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Recurrent stroke and cardiac risks after first ischemic stroke

The Northern Manhattan Study

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Abstract—Background: Few population-based studies with long-term follow-up have compared risk of recurrent stroke and cardiac events after first ischemic stroke. The relative risk of these two outcomes may inform treatment decisions. **Methods:** In the population-based Northern Manhattan Study, first ischemic stroke patients age 40 or older were prospectively followed for recurrent stroke, myocardial infarction (MI), and cause-specific mortality. Fatal cardiac events were defined as death secondary to MI, congestive heart failure, sudden death/arrhythmia, and cardiopulmonary arrest. Risk of events (with 95% CIs) was calculated using Kaplan–Meier survival analysis and adjusted for sex and age using Cox proportional hazard models. **Results:** Mean age ($n = 655$; median follow-up 4.0 years) was 69.7 ± 12.7 years. The risk of recurrent stroke was more than twice that of cardiac events (including nonfatal MI) at 30 days and approximately twice cardiac risk at 5 years. The age- and sex-adjusted 5-year risk of fatal or nonfatal recurrent stroke was 18.3% (14.8 to 21.7%), and the 5-year risk of MI or fatal cardiac event was 8.6% (6.0 to 11.2%). The adjusted 5-year risk of nonfatal stroke (14.8%, 11.6 to 17.9%) was approximately twice as high as fatal cardiac events (6.4%, 4.1 to 8.6%) and four times higher than risk of fatal stroke (3.7%, 2.1 to 5.4%). **Conclusions:** Cardiac mortality is nearly twice as high as mortality owing to recurrent stroke, but long-term risk of all stroke, fatal or nonfatal, is approximately twice the risk of all cardiac events. The high risk of nonfatal recurrent stroke reinforces the importance of therapies aimed at preventing stroke recurrence in addition to preventing cardiac events.

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Cerebrovascular disease and coronary artery disease (CAD) share common risk factors and pathophysiologies, and CAD is a significant cause of morbidity and mortality in stroke patients.¹ The risk of CAD in patients with cerebrovascular disease is important for determining prognosis, and it affects decisions concerning diagnostic testing and treatment. The ability to stratify stroke patients based on risk of future cardiovascular events should allow more effective, targeted, and cost-effective treatment. For example, among patients who have had a first ischemic stroke, identification of those at high risk of myocardial infarction (MI) or fatal cardiac events would justify use of secondary preventive strategies shown to reduce risk of coronary events, such as statin therapy, according to recent guidelines.^{2,3}

At the same time, recurrent stroke is also an important predictor of functional outcomes as well as mortality after first stroke.^{4,5} Some have argued that recurrent stroke is a better marker than cardiac events or mortality of the effect of therapy in clinical trials in a stroke patient population.⁶ Understanding

the balance between the risk of cardiac and cerebrovascular events after a first stroke may help in the design of secondary prevention studies and in the direction of limited health resources. Few long-term population-based studies have provided data on the differential risk of recurrent stroke and cardiac events after incident ischemic stroke to date. We sought to determine the absolute risk of nonfatal and fatal recurrent stroke, nonfatal and fatal MI, and MI or other fatal cardiac events in a multiethnic cohort at early and late time intervals post stroke.

Methods. The Northern Manhattan Study (NOMAS) includes a population-based incident ischemic stroke follow-up study designed to determine predictors of stroke recurrence and prognosis in a multiethnic, urban population, as previously described.^{7,8} The race-ethnic mixture of the northern Manhattan community consists of 63% Hispanic, 20% black, and 15% white residents.

Selection of NOMAS cohort. The methods of patient identification and enrollment have been described in previous publications.^{9,10} In brief, stroke patients were enrolled if they were 1) diagnosed with a first stroke, age 40 or older, and 3) resided in northern Manhattan for ≥ 3 months in a household with a telephone. For this analysis, only ischemic stroke cases were included.

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Over 80% of patients with acute ischemic stroke in northern Manhattan are hospitalized at the Columbia University Medical Center (CUMC). Subjects hospitalized at other local hospitals were identified through active surveillance of admissions to those hospitals and through agreements with local physicians. Approximately 5% of incident ischemic stroke patients in northern Manhattan were not hospitalized and were also included.^{7,10} Evaluation of patients was performed at the hospital; those subjects either not hospitalized or hospitalized elsewhere were evaluated in the outpatient research clinic. The study was approved by the CUMC Institutional Review Board. All participants gave consent directly or through a surrogate when appropriate.

Index evaluation of subjects. Data were collected through interviews by trained research assistants, and physical and neurologic examinations were conducted by study neurologists, as previously described.^{9,10} Assessments were conducted in English or Spanish depending upon the primary language of the participant. Race-ethnicity was based upon self-identification. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System¹¹ by the Centers for Disease Control and Prevention regarding the following conditions: hypertension, diabetes, hypercholesterolemia, peripheral vascular disease, TIA, cigarette smoking, and cardiac conditions such as myocardial infarction, coronary artery disease, angina, congestive heart failure, atrial fibrillation, other arrhythmias, and valvular heart disease.

Stroke severity was assessed using a NIH Stroke Scale (NIHSS) score derived from a standardized neurologic examination and was categorized into mild (NIHSS < 6), moderate (NIHSS 6 to 13), and severe (NIHSS ≥ 14). This categorization was based on previous analyses of stroke severity in relation to stroke outcome from our population¹² as well as use in a recent clinical trial of a neuroprotective agent.¹³ Stroke diagnostic evaluation included CT or MRI of the brain and ultrasound evaluation or MR angiography of the extracranial and intracranial cerebral vessels and transthoracic or transesophageal echocardiogram as appropriate. A consensus of stroke neurologists assessed stroke subtype using modified Stroke Data Bank criteria and all available information, as described in a previous publication.^{14,15}

Follow-up and outcomes assessment. Follow-up evaluations were conducted at 6 months and then annually for 5 years. The 6-month evaluation was conducted by telephone and consisted of an interview of the patient, family member, or caregiver. Information on vital status, functional status, and intercurrent symptoms, illness, or hospitalization was collected. Annual in-person follow-up visits were conducted at the medical center and included interviews as at the 6-month follow-up visit as well as measurement of vital signs and physical and neurologic examination. Patients unable or unwilling to come to the medical center were visited by a member of the research staff, and the evaluation was conducted at home or in an alternative place of residence (e.g., nursing home). An ongoing surveillance system of admissions to the CUMC and other local hospitals, described in a previous publication,⁷ was also used to identify study participants who experienced recurrent stroke, MI, hospitalization, or death. When available, medical records were reviewed for all outcome events including death. All outcome events were reviewed by a specially trained research assistant. MI was validated by review by a study cardiologist, strokes were validated by a study neurologist, and deaths were also validated by a study cardiologist or neurologist. Deaths were classified using death certificates, medical records, and family interviews. Where necessary, cause of death was determined by consensus among the study physicians.

Death was due to stroke if there was clear documentation of a stroke from the death certificate or hospitalization records or if the death occurred within 30 days of the event. Deaths that occurred more than 30 days after the initial event were considered related to the event based on clinical judgment that relied on a clearly documented relationship in medical records of the stroke or its complications to the death. Death from MI was determined by clear documentation of an MI from the death certificate or hospitalization records or by the death occurring within 30 days of the event (or beyond, as above). Fatal congestive heart failure was determined in cases where the patient died at home with previously diagnosed heart failure/dilated cardiomyopathy or was hospitalized with symptoms, radiographic or echocardiographic findings, or clinical signs of heart failure. Fatal pulmonary embolus was determined in cases of sudden shortness of breath, col-

lapse, or sudden death after a long period of bed rest. This diagnosis was supported by a ventilation-perfusion (VQ) scan, an EKG, a spiral CT, or an MRI. Death from arrhythmia or sudden death was ascribed in cases of a documented arrest in a medical setting if the death did not meet the above criteria and in cases of a sudden, unexpected death. In those cases in which it was difficult to make a determination whether death was due to stroke or cardiac disease, consensus was reached after discussion using best available information.

Statistical analyses. Statistical analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC). For descriptive purposes, means were calculated for continuous variables and proportions for categorical variables among the cohort of stroke patients. Cumulative 5-year risk and 95% CIs were calculated separately for first occurrence of fatal and nonfatal recurrent stroke, fatal and nonfatal MI, and the composite outcome of MI or fatal cardiac event using Kaplan-Meier survival analysis. Risks were calculated for the entire cohort of participants and separately for those who survived at least 30 days. Risk data were also adjusted for sex and age using Cox proportional hazard models after checking that the assumption of proportionality was satisfied. Analyses were further conducted for subgroups stratified by age <70 and ≥70 years, sex, and race-ethnicity.

Results. Baseline characteristics of the study population are shown in table 1. Mean age of the 655 subjects was 69.7 ± 12.7 years, and 44.6% were men. Participants were 51.3% Hispanic, 27.6% black, and 18.9% white. Mean age of non-Hispanic whites was 77.0 ± 12.5, non-Hispanic blacks 70.4 ± 11.6, and Hispanics 65.7 ± 12.5. The prevalence of vascular risk factors was high, as was previous history of cardiovascular disease: 16.2% had a history of MI, 33.4% CAD, 13.8% congestive heart failure, 11.0% atrial fibrillation, and 21.6% peripheral arterial disease. Most participants were nondrinkers (72.2%). Half of incident strokes were mild and 16.5% severe.

Median follow-up in those who did not experience an event was 4.0 years. Unadjusted risks were similar to sex- and age-adjusted risks. Cumulative risks of outcome events, adjusted for age and sex, among all participants at 30 days, 1 year, 3 years, and 5 years are shown in table 2. The adjusted risk of recurrent stroke was higher than the risk of cardiac events: approximately 2.5 times the risk of cardiac events at 30 days (1.5 vs 0.6%) and more than twice the risk at 5 years (18.3 vs 8.6%; table 2 and figure 1). The 5-year risk of nonfatal stroke (14.8%, 11.6 to 17.9%) was approximately twice as high as fatal cardiac events (6.4%, 4.1 to 8.6%) and four times higher than risk of fatal stroke (3.7%, 2.1 to 5.4%). The risk of nonfatal stroke was approximately four times the risk of nonfatal MI at 5 years (table 2). Among those who survived at least 30 days after stroke, the risk of recurrent stroke was higher than the risk of a cardiac event throughout the period of follow-up (figure 2A).

For fatal outcomes, throughout the period of follow-up, the 5-year risk of a fatal cardiac event was twice the risk of a fatal stroke (6.4 vs 3.7%; table 2). A similar pattern of risk was observed among those who survived at least 30 days (figure 2B).

Table 3 shows the cumulative 5-year risk of recurrent stroke and MI or fatal cardiac events stratified by age, sex, and race-ethnicity. The total stroke risk was greater than cardiac risk among those <70 and ≥70 years old. Men had a greater risk of MI or fatal cardiac events than women, whereas the risk of recurrent stroke was similar. Non-Hispanic whites had a higher risk of MI or fatal cardiac events at 5 years compared with other ethnic groups, probably reflecting the higher mean age of the white popula-

Table 1 Baseline characteristics of study population

Demographics	N = 655
Age, mean (SD); y	69.7 (12.7)
Male, no. (%)	292 (44.6)
High school education as highest attainment (n = 640), no. (%)	213 (33.3)
Race	
Non-Hispanic white, no. (%)	124 (18.9)
Non-Hispanic black, no. (%)	181 (27.6)
Hispanic, no. (%)	336 (51.3)
Other, no. (%)	14 (2.1)
Risk factors, no. (%)	
History of myocardial infarction (n = 654)	106 (16.2)
History of coronary artery disease	219 (33.4)
History of congestive heart failure (n = 653)	90 (13.8)
History of atrial fibrillation (n = 654)	72 (11.0)
History of peripheral arterial disease (n = 653)	141 (21.6)
Current smoking (n = 626)	133 (21.3)
Past smoking (n = 652)	349 (53.5)
Diabetes mellitus (n = 654)	284 (43.4)
Hypertension	512 (78.2)
Hypercholesterolemia (n = 648)	224 (34.6)
Total cholesterol, mean (SD); mg/dL [mmol/L]	192 (46) [4.97 (1.19)]
LDL, mean (SD); mg/dL [mmol/L]	120 (40) [3.11 (1.04)]
HDL, mean (SD); mg/dL [mmol/L]	40 (12) [1.04 (0.31)]
LDL >130 mg/dL (3.37 mmol/L) (n = 450), no. (%)	162 (36.0)
HDL <40 mg/dL (1.04 mmol/L) (n = 450), no. (%)	249 (55.3)
Stroke etiologic subtypes (n = 628), no. (%)	
Atherosclerotic	100 (15.9)
Lacunar	148 (23.6)
Embolic	126 (20.1)
Cryptogenic	254 (40.4)
Stroke severity (n = 620), no. (%)	
NIHSS rating 0 to 5	318 (51.3)
NIHSS rating 6 to 13	200 (32.3)
NIHSS rating ≥14	102 (16.5)

All percentages calculated with n = 655 unless otherwise noted.

LDL = low-density lipoprotein; HDL = high-density lipoprotein; NIHSS = NIH Stroke Scale; risk factor definitions in text.

tion in northern Manhattan compared with other ethnic groups.

Discussion. Our study provides evidence that after a first ischemic stroke, the pattern of risk of recurrent stroke differs from that of cardiac events. The overall risk of recurrent stroke (fatal or nonfa-

tal) is high (approximately 20% at 5 years). At 30 days, the risk of recurrent stroke was approximately 2.5 times the risk of MI or fatal cardiac event, and this ratio fell slightly to about twice the risk of MI or fatal cardiac event by 5 years. Although risk of recurrent stroke predominated even at 5 years, this pattern suggests that there may be an increasing importance of cardiac disease, both nonfatal and fatal, relative to recurrent stroke in the long term after an ischemic stroke.

Although recurrent strokes occur more commonly than cardiac events over the long term after a first stroke, cardiac events still account for a greater proportionate mortality after stroke. Among those who survived a first ischemic stroke, cardiac mortality was higher than stroke mortality throughout the period of follow-up, with the risk of fatal cardiac events approximately twice the risk of fatal stroke at 5 years.

Previous population-based epidemiologic studies compared mortality due to stroke and cardiac disease after a first stroke and generally found that early mortality after stroke is usually related to stroke or recurrent stroke, but that mortality at later time points is more often related to cardiovascular causes.¹⁶⁻²⁰ These trends were seen in populations and time periods that were similar to^{21,23} as well as different from^{19,20,22} our study. In a prior analysis of causes of mortality among stroke patients in northern Manhattan, death during the first month after stroke was due to stroke three times as often as cardiac causes, but during longer follow-up cardiac mortality was twice as common as stroke-related death.⁸ In another population,²¹ 30-day mortality was due to the initial stroke 51% of the time and to cardiovascular events only 12% of the time, whereas later cardiovascular events caused twice the deaths (22%) as recurrent stroke (9%). In a study with 10 years of follow-up,²² 41% of deaths were due to cardiovascular events and 25% to recurrent stroke. A retrospective analysis of a large administrative database showed that 11.8% of those with a first ischemic stroke or TIA had a recurrent stroke and 7.7% had a cardiac events 2 years after the incident event.²³ In contrast to the above findings, a greater proportionate mortality due to recurrent stroke rather than cardiac causes of death was found in Rochester, MN.²⁴ This could be due to the greater mean age at enrollment in that study (74.5 ± 13.0 years) compared with our study (69.7 ± 12.7 years) as well as longer follow-up, which may have increased the proportion of noncardiac causes of death among the entire study population when the study was terminated. Also, the populations differ in terms of demographics and pre-existing risk factors.

The differential impact of fatal recurrent stroke and fatal cardiac events in our study is also supported by evidence from randomized clinical trials in stroke patients. Data from most trials with short-term follow-up in which data on cardiac outcomes are available²⁵⁻³³ show a ratio of fatal cardiac events

Table 2 Cumulative risk of outcome events among ischemic stroke patients, adjusted for age and sex*

Cerebrovascular events	Age- and sex-adjusted cumulative risk, % (95% CI)			
	30 d	1 y	3 y	5 y
Nonfatal or fatal recurrent stroke	1.5 (0.6–2.5)	7.7 (5.5–9.8)	15.0 (12.0–18.0)	18.3 (14.8–21.7)
Nonfatal stroke	1.2 (0.4–2.1)	6.6 (4.6–8.6)	12.1 (9.3–14.8)	14.8 (11.6–17.9)
Fatal stroke	0.3 (0.0–0.7)	1.1 (0.3–2.0)	3.0 (1.6–4.5)	3.7 (2.1–5.4)
Cardiac events				
Nonfatal MI or fatal cardiac event†	0.6 (0.0–1.1)	3.3 (1.9–4.7)	6.6 (4.7–8.8)	8.6 (6.0–11.2)
Nonfatal MI	0.2 (0.0–0.4)	0.7 (0.0–1.3)	2.7 (1.3–4.1)	3.4 (1.7–5.1)
Nonfatal or fatal MI	0.3 (0.0–0.6)	1.3 (0.4–2.2)	3.9 (2.1–5.5)	4.7 (2.6–6.7)
Fatal cardiac event	0.4 (0.0–0.8)	2.9 (1.5–4.2)	5.0 (3.1–6.8)	6.4 (4.1–8.6)

* Adjusted risk is the risk of each outcome at mean levels of age (70 years) and sex (45% male).

† Fatal cardiac event includes fatal myocardial infarction, death due to heart failure, sudden death or arrhythmia, and cardiopulmonary arrest.

MI = myocardial infarction.

to fatal strokes of less than 1, reflecting the high early stroke mortality that is a result of the incident stroke. Most trials with longer follow-up show that fatal cardiac events either equal or outnumber fatal strokes,^{34–47} with risk of fatal cardiac events approximately one to five times the risk of fatal recurrent strokes in each study. In our study, the risk of fatal cardiac events was 1.6 times that of fatal recurrent stroke at 5 years. Disadvantages of using clinical trial data for long-term estimates of risk, however, include selection bias and inclusion of healthier individuals than in population-based studies. Our study provides similar evidence to clinical trials but from a population-based epidemiologic study.

Although proportionally less important as a cause of mortality, the high risk of recurrent nonfatal strokes has major clinical implications. As in our study, in those clinical trials that collected data about nonfatal recurrent stroke, nonfatal recurrent strokes occurred more often than nonfatal cardiac events. Two trials with short-term follow-up that reported nonfatal recurrent stroke data showed ratios

of nonfatal recurrent stroke to nonfatal MI of 2.5²⁸ and 3.5,²⁹ and all trials with longer-term follow-up showed ratios of greater than 1, ranging from 1.4 to 10.6.^{34–47} Not all events are equal in terms of their impact on quality of life. Nonfatal cardiac events may be less disabling than nonfatal recurrent strokes. The occurrence of nonfatal strokes, although they do not result in death, leads to disability as

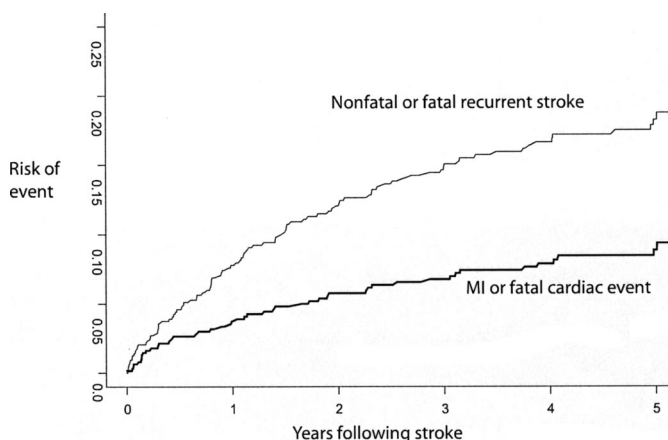


Figure 1. Kaplan–Meier survival curve comparing risk of nonfatal or fatal recurrent stroke with risk of myocardial infarction or fatal cardiac events.

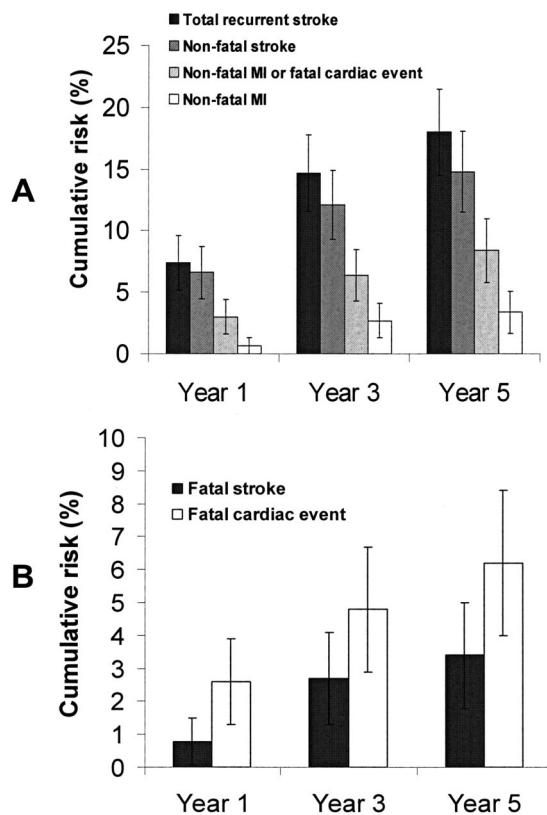


Figure 2. Cumulative risk of outcome events among 30-day survivors of first ischemic stroke, adjusted for age and sex. (A) Total and nonfatal stroke and cardiac events; (B) fatal stroke and cardiac events.

Table 3 Kaplan–Meier survival analysis: cumulative risk of outcome events among subgroups of population

Outcome	5-Year cumulative risk, % (95% CI)	
	Recurrent stroke (nonfatal or fatal)	Nonfatal MI or fatal cardiac event*
Age <70 y	16.0 (11.6–20.3)	6.7 (3.5–9.8)
Age >70 y	21.1 (15.7–26.4)	12.3 (8.2–16.3)
Male	17.7 (12.7–22.8)	11.8 (7.6–16.0)
Female	18.6 (14.0–23.2)	7.3 (4.3–10.4)
Hispanic	19.2 (14.4–24.0)	7.5 (4.2–10.8)
Non-Hispanic black	16.6 (10.5–22.7)	9.6 (4.7–14.4)
Non-Hispanic white	19.5 (11.1–28.0)	15.3 (7.8–22.8)

* Fatal cardiac event includes fatal myocardial infarction, death due to heart failure, sudden death or arrhythmia, and cardio-pulmonary arrest.

MI = myocardial infarction.

deficits from repeated strokes accumulate over time.^{4,5}

Our study has limitations. The northern Manhattan population has a high prevalence of cardiac- and stroke-related risk factors such as prior cardiac disease, hypertension, and diabetes mellitus. Patients included in our analysis were also age ≥ 40 years. As a result, the risk data in our population may be higher than in other lower-risk populations. Because most strokes occur in patients older than 40 years, however, our results are likely to be generalizable. There may also be a small number of nonhospitalized stroke cases that were not captured by our study, and our risk estimates may be slightly higher because some minor strokes were missed. We also chose the category of “fatal cardiac event” to include fatal MI, death due to heart failure, and sudden death or arrhythmia. Cardiac event rates would be lower if we further limited the category of “fatal cardiac events.” Cardiac events are not uniformly defined in the literature, limiting comparisons of risk across studies.

Our findings confirm that early mortality after stroke is due to the initial stroke itself and that the relative importance of mortality due to cardiac causes increases as one survives longer after stroke. However, the risk of nonfatal recurrent stroke remains high even after 5 years following stroke. Hence, secondary prevention strategies focused on stroke prevention are warranted in addition to strategies specific to cardiac disease. Aggressive blood pressure control, even in patients without overt hypertension, was shown to benefit patients in the PROGRESS trial.⁴⁸ There may also be antiplatelet agents, such as dipyridamole, that are effective in stroke prevention but have not been convincingly shown to prevent coronary disease.⁴⁹

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