High Myeloid-Related Protein
8/14 Levels Are Related to an Increased Risk of Cardiovascular Events After Carotid Endarterectomy

Mihaela G. Ionita, MD; Louise M. Catanzariti, MSc; Michel L. Bots, MD, PhD; Jean-Paul P.M. de Vries, MD, PhD; Frans L. Moll, MD, PhD; Siu Kwan Sze, PhD; Gerard Pasterkamp, MD, PhD; Dominique P.V. de Kleijn, PhD

Background and Purpose—Myeloid-related protein (Mrp) 8/14 complex is the functional relevant form of Mrp-8 and Mrp-14. Mrp-8/14 complex is actively formed in the cytoplasm of circulating neutrophils and monocytes and then secreted. Plasma Mrp-8/14 complex is emerging as a new biomarker that may discriminate between patients with an acute coronary syndrome and those with stable coronary heart disease. Little is known about the predictive value of Mrp-8/14 plaque and plasma levels for cardiovascular events after atherectomy.

Methods and Results—Plasma and plaque Mrp-8/14 levels were determined by ELISA in 230 consecutive patients (mean age 73) who underwent carotid endarterectomy. Patients were followed for 3 years for recurrent cardiovascular events (vascular death, nonfatal vascular event, and peripheral intervention). During follow-up, 62 patients experienced an event. Baseline Mrp-8/14 levels were higher in patients who experienced an event than in event-free patients (plasma 0.78±0.63 versus 0.57±0.67 mg/L; P=0.030 and plaque 0.54±1.23 versus 0.08±1.51 mg/kg; P=0.027). In a Cox model, a 1 U increase in log Mrp-8/14 was associated with an increased risk of recurrent events (plasma, hazard ratio [HR], 1.51; 95% CI, 1.02 to 2.23; P=0.040; and plaque, HR, 1.23, 95% CI, 1.04 to 1.46, P=0.018). After multivariate adjustment for risk factors (both plasma and plaque Mrp-8/14) and plaque characteristics (only plaque Mrp-8/14), the HR remained the same for both plasma (HR, 1.50, 95% CI, 1.01 to 2.30; P=0.046) and plaque (HR, 1.20, 95% CI, 1.01 to 1.44; P=0.042).

Conclusion—High Mrp-8/14 plasma and plaque levels are related to an increased risk of adverse cardiovascular events after a carotid endarterectomy, independent of traditional cardiovascular risk factors. (Stroke. 2010;41:2010-2015.)

Key Words: atherosclerosis ▪ carotid artery ▪ carotid endarterectomy ▪ outcome ▪ statins ▪ symptomatic carotid stenosis ▪ vascular surgery ▪ myeloid related protein ▪ recurrent cardiovascular events

Disruption and thrombosis of an atherosclerotic plaque may lead to severe clinical presentations such as acute ischemic attacks in the heart and brain, with morbidity and mortality for the patient. Inflammation is pivotal for the development and destabilization of an atherosclerotic plaque; therefore, a large number of inflammatory proteins have been investigated in prospective studies, and they have been found to relate to cardiovascular events.1

Myeloid-related protein (Mrp) 8 and Mrp-14 are inflammation-associated proteins, expressed by inflammatory cells such as neutrophils, monocytes,2 and macrophages.3 On cell activation, Mrp-8 and Mrp-14 form the Mrp-8/14 complex, which is transferred to the cell membrane or secreted.4 The Mrp-8/14 complex is considered the functional relevant form of Mrp-8 and Mrp-14, being a cytokine- and chemokine-like protein.5 Mrp-8/14 is expressed in both mouse6 and human atherosclerotic plaques.7 Mice lacking the Mrp-8/14 have reduced atherosclerotic lesion area and macrophage accumulation within the lesions,6 supporting a role for Mrp in plaque formation and development. In human carotid endarterectomy (CEA) specimens, we previously described an association among high Mrp-8, Mrp-14, and Mrp-8/14 levels and the features of the rupture-prone lesions,7 suggesting a role for high levels of Mrp proteins in plaque destabilization and disruption.

In human plasma, Mrp-8/14 levels were shown to be useful markers for monitoring disease activity in inflammatory diseases such as rheumatoid arthritis and Crohn disease.8 In addition, plasma as well as local (thrombi) Mrp-8/14 levels are elevated in patients with an acute coronary syndrome...
compared with patients with stable coronary artery disease or patients with normal coronary arteries. Moreover, levels of systemic Mrp-8/14 appear to increase before markers of myocardial necrosis (myoglobin, creatine kinase–MB, and troponin), and high levels are associated with increased risk of recurrent cardiovascular events. Plasma Mrp-8/14 levels were higher in patients with ST-segment elevation myocardial infarction (MI) compared with patients with stable coronary artery disease, and the risk of the first cardiovascular event increased with each quartile of plasma Mrp-8/14. Together, these studies demonstrate that high Mrp-8/14 plasma levels are related to an increased risk of cardiovascular events in healthy (primary event) patients and patients with coronary disease (secondary event). Mrp-8/14 is expressed in human carotid plaques, and high levels are associated with rupture-prone lesions; this might point to Mrp-8/14 as a marker for plaque vulnerability. No study so far has evaluated the association of high Mrp-8/14 plaque levels and the occurrence of recurrent cardiovascular events after atherectomy.

To investigate this, we measured Mrp-8/14 levels locally (carotid plaque) and systemically (plasma) in patients undergoing CEA and studied the association with the occurrence of recurrent cardiovascular events during 3 years of follow-up.

Methods
Study Population and Design
Athero-Express is an ongoing longitudinal cohort study, initiated in 2002 by 2 Dutch hospitals: the University Medical Center Utrecht and the St. Antonius Hospital in Nieuwegein. The study has been approved by the institutional boards of both hospitals, and written informed consent was obtained from all participants. The study is designed to investigate, in patients undergoing CEA, the expression of atherosclerotic tissue–derived biological markers in relation to plaque phenotype and the recurrence of cardiovascular events during follow-up, as described previously.

In this study, a set of 230 consecutive patients undergoing CEA between April 1, 2002, and March 1, 2006, were included. At baseline, clinical parameters including cardiovascular risk factors and medication use were documented and recorded. Exclusion criteria for follow-up were unwillingness or physical incapability to participate (eg, severe dementia).

Clinical Presentations of Atherosclerotic Carotid Disease Before CEA
Patients included for CEA were asymptomatic (no clinical symptoms related to the carotid luminal stenosis >75%; n = 47) and symptomatic (n = 183), with minor clinical presentations (ie, transient ischemic attack, amaurosis fugax, and retinal infarction; n = 127) or major presentations (ie, stroke; n = 56). The time between the onset of symptoms and CEA (in days) was recorded as described previously. We reported an association between the time of symptom onset until CEA and cellular and molecular changes in plaques. In short, we showed that symptomatic plaques are associated with a rupture-prone phenotype and remodel into more stable plaques over time after stroke; therefore, these temporal plaque phenotypic changes should be taken into account when analyzing plaque Mrp-8/14 as a biomarker.

Follow-Up
Patients underwent clinical follow-up 1 year after CEA and completed postal questionnaires 1, 2, and 3 years after the surgery. Adjudication of the outcome events was done by a committee consisting of 3 surgeons who were blinded to laboratory results. All end points were assessed independently by 2 committee members.

Clinical Outcome
The primary outcome was defined as a composite of events including: any death of vascular origin (fatal stroke, fatal MI, sudden death, and other vascular death), nonfatal stroke, nonfatal MI, and any arterial vascular intervention that had not already been planned at the time of inclusion (ie, carotid surgery or angioplasty, coronary artery bypass, percutaneous coronary artery intervention, peripheral vascular surgery, or angioplasty). In addition, we defined 3 subgroups regarding the clinical outcome in different vascular territories (coronary, stroke, and peripheral) and a composite group of major outcomes. Coronary outcomes include MI (fatal and nonfatal), coronary artery bypass, coronary artery intervention, and sudden death. Stroke outcomes include nonfatal and fatal stroke. Peripheral outcomes include leg amputation and peripheral arterial intervention that had not been planned at the time of inclusion. Major outcomes include MI (fatal and nonfatal), stroke (fatal and nonfatal), coronary artery bypass, coronary artery intervention, and sudden death.

CEA Specimens and Blood Collection
All carotid plaques were dissected from the carotid arteries during surgery and immediately transferred to the laboratory for further processing as described previously. In short, in the laboratory, the atherosclerotic fragments were dissected, by a dedicated technician, into 0.5 cm-thick cross-sectional segments along the longitudinal axis of the vessel. The plaque segment showing the largest plaque burden was called the culprit lesion and was used for histological analysis to determine plaque morphology; adjacent segments were used for protein isolation. Plaques were categorized as no/minor staining or moderate/heavy staining for the following stains: hematoxylin and eosin, Pico Sirius red (for total collagen), anti–CD68 immunostain (for macrophages) and anti–α-1 actin immunostain (for vascular smooth muscle cells [SMCs]). Using the hematoxylin and eosin and Pico Sirius red stains, the size of the lipid core was estimated as percentage of total plaque area and divided into 3 categories: <10%, 10% to 40%, and >40%. Overall plaque phenotype is based on the size of the lipid core, the amount of collagen, and the extent of macrophage and SMC infiltration. Plaques with a lipid core size >40% of the plaque area, with high macrophage infiltration, low collagen levels, and low SMC infiltration, were identified as rupture-prone plaques. Intraplaque hemorrhage was scored using hematoxylin and eosin, fibrin (Mallory’s phosphotungstic acid–hematoxylin), and anti-smooth muscle actin; immunostains are reported in this study as absent (no) or present (yes).

Blood is withdrawn before surgical incision for CEA, and plasma is stored at −80°C until further use.

Immunoassays for Mrp-8/14
Levels of Mrp-8/14 heterodimers were measured with a commercial ELISA (Bühlmann Laboratories AG). For each patient, 50 µg of plaque Tris-protein and 5 µL of heparin plasma were used. The detection limits for plaque and plasma Mrp-8/14 were 10 pg/g and 4 ng/mL, respectively. The average interassay variability was 2.5%. The ELISA kit is specific for the Mrp-8/14 heterodimers, and the cross-reactivity with Mrp-8 and Mrp-14 homodimers is minimal (according to the manufacturer).

Data Analysis
Medians with interquartile ranges, means with SDs, or proportions for baseline clinical characteristics were computed for patients with and without secondary cardiovascular events during 3 years of follow-up. The distributions of plasma and plaque Mrp-8/14, low-density lipoprotein, triglycerides, and high-sensitivity C-reactive protein were skewed, therefore, they were log transformed. The differences between 2 variables were tested by the t test (continuous versus continuous/categorical) or by χ² (categorical versus categorical). The correlation between 2 variables was assessed by the Spearman or Pearson correlation test. Cox proportional hazard
models were used to assess the independent relationship with recurrent cardiovascular events for a 1 U increase of log-transformed Mrp-8/14 (plasma or plaque) data. Results are presented as hazard ratios (HRs) with their 95% CIs. First, crude HRs were calculated (Cox-regression, Enter method). Next, results were adjusted for age (continuous), male gender (yes/no), smoking status (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), diabetes mellitus (yes/no), history of coronary interventions, peripheral interventions, stroke or MI (yes/no), and the use of statins before operation (yes/no). Results for plasma Mrp-8/14 were further adjusted for serum C-reactive protein (continuous). Results for plaque Mrp-8/14 were further adjusted for plaque characteristics (ie, large lipid core [yes/no], high macrophage infiltration [yes/no], low collagen [yes/no], low SMC infiltration [yes/no], intraplaque hemorrhage [yes/no]) and for time between symptom onset and CEA (continuous). A backward method, leaving variables with a P value >0.1 step-wise out, was used. Statistically significant associations with clinical outcome were defined as a 95% CI, not including 1 or a P value <0.05. For statistical analyses, SPSS 15.0 was used (SPSS Inc.).

Results

Baseline Characteristics

The current study is based on a cohort of 230 patients experiencing carotid atherosclerotic disease. The cohort was 68% male, with an average age of 73 years, a mean body mass index of 26.3 (± 3.9), 70% were hypertensive, 54% had hypercholesterolemia, and 19% had diabetes mellitus. Baseline characteristics are provided in Table 1. A total of 20% of the patients reported a previous manifestation of atherosclerotic disease (ie, previous stroke, MI, or coronary or peripheral intervention). At the time of inclusion for CEA, 80% of the patients were symptomatic with minor clinical presentations (ie, transient ischemic attack, amaurosis fugax, and retinal infarction; n = 127) or major presentations (ie, stroke; n = 56); 47 patients were asymptomatic. Before CEA, 67%...
were on statin therapy, whereas a smaller percentage was using aspirin (43%) or oral anticoagulants (15%; Table 1).

During 3 years of follow-up (mean follow-up 2.46 years; range 0.01 to 3.00), 62 patients reached a primary outcome, 14 patients had a nonfatal or fatal stroke, 11 patients had nonfatal or fatal MI, 26 patients had a peripheral intervention, and 21 patients died of cardiovascular disease. Patients who developed a recurrent event during follow-up were significantly older, were more frequently men, had lower high-density lipoprotein levels, and had more coronary interventions (percutaneous coronary intervention or surgery) in the past (Table 1). Mrp-8/14 (plasma and plaque) levels were considerably higher in patients with recurrent events than in those without (Table 1). Serum C-reactive protein levels were elevated in patients who developed a recurrent cardiovascular event compared with those who remained free of events. Both markers were strongly and independently related to an increased risk of recurrent cardiovascular events even after adjustment for traditional risk factors, history of previous events or interventions, medication, and plaque characteristics.

The finding that Mrp-8/14 levels measured in plaque relate to an increased risk of recurrent cardiovascular events in any vascular territory underlies the previously described concept postulating that local plaque protein levels may reflect a person’s constitution to build unstable plaques.14 It would be interesting to know whether Mrp-8/14 plasma levels change once the plaque is removed from the patient. In the present study, we were unable to measure plasma Mrp-8/14 levels after CEA because we only collect blood before CEA. Nevertheless, a correlation between plasma and plaque Mrp-8/14 was not seen, which may suggest that only a small proportion of the circulating Mrp-8/14 levels originate from atherosclerotic plaque. In addition, we analyzed plasma and

Mrp-8/14 Levels and the Risk of Recurrent Cardiovascular Events

We determined whether Mrp-8/14 levels (plasma and plaque) differed between patients who developed a recurrent cardiovascular event during the 3 years following their CEA and patients who remained free of events.

In a model containing only plasma Mrp-8/14, a 1 U increase in log Mrp-8/14 was associated with a 51% increase in risk of any recurrent cardiovascular event (HR, 1.51; 95% CI, 1.02 to 2.23; P = 0.040). Multivariate adjustments for traditional risk factors did not attenuate the relationship (HR, 1.50; 95% CI, 1.01 to 2.30; P = 0.046). Addition of serum C-reactive protein to the multivariable model led to similar findings (HR, 1.57; 95% CI, 1.05 to 2.36; P = 0.030; Table 2).

Similar analysis was done for plaque Mrp-8/14: a model containing only plaque Mrp-8/14 showed that a 1 U increase in log Mrp-8/14 was associated with a 23% increase in risk of any recurrent cardiovascular event (HR, 1.23; 95% CI, 1.04 to 1.46; P = 0.018). Adjustments for traditional risk factors and plaque characteristics did not change the risk (HR, 1.20; 95% CI, 1.01 to 1.44; P = 0.042). Further, addition of time between symptom onset and CEA to the multivariable model did not materially affect the relationship (HR, 1.26; 95% CI, 1.01 to 1.57; P = 0.038; Table 2).

Discussion

In the present cohort of patients with severe carotid atherosclerotic disease undergoing CEA, we investigated the risk of recurrent cardiovascular events associated with Mrp-8/14 plasma and plaque levels. Both plasma and plaque Mrp-8/14 were on statin therapy, whereas a smaller percentage was using aspirin (43%) or oral anticoagulants (15%; Table 1).

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<table>
<thead>
<tr>
<th>Table 2. HR for Any Cardiovascular Events (Combined Outcome) by 1-U Increase in Log Mrp-8/14 Plasma or Plaque</th>
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<tbody>
<tr>
<td>Model</td>
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<tr>
<td>Plasma Mrp-8/14</td>
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<tr>
<td>Unadjusted</td>
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<tr>
<td>Multivariable adjustment*</td>
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<tr>
<td>Multivariable and CRP adjustment</td>
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<tr>
<td>Plaque Mrp-8/14</td>
</tr>
<tr>
<td>Unadjusted</td>
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<tr>
<td>Multivariable adjustment†</td>
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<td>Multivariable and time between symptom and CEA</td>
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*Multivariable adjustment for age, male gender, smoking status, hypertension, hypercholesterolemia, diabetes mellitus, history of coronary or peripheral intervention, history of stroke or MI, use of statins, plaque characteristics, and intraplaque hemorrhage.
†Further adjustment for lipid core size of plaque, collagen amount, macrophage and SMC infiltration, and intraplaque hemorrhage.
plaque Mrp-8/14 levels by the elapsed time from symptom onset (stroke or transient ischemic attack) to CEA. We found that plaque Mrp-8/14 levels slightly decreased over this time ($r = -0.16; P = 0.045$), whereas plasma Mrp-8/14 levels remained constant ($r = -0.018; P = 0.824$). This observation suggests that the local carotid plaque may not be the dominant source of Mrp-8/14 in plasma; however, we cannot rule out plaques as a source. The possibility of other tissue origins of Mrp-8/14 in plasma from our patients remains uncertain.

Two studies, both focusing on coronary events (first or second manifestation) showed that plasma Mrp-8/14 was related to future coronary events. In an acute coronary syndrome cohort, high plasma Mrp-8/14 levels were related to the risk of a first cardiovascular event in apparently healthy postmenopausal women. In this prospective, nested-case control study ($n = 255$ case-control pairs), apparently healthy women, matched for age and smoking, were included and followed for $\approx 3$ years, and any cardiovascular events (non-fatal MI, stroke, and cardiovascular death) were documented. Women who developed cardiovascular events during follow-up had higher Mrp-8/14 plasma levels at baseline than women who remained free of events; the relative risks according to increasing quartiles of Mrp-8/14 were 1.0, 1.7, 2.3, and $2.3 (P = 0.03)$.

Another nested case-control study ($n = 237$ case control pairs) included patients with a first presentation of MI or unstable angina and discharged with moderate/intensive statin treatment; patients were matched for age, gender, and smoking status. At 30 days after the acute coronary syndrome, the Mrp-8/14 plasma levels were measured. Patients were then followed for 24 months, and end points such as cardiovascular death or new MI were documented. The authors found significantly higher Mrp-8/14 plasma levels in patients with end points than in patients without; after adjusting for risk factors, the relative odds of cardiovascular death or MI increased significantly with each increasing quartile of Mrp-8/14: 1.0, 1.7, and 2.0 ($P = 0.024$).

In our study, we also investigated the association between plasma Mrp-8/14 and the risk of coronary events and interventions after CEA. We found that a 1 U increase of log Mrp-8/14 was related to a 108% increase in risk of coronary events or interventions; however, after multivariate adjustments for traditional risk factors, the risk decreased to 98% and was not statistically significant (Table 3). The present study has a small number of recurrent coronary events, and this might diminish the power of the study.

Our cohort is different from those used in previous studies, which were based on healthy cohorts or cohorts of patients with coronary disease. The current study included patients with recent cerebral ischemia (stroke or transient ischemic attack). We followed patients for 3 years after CEA and, compared with the study of Morrow et al., we did not focus on recurrent coronary events, but we documented all cardiovascular events in the follow-up. For the first time, we measured Mrp-8/14 levels in plasma and plaque in the same patient, and we showed that both are related to recurrent cardiovascular events. Our findings indicate that plasma Mrp-8/14 reflects the patient’s instability rather than just the instability of a local plaque.

Table 3. HR for Different Cardiovascular Events of 1 U Increase in Log Mrp-8/14 Plasma or Plaque

<table>
<thead>
<tr>
<th>Event (Follow-Up)</th>
<th>Plasma Mrp-8/14</th>
<th>Plaque Mrp-8/14</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI; P Value)</td>
<td>HR (95% CI; P Value)</td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.624 (0.950–2.777; 0.076)</td>
<td>1.065 (0.843–1.346; 0.598)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>1.543 (0.906–2.626; 0.110)</td>
<td>0.871 (0.657–1.514; 0.336)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
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<tr>
<td>Crude</td>
<td>1.385 (0.620–3.09; 0.427)</td>
<td>0.950 (0.664–1.361; 0.782)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>1.071 (0.462–2.482; 0.872)</td>
<td>0.885 (0.611–1.282; 0.519)</td>
</tr>
<tr>
<td>Coronary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>2.086 (1.036–4.200; 0.039)</td>
<td>1.255 (0.924–1.705; 0.145)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>1.984 (0.970–4.061; 0.061)</td>
<td>1.219 (0.782–1.900; 0.383)</td>
</tr>
<tr>
<td>Peripheral</td>
<td></td>
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</tr>
<tr>
<td>intervention</td>
<td></td>
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<tr>
<td>Crude</td>
<td>1.471 (0.808–2.766; 0.206)</td>
<td>1.365 (1.042–1.788; 0.024)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>1.432 (0.773–2.652; 0.254)</td>
<td>1.470 (0.901–2.398; 0.123)</td>
</tr>
<tr>
<td>MI</td>
<td></td>
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</tr>
<tr>
<td>Crude</td>
<td>1.801 (0.718–4.520; 0.210)</td>
<td>1.04 (0.696–1.570; 0.830)</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>1.800 (0.670–4.836; 0.244)</td>
<td>0.955 (0.647–1.408; 0.815)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, smoking status, hypertension, hypercholesterolemia, diabetes mellitus, history of stroke, MI, coronary and peripheral interventions, use of statins, plaque characteristics, and intraplaque hemorrhage.†Plaque Mrp-8/14 was further adjusted for lipid core size of plaque, collagen amount, macrophage and SMC infiltration, and intraplaque hemorrhage.

The findings presented here could have clinical implications. We bring proof to support the concept that high Mrp-8/14 levels measured in plasma are a clinically useful tool in estimating the risk of recurrent cardiovascular events in severely diseased atherosclerotic patients. Further, we show for the first time that high Mrp-8/14 levels measured also locally in plaque are associated with an increased risk of recurrent events. For imaging techniques (eg, MRI, single-photon emission CT), which aim to target plaque proteins and use them to stratify patients at risk of recurrent events, plaque Mrp-8/14 might be a potential target.

In conclusion, we expanded the existing evidence by showing that high Mrp-8/14 levels (local [plaque] and systemic [plasma]) are independently related to an increased risk of adverse cardiovascular events following a CEA.

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Disclosures

D.P.V.d.K., F.M., and G.P. are cofounders of Cavadis, a biomarker company. The other authors report no significant conflicts of interest.

References


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/content/41/11/e599.full.pdf

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2010/07/29/STROKEAHA.110.582122.DC1

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In the article entitled “High Myeloid-Related Protein: 8/14 Levels Are Related to an Increased Risk of Cardiovascular Events After Carotid Endarterectomy” by Ionita et al, an author’s name appears incorrectly. The correct name is Siu Kwan Sze, not Siu Sze Kwan. The authors regret this error.

The corrected version can be viewed online at http://stroke.ahajournals.org/cgi/reprint/41/9/2010.