Cerebral Small Vessel Disease MRI Features Do Not Improve the Prediction of Stroke Outcome

Juliette Coutureau, MD, Julien Asselineau, MSc, Paul Perez, MD, PhD, Gregory Kuchcinski, MD, Sharmila Sagnier, MD, PhD, Pauline Renou, MD, Fanny Munsch, PhD, Renaud Lopes, PhD, Hilde Henon, MD, Regis Bordet, MD, PhD, Vincent Dousset, MD, PhD, Igor Sibon, MD, PhD, and Thomas Tourdias, MD, PhD

Neurology® 2021;96:e527-e537. doi:10.1212/WNL.0000000000011208

Abstract

Objective
To determine whether the total small vessel disease (SVD) score adds information to the prediction of stroke outcome compared to validated predictors, we tested different predictive models of outcome in patients with stroke.

Methods
White matter hyperintensity, lacunes, perivascular spaces, microbleeds, and atrophy were quantified in 2 prospective datasets of 428 and 197 patients with first-ever stroke, using MRI collected 24 to 72 hours after stroke onset. Functional, cognitive, and psychological status were assessed at the 3- to 6-month follow-up. The predictive accuracy (in terms of calibration and discrimination) of age, baseline NIH Stroke Scale score (NIHSS), and infarct volume was quantified (model 1) on dataset 1, the total SVD score was added (model 2), and the improvement in predictive accuracy was evaluated. These 2 models were also developed in dataset 2 for replication. Finally, in model 3, the MRI features of cerebral SVD were included rather than the total SVD score.

Results
Model 1 showed excellent performance for discriminating poor vs good functional outcomes (area under the curve [AUC] 0.915), and fair performance for identifying cognitively impaired and depressed patients (AUCs 0.750 and 0.688, respectively). A higher SVD score was associated with a poorer outcome (odds ratio 1.30 [1.07–1.58], \(p = 0.0090\) at best for functional outcome). However, adding the total SVD score (model 2) or individual MRI features (model 3) did not improve the prediction over model 1. Results for dataset 2 were similar.

Conclusions
Cerebral SVD was independently associated with functional, cognitive, and psychological outcomes, but had no clinically relevant added value to predict the individual outcomes of patients when compared to the usual predictors, such as age and baseline NIHSS.
The number of survivors living with the consequences of stroke is increasing worldwide.1 Rapidly predicting outcome following stroke is crucial to the management of these patients.2 Increasing attention, in this regard, has been given to cerebral small vessel disease (SVD),3 as it could affect outcome by disrupting network and neuronal plasticity capabilities.4 The total SVD score5,6 has become increasingly used as a convenient way to assess the global burden of cerebral SVD through a neuroimaging evaluation of white matter hyperintensity (WMH), lacunes, perivascular spaces (PVS), and cerebral microbleeds (CMBs). Despite the finding that cerebral SVD has been shown to be associated with clinical outcome,7–16 whether it actually adds information to the prediction of stroke outcome is unknown. Major methodologic considerations are that (1) associations measured in terms of odds ratios (ORs) do not necessarily imply that the markers will be able to distinguish patients with different outcomes accurately17 and (2) markers should be evaluated for their incremental value on top of the already known predictors.2,18

We quantified the prognostic value of cerebral SVD in terms of functional, cognitive, and psychological outcomes after stroke. We first developed prognostic models based on already known predictors,2 including age, initial severity, and infarct volume in a prospective longitudinal cohort. Then, the potential added value of cerebral SVD19 was assessed and models were compared in terms of calibration and discrimination. Some analyses were replicated on an external cohort for generalizability.

Methods

Study Populations

The first dataset (dataset 1) included patients from the “brain before stroke” cohort. The study recruited 428 patients, prospectively and consecutively, who presented for suspected ischemic stroke at the University Hospital of Bordeaux, France, from June 2012 to February 2015. Primary inclusion criteria were men and women >18 years of age with a clinical diagnosis of minor to severe supratentorial cerebral infarct (NIH Stroke Scale [NIHSS] score 1–25). Exclusion criteria were history of symptomatic cerebral infarct with functional deficit (prestroke modified Rankin Scale [mRS] score ≥1), infratentorial stroke or no stroke on research MRI performed between 24 and 72 hours after stroke onset, history of severe cognitive impairment (dementia) or psychiatric disorder, coma, pregnancy, and contraindications to MRI.

A second independent dataset (dataset 2) was used for generalizability and included 197 patients from the Strokdem cohort, who were recruited prospectively at the University Hospital of Lille, France, with similar inclusion criteria.

Clinical Assessment

Demographic data, vascular risk factors, treatments, and the NIHSS score were recorded between 24 and 72 hours after stroke onset (baseline evaluation). Level of education and pre-cognitive state were also recorded using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), which was completed by the patient’s relative at the time of admission.

In dataset 1, all patients underwent a standardized battery of clinical testing at the 3-month follow-up that included the mRS25 score to assess functional outcome, the Montreal Cognitive Assessment (MoCA)26 to assess cognitive outcome, and the Hospital Anxiety and Depression Scale (HADS)27 to assess psychological outcome. In dataset 2, follow-up was performed at 6 months with the same clinical tests, except for the presence of depression, which was assessed by the Center for Epidemiologic Studies–Depression score.

Brain MRI Acquisition and Analyses

Acquisition

Standardized MRI examinations were performed between 24 and 72 hours after stroke onset on a 3T scanner (Discovery MR 750w, GE Healthcare, Milwaukee, WI) for dataset 1 and on a 3T scanner (Achieva, Philips, Best, the Netherlands) for dataset 2. Imaging protocols included, among others, diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR), gradient echo T2*-weighted imaging (T2*WI), susceptibility-weighted imaging (SWI), and 3D T1-weighted imaging (3D-T1WI). Scan parameters have been detailed elsewhere20–24 and are also available in table e-1 (available from Dryad, doi.org/10.5061/dryad.2547d7wnj).
Image Analyses

All images were reviewed centrally and independently by 2 radiologists blinded to the clinical data at baseline and at follow-up. Recent infarcts were defined as hyperintense areas on DWI with a corresponding low apparent diffusion coefficient and were segmented using a semiautomatic tool available in 3D Slicer. Cerebral SVD features were assessed according to the standards for reporting vascular changes on neuroimaging. WMHs were defined as hyperintensity on FLAIR, distinct from cavitation; their severity was determined according to the Fazekas scale. Lacunes were manually counted by looking for rounded or ovoid subcortical lesions, between 3 and 20 mm in diameter, with a CSF signal on T1WI and FLAIR. PVS were defined as small (<3 mm) punctate or linear lesions, with intensity similar to CSF on all sequences in the basal ganglia or centrum semiovale and were rated on 3D-T1WI based on a previously validated semiquantitative scale from 0 to 4. CMBs were defined as small (up to 10 mm) areas of signal void with associated blooming artifacts seen on gradient echo imaging and were independently counted on T2*WI and SWI according to current guidelines. Sequelae of previous strokes were also rated. The interrater weighted κ values from a subset of 200 randomly selected scans were good and ranged from 0.72 for PVS to 0.88 for WMH.

The total SVD score was rated from these features by allocating 1 point to each of the following: (1) confluent deep WMH (Fazekas score 2 or 3) or irregular periventricular WMHs extending into the deep white matter (Fazekas score 3), (2) presence of 1 or more lacune, (3) moderate to severe (>10) PVS in the basal ganglia, and (4) presence of any CMBS on T2*WI.

For volumetric analyses, FLAIR and 3D-T1WI were processed using the VolBrain system. The automatically segmented WMHs were quality controlled and manually corrected, particularly by excluding the acute infarct. Brain volume was also automatically computed and normalized for atrophy using intracranial cavity volume to control for variations in head size.

Statistical Analysis

Statistical analyses were performed with SAS v9.4 software (SAS Institute, Cary, NC).

Sample Size Calculation

The sample size of dataset 1 was powered for the primary objective, to predict poor functional outcome (mRS > 2) at 3 months, with 12–15 possible predictors, without overfitting the models. Considering that at least 10 outcomes should be observed for each degree of freedom, 120–150 patients with mRS >2 at 3 months were needed, which required including 343–429 patients for an estimated 35% prevalence of poor outcome.

Model Variables

Three dependent variables were prespecified to quantify the capability to predict a handicap following stroke within the functional, cognitive, and psychological domains. We used the mRS, MoCA, and HADS collected at follow-up, which were dichotomized based on clinically relevant and literature-supported thresholds. Poor status at follow-up was defined as mRS >2, as MoCA <26, and as HADS >7 for the functional, cognitive, and psychological outcomes, respectively. Because aphasia could possibly bias the evaluation of MoCA and HADS, additional analyses were also conducted by excluding aphasic patients, defined as those who had at least 1 point on the item 9 of NIHSS at follow-up.

Independent variables consisted of (1) age, (2) initial NIHSS, and (3) infarct volume from baseline DWI considering that these predictors are the most consistently reported in the literature. This set of 3 independent variables was used to build model 1. The total SVD score was added to model 1 to generate model 2. Because refinement of the total SVD score has been hypothesized as a method to improve quantification of the total burden of cerebral SVD, we also tested (model 3) all cerebral SVD MRI features added to model 1, instead of the total SVD score, which is based on specific criteria and thresholds. Therefore, the following imaging variables were included in model 3: (1) deep white matter Fazekas score (0, 1, 2, or 3), (2) periventricular Fazekas score (0, 1, 2, or 3), (3) volumetric analysis of WMH (in cm³), (4) number of lacunes, (5) number of PVS in basal ganglia (0, 1–10, 11–20, 21–40, and >40) and in centrum semiovale ganglia (0, 1–10, 11–20, 21–40, and >40), (6) number of CMBS on T2*WI (0, 1–4, and >4), (7) number of CMBS on SWI (0, 1–4, and >4), (8) sequel of previous stroke, and (9) and atrophy (% of intracranial cavity).

Analyses

We used multivariate logistic regression analyses to estimate predictive models for the 3 dependent variables following the TRIPOD recommendations. For the independent quantitative variables, the shapes of the association with the clinical outcomes were analyzed using fractional polynomials implemented in a bootstrapping approach to select a more robust shape. Transformations, such as log-transformation, were applied if they improved the shape of the association. The independent variables for model 1 were introduced simultaneously. The SVD score was added to model 1 for model 2. A backward and stepwise selection of each of the cerebral SVD features was applied in model 3 using the Akaike information criterion (corresponding to \( p = 0.135 \) for one degree of freedom).

Missing data were not excluded but they were replaced using a multiple imputation method during development of the models. The number of imputations was proportional to the percentage of patients with at least one missing datum. If the outcome measure at follow-up was missing, baseline data were still included to implement the imputation model. Results of the imputed datasets were aggregated using the Rubin rule.

Model Performance

The strengths of the associations were measured using ORs and their 2-sided 95% confidence intervals (CIs). Then, the predictive performances of the models were assessed through their calibration and discrimination capabilities. For calibration, we used the plots of predicted probability of outcome vs the actual
outcome. For discrimination, we used the area under the receiver operating characteristic curve (AUC) and its 2-sided 95% CI.\textsuperscript{40} We also used reclassification tables to assess the clinical pertinence of the models by quantifying the number of reclassified patients when new variables were added to the previous model.

An internal validation was used through a repeated 10-fold cross-validation procedure to correct the AUC of each model for optimism. The bootstrap technique was performed with 1,000 replications to estimate 2-sided 95% CIs of each AUC and the added value.\textsuperscript{41}

The second dataset was analyzed to assess the degree of replication of the model 1 and model 2 results.

Data Availability
Anonymized data will be shared by request from any qualified investigator.

Results

Among the 428 patients recruited for dataset 1, 80 were excluded, leaving 348 patients for analyses (n = 30, no infarct; n = 27, no baseline MRI; n = 9, posterior fossa infarct; n = 4, claustrophobia; n = 6, uninterpretable MRI data and agitation; n = 4, violation of other inclusion criteria). Among the 197 patients in independent dataset 2, 60 were excluded for similar reasons, leaving 137 patients for the analyses.

Patient Characteristics and Imaging Features

The clinical and imaging characteristics at baseline and the clinical outcomes at follow-up were compared between the 2 datasets in table 1.

None of the patients had prestroke cognitive impairment based on the IQCODE score. The median NIHSS at baseline and infarct volume suggested mild to moderate neurologic deficit in the 2 datasets with younger patients and with a lower deficit in dataset 2. White matter disease and PVS had the highest prevalence among the cerebral SVD features, with a predominance of low-grade anomalies in the 2 datasets. For instance, the Fazekas score of periventricular WMH was >1 in about 35% of the patients, and more than 20 PVS were found in 13.2% and 8.1% of the patients in datasets 1 and 2, respectively. Lacunes were described in <20% of patients, and CMBs in 12% and 21% of the patients in datasets 1 and 2, respectively. Despite differences in the individual components, the total SVD scores showed relatively comparable distribution in the 2 datasets. At follow-up, patients from dataset 2 had less severe disease than those from dataset 1, in which 95/348 (27.4%) patients had a mRS >2, 167/288 (58.0%) patients had a MoCA <26, and 58/288 (20.1%) patients had a HADS score >7.

Age, Baseline NIHSS, and Infarct Volume Were Associated With, and Predicted, Patient Outcome

Table 2 shows model 1 for the 3 clinical outcomes in dataset 1. As expected, higher age and higher baseline NIHSS were significantly associated with a poor mRS at 3 months, with a predominant effect of the NIHSS (OR for log-transformed NIHSS, 10.56 [5.83–19.14], p < 0.0001). Higher age and higher NIHSS were also significantly associated with poor cognitive performance and with depression at 3 months. Infarct volume was not associated with any of the clinical outcome variables.

Overall, the combination of these 3 variables (actually, mainly age and baseline NIHSS) translated into predictive performance. The calibration curves showed that the predicted outcome probability based on the combination of the 3 variables was very close to the observed outcome probability (see below). The prediction ranged from excellent to discriminate between poor and good mRS at 3 months (AUC, 0.915 [0.868–0.943]) to fair to discriminate cognitively impaired and depressed patients at 3 months (AUC, 0.750 [0.644–0.797] and 0.688 [0.557–0.759], respectively). A sensitivity analysis was also conducted by running the same models with the addition of acute treatments (thrombolysis or thrombectomy) which did not significantly change the AUCs (data not shown) possibly because part of the effect is captured by NIHSS and infarct volume measured between 24 and 72 hours after stroke onset.

Total SVD Score Was Associated With Patient Outcome, but Did Not Provide Significant Improvement of Prediction

A shift toward higher total SVD scores was observed in patients with poor outcomes (functional, cognitive, and psychological) compared to patients with good outcomes at 3 months (figure 1). Accordingly, univariate logistic regressions showed slight but significant associations between the SVD score and functional and cognitive outcome (OR, 1.30 [1.07–1.58], p = 0.0090; and OR, 1.23 [1.00–1.50], p = 0.05, respectively) while the association did not reach significance for psychological outcome (OR, 1.16 [0.92–1.45], p = 0.2077).

However, in multivariate analyses, adding the total SVD score to model 1 did not improve the prediction of the 3 outcomes (table 3). Indeed, these combined models produced AUCs that were not statistically different from those of model 1, with a difference in the AUCs of 0.003 (−0.006 to 0.014) for functional outcome, −0.004 (−0.018 to 0.010) for cognitive outcome, and −0.004 (−0.030 to 0.023) for psychological outcome. Results were consistent when the analyses were reconducted after exclusion of patients with aphasia at follow-up (ΔAUC of 0.003 for both cognitive and psychological outcomes).

To understand whether the lack of improvement of the prediction by adding SVD could be related to collision with the other variables (age, baseline NIHSS, and infarct volume), we also tested the predictive performances of the total SVD score alone and found they were close to random for functional, cognitive, and psychological outcome (AUC of 0.577...
MRI Features of Cerebral SVD Were Associated With Patient Outcome, but Did Not Provide Significant Improvement of the Prediction

Table 4 shows model 3 for the 3 clinical outcomes in dataset 1. The rationale was to keep the predictors of model 1 and to identify, through a backward and stepwise selection, the MRI features of the underlying brain that showed an association with outcomes using detailed MRI features beyond strict utilization of the SVD score.

WMH was a feature consistently associated with a poor outcome, with various definitions showing up (Fazekas grade for deep white matter, Fazekas grade for periventricular white matter or volumetric quantification), depending on the outcome score that was considered. Among the variables not evaluated by the total SVD score, we also found a
A significant association between brain volume loss and poor functional outcome at 3 months (OR, 1.18 [1.06–1.31], \(p = 0.0029\)).

Importantly, these combined models did not improve the predictive performance of model 1 either. Indeed, on the calibration curves, the excellent correspondence between the predicted probability and the observed probability of the outcome observed in model 1 did not improve in model 3 (figure 2, upper row). Similarly, the AUCs for model 1 vs model 3 were not significantly different: \(\Delta\)AUC of 0.007 (−0.027 to 0.027) for functional outcome, −0.010 (−0.069 to 0.014) for cognitive outcome, and 0.027 (−0.083 to 0.084) for psychological outcome (figure 2, lower row).

While the predicted outcomes were similar in model 3 compared to model 1 based on these calibration and discrimination metrics, we hypothesized that model 3 might help to classify clinically the patients with more certainty than model 1. To test this hypothesis, we considered that only patients

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### Table 2 Prognostic Values of Age, Baseline NIH Stroke Scale Score (NIHSS), and Infarct Volume to Assess Functional, Cognitive, and Psychological Outcomes at 3 Months in Dataset 1 (Model 1)

| Dependent variables | Independent variables | OR      | 95% CI       | \(p\) Value | AUC \(^a\) (95% CI) (bootstrap corrected) |
|---------------------|-----------------------|---------|--------------|-------------|----------------------------------------|
| **Functional outcome** | Age (+5 y)            | 1.30    | 1.14; 1.48   | 0.0001\(^b\) | 0.915 (0.868; 0.943)                   |
|                     | Baseline NIHSS (+1 log)\(^c\) | 10.56   | 5.83; 19.14  | <0.0001\(^b\) | 0.8178                                 |
|                     | Infarct volume (+1 cm\(^3\)) | 1.00    | 0.99; 1.01   |             |                                        |
| **Cognitive outcome** | Age (+5 y)            | 1.28    | 1.15; 1.43   | <0.0001\(^b\) | 0.750 (0.644; 0.797)                   |
|                     | Baseline NIHSS (+1 point) | 1.15    | 1.06; 1.25   | 0.0012\(^b\) |                                        |
|                     | Infarct volume (+1 cm\(^3\)) | 1.00    | 0.99; 1.01   | 0.8530      |                                        |
| **Psychological outcome** | Age (+5 y)            | 1.18    | 1.05; 1.32   | 0.0064\(^b\) | 0.688 (0.557; 0.759)                   |
|                     | Baseline NIHSS (+1 point) | 1.10    | 1.04; 1.16   | 0.0015\(^b\) |                                        |
|                     | Infarct volume (+1 cm\(^3\)) | 1.00    | 0.99; 1.01   | 0.8078      |                                        |

Abbreviations: AUC = area under the receiver operating characteristic curve; CI = confidence interval; OR = odds ratio. Predictions are shown for poor outcome at 3 months assessed by modified Rankin Scale score >2 for functional outcome, Montreal Cognitive Assessment score <26 for cognitive outcome, and Hospital Anxiety and Depression Scale score >7 for psychological outcome. The 3 independent variables were introduced simultaneously.

\(^a\) AUCs were corrected for optimism through a repeated 10-fold cross-validation procedure and with a bootstrap technique (1,000 replications) to estimate the 2-sided 95% CIs.

\(^b\) \(p < 0.05\).

\(^c\) Baseline NIHSS was log transformed in this model, as it improved the association with the outcome.

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**Figure 1 Distribution of Small Vessel Disease (SVD) Scores**

Distribution of SVD scores in dataset 1 according to functional (modified Rankin Scale [mRS]), cognitive (Montreal Cognitive Assessment [MoCA]), and psychological (Hospital Anxiety and Depression Scale [HADS]) outcomes at 3-month follow-up. Outcomes were dichotomized as described in the Methods. A mild shift toward a higher score was observed in patients with worse outcome.
with a predicted probability >70% or <30% could be considered at high risk or low risk to evolve toward a poor outcome, while patients with a predicted probability of 30%–70% would have an uncertain outcome. Actually, only 3 patients (of the 348) were reclassified in the ranges of high certainty (>70% or <30%) when model 3 was compared to model 1 for

**Table 3 Prognostic Values of the Total Small Vessel Disease (SVD) Score to Assess Functional, Cognitive, and Psychological Outcomes at 3 Months in Dataset 1 (Model 2)**

| Dependent variables | Independent variables | OR     | 95% CI  | p Value   | AUC (95% CI) (bootstrap corrected) |
|---------------------|-----------------------|--------|---------|-----------|-------------------------------------|
| **Functional outcome** | Age (+5 y)            | 1.27   | 1.11; 1.45 | 0.0006b | 0.917 (0.869; 0.945)               |
|                     | Baseline NIHSS (+1 log)c | 10.70 | 5.83; 19.62 | <0.0001b |                                      |
|                     | Infarct volume (+1 cm³) | 1.00   | 1.01; 1.02 | 0.3943   |                                      |
|                     | Total SVD score (+1)d  | 1.44   | 1.05; 1.96 | 0.0219b |                                      |
| **Cognitive outcome** | Age (+5 y)            | 1.28   | 1.14; 1.43 | <0.0001b | 0.745 (0.637; 0.793)               |
|                     | Baseline NIHSS (+1 point) | 1.15  | 1.06; 1.25 | 0.0014d |                                      |
|                     | Infarct volume (+1 cm³) | 1.00   | 0.99; 1.01 | 0.8978   |                                      |
|                     | Total SVD score (+1)   | 1.04   | 0.82; 1.31 | 0.7638   |                                      |
| **Psychological outcome** | Age (+5 y)            | 1.17   | 1.03; 1.32 | 0.0120b | 0.685 (0.551; 0.756)               |
|                     | Baseline NIHSS (+1 point) | 1.10  | 1.04; 1.16 | 0.0017d |                                      |
|                     | Infarct volume (+1 cm³) | 1.00   | 0.99; 1.01 | 0.8875   |                                      |
|                     | Total SVD score (+1)   | 1.07   | 0.83; 1.38 | 0.5975   |                                      |

Abbreviations: AUC = area under the receiver operating characteristic curve; CI = confidence interval; NIHSS = NIH Stroke Scale; OR = odds ratio; WMH = white matter hyperintensity.

Predictions are shown for poor outcomes at 3 months assessed by modified Rankin Scale score >2 for functional outcome, Montreal Cognitive Assessment score <26 for cognitive outcome, and Hospital Anxiety and Depression Scale score >7 for psychological outcome. The models are shown with SVD combined with age + baseline NIHSS + infarct volume, forced in final model 2.

* AUCs were corrected for optimism through a 10-fold cross-validation procedure and with a bootstrap technique (1,000 replications) to estimate the 2-sided 95% CIs.

**Table 4 Prognostic Values of MRI Features of Cerebral Small Vessel Disease (SVD) to Assess Functional, Cognitive, and Psychological Outcomes at 3 Months in Dataset 1 (Model 3)**

| Dependent variables | Independent variables | OR     | 95% CI  | p Value   | AUC (95% CI) (bootstrap corrected) |
|---------------------|-----------------------|--------|---------|-----------|-------------------------------------|
| **Functional outcome** | Age (+5 y)            | 1.15   | 0.96; 1.38 | 0.1268b | 0.921 (0.861; 0.947)               |
|                     | Baseline NIHSS (+1 log)c | 9.66  | 5.23; 17.83 | <0.0001b |                                      |
|                     | Infarct volume (+1 cm³) | 1.01   | 1.00; 1.02 | 0.0795b |                                      |
|                     | Brain volume (+1%)    | 1.18   | 1.06; 1.31 | 0.0029b |                                      |
|                     | Fazekas deep white matter (+1 point) | 1.97 | 1.18; 3.30 | 0.0101b |                                      |
|                     | Number of microbleed (1–4 vs 0) | 2.77  | 0.87; 8.83 | 0.0124m |                                      |
|                     | Number of microbleed (>4 vs 0) | 3.90   | 0.49; 30.92 | 0.0256m |                                      |
|                     | Total PVS (+1 point)   | 0.53   | 0.3; 0.93 | 0.397b |                                      |
| **Cognitive outcome** | Age (+5 y)            | 1.25   | 1.11; 1.40 | 0.0001b | 0.739 (0.603; 0.781)               |
|                     | Baseline NIHSS (+1 point) | 1.14  | 1.05; 1.24 | 0.0022b |                                      |
|                     | Infarct volume (+1 cm³) | 1.00   | 0.99; 1.01 | 0.9584   |                                      |
|                     | WMH (+5 cm³)           | 1.07   | 0.98; 1.18 | 0.1336b |                                      |
| **Psychological outcome** | Age (+5 y)            | 1.15   | 1.01; 1.32 | 0.0383b | 0.715 (0.539; 0.774)               |
|                     | Baseline NIHSS (+1 point) | 1.10  | 1.03; 1.17 | 0.0047b |                                      |
|                     | Infarct volume (+1 cm³) | 1.00   | 0.99; 1.01 | 0.9340   |                                      |
|                     | Fazekas periventricular (1 vs 0) | 0.52 | 0.20; 1.33 | 0.0018b |                                      |
|                     | Fazekas periventricular (2 vs 0) | 1.08 | 0.37; 3.14 | 0.0515b |                                      |
|                     | Fazekas periventricular (3 vs 0) | 3.43 | 0.96; 12.24 | 0.0001b |                                      |
|                     | Basal ganglia PVS (2 vs 0–1) | 0.41 | 0.17; 0.97 | 0.0002b |                                      |
|                     | Basal ganglia PVS (3–4 vs 0–1) | 0.51  | 0.17; 1.57 | 0.0002b |                                      |

Abbreviations: AUC = area under the receiver operating characteristic curve; CI = confidence interval; NIHSS = NIH Stroke Scale; OR = odds ratio; PVS = perivascular space; WMH = white matter hyperintensity.

Predictions are shown for poor outcome at 3 months assessed by modified Rankin Scale score >2 for functional outcome, Montreal Cognitive Assessment score <26 for cognitive outcome, and Hospital Anxiety and Depression Scale score >7 for psychological outcome. The models are shown with age + baseline NIHSS + infarct volume forced in the final model 3 and associated with individual MRI features of cerebral SVD that were added according to a backward and stepwise selection.

* AUCs were corrected for optimism through a 10-fold cross-validation procedure and with a bootstrap technique (1,000 replications) to estimate the 2-sided 95% CIs.

* p < 0.135 (according to Akaike information criteria for 1 degree of freedom).

* Baseline NIHSS was log-transformed in this model, as it improved the association with outcome.
The Results Were Confirmed Using Independent Dataset 2

Similar results were found when models 1 and 2 were replicated on dataset 2. The total SVD score confirmed a low predictive value, with differences in AUCs between model 1 and model 2 of $-0.009$ ($-0.120$ to $0.063$), $0.044$ ($-0.154$ to $0.145$), and $-0.023$ ($-0.128$ to $0.178$) for the functional, cognitive, and psychological outcomes, respectively. Calibration curves and AUCs for models 1 and 2 based on dataset 2 can be found in figure e-1 (available from Dryad, doi.org/10.5061/dryad.2547d7wnj).

Discussion

Our results show that cerebral SVD (assessed by the total SVD score or by detailed SVD MRI features) was associated with functional, cognitive, and psychological outcomes but did not provide any clinically relevant added value to predict the individual outcomes of patients when compared to the usual validated predictors, such as age and baseline NIHSS.

Models that accurately predict clinical outcome after stroke could have several uses. Such models could help to provide rapid, realistic prognostic expectations to the patients and families, which could be useful for anticipating home adjustments. These models could also help in the planning of long-term care, such as access to intensive rehabilitation, cognitive training, or introduction of behavioral therapy depending on the domain that is most at risk. They could also help to allocate resources more specifically, to reduce costs. Furthermore, such models could be useful for selecting homogeneous patient populations to improve statistical power and reduce the required sample size when assessing interventions for clinical trials.

We reaffirmed that age and baseline NIHSS are very strong predictors of functional outcome determined by the 3- to 6-month mRS, but at a lower degree for cognitive and psychological outcomes. In line with previous studies, infarct volume on DWI did not contribute to the predictive models.

The main goal of this study was to evaluate the predictive value of the underlying brain that we call the “brain before stroke” to refer to modifications related to cerebral SVD. Consistent with the literature, the total SVD score was significantly associated with some aspects of poststroke outcome. Refinements in the total SVD score have been discussed by several authors to redefine the thresholds for each feature, to avoid redundancy between the features, or to consider atrophy as an additional criterion of the ageing brain. Therefore, we also tested the value of all MRI features independently of the total SVD score in model 3 and found that WMH was the most consistent marker.
associated with 3-month functional, cognitive, and psychological outcomes, which agrees with previous literature.\textsuperscript{11,46} Cerebral atrophy was also associated with functional outcome.

Despite these associations, adding cerebral SVD neuroimaging markers to validated predictors (age and baseline NIHSS) did not significantly improve the accuracy of predicting a patient’s individual outcome (no significant modification of the calibration curves or of the AUC). There are several probable reasons why cerebral SVD does not add information to the prediction of stroke outcome. First, our results indicate that statistical associations between a marker and an outcome do not necessarily imply that the marker can discriminate between individuals likely, or otherwise, to have the outcome. This is the major difference between the concept of statistical association and the concept of prediction. Strong associations are needed for a marker to classify subjects, and the OR is a simple scalar measure of association that corresponds to many different pairs of sensitivity and specificity on the receiving operating characteristic curve.\textsuperscript{17} This may explain the poor performance of cerebral SVD features that could have been improperly described in the literature as “predictive” factors of stroke outcome, given that such conclusions were only based on logistic models or regression analyses.\textsuperscript{7–13,15,16} In our analyses, the ORs for WMH ranged from 1.07 to 3.43, and the ORs for the total SVD score were relatively weak but actually in line with many others.\textsuperscript{7,8,10–12} This result is insufficient to affect the prediction, as compared to NIHSS and age, which together dominate the prediction.\textsuperscript{47} This is particularly true for functional outcome, as shown by the high AUC of the model that included those 2 markers alone (AUC 0.915). Lower performance was found with age and baseline NIHSS for predicting cognitive and psychological outcomes, pointing to other possible predictors.\textsuperscript{20} We would have expected that cerebral SVD markers would contribute more to prediction in these fields by altering the networks involved in information processing speed, executive functions, or plasticity following stroke, but this was not the case. Importantly, we only selected patients without premorbid cognitive deficits, which is an important methodologic point to avoid improper interpretation of preexisting deficit as cognitive decline in the context of cerebral SVD and stroke. Another reason why cerebral SVD does not add information to the prediction might have been that age and cerebral SVD are correlated\textsuperscript{5,11} (which is true in our data; data not shown) and one could have assumed that age, which was included in our models, was conveying most of the information. This phenomenon has been suggested to explain the small magnitude of the effect of infarct volume when NIHSS is included in the same model because it captures the same information.\textsuperscript{44,46} The strengths of associations between SVD and cognitive and psychological outcomes indeed decreased when age was included (lower OR) but this cannot be the sole explanation because even the SVD score alone did not show any significant predictive performances.

We could demonstrate, in line with the current literature, that cerebral SVD is associated with stroke outcome, but we could not find a significant predictive role of SVD imaging features compared to validated predictors of outcome such as age and NIHSS. Such a “negative” result is of substantial value because our study included a large dataset of patients, prospectively and longitudinally followed over time, with applications of all major methodologic requirements for prognostic research design and analysis,\textsuperscript{36} including an adequate sample size calculation, appropriate handling of missing data with statistical imputation, and internal validation and confirmation on an independent dataset. However, the limitations of this study should be acknowledged. The main limitation is that the 2 datasets included patients with mild severity at baseline and rather good functional outcomes, which is not representative of the general stroke population. This might be because patients with more severe stroke sometimes do not consent to participate or do not tolerate the longer MRI examination used here for research purposes. Otherwise, all patients with a suspected diagnosis of stroke were included; patients unable to be scanned with the research protocol or with images not assessable were secondarily excluded. These results cannot be extrapolated to patients with hemorrhagic, infratentorial, or DWI-negative strokes who were not included in this study. Second, the burden of cerebral SVD was also rather low, with <15% of the population having Fazekas grade 3 WMH, or a SVD score >2, which could have altered the strength of associations and the predictive effect of the cerebral SVD factors. Nevertheless, these imaging characteristics were similar to those described in previous studies\textsuperscript{7,45,49} and correspond to a relevant category of the population frequently encountered. Third, cognitive outcomes should be assessed with a broader neuropsychological battery in the future because the MoCA, while validated for screening cognitive impairment after stroke,\textsuperscript{26} cannot capture all nuances of cognition. A longer follow-up would also be preferred,\textsuperscript{40} even though much of the recovery has already occurred at 3–6 months. Fourth, the outcomes were considered as dichotomous variables using clinically relevant cutpoints based on the literature,\textsuperscript{25–27} and not used as continuous variables. This approach may have weakened the statistical power to detect the associations between the SVD score and outcome, but is the best way to evaluate the performances of predictive models in terms of classification errors in the clinical decision process.\textsuperscript{17} Finally, other metrics to quantify cerebral SVD could be used in the future, including diffusion tensor imaging to capture diffuse microstructural alterations, even in normal-appearing white matter.

Overall, in our cohorts of patients with moderately severe stroke, we demonstrated that, although imaging features of cerebral SVD and total SVD score were associated with the patient’s prognosis and could be interesting from a pathophysiologic point of view, adding these neuroimaging markers to validate clinical predictors did not improve accuracy of prediction of the outcome for an individual patient.

Study Funding

The study was supported by public grants from the French Agence Nationale de la Recherche within the context of the Investments for the Future Program, referenced ANR-10-
LABX-57, and named TRAIL (Translational Research and Advanced Imaging Laboratory). The development cohort was funded by a public grant from the French government (PHRC [Programme Hospitalier de Recherche Clinique Inter-régional]) funded in 2012. The validation cohort was funded by the Hauts-de-France Regional Council, the Coeur et Artères foundation, and the French Ministry of Health. The authors thank the In-vivo Imaging and Functions core facility (ci2c.fr) for the MRI acquisitions of Strokdem database.

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History
Received by Neurology February 13, 2020. Accepted in final form September 11, 2020.

Appendix

Table: Authors

| Name                  | Location                        | Contribution                                                                 |
|-----------------------|---------------------------------|------------------------------------------------------------------------------|
| Juliette Coutureau, MD, PhD | University Hospital of Bordeaux, France | Analyzed the data, interpreted the data, drafted the manuscript for intellectual content |
| Julien Asselineau, MSc | University Hospital of Bordeaux, France | Designed and conceptualized study, performed biostatistical analyses, revised the manuscript critically for intellectual content |
| Paul Perez, MD, PhD   | University Hospital of Bordeaux, France | Designed and conceptualized study, biostatistical review of results, revised the manuscript critically for intellectual content |
| Gregory Kuchcinski, MD | University Hospital of Lille, France | Coordinated imaging for site, major role in the acquisition of data, participated in MRI review, revised the manuscript critically for intellectual content |
| Sharmila Sagner, MD, PhD | University Hospital of Bordeaux, France | Major role in the acquisition of data, participated to MRI review, revised the manuscript critically for intellectual content |
| Pauline Renou, MD     | University Hospital of Bordeaux, France | Major role in the acquisition of data, revised the manuscript critically for intellectual content |
| Fanny Munsch, PhD      | Beth Israel Deaconess Medical Center, Boston, MA | Major role in the acquisition of data, participated to MRI review, revised the manuscript critically for intellectual content |
| Renaud Lopes, PhD      | University Hospital of Lille, France | Major role in the acquisition of data, revised the manuscript critically for intellectual content |
| Hilde Henon, MD        | University Hospital of Lille, France | Major role in the acquisition of data, revised the manuscript critically for intellectual content |
| Regis Bordet, MD, PhD  | University Hospital of Lille, France | Design and conceptualized study, revised the manuscript critically for intellectual content |
| Vincent Dousset, MD, PhD | University Hospital of Bordeaux, France | Design and conceptualized study, revised the manuscript critically for intellectual content |

Appendix (continued)

| Name                  | Location                        | Contribution                                                                 |
|-----------------------|---------------------------------|------------------------------------------------------------------------------|
| Igor Sibon, MD, PhD   | University Hospital of Bordeaux, France | Design and conceptualized study, revised the manuscript critically for intellectual content |
| Thomas Tourdias, MD, PhD | University Hospital of Bordeaux, France | Design and conceptualized study, Interpreted the data, drafted the manuscript for intellectual content |

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