Carotid artery disease and stroke in patients with peripheral arterial disease. The role of inflammation

Patologia carotidea e Ictus in pazienti con arteriopatia ostruttiva periferica. Il ruolo della infiammazione

Giusy Sirico, Lucrezia Spadera, Mario De Laurentis, Gregorio Brevetti


Although during the last decade there have been great advances in our knowledge of the epidemiology and pathophysiology of multi-district atherosclerotic disease, little is known about the association between peripheral arterial disease and carotid artery disease. This review was conceived to cast some light on this topic, paying special attention to inflammation which plays a pivotal role in atherosclerosis. An aspect of pathophysiologic and clinical relevance is that the coexistence of carotid disease is more frequent in peripheral arterial disease than in coronary artery disease, not only in terms of carotid stenosis, but also with respect to the presence of hypoechoic unstable plaque. These latter plaques present a large infiltration of macrophages and are associated to high levels of inflammatory markers. In particular, the greater prevalence of hypoechoic carotid plaques in peripheral arterial disease compared to patients with carotid artery disease was poorly related to classic risk factors, but showed an independent association with an increased number of leucocyte and neutrophil cells, which are reliable markers of inflammation. The greater prevalence of hypoechoic unstable carotid plaques could explain why peripheral arterial disease portends higher risk of stroke than coronary artery disease.

Keywords: peripheral arterial disease, carotid artery disease, stroke, polyvascular disease, inflammation.

vere (75%-100%) carotid stenoses increased in a graded stepwise fashion as the ABI decreased. Mostaza Jose M. et al. [19] reported that it was 14.3% in PAD patients and only 4.7% in the control subjects, matched for age, sex, and major risk factors. Similarly, in our experience, the presence of > 50% carotid stenosis in PAD was 18.6% [20]. A lower prevalence was found in the Lower Extremity Arterial Disease (LEAD) substudy of the Bypass Angioplasty Revascularization Investigation (BARI) trial which reported carotid stenosis in 7% of PAD patients (BARI). In any case, such prevalence was markedly higher than in no PAD (0.3%, \( P < 0.001 \)) [21].

An aspect of pathophysiologic and clinical relevance is that the coexistence of carotid disease is more frequent in PAD than in CAD. In particular, the Second Manifestation of ARterial (SMART) disease study [22] showed that the prevalence of carotid stenosis \( \geq 70\% \) was 12.5% in PAD and only 3.1% in CAD. Similarly, in another series, carotid stenosis \( \geq 70\% \) was present in 24.5% of PAD patients and 11.1% of CAD patients [23].

These data may partly explain the higher incidence of stroke in PAD vs CAD [7, 24]. However, many cerebrovascular events are associated with carotid stenoses <75%, thus indicating that other mechanisms are involved such as cardiac or aortic embolism, lacunar infarction, valvular disease with atrial fibrillation, and embolism from carotid bifurcation. The latter event appears to be the most common pathogenetic mechanism for cerebral ischemia [25, 26]. Actually, histopathologic data have led to the concept that plaques with a soft lipid-rich core, a thin cap, and inflammation in cap and shoulder are unstable and prone to rupture [27-35].

This type of plaques may be identified at B-mode ultrasound scanning. Plaques that appear with low echogenicity have an increased lipid content, while plaques with high echogenicity consist mainly of fibrin and collagen, which make them more stable [36, 37]. More in detail, plaques may be divided as echolucent (type 1), predominantly echolucent (type 2), predominantly echogenic (type 3), echogenic (type 4), or calcified (type 5) [38] (Fig. 1).

To the best of our knowledge, only two studies compared the prevalence of carotid plaque echogenicity in patients affected by PAD [20, 39] to that observed in CAD subjects. In the first paper, PAD patients with carotid atherosclerosis but without CAD, showed a prevalence of hypoechoic plaques (type 1 + type 2) of 39.5% [20]. A similar result was obtained when carotid plaque echogenicity was assessed by grey-scale median (GSM) analysis (34.9%). Both these proportions were markedly higher than those observed in CAD patients without PAD [20]. Actually, in the latter, the percentage of patients with hypoechoic carotid plaques was only 18.6% at visual (\( p=0.033 \)) and 14.0% at GSM analysis (\( p=0.024 \)) [20]. Compared to CAD patients, those with PAD showed an increased risk of having hypoechoic plaque both at visual (OR 4.39, 95% CI 1.21-15.92) and GSM (OR 5.13, 95% CI 1.27-20.67) analysis, after adjustment for age, male, sex, hypertension and body mass index [15]. Given these results, it is not surprising that, in the second paper, hypoechoic carotid plaques (i.e. those with a GSM < 25th percentile) resulted more prevalent in CAD+PAD patients than in those with isolated CAD (38.0% vs 11.4%, \( p<0.001 \)) [39].

- **Type 1:** echolucent
- **Type 2:** predominantly echolucent
- **Type 3:** predominantly echogenic
- **Type 4:** echogenic
- **Type 5:** calcified

Figure 1. - Carotid plaque classified according to their echogenicity.
In both the aforementioned studies [20, 39] the greater prevalence of hypoechoic carotid plaques in PAD vs CAD patients was poorly related to classic risk factors but showed an independent association with an increased number of leukocyte and neutrophil cells, which are reliable markers of inflammation. This is consistent with previous results showing that in PAD subjects the inflammatory profile is more pronounced than in CAD patients [20].

2. Inflammation and carotid disease

Atherosclerosis can be considered as an expression of chronic inflammation which, in addition to favor the development of plaques, plays a prominent role in their instability [40-43]. Several clinical and histopathological studies indicate that the severity of the carotid artery disease is related to inflammation. In 5201 participants in the Cardiovascular Health Study (CHS) [44], a weak but significant correlation was found between C-Reactive Protein (CRP) levels and carotid IMT ($r=0.12, \ P=0.001$). Mullinex et al. [45] compared 72 patients with carotid stenosis with 74 healthy subjects without carotid stenosis, and found that in the formers CRP levels roughly doubled those observed in patients without carotid stenosis (3.7 ± 6.1 vs 1.9 ± 2.1 mg/L, \(p=0.02\)). Even more important, increased levels of CRP paralleled an increase in the degree of carotid artery stenosis. Actually, each additional 1 mg/dL of baseline serum CRP level corresponded with a 5.2-cm/s increase in carotid duplex velocity magnitude ($P < 0.01$) [45]. Similarly, in the Inflammation and Carotid Artery-Risk for Atherosclerosis Study (ICARAS) [46], levels of CRP and serum amyloid A (SAA) at baseline and follow-up, and the change from baseline to follow-up were significantly associated with progression of carotid atherosclerosis assessed by Peak Systolic Velocity of internal carotid artery and NASCET criteria [47]. Actually, adjusted Odds Ratios (ORs) for atherosclerosis progression for increased quintiles of baseline CRP were 1.65 (0.71 to 3.84), 1.87 (0.8 to 4.37), 3.32 (1.49 to 7.39), and 3.65 (1.65 to 8.08), respectively, compared with the lowest quintiles [46]. The corresponding ORs for baseline SAA were 0.86 (0.38 to 1.92), 0.99 (0.49 to 1.99), 1.72 (0.91 to 3.28), and 2.28 (1.24 to 4.20) [46].

However, inflammation is related not only to the degree of plaque stenosis but also to the plaque morphology, which plays a distinct pathophysiological role in the development of stroke [44, 48, 49]. Indeed, for a given critical stenosis plaque surface and composition may be responsible for plaque disruption and distal embolization [25, 26] (Fig. 2).

The CHS reported that, when patients were classified as having high-risk carotid plaques (irregular or ulcerated surface of hypoechoic plaques), intermediate-risk plaques (hyperdense, calcified plaques or those with mildly irregular surface) and no plaques, CRP levels increased from the group without plaques, group with intermediate-risk plaques, to plaques at high-risk [44]. Consistently, Alvarez Garcia et al. [49] measured CRP levels 48 hours before carotid surgery, and found that patients with histologically defined unstable plaques had a higher median CRP value (27.1 mg/L) than those with stable plaques (4.1 mg/L) ($p < 0.001$). Similarly, Lombardo et al. [50] reported that in CAD, CRP levels were higher in pa-
patients with echocardiographically complex unstable carotid plaques than in those with stable plaques. A more direct evidence of the relationship between unstable carotid plaques and inflammation emerges from histopathological studies. Jander et al. [51] performed a quantitative immunocytochemical analysis of inflammatory infiltration in endarterectomy specimens from 37 patients undergoing carotid surgery and asked whether the extent of inflammation correlated to plaque instability as evidenced clinically by both the presence of ischemic symptoms and the rate of cerebral microembolism assessed by transcranial Doppler ultrasonography. Statistical analyses revealed that the percentage of macrophage-rich areas and the number of T-cells per mm² section area were significantly higher in recently symptomatic than in asymptomatic patient. Furthermore, macrophage infiltration was more pronounced in micro-embolism-positive than in micro-embolism-negative patients. Consistently, in a series of 106 patients undergoing carotid endoarterectomy, macrophages were found to be particularly common in plaques with a high content of lipid and hemorrhage and, conversely, rare in plaques dominated by calcification and fibrous tissue [52]. In addition, macrophage density in carotid artery plaques classified by B-mode ultrasound images as echolucent, intermediate, or echogenic was 1.8%±0.2%, 1.5%±0.4% and 1.0%±0.2% (P=0.02 at analysis of variance). A recent immunohistochemistry study reports that CD36, a scavenger receptor involved in lipid uptake and inflammation, is localized to macrophages-rich area of intima within the carotid atherosclerotic lesions. Furthermore, plasma levels of soluble CD36 were markedly higher in patients with recent cerebrovascular symptoms (≤2 months) [53].

Finally, and extremely important from a therapeutic point of view, macrophage density in carotid artery was significantly lower in patients using aspirin than in non users (1.2%±0.2% vs 1.8%±0.2%, P=0.01) [51]. Relevant in this regard are the data of a recent paper which, in addition to confirm the inflammatory infiltration in unstable carotid plaques, demonstrated that patients treated with statins had lower percentage values of macrophage area and metalloproteinase-9 area than untreated patients. This provides further evidence to support the hypothesis that statins reduce the inflammatory response and thereby stabilize carotid atherosclerotic plaques [54].

3. PAD, inflammation and Carotid disease

Despite the large evidence of the strict relationship between inflammation and carotid artery disease, this aspect has been poorly investigated in PAD, although affected individuals have a more severe inflammatory status than controls [55-57] and a higher prevalence of carotid disease [22, 23].

In our laboratory, we found a significant inverse relationship between the echogenicity of carotid plaques measured by GSM analysis and the number of neutrophils (p=–0.423, P<0.01). Thus, the greater the plaque instability, the higher inflammatory status. Indeed, the number of neutrophils was higher in type 1 and 2 plaques (considered collectively) than in the subgroup comprising type 3 and 4 plaques (4.9 ± 1.0 vs 3.8 ± 1.1 10⁹/l, P < 0.01) [20], and the hypochoic plaques were much more common in the group of patients with neutrophil number exceeding the median than in those with lower neutrophil levels (48.8% vs 9.3%, P < 0.01, for visual analysis, and 41.9% vs 7.0%, P < 0.01, for GSM analysis). Notably, the increased risk associated with PAD of having hypochoic plaques was no longer significant when the neutrophil number exceeding the median was added to the multivariate analyses. In this model, only an increased neutrophil count was independently associated with the presence of hypochoic plaques. Indeed, PAD patients showed a greater number of neutrophils than those with CAD (4.4 ± 1.0 vs 3.9 ± 1.2 10⁹/l, p = 0.03). Therefore, the finding that the prevalence of hypochoic carotid plaques was higher in PAD than in CAD patients was probably because, consistent with previous studies [58, 59], the PAD group had a more pronounced inflammatory profile than CAD patients. Similar findings were observed in a subsequent study [39] comparing CAD patients with a coexistent PAD vs those with CAD alone. Indeed, the leucocyte number was greater in CAD+PAD than in CAD alone, and when the leucocyte number higher than the median was included in multivariate analysis, it showed an association with hypochoic plaques (OR 6.70, 95% CI 2.13 to 21.10, p=0.008) [39]. These data are consistent with those of a previous study showing that in patients with acute myocardial infarction, the leucocyte number increase proportionally to the number of carotid plaques defined unstable on B-mode ultrasound [60].

Therefore, in patients with CAD, the coexistence of PAD entails not only a more severe CAD [58, 59, 14], but even a more severe carotid disease [39]. Conceivably, this is due to a more aggressive atherosclerosis, which however is only in part due to classic risk factors [58, 14]. Rather, it appears to be independently associated with inflammation. [61,62] What remains to be determined is whether and to what extent the high levels of inflammatory markers result from a primary “extravascular” activation of the acute phase response, or whether they originate from the site of the active plaques. The two mechanisms are not mutually exclusive. However, because inflamed plaques are common in femoral arteries [63, 64], and the peripheral vascular bed provides a large surface for the release of inflammatory molecules, it is intriguing to speculate that an inflammatory response generated in the affected limb of PAD patients could impair arterial vessels at distant sites. In actual fact, CAD + PAD who had, in the affected limb, a transfemoral gradient of interleukin-6 (IL-6) and myeloperoxidase (MPOX) greater than the median showed a more severe CAD than those with a lower local inflammatory status [58, 65]. Furthermore, serum from the claudicant limb of CAD+PAD patients induced a proinflammatory state in human coronary artery endothelial cells (HCAECs) in vitro. HCAECs released more MCP-1 when incubated with serum from healthy legs or the aorta of CAD-alone patients [58]. Therefore, it is reasonable to assume that, consequent to the presence of inflamed
plaques, the blood leaving the affected limb of PAD patients contains substances that affect the endothelial cells of the other vascular districts. Accordingly, we investigated whether hypoechoic, presumably inflamed, femoral plaques, entail a high risk of hypoechoic carotid plaques. Femoral and carotid plaques of 102 consecutive patients with peripheral artery disease (PAD) were studied echoically and classified as echoluent or echorich according to the GSM value, which was 53.6 for femoral and 55.2 for carotid plaques. Serum CRP and neutrophil count were also measured. Echoluent carotid plaques were more frequent in patients with echoluent than in those with echorich femoral plaques (55.8% vs 32.0%, p<0.01). Compared to patients with echorich femoral plaques, those with echoluent femoral plaques showed higher levels of both high-sensitivity CRP (2.0 [1.4-3.5] mg/L vs 3.6 [2.5-5.8] mg/L (p<0.01)) and neutrophil count (4.1 [2.9-4.9] x 10^3/µL vs 4.5 [3.9-5.4] x 10^3/µL (p=0.029)) [66]. At multivariate analysis, adjusted for age, sex, diabetes, active smoking, hypercholesterolemia, and hypertension, when hs-CRP and neutrophil count were added to the other covariates, only the latter was associated with echoluent carotid plaques (OR 5.71, 95% CI 1.37-23.85, p=0.017). Noteworthy, in this model the association between femoral and carotid echolucency was attenuated (OR 3.75, 95% CI 0.98-14.43, p=0.05) [66]. Thus, the higher prevalence of echoluent carotid plaques in patients with echoluent femoral plaques is likely consequent to the marked inflammatory profile of the latter. Therefore, it remains to be established whether the coexistence of echoluent plaques in the femoral and carotid arteries individuates a vulnerable patient or is consequent of the release of inflammatory molecules from the arterial bed of the affected limb.

On the other hand, high-risk plaque has been suggested to be a multivessel phenomenon [50, 65, 67, 68]. However, whichever of the two mechanisms is operating, there is need of future prospective studies to assess whether echoluent femoral plaque portents a higher risk of ischemic cerebral events, as compared to echorich femoral plaque [66].

4. PAD and stroke

Stroke is the second most common cause of death after ischemic heart disease, represents a major cause of disability, and accounts for more than 4% of direct health costs in industrialized countries [69]. PAD carries an increased stroke risk, which at least in the Northern Manhattan Study [70], appears to be less striking than myocardial infarction. Actually, patients with self-reported PAD showed a higher incidence of myocardial infarction vs those without PAD (p=0.003 at Log Rank Test), while no group difference was observed for ischemic stroke (p=0.604). In the Atherosclerosis Risk in Community (ARIC) Study [71], the strong association between PAD and stroke at univariate analysis was no longer significant after adjustment for major risk factors. Similarly, the CHS [18] reported that PAD was associated with 60% increased risk of stroke in those without previously diagnosed cardiovascular disease, but this association disappeared after adjustment for confounding factors. Also the Edinburgh Artery Study [15], after adjustment for age, did not show any association between PAD and risk of stroke. Different from what reported above, other studies testify that PAD and its severity show an incidence of ischemic stroke even greater than that observed in CAD. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study [24] showed that the occurrence of fatal and non fatal stroke at follow up in the PAD subgroup was double that in the myocardial infarction subgroup, in both the clopidogrel and aspirin arm. Furthermore, the Reduction of Atherothrombosis for Continued Health (REACH) Registry reported a greater 1-year stroke incidence in PAD patients with concomitant cerebrovascular disease than in patients with CAD and cerebrovascular disease [7].

With respect to the relationship between ABI and stroke risk, retrospective data from the National Health and Nutrition and Examination Survey [72] showed that more subjects with ABI ≤ 0.9 versus those with ABI > 0.9 had experienced a stroke (12.7% vs 5.4%, p<0.001). With the full ABI range, stroke presence rose with decreasing ABI, although, after adjustment for potential confounders, only ABI ≤ 0.9 and 0.9-0.99 remained significantly associated with the presence of stroke as compared with the reference group (ABI 1.1-1.29). Consistently, the Honolulu Heart program found a significant 2-fold increased risk of stroke in men with PAD among 2767 men aged 71 to 93 years during 3 to 6 years of follow-up [73]. The rate of fatal and non fatal stroke was 6% in men with PAD (ABI <0.9) compared with 2.9% in men without PAD [73]. After adjustment for other risk factors, the risk of total and thromboembolic stroke increased with declining ABI [73]. Therefore, studies on the relationship between PAD and stroke risk provide conflicting results. In any case, although PAD may not be predictor of stroke, it is a marker of disease and future events.

5. PAD, inflammation and stroke

Inflammation plays a role in the genesis of brain ischemia and inflammatory processes and may facilitate serious and life-threatening complication in stroke patients [74]. However, few is known about the association between inflammation and stroke in PAD patients. This because the large majority of studies investigating the relationship between inflammation and natural history of PAD included stroke in a composite of cardiovascular events.

Between 1996 and 2003, 384 patients with symptomatic PAD or symptomatic cerebrovascular disease or both were enrolled in National Institutes of Health-sponsored blinded prospective trial evaluating the effects of multiple atherosclerotic risk factors on progression of symptomatic PAD [75]. Baseline levels of CRP and D-dimer were obtained in 332 subjects. Results showed no relationship between the baseline levels of these inflammatory markers and stroke [75]. More recently, a prospective study including specifically patients with symptomatic PAD showed an increased incidence of stroke for each increasing quartile of CRP [76]. However no significant group difference was observed. On the contrary, inflammation has been found to predict the risk of first ischemic stroke in apparently healthy men [77], future is-
chimic stroke and TIA in the elderly [78] and fatal stroke in the elderly [79]. The importance of inflammation in stroke is highlighted by the finding that levels of inflammatory molecules are increased within 24 hours after the onset of stroke [80-82]. Sequential blood studies demonstrate significantly elevated CRP and white blood cell (WBC) counts even 3 months after the onset of stroke [83]. Furthermore, histopathologic studies report that neutrophil recruitment starts from the first day after stroke, comes to its peak within 2-3 days and disappears after 1 week. Macrophage infiltration starts about 3 days after symptom onset and lasts for several years or decades, in the region infarction [84,85].

**Conclusion**

Although during the last decade there have been great advances in our knowledge on the epidemiology and pathophysiology of carotid arteriopathy, little is known about the association between PAD and carotid artery disease. This review was conceived to cast some light on this topic, but many issues remain to be confirmed or clarified. In particular, more extensive studies are needed to ascertain whether the greater severity of carotid atherosclerosis in PAD vs CAD patients is only due to the more pronounced inflammatory profile of the formers.

Furthermore, it remains to be established whether, among PAD patients, a lower ABI portends a higher risk of stroke. Finally, it should be investigated the role of CRP and other inflammatory molecules as specific markers of stroke risk in PAD.

**Riassunto**

Benché il carattere polidistrettuale dell’aterosclerosi sia ben definito, pochi sono i dati a riguardo della specifica associazione tra arteriopatia periferica e malattia carotidea. Lo scopo di questo articolo è di riassumere i dati epidemiologici sulla coesistenza delle due malattie e di cercare di far luce su alcuni meccanismi fisiopatologici che favoriscono la loro associazione, con particolare attenzione per l’inflammazione che occupa un ruolo strategico nella malattia aterosclerotica. Un aspetto degno di attenzione è il fatto che la malattia carotidea si manifesti con più frequenza e con maggiore severità nei pazienti arteriopatici che in quelli affetti da cardiopatia ischemica.

Infatti, all’esame ecocolor Doppler, i pazienti con arteriopatia degli arti inferiori presentano una maggiore prevalenza di placche ipoecochee, che essendo caratterizzate da un elevato contenuto lipidico ed infiltrato di macrofagi, risultano instabili e quindi suscettibili alla formazione di trombi ed alla embolizzazione nel territorio vascolare cerebrale. Questo dato risulta associato in maniera indipendente ad elevati livelli sierici di leucociti e neutrofili, dimostrando negli arteriopatici un profilo inflammatory molto severo. Tale risultato potrebbe contribuire a spiegare il motivo per il quale i pazienti affetti da arteriopatia periferica presentino un più alto rischio di stroke rispetto a quelli portatori di malattia coronarica.

Parole chiave: arteriopatia obliterante degli arti inferiori, malattia carotidea, ictus cerebri, malattia polidistrettuale, inflammmazione.

**ABBREVIATION LIST**

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<tr>
<th><strong>Abbreviation</strong></th>
<th><strong>Description</strong></th>
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<tr>
<td>PAD</td>
<td>Peripheral Arterial Disease</td>
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<td>CVD</td>
<td>Cerebrovascular Disease</td>
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<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>ABI</td>
<td>Ankle Brachial Index</td>
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<td>IMT</td>
<td>Intimal Medial Thickness</td>
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<td>IC</td>
<td>Intermittent Claudication</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>GSM</td>
<td>Grey-Scale Median</td>
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<td>WBC</td>
<td>White Blood Cell</td>
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<td>CRP</td>
<td>C-Reactive Protein</td>
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<td>myeloperoxidase</td>
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<td>HCAECs</td>
<td>human coronary endothelial cells</td>
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<td>REACH</td>
<td>The REduction of Atherothrombosis for Continued Health</td>
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<td>CHS</td>
<td>Cardiovascular Health Study</td>
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<td>LEAD</td>
<td>Lower Extremity Arterial Disease</td>
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<td>BARI</td>
<td>Bypass Angioplasty Revascularization Investigation</td>
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<td>SMART</td>
<td>the Second Manifestation of ATRial disease</td>
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<td>ICARAS</td>
<td>Carotid Artery-Risk for Atherosclerosis Study</td>
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<td>NASCET</td>
<td>North American Symptomatic Carotid Endarterectomy Trial Collaborators</td>
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<td>ARIC</td>
<td>Atherosclerosis Risk in Community</td>
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<td>CAPRIE</td>
<td>The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events</td>
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