, diabetes, body mass index, total/high-density lipoprotein cholesterol, physical activity, and history of CVD.
†Change in the −2log likelihood from the model with cardiovascular risk factors using only the χ² test.
A number of markers were associated with future CVD after adjustment for an indicator of asymptomatic atherosclerosis as well as classic risk factors and clinical baseline disease. Inclusion of multiple markers, but not single markers, was found to add to the predictive ability of traditional cardiovascular risk factors for CVD.

Conclusions

Acknowledgments

We thank all participants, staff, and general practitioners involved in the Edinburgh Artery Study.

Sources of Funding

We acknowledge financial support from the British Heart Foundation. Dr Ioanna Tzoulaki was funded by the Scottish Executive (Chief Scientist Office).

Disclosures

None.

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Circulation. 2007;115:2119-2127; originally published online April 2, 2007; doi: 10.1161/CIRCULATIONAHA.106.635029

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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