Treatment of vascular risk factors is associated with slower decline in Alzheimer disease

Yan Deschaintre, MD
Florence Richard, MD, PhD
Didier Leys, MD
Florence Pasquier, MD, PhD

Address correspondence and reprint requests to Dr. Florence Richard, Université Lille Nord de France, INSERM UMR 744, Institut Pasteur de Lille, 1 rue Calmette, 59019 Lille Cedex, France
florence.richard@pasteur-lille.fr

ABSTRACT

Background: There is growing evidence that vascular risk factors (VRF) contribute to cognitive decline. Whether their treatment can slow down the progression of Alzheimer disease (AD) remains unsettled. The aim of this observational study was to evaluate whether the treatment of VRF is associated with a slower cognitive decline in patients who have AD without cerebrovascular disease (CVD).

Methods: We recruited 301 consecutive patients who had AD without CVD (mean age 71.7 years; 69.4% women; first Mini-Mental State Examination [MMSE] mean score 21.6; mean follow-up 2.3 years), who had attended a memory clinic between 1997 and 2003. VRF sought were high blood pressure, dyslipidemia, diabetes mellitus, tobacco smoking, and atherosclerotic disease. Only 21 patients (7.0%) had no VRF. Others were classified as having no VRF treated (n = 72; 25.7%), some VRF treated (n = 119; 42.5%), or all VRF treated (n = 89; 31.8%). We compared MMSE progression over time among these 3 groups using a mixed random effects regression model.

Results: Baseline MMSE scores were similar in the 3 groups. With adjustment for confounding factors, MMSE progression over time differed significantly between groups ($p = 0.002$). Patients with all their VRF treated declined less than those with none of their VRF treated. Those with some VRF treated tended to have an intermediate decline.

Conclusions: In patients who have Alzheimer disease without CVD, treatment of vascular risk factors (VRF) is associated with a slower decline in Mini-Mental State Examination score. Randomized controlled trials are needed to confirm this association, but our data suggest that dementia should not prevent treatment of VRF. *Neurology*® 2009;73:674–680

GLOSSARY

AD = Alzheimer's disease; **ANOVA** = analysis of variance; **ChEI** = cholinesterase inhibitor; **CVD** = cerebrovascular disease; **DRS** = Dementia Rating Scale; **MMSE** = Mini-Mental State Examination; **RR** = relative risk; **VRF** = vascular risk factors.

In 2003, dementia affected approximately 27.7 million people worldwide and had a direct cost of US $156 billion (114 billion Euros).[1] With the aging population, dementia prevalence will almost double within the next 20 years.[2] Slowing dementia progression could reduce both its prevalence and the prevalence of its later severe stages.[3] These later stages being responsible for most of dementia burden, any intervention modifying dementia progression could have a tremendous effect.[4]

Alzheimer disease (AD) is the most common type of dementia.[5] Currently approved drugs for its treatment (cholinesterase inhibitors and memantine) offer symptomatic relief but lack evidence of a disease-modifying effect.[6] Classic vascular risk factors (VRF) such as high blood pressure,[7,8] dyslipidemia,[8] diabetes mellitus,[9] tobacco smoking,[10] and the presence of athero-

Supplemental data at www.neurology.org

From the Université Lille Nord de France (Y.D., F.P.), EA 2691, Centre Mémoire de Ressources et de Recherche, CHRU de Lille; Stroke Team (Y.D.), Centre Hospitalier de l'Université de Montréal; Université Lille Nord de France (F.R.), INSERM, UMR744, Institut Pasteur de Lille; and Université Lille Nord de France (D.L.), EA 2691, Service de neurologie vasculaire, CHRU de Lille, France.

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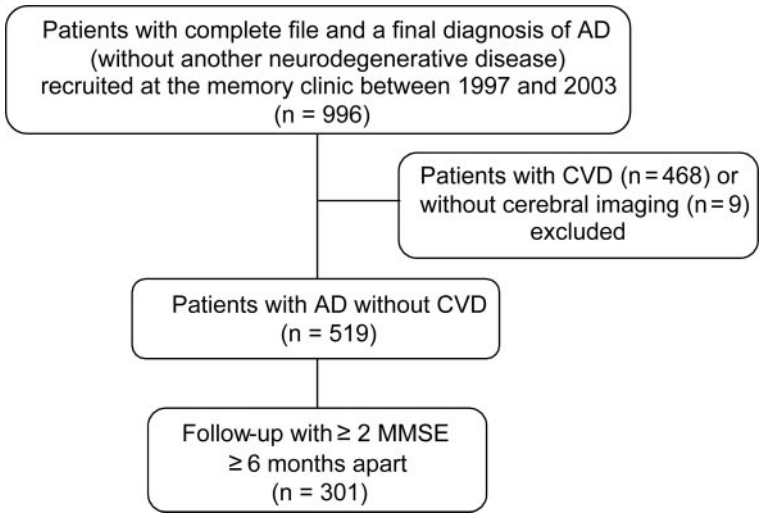
Figure 1 Patient inclusion flowchart



AD = Alzheimer disease; CVD = cerebrovascular disease; MMSE = Mini-Mental State Examination.

sclerotic disease[11] have all been associated with an increased risk of AD.[12] High blood pressure and angina have also been associated with a more rapid cognitive decline once AD is overt.[13]

These findings raise the question of whether VRF treatment could slow down cognitive decline in AD. Studies have shown that treating high blood pressure could reduce the incidence of dementia.[14] The effect of treatment in patients already demented and in patients without cerebrovascular disease (CVD) is less clear.[15]

The aim of this observational study was to evaluate whether the treatment of VRF is associated with a slower progression of cognitive decline in patients who have AD without CVD. Because aggregation of multiple VRF further increases the risk of dementia,[16,17] both the impact of individual VRF and global treatment of all VRF could be important.

METHODS To carry out this observational study, we used the computerized database of the University outpatient memory clinic of Lille, France. Since its opening in 1992, all patients are first assessed with a comprehensive clinical examination conducted by a senior staff neurologist, a psychiatrist, a neuropsychologist, a speech therapist, and a nurse. They have cerebral imaging (with CT scan or MRI) and laboratory investigation, including fasting serum total cholesterol, triglycerides, and glucose. These results, along with demographic data, personal medical history (especially VRF), previous and current treatment, and clinical examination, including the Mini-Mental State Examination (MMSE),[18] are consigned in a standardized file. During confrontation meetings with all the staff, a consensual diagnosis is given for each patient according to existing diagnostic criteria.[19-22] Most patients are then followed up on a regular basis (every 6–12 months). If patients are lost during follow-up, living status is ascertained by all available sources (general practitioners, nursing homes, patients, and families). Previous studies have been conducted from the same database.[23,24]

For the purpose of this study, all patients meeting the following criteria were included: complete file, final diagnosis (definite, probable, or possible) of AD according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria,[19] first visit between 1997 and 2003 inclusively, and follow-up with at least 2 MMSEs at least 6 months apart. The last follow-up visit taken into account was the last visit performed before January 1, 2007. Patients who had a stroke before first visit or during follow-up and patients both meeting AD criteria and showing significant vascular lesions on brain imaging (strategic lesion, multiple lesions, or diffuse white matter lesions)[5,20] were considered to have CVD and were excluded (figure 1). Patients with the posterior cortical atrophy variant of AD[25] or with both AD and another neurodegenerative disease were not included.

We recorded the presence, at the first evaluation, of high blood pressure, dyslipidemia, diabetes mellitus (type I or type II), tobacco smoking, and atherosclerotic disease. High blood pressure was defined as a history of high blood pressure, a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or the use of an antihypertensive medication (diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, calcium channel blocker, or other); dyslipidemia was defined as a history of dyslipidemia, a fasting serum total cholesterol ≥6.22 mmol/L (2.4 g/L) or triglycerides ≥2.26 mmol/L (2 g/L), or the use of a statin or fibrate; diabetes mellitus was defined as a history of diabetes mellitus, a fasting serum glucose >7.0 mmol/L (1.26 g/L), or the use of an oral antihyperglycemic or insulin; tobacco smoking was defined as a history of past or active tobacco smoking; and atherosclerotic disease was defined as a history of angina pectoris, past myocardial infarction, TIA, peripheral arterial disease, angioplasty, endarterectomy or artery bypass graft, or the use of an antiplatelet treatment.

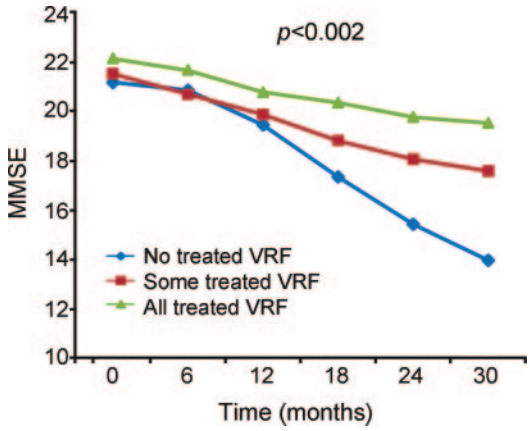
Each VRF was considered treated if it received a specific medication at the first evaluation: diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, calcium channel blocker, or other antihypertensive medication for high blood pressure; statin or fibrate for dyslipidemia; oral antihyperglycemic or insulin for diabetes; antiplatelet or anticoagulant for atherosclerotic disease; tobacco smoking was considered "treated" if the patient had stopped smoking. To evaluate how all VRF were treated, patients with VRF were divided into 3 groups: patients with none of their VRF treated, patients with some of their VRF treated, and patients with all their VRF treated.

Cognitive decline was assessed with the MMSE score recorded at each visit. The Dementia Rating Scale (DRS)[26] was also performed at baseline but was not systematically repeated. The mean annual decline on the MMSE was calculated as the difference between the first and last score, divided by the time, expressed in years, between the 2 measurements.

This was a retrospective review of anonymous patient data, which was approved by the CPP (local ethics committee).

Statistical analysis. Means of quantitative variables were compared with a 1-way analysis of variance (ANOVA), with

Figure 2 **Multivariate mixed random effects regression model of MMSE progression over time in patients with AD without CVD**



Model is adjusted for age, sex, education level, first Mini-Mental State Examination (MMSE) score, cholinesterase inhibitor use, number of vascular risk factors (VRF), year of first visit, duration of symptoms before first visit, and propensity score. AD = Alzheimer disease; CVD = cerebrovascular disease.

Tukey correction for multiple comparisons between groups, whereas frequencies of qualitative variables were compared with a χ^2 or Fisher exact test. Initial characteristics of the 3 treatment groups were also compared in a multivariate multinomial model.

To take into account correlation between repeated MMSE in the same patient, MMSE decline was analyzed with a multivariate mixed random effects regression model. This model is robust with missing data and allows analysis of repeated data with variable numbers of measurements per subject, as in our data set. In this model, a significant time effect indicates a change in MMSE score over time, and a significant interaction between group and time indicates a differential change in MMSE according to group. To ensure sufficient MMSE evaluations in each group, MMSE decline was analyzed from baseline evaluation up to a maximum of 2.5 years. The "time" variable was analyzed in months but, to maximize clarity, figure 2 presents the means of predicted adjusted values for 6-month periods.

Adjustment variables included age, sex, education level, first MMSE score, year of first visit, cholinesterase inhibitor (ChEI) use during follow-up, duration of symptoms before the first visit, number of VRF, and propensity score. To address the possible nonlinearity of cognitive decline, we added an adjustment with a time-squared term. We also checked for interactions between time or time squared and each of the adjustment variables. To avoid overadjustment, we did not include the number of VRF in the model used to analyze relationships between each VRF and cognitive decline.

Propensity score describes the probability for any given patient, based on his or her characteristics, of receiving a treatment for his or her VRF. It is a statistical technique reducing bias resulting from the nonrandom nature of treatment assignment seen in observational studies.[27-30] Variables for the propensity score were included step-by-step using an α value of 0.2: age, sex, education level, year of first visit, first MMSE score, and number of VRF were included in this way. Because of its known effect on the MMSE, the use of a ChEI was also included even if it had a $p > 0.2$.

For survival analysis, we used time since onset of dementia (i.e., duration of the disease as reported by the patient and his/her caregiver) rather than time since first visit. Cox proportional hazard model with "delayed entry" adjustment was used to assess the relative risk (RR) of mortality according to treatment group,[31] and actuarial analysis was used to predict survival curves for them. Data were right-censored 7 years after disease onset.

RESULTS A total of 996 patients with a complete file and a final diagnosis of AD (without another neurodegenerative disease) were seen at the memory clinic between 1997 and 2003. From these, 468 patients with CVD (337 [72.0%] had an MRI) and 9 patients without cerebral imaging were excluded. From the remaining 519 patients, 301 met our follow-up criteria with at least 2 MMSEs at least 6 months apart (figure 1). Most of the 218 patients not fulfilling our follow-up criteria were already followed at another center and were only referred for an expert opinion: at their first visit in our center, they were older, had symptoms for a longer time, and had a lower MMSE score.

Among the 301 patients included, 222 (73.8%) had a MRI. Only 21 patients (7.0%) did not have any VRF. Because of their small number, they were excluded from the following analysis, leaving 280 patients with at least 1 VRF. Characteristics of each treatment group are shown in table 1 and figure e-1 on the *Neurology*® Web site at www.neurology.org. The 3 treatment groups were similar for education level, use of a ChEI during follow-up, duration of symptoms before the first visit, first MMSE score, first DRS score, number of visits, and follow-up duration. Patients with no VRF treated were significantly younger, were more often women, and had fewer VRF than patients with some or all of their VRF treated (one-way ANOVA with Tukey correction, $p < 0.05$). On the multinomial adjusted model, only age and number of VRF were significantly different between the 3 groups.

Overall, the crude mean ± SD annual decline on MMSE was 1.6 ± 2.3 points, with no significant difference between treatment groups. In the adjusted mixed model (figure 2), MMSE scores declined over time ($p < 0.0001$), and the decline rate was different between groups ($p = 0.002$). Decline was slowest for patients with all VRF treated compared with no VRF treated (β estimate = +0.03 ± 0.01 per month, $p < 0.002$). Although the decline of the group with some VRF treated was intermediate, it did not differ from patients with no VRF treated (β = +0.01 ± 0.01 per month, $p < 0.39$). Adding a time-squared term did not improve the goodness of fit of the model. Additional adjustment on initial DRS score or re-

Table 1 Characteristics of patients according to their treatment group

	No VRF treated (n = 72)	Some VRF treated (n = 119)	All VRF treated (n = 89)	*p* Value
Age at first visit, y	69.2 (9.4)	72.7 (7.8)	73.4 (6.6)	<0.003
Men, %	20.8	37.0	32.6	<0.07
Higher education*, %	23.6	23.7	22.5	0.98
Duration of symptoms before the first visit, y	3.6 (2.8)	3.0 (2.0)	2.9 (2.4)	<0.11
First MMSE score	20.9 (5.7)	21.5 (5.1)	22.2 (4.1)	<0.25
First DRS score	111.3 (21.2)	113.3 (22.3)	115.3 (20.0)	<0.54
No. of visits	4.8 (2.0)	4.9 (2.1)	5.2 (1.9)	<0.36
Follow-up duration, y	2.2 (0.6)	2.3 (0.5)	2.3 (0.5)	<0.48
ChEI use during follow-up, %	79.2	77.3	84.3	0.45
No. of VRF	1.6 (0.6)	2.8 (0.8)	2.2 (0.9)	<0.0001
Lost at 2.5 y of follow-up, %	18.3	10.9	11.2	0.29
Death at follow-up, %	5.6	6.7	3.4	0.57
Death within 7 y of disease onset, %	11.1	17.7	16.9	0.46
Mean annual decline on MMSE	1.8 (2.2)	1.5 (2.4)	1.6 (2.1)	0.57

Values are given as mean (SD) or percentage.
*Higher education was considered education beyond primary school.
VRF = vascular risk factor; MMSE = Mini-Mental State Examination; DRS = Dementia Rating scale; ChEI = cholinesterase inhibitor.

moval of the adjustment on propensity score did not change the results.

When VRF were analyzed individually, only dyslipidemia treatment was globally significantly associated with cognitive decline (table 2). Treated patients with dyslipidemia had a slower decline than patients without dyslipidemia ($\beta = +0.03 \pm 0.01$, $p = 0.003$). The trend was similar for both statins (n = 46, $p = 0.06$) and fibrates (n = 34, $p = 0.0503$). Patients with untreated atherosclerosis ($\beta = -0.03 \pm 0.01$, $p = 0.02$) had a faster decline than patients with no atherosclerosis, while treated patients with atherosclerosis did not significantly differ from patients without atherosclerosis, suggesting that atherosclerosis treatment reduces the rate of cognitive decline back to that of patients without atherosclerosis. We did not find significant effect for hypertension, diabetes mellitus, or tobacco smoking treatments. However, untreated patients with diabetes tended to have a faster decline than patients without diabetes ($\beta = -0.03 \pm 0.02$, $p = 0.06$), whereas treated patients with diabetes did not differ from patients without diabetes ($\beta = +0.004 \pm 0.02$, $p = 0.79$). Interestingly, in patients without dyslipidemia, the decline rate was different between VRF groups ($p < 0.002$). Patients with all other VRF treated (i.e., tobacco smoking and/or hypertension and/or diabetes and/or atherosclerosis) declined more slowly than patients with no VRF treated ($\beta = +0.06 \pm 0.02$ per month, $p < 0.002$), although patients with some VRF treated were similar to patients with no VRF treated ($\beta = 0.01 \pm 0.02$ per month, $p < 0.58$). The same finding was observed in analysis restricted to patients without atherosclerosis.

Forty-four patients died within 7 years of disease onset. Duration of their disease was similar for all 3 treatment groups (no VRF treated: 5.4 ± 1.8 years; some VRF treated: 5.8 ± 1.5; all VRF treated: 5.2 ± 1.3; p = not significant). After adjustment, the risk of mortality was similar for patients with some VRF treated (RR 0.5, 95% confidence interval [CI] 0.2–1.5, $p < 0.23$) or all VRFs treated (RR 0.8, 95% CI 0.2–2.4, $p < 0.66$), compared with patients with no VRF treated.

DISCUSSION This study found an association between VRF treatment and slower cognitive decline in patients who had AD without CVD. Moreover, a progressive gradient of cognitive decline was seen from all VRF treated to some VRF treated and no VRF treated, as would be expected in a causal relationship.

Whereas the rate of cognitive decline in vascular dementia is thought to result from new vascular brain lesions,[5,20] in AD the relationship is less clear.[32]

Table 2 Summary of mixed random effects regression model testing the effect of each VRF on monthly change of MMSE

	Untreated			Treated			
	No. (%)	β ± SE	*p*	No. (%)	β ± SE	*p*	Global *p*
High blood pressure (n = 190)	58 (30.5)	−0.01 ± 0.01	0.23	132 (69.5)	−0.004 ± 0.01	0.63	0.48
Dyslipidemia (n = 207)	127 (61.4)	+0.01 ± 0.01	0.11	80 (38.6)	+0.03 ± 0.01	0.003	0.02
Diabetes mellitus (n = 36)	17 (47.2)	−0.03 ± 0.02	0.06	19 (52.8)	+0.004 ± 0.02	0.79	0.15
Tobacco smoking (n = 90)	29 (32.2)	−0.01 ± 0.01	0.43	61 (67.8)	+0.01 ± 0.01	0.55	0.51
Atherosclerotic disease (n = 118)	43 (36.4)	−0.03 ± 0.01	0.02	75 (63.6)	−0.01 ± 0.01	0.30	0.08

Values are β estimate ± SE and *p* value of interaction with time compared with patient without the vascular risk factor (VRF). Model is adjusted for age, sex, education level, first Mini-Mental State Examination (MMSE) score, year of first consultation, cholinesterase inhibitor use during follow-up, duration of symptoms before the first visit, and propensity score.

We tried to exclude patients with CVD, but even on MRI small vascular lesions could be missed. Autopsies series of patients with AD report a high prevalence of undiagnosed vascular lesions.[33,34] In addition, because most patients only had brain imaging at their initial visit, silent vascular brain lesions could have appeared during follow-up. Whether VRF treatment slowed cognitive decline by reducing the appearance of new vascular brain lesion or by other mechanisms could not be ascertained with this study.

We chose to aggregate VRF treatment because the risk of dementia associated with aggregated VRF is higher than with their individual addition.[16,17] The resulting classification from no VRF treated to all VRF treated is simple and could easily be used in clinical practice. A more robust model would have taken into account the relative importance of each VRF treatment as well as their reciprocal interactions, but such a model would have required a much larger sample size.

Assessment of individual VRF found a significant effect only for dyslipidemia treatment and atherosclerosis. For dyslipidemia, treated patients declined less than patients without dyslipidemia, suggesting that effects other than cholesterol lowering might be at work. Previous studies found similar results,[23] and results from large randomized controlled trials are awaited.[35] For atherosclerosis, untreated patients declined faster than patients without atherosclerosis. Atherosclerotic disease is considered a risk factor for vascular brain lesions, but it could also be the end result of other VRF. Its presence could therefore be the marker of an overall higher vascular risk, with stronger effect on cognitive decline. The absence of significant effects for high blood pressure, diabetes mellitus, and tobacco smoking could be due to a lack of power for less important effects. Because global treatment was still associated with a slower cognitive decline in patients without atherosclerosis or dyslipidemia, other VRF treatments still have an impact.

Because of its widespread use and ease of administration, the MMSE was the only neuropsychological test repeated for all patients. It gives a rough measure of cognitive function and may be insensitive to change, especially for the executive dysfunction expected in vascular cognitive impairment. A more extensive testing would have help to determine which cognitive domains were influenced by VRF treatment.

Most of our patients (93.0%) had at least 1 VRF. This high prevalence could result from an elevated detection rate with the use of a thorough standardized medical evaluation and/or from the criteria used to define VRF (i.e., some patients take an antiplatelet treatment for primary vascular prevention without atherosclerosis). The indications leading to drug prescriptions could not be retraced from our data, but we infer that patients with VRF treatment do have some vascular risk. We recognize that the VRF and their treatment could have changed during follow-up. But if treatment changes did occur, they would have rather lessened the difference observed, as in intention-to-treat analysis.

Similar low mortality rates were found between treatment groups. Our patients were relatively young (mean age 71.7 years) and still in mild or moderate stages of AD. Although the rate of cognitive decline has been reported to influence mortality in AD,[36] its effect is more pronounced in the later severe stages.[37] Because patients with treated VRF had more VRF, any beneficial effect from treatment could have been offset by a higher risk of vascular death.

A definite answer to whether treating VRF slows dementia progression would require a randomized controlled trial. This study was observational because it would have been unethical to deliberately leave a VRF untreated. However, such an observational design exposes to numerous biases. Patients treated for their VRF seemed to have a higher vascular risk: they were older, were more frequently male, and had more VRF. They were more likely to have CVD, although we precisely tried to exclude patients with CVD. This could introduce an indication bias if AD + CVD declines less than AD.[32,38] However, when restricting analysis to patients with only 1 or 2 VRF (i.e., with lower vascular risk), results go in the same direction.

Other unmeasured variables such as social support, depression, or attitude toward health care could have biased the results. Better VRF treatment could also simply reflect better global patient care. In agreement with the assumption of improved patient care over time, patients referred more recently were more often treated for both their VRF and their dementia (with increasing use of a ChEI). In patients treated for all their VRF, only a nonsignificant trend toward a higher use of ChEI was seen. Other indicators of good patient care, such as number of visit and follow-up duration, were similar across treatment groups, suggesting no obvious differences in overall care.

Previous studies have shown that stroke patients with cognitive impairment or dementia are less likely to be prescribed drugs for stroke prevention such as aspirin.[39,40] A prescription bias in our cohort is thus possible. However, education level, first MMSE score, and first DRS score were similar across treatment groups, suggesting that there was no obvious cognitive difference at the time of first evaluation, when the treatment had been assessed. We nonethe-

less tried to correct this bias by adding an adjustment for the probability of each patient to be treated (propensity score).

Despite all these limitations, our data add up to the existing evidence and suggest that treating VRF could at least partially offset their effect on cognitive decline. At least, dementia should not prevent from treating VRF.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Florence Richard (INSERM U744, Université de Lille 2, Institut Pasteur de Lille) and Yan Deschaintre (EA 2691, Université de Lille 2, Centre Mémoire de Ressources et de Recherche, CHRU de Lille and Stroke team, Centre Hospitalier de l'Université de Montréal).

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DISCLOSURE

Dr. Pasquier has served on scientific advisory boards for and received funding for travel from Bayer Healthcare (International), Eisai, Janssen-Cilag (National: French), and Ipsen; and receives research support from the University Research Group EA 2691 (Codirector). Dr. Deschaintre gave expert testimony using slides from the present study. He has served on a scientific advisory board for and received travel funding from Janssen Ortho and speaker honoraria from Janssen Ortho and Pfizer. Dr. Richard reports no disclosures. Dr. Leys has served on speakers' bureaus for and received funding for travel from Boehringer Ingelheim, Sanofi Aventis, Servier, and Novo Nordisk; serves as an Associate Editor of the *Journal of Neurology, Neurosurgery and Psychiatry* and as an editorial board member of *Stroke*; formerly served as an editorial board member of *Cerebrovascular Diseases*, the *Journal of Neurology*, and *La Revue Neurologique*; received payment for authoring a textbook (Leys D, Defebvre L. Préparer l'examen classant national: neurologie. Editions Ellipse. 2008) and 2 chapters in a book (Mas JL, Bousser MG. Accidents vasculaires cérébraux. Doin ed. 2009); has received an honorarium from the Canadian Stroke Council for evaluation of grant applications; and receives research support from the University Research Group EA 2691 (Codirector).

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