Atherogenic Dyslipidemia in Patients With Transient Ischemic Attack

Gaia Sirimarco, MD; Dominique Deplanque, MD, PhD; Philippa C. Lavallée, MD; Julien Labreuche, BS; Elena Meseguer, MD; Lucie Cabrejo, MD; Céline Guidoux, MD; Jean-Marc Olivot, MD, PhD; Halim Abboud, MD; Bertrand Lapergue, MD; Isabelle F. Klein, MD, PhD; Mikael Mazighi, MD, PhD; Pierre-Jean Touboul, MD; Eric Bruckert, MD; Pierre Amarenco, MD

Background and Purpose—There is mounting evidence that atherogenic dyslipidemia (ie, low high-density lipoprotein cholesterol combined with high triglyceride concentrations) is an independent predictor of high cardiovascular risk and possibly of stroke.

Methods—All patients included in the SOS-TIA cohort underwent an initial standardized evaluation, including medical history, physical examination, routine blood biochemistry, and diagnostic testing, and were followed for 1 year. Lipid profile was evaluated under fasting conditions. Atherogenic dyslipidemia was defined as high-density lipoprotein cholesterol blood concentration ≤40 mg/dL and triglycerides ≥150 mg/dL.

Results—Among 1471 consecutive patients with transient ischemic attack (TIA) or minor stroke, overall prevalence of atherogenic dyslipidemia was 5.8%, but varied from 4.6% to 11.1%, depending on final diagnosis (possible TIA or TIA with a cerebral ischemic lesion, respectively). Prevalence of atherogenic dyslipidemia was independently associated with male sex, diabetes, and body mass index, but not with ABCD2 score. Atherogenic dyslipidemia also strongly associated with symptomatic intracranial stenosis ≥50% (adjusted odds ratio, 2.77; 95% CI, 1.38–5.55), but not with symptomatic extracranial stenosis ≥50% (adjusted odds ratio, 1.20; 95% CI, 0.64–2.26). Despite appropriate secondary prevention treatment, 90-day stroke risk was greater in patients with versus without atherogenic dyslipidemia (4.8% versus 1.7%; P=0.04).

Conclusions—The atherogenic dyslipidemia phenotype in patients with TIA may be associated with intracranial artery stenosis and higher risk of early recurrent stroke. Additional data are needed to confirm these findings and to assess the best way to reduce important residual risk in such patients. (Stroke. 2011;42:2131-2137.)

Key Words: transient ischemic attack • atherogenic dyslipidemia • intracranial atherosclerosis

The risk of recurrent stroke following transient ischemic attack (TIA) is approximately 5% at 7 days and 10% to 15% at 90 days.1 Urgent assessment and combined use of preventive treatments in appropriate patients can reduce this risk significantly.2,3 However, despite best medical treatment, including antiplatelet drugs, statins, and blood pressure-lowering medications, there is a high residual risk of cardiovascular disease.4,5

One explanation may be that beyond low-density lipoprotein cholesterol (LDL-C), other factors such as high triglycerides, low high-density lipoprotein cholesterol (HDL-C), and elevated apolipoprotein B are also involved.6 Even though low HDL-C and high triglyceride concentrations have been separately discussed as possible independent predictors of cardiovascular disease,7-11 the combination of these 2 conditions, also called atherogenic dyslipidemia, may be even more deleterious.6 Such atherogenic dyslipidemia profile is particularly prevalent in patients with type 2 diabetes mellitus, obesity, metabolic syndrome, and/or established cardiovascular disease—a number of conditions associated with a high vascular risk.12-14 In contrast, in the Action in Control Cardiovascular Risk in Diabetes (ACCORD) study, in which fenofibrate or placebo on top of statin therapy was evaluated (a study that was negative overall), the subgroup analysis of

Received November 30, 2010; accepted March 1, 2011.
Ralph L. Sacco, MD, MS, was the Consulting Editor for this paper.
From the INSERM U-698 and Paris-Diderot University (G.S., D.D., P.C.L., J.L., E.M., L.C., C.G., J.-M.O., H.A., B.L., I.K., M.M., P.-J.T., P.A.), Department of Neurology and Stroke Centre, Bichat University Hospital, Paris, France; Department of Neurological Sciences (G.S.), Sapienza University of Rome, Rome, Italy; University Lille-North of France (D.D.), Department of Medical Pharmacology, Faculty of Medicine, Lille, France; Department of Endocrinology, Pitié-Salpêtrière University Hospital (E.B.), Pierre and Marie Curie University, Paris, France.
The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.609727/DC1.
Correspondence to Pierre Amarenco, MD, Department of Neurology and Stroke Centre, Bichat University Hospital, 46 rue Henri Huchard, 75018 Paris, France. E-mail pierre.amarenco@bch.aphp.fr

© 2011 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org
DOI: 10.1161/STROKEAHA.110.609727
individuals with both low HDL-C and high triglyceride concentrations suggested a possible benefit of adjunctive fenofibrate treatment. In a meta-analysis of fibrate trials, we have also shown a significant treatment by atherogenic dyslipidemia interaction, suggesting that this group of patients could be a target for effective fibrate therapy. Hence, as recently discussed, the presence of atherogenic dyslipidemia may contribute to residual cardiovascular disease risk, and the management of all atherogenic lipoproteins, in addition to lowering of LDL-C, may help reduce cardiovascular risk.

Because few data were available regarding the possible role of atherogenic dyslipidemia in stroke patients, the aim of the present study was to investigate the prevalence and clinical implication of atherogenic dyslipidemia phenotype (low HDL-C together with high triglycerides) in the SOS-TIA cohort (ie, patients at high risk of recurrent stroke).

Methods

Patients

Both the design of the SOS-TIA clinic and the initial results had been described in detail elsewhere. The present report concerns all patients admitted to the SOS-TIA clinic between January 2003 and December 2008 with a final vascular diagnosis of TIA or minor stroke. Briefly, SOS-TIA is a TIA clinic with round-the-clock (24-hour) access; it is located in a “day” hospital (also open at night), nested in a neurology department that also has a stroke unit. Primary care physicians (ie, general practitioners, cardiologists, neurologists, and ophthalmologists) and emergency department physicians in Paris and its administrative regions can contact the SOS-TIA clinic via a toll-free telephone number. Patients are admitted to the SOS-TIA clinic if the suspicion of TIA is confirmed by a trained nurse or vascular neurologist after a brief telephone interview. After triage based on etiologic work-up performed in fewer than 4 hours, patients are either discharged home from the day hospital or are then admitted to the stroke unit according to published criteria.

Data Collection

Each patient’s demographics, baseline characteristics, clinical information, examination findings, final vascular diagnosis, medications, and follow-up information were collected using a structured questionnaire. TIA was defined as an acute loss of focal cerebral or ocular neurological symptoms whose clinical and radiological features did not allow designation as definitive TIA were categorized as possible TIA. Patients with incomplete recovery were judged to have had a minor ischemic stroke regardless of brain imaging results. Neurologists in the outpatient clinic obtained follow-up information via telephone calls on the occurrence of any vascular events or death during face-to-face interviews or by research nurses. In all cases of a reported vascular event, medical records were obtained whenever possible. Adjudication of predefined end points (stroke, myocardial infarction, and vascular death) was validated by consensus between 2 neurologists (P.C.L. and P.A.).

Investigations

All patients had an initial standardized evaluation including medical history, physical examination, routine blood biochemistry, and diagnostic testing. Blood samples were collected in fasting conditions for evaluation of the lipid profile at admission, or during a second set of investigations before any change in lipid-lowering treatment. Brain imaging was performed immediately (either magnetic resonance imaging or a default computed tomography scan). Cervical duplex ultrasonography and transcranial Doppler were performed systematically and immediately by a fully trained senior vascular neurologist. Intracranial stenosis ≥50% or occlusion corresponding to clinical symptoms was considered symptomatic when confirmed by another method of cerebral vascular imaging (magnetic resonance angiography or computed tomographic angiography or high-resolution magnetic resonance imaging). Cardiac evaluation included a 12-lead electrocardiogram, and transesophageal echocardiography. Echocardiography was performed on the same day in cases where a high-risk cardiac source of embolism was clinically suspected, and later in other cases.

Atherogenic Dyslipidemia Subgroup

The atherogenic dyslipidemic subgroup was defined as patients with both high triglycerides and low HDL-C according to prespecified cutoff values. According to the lack of clear consensus and to results of a previous meta-analysis, these cutoffs were defined as triglycerides ≥150 mg/dL and HDL-C ≤40 mg/dL, regardless of patient’s sex.

Statistical Analysis

Data analysis was based on 1471 patients with diagnosis of TIA or minor stroke for whom both HDL-C and triglyceride measures were available. Bivariate comparisons were made using the chi-square tests (Fisher exact test was used when expected cell frequency was <5) for categorical variables and Student t-test for continuous variables. To assess the selection bias related to missing HDL-C and triglyceride data, clinical characteristics were compared between included and nonincluded TIA and minor stroke patients. We calculated the prevalence of individual and combined criteria for diagnosis of atherogenic dyslipidemia phenotype in the overall study sample and in each final vascular diagnosis. Among the overall study group, we studied the independent association of conventional vascular risk factors with atherogenic dyslipidemia phenotype using a stepwise logistic regression analysis with entry and removal values set to 0.10. ORs and their 95% CIs for the presence of significant atherosclerosis (overall and by arterial territory) associated with atherogenic dyslipidemia phenotype were calculated using logistic regression analysis adjusted on hypertension, LDL-C, and other risk factors associated with atherogenic dyslipidemia phenotype. Primary analyses were conducted using the combined criteria for diagnosis of atherogenic dyslipidemia phenotype; they were repeated using individual criteria. Finally, we estimated and compared the 90-day stroke risk and the 1-year composite outcome (stroke, myocardial infarction, vascular death) between patients with and without atherogenic dyslipidemia phenotype using the Kaplan-Meier method and the logrank test. Patients who died from causes other than stroke or vascular disease were censored at the time of death, depending on the outcome. Statistical testing was performed at the 2-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.1 (SAS Institute).

Role of the Funding Source

The sponsor had no role in the study design; in the collection, analysis, interpretation of data; writing of the report; or in the decision to submit the article for publication.

Results

Of 2398 patients admitted from January 2003 to December 2008 at the SOS-TIA clinic for suspected TIA, 1850 patients had a final vascular diagnosis of TIA (definite or possible) or minor ischemic stroke. Of them, 1471 patients with available fasting HDL-C and triglyceride measurements (80%) were included in the present study. Compared with the 379 excluded TIA or minor stroke patients, included patients were
younger and more likely to have neurological weakness (Supplemental Table S1, http://stroke.ahajournals.org).

Prevalence of Atherogenic Dyslipidemia
Table 1 reports the prevalence of individual and combined criteria of atherogenic dyslipidemia, overall and by final vascular diagnosis. Using prespecified definition of lipid profile abnormalities (HDL-C =40 mg/dL and triglycerides ≥150 mg/dL), 160 patients had low HDL-C (11%), 288 patients had high triglycerides (20%), and 85 patients had both low HDL-C and high triglycerides (6%). Regarding final vascular diagnosis, the higher prevalence of atherogenic dyslipidemia phenotype was found in definite TIA patients with an ischemic lesion detected on computed tomography scan or magnetic resonance imaging examination (Table 1).

Atherogenic Dyslipidaemia, Vascular Risk Factors, and Clinical Features
As shown in Table 2, atherogenic dyslipidemia phenotype was associated, in univariate analysis, with all conventional vascular risk factors, with the exception of age. To evaluate further the relationship between body mass index (BMI) and atherogenic dyslipidemia phenotype, we used the World Health Organization classification of BMI, and found a gradual increase in the prevalence of atherogenic dyslipidemia phenotype from 3% in patients not overweight (BMI

### Table 1. Prevalence of Atherogenic Dyslipidemia Subgroups, Overall and by Final Vascular Diagnosis

<table>
<thead>
<tr>
<th>Atherogenic Dyslipidemia</th>
<th>Overall (N=1471)</th>
<th>Definite TIA(+)</th>
<th>Definite TIA(−)</th>
<th>Possible TIA</th>
<th>Minor Ischemic Stroke (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Low HDL-C (&lt;40 mg/dL)</td>
<td>160</td>
<td>10.9</td>
<td>37</td>
<td>17.9</td>
<td>94</td>
</tr>
<tr>
<td>High triglycerides (&gt;150 mg/dL)</td>
<td>288</td>
<td>19.6</td>
<td>51</td>
<td>24.6</td>
<td>188</td>
</tr>
<tr>
<td>Low HDL-C and high triglycerides</td>
<td>85</td>
<td>5.8</td>
<td>23</td>
<td>11.1</td>
<td>47</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; HDL-C, high-density lipoprotein cholesterol.

*Transient ischemic attack with ischemic lesion on CT/MRI examination.
†TIA without ischemic lesion at CT/MRI examination; HDL-C, high-density lipoprotein cholesterol.
‡P for comparison between the four vascular diagnoses.
§P=0.017 for post-hoc comparison with definite TIAs(+).

Table 2. Patient Characteristics According to Atherogenic Dyslipidemia Phenotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (N=1386)</th>
<th>Yes (N=85)</th>
<th>Univariate P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y), mean±SD</td>
<td>63.8±15.6</td>
<td>62.6±14.2</td>
<td>0.48</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>723 (52.2)</td>
<td>65 (76.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean±SD</td>
<td>25.3±4.4</td>
<td>28.2±4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)†</td>
<td>916 (66.1)</td>
<td>66 (77.7)</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>139 (10.1)</td>
<td>21 (25.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)‡</td>
<td>596 (43.0)</td>
<td>45 (52.9)</td>
<td>0.073</td>
</tr>
<tr>
<td>Former or current smoker, n (%)</td>
<td>690 (52.1)</td>
<td>58 (71.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical feature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness, n (%)</td>
<td>553 (38.5)</td>
<td>44 (51.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>Speech disturbance, n (%)</td>
<td>529 (38.2)</td>
<td>35 (41.2)</td>
<td>0.58</td>
</tr>
<tr>
<td>Visual deficit, n (%)</td>
<td>395 (28.6)</td>
<td>17 (20.0)</td>
<td>0.088</td>
</tr>
<tr>
<td>Dual TIA, n (%)</td>
<td>272 (19.6)</td>
<td>20 (23.5)</td>
<td>0.38</td>
</tr>
<tr>
<td>TIA duration ≥60 min, n (%)</td>
<td>405 (30.1)</td>
<td>23 (27.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Lipid-lowering treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>319 (23.5)</td>
<td>24 (29.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Fibrate, n (%)</td>
<td>70 (5.2)</td>
<td>8 (9.8)</td>
<td>0.080</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; SD, standard deviation.

*Defined as high-density lipoprotein cholesterol ≤40 mg/dL and triglycerides ≥150 mg/dL.
†Defined as a history of treated hypertension or admission blood pressure values ≥140/90 mm Hg.
‡Defined as history of treated hypercholesterolemia or admission low-density lipoprotein cholesterol ≥160 mg/dL.
¶Defined as previous TIA ≥1 wk of the last symptom onset.
<25 kg/m²) to 13% in patients with class III obesity (BMI ≥40 kg/m²; P for trend <0.0001). In multivariate analysis, male sex (odds ratio [OR], 2.35; 95% CI, 1.33–4.16), BMI (OR per 1 SD increase, 1.56; 95% CI, 1.26–1.92), and diabetes (OR, 2.40; 95% CI, 1.34–4.31) remained significantly associated with atherogenic dyslipidemia phenotype; a borderline association was found with smoking (OR, 1.61; 95% CI, 0.94–2.76). Similar results were found in additional stepwise logistic regression analyses using individual criteria as dependent variables; the exception was with associations between high triglycerides and hypercholesterolemia, which also reached significance (data not shown).

Concerning TIA symptoms, we only found a higher proportion of neurological weakness in patients with atherogenic dyslipidemia phenotype. However, this difference disappeared after adjustment for vascular risk factors (P=0.15). Regarding ABCD2 score, 48% of patients (n=39) with atherogenic dyslipidemia phenotype had an ABCD2 score ≥4 compared with 43% of patients (n=566) without (P=0.33).

**Atherogenic Dyslipidaemia and Atherosclerosis Disease Feature**

As shown in Table 3, significant atherosclerotic disease was more frequently documented in patients with versus without the atherogenic dyslipidemia phenotype (51% versus 31%; P=0.0001). However, this difference disappeared after adjustment for hypertension, LDL-C, and other vascular risk factors associated with atherogenic dyslipidemia phenotype (adjusted OR, 1.58; 95% CI, 0.94–2.66). Among cerebral, coronary, and peripheral artery territories, the strongest between-group difference was found for cerebral artery territory, which remained significant in multivariate analysis (adjusted OR, 1.86; 95% CI, 1.08–3.20). When extracranial and intracranial arteries were considered separately, a specific relationship was found between atherogenic dyslipidemia phenotype and symptomatic intracranial atherosclerotic disease, with an adjusted OR of 2.77 (1.38–5.55). The adjusted OR for presence of symptomatic extracranial atherosclerotic disease was 1.20 (0.64–2.26). Regarding individual criteria, the same specific relationships with intracranial atherosclerotic disease were observed (Figure 1).

**Atherogenic Dyslipidemia and Risk of Recurrent Vascular Events**

After presentation at the TIA clinic, 98% of included TIA and minor stroke patients (n=1443) were followed for a median of 13 months (interquartile range 12–16). At 1-year follow-up, 39 strokes (27 within 90 days, 5 fatal), 6 myocardial infarctions (2 fatal), and 6 other vascular deaths had occurred. Nine nonvascular deaths and 3 deaths of unknown cause also occurred within 1 year of presentation.

Four strokes occurred within 90 days after admission in patients with atherogenic dyslipidemia phenotype, giving an estimated early risk of stroke of 4.8% compared with 1.7% (n=23) in patients without atherogenic dyslipidemia phenotype (logrank, P=0.04). Only 1 additional vascular event occurred within 1 year of follow-up in patients with atherogenic dyslipidemia phenotype, whereas 22 additional vascular events occurred in patients without atherogenic dyslipidemia phenotype (Figure 2). Clinical characteristics of patients with atherogenic dyslipidemia phenotype and vascular events during 1-year follow-up are available in Supplemental Table S2.

**Discussion**

In this large, consecutive series of patients with TIA or minor stroke, the prevalence of atherogenic dyslipidemia (triglycerides ≥150 mg/dL and HDL-C ≤40 mg/dL) was 6%. This prevalence was higher in patients with ischemic brain lesion (11%) as well as in patients with other metabolic diseases
such as class III obesity or diabetes mellitus (13% each). The atherogenic dyslipidemia phenotype was also associated with diffuse atherosclerosis and, strikingly, with symptomatic intracranial artery stenosis, and with an increase in early recurrent stroke.

To the best of our knowledge, the present study is the first to report the prevalence of atherogenic dyslipidemia in a population at high risk of stroke, ie, patients with a recent TIA. Prevalence varied from 4.6% to 11.1% according to the presence or absence of an acute ischemic brain lesion. Compared with other studies conducted in different population settings, the prevalence of atherogenic dyslipidemia was lower than was expected. Beyond the heterogeneity in cutoff values used to define such a disease, particular or associated factors in the different population sets may also explain the differences reported. The present results also confirm the particular place of other metabolic diseases. In past years, there has been speculation that the risk factor profile of the general population is deteriorating, in response to higher rates of obesity, diabetes, and a combination thereof. It could also be assumed that high concentrations of triglycerides, low concentrations of HDL-C and apolipoprotein A1, and small, dense LDL-C comprise a metabolic pattern that may be driven by insulin resistance, which ultimately leads to accelerated progression of atherosclerotic vascular disease.

In the present study, atherogenic dyslipidemia was associated with diffuse atherosclerosis. Nevertheless, patients may have a particular profile according to an association with intracranial artery stenosis. When adjusting for confounding factors, symptomatic intracranial atherosclerosis remained strongly associated with low HDL-C, high triglyceride, and the combination of both, whereas extracranial atherosclerosis was not. Another recent study also highlighted that intracranial arterial stenosis may be associated with lipid disorders. A number of other factors were already known to be associated with intracranial stenosis, such as hypertension, hypercholesterolemia, tobacco use, diabetes, black race, and male sex, which are for some also associated with atherogenic dyslipidemia. Mechanisms by which these risk factors contribute to the high risk of stroke in patients with intracranial stenosis still remain unclear. One explanation may be that the association of atherogenic dyslipidemia with a proinflammatory state and oxidative stress contribute to the residual vascular risk, particularly in patients with type 2 diabetes or metabolic syndrome. Nevertheless, it was not possible to measure specifically the weight of metabolic syndrome characteristics in the present study because waist-hip circumferences were not measured. Moreover, because French law does not permit recording of ethnicity in databases, the present study did not contain any information regarding race...
or ethnic identity that may also interfere with cervicocephalic atherosclerosis development. From a pathophysiological point of view, it may be that according to the characteristics of both adventitia and media of the intracranial arteries, small, dense LDL particles penetrate the arterial wall more easily and bind to proteoglycans, rendering the arteries more susceptible to oxidative modifications. Early diagnosis and effective treatment of lipid disorders, particularly of atherogenic dyslipidemia phenotype, may then help prevent the progression of intracranial atherosclerosis.

One of the last and most important findings of the present study was that TIA patients with atherogenic dyslipidemia phenotype had a higher risk of early recurrent stroke despite optimal diagnosis and treatment procedures. Taking into account limitations associated with low statistical power, it should be emphasized that most cases of recurrent stroke in atherogenic dyslipidemia population occurred within 10 days of TIA onset. Besides the possible deleterious impact of symptomatic intracranial artery stenosis, which is known to be associated with at least a 2-fold increase in the risk of early stroke recurrence, atherogenic dyslipidemia may also have its own deleterious effect as discussed above. This is consistent with recent meta-analysis of nicotinic acid trials which showed a significant stroke risk reduction. In terms of prediction, the ABCD2 score may be a good tool to discriminate TIA patients at high risk for early recurrence of stroke. Nevertheless, ABCD2 score values in the present study were similar, irrespective of the presence or absence of atherogenic dyslipidemia profile. However, the possible improvement achieved by including such variables needs to be tested in a larger TIA registry.

The strengths of our study include its prospective design, the systematic review of all patients by a vascular neurologist, and the low loss-to-follow-up rate. However, several limitations need to be considered. First, the SOS-TIA cohort was not formally population-based, because not all cases of TIA in the Paris area were recorded. However, the patients’ characteristics were similar to those of another population-based TIA cohort. Second, we could not exclude a selection bias because not all patients had a lipid-profile evaluation. Finally, there was limited statistical power for survival analysis. This was caused by a low event rate that was a consequence of fast access to clinic and management, as well as the short follow-up period. Additional larger studies with longer follow-up are needed to replicate these findings and to establish independent contribution of atherogenic dyslipidemia in residual risk.

In conclusion, the present study in consecutive patients treated in a TIA clinic suggests the deleterious role of atherogenic dyslipidemia on the risk of early stroke recurrence. Associated intracranial artery stenosis may be a key factor, but atherogenic dyslipidemia may also contribute independently to the risk of stroke recurrence. Because the risk of early stroke recurrence develops despite optimal medical management, atherogenic dyslipidemia identifies TIA patients with higher risk of recurrence, and targeting these patients in clinical trials evaluating compounds that increase HDL-C and decrease triglycerides may help reduce residual risk.

Acknowledgments
Sophie Rushton-Smith, PhD, provided editorial assistance on the final version of this manuscript, and was funded by SOS-ATTAQUE CEREBRALE.

Sources of Funding
This work was funded in part by SOS-ATTAQUE CEREBRALE (a not-for-profit patient and research association).

Disclosures
None.

References


Atherogenic Dyslipidemia in Patients With Transient Ischemic Attack
Gaia Sirimargo, Dominique Deplanque, Philippa C. Lavallée, Julien Labreuche, Elena Meseguer, Lucie Cabrejo, Céline Guidoux, Jean-Marc Olivot, Halim Abboud, Bertrand Lapergue, Isabelle F. Klein, Mikael Mazighi, Pierre-Jean Touboul, Eric Bruckert and Pierre Amarenco

Stroke. 2011;42:2131-2137; originally published online July 7, 2011;
doi: 10.1161/STROKEAHA.110.609727

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/8/2131

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/07/07/STROKEAHA.110.609727.DC1
http://stroke.ahajournals.org/content/suppl/2012/08/21/STROKEAHA.110.609727.DC2
http://stroke.ahajournals.org/content/suppl/2013/10/08/STROKEAHA.110.609727.DC3

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
**Supplemental Tables**

<table>
<thead>
<tr>
<th>Vascular risk factor</th>
<th>Included (n=1471)</th>
<th>Non-included* (n=379)</th>
<th>Univariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63·8±15·6</td>
<td>66·2±15·6</td>
<td>0·007</td>
</tr>
<tr>
<td>Male sex</td>
<td>788 (53·6)</td>
<td>186 (49·1)</td>
<td>0·12</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25·5±4·5</td>
<td>25-4±4·5</td>
<td>0·81</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>982 (66·8)</td>
<td>266 (70·4)</td>
<td>0·18</td>
</tr>
<tr>
<td>Diabetes</td>
<td>160 (10·9)</td>
<td>39 (10·5)</td>
<td>0·79</td>
</tr>
<tr>
<td>Hypercholesterolaemia‡</td>
<td>453 (31·3)</td>
<td>97 (26·7)</td>
<td>0·087</td>
</tr>
<tr>
<td>Former or current smoker</td>
<td>748 (53·2)</td>
<td>174 (47·9)</td>
<td>0·073</td>
</tr>
<tr>
<td>Clinical feature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>577 (39·3)</td>
<td>126 (33·3)</td>
<td>0·032</td>
</tr>
<tr>
<td>Speech disturbance</td>
<td>564 (38·3)</td>
<td>154 (40·7)</td>
<td>0·39</td>
</tr>
<tr>
<td>Visual deficit</td>
<td>412 (28·1)</td>
<td>113 (29·8)</td>
<td>0·51</td>
</tr>
<tr>
<td>Dual TIA#</td>
<td>292 (19·9)</td>
<td>76 (20·1)</td>
<td>0·93</td>
</tr>
<tr>
<td>TIA duration ≥60 min</td>
<td>471 (32·0)</td>
<td>116 (30·7)</td>
<td>0·83</td>
</tr>
<tr>
<td>Lipid lowering treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>343 (23·8)</td>
<td>76 (20·9)</td>
<td>0·24</td>
</tr>
<tr>
<td>Fibrate</td>
<td>78 (5·4)</td>
<td>12 (3·3)</td>
<td>0·098</td>
</tr>
</tbody>
</table>

Data are mean±SD or number (%). TIA, transient ischemic attack. *Patients with no high-density lipoprotein cholesterol and triglyceride measurements. †Defined as a history of treated hypertension or admission blood pressure values ≥140/90 mmHg. ‡Defined as history of treated hypercholesterolaemia or admission low-density lipoprotein cholesterol ≥160 mg/dL. #Defined as previous TIA ≤1 week of the last symptom onset.

**Supplemental Table 1**: Comparison of clinical characteristics of included and non-included patients with a definite or possible TIA or minor stroke.
<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>86</td>
<td>58</td>
<td>65</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>Sex</td>
<td>Men</td>
<td>Men</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24</td>
<td>32</td>
<td>23</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Smoking</td>
<td>Former</td>
<td>Former</td>
<td>Former</td>
<td>Never</td>
<td>Never</td>
</tr>
<tr>
<td>Prior vascular history</td>
<td>Stroke</td>
<td>MI</td>
<td>MI</td>
<td>No</td>
<td>MI</td>
</tr>
<tr>
<td>Admission LDL-C (mg/dL)</td>
<td>126</td>
<td>124</td>
<td>34</td>
<td>111</td>
<td>109</td>
</tr>
<tr>
<td>Admission HDL-C (mg/dL)</td>
<td>35</td>
<td>33</td>
<td>28</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Admission triglycerides (mg/dL)</td>
<td>181</td>
<td>254</td>
<td>165</td>
<td>150</td>
<td>167</td>
</tr>
<tr>
<td>ABCD² score</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Initial CT/MRI scan</td>
<td>Acute lesion</td>
<td>Acute lesion</td>
<td>Acute lesion</td>
<td>Acute lesion</td>
<td>Negative</td>
</tr>
<tr>
<td>Intracranial stenosis ≥50%</td>
<td>Symptomatic</td>
<td>No</td>
<td>No</td>
<td>Symptomatic</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Vascular recurrence</td>
<td>Stroke at 4 days. Died at 47 days</td>
<td>Stroke at 7 days</td>
<td>Stroke at 8 days</td>
<td>Stroke at 9 days. Died at 298 days</td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging.

**Supplemental table 2:** Main characteristics of patients with atherogenic dyslipidaemia phenotype and 1-year vascular recurrence.
一過性脳虚血発作患者におけるアテローム性脂質異常症

Atherogenic Dyslipidemia in Patients With Transient Ischemic Attack

Gaia Sirimarco, MD1,2; Dominique Deplanque, MD, PhD1,3; Philippa C. Lavallée, MD1; Julien Labreuche, BS1; Elena Meseguer, MD1; Lucie Cabrejo, MD1; Céline Guidoux, MD1; Jean-Marc Olivot, MD, PhD1; Halim Abboud, MD1; Bertrand Lapergue, MD1; Isabelle F. Klein, MD, PhD1; Mikael Mazighi, MD, PhD1; Pierre-Jean Touboul, MD1; Eric Bruckert, MD4; Pierre Amarenco, MD1

1 INSERM U-698 and Paris-Diderot University, Department of Neurology and Stroke Centre, Bichat University Hospital, Paris, France; 2 Department of Neurological Sciences, Sapienza University of Rome, Rome, Italy; 3 University Lille-North of France, Department of Medical Pharmacology, Faculty of Medicine, Lille, France; 4 Department of Endocrinology, Pitié-Salpêtrière University Hospital, Pierre and Marie Curie University, Paris, France

Abstract

一過性脳虚血発作（TIA）または脳卒中を初発症状とする成人患者（患者数1,471例）のアテローム性脂質異常症の有無を調査した。視力検査、血栓形成、血圧、血中脂質（HDL-C、LDL-C、TG）、動脈硬化度、全身冠動脈硬化をNHE-27の基準で評価した。結果：アテローム性脂質異常症の有無は、患者の生存率を異なると推定された。TIA患者の脳卒中再発リスクは、アテローム性脂質異常症の有無で異なる。
일과성혈혈발작 환자에서 죽종을 발생시키는 이상지질혈증

Atherogenic Dyslipidemia in Patients With Transient Ischemic Attack

Gaia Sirimarco, MD; Dominique Deplanque, MD, PhD; Philippa C. Lavallée, MD; Julien Labreuche, BS; Elena Meseguer, MD; Lucie Cabrejo, MD; Céline Guidoux, MD; Jean-Marc Olivot, MD, PhD; Halim Abboud, MD; Bertrand Lapergue, MD; Isabelle F. Klein, MD, PhD; Mikael Mazighi, MD, PhD; Pierre-Jean Touboul, MD; Eric Bruckert, MD; Pierre Amarenco, MD

(Stroke. 2011;42:2131-2137.)

Key Words: transient ischemic attack ■ atherogenic dyslipidemia ■ intracranial atherosclerosis

배경과 목적

죽종을 발생시키는 이상지질혈증(atherogenic dyslipidemia)은, 저고밀도지질단백질 콜레스테롤(low high-density lipoprotein cholesterol) 및 고중성지방(high triglyceride)이 심혈관질환(cardiovascular) 및 뇌졸중의 위험에 대한 독립적 예측인자라는 증거가 축적되고 있다.

방법

SOS-TIA 코호트에 포함된 모든 환자들이, 병력 청취, 신체 검진, 정규 혈액 검사 및 진단적 검사를 받았으며, 이를 1년 후 추적 관찰하였다. 지질 분석은 금식 후에 시행하였다. 죽종을 발생시키는 이성지질혈증은 고밀도지질단백질 콜레스테롤 농도 40 mg/dL 이하 및 중성지방 150 mg/dL 이상으로 정의하였다.

결과

일과성혈혈발작(transient ischemic attack, TIA) 혹은 경미한 뇌졸중을 보인 환자 1,471명 중, 죽종을 발생시키는 이성지질혈증의 유병률은 5.8%였으며, 최종 진단(잠재적인 TIA 혹은 허혈성 병변이 확인된 TIA)에 따라 4.6~11.1%를 보였다. 죽종을 발생시키는 이성지질혈증의 유병률은 남성, 당뇨병의 병력, 체질량지수와 독립적으로 연관되어 있었으나, ABCD2 점수와는 연관이 없었다. 죽종을 발생시키는 이성지질혈증은 또한 중상성 두개내 혈착 50% 이상과 강한 연관(보정 교차비, 2.77; 95% CI, 1.38~5.55)을 보였으나, 중상성 두개내 혈착 50% 이상과 관련되어 있지 않았다(보정 교차비, 1.20; 95% CI, 0.64~2.26). 적절한 이차 예방 치료에도 불구하고, 90일 뇌졸중 위험도는 죽종을 발생시키는 이성지질혈증을 가진 환자에서 더 높았다(4.8% vs. 1.7%; P=0.04).

결론

죽종을 발생시키는 이성지질혈증은 TIA 환자에서 두개내동맥 혈착(intracranial artery stenosis) 및 높은 경미한 뇌졸중 재발과 연관되어 있었다. 이러한 환자에서 뇌졸중 위험을 더 낮출 수 있는 최선의 전략을 찾기 위하여 추가적인 데이터가 필요하다.
Table 1. Prevalence of Atherogenic Dyslipidemia Subgroups, Overall and by Final Vascular Diagnosis

<table>
<thead>
<tr>
<th>Atherogenic Dyslipidemia</th>
<th>Overall (N=1471)</th>
<th>Definite TIA(+)† (N=207)</th>
<th>Definite TIA(−)† (N=966)</th>
<th>Possible TIA (N=220)</th>
<th>Minor Ischemic Stroke (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low HDL-C (≤40 mg/dL)</td>
<td>160</td>
<td>10.9</td>
<td>37</td>
<td>17.9</td>
<td>9.7§</td>
</tr>
<tr>
<td>High triglycerides (≥150 mg/dL)</td>
<td>288</td>
<td>19.6</td>
<td>51</td>
<td>24.6</td>
<td>18.8</td>
</tr>
<tr>
<td>Low HDL-C and high triglycerides</td>
<td>85</td>
<td>5.8</td>
<td>23</td>
<td>11.1</td>
<td>4.9§</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; HDL-C, high-density lipoprotein cholesterol. *Transient ischemic attack with ischemic lesion on CT/MRI examination. †TIA without ischemic lesion at CT/MRI examination; HDL-C, high-density lipoprotein cholesterol. §P for comparison between the four vascular diagnoses. §P<0.017 for post-hoc comparison with definite TIAs(†).

**Figure 1.** Association of extracranial and intracranial atherosclerosis and atherogenic dyslipidemia. Prevalence of atherosclerotic disease and univariate probability values for comparison between atherogenic dyslipidemia subgroups (*) are reported. Odds ratios for atherosclerotic disease adjusted for sex, hypertension, body mass index, diabetes, low-density lipoprotein cholesterol (LDL-C), and smoking are plotted. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; TGs, triglycerides.