Carotid Intima-Media Thickness, Plaques, and Framingham Risk Score as Independent Determinants of Stroke Risk

Pierre-Jean Touboul, MD; Julien Labreuche, BS; Eric Vicaut, MD, PhD; Pierre Amarenco, MD; on behalf of the GENIC Investigators*

Background and Purpose—The Framingham stroke risk score (FSRS) and Framingham cardiovascular risk score (FCRS) estimate the individual absolute cardiovascular and stroke risks. Common carotid artery intima-media thickness (CCA-IMT) and carotid plaques (CPs) are markers of subclinical atherosclerosis and help in the early identification of presymptomatic individuals. The purpose of this study was to correlate Framingham risk score (FRS) with CCA-IMT and CPs and evaluate their respective contribution to stroke risk.

Methods—In 510 consecutive patients with brain infarction and 510 matched controls, we calculated the FSRS and FCRS for each individual and performed carotid ultrasonography. Mean CCA-IMT was measured off-line at a central core laboratory, and presence of CPs was assessed.

Results—FRS progressively increased according to tertiles of CCA-IMT (P for trend <0.0001). The part of the variances of FSRS and FCRS explained by CCA-IMT was respectively 11% and 20%. The relationships between CCA-IMT and FRS were significantly different between patients with or without CPs (P for interaction <0.005). With increasing CCA-IMT, the 10-year FRS gradually increased between 10% and 20% in the presence of CPs and between 5% and 20% in the absence of CPs. Multiple conditional logistic regression for matched sets showed that CCA-IMT, FCRS, and CPs were independently associated with stroke risk, with an odds ratio of 1.68 (1.25 to 2.26; P=0.0006), 2.16 (1.57 to 2.98; P<0.0001), and 2.73 (1.68 to 4.44; P<0.0001), respectively, meaning that each of them may be important for evaluation of the individual cardiovascular risk.

Conclusions—CCA-IMT, CPs, and FRSSs correlated well. The CCA-IMT value may help discriminate between subjects at low or high 10-year risk. (Stroke. 2005;36:1741-1745.)

Key Words: atherosclerosis ▼ intima-media thickness ▼ carotid artery plaque ▼ cerebrovascular disorders

Estimation of the individual 10-year absolute cardiovascular risk is currently based either on counting the number of risk factors or on calculating scores such as the Framingham scores.1,2 These approaches are limited by their number of risk factors or on calculating scores such as the Framingham scores.1,2 These approaches are limited by their number of risk factors or on calculating scores such as the Framingham scores.1,2 These approaches are limited by their number of risk factors or on calculating scores such as the Framingham scores.1,2 These approaches are limited by their number of risk factors or on calculating scores such as the Framingham scores.1,2 These approaches are limited by their number of risk factors or on calculating scores such as the Framingham scores.1,2 These approaches are limited by their number of risk factors or on calculating scores such as the Framingham scores.1,2 These approaches are limited by their number of risk factors or on calculating scores such 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such as the Framingham scores.1,2 These approaches are limited by their number of risk factors or on calculating scores such as the Framingham scores.

Other approaches exist to estimate the risk of an individual. Common carotid artery intima-media thickness (CCA-IMT) represents a marker for subclinical atherosclerosis and an opportunity for early detection of presymptomatic individuals.5–8 CCA-IMT has been associated with all modifiable (eg, blood pressure, blood cholesterol, smoking, diabetes, and obesity) and nonmodifiable risk factors (including age, gender, genes, and currently unknown risk factors).9 with all ischemic stroke subtypes,10 with occurrence of future carotid plaque (CP),11 and with a high risk of incident myocardial infarction, stroke, and vascular death.12,13 Therapeutic interventions with blood pressure–lowering agents,14,15 lipid-lowering agents,16,17 as well as multifactorial interventions in diabetics18 can slow the progression of or even reduce carotid IMT. Carotid IMT has been recognized recently as a surrogate marker by which to evaluate therapeutic interventions in atherosclerotic disease. However, the association between the FRS and CCA-IMT has not yet been evaluated in relation to incident strokes. Because risk factor history, CCA-IMT, and CPs are unlikely to be modified by a stroke event, we used the GENIC cohort to examine the relationships between FRS and carotid atherosclerosis (ie, mean CCA-IMT and presence of CPs). We also compared stroke risk according to FRS, mean CCA-IMT, and CPs.

Methods
The design of the GENIC study has been reported previously.10,19 The research protocol was approved by the ethics committee of
Cochin Hospital in Paris, and all subjects signed an informed consent form. A total of 510 patients with brain infarct (BI) proven by MRI were recruited consecutively in 12 French neurological centers together with 510 age-, sex-, and center-matched controls. Cases were included in the week interval after the event.

Data Collection and Risk Factor Definition
Information on demographic characteristics and risk factors was collected using a structured questionnaire. Blood pressure was measured in a sitting position, and hypertension treatment at admission was recorded. Smoking history was coded as never, previous, or current. Current smokers were those who still smoked or who had stopped smoking <6 months before the qualifying stroke. Subjects were classified as diabetic when treated for insulin-dependent or noninsulin-dependent diabetes. Blood was drawn in the morning from fasting subjects for the blood cell count and for lipid profile determination in a central laboratory. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. Use of lipid-lowering drugs was assessed. History of myocardial infarction, angina pectoris, coronary artery bypass surgery, or lower-limb arterial disease was recorded; a positive cardiovascular history was defined as the presence of any of these diseases. History of stroke or transient ischemic attacks was obtained in the cases. History of atrial fibrillation was noted, and an ECG was required to diagnose previously unknown atrial fibrillation.

FRS Calculation
Framingham stroke risk score (FRS) and the Framingham cardiovascular risk score (FCRS) were calculated according to D’Agostino et al and Wilson et al. The risk factors included in the Framingham calculation of 10-year stroke risk are age, systolic blood pressure, treatment for hypertension, diabetes mellitus, cigarette smoking, history of cardiovascular disease, history of atrial fibrillation, and left ventricular hypertrophy. The risk factors included in the Framingham calculation of 10-year cardiovascular risk are age, LDL cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, diabetes, and cigarette smoking.

Carotid Ultrasonography Studies
Carotid ultrasonography studies were performed on all stroke patients; details of the method have been reported previously. Examination included measurement of the CCA-IMT in a region free of plaque and assessed the presence of CPs. Plaque was defined as a localized echostructure that encroached into the vessel >1 mm beyond the interface between lumen and intima (it was 10 years before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment20). All centers were trained and certified before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment.20 All centers were trained and certified before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment.20 All centers were trained and certified before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment.20 All centers were trained and certified before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment.20 All centers were trained and certified before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment.20 All centers were trained and certified before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment.20 All centers were trained and certified before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment.20 All centers were trained and certified before the 2004 Mannheim consensus on the definition of carotid IMT and plaque, which has chosen the cut-off of 0.5 mm for the encroachment.20

Statistical Analysis
FSRS was determined for 373 cases and 346 controls aged 54 to 85 years who had complete information on risk factors, CCA-IMT, and CP assessments. FCRS was determined for 324 cases and 310 controls aged 30 to 74 years who had complete information on risk factors, CCA-IMT, and CP assessments. General characteristics are given for both study samples, separately in cases and controls.

Scores were log-transformed to reduce skewness; geometric means were therefore calculated. We used 2-way ANOVA to examine whether the relationship between scores and CCA-IMT divided according to tertiles and whether the relationship of scores to CP was modified according to case/control status. Because the relationships between scores, CCA-IMT, and CPs were similar in cases and controls, results were presented in cases and controls combined. Multiple linear regressions of Framingham scores were performed by including in the models CCA-IMT as a continuous variable and CPs. Interaction terms were introduced in the models to test whether the relationship between Framingham scores and CCA-IMT was modified by the presence of CPs.

Conditional logistic regression for matched sets was used to study the relationships between BI and scores, CCA-IMT, and CPs. Analyses including FSRs were based on 304 matched pairs of cases and controls and analyses including FCRS on 254 pairs. In univariate analysis, the relative risk of BI associated with tertiles of FRS, CCA-IMT, and CPs was estimated by calculation of the odds ratios (ORs) and 95% CIs. Because we found that ORs for BI increased regularly with increasing Framingham scores and CCA-IMT, we also computed the OR associated with an increase of 1 SD in Framingham scores and CCA-IMT in univariate and multivariate analysis.

Because the 2 Framingham scores were developed for first incident stroke and myocardial infarction, sensitivity analysis was performed on matched pairs of cases and controls free of cardiovascular and cerebrovascular history.

Statistical testing was done at the 2-tailed α-level of 0.05. Data were analyzed using the SAS package (version 8.2; SAS Institute Inc).

Results
Table 1 describes the general characteristics of study subjects according to case/control status. Cases had a higher prevalence of cerebrovascular risk factors and reported a previous cardiovascular history more frequently than controls.

Relationships Between FRSs, CCA-IMT, and CPs
As shown in Figure 1, there was a progressive increase in FCRS and FSRs according to tertiles of CCA-IMT (P for trend <0.0001). The increase in Framingham risk with CCA-IMT was not significantly different between cases and controls (P for interaction >0.20 for both Framingham scores). CCA-IMT explained 20% and 11% of the variance in the FCRS and FSRs, respectively. We found a higher Framingham risk in patients with CPs (FCRS and FSRs, 20% and 16%, respectively, versus 12% and 10% without plaque; P<0.0001). As shown by the multivariate analysis presented in Table 2, CCA-IMT and the presence of CPs appeared to be independently related to FCRS and FSRs. Altogether, CCA-IMT and the presence of CPs explained 24% of the variance in the FCRS and 18% of the variances in the FSRs. Small changes in regression parameters were found after adjustment for case/control status and cardiovascular and cerebrovascular history (Table 2).

We observed that the relationships between CCA-IMT and Framingham risk were significantly different between patients with or without CPs (Figure 2; P for interaction <0.005). The slopes±SE were lower in patients with CPs (1.24±0.23 for FCRS and 1.07±0.23 for FSRs) than in patients without CPs (2.77±0.31 for FCRS and 2.17±0.30 for FSRs). Patients with CPs had a high 10-year FCRS ranging from 10% to >20%; interestingly, if one adds the presence of CPs and the highest values of CCA-IMT, these patients have a 10-year coronary heart disease risk equivalent to 20%. For patients without CPs, the 10-year FCRS increased gradually from 5% to 20% according to CCA-IMT, with a 10-year FCS above 10% for CCA-IMT >0.75 and a coronary heart disease risk equivalent to the highest values of CCA-IMT.

Relationships Between BI, FRS, CCA-IMT, and CPs
As shown in Figure 3, the ORs of BI increased gradually with tertiles of FCRS and CCA-IMT. FCRS, CCA-IMT, and CPs
were independently associated with BI (Table 3). It can be calculated that the increase in OR attributable to presence of CPs (OR, 2.73) is similar to the 15.8% increase in the FCRS or to the 0.297-mm increase in CCA-IMT. Sensitivity analyses restricted to 155 matched pairs free of previous cardiovascular or cerebrovascular history gave similar results (Table 3).

Analogous conclusions can be made when analyzing FSRS. In univariate analysis, all ORs were significantly /H11022 1.00 (P/H11021 0.0001). In multivariate analysis, CCA-IMT, FSRS, and CPs were independently associated with BI (OR, 1.94 and 95% CI, 1.46 to 2.58 for 1 SD of FSRS; OR, 1.42 and 95% CI, 1.13 to 1.77 for 1 SD of CCA-IMT; OR, 2.91 and 95% CI, 1.89 to 4.47 for presence of CPs). Sensitivity analyses restricted to 157 matched pairs free of previous cardiovascular or cerebrovascular history gave similar results (FSRS OR, 2.35; CCA-IMT OR, 1.41; CP OR, 3.24; P/H11021 0.04).

Discussion

The Framingham risk scoring system is currently the recommended approach to evaluate the 10-year absolute stroke and cardiovascular risk. However, it overestimated the risk in the INSIGHT trial, and in the placebo group of the ASCOT-LLA trial, the actual risk was far below that expected by Framingham risk calculation, even after taking into account the fact that the best medical care also decreased the risk in this group.4,21 Although the Framingham scores can be recalibrated to take into account a lower risk in European countries than in the Framingham cohort,3 this calculation may not be precise enough for individuals. Another approach would be to evaluate the correlation between the Framingham risk and a standard measure such as mean IMT of the CCA or the presence of CPs.

In this study, we found a good correlation between FSRS and FRCS and mean CCA-IMT. However, there was a large dispersion of the individual risk score distribution in each tertile of CCA-IMT, and the correlation coefficient, although highly significant, was rather low (Figure 1). This indicates that Framingham risk and CCA-IMT may not mirror exactly the same component of the absolute stroke and cardiovascular risks. This is in agreement with all studies showing that IMT is a marker of cardiovascular risk, independently of modifiable and nonmodifiable cardiovascular risk factors.10,12 When

### Table 1. General Characteristics of Study Subjects According to Case/Control Status

<table>
<thead>
<tr>
<th>Subjects Included in Analyses of FSRS</th>
<th>Subjects Included in Analyses of FCRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n=373)</td>
<td>Controls (n=346)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>71 (8)</td>
</tr>
<tr>
<td>Male sex, % (no.)</td>
<td>62.4 (229)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>25.3 (4.2)</td>
</tr>
<tr>
<td>History of hypertension, % (no.)</td>
<td>56.6 (211)</td>
</tr>
<tr>
<td>History of diabetes, % (no.)</td>
<td>18.8 (70)</td>
</tr>
<tr>
<td>Current smokers, % (no.)</td>
<td>23.1 (86)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL, mean (SD)</td>
<td>200 (42)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL, mean (SD)</td>
<td>125 (34)</td>
</tr>
<tr>
<td>Cardiovascular history, % (no.)</td>
<td>23.1 (86)</td>
</tr>
<tr>
<td>Stroke history, % (no.)</td>
<td>23.3 (87)</td>
</tr>
<tr>
<td>CCA-IMT, mm, mean (SD)</td>
<td>0.830 (0.142)</td>
</tr>
<tr>
<td>Carotid plaques, % (no.)</td>
<td>74.3 (277)</td>
</tr>
</tbody>
</table>

χ² analysis and Student t test were used to compare proportions and continuous variables, respectively.

†P<0.001; ‡P<0.05

### Table 2. Multiple Linear Regression of FRS (After Log-Transformation) on CCA-IMT and Carotid Plaques

<table>
<thead>
<tr>
<th>Regression Coefficient (95% CI)</th>
<th>Standardized Regression Coefficient</th>
<th>P</th>
<th>Standardized Regression Coefficient*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA-IMT</td>
<td>1.93 (1.55–2.30)</td>
<td>0.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>0.34 (0.22–0.45)</td>
<td>0.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FSRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA-IMT</td>
<td>1.43 (1.07–1.79)</td>
<td>0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>0.42 (0.31–0.52)</td>
<td>0.27</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted on case/control status and cardiovascular and cerebrovascular history.
the cohort was divided according to the presence of CPs, we found that subjects with plaques had a 10-year Framingham risk, which gradually increased from 10% to >20% according to CCA-IMT values, meaning that inclusion of these 2 variables (presence of plaques and CCA-IMT value) provides a complementary evaluation of 10-year Framingham risk compared with CCA-IMT or CPs alone (Figure 2). For patients without CP, the 10-year Framingham risk gradually increased from 5% to almost 20% with CCA-IMT values, highlighting the potential importance of CCA-IMT to discriminate between patients at high and low 10-year risk (ie, patients at intermediate risk). In patients without CPs, a mean CCA-IMT <0.75 mm was associated with a low 10-year Framingham risk, whereas a mean CCA-IMT >0.75 mm was associated with a high 10-year Framingham risk >10%. This is consistent with the finding in the Etude du Vieillissement Arteriel (EVA) Study that thick IMT is a strong predictor for future occurrence of a new plaque,11 (ie, that it could be viewed as a “stroke risk equivalent”). Future interventional study should aim at evaluating prevention of plaque occurrence in patients with thick CCA-IMT.

Finally, to explore which of the 3 parameters among FRS/FCRS, mean CCA-IMT, and CPs best predicts the risk of stroke and cardiovascular events, we performed a multiple conditional logistic regression for matched sets and found that each parameter was associated independently with the risk of stroke (Table 3). Even keeping in mind the limitations of case/control studies, which are less robust than prospective studies, the present results strongly suggest that each of these parameters explained one part of the risk, and that these 3 approaches may be not redundant but synergistic for evaluation of the individual absolute risk.

Another limitation of our study was its case/control design, which brings in numerous issues related to prevalence/incidence bias. The risk equations, developed as they were to predict incident events, would also predict incident fatal events, which were included in this study, but stroke deaths before admission to the hospital have not been captured. These events are better evaluated in a prospective study.

In the British Regional Heart Study, measurements of IMT were performed on the CCA and the carotid bifurcation.13 The authors found that both measures were correlated to the presence of plaques. However, they identified 2 different patterns. CCA-IMT was strongly associated with risk factors for stroke and with prevalent stroke, whereas IMT measured at the bifurcation, and plaques were more directly associated with ischemic heart disease risk factors and prevalent ischemic heart disease.13 Cross-sectional and prospective epidemiologic studies of carotid atherosclerosis showed that increased IMT was the first change to appear before plaque occurrence.22 To prevent plaque occurrence and its resultant high absolute cardiovascular and stroke risk status, increased IMT in the absence of plaque may represent a way to detect and target intermediate-risk populations in which prevention could be more efficient. Prospective interventional studies looking at these different stages of carotid atherosclerosis and clinical events are needed to explore such a hypothesis.

**Figure 2.** Relationship between FRS and CCA-IMT according to CP status. Predictive values for FCRS (left panel) and FSRS (right panel) were plotted.

**Figure 3.** OR of BI associated with tertiles of FCRS, CCA-IMT, and CPs

**TABLE 3.** Associations Between BI and FCRS, CCA-IMT and Carotid Plaques

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)*</th>
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<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
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<tr>
<td>FCRS</td>
<td>2.46 (1.83–3.29)†</td>
<td>&lt;0.0001</td>
<td>2.31 (1.58–3.37)†</td>
</tr>
<tr>
<td>CCA-IMT</td>
<td>2.05 (1.57–2.66)‡</td>
<td>&lt;0.0001</td>
<td>2.10 (1.49–2.94)‡</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>3.49 (2.25–5.43)</td>
<td>&lt;0.0001</td>
<td>3.37 (1.95–5.83)</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCRS</td>
<td>2.16 (1.57–2.98)†</td>
<td>&lt;0.0001</td>
<td>1.98 (1.31–2.98)†</td>
</tr>
<tr>
<td>CCA-IMT</td>
<td>1.68 (1.25–2.26)‡</td>
<td>0.0006</td>
<td>1.76 (1.20–2.58)‡</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>2.73 (1.68–4.44)</td>
<td>&lt;0.0001</td>
<td>2.67 (1.47–4.86)</td>
</tr>
</tbody>
</table>

ORs were computed using conditional logistic regression for matched sets.

*In cases and matched controls free of cardiovascular and cerebrovascular history (n=150); †OR per 1 SD increase of FCRS (12.1%); ‡OR per 1 SD increase of CCA-IMT (0.153 mm).
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References
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