Recurrent stroke in midlife is associated with not having a primary care physician

Rebecca J. Lank, BS, Lynda D. Lisabeth, PhD, Brisa N. Sánchez, PhD, Darin B. Zahuranec, MD, Kevin A. Kerber, MD, Lesli E. Skolarus, MD, James F. Burke, MD, Deborah A. Levine, MD, Erin Case, BA, Devin L. Brown, MD, and Lewis B. Morgenstern, MD

Correspondence
Dr. Morgenstern
lmorgens@umich.edu

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Abstract

Objective

To determine using a population-based study whether midlife stroke patients having a primary care physician (PCP) at the time of first stroke have a lower risk of stroke recurrence and mortality than those who do not have a PCP.

Methods

First-ever ischemic stroke patients 45 to 64 years of age at stroke onset were ascertained through the Brain Attack Surveillance in Corpus Christi (BASIC) project from 2000 to 2013 in Texas. Cox proportional hazards models were used to examine the association between not having a PCP and stroke recurrence or all-cause mortality in separate models. Cases were followed up for up to 5 years or until December 31, 2013, whichever came first. Cases were censored for recurrence if they died before experiencing a recurrent event. We adjusted for clinical risk factors that could be associated with having a PCP and recurrence or mortality.

Results

There were 663 first-occurrence ischemic stroke cases. Of these, 77% had a PCP, 43% were female, and average age was 55.6 years. Five-year recurrence risk was 14.6%, and mortality risk was 19.2%. Not having a PCP was associated with higher recurrence risk (adjusted hazard ratio 1.75, 95% confidence interval 1.02–3.02). Having a PCP was not associated with mortality. Sensitivity analyses showed that results were robust to different ways to adjust for chronic conditions.

Conclusion

This study found lower rates of stroke recurrence among those with a PCP at the time of first stroke. Future studies could determine the value of establishing a PCP before stroke hospital discharge for secondary stroke prevention.

From the Stroke Program (R.J.L., L.D.L., D.B.Z., K.A.K., L.E.S., J.F.B., D.A.L., D.L.B., L.B.M.), Department of Epidemiology (L.D.L., E.C.C., L.B.M.), Department of Biostatistics (B.N.S.), and Department of Internal Medicine (D.A.L.), University of Michigan, Ann Arbor.

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Glossary

BASIC = Brain Attack Surveillance in Corpus Christi; **CI** = confidence interval; **HR** = hazard ratio; **ICD** = *International Classification of Diseases*; **IRB** = Institutional Review Board; **NIHSS** = NIH Stroke Scale; **PCP** = primary care physician.

There are 795,000 strokes in the United States annually, 185,000 of which are recurrent strokes.¹ Compared to first stroke, recurrent stroke is associated with greater disability, cost, and mortality.^{2,3}

During initial stroke hospitalization, neurologists are actively engaged in stroke patient care, which includes identifying stroke etiology to tailor secondary prevention measures. Primary care physicians (PCPs) are often optimal coordinators of long-term postdischarge secondary stroke prevention.^{4,5} This care includes management of stroke risk factors such as hypertension, high cholesterol, and atrial fibrillation, as well as behavioral risk factors such as smoking and excessive alcohol intake.^{5,6} Improved management of these conditions has largely been credited for the overall reduced stroke recurrence and mortality in developed countries.⁷

Although stroke incidence is decreasing in the United States, first-ever and overall stroke incidence in the midlife is stable or increasing.^{1,8–10} Midlife stroke can be especially damaging for the patient, family, and society because patients are at working and parenting age and may not be able to maintain these supportive roles.¹¹ Moreover, stroke patients <65 years of age and those with recurrent stroke are more likely to be depressed.¹² Furthermore, midlife stroke patients have relatively prolonged risk for recurrent stroke because they are expected to live longer than older stroke patients. Thus, it is critical that secondary stroke prevention be properly managed in this vulnerable young population.

Using a population-based study, we sought to determine the association between having a PCP at the time of first stroke and the risk of ischemic stroke recurrence and mortality in midlife stroke patients.

Methods

The Brain Attack Surveillance in Corpus Christi (BASIC) project is a population-based surveillance study that aims to capture every stroke case in Nueces County, Texas. Nueces County is a biethnic community of ≈361,000 people; 90% of the county population resides in the urban city of Corpus Christi, with ≈63% of people identifying as Mexican American and 29% identifying as non-Hispanic white.¹³

BASIC methods have been described extensively elsewhere.^{9,14} Briefly, midlife ischemic stroke patients (age 45–64 years) during 2000 to 2013 were identified by trained abstractors through active screening of hospital emergency department and inpatient logs for stroke symptoms and passively through

ICD-9 and -10 codes in discharge logs. At the time of first stroke, charts were abstracted for demographic and clinical information, including age, sex, ethnicity, insurance status, comorbid conditions, excessive alcohol intake, smoking status, tissue plasminogen activator administration, and initial NIH Stroke Scale (NIHSS) score. If no NIHSS score was recorded in the medical record, trained abstractors calculated the score from recorded clinical information.¹⁵ First-ever ischemic strokes were validated by stroke physicians using source documentation masked to age and ethnicity. Stroke patients were asked to participate in an in-person baseline interview. From 2000 to 2008, 75% were random sampled, and 100% were included from 2009 through the end of the study period.

Eligible patients were approached by a trained abstractor for study participation. Baseline interviews were completed soon after the first stroke, during which patients (or proxies) were asked if they had a routine place or physician they saw for routine medical needs before the stroke. They were able to respond “yes,” “no,” or “don’t know.” Patients’ education was also recorded during the interview. Incident cases were followed up for up to 5 years from the date of onset of first stroke or until December 31, 2013, whichever came first. Because of small numbers of people reporting ethnicity different from Hispanic or non-Hispanic white, all other racial/ethnic groups were excluded in this analysis.

Standard protocol approvals, registrations, and patient consents

This study was approved by the University of Michigan Institutional Review Board (IRB) and the IRB of both hospital systems in Corpus Christi (Christus Spohn Health System and Corpus Christi Medical Center). Written informed consent was obtained for all participants (or proxies) in the study.

Data availability statement

The deidentified data that support the findings of this study are available from the corresponding author on reasonable request from a qualified investigator as long as it conforms to Health Insurance Portability and Accountability Act of 1996 protection, IRB study approvals, and data-use agreements that the study team has with the participating hospitals.

Data analysis

Cox proportional hazards models were used to examine the association between not having a PCP and stroke recurrence or all-cause mortality in separate models. Cases were censored for recurrence if they died before experiencing a recurrent event within the 5 years of follow-up. For the 5-year mortality outcome, patients continued to be followed up until death,

despite having a recurrence. If the recurrent stroke was fatal, it was counted as a death in the mortality model and as a recurrent event in the recurrence model.

We adjusted for variables determined a priori to be potential confounders of the PCP-outcome associations, including demographic variables (age, ethnicity, sex). On the basis of the cumulative sum of residual diagnostics, age was found to follow a nonlinear association with mortality and recurrence and was modeled by including linear and quadratic terms in the model. Furthermore, because patients with comorbid chronic conditions may be more likely to have a PCP and may also have higher recurrence and mortality risk, we additionally

decided a priori to adjust for diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, and high cholesterol. Chronic conditions were included in the model by treating them as stratification variables to allow the baseline hazards to differ across subgroups with the various chronic conditions (i.e., does not assume proportional hazards for the chronic conditions).

In additional analyses, we further adjusted for smoking status, excessive alcohol use, insurance status (uninsured, private insurance, and insurance coverage through Medicare, Medicaid, or the Veterans Affairs), and education, categorized as less than high school, completed high school, and more than

Table 1 Demographic and clinical characteristics of participants with and without a PCP: The BASIC study, 2000 to 2013

Characteristic	Does not have routine PCP (n = 151)	Has routine PCP (n = 512)	p Value
Mexican American, %	63.6	70.1	0.13
Female, %	37.1	44.9	0.09
Age, y	56.00 (50.00–60.00)	56.00 (52.00–60.00)	0.11
Education, y ^a	12.00 (9.00–13.00)	12.00 (11.00–14.00)	<0.01
Education categories, %			<0.01
More than high school	25.8	39.3	
High school diploma/GED	29.8	31.2	
Less than high school	44.4	29.5	
Insurance, % ^a			<0.001
Private	32.0	54.5	
Medicaid, Medicare, or VA	10.6	20.6	
Uninsured	57.4	24.9	
Atrial fibrillation, %	2.0	3.7	0.30
Excessive alcohol use, %	21.9	7.4	<0.001
CAD, %	11.9	23.2	<0.01
High cholesterol, %	19.2	38.5	<0.001
Diabetes mellitus, %	36.4	56.1	<0.001
Hypertension, %	55.0	76.0	<0.001
NIHSS score	4.00 (1.00–7.00)	3.00 (2.00–6.00)	0.71
Smoking, %			<0.001
Current	4.6	10.0	0.04
Former	52.3	31.3	<0.001
Never	43.0	58.8	<0.01
tPA, %	2.6	5.9	0.12
Proxy interview, %	15.5	17.2	0.61

Abbreviations: BASIC = Brain Attack Surveillance in Corpus Christi; CAD = coronary artery disease; GED = General Educational Development; NIHSS = NIH Stroke Scale; PCP = primary care physician; tPA = tissue plasminogen activator; VA = Veterans Affairs.

Data obtained at time of first stroke.

^a Three patients were missing education and 1 patient was missing insurance information.

high school. The model for mortality also adjusted for NIHSS score as a continuous measure. Because NIHSS score violated the proportional hazards assumption, its interaction with time in follow-up was also included.

Sensitivity analyses were conducted to investigate whether the approach to adjusting for chronic conditions had an effect on the results. First, we followed an alternative sequential approach to entering adjustment factors in the model, following the Andersen model,¹⁶ to examine which factors (predisposing patient characteristics including age, sex, ethnicity, and education; enabling patient characteristics such as insurance; health behaviors; or chronic conditions) were the most potent confounders of the PCP-outcome association. Second, while chronic conditions were entered as stratification variables in the primary Cox regression models, we also examined alternatives to adjusting for chronic conditions, namely including chronic conditions as covariates in the model; including a chronic conditions risk score, created by adding the number of chronic conditions as a covariate; and using the risk score as a stratification variable. Because there was no meaningful difference in the final model due to method of adjustment, we used simplified models that treated chronic conditions as covariates to obtain estimated recurrence or mortality risk and to graphically display the association between mortality or recurrence and having a PCP; all other covariates were set at their mean.

We also conducted a sensitivity analysis for mortality, treating recurrence as a time-varying covariate. For recurrence, a sensitivity analysis treated mortality as a competing event.

Results

First-ever midlife ischemic stroke patients ($n = 1,134$) were identified during the study period. Of these, 207 were ineligible to participate in the baseline interview (188 were randomized to no interview, 11 had the interview >6 months after initial stroke, and 8 for other prespecified reasons). Of the remaining 927 eligible patients, 96 (8.5%) could not be located, and 168 (14.5%) refused the interview. The remaining 663 first-ever stroke cases had complete data on whether the patient had a PCP. Those included were more likely to be female (43.1% vs 36.6%, $p = 0.03$), but they were otherwise similar in terms of 5-year recurrence rate (log-rank test $p = 0.95$) and other demographic characteristics and risk factors (all $p > 0.05$) compared with those not included. Among the 663 included in the analysis, median follow-up was 1,282 days; 5-year recurrence was 14.6% (86 recurrent strokes) and mortality was 19.2% (115 deaths); 77% had a PCP at the time of first stroke; 67% were Mexican American; 43% were female; patients were on average 55.6 years of age at first stroke; and 15.9% of interviews were completed by proxies. Table 1 shows patient characteristics of those with and without a PCP.

From the final adjusted model, the cumulative 5-year recurrence risk was 75% greater for those without a PCP

compared to those with a PCP (hazard ratio [HR] 1.75, 95% confidence interval [CI] 1.02–3.02, $p = 0.04$). Adjustment for alcohol use and smoking did not meaningfully influence these findings, and neither did adjustment for insurance or education (table 2). There were no associations between recurrence and other factors included in the model (table 3).

The alternative sequential approach to entering adjustment factors in the model revealed that chronic conditions were the most potent confounder of the PCP-recurrence association (table 4). The sensitivity analyses for different ways to account for the influence of chronic conditions (i.e., stratification or risk score) showed that results were robust to the a priori approach of the study (data not shown). Adjusting for mortality as a competing event slightly strengthened the association between not having a PCP and recurrence (table 4). The figure shows survival curves for recurrence by PCP status estimated from a fully adjusted model with all covariates set at their mean.

Not having a PCP was not associated with all-cause mortality (HR 0.91, 95% CI 0.54–1.54, $p = 0.72$) (table 5). Additional adjustment for recurrence as a time-varying covariate did not influence the results (table 5), and neither did other sensitivity analyses (data not shown).

Discussion

This population-based study found a relative 75% increase (and nearly 10% absolute increase) in 5-year ischemic stroke recurrence risk associated with not having a PCP at the time of first stroke, even after adjustment for demographic and clinical factors, including insurance status. This demonstrates the potentially positive role a PCP can have on patients' long-term secondary stroke prevention. This study focused on midlife stroke survivors because recent data suggest that this group is not experiencing the same stroke incidence and mortality reductions as older stroke patients.^{8,9,17} Secondary

Table 2 HRs for stroke recurrence comparing those without a PCP to those with a PCP

Adjustment	HR	p Value
Unadjusted	1.28 (0.79–2.07)	0.31
Model 1: ethnicity, age, sex, chronic conditions^a	1.71 (1.03–2.84)	0.04
Model 1 + smoking	1.68 (1.00–2.80)	0.05
Model 1 + insurance	1.81 (1.06–3.09)	0.03
Model 1 + education	1.69 (1.01–2.82)	0.05
Final model: model 1 + all above	1.75 (1.02–3.02)	0.04

Abbreviations: CI = confidence interval; HR = hazard ratio; PCP = primary care physician.

^a All covariates were indicator variables except continuous age, which was modeled with a quadratic term. Chronic conditions entered as stratification variables in the Cox regression model: diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, and high cholesterol.

Table 3 HRs from fully adjusted^a final model for stroke recurrence comparing those without a PCP to those with a PCP

Exposure	HR (95% CI)	p Value
No PCP	1.75 (1.02–3.02)	0.04
Mexican American (vs non-Hispanic white)	1.60 (0.90–2.86)	0.11
Female	1.34 (0.84–2.14)	0.21
Education (reference: less than high school)		
High school education	1.03 (0.60–1.77)	0.91
More than high school	0.91 (0.51–1.62)	0.74
Insurance (reference: public insurance)		
Uninsured	0.87 (0.44–1.72)	0.69
Private insurance	1.03 (0.56–1.90)	0.92
Current smoker	1.03 (0.62–1.69)	0.92
Alcohol	1.21 (0.57–2.54)	0.62
Age^b		
Older age	0.94 (0.70–1.26)	0.70
Younger age	1.34 (0.96–1.88)	0.09

Abbreviations: CI = confidence interval; HR = hazard ratio; PCP = primary care physician.

Public insurance: Medicaid, Medicare, or Veterans Affairs combined.

^a Chronic conditions were treated as stratification factors.

^b Age demonstrated a nonlinear effect and was modeled with a quadratic term. Effects shown represent the comparisons of 5 years above or below the mean, compared to the mean age.

stroke prevention can be a complex combination of pharmaceutical, behavioral, and sometimes surgical interventions.^{4,6} Previous research found younger age to be a predictor of poor adherence to recurrent stroke prevention medication.¹⁸ These hypotheses-generating data suggest that proper management may be optimized with the help of a PCP, particularly in these younger patients.

While our study found a lower rate of recurrence in stroke recurrence associated with having a PCP, the overall recurrence rate was still high at 14%, and there was no associated reduction in all-cause mortality, which was also considerably high for people in their midlife at 19.2% over 5 years. In another study, more than half of deaths 5 years after stroke in young patients was due to a recurrent stroke or other cardiovascular disease, indicating that death could be attributed to cerebrovascular risk factors.¹⁹ Some researchers suggest that a gap between evidence-based interventions in secondary stroke care and clinical practice could contribute to persistent levels of stroke recurrence and mortality.^{4,20} Results are mixed on whether adherence to guidelines improves patient outcomes.^{21,22} As a result of this controversy, several studies have developed interventions that add new

components to secondary stroke care such as weekly visits to a stroke nurse for patient education.^{22–25} These studies have had limited efficacy, and the anticipated difficulty to widely implement these interventions may make them infeasible.

In 1 randomized controlled study, stroke patients assigned to a shared-care intervention, which included enhanced communication between stroke neurologists and general practitioners and scheduled appointments with the general physician, had improved vascular risk factor management and cognition compared to patients receiving standard care from their PCP.²⁶ This may indicate the crucial role of the neurologist in secondary stroke prevention. Further work is critical to identify modifiable care practices that can reduce stroke recurrence.

There are several limitations to our study. Because this is an observational study, we cannot determine causality between having a PCP and the associated reduction in stroke recurrence risk. This association makes intuitive sense under the assumptions that patients with a PCP visit their PCP, the PCP prescribes appropriate regimens for stroke prevention, and the patient adheres to these regimens. However, our data do not measure the type or quality of care received by PCPs. The very definition of PCP is somewhat vague and open to the respondent's definition of routine medical needs. In addition, our data do not directly or indirectly measure regimen adherence. Therefore, we cannot confirm that our assumptions about PCPs are true, and future studies should investigate the association between the quality of secondary stroke

Table 4 HRs for stroke recurrence comparing those without a PCP to those with a PCP using the Andersen Behavioral Model for adjustment and sensitivity analysis treating mortality as a competing event

Adjustment	HR (95% CI)	p Value
Unadjusted	1.28 (0.79–2.07)	0.31
Model 1: age, ^a sex, ethnicity, education	1.35 (0.83–2.21)	0.23
Model 1 + insurance	1.41 (0.85–2.34)	0.18
Model 1 + insurance and chronic conditions ^b	1.78 (1.04–3.06)	0.04
Final model: model 1 + insurance, chronic conditions, smoking, and alcohol	1.75 (1.02–3.02)	0.04
Sensitivity analysis: final model with mortality treated as a competing event	1.80 (1.12–2.90)	0.016

Abbreviations: CI = confidence interval; HR = hazard ratio; PCP = primary care physician.

^a All covariates were indicator variables except continuous age, which was modeled with linear and quadratic terms.

^b Chronic conditions entered as stratification variables in the model diabetes mellitus, atrial fibrillation, coronary artery disease, high cholesterol, and hypertension.

Figure Probability of remaining without recurrence during follow-up for those with and without a PCP, estimated from final adjusted model with covariates set at the mean

PCP = primary care physician.

prevention care from PCPs, adherence to prevention regimens, and risk for stroke recurrence and mortality among first-time stroke patients.

Although the large study population allowed for adjustment of many potential confounders, residual confounding may

Table 5 HRs for all-cause mortality comparing those without a PCP to those with a PCP

Adjustment	HR (95% CI)	p Value
Unadjusted	0.77 (0.48–1.23)	0.27
Model 1: ethnicity, age, sex, chronic conditions ^a	0.87 (0.53–1.44)	0.59
Model 1 + smoking	0.83 (0.50–1.38)	0.48
Model 1 + insurance	0.97 (0.58–1.63)	0.91
Model 1 + education	0.81 (0.49–1.34)	0.41
Model 1 + all the above	0.92 (0.54–1.55)	0.74
Final model: model 1 + all the above + NIHSS ^b	0.91 (0.54–1.54)	0.72
Sensitivity analysis: final model with recurrence treated as a time-varying covariate	0.90 (0.53–1.54)	0.71

Abbreviations: CI = confidence interval; HR = hazard ratio; NIHSS = NIH Stroke Scale; PCP = primary care physician.

^a All covariates were indicator variables except continuous age, which was modeled with a quadratic term. Chronic conditions entered as stratification variables in the Cox regression model: diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, and high cholesterol.

^b NIHSS modeled as a continuous variable demonstrated lack of proportional hazards; thus, its interaction with time in follow-up was also included in the model.

remain. This is a particular limitation for our adjustment of comorbid conditions. It is possible that patients without a PCP may not know their comorbid conditions and thus underreport these conditions. In this case, our findings may overestimate the association between having a PCP and recurrence. However, it is also probable that patients without a PCP choose not to have one because they do not have chronic conditions. Because there is no way to distinguish the degree of underreporting chronic conditions in patients without PCPs, and because there is no existing literature on this issue, we must interpret our findings with caution. Our multiple sensitivity analyses indicate that our results are robust to different methods to account for comorbid conditions. It is crucial for future studies to assess the rates of undiagnosed risk factors in patients with and without a PCP.

Our current study examined only the association between having a PCP near the point of first ischemic stroke and recurrence. We are therefore unable to comment on whether changes over time in having a PCP could affect stroke recurrence risk. However, risk for recurrent stroke is highest soon after the first stroke, so we would expect that having a PCP would be most important as soon after the first stroke as possible.^{3,27,28} Given the expectation that at least some patients who did not have a routine physician at the time of the baseline interview would later establish a PCP within 5 years, our findings of lower stroke recurrence among those with a PCP at the time of the baseline interview are noteworthy.

Because we monitor only recurrent stroke identified in Corpus Christi hospitals, there is possible loss to follow-up for stroke recurrence. However, Nueces County is geographically isolated, making capture of initial stroke very likely. Furthermore, migration out of this community is rare with a stable population of US citizen Mexican Americans. Because we ascertain mortality through the death index, mortality data are relatively insulated from loss to follow-up.

This population-based study comes from a single community, which limits its generalizability to other communities. Future work should be done in different communities and in different age and racial/ethnic groups to determine whether the association between having a PCP and stroke recurrence holds.

Midlife stroke patients need to manage their secondary stroke risk factors to live a long, healthy life. Having a PCP at the time of first stroke was associated with lower rates of stroke recurrence. Future studies could determine the value of establishing a PCP before stroke hospital discharge for secondary stroke prevention.

Author contributions

Rebecca Lank: drafting/revising manuscript for content, interpretation of data. Lynda Lisabeth: drafting/revising manuscript for content, study supervision, and obtaining funding. Brisa Sánchez: drafting/revising manuscript for content,

analysis and interpretation of data, statistical analysis. Darin Zahuranec, Kevin Kerber, Lesli Skolarus, James Burke, and Deborah Levine: drafting/revising manuscript for content. Erin Case: drafting/revising manuscript for content, study supervision, and coordination. Devin Brown: drafting/revising manuscript for content. Lewis Morgenstern: drafting/revising manuscript for content, study concept and design, study supervision, obtaining funding.

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Disclosure

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