**Serum Matrix Metalloproteinase-8 Concentrations Are Associated With Cardiovascular Outcome in Men**

Anita M. Tuomainen, Kristiina Nyysönen, Jari A. Laukkanen, Taina Tervahartiala, Tomi-Pekka Tuomainen, Jukka T. Salonen, Timo Sorsa, Pirkko J. Pussinen

**Objective**—In culture studies matrix metalloproteinase (MMP)-8 thins the protecting fibrous cap of the atherosclerotic plaque thereby increasing its vulnerability. Results on the association of serum MMP-8 concentrations and cardiovascular diseases (CVD) are, however, scarce and contradictory.

**Methods and Results**—We analyzed the association between CVD or subclinical atherosclerosis and serum MMP-8 and tissue inhibitor of metalloproteinase-1 (TIMP-1) concentrations of 1018 men with the follow-up time of 10 years. MMP-8 concentrations or MMP-8/TIMP-1 ratios were higher in men with prevalent CVD or subclinical atherosclerosis at baseline than those without. In men free of CVD at baseline, MMP-8 concentrations associated with acute myocardial infarction, death from coronary heart disease (CHD), CVD, or from any cause with relative risks (RR) (95% CI) of 1.138 (1.009 to 1.284), 1.188 (1.034 to 1.365), 1.171 (1.026 to 1.338), and 1.136 (1.018 to 1.269), respectively, and MMP-8/TIMP-1 ratio with CHD death with an RR of 1.206 (1.028 to 1.414) per standard deviation (SD) increase. In men with no prevalent CVD but with subclinical atherosclerosis at baseline, elevated serum MMP-8 concentration predicted CVD death with an RR of 3.03 (1.09 to 8.44). TIMP-1 concentrations alone had no predictive value.

**Conclusions**—The results indicate that serum MMP-8 concentrations are elevated in prevalent or subclinical atherosclerosis and associate with the worst cardiovascular outcome. (*Arterioscler Thromb Vasc Biol. 2007;27:2722-2728.*)

**Key Words:** inflammation • atherosclerosis • cardiovascular diseases • myocardial infarction • metalloproteinases

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Matrix metalloproteinases (MMPs) are involved in the breakdown of the extracellular matrix occurring during, eg, tissue repair but also in pathogenic conditions such as rheumatoid arthritis, periodontitis, and atherosclerosis.\(^1^\) Collagenase MMP-8 (neutrophil collagenase or collagenase-2) is capable to initiate the degradation of the fibrillar collagens such as collagen type I, which is the major load-bearing molecule of the fibrous cap in atherosclerotic lesions. Several other MMPs, such as MMP-2 and MMP-9, can further degrade the cleaved collagen fragments.\(^3^\) Additionally, MMP-8 can process various noncollagenous molecules thereby participating also in immune responses.\(^4^\)

Tissue inhibitors of metalloproteinases (TIMPs) are specific MMP inhibitors. TIMPs also exert a wide range of additional biological functions such as effects on cell growth and viability.\(^5^\) In humans, plasma TIMP-1 concentration is increased in acute coronary syndrome, and serum TIMP-1 associates with the presence of carotid lesions.\(^6^\) Expression of TIMP-1 is slightly upregulated in abdominal aortic aneurysm.\(^8^\)

In cell culture studies, MMP-8 has been implicated in atherosclerotic plaque destabilization through its capacity to thin the protecting fibrous cap, thus rendering it more vulnerable to rupture.\(^9^\) In human atherosclerotic plaque samples, MMP-8 protein and mRNA colocalize with macrophages.\(^10^\) In addition, abdominal aorta aneurysm contains significantly higher MMP-8 concentrations than normal aortic tissue.\(^11^\) Increased plaque MMP-8 activity has been observed in asymptomatic patients with plaque progression.\(^12^\) Also plaques prone to rupture express more immunoreactive MMP-8 compared with lesions with more stable morphology.\(^9^\)

Hitherto, however, only a few studies have investigated the associations of serum MMP-8 concentrations with cardiovascular diseases (CVD). Results from 2 case–control studies with small populations suggest that serum MMP-8 concentrations of patients with heart failure and cerebral ischemia are decreased.\(^13^\) In 2 most recent larger studies, plasma MMP-8 concentration has been positively associated with presence and severity of CAD\(^1^5\) and with carotid artery plaque progression.\(^12^\)

The aim of our study was to analyze whether serum MMP-8 and TIMP-1 concentrations or their ratio are associated with risk for CVD event in a prospective population-based study and their suitability as serum markers for cardiovascular outcome.
Materials and Methods

Subjects

Altogether 2682 Finnish men were enrolled in the Kuopio Ischemic Heart Disease Risk Factor (KIHD) study between 1984 and 1989, and data on their socioeconomic status were collected at the time of sampling. The study was approved by the Research Ethics Committee of the University of Kuopio, Finland, and all subjects gave their written informed consent.

Study Design

The study comprised 1018 men aged 46 to 64 years, who participated in the KIHD study from 1987 to 1989 and were reexamined 4 years later, from 1991 to 1993 (baseline of the present study). For this reexamination the subjects were studied twice with a 7-day interval. At the first visit, blood pressure and body mass index (BMI) were measured, whereas blood samples were taken and intima media thickness (IMT) of the common carotid artery was scanned ultrasonographically during the second visit as described in detail. The inter- and intraobserver variabilities of the measurements have been reported earlier. Data on sociodemographic background, diseases, medications, and smoking habit were obtained from self-administered questionnaires.

The eligible sample size of the present study was 1229, but 191 (15.5%) were lost because of death, severe illness, migration, refusal, or other reason. From the 1038 men who participated in the present study, 20 (1.9%) were excluded because of missing variables.

Of the 1018 men, 113 were classified as having CVD at baseline, because of their diagnosed or self-reported coronary heart disease (CHD), angina pectoris, coronary bypass, or other coronary disease. The rest, 905 men who were free from CHD at baseline, were included in the follow-up study of 10 years. Among them, 153 experienced a registered end point, ie, fatal or nonfatal acute myocardial infarction (AMI), CHD or CVD event, or death from other causes during the follow up until 2002. If a subject had multiple nonfatal coronary events during the follow-up, the first was considered the end point.

Deaths were ascertained by computer linkage to the National death registry using the social security number. All deaths that occurred by the end of the follow-up were included. CVD and CHD deaths were coded using the Ninth International Classification of Diseases (ICD) codes (390 to 459 and 410 to 414, respectively) or the Tenth ICD codes (I00-I99 and I20-I25, respectively). The present sample included 53 CVD deaths, 33 of which were attributable to CHD.

Data on nonfatal AMI were obtained from the National Hospital Discharge Data Register. The diagnostic classification of coronary events was based on symptoms, electrocardiographic findings, and cardiac enzyme elevations. Each suspected coronary event (ICD-9 codes 410 to 414 and ICD-10 codes I20-I25) was classified into (1) a definite AMI, (2) a probable AMI, (3) a typical acute chest pain episode of more than 20 minutes indicating CHD, (4) an ischemic cardiac arrest with successful resuscitation, or (5) no acute coronary event. In the present population, 86 definite AMIs were included.

Serum and Plasma Determinations

Baseline (1991–1993) venous blood samples were taken after 12-hour fasting. Serum total and HDL cholesterol, and triglyceride concentrations were determined enzymatically. Data on plasma fibrinogen concentrations and serum IgG-class antibody levels against major periodontal pathogens, Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis, were available from our previous study.

MMP-8 and TIMP-1 Determinations

Serum MMP-8 concentration was determined by a time-resolved immunofluorometric assay (Medix Biochemicals, Kauniainen, Finland) according to the manufacturer’s instructions with a serum dilution of 1:5. The interassay coefficient of variation (CV)% was 7.3% (n = 28) and detection limit for the assay 0.08 μg/L. MMP-8 (R&D Systems) was performed according to the manufacturer’s instructions with 1:300 dilutions of the serum. The interassay CV% was 8.2% (n = 28) and detection limit 0.08 ng/mL.

Statistical Analyses

The significance of differences between men with and without end point was tested using Mann–Whitney U test or Chi-square test. Two linear regression models were used to analyze the association of MMP-8, TIMP-1, and MMP-8/TIMP-1 (dependent) with selected CVD risk factors (independent) Model I as the basic model and Model II as a more extensive one. Cox model was used to estimate the linear association between one standard deviation (SD) increment of MMP-8, TIMP-1, and MMP-8/TIMP-1 as continuous variables (independent) and the risk (RR) and the 95% confidence intervals (95% CI) of end points registered (dependent) in men free from CVD at baseline. The model was adjusted for age, BMI, smoking (non-smokers versus former and current smokers), diabetes (no versus yes), systolic blood pressure, and serum cholesterol, HDL cholesterol, and plasma fibrinogen concentrations. The associations of MMP-8 concentrations with secondary CVD event in men with CVD at baseline were analyzed separately. Cumulative survival as well as the RR and their 95% CI of cardiac end points in quartiles of MMP-8, TIMP-1, and MMP-8/TIMP-1 were also determined using Cox regression models adjusted first by age only. In the second step the models were further adjusted for BMI, smoking, and plasma fibrinogen concentration. The analyses were done separately for men with and without CVD at baseline. The receiver operating characteristic (ROC) analysis was performed to evaluate the usefulness of MMP-8, TIMP-1, and MMP-8/TIMP-1 ratio in predicting CVD outcome. The statistical analyses were carried out using SPSS program version 12.0 for Windows.

Results

Serum MMP-8 and TIMP-1 concentrations were determined at baseline of the KIHD Study. Serum MMP-8 concentrations were significantly (P = 0.043) higher in men with (n = 113) than without (n = 905) CVD at baseline, 10.3 (5.0 to 15.0) versus 8.4 (4.1 to 12.4) μg/L (median, 1st–3rd quartile), respectively. High MMP-8 concentrations, however, did not significantly predict secondary CVD end point in men with CVD at baseline (data not shown). Therefore, they were excluded from further analyses.

The baseline characteristics of men free of CVD are presented in Table 1. Compared with men who had no subclinical atherosclerosis at baseline (mean IMT <1.0 mm), men with subclinical atherosclerosis (mean IMT ≥1 mm) had higher MMP-8/TIMP-1 ratios (Table 2). MMP-8 or TIMP-1 concentrations did not differ at baseline between the men with or without a CVD end point during the follow-up. Current smokers, however, had higher serum concentrations of MMP-8, TIMP-1, and MMP-8/TIMP-1 than nonsmoking men.

The basic multivariate linear regression model (Table 3, Model I) for men free from CVD at baseline revealed significant associations between MMP-8 concentrations as a continuous variable, and BMI and plasma fibrinogen concentration. In a more extensive model (Model II), significant predictors of MMP-8 concentrations remained the same. TIMP-1 concentrations had a positive association with smoking, and triglyceride and HDL cholesterol concentration, and a negative association with age and total cholesterol concentration. The only predictors that remained significant for the MMP-8/TIMP-1 ratio in Model II were age and plasma fibrinogen concentration.
antibody levels to periodontal pathogens, were higher in men with periodontal disease, namely presence of dentures and serum gen concentrations. Parameters describing past or present habits, as well as triglyceride, HDL cholesterol, and fibrinogen concentrations, did not interact with each other.

Cox models were used to estimate the linear association of MMP-8, TIMP-1 concentrations, and their ratio with the end points registered during the follow-up (Table 4). After multiple adjustments for CVD risk factors, MMP-8 concentration was linearly associated with all end points. The RRs/1 SD increment (95% CI, p) for AMI, CHD death, CVD death, and all cause death were 1.284, 0.036), 1.188 (1.034 to 1.365, 0.015), 1.171 (1.026 to 1.338, 0.020), and 1.136 (1.018 to 1.269, 0.023), respectively. MMP-8/TIMP-1 ratio was associated only with CHD death with an RR of 1.206 (1.028 to 1.414, 0.020), and 1.136 (1.018 to 1.269, 0.023), respectively. The predictive value of MMP-8/TIMP-1 ratio for these end points was 2.64 (0.85 to 8.19, 0.093) and 2.60 (0.98 to 6.95, 0.056), respectively. In men with IMT <1 mm, neither MMP-8 concentrations nor MMP-8/TIMP-1 ratio were associated with incident end points after adjustment with age (Table 5). When the Cox regression models were further adjusted for CVD risk factors, high MMP-8 concentrations predicted CVD death in men with IMT ≥1 mm, aortic atherosclerotic plaques of symptomatic patients,10 the aorta of

The characteristics of men free from prevalent CVD at baseline, with or without subclinical atherosclerosis are summarized in Table 1. Between these subgroups, there were significant differences in age, blood pressure values, smoking habits, as well as triglyceride, HDL cholesterol, and fibrinogen concentrations. Parameters describing past or present periodontal disease, namely presence of dentures and serum antibody levels to periodontal pathogens, were higher in men with subclinical atherosclerosis at baseline: high serum MMP-8 concentration is an independent risk factor for AMI, and CHD, CVD, and all cause death. The increased risk for CVD death was especially substantial in the men, with subclinical atherosclerosis at baseline: high serum MMP-8 concentration increased the risk for CVD death during the follow-up by 3-fold independently of other CVD risk factors.

Compared with healthy human tissues, unstable carotid atherosclerotic plaques of symptomatic patients,10 the aorta of
abdominal aortic aneurysm patients,\textsuperscript{11} the site of ruptured abdominal aortic aneurysm,\textsuperscript{21} and the shoulder regions of advanced atherosclerotic lesions\textsuperscript{9} display increased MMP-8 protein or mRNA expression levels. These studies suggest that MMP-8 is involved in matrix remodelling in atherosclerosis and relates to rupture of unstable plaque—the basic pathology behind the acute coronary syndromes. The findings are in a good agreement with our present results that high serum MMP-8 concentrations predicted death from cardiovascular causes both in the men free from CVD at baseline, and especially in those with subclinical atherosclerosis at baseline.

Serum or plasma MMP-8 concentrations have only rarely been determined in the context of CVD, especially in prospective setting. Plasma MMP-8 concentrations have been found to correlate with the presence and severity of coronary artery disease,\textsuperscript{15} and associate with carotid plaque instability, morphology, and the time delay after stroke.\textsuperscript{12} Decreased plasma MMP-8 levels have been reported in patients with congestive heart failure and with cerebral ischemia.\textsuperscript{13,14} Some of these contradictory results may arise from small sample sizes with inadequate statistical power. Therefore, the strengths of the present study include its sufficient sample size, prospective population-based design, and the long and complete follow-up. Limitations of the study include a relatively small number of end points, in particular CHD deaths. Yet the results are clearly significant and can therefore be considered reliable. In addition, as the present study comprises only men, further analyses are needed to confirm the relevance of MMP-8 in CVD in women.

We divided the men according to their IMT values to those without and those with subclinical atherosclerosis. Several studies have shown that an increase in carotid artery IMT reflects the overall presence of subclinical atherosclerosis, \(1 \text{ mm}\) being the threshold value.\textsuperscript{22,23} High IMT has been shown to associate for example with MI and stroke.\textsuperscript{24} At the baseline of the present study, the men with IMT \(>1 \text{ mm}\) had several established CVD risk factors compared with the men with IMT \(\leq 1 \text{ mm}\), such as high fibrinogen concentration, which is an independent predictor of IMT.\textsuperscript{25}

After adjusting for main CVD risk factors, serum MMP-8 concentration and MMP-8/TIMP-1 ratio correlated strongly and positively with plasma fibrinogen concentrations. CHD, AMI and stroke cause or result from an elevated fibrinogen concentration, a marker of inflammation and an independent risk factor for CHD events.\textsuperscript{26} In the present study, high fibrinogen concentration predicted AMI in men without subclinical atherosclerosis with a multivariate RR of 1.65.
(1.05 to 2.60, \( P = 0.029 \)), but for other end points or for men with subclinical atherosclerosis its predictive value did not reach statistical significance. In addition, MMP-8 concentration had a strong positive correlation with fibrinogen concentration also after adjustment for smoking, a major cause of increased fibrinogen concentration. Serum MMP-8 levels in smokers were recently shown to be slightly but not significantly higher relative to those of nonsmokers, but serum MMP-8 levels did not correlate with the amount of urinary nicotine metabolites or number of smoking years.27

In addition to the inflammation caused by subclinical atherosclerosis, the sources of MMP-8 found in serum may be various. For example, the host response to the insult of periodontal pathogens involves local increases of MMP-8,28 which may most probably leak to circulation through inflamed periodontal tissues. The extent and severity of periodontitis, as well as seropositivity to periodontal pathogens were recently found to correlate with measures of subclinical atherosclerosis.20,29 Considering these associations as well as the fact that periodontitis and seropositivity to periodontal pathogens are independent risk factors for CVD,20,30 combined serum antibody level to major periodontal pathogens was included in the linear regression analysis as a confounding factor. No obvious association, however, was found between these antibody levels and MMP-8 concentrations. Anyhow, in crude analyses the subjects with subclinical atherosclerosis at baseline had nonsignificantly higher antibody levels to periodontal pathogens than those without with IMT \( \geq 1 \) mm, which is in line with our earlier results concerning the same population.20

TIMPs participate in the regulation of extracellular matrix metabolism by inhibiting MMPs, thereby also suppressing the

Table 3. Multivariate Linear Regression Models for MMP-8 and TIMP-1 Concentrations in Men Free of CVD at Baseline (\( n = 905 \))

<table>
<thead>
<tr>
<th>( \beta ), ( P ) Value</th>
<th>Model I*</th>
<th>Model II†</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta ), ( P ) Value</td>
<td>MMP-8 (( \mu )g/mL)</td>
<td>TIMP-1 (ng/mL)</td>
</tr>
<tr>
<td>Age, y</td>
<td>-0.020, 0.552</td>
<td>-0.155, &lt;0.001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>-0.050, 0.125</td>
<td>-0.035, 0.280</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>-0.002, 0.954</td>
<td>0.066, 0.061</td>
</tr>
<tr>
<td>Smoking, cigarettes/d</td>
<td>0.051, 0.134</td>
<td>0.143, &lt;0.001</td>
</tr>
<tr>
<td>Diabetes, no/yes</td>
<td>-0.007, 0.834</td>
<td>-0.038, 0.244</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>-0.097, 0.005</td>
<td>-0.037, 0.467</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>0.252, &lt;0.001</td>
<td>-0.025, 0.286</td>
</tr>
</tbody>
</table>

*Independents added by the enter method; †Independents added by the backward selection method, excluded variables included systolic blood pressure, diabetes, socioeconomic status, mean IMT, and serum antibody levels to major periodontal pathogens. The 5 best predictors remaining are shown.

Table 4. Relative Risk (RR) for an End Point per 1 SD of Increasing Serum MMP-8 Concentrations in Men Free From CVD at Baseline (\( n = 905 \))

<table>
<thead>
<tr>
<th>End Point</th>
<th>With/Without</th>
<th>MMP-8 (( \mu )g/L)</th>
<th>MMP-8/TIMP-1 (mol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>86/819</td>
<td>1.138 (1.009–1.284), 0.036</td>
<td>1.112 (0.957–1.293), 0.166</td>
</tr>
<tr>
<td>CHD death</td>
<td>33/872</td>
<td>1.188 (1.034–1.365), 0.015</td>
<td>1.206 (1.028–1.414), 0.022</td>
</tr>
<tr>
<td>CVD death</td>
<td>53/852</td>
<td>1.171 (1.026–1.338), 0.020</td>
<td>1.160 (0.986–1.364), 0.073</td>
</tr>
<tr>
<td>All cause death</td>
<td>103/802</td>
<td>1.136 (1.018–1.269), 0.023</td>
<td>1.127 (0.991–1.281), 0.068</td>
</tr>
</tbody>
</table>

Adjusted for age, BMI, smoking, diabetes, systolic blood pressure, serum cholesterol concentration, HDL, and plasma fibrinogen concentration.
vulnerability of plaque to rupture. Our results suggest at serum level that disturbances in MMP-8 and TIMP-1 ratio favoring the former are a significant part of progression of subclinical atherosclerosis into clinical stage.

The course of CVD has been shown to associate with several biomarkers of systemic inflammation.31,32 The present study indicates that serum MMP-8 may be an indicator of plaque vulnerability. In many cases, thrombosis occurs in a vessel area with no substantial occlusion (eg, less than 50%), yet the vessel wall may be weak resulting in plaque rupture; therefore, there is still an urgent need for new diagnostic tools to predict CVD outcome. To our knowledge the present work is the first prospective population-based study showing the relevance of serum MMP-8 in CVD, especially in predicting the CVD outcome. According to our study, serum MMP-8 concentration and MMP-8/TIMP-1 ratio, but not TIMP-1 concentration alone, predict the worst CVD outcome in men, especially in those with subclinical atherosclerosis. Determining MMP-8 concentrations or MMP-8/TIMP-1 ratios may therefore have prognostic and diagnostic significance in assessing the patient’s risk for CVD events.

Sources of Funding
This work was supported by grants from the Academy of Finland (211129, 205987, 118391, 45155), Hospital District of Helsinki and Uusimaa (HUS-EVO, TYH 5306, TYH 6104, TYH 7114, TI 020Y0002), Finnish Foundation for Cardiovascular Research, and Ministry of Education of Finland.

Disclosures
None.

References

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Table 5. Relative Risks (RR) for an End Point in Men Free From CVD at Baseline (n=905) and Mean IMT<1.0 (n=753) or ≥1.0 mm (n=152)  

<table>
<thead>
<tr>
<th>End Point</th>
<th>With/Without End Point</th>
<th>RR (95% CI) in the Highest Quartile vs Quartiles 1–3, P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>†IMT&lt;1, 62/688</td>
<td>1.27 (0.73–2.20), 0.394</td>
</tr>
<tr>
<td></td>
<td>†IMT≥1, 24/128</td>
<td>1.43 (0.61–3.35), 0.411</td>
</tr>
<tr>
<td></td>
<td>†IMT≥1, 24/128</td>
<td>1.33 (0.56–3.18), 0.518</td>
</tr>
<tr>
<td>CHD death</td>
<td>†IMT&lt;1, 12/140</td>
<td>0.89 (0.33–2.44), 0.822</td>
</tr>
<tr>
<td></td>
<td>†IMT≥1, 12/140</td>
<td>3.27 (1.05–10.16), 0.041</td>
</tr>
<tr>
<td></td>
<td>†IMT≥1, 12/140</td>
<td>2.72 (0.84–8.82), 0.095</td>
</tr>
<tr>
<td>CVD death</td>
<td>†IMT&lt;1, 37/116</td>
<td>1.26 (0.57–2.76), 0.564</td>
</tr>
<tr>
<td></td>
<td>†IMT≥1, 16/136</td>
<td>3.20 (1.20–8.56), 0.020</td>
</tr>
<tr>
<td></td>
<td>†IMT≥1, 16/136</td>
<td>3.03 (1.09–8.44), 0.034</td>
</tr>
<tr>
<td>All cause death</td>
<td>†IMT&lt;1, 77/673</td>
<td>0.95 (0.56–1.60), 0.841</td>
</tr>
<tr>
<td></td>
<td>†IMT≥1, 25/127</td>
<td>1.47 (0.63–3.42), 0.369</td>
</tr>
<tr>
<td></td>
<td>†IMT≥1, 25/127</td>
<td>1.28 (0.54–3.06), 0.576</td>
</tr>
</tbody>
</table>

*P value for the fourth quartile vs quartiles 1–3; †adjusted for age; ‡adjusted for age, BMI, smoking, and plasma fibrinogen concentration.

Figure. Cumulative survival rate for CVD death. The cumulative survival rate of CVD death in men with IMT ≥1 in the highest quartiles (black line) of MMP-8 concentration versus the corresponding lower quartiles (gray line) were analyzed by Cox regression model adjusted for age, BMI, smoking, and plasma fibrinogen concentration.
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Arterioscler Thromb Vasc Biol. 2007;27:2722-2728; originally published online October 11, 2007; doi: 10.1161/ATVBAHA.107.154831

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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