Vascular risk factors and cognitive impairment in a stroke-free cohort

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ABSTRACT

Objective: To examine vascular risk factors, as measured by the Framingham Stroke Risk Profile (FSRP), to predict incident cognitive impairment in a large, national sample of black and white adults age 45 years and older.

Methods: Participants included subjects without stroke at baseline from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study with at least 2 cognitive function assessments during the follow-up (n = 23,752). Incident cognitive impairment was defined as decline from a baseline score of 5 or 6 (of possible 6 points) to the most recent follow-up score of 4 or less on the Six-item Screener (SIS). Subjects with suspected stroke during follow-up were censored.

Results: During a mean follow-up of 4.1 years, 1,907 participants met criteria for incident cognitive impairment. Baseline FSRP score was associated with incident cognitive impairment. An adjusted model revealed that male sex (odds ratio [OR] = 1.59, 95% confidence interval [CI] 1.43–1.77), black race (OR = 2.09, 95% CI 1.88–2.35), less education (less than high school graduate vs college graduate, OR = 2.21, 95% CI 1.88–2.60), older age (10-year increments, OR = 2.11, per 10-year increase in age, 95% CI 2.05–2.18), and presence of left ventricular hypertrophy (LVH, OR = 1.29, 95% CI 1.06–1.58) were related to development of cognitive impairment. When LVH was excluded from the model, elevated systolic blood pressure was related to incident cognitive impairment.

Conclusions: Total FSRP score, elevated blood pressure, and LVH predict development of clinically significant cognitive dysfunction. Prevention and treatment of high blood pressure may be effective in preserving cognitive health. *Neurology*® 2011;77:1729–1736

GLOSSARY

CES-D = Center for Epidemiologic Studies–Depression; **CI** = confidence interval; **FSRP** = Framingham Stroke Risk Profile; **LVH** = left ventricular hypertrophy; **MI** = myocardial infarction; **OR** = odds ratio; **REGARDS** = Reasons for Geographic and Racial Differences in Stroke; **SIS** = Six-item Screener.

Vascular risk factors like hypertension and diabetes are common among older adults,[1,2] affect brain structure,[3] and have been associated with incident cognitive decline,[4] incident cognitive impairment,[5–7] and incident dementia.[8–10] The Framingham Stroke Risk Profile (FSRP) provides an estimate of the 10-year risk for future stroke based on age and presence and severity of several cardiovascular risk factors.[11,12] Among stroke-free individuals, high FSRP score is related to lower cognitive function.[13,14]

We examined the relation of the FSRP and its components in predicting incident cognitive impairment, using a brief and easily administered cognitive screening test, in a large, demographically and regionally diverse sample of older adults in the continental United States. The

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FSRP score and its components were selected by the Framingham group to be most predictive of stroke. While it is likely that the coefficients for cognitive impairment will differ somewhat, our interest is to determine if the formula will also capture cognitive impairment and if so which, if any, of the component scores selected to be predictive for stroke also perform well in the prediction of cognitive impairment. We hypothesized that FSRP total score and its components would be related to incident cognitive impairment.

METHODS

Design and sampling frame. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a national, population-based, longitudinal cohort study designed to investigate the factors associated with the excess stroke mortality observed among African Americans and residents of the Southeastern stroke belt region (see[15] for details). Participants were randomly selected from commercially available lists. Community-dwelling individuals aged 45 years or older, and either African American or white, were eligible for the study. Exclusion criteria included self-reported medical conditions (such as cancer) that would prevent long-term participation, or being on a waiting list for a nursing home. The sample size was calculated to provide sufficient incident stroke events to detect relatively small risk effects. The sample was recruited between January 2003 and December 2007 using mail and telephone contact (33% response rate, 49% cooperation rate[16]). Enrollment resulted in a cohort of 30,239 individuals with 56% residents in stroke belt states (NC, SC, GA, AL, MS, TN, AR, and LA), 45% men, and 42% African American.

Standard protocol approvals, registrations, and patient consents. Study procedures were reviewed and approved by the institutional review boards at the collaborating institutions. All subjects provided informed consent to participate in the study.

Procedures. Demographic data (age, education [years completed], race [African American or white], and sex), health history including use of antihypertensive medications, and depressive symptoms were gathered via telephone interview at baseline. An in-home examination was used to gather physical measures including blood pressure, blood and urine samples, EKG, and an inventory of current medications. Incident stroke was ascertained via telephone follow-up every 6 months using the Questionnaire for Verifying Stroke-free Status[17] and verified by medical record review and adjudication by a panel of neurologist stroke experts.

Measures. The Six-item Screener (SIS) is a global measure of cognitive status that assesses 3-item recall and orientation to year, month, and day of the week.[18] Scores range from 0 to 6 with a score of 4 or fewer correct indicative of cognitive impairment. The SIS was first administered at baseline in REGARDS in December 2003 and then annually to all participants. Incident cognitive impairment was defined as decline from an initial score of 5 or better to the most recent follow-up score of 4 or less. The SIS has been validated against clinical diagnoses of dementia and mild cognitive impairment (74% sensitivity and 80% specificity for both groups combined vs cognitively normal elders).[18] The SIS has been used to document cognitive impairment in older patients seen in emergency departments[19] and older depressed patients in a large randomized controlled trial.[20] SIS scores are related to self-reported stroke symptoms and health behaviors,[21] cardiovascular risk factors,[22,23] and kidney dysfunction.[24] Self-reported depressive symptoms were measured with the Center for Epidemiologic Studies–Depression (CES-D) scale, 4-item version.[25]

The FSRP[11,12] was calculated as an estimate of the 10-year risk of stroke. It incorporates age, measured systolic blood pressure (in mm Hg recoded into 10 groupings from 95 to 204 mm Hg), presence of diabetes mellitus, current cigarette smoking, history of heart disease, atrial fibrillation, LVH, and the use of antihypertensive medication. Diabetes was defined as fasting glucose greater than or equal to 126 mL/dL, nonfasting glucose greater than or equal to 200 mL/dL, or self-reported use of diabetes medications. Current cigarette smoking (at the baseline) and current use of antihypertension medications (at the baseline) were determined by interview. History of heart disease was determined by self-reported myocardial infarction (MI), coronary artery bypass graft, angioplasty or stenting, or evidence of MI from baseline ECG. Atrial fibrillation was defined as self-reported or via ECG evidence. LVH was defined as presence on ECG (12 lead or 7 lead).[26] Given our dichotomous outcome, we did not log transform scores though some studies with a continuous outcome have used transformed scores.[14]

Statistical analyses. Our aim was to relate vascular risk factors to incident cognitive impairment in an initially cognitively intact and stroke-free cohort. Of 30,239 REGARDS participants, we excluded 8 due to anomalous data, 1,931 due to self-reported stroke at baseline, 2,322 due to cognitive impairment at baseline (SIS score of 4 or fewer correct), 500 due to missing SIS measurements, 1,603 due to only 1 SIS assessment, and 113 due to incident stroke prior to first SIS assessment. Thus 23,752 participants remained for analysis. Of note, 196 participants in the remaining 23,752 subsequently had an adjudicated stroke during the follow-up. The SIS assessments for these participants were included until the time at which their stroke occurred, but were censored afterward. To examine the effect of a more stringent case definition on outcomes, we conducted a sensitivity analysis focusing on participants with a minimum of 3 SIS assessments, the last 2 with SIS <5 ($n = 20{,}803$); the pattern of results did not differ and are not presented below.

Analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC). Descriptive statistics were computed for continuous categorical variables, and t tests or χ^2 tests of association were used as appropriate to assess whether differences in baseline characteristics existed between those with and without incident cognitive impairment. Logistic regression models were used to examine whether the odds of cognitive impairment differed by demographic characteristics, FSRP total score, and by FSRP factors, in univariate models, in models adjusted only for demographic factors, and in a single multivariable model. We assessed interactions between the FSRP total score and each of race, region, and gender, in order to determine whether differences in the relationship between the FSRP total score and incident impairment differed as a function of each of these factors. In addition, we examined the interaction between SBP and LVH, and the interaction between SBP and antihypertensive medication use. A sensitivity analysis excluding those with LVH was conducted to determine the impact this had on results. Odds ratios and 95% confidence intervals were computed.

Baseline characteristics included age, sex, race, region, education (< high school, high school graduate, some college, college

Table 1 Baseline characteristics

	All subjects (n = 23,752)	Incident cognitive impairment (n = 1,907, 8%)	No cognitive impairment (n = 21,845, 92%)	p Value[a]
Age, y	64.3 (9.2)	69.9 (9.4)	63.8 (9.0)	<0.0001
Male gender, n (%)	10,350 (44)	983 (52)	9,367 (43)	<0.0001
African American, n (%)	8,948 (38)	990 (52)	7,958 (36)	<0.0001
Region, n (%)				
Stroke belt[b] state	8,180 (34)	709 (37)	7,471 (34)	0.001
Stroke buckle[c]	5,016 (21)	345 (18)	4,671 (21)	
Non-belt state	10,556 (44)	843 (45)	9,703 (44)	
Education, n (%)				<0.0001
< High school	2,370 (10)	407 (21)	1,963 (9)	
High school graduate	5,975 (25)	551 (29)	5,424 (25)	
Some college	6,466 (27)	443 (23)	6,023 (28)	
College graduate	8,929 (38)	503 (26)	8,426 (39)	
Alcohol use, n (%)				
None	14,192 (61)	1,278 (69)	12,914 (60)	<0.0001
Moderate	8,160 (35)	524 (28)	7,636 (36)	
Heavy	972 (4)	59 (3)	913 (4)	
Baseline SIS score	5.8 (0.42)	5.6 (0.49)	5.8 (0.41)	<0.0001
CES-D-4	1.0 (1.9)	1.3 (2.1)	1.0 (1.9)	<0.0001
Assessment interval, y	4.1 (1.4)	4.1 (1.4)	4.1 (1.3)	0.33

Abbreviations: CES-D-4 = 4-item Center for Epidemiologic Studies–Depression scale; SIS = Six-item Screener.
[a] Difference between incident cognitive impairment and no cognitive impairment.
[b] Stroke belt = North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas.
[c] Stroke buckle = coastal plains of North Carolina, South Carolina, and Georgia.

graduate or higher), alcohol use (National Institute on Alcohol Abuse and Alcoholism classification: none, moderate [0–7/week, women; 0–14/week, men], heavy [7+/week, women; 14+/week, men]), baseline SIS score, CESD-4, SBP, and FSRP indicators.

RESULTS Table 1 presents the baseline characteristics overall and by final cognitive status. The average age was 64 (SD = 9.2) years and the average length of follow-up was 4.1 (SD = 1.4) years. Eleven percent of the participants completed 2 SIS assessments during the follow-up, 22% had 3 assessments, 24% had 4 assessments, 24% had 5, and 19% had 6 or more. The group of 1,907 participants with incident cognitive impairment was significantly older and more likely to be male, African American, resident in the stroke belt, and to have completed fewer years of education than the group without incident cognitive impairment. Just over 78% (1,497/1,907) of incident cognitive participants met criteria by a decline of 2 or more points in the SIS. Baseline SIS scores were only slightly lower in the incident cognitive impairment group (mean of 5.6 vs 5.8) compared to the no decline group. The incident cognitive impairment group also had a slightly higher depressive symptoms score, and less alcohol use than the group with no cognitive decline.

Table 2 shows the mean scores for the FSRP and systolic blood pressure and percent with component FSRP conditions for the whole sample and by incident cognitive impairment status. The total FSRP score and each of the FSRP factors, except current smoking, were related to incident cognitive decline. Specifically, the group with incident cognitive impairment had higher systolic blood pressure, more use of antihypertensive medications, and higher prevalence of diabetes, LVH, atrial fibrillation, and history of heart disease than the group that stayed cognitively intact. The figure depicts the frequency of incident cognitive impairment according to FSRP score quartile. A total of 21,936 participants had a FSRP score and 1,732 were cognitively impaired (1,816 participants did not have a total FSRP score due to missing one of the components). The rate of impairment increases in a nearly linear fashion across the FSRP quartiles to 14.5% in the highest quartile.

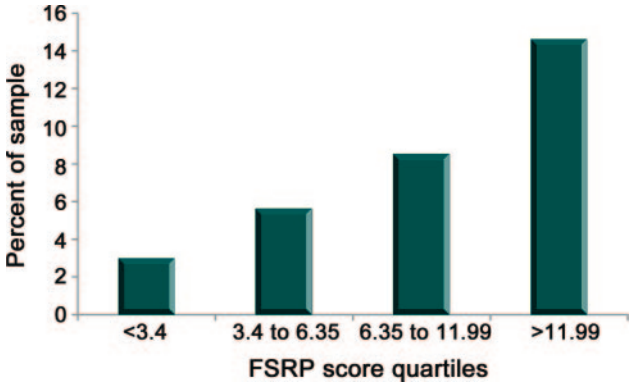
Table 3 presents the results from the fitted logistic regression models. In the univariate models, each of

Table 2 Framingham Stroke Risk Profile factors at baseline

	All subjects (n = 23,752)	Incident cognitive impairment (n = 1,907, 8%)	No cognitive impairment (n = 21,845, 92%)	p Value[a]
Framingham Stroke Risk Profile score	9.6 (10.0)	15.2 (13.3)	9.1 (9.5)	<0.0001
Systolic blood pressure[b]	127 (16)	130 (17)	127 (16)	<0.0001
Antihypertensive medication, n (%)	1,823 (8)	1,059 (9)	764 (7)	<0.0001
Diabetes, n (%)	4,547 (20)	469 (26)	4,078 (19)	<0.0001
Left ventricular hypertrophy, n (%)	1,169 (5)	153 (8)	1,016 (5)	<0.0001
Atrial fibrillation, n (%)	1,878 (8)	191 (10)	1,687 (8)	0.0005
Heart disease, n (%)	4,884 (21)	515 (28)	4,369 (20)	<0.0001
Current smoker, n (%)	3,321 (14)	239 (13)	2,982 (14)	0.18

[a] Difference between incident cognitive impairment and no cognitive impairment.
[b] Measured blood pressure in mm Hg recoded into 10 groupings from 95 to 204 mm Hg.

Figure Percent incident cognitive impairment by Framingham Stroke Risk Profile (FSRP) score quartiles



A total of 21,936 participants had a FSRP score and 1,732 were cognitively impaired (1,816 participants did not have a total FSRP score due to missing one of the components).

the demographic and FSRP factors, with the exception of current smoking, was related to incident cognitive impairment, and remained so after adjustment for demographic factors. After multivariable adjustment, the demographic factors (male sex, black race, stroke belt residence, and less education) and only the FSRP factors of older age and presence of LVH were significantly related to incident cognitive impairment. A separate multivariable analysis excluding subjects with LVH revealed that higher systolic blood pressure (odds ratio 1.04 for each 10-mm Hg increase, 95% confidence interval 1.02–1.06) and age (odds ratio 2.10 for each 10-year increase, 95% confidence interval 2.04–2.17) were related to incident cognitive impairment.

The mean (SD) baseline FSRP score was 15.2 (13.3) in those who developed cognitive impairment and 9.1 (9.5) in those who did not. For each SD higher baseline FSRP score, the risk of incident cognitive impairment increased by 41% (95% confidence interval 37%–46%) after adjustment for demographic factors. None of the interactions assessed were statistically significant.

DISCUSSION In a large, national sample that was stroke-free and cognitively normal at baseline, followed for an average of 4 years, and culled of participants who developed clinical stroke in the interval, FSRP score, which is composed of vascular risk factors, was linearly related to rate of incident cognitive impairment. In the highest FSRP quartile (scores >11.99), almost 3 in 20 participants de-

Table 3 Odds of incident cognitive impairment as a function of demographics, region, and Framingham Stroke Risk Profile component scores (n = 23,752)

	Unadjusted models		Adjusted only for demographics[a]		Fully adjusted models[b]	
	OR	95% CI	OR	95% CI	OR	95% CI
Sex (male vs female)	1.42[c]	1.29-1.57[c]	1.62[c]	1.47-1.78[c]	1.59[c]	1.43-1.77[c]
Race (African American vs white)	1.88[c]	1.72-2.07[c]	1.72[c]	1.56-1.90[c]	2.09[c]	1.87-2.47[c]
Region of residence						
Stroke belt vs non-belt	1.08	0.97-1.20	1.08	0.97-1.20	1.20[c]	1.06-1.34[c]
Stroke buckle vs non-belt	0.84[c]	0.74-0.96[c]	0.86[c]	0.76-0.99[c]	1.01	0.86-1.16
Education						
< High school vs college graduate	3.47[c]	3.02-3.99[c]	3.14[c]	2.72-3.63[c]	2.21[c]	1.88-2.60[c]
High school graduate vs college graduate	1.70[c]	1.50-1.92[c]	1.68[c]	1.48-1.91[c]	1.55[c]	1.35-1.78[c]
Some college vs college graduate	1.23[c]	1.08-1.41[c]	1.22[c]	1.07-1.39[c]	1.16[c]	1.00-1.34[c]
FSRP (+1 SD difference)	1.49[c]	1.44-1.57[c]	1.41[c]	1.37-1.46[c]	—	—
Age (10-year intervals)	2.05[c]	1.95-2.17[c]	2.10[c]	1.99-2.22[c]	2.11[c]	2.05-2.18[c]
Systolic blood pressure (10 mm Hg)	1.15[c]	1.12-1.18[c]	1.08[c]	1.05-1.11[c]	1.00	1.00-1.01
Antihypertensive medication	1.36[c]	1.23-1.50[c]	1.16[c]	1.04-1.28[c]	0.94	0.84-1.05
Diabetes	1.44[c]	1.29-1.61[c]	1.15[c]	1.02-1.28[c]	1.11	0.98-1.26
Left ventricular hypertrophy	1.79[c]	1.50-2.14[c]	1.60[c]	1.33-1.92[c]	1.29[c]	1.05-1.58[c]
Atrial fibrillation	1.33[c]	1.14-1.56[c]	1.35[c]	1.15-1.59[c]	1.10	0.92-1.31
Heart disease	1.49[c]	1.34-1.66[c]	1.37[c]	1.23-1.53[c]	1.09	0.97-1.23
Current smoker	0.91	0.80-1.05	0.77[c]	0.66-0.89[c]	1.07	0.91-1.26

Abbreviations: CI = confidence interval; FSRP = Framingham Stroke Risk Profile; OR = odds ratio.
[a] Includes sex, race, region, and education.
[b] After adjusting for each of the other variables in the table.
[c] 95% CI that does not include 1.0.

veloped incident cognitive impairment during the follow-up.

All the elements of the FSRP are significant predictors of cognitive impairment individually, and the more individual risk factors a person has, the greater the risk of cognitive impairment. Age and presence of LVH were the only FSRP component factors independently associated with future development of cognitive impairment. The association between LVH and cognitive impairment remained after controlling for age, sex, race, region of residence, and education. Consistent with the notion that LVH is a late developing marker of long-term exposure to high blood pressure,[27] we also found that high systolic blood pressure was related to incident cognitive impairment in persons without LVH. This suggests that hypertension may be a very important risk factor to address in order to prevent cognitive impairment. Overall, it appears that the total FSRP score and its components, while initially derived to predict stroke, are also useful in the prediction of cognitive impairment.

Other studies have shown that increased stroke risk as measured by total FSRP score is related to lowered cognitive performance cross-sectionally[13,14] and longitudinally.[28] The longitudinal study[28] consisted of 235 stroke- and dementia-free men at the baseline who were reassessed on a cognitive battery 3 years later. The FSRP was inversely related to verbal fluency but not word list learning, word list recall, pattern comparison, or digit span. Our study extends these findings by including a larger, more diverse population (23,752 participants, of whom 56% were female and 38% were African American), and longer follow-up (average of 4 and up to 6 years).

LVH is a pathologic reaction to cardiovascular disease including high blood pressure. Elevated blood pressure increases the load the heart contracts against and over time results in increased volume of heart muscle and functional degradation of the heart including heart failure. An earlier cross-sectional analysis of the Framingham Offspring Study cohort showed an inverse relation between left ventricular mass (as determined by heart wall thickness and chamber volume) and cognition.[29] The relationship was attenuated when blood pressure was considered and eliminated when prevalent heart disease (coronary artery disease, claudication, and heart failure) and risk factors (diabetes, cholesterol, alcohol use, smoking, homocysteine, and depressed mood) were included in the modeling. Our study extends this finding by showing a longitudinal relationship between LVH and clinically significant incident cognitive impairment that is independent of other demographic and cardiovascular risk factors.

Our subgroup analysis suggested that elevations in systolic blood pressure were associated with incident cognitive impairment even in those without LVH. This is consistent with other studies of blood pressure and cognitive decline[4,30,31] incident cognitive impairment,[5–7] and incident dementia.[9] Our data suggest an early role for elevated blood pressure in the relationship of LVH and longitudinal changes in cognition.

In contrast to other studies that reported a relationship of diabetes to cognitive decline,[4,31–34] incident cognitive impairment,[5,31–34] and incident dementia,[8,10] diabetes was not independently associated with risk of incident cognitive impairment in this study (others have also failed to see an association[35]). This may be due to a limitation of the SIS in assessing cognitive impairment as a recent systematic review of prospective observational studies on diabetes and cognitive decline indicated that the broad measure MMSE (from which the SIS is derived) was less sensitive than a psychomotor speed-based cognitive test for diabetes-associated cognitive decline.[36] It is also possible that diabetes as reflected in the FSRP (present vs absent), while sensitive to stroke risk, requires additional elaboration and specification in order to be a marker of cognitive decline. For example, it may be necessary to capture the duration of exposure to diabetes or the quality of treatment and control of diabetes.

Subclinical cerebrovascular disease including white matter abnormalities, silent cerebral infarction, and brain atrophy may underlie the association we saw between stroke risk factors and cognition. Other studies with neuroimaging verification in stroke-free participants with FSRP risk have found that FSRP scores are correlated with silent cerebral infarctions[37] and changes in cerebral brain volume over time.[38]

This study has strengths including a very large, diverse sample that was free of clinical stroke at the baseline, censoring subjects at the time of incident stroke during the follow-up interval, longitudinal analysis with moderate length of follow-up interval, and use of a robust marker of clinically important cognitive dysfunction. Limitations include attrition over the follow-up interval. The attrition rate in REGARDS is about 3% per year which is not atypical for a large study with high proportion of older adults. To the extent that less cognitively able subjects were over-represented among the dropouts, a likely situation,[39] our findings would underestimate the relation between cardiovascular risk factors and cognition. Our use of a global cognitive marker focused on memory means that we are unable to examine the effects of stroke risk factors on other cognitive domains sensitive to cardiovascular dysfunction in-

cluding executive, psychomotor, and visuospatial function. Our definition of cognitive impairment is based on a screening test and not a clinical diagnosis of mild cognitive impairment or dementia. While screening tests such as the SIS do have reasonable correspondence to clinical diagnosis,[18,40] there is some loss of precision, which would make it less likely that correlates of cognitive impairment could be detected. We found that current smoking (as coded in the FSRP) was not related to cognitive status. Since relatively few people are current smokers and former smokers are common, future research could examine smoking in a more differentiated way, for example, current smoker, former smoker, or never smoked, or smoking could be scaled in terms of pack-years. Finally, 25% of our participants received a 7-lead ECG which requires calculation of Cornell voltage using S-wave amplitude in the midsternal lead (SV) instead of SV3 in the formula to calculate LVH. While this approach to LVH has demographic and clinical associations that are similar to that calculated from a standard 12-lead ECG (using SV3),[26] some loss of precision in that portion of the sample is possible, which would lead to underestimation of the relationships between LVH and cognition.

Our findings suggest that the vascular risk factors measured by the FSRP, elevated blood pressure and its long-term consequence, left ventricular hypertrophy, may provide a simple and efficient means of identifying adults who are at risk for future cognitive impairment and lends support to the notion that increased attention to prevention and treatment of high blood pressure may be effective in preserving cognitive health.

AUTHOR CONTRIBUTIONS

Dr. Unverzagt: drafting/revising the manuscript for content, including medical writing for content, analysis or interpretation of data. Dr. McClure: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, statistical analysis, obtaining funding. Dr. Wadley: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, obtaining funding. Dr. Jenny: drafting/revising the manuscript for content, including medical writing for content. Dr. Go: drafting/revising the manuscript for content, including medical writing for content. Dr. Cushman: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, obtaining funding. Dr. Kissela: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, obtaining funding. Dr. Kelley: drafting/revising the manuscript for content, including medical writing for content. Dr. Kennedy: drafting/revising the manuscript for content, including medical writing for content, analysis or interpretation of data. Dr. Moy: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, obtaining funding. Dr. V. Howard: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, acquisition of data, study supervision or coordination, obtaining funding. Dr. G. Howard: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision or coordination, obtaining funding.

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DISCLOSURE

Dr. Unverzagt has served as a consultant to Eli Lilly and Company; serves on the editorial boards of the *Journal of the International Neuropsychological Association* and *Neuropsychology*; receives research support from the NIH and Posit Science Inc; and holds stock in Eli Lilly and Company. Dr. McClure serves on a Data Monitoring Committee for the NIH/NINDS and receives research support from Genzyme Corporation, the NIH (NINDS, NICHD, NHLBI), and NASA. Dr. Wadley has received funding for travel from Amgen; serves on the editorial board of *Current Gerontology and Geriatrics Research*; and receives research support from Genzyme Corporation, the NIH, and the Jefferson County Office of Senior Citizens Services. Dr. Jenny serves on the editorial board of *Arteriosclerosis, Thrombosis and Vascular Biology*; serves as a consultant for Tethys Bioscience, Inc.; receives research support from GlaxoSmithKline, the NIH, and the American Diabetic Association; and holds stock in Haematologic Technologies, Inc. Dr. Go receives research support from the NIH/NINDS. Dr. Cushman serves on the editorial boards of the *Journal of Thrombosis and Haemostasis*, *Circulation*, *Archives of Internal Medicine*, and the *Journal of Thrombosis and Thrombolysis*; and receives/has received research support from Amgen, GlaxoSmithKline, and the NIH. Dr. Kissela serves on scientific advisory boards for Northstar Neuroscience and Allergan, Inc.; has received funding for travel and speaker honoraria from Allergan, Inc.; has received research support from NexStim and the NIH; and provides medico-legal reviews. Dr. Kelley receives/has received research support from Novartis and the NIH. Dr. Kennedy receives research support from the NIH (NINDS, NIA, NIDDK). Dr. Moy reports no disclosures. Dr. V. Howard serves/has served on scientific advisory boards for Amgen, Boehringer-Ingelheim, Mitsubishi, PhotoThera, and MediciNova; her spouse serves on a scientific advisory boards for Bayer Schering Pharma; has received funding for travel from Amgen; serves as a consultant for NIH review committees; her spouse has provided legal consulting for Merck Serono; and receives research support from the NIH (NINDS, NIDDK, NIOSH). Dr. G. Howard serves/has served on scientific advisory boards for Bayer Schering Pharma, Abbott, Boehringer Ingelheim, BrainsGate, Cerevast Therapeutics, Inc., CoAxia, Inc., MediciNova, Inc., Mitsubishi Tanabe Pharma Corporation, and PhotoThera; serves as Stroke Section Editor for the *Journal of The American Society of Hypertension*; and receives research support from Amgen and the NIH (NINDS, NIAMS, NICHD, NHLBI).

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CELEBRATING 60 YEARS OF PUBLICATION
Neurology

Historical Abstract: December 12, 2000

EARLY STROKE TREATMENT ASSOCIATED WITH BETTER OUTCOME: THE NINDS rt-PA STROKE STUDY

J.R. Marler, B.C. Tilley, M. Lu, T.G. Brott, P.C. Lyden, J.C. Grotta, J.P. Broderick, S.R. Levine, M.P. Frankel, S.H. Horowitz, E.C. Haley, Jr., C.A. Lewandowski, T.P. Kwiatkowski, for the NINDS rt-PA Stroke Study Group

Neurology **2000;55:1649-1655**

Background: The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study showed a similar percentage of intracranial hemorrhage and good outcome in patients 3 months after stroke treatment given 0 to 90 minutes and 91 to 180 minutes after stroke onset. At 24 hours after stroke onset more patients treated 0 to 90 compared to 91 to 180 minutes after stroke onset had improved by four or more points on the NIH Stroke Scale (NIHSS). The authors performed further analyses to characterize the relationship of onset-to-treatment time (OTT) to outcome at 3 months, early improvement at 24 hours, and intracranial hemorrhage within 36 hours. ***Methods:*** Univariate analyses identified potentially confounding variables associated with OTT that could mask an OTT–treatment interaction. Tests for OTT–treatment interactions adjusting for potential masking confounders were performed. An OTT–treatment interaction was considered significant if $p \leq 0.10$, implying that treatment effectiveness was related to OTT. ***Results:*** For 24-hour improvement, there were no masking confounders identified and there was an OTT–treatment interaction ($p = 0.08$). For 3-month favorable outcome, the NIHSS met criteria for a masking confounder. After adjusting for NIHSS as a covariate, an OTT–treatment interaction was detected ($p = 0.09$): the adjusted OR (95% CI) for a favorable 3-month outcome associated with recombinant tissue-type plasminogen activator (rt-PA) was 2.11 (1.33 to 3.35) in the 0 to 90 minute stratum and 1.69 (1.09 to 2.62) in the 91 to 180 minute stratum. In the group treated with rt-PA, after adjusting for baseline NIHSS, an effect of OTT on the occurrence of intracranial hemorrhage was not detected. ***Conclusions:*** If the NINDS rt-PA Stroke Trial treatment protocol is followed, this analysis suggests that patients treated 0 to 90 minutes from stroke onset with rt-PA have an increased odds of improvement at 24 hours and favorable 3-month outcome compared to patients treated later than 90 minutes. No effect of OTT on intracranial hemorrhage was detected within the group treated with rt-PA, possibly due to low power.

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Comment from Kevin Barrett, MD, MSc: *This analysis of The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study established the clinical relationship between time to treatment and stroke outcome. The manuscript includes an often-cited figure that clearly demonstrates the improved odds of a favorable 3-month outcome with earlier rt-PA treatment.*