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 FRSs correlated well. The CCA-IMT value may help discriminate between subjects at low or high 10-year risk. (Stoke. 2005;36:1741-1745.)

Key Words: atherosclerosis ■ intima-media thickness ■ carotid artery plaque ■ cerebrovascular disorders
The relationships between BI and scores, CCA-IMT, and CPs were studied by Conditional logistic regression for matched sets. Analyses using FCRS were based on 304 matched pairs of cases and controls and analyses using FSRS 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 FCRS 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 \( P<0.0001 \). 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; \( P<0.001 \);

**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. Although the Framingham scores can be recalibrated to take into account a lower risk in European countries, 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.

![Figure 1. Geometric means of FCRS (left panel) and FSRS (right panel) by tertiles of CCA-IMT. Upper bounds of 95% CI are indicated.](image_url)

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

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficient (95% CI)</th>
<th>Standardized Regression Coefficient</th>
<th>( P )</th>
<th>Standardized Regression Coefficient*</th>
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<tr>
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<tr>
<td><strong>FCRS</strong></td>
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<tr>
<td>CCA-IMT</td>
<td>1.93 (1.55–2.30)</td>
<td>0.37</td>
<td>&lt;0.0001</td>
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<td>Carotid plaques</td>
<td>0.34 (0.22–0.45)</td>
<td>0.21</td>
<td>&lt;0.0001</td>
<td>0.19</td>
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<tr>
<td><strong>FSRS</strong></td>
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<tr>
<td>CCA-IMT</td>
<td>1.43 (1.07–1.79)</td>
<td>0.27</td>
<td>&lt;0.0001</td>
<td>0.23</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>0.42 (0.31–0.52)</td>
<td>0.27</td>
<td>&lt;0.0001</td>
<td>0.21</td>
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*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 FSRS/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.
Acknowledgments

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References

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