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Long-term predictive value of the Framingham Risk Score for Stroke in HIV-positive vs HIV-negative men

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ABSTRACT

Objective: To test the predictive accuracy of the Framingham Risk Score for Stroke (FRS-S) in HIV-infected (HIV+) vs HIV-uninfected (HIV−) men.

Methods: The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective study of HIV+ and HIV− men who have sex with men (MSM) enrolled in 4 US cities. We ascertained all reported stroke events during a recent 15-year timeframe (July 1, 1996 to June 30, 2011) among 3,945 participants (1,776 HIV+ and 2,169 HIV−). For those with strokes, FRS-S were calculated 10 years before the stroke event and assessed according to HIV status.

Results: A total of 114 stroke events occurred, including 57 HIV+ and 37 HIV− participants with first-ever strokes and 19 fatal strokes. The incidence of first-ever stroke was 1.7/1,000 person-years among HIV− and 3.3/1,000 person-years among HIV+ participants. Among those with strokes, HIV+ participants were younger than HIV− participants (median age 51.3 vs 61.8 years, $p < 0.0001$). For these men with stroke, the average 10-year risk of stroke was higher for HIV− MSM (6.6% [range 3%–26%] vs 4.9% for HIV+ MSM [range 0%–15%], $p < 0.04$). Traditional risk factors for stroke were similar among the Framingham cohort and the MACS HIV+ and HIV− participants.

Conclusions: FRS-S prediction was systematically different in HIV+ vs HIV− men with stroke events. The FRS-S underestimates the long-term risk of stroke in HIV+ men. ***Neurology*® 2013;81:2094–2102**

GLOSSARY

FRS-S = Framingham Risk Score for Stroke; **HAART** = highly active antiretroviral therapy; ***ICD-9*** = *International Classification of Diseases*, ninth revision; **MACS** = Multicenter AIDS Cohort Study; **MSM** = men who have sex with men.

The Framingham Risk Score for Stroke (FRS-S) was developed in the early 1990s to identify individuals at substantially increased long-term stroke risk. The score provided impetus for risk factor modification and drew attention to individuals who were at risk of stroke due to borderline levels of multiple factors.[1] In the early 1990s, survival of people with HIV infection was limited, and the Framingham Heart Study Cohort, in whom the FRS-S was developed, was not tested for HIV serostatus.

With the advent of highly active antiretroviral therapy (HAART) and longer survival of HIV-infected (HIV+) individuals, the relationships among chronic HIV infection, HAART use, and vascular disease have become increasingly important.[2–6] The influence of HIV on long-term stroke risk remains unresolved[7–11] even though >50% of all prevalent HIV cases in the United States will be older than 50 years by 2015.[12] Longitudinal studies that prospectively ascertain the effect of HIV on stroke risk in the HAART era are not reported.[5]

Here, we test the long-term predictive value of the FRS-S in a large prospectively followed cohort of HIV+ vs HIV-uninfected (HIV−) men who have sex with men (MSM). First,

Supplemental data at www.neurology.org

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MACS coinvestigators are listed on the *Neurology*® Web site at www.neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

we compare the baseline characteristics of the Framingham cohort vs the Multicenter AIDS Cohort Study (MACS) participants for important stroke risk factor differences. Second, we report the stroke incidence in HIV+ and HIV− men and determine whether the FRS-S 10 years earlier differed by HIV serostatus among participants with strokes. Finally, as a separate analysis, we calculate the FRS-S at the beginning of the HAART era for all MACS participants and compare it between HIV+ and HIV− groups.

METHODS

Standard protocol approvals, registrations, and patient consents. The MACS was approved by the Institutional Review Board at each study site. Each participant provided his own informed consent to participate in the MACS.

Cohort. The MACS began in 1984 to study the natural history of AIDS. The enrollment, recruitment, and goals of the MACS have been reported.[13,14] MSM were recruited in Baltimore, Chicago, Los Angeles, and Pittsburgh. Cumulative enrollment is now at >7,000 participants. MSM were chosen because they represented a group at high risk of AIDS and could reliably participate in a longitudinal follow-up study. The HIV status of the men at enrollment was unknown. MSM who remained HIV− served as a comparison group in the present study.

MACS participants are followed every 6 months via standardized in-person interviews, clinical assessments, neuropsychological screening tests, and laboratory evaluation, including measurements of HIV viral load and T-cell subsets (Roche ultrasensitive assay, <50 copies/mL, and standardized and quality-controlled flow cytometry).[13] By late 1996, HAART was initiated by >50% of all participants, considered as the beginning of the HAART era.[15] Stroke events during a 15-year period of the HAART era (July 1, 1996 to June 30, 2011) were used here.

Definition of stroke. Stroke was ascertained by either self-report at the study visit, prospective active reporting by participants between visits, review of causes of death, or ad hoc when reviewing medical records to confirm other diagnoses. At each MACS visit, participants were asked whether they were diagnosed with stroke since their last visit, and, in April 2004 through March 2005, they were asked about lifetime history of stroke. Hospitalizations and diagnoses for vascular and neurologic problems are continuously monitored. Events are recorded using *ICD-9* codes. Reported strokes were followed up by each study site's investigators, including neurologists, via correspondence to the participant's physician.

Death of MACS participants is also continuously monitored. For deaths that were reported by the participant's contact (e.g., partner, physician), death certificates were ascertained and systematically searched for the diagnosis of stroke. Deaths in the MACS are also captured and verified via the National Death Index, Social Security Death Index, credit databases, and scanning of obituaries. Medical records before death were requested. Fatal stroke was defined as a stroke with a reported death within 30 days after the date of first presentation of stroke.

Any event that fit the definition of "silent stroke," defined as imaging findings representative of stroke that were not correlated with clinical symptoms of stroke, were excluded. Self-reported stroke events that could not be confirmed were included, and sensitivity analyses were performed (table e-1 on the *Neurology*® Web site at www.neurology.org).

Framingham Risk Score for Stroke. The original FRS-S was sex-specific and based on 36 calendar years of follow-up of 2,372 men and 3,362 women aged 55 to 84 years.[1] There were 213 strokes in men and 259 strokes in women in the Framingham Heart Study's original cohort. The distribution of events diagnosed in men was atherothrombotic brain infarction (46%), TIA only (24%), cerebral embolus (19%), intracerebral hemorrhage (5%), subarachnoid hemorrhage (4%), and other (2%). Points for sex-specific FRS-S were ascribed based on 8 baseline risk factors, identified via Cox proportional hazards regression models: age, systolic blood pressure (mm Hg), antihypertensive therapy, diabetes mellitus, cigarette smoking, atrial fibrillation on ECG, left ventricular hypertrophy on ECG, and history of previously diagnosed cardiovascular disease (table e-2). Cardiovascular disease in the original score included coronary heart disease, history of myocardial infarction, angina pectoris, coronary insufficiency, cardiac failure, and intermittent claudication.

Vascular risk factor definitions. In the MACS, risk factors for stroke were defined according to the Framingham Study whenever possible. For participants who were younger than 55 years, the number of points ascribed for age was zero. Diabetes mellitus was defined as 1) measured fasting glucose levels ≥126 mg/dL, 2) measured nonfasting glucose levels ≥200 mg/dL when fasting samples were unavailable, or 3) self-reported diagnosis of diabetes treated with medications. Diabetes was ascertained at study entry and during regular study visits after April 1, 1999. Cigarette smokers were current smokers. Consistent with the FRS-S, former cigarette smokers were not given risk points. Specific cardiac conditions used in the original FRS were not regularly evaluated clinically by MACS investigators. ECGs were also not performed as part of the MACS. It was assumed here that no MACS participants had atrial fibrillation or left ventricular hypertrophy; therefore, no MACS participants received points for these conditions. However, within the MACS, participants were asked to report their lifetime history between April 2004 and March 2005—and follow-up information on subsequent visits—on whether or not they had experienced 1) myocardial infarction, 2) angina or chest pain caused by the heart, and 3) congestive heart failure. Participants who responded affirmatively to these questions were ascribed the 3 points for cardiovascular disease defined in the FRS-S (table e-1). All other participants were ascribed zero points. The FRS-S risk score conversion to the 10-year predicted risk of stroke is based on the percentage points derived from the original Framingham cohort.[1]

Statistical analysis. Participants with prevalent stroke at the time of study entry or stroke in the pre-HAART era were excluded. Among participants with a first-ever stroke during the HAART era, FRS was calculated using risk factors and characteristics from the study visit closest to 10 years before the date of the stroke event. The algorithm provided by the FRS cohort was used (table e-1). Participants in whom risk factor information was missing were considered not to have the risk factor of interest.

As a second measure of stroke risk, calculation of the baseline FRS-S among the entire MACS cohort was performed and compared between HIV+ and HIV− participants. This was done on all MACS participants, whether they had a stroke event or not, and calculated at the beginning of the HAART era (July 1, 1996) or, if the participant entered the MACS afterward, at the participant's first date of study entry in the HAART era.

Comparison between groups was performed using the Wilcoxon rank sum tests and 2-sample binomial tests for proportions. To reconstruct the FRS-S in the MACS, Cox

proportional hazards models were used, stratified by serostatus and combined using serostatus as a binary predictor. The date of data censoring was death, study dropout, or the last follow-up visit of the participant on or before June 30, 2011.

RESULTS There were 3,945 participants (1,776 HIV+ and 2,169 HIV−) in the MACS during the study timeframe. The baseline characteristics of this cohort and incidence of all neurologic disease have been reported[7] and are provided by stroke and HIV serostatus in table 1. There were 114 strokes in MACS participants recorded, including 19 fatal strokes among HIV+ participants (n = 12) and HIV− participants (n = 7). The stroke events occurred throughout the study observation period (figure e-1).

There were 94 first-ever strokes among 57 HIV+ and 37 HIV− participants with an incidence rate of first-ever stroke of 1.7/1,000 person-years in HIV− and 3.3/1,000 person-years in HIV+ participants (table 1). The median age at the time of first stroke diagnosis was 55.6 years (range 34.5–8.5 years). Among HIV+ participants, the median age of first stroke was 51.4 compared with 61.8 years in HIV− participants ($p < 0.0001$). A total of 70 (74%) were

Table 1 Comparison of baseline demographic and clinical features related to stroke risk in the FHS and MACS

Risk factor	FHS original cohort (men only), 1954–1990	MACS, HIV+, 1996–2011		MACS, HIV−, 1996–2011		Comparison of HIV+ and HIV− MACS participants
		Entire cohort (n = 1,776)	Stroke subjects (n = 57)	Entire cohort (n = 2,169)	Stroke subjects (n = 37)	
Variables in FRS-S						
Mean age (range), y[a]	65.4 (55–84)	41.0 (17–69)	45.4 (30–66)	43.4 (18–82)	53.4 (38–72)	<0.001
Systolic BP, mean (range), mm Hg	139.3	121.7 (83–180)	122.5 (94–150)	122.6 (80–201)	128.2 (100–178)	0.06
Antihypertensive therapy, %	16.1	8.9	21.4	5.2	13.2	0.41
Diabetes mellitus, %	10.6	1.5	1.8	1.5	2.6	0.98
Cigarette smoking, %	33.8	39.5	42.9	33.2	36.8	<0.001
Cardiovascular disease, %[b]	22.2	2.7	8.9	1.5	7.9	1
Atrial fibrillation, %	2.8	Unknown	Unknown	Unknown	Unknown	—
Left ventricular hypertrophy, %	3.5	Unknown	Unknown	Unknown	Unknown	—
Other variables, not in FRS-S						
HIV-related variables						
HIV, %	Unknown	100	100	0	0	<0.001
HIV viral load at baseline, mean (IQR), copies/mL[c]	NA	24,130 (7,770)	7,194 (340)	NA	NA	NA
CD4 count at baseline, mean (IQR), cells/mL	NA	688 (401)	760 (481)	957 (450)	947 (381)	<0.001
No. of years since HIV diagnosis, mean (IQR)	NA	5.9 (11.6)	6.4 (11.6)	NA	NA	NA
Duration on HAART, mean (IQR), y	NA	0.9 (0.3)	1.0 (0.2)	NA	NA	NA
Other variables						
Race, % Caucasian-black-other	Predominantly Caucasian	65-29-7	75-20-5	79-18-4	82-16-3	<0.001
Body mass index, mean (IQR), kg/m^2	Unknown	24.2 (4.0)	24.4 (5.1)	24.6 (4.4)	25.2 (3.5)	0.05
Alcohol, average no. drinks/wk, mean (IQR)	NA	7.0 (10.0)	7.1 (10.1)	7.4 (9.6)	6.6 (8.4)	<0.001
Use of cocaine or crack in the past 2 y or the previous study visit, %	NA	35	20	29	29	<0.001
Any other drug abuse by history, including poppers, marijuana, hash, "uppers," or other drugs, %[d]	NA	68	71	69	74	0.37

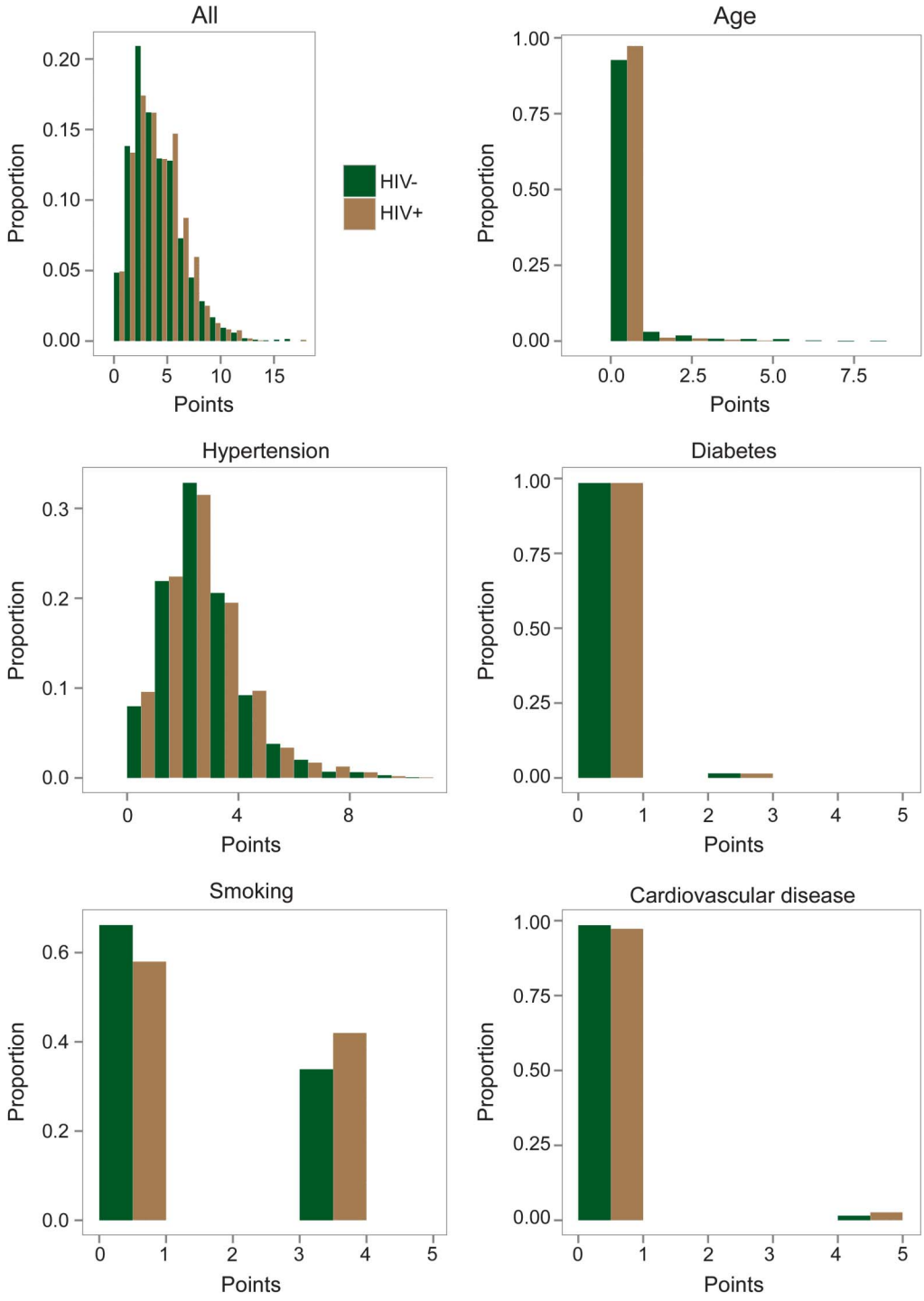
Abbreviations: BP = blood pressure; FHS = Framingham Heart Study; FRS-S = Framingham Risk Score for Stroke; HAART = highly active antiretroviral therapy; IQR = interquartile range; MACS = Multicenter AIDS Cohort Study; NA = not applicable.
[a] At the time of study entry in the HAART era.
[b] As stated in methods section in the MACS.
[c] More than 50% of participants had missing values.
[d] Includes crystal meth, meth, speed, and ice.

enrolled in the MACS for ≥10 years before their first stroke event.

Among HIV+ participants with first-ever stroke, 52 (91%) occurred while the participant was taking HAART. CD4 count within 60 days before the stroke event was available for 42 of 57 HIV+ participants with stroke (mean 484 cells/mL, range 17–1,256). Among this group, 8 had a CD4 count <200 cells/mL of whom 7 reported being on HAART.

For HIV+ participants with stroke, the FRS-S 10 years before stroke, for 10-year prediction of stroke, averaged 4.9% (range 0%–15%) compared with HIV− participants with stroke whose baseline FRS-S averaged 6.6% (range 3%–26%) ($p < 0.04$). When

Figure 1 **Histograms of FRS-S point composition of the entire MACS cohort at the beginning of the HAART era**

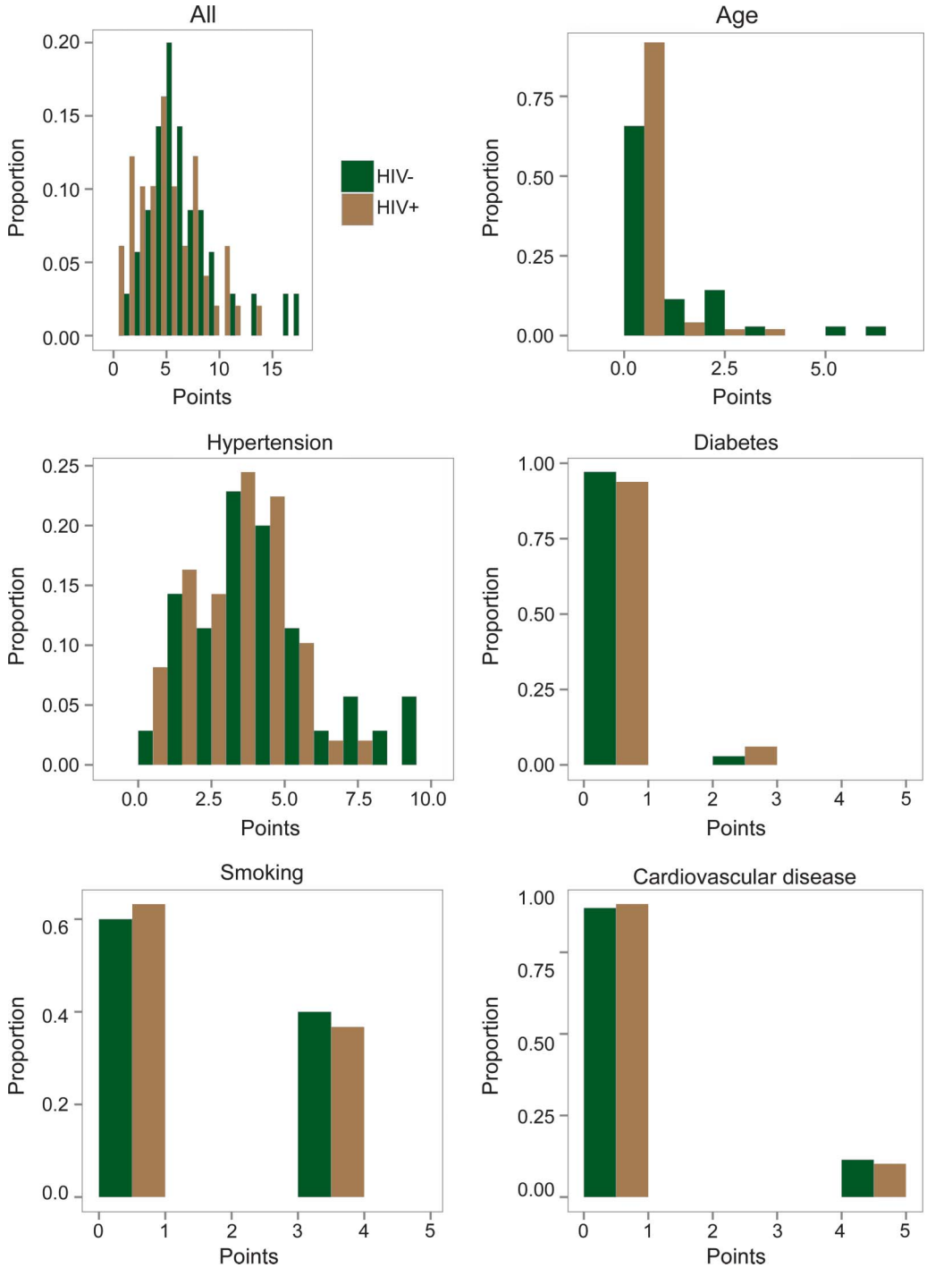


FRS-S points for all MACS participants by HIV serostatus. FRS-S = Framingham Risk Score for Stroke; HAART = highly active antiretroviral therapy; MACS = Multicenter AIDS Cohort Study.

considering only the subgroup of MACS participants who were enrolled in the cohort study for 10 years or longer, the difference in mean FRS-S between HIV+ and HIV− participants was still significant (4.0% vs 5.9%, $p < 0.02$). Notably, 3 HIV+ participants with strokes and more than 10 years of follow-up had an FRS-S predicted risk of zero.

The distribution of risk factors for HIV+ and HIV− men with stroke events is reported in figure 1. Overall, HIV+ participants were more likely to be younger and smoke cigarettes. HIV− participants were marginally more likely to have hypertension. The distribution of history of diabetes and history of myocardial infarction was similar between HIV+ and HIV− men with strokes.

Figure 2 **Histograms of FRS-S point composition of the MACS participants who experienced a stroke during the study timeframe**



FRS-S points for MACS participants with stroke by HIV serostatus. FRS-S = Framingham Risk Score for Stroke; MACS = Multicenter AIDS Cohort Study.

Table 2 Regression coefficients and relative risks for significant risk factors in Cox proportional hazards regressions for stroke profiles in male Framingham participants aged 55 to 84 years and MACS participants

	Framingham Heart Study (n = 2,372)		MACS HIV+ (n = 2,042), relative risk (95% CI)	MACS HIV− (n = 1,531), relative risk (95% CI)	Total MACS cohort (n = 3,945)	
Risk factor	Coefficient	Relative risk (95% CI)[a]			Relative risk (95% CI)	p Value
Age, per 10 y	0.049	1.63 (1.33–1.99)[a]	1.80 (1.26–2.55)	2.55 (1.89–3.46)	2.19 (1.74–2.75)	<0.001
Systolic BP	0.015	1.16 (1.10–1.24)[a]	0.97 (0.78–1.20)	1.10 (0.76–1.18)	1.03 (0.89–1.20)	0.77
Antihypertensive therapy/systolic BP term (per 10 mm Hg increase)	0.00019	—	3.3×10^{-4}[b] (1.5×10^{-4}, 1.4×10^{-3})	8.0×10^{-4}[b] (1.6×10^{-4}, 1.4×10^{-3})	4.5×10^{-4}[b] (-8.0×10^{-6}, 9.1×10^{-4})	0.05
Diabetes mellitus	0.34	1.41 (0.97–2.04)	0.83 (0.11–6.28)	0.38 (0.04–3.62)	0.75 (0.17, 3.25)	0.66
Cigarette smoking	0.52	1.69 (1.27–2.23)	1.20 (0.69–2.10)	1.29 (0.66–2.55)	1.24 (0.80–1.90)	0.33
Cardiovascular disease[c]	0.55	1.73 (1.68–1.78)	3.11 (1.09–8.9)	3.78 (0.98–14.6)	3.12 (1.38–7.04)	<0.01
Atrial fibrillation	0.60	1.82 (1.01–3.29)	—	—	—	—
Left ventricular hypertrophy	0.79	2.20 (1.26–3.84)	—	—	—	—
HIV	—	—	—	—	2.16 (1.39–3.31)	<0.001

Abbreviations: BP = blood pressure; CI = confidence interval; MACS = Multicenter AIDS Cohort Study.
[a] Given for 10-unit changes, per the original Framingham study; all other variables reported dichotomously. In The Framingham Heart Study, all variables were significant at a $p < 0.05$ level.
[b] Coefficient from predictive model, as opposed to relative risk of stroke, because of nonlinearity.
[c] In MACS, limited to self-reported myocardial infarction ascertainment.

In the entire cohort of HIV+ men without a stroke (median and mean age at first visit during the HAART era 41 years), the mean 10-year predicted risk of stroke was 4.11% (range 0%–26%) vs 4.05% (0%–22%) in HIV− men (median and mean age 43 years) ($p < 0.02$). In participants without known stroke, hypertension and cigarette smoking were more likely among HIV+ men (figure 2).

In the analysis of baseline stroke prediction, the association between stroke and traditionally measured risk factors in the FRS-S was similar between the Framingham cohort participants and the MACS participants, but there was a significant added risk of HIV status among HIV+ MACS participants ($p < 0.0001$, table 2).

DISCUSSION Several studies have suggested an increased risk of stroke in HIV+ adults,[4,9,10,16–18] but prospectively followed HIV+ individuals over ≥10 years with incident stroke have not previously been available. Many studies of HIV+ adults are limited to small numbers of stroke,[9,10,16,19,20] and none has had the opportunity to compare baseline risk with long-term incidence of stroke. The comparison of baseline risk and long-term outcome remains of critical importance to HIV+ individuals. Traditional scores for risk prediction appear to be insufficient to accurately inform long-term cerebrovascular health status in chronic HIV infection. We observed a higher incidence of first-ever strokes in HIV+ vs HIV− participants (3.3 vs 1.7/1,000 person-years); however, the average 10-year FRS-S predicted risk at baseline was lower in HIV+ vs HIV− subjects (4.9% vs 6.6%). Remodeling of the baseline stroke risk in the MACS demonstrates that HIV adds a significant risk of stroke.

There are several reasons that the FRS-S may have underestimated stroke risk in HIV+ men in this study. Risk difference using the FRS-S between HIV+ and HIV− men may be partly accounted for by the younger onset of stroke in HIV+ men therefore leading to lower FRS-S point calculation at 10 years before the event. The original FRS-S was designed in men aged 55 to 84 years and was not modeled for young-onset stroke prediction. In the current study, the median age for stroke was in the fifth and sixth decades of life for both HIV+ and HIV− MSM.

HIV+ individuals may have unique risk factors for stroke that are measurable and can therefore lead to adjustment in their FRS-S. One study from Spain[10] found that high alcohol intake, a history of a diagnosis of AIDS, and fewer months on HAART increased the risk of stroke, although only 25 patients with stroke were identified. HIV infection itself may portend a higher stroke risk, even when accounting for demographic and traditional stroke risk factors.

Most studies in high-income settings suggest that HIV increases stroke risk (table 3).[4,9,10,16–24] In South Africa, however, most studies report similarities in patient characteristics and stroke incidence between HIV+ and HIV− groups.[19–21]

The reasons for increased rates of stroke among HIV+ men could include such mechanisms as chronic inflammation leading to atherogenic tendency of the endothelium, remodeling of the intracranial and carotid vasculature, and higher frequency of circulating inflammatory markers.[22,25–27] In the multinational STACCATO study,[28] inflammatory markers associated with increased cardiovascular risk, such as sVCAM-1 (soluble vascular adhesion molecule-1), were associated with HIV RNA replication and decreased with HAART initiation. In a separate study by the SMART/INSIGHT and D.A.D. working groups,[29] abacavir, found in some HAART regimens, was associated with an increased risk of all-cause cardiovascular disease, which included stroke. The relationship between HAART and long-term stroke risk requires further investigation.

There may be important risk factors that confound the relationship between stroke and HIV such as injection drug abuse with cocaine, excessive alcohol use, or poor medication adherence. Given that the majority of the HIV+ cohort with strokes was HAART-treated, it is unlikely that the strokes were caused by opportunistic infections; however, a fraction of the HIV+ participants with stroke had lower than expected CD4 counts and should be considered immunosuppressed. The MACS represents mostly HAART-treated adults, a situation that almost certainly mimics the clinical scenario in most high-income settings.

Our study had several limitations. Stroke ascertainment in this cohort was partially dependent on self-reported events that were later verified by physicians and study investigators. In some cases, medical records from the patient could not be verified by the study site and diagnosis could only be based on the participant's provided information. Although a majority of strokes received an *ICD-9* designation by the treating physician, there were several events that were not subclassified by mechanism or stroke type. We were unable to report the number of strokes by subtype and compare them with the original Framingham Heart Study cohort; nonetheless, the FRS-S is useful for general risk of stroke and not specific to subtype. Assessments related to stroke

Table 3 Selected clinical studies of stroke in HIV-infected adult patients performed in the HAART era with ≥10 HIV-infected stroke patients (July 1996 to June 2013)

Year of publication and ref. no.	Study design	Study location	No. of stroke events in HIV+ individuals	Conclusions
2000[19]	Retrospective case control	KwaZulu Natal, South Africa	22	Incidence rate similar between HIV+ and HIV− young Africans but higher incidence of large-vessel cryptogenic strokes in HIV+
2003[16]	Prospective academic medical center–based cohort	Münster, Germany	15	Ischemic stroke more common in HIV+ individuals
2003[20]	Prospective hospital-based study	Johannesburg, South Africa	35	Similar patient characteristics between HIV+ and HIV− patients
2004[9]	Retrospective medical records review of 46 hospitals	Central Maryland and Washington, DC	12	AIDS is strongly associated with both ischemic and hemorrhagic stroke
2005[21]	Hospital-based retrospective chart review	KwaZulu Natal, South Africa	56	No difference in angiographic, cardiac, or serologic tests between HIV+ and HIV− groups
2007[22]	Hospital-based retrospective chart review	Miami	82	High incidence of vasculopathy and hypercoagulability but mostly immunocompromised patients
2007[23]	Prospective hospital-based study	Cape Town, South Africa	67	HIV vasculopathy occurred in 20% of patients
2009[10]	Retrospective hospital-based cohort study	Madrid, Spain	25	Stroke incidence is increased in HIV treated with HAART
2010[24]	Events recorded in a clinical trial of HIV+ participants	US, multicenter	38	55% of strokes were confirmed based on defined criteria vs 5% probable and 39% unconfirmed
2011[4]	Population-based cohort using active register	Denmark	140	Increased risk of ischemic stroke in HIV, with and without proven risk factors
2011[11]	Retrospective hospital-based national registry	Nationwide inpatient sample, US	10,944	Increased no. of admitted stroke patients with HIV in recent years
2012[17]	Cohort study	Boston	132	Ischemic stroke rates increased in HIV, especially younger patients and women
2013[18]	Retrospective cohort study with scheduled chart reviews	North Carolina	53	Ischemic stroke incidence ~1.5 times higher than a population-based cohort; risk not associated with antiretroviral therapy

Abbreviation: HAART = highly active antiretroviral therapy.

severity, functional outcome, and neuroimaging confirmation were not consistently available in the MACS. This is true in most study cohorts of HIV+ individuals in whom vascular disease, particularly stroke, was not a priority condition to study. Because MACS began studying self-reported strokes in detail in 2006, it is possible that strokes that occurred earlier in the HAART era were not all ascertained. However, given our definition of the HAART era as 1996 and beyond, the inclusion of stroke in 2006 on interview forms is still appropriate for assessment of risk at the required time point of 10 years earlier.

Some MACS participants had a stroke event before 2006, and pre-HAART era years were included in their risk period. This occurred in a minority of cases. Diabetes mellitus was ascertained regularly from April 1999 onward and at the time of the participant's entry into the MACS. Notably, a participant who developed diabetes between his study entry and April 1999 may not have the date of diabetes diagnosis recorded with the MACS cohort until 1999. This would lead to underestimation of his FRS-S because points would not have been ascribed for diabetes in that individual in that timeframe.

Our study was limited to adult MSM. It is possible that our findings are not generalizable to other HIV+ populations such as women, or persons with other high-risk behaviors for stroke such as injection drug abuse. There are more African Americans in the MACS compared with the Framingham Heart Study, which may lead to a differing baseline risk of stroke. Race is not part of the FRS-S but has been studied in cardiovascular disease prediction.[30] Also, access to care may be better among MACS participants.

This study had several strengths. The MACS has the advantage of enrollment of both HIV+ and HIV− MSM in the same prospective cohort study and does not derive its control group from other databases or registries. Many other cohorts lack an HIV− control group, making it difficult to discern the relative contributions of age, other HIV-related risk factors, and HIV infection. The number of strokes in the MACS is among the highest of any HIV+ cohort with well-described cardiovascular risk factor variables and HIV status information. Despite the high number of reports suggesting that HIV is an important risk factor for stroke, the number of reported patients with both HIV and stroke is small. Other studies have survival bias, such that an increased number of HIV+ individuals experiencing stroke in the HAART era may be inaccurately equated with HIV as a risk factor for stroke. In the MACS, we had the unique opportunity to retrospectively calculate the FRS-S in participants 10 years before stroke events. Because events were ascertained prospectively, there is no recall bias. Also, our finding that some individuals with stroke had an FRS-S of zero suggests that there are particular individuals at high risk, which is difficult to predict using standard scores.

Adjustment and calibration of the FRS-S may be of high future utility in the HIV+ adult population.[31–34] Follow-up of existing cohorts, with dedicated attention to vascular outcomes, is imperative to understand the accuracy of stroke prediction in HIV+ populations with various baseline risks.

AUTHOR CONTRIBUTIONS

F.J.M. was involved in the study design, study conception, data analysis, data interpretation, writing, and editing of the manuscript. W.S.P., N.S., and A.G.A. were involved with the data interpretation and editing of the manuscript. J.T.B. was involved with the data collection, data interpretation, and editing of the manuscript. B.R.S. was involved with the data interpretation and editing of the manuscript. R.D. and E.M. were involved with the data collection, data interpretation, and editing of the manuscript. J.P.P. was involved with the study conception, data interpretation, and editing of the manuscript. R.T.S. was involved in the study design, data analysis, data interpretation, writing, and editing of the manuscript.

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DISCLOSURE

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

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REFERENCES

1. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312–318.
2. Friis-Møller N, Thiébaut R, Reiss P, et al; DAD Study Group. Predicting the risk of cardiovascular disease in HIV-infected patients: the Data Collection on Adverse Effects of Anti-HIV Drugs Study. Eur J Cardiovasc Prev Rehabil 2010;17:491–501.
3. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV Cohort Study. Clin Infect Dis 2011;53:1130–1139.
4. Rasmussen LD, Engsig FN, Christensen H, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS 2011;25:1637–1646.
5. Benjamin LA, Bryer A, Emsley HC, Solomon T, Connor MD. HIV infection and stroke: current perspectives and future directions. Lancet Neurol 2012;11:878–890.
6. Cruse B, Cysique LA, Markus R, Brew BJ. Cerebrovascular disease in HIV-infected individuals in the era of

highly active antiretroviral therapy. J Neurovirol 2012; 18:264–276.
7. Mateen FJ, Shinohara RT, Carone M, et al; Multicenter AIDS Cohort Study (MACS) Investigators. Neurologic disorders incidence in HIV+ vs HIV− men: Multicenter AIDS Cohort Study, 1996–2011. Neurology 2012;79: 1873–1880.
8. Berger JR, Harris JO, Gregorios J, Norenberg M. Cerebrovascular disease in AIDS: a case-control study. AIDS 1990;4:239–244.
9. Cole JW, Pinto AN, Hebel JR, et al. Acquired immunodeficiency syndrome and the risk of stroke. Stroke 2004; 35:51–56.
10. Corral I, Quereda C, Moreno A, et al. Cerebrovascular ischemic events in HIV-1-infected patients receiving highly active antiretroviral therapy: incidence and risk factors. Cerebrovasc Dis 2009;27:559–563.
11. Ovbiagele B, Nath A. Increasing incidence of ischemic stroke in patients with HIV infection. Neurology 2011; 76:444–450.
12. Centers for Disease Control and Prevention (CDC). HIV testing among men who have sex with men: 21 cities, United States, 2008. MMWR Morb Mort Wkly Rep 2011;60:694–699.
13. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol 1987;126:310–318.
14. Detels R, Jacobson L, Margolick J, et al. The Multicenter AIDS Cohort Study, 1983 to …. Public Health 2012;126: 196–198.
15. Jacobson LP, Li R, Phair J, et al. Evaluation of the effectiveness of highly active antiretroviral therapy in persons with human immunodeficiency virus using biomarker-based equivalence of disease progression. Am J Epidemiol 2002;155:760–770.
16. Evers S, Nabavi D, Rahmann A, Heese C, Reichelt D, Husstedt IW. Ischaemic cerebrovascular events in HIV infection. Cerebrovasc Dis 2003;15:199–205.
17. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. J Acquir Immune Defic Syndr 2012;60:351–358.
18. Vinikoor MJ, Napravnik S, Floris-Moore M, Wilson S, Huang DY, Eron JJ. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the Southeastern United States. AIDS Res Hum Retroviruses 2013;29:1068–1074.
19. Hoffmann M, Berger JR, Nath A, Rayens M. Cerebrovascular disease in young, HIV-infected, black Africans in the KwaZulu Natal Province of South Africa. J Neurovirol 2000;6:229–236.
20. Mochan A, Modi M, Modi G. Stroke in Black South African HIV-positive patients: a prospective analysis. Stroke 2003;34:10–15.
21. Patel VB, Sacoor Z, Francis P, Bhigjee AI, Connolly C. Ischemic stroke in young HIV-positive patients in KwaZulu-Natal, South Africa. Neurology 2005;65:759–761.
22. Ortiz G, Koch S, Romano JG, Forteza AM, Rabinstein AA. Mechanisms of ischemic stroke in HIV-infected patients. Neurology 2007;68:1257–1261.
23. Tipping B, de Villiers L, Wainwright H, Candy S, Bryer A. Stroke in patients with human immunodeficiency virus infection. J Neurol Neurosurg Psychiatry 2007;78: 1320–1324.
24. Lifson AR, Belloso WH, Davey RT, Duprez D, et al; INSIGHT Endpoint Review Committee Writing Group; INSIGHT Study Group. Development of diagnostic criteria for serious non-AIDS events in HIV clinical trials. HIV Clin Trials 2010;11:205–219.
25. Falcone EL, Mangili A, Skinner S, Alam A, Polak JF, Wanke CA. Framingham risk score and early markers of atherosclerosis in a cohort of adults infected with HIV. Antivir Ther 2011;16:1–8.
26. Seaberg EC, Benning L, Sharrett AR, et al. Association between human immunodeficiency virus infection and stiffness of the common carotid artery. Stroke 2010;41: 2163–2170.
27. Sen S, Rabinstein AA, Elkind MS, Powers WJ. Recent developments regarding human immunodeficiency virus infection and stroke. Cerebrovasc Dis 2012;33:209–218.
28. Calmy A, Gayet-Ageron A, Montecucco F, et al; STACCATO Study Group. HIV increases markers of cardiovascular risk: results from a randomized, treatment interruption trial. AIDS 2009;23:929–939.
29. Strategies for Management of Anti-Retroviral Therapy/ INSIGHT; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. AIDS 2008;22:F17–F24.
30. D'Agostino RB, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286: 180–187.
31. Bergersen BM, Sandvik L, Bruun JN, Tonstad S. Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: results from a Norwegian study of 721 subjects. Eur J Clin Microbiol Infect Dis 2004;23:625–630.
32. Kaplan RC, Kingsley LA, Sharrett R, et al. Ten-year predicted coronary heart disease risk in HIV-infected men and women. Clin Infect Dis 2007;45:1074–1081.
33. Kim DJ, Westfall AO, Chamot E, et al. Multimorbidity patterns in HIV-infected patients: the role of obesity in chronic disease clustering. J Acquir Immune Defic Syndr 2012;61:600–605.
34. Gutierrez J, Elkind MS, Marshall RS. Cardiovascular profile and events of US adults 20–49 years with HIV: results from the NHANES 1999–2008. AIDS Care Epub 2013 Feb 21.