JAMA Neurology | Original Investigation

Sex Differences in Presentation and Outcome After an Acute Transient or Minor Neurologic Event

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IMPORTANCE Sex differences have been described in the presentation, care, and outcomes among people with acute ischemic strokes, but these differences are less understood for minor ischemic cerebrovascular events. The present study hypothesized that, compared with men, women are more likely to report nonfocal symptoms and to receive a stroke mimic diagnosis.

OBJECTIVE To evaluate sex differences in the symptoms, diagnoses, and outcomes of patients with acute transient or minor neurologic events.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study of patients with minor ischemic cerebrovascular events or stroke mimics enrolled at multicenter academic emergency departments in Canada between December 2013 and March 2017 and followed up for 90 days is a substudy of SpecTRA (Spectrometry for Transient Ischemic Attack Rapid Assessment). In total, 1729 consecutive consenting patients with acute transient or minor neurologic symptoms were referred for neurologic evaluation; 66 patients were excluded for protocol violation (n = 46) or diagnosis of transient global amnesia (n = 20).

EXPOSURES The main exposure was female or male sex.

MAIN OUTCOMES AND MEASURES The main outcome was the clinical diagnosis (cerebral ischemia vs stroke mimic). Secondary outcomes were 90-day stroke recurrence and 90-day composite outcome of stroke, myocardial infarction, or death. The association between presenting symptoms (focal vs nonfocal) and clinical diagnosis was also assessed. Research hypotheses were formulated after data collection.

RESULTS Of 1648 patients included, 770 (46.7%) were women, the median (interquartile range) age was 70 (59-80) years, 1509 patients (91.6%) underwent brain magnetic resonance imaging, and 1582 patients (96.0%) completed the 90-day follow-up. Women (522 of 770 [67.8%]) were less likely than men (674 of 878 [76.8%]) to receive a diagnosis of cerebral ischemia (adjusted risk ratio [aRR], 0.88; 95% CI, 0.82-0.95), but the 90-day stroke recurrence outcome (aRR, 0.90; 95% CI, 0.48-1.66) and 90-day composite outcome (aRR, 0.86; 95% CI, 0.54-1.32) were similar for men and women. No significant sex differences were found for presenting symptoms. Compared with patients with no focal neurologic symptoms, those with focal and nonfocal symptoms were more likely to receive a diagnosis of cerebral ischemia (aRR, 1.28; 95% CI, 1.15-1.39), but the risk was highest among patients with focal symptoms only (aRR, 1.45; 95% CI, 1.34-1.53). Sex did not modify these associations.

CONCLUSIONS AND RELEVANCE The results of the present study suggest that, despite similar presenting symptoms among men and women, women may be more likely to receive a diagnosis of stroke mimic, but they may not have a lower risk than men of subsequent vascular events, indicating potentially missed opportunities for prevention of vascular events among women.

JAMA Neurol. doi:10.1001/jamaneurol.2019.1305
Published online May 22, 2019.

Supplemental content

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Sex differences exist in the presentation and outcome of moderate to severe stroke.[1] Compared with men, women are less likely to report typical symptoms of stroke, such as weakness, numbness, or language disturbances,[2,3] and are more likely to receive a diagnosis of stroke mimic.[4,5] In addition, the quality of stroke care is lower for women, and they are more likely to have increased disability and poorer quality of life after stroke.[1,6,7]

By contrast, the differences in the presenting symptoms and diagnosis of men and women with minor strokes and transient ischemic attacks (TIAs) are less well understood. Minor ischemic cerebrovascular events account for more than half of all ischemic strokes and are associated with a high risk of stroke recurrence, progression, and disability.[8-10] Diagnosing minor events is often challenging, even for neurologists, because symptoms can be subtle or transient.[5,11] At least one-third of patients with transient or mild neurologic symptoms are eventually given a diagnosis other than stroke or TIA (ie, a stroke mimic) after investigations.[12,13] Potential differences in presenting symptoms between men and women add another layer of complexity and may result in sex differences in clinical investigation, final diagnosis, and outcome after a minor ischemic cerebrovascular event.

We aimed to understand the sex differences in the symptoms, diagnoses, and outcomes of patients presenting to the emergency department with acute transient or minor neurologic events. We hypothesized that, compared with men, women more frequently report nonfocal symptoms and are more likely to receive a diagnosis of a stroke mimic. We also assessed the sex differences in stroke recurrence within 90 days as well as the composite outcome of stroke, myocardial infarction, or death within 90 days.

Key Points

Question Are there sex differences in the presenting symptoms of minor ischemic cerebrovascular events, and if so, do they contribute to sex disparity in stroke outcome?

Findings In this cohort study of 1648 patients, despite having similar symptoms at presentation, women with acute transient or minor neurologic events were more likely than men to receive a diagnosis of stroke mimic, but the risks of stroke recurrence or of stroke, myocardial infarction, or death within 90 days of the event were similar between women and men.

Meaning These findings call for attention to potential missed opportunities for prevention of stroke and other adverse vascular events among women.

Methods

This is a substudy of SpecTRA (Spectrometry for Transient Ischemic Attack Rapid Assessment), a multicenter, prospective study aiming to identify a blood biomarker differentiating TIAs or minor strokes from stroke mimics in patients presenting within 24 hours of symptom onset and referred for an acute neurologic assessment.[14] The SpecTRA study received institutional approvals from the participating hospitals' ethics review board for research using human subjects, and written informed consent was obtained from all patients enrolled.

Study Participants

Between December 2013 and March 2017, SpecTRA investigators enrolled 1729 patients who presented with acute transient or minor neurologic symptoms and who were suspected of having experienced either a minor ischemic cerebrovascular event or a stroke mimic, such as syncope, seizure, migraine, peripheral neuropathy. There were 66 patients (3.8%) excluded from the final analyses (46 patients excluded for protocol violations, eg, incorrect or missing tests, blood drawn out of time window, or blood biomarker sample processing issues, and 20 patients excluded for diagnosis of transient global amnesia because of the ambiguity of this diagnosis and its association with cerebral ischemia).[15] A minor symptom was defined as a National Institutes of Health Stroke Scale score of 3 or lower. The SpecTRA study required a clinical evaluation by a neurologist with stroke expertise at least once between symptom onset and 90 days after onset as well as having brain magnetic resonance imaging (MRI) within 7 days of the event or computed tomography and computed tomographic angiography within 24 hours of the event. All other investigations and clinical follow-up were completed as was clinically routine.

The 3 categories for symptom types were absence of focal neurologic symptoms, both focal and nonfocal symptoms, and focal symptoms only. Focal neurologic symptoms included any motor, sensory, vision, or speech (aphasia or dysarthria) deficits. Nonfocal symptoms included the migration of symptoms that took longer than 2 minutes, symptoms affected by changes in head position, headache, neck pain, photophobia, eyelid droop, vertigo, unsteady gait, nausea, vomiting, feeling "drunk," confusion, disorientation, difficulty concentrating, visuospatial difficulties, amnesia, fatigue, dizziness, involuntary movement, anxiety, or cardiac symptoms (shortness of breath, anxiety, chest pain, palpitations, syncope, or presyncope). Symptoms were ascertained by study coordinators and investigators (A.Y.X.Y., A.M.P., M.L.P., V.S., J.H., C.Z., E.K., L.B., and S.B.C.) at the time of enrollment.

The primary outcome was the final clinical diagnosis of minor ischemic cerebrovascular event (ie, TIA or minor stroke) or stroke mimic. This was determined by 2-person adjudication committees (A.Y.X.Y., J.H., C.Z., and E.K.) on the basis of detailed medical record review, which included the neuroimaging results, all investigations completed in the context of clinical care, and the clinical notes of the treating physicians detailing their impressions of the final diagnosis and stroke etiology. Any disagreement was resolved by a third adjudicator (A.M.P. and S.B.C.). All adjudicators were neurologists with stroke fellowship training. Among people with TIA or minor stroke, stroke subtype was recorded according to the Trial of Org 10172 in Acute Stroke Treatment classification.[16] The patients were given the classification of the most likely cause of stroke based on investigations completed in clinical care if one was found (eg, atrial fibrillation, symptomatic dissection). If 2 causes of the stroke were found, patients were classified as

Table 1. Baseline Characteristics and Investigations of 1648 Patients by Sex

Characteristic or Investigation	No. (%) of Patients		*P* Value
	Women (n = 770)	Men (n = 878)	
Age, median (IQR), y	71 (58-81)	69 (59-79)	.09
Race/ethnicity			
White	705 (91.6)	791 (90.1)	.03
Black	7 (0.9)	7 (0.8)	
Asian	25 (3.2)	52 (5.9)	
Aboriginal	19 (2.5)	10 (1.1)	
Other	14 (1.8)	18 (2.0)	
Hypertension	401 (52.1)	513 (58.4)	.01
Diabetes	118 (15.3)	179 (20.4)	.01
Dyslipidemia	227 (29.5)	351 (40.0)	<.001
Coronary artery disease	74 (9.6)	166 (18.9)	<.001
Atrial fibrillation	92 (11.9)	115 (13.1)	.53
Active smoking	91 (11.8)	126 (14.4)	.15
History of stroke	59 (7.7)	87 (9.9)	.13
History of migraines	193 (25.1)	107 (12.2)	<.001
Self-reported psychiatric condition or recent stressor	177 (23.0)	158 (18.0)	.01
Baseline medication			
Antiplatelet for the past ≥7 d	210 (27.3)	339 (38.6)	<.001
Vitamin K antagonist	22 (2.9)	27 (3.1)	.91
Direct oral anticoagulant	27 (3.5)	50 (5.7)	.05
Antihypertensive	378 (49.1)	469 (53.4)	.09
Statin for the past ≥30 d	190 (24.7)	337 (38.4)	<.001
Brain parenchymal imaging	768 (99.7)	877 (99.9)	.42
Computed tomography	697 (90.5)	822 (93.6)	.003
Magnetic resonance imaging	705 (91.6)	804 (91.6)	.93
Computed tomographic angiography or carotid Doppler tests	659 (85.6)	794 (90.4)	.001
Echocardiogram	306 (39.7)	402 (45.8)	.02
Holter monitoring if no baseline atrial fibrillation	357 (46.4)	443 (50.4)	.05

Abbreviation: IQR, interquartile range.

having competing etiologies. Patients were classified as incompletely investigated only if no clear cause of the stroke was identified and they did not have a minimum of vascular imaging, echocardiogram, and 24-hour Holter monitoring within 90 days of their event. Secondary outcomes included the presence of an MR diffusion-weighted imaging (DWI) lesion indicating acute infarction, stroke recurrence within 90 days, and a 90-day composite outcome of stroke, myocardial infarction, or all-cause death. The 90-day outcomes were determined by a study coordinator via telephone follow-up or medical record review. We report patient race/ethnicity in this study as classified by investigators or by participants in the table of baseline characteristics (**Table 1**).

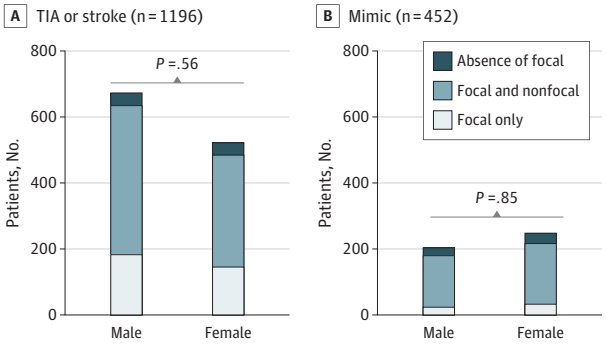
Statistical Analysis

We compared baseline characteristics between male and female patients using the Wilcoxon signed rank test for continuous variables and the χ^2 test for categorical variables. We evaluated the association between sex and the outcomes by calculating risk differences and 95% CIs derived from the Wilson score interval with continuity correction.[17] We used multivariable logistic regression with adjustment for age, hypertension, diabetes, atrial fibrillation, coronary artery disease, smoking, and history of stroke to obtain adjusted odds ratios, and we derived adjusted risk ratios (aRRs) and 95% CIs using previously described methods.[18] We also determined the association between presenting symptoms and the final clinical diagnosis as well as the association between symptoms and the presence of acute infarct evidence on MRI with adjustment for the same covariates. We tested for effect modification by sex using multiplicative interaction terms. Study data were managed using REDCap, and all analyses were performed using R, version 3.3.1 (The R Foundation).[19] A 2-sided $P < .05$ was considered statistically significant.

Results

We included 1648 patients (770 [46.7%] women; median [interquartile range] age, 70 [59-80] years) who presented to the emergency department with acute minor neurologic symptoms. Table 1 provides patient baseline characteristics and clinical investigations performed stratified by sex. Compared with 878 men, fewer of the 770 women had a history of hypertension (401 [52.1%] vs 513 [58.4%]; $P = .01$), diabetes (118 [15.3%] vs 179 [20.4%]; $P = .01$), dyslipidemia (227 [29.5%] vs 351

Figure. Presenting Symptoms by Sex and Final Diagnosis



Symptom distribution by sex among patients with transient ischemic attack (TIA) or minor stroke (A) or with stroke mimic (B).

[40.0%]; $P < .001$), and coronary artery disease (74 [9.6%] vs 166 [18.9%]; $P < .001$), but more women reported a history of migraine headaches (193 [25.1%] vs 107 [12.2%]; $P < .001$) as well as a psychiatric condition or recent stressor (177 [23.0%] vs 158 [18.0%]; $P = .01$). An MRI of the brain was obtained in 1509 patients (91.6%) within 7 days of symptom onset, and the median (interquartile range) time to MRI was 0.82 (0.29-1.27) days. The majority of patients reported both focal and nonfocal symptoms, and the sex differences in presenting symptoms by final diagnosis were not significantly different (**Figure**). For 522 women diagnosed as having TIA or stroke, 38 (7.3%) had an absence of focal symptoms, 338 (64.8%) had focal and nonfocal symptoms, and 146 (28.0%) had focal symptoms only. For 674 men diagnosed as having TIA or stroke, 40 men (5.9%) had an absence of focal symptoms, 452 (67.1%) had focal and nonfocal symptoms, and 182 (27.0%) had focal only symptoms. For 248 women diagnosed as having stroke mimic, 31 (12.5%) had an absence of focal symptoms, 184 (74.2%) had focal and nonfocal symptoms, and 33 (13.3%) had focal only symptoms. For 204 men diagnosed as having stroke mimic, 24 (11.8%) had an absence of focal symptoms, 156 (76.5%) had focal and nonfocal symptoms, and 24 (11.8%) had focal only symptoms. Headache (women, 285 [37.0%] vs men, 265 [30.2%]; $P = .004$) and photophobia (women, 55 [7.1%] vs men, 35 [4.0%]; $P = .007$) were more frequently reported by women than by men, but the frequency of other reported nonfocal symptoms was similar (eTable 1 in the Supplement).

The clinical diagnosis of the presenting event was ascertained for all 1648 patients, and 1582 patients (96.0%) completed the 90-day follow-up. Overall, 1196 patients received a diagnosis of a minor ischemic cerebrovascular event, and 452 patients received a diagnosis of a stroke mimic. **Table 2** shows the risk differences comparing women with men for all outcomes and aRRs with 95% CIs. A diagnosis of minor ischemic cerebrovascular event was given to a lower percentage of the women (522 of 770 [67.8%]) than men (674 of 878 [76.8%]), and 247 of these events for women (47.3%) were DWI-negative clinical TIA, whereas 268 of these events for men (39.8%) were DWI-negative clinical TIA. The 3 most common stroke mimic diagnoses received by women were migraine, peripheral vestibulopathy, and anxiety or other psychiatric condition, whereas for men they were migraine, peripheral vestibulopathy, and seizure (eTable 2 in the Supplement).

Even after adjustment for baseline differences, women were less likely than men to receive a diagnosis of minor ischemic cerebrovascular event (aRR, 0.88; 95% CI, 0.82-0.95), and women were less likely than men to have evidence of acute infarction on MRI (aRR, 0.77; 95% CI, 0.67-0.87) (Table 2). Despite these findings, women and men had similar recurrence of stroke within 90 days (aRR, 0.90; 95% CI, 0.48-1.66) and had similar 90-day composite outcome of stroke, myocardial infarction, or death (aRR, 0.86; 95% CI, 0.54-1.32). Among patients with 90-day recurrent stroke (18 women and 23 men), 16 women (88.9%) and 23 men (100%) initially received a diagnosis of minor ischemic cerebrovascular event. Among patients with 90-day stroke, myocardial infarction, or death (35 women and 46 men), 29 women (82.9%) and 42 men (91.3%) initially received a diagnosis of a minor ischemic cerebrovascular event. Similarly, among patients with 90-day recurrent stroke, 6 women (33.3%) and 17 men (73.9%) had DWI-positive scan results; among those with 90-day stroke, myocardial infarction, or death, 14 women (40.0%) and 29 men (63.0%) had DWI-positive scan results. We found that women with no MRI evidence of a cerebrovascular event were more likely than men to be incompletely investigated (54 [25.4%] vs 29 [13.1%]; $P = .002$) (**Table 3**).

Presenting symptoms were associated with the final diagnosis or with evidence of presence of infarct on MRI, and these associations were not modified by sex (all interactions, $P > .60$). Compared with patients with no focal neurologic symptoms, the presence of both focal and nonfocal stroke symptoms in patients was associated with an increased risk of diagnosis of minor ischemic cerebrovascular event (aRR, 1.28; 95% CI, 1.15-1.39), but the risk was highest among patients with focal symptoms only (aRR, 1.45; 95% CI, 1.34-1.53). Similarly, patients with isolated focal stroke symptoms were at highest risk of acute infarct evidence on MRI brain scan (aRR, 3.00; 95% CI, 2.40-3.58), but patients with both focal and nonfocal symptoms were still at higher risk (aRR, 2.27; 95% CI, 1.73-2.88).

Discussion

In this cohort of 1648 patients presenting to an emergency department with acute transient or minor neurologic deficits, we found that women were more likely than men to receive a diagnosis of a stroke mimic, but the 90-day stroke recurrence and composite outcome of stroke, myocardial infarction, or death risks were similar between the sexes.

There are a number of potential explanations for these observations. First, our findings suggested a greater risk of missed diagnosis of cerebral ischemia in women compared with men who presented with minor or transient neurologic symptoms, and women may have been particularly vulnerable to misdiagnosis when there was no evidence of acute infarct on MRI. These explanations are consistent with other studies that have reported female sex to be a risk factor for stroke

Table 2. Multivariable Analysis of Diagnosis and 90-Day Outcomes Comparing 1648 Female vs Male Patients

Diagnosis or Outcome	No. (%) of Patients		Unadjusted RD, % (95% CI)	Adjusted RR (95% CI)[a]
	Women (n = 770)	Men (n = 878)		
Minor ischemic cerebrovascular event	522 (67.8)	674 (76.8)	−9.0 (−13.4 to −4.5)	0.88 (0.82 to 0.95)
Infarct evident on MRI	275 (35.7)	406 (46.2)	−10.5 (−15.4 to −5.7)	0.77 (0.67 to 0.87)
Stroke recurrence within 90 d	18 (2.3)	23 (2.6)	−0.25 (−1.94 to 1.45)	0.90 (0.48 to 1.66)
90-d Stroke, myocardial infarction, or death	35 (4.5)	46 (5.2)	−0.63 (−2.93 to 1.67)	0.86 (0.54 to 1.32)

Abbreviations: MRI, magnetic resonance imaging; RD, risk difference; RR, risk ratio.

[a] Adjusted for baseline covariates of age, hypertension, diabetes, atrial fibrillation, coronary artery disease, smoking, and history of stroke.

Table 3. Cause of Minor Cerebral Ischemic Event by Sex and Evidence of Acute Infarct on MRI[a]

Cause of Cerebral Ischemia	No. (%) of Patients		*P* Value[b]
	Women	Men	
Negative on MRI			
No.	213	222	
Cardioembolic	32 (15.0)	31 (14.0)	.86
Large-artery atherosclerosis	25 (11.7)	44 (19.8)	.03
Small-vessel disease	4 (1.9)	8 (3.6)	.42
Other	7 (3.3)	5 (2.3)	.72
Cryptogenic	87 (40.8)	95 (42.8)	.75
Competing etiologies	4 (1.9)	10 (4.5)	.20
Incomplete investigations	54 (25.4)	29 (13.1)	.002
Positive on MRI			
No.	275	406	
Cardioembolic	52 (18.9)	62 (15.3)	.25
Large artery atherosclerosis	42 (15.3)	63 (15.5)	>.99
Small vessel disease	38 (13.8)	71 (17.5)	.24
Other	9 (3.3)	18 (4.4)	.57
Cryptogenic	103 (37.5)	145 (35.7)	.70
Competing etiologies	7 (2.5)	16 (3.9)	.44
Incomplete investigations	24 (8.7)	31 (7.6)	.71

Abbreviation: MRI, magnetic resonance imaging.

[a] People without MRI excluded (n = 80).

[b] Pearson χ^2 test with Yates continuity correction.

misdiagnosis.[5,20] Although MRI is the most sensitive test for acute cerebral ischemia, the sensitivity of the technology is limited for people with minor events. Prior studies have shown that up to two-thirds of people who receive a diagnosis of clinical TIA have no acute DWI lesion.[21] Furthermore, a medical history evoking alternative diagnoses, such as migraine or anxiety, may contribute to misdiagnosis in women more than men because migraine and psychosocial stressors are more common in women.[22,23] Our results also raise the possibility of implicit sex and gender bias in the evaluation of this population, such that a symptom or element of the clinical history may raise suspicion for cerebral ischemia in men, but not in women.

Second, consistent with prior studies, we found sex differences in the treatment management among patients with a minor cerebrovascular event.[7,23] We observed that women who received a diagnosis of cerebral ischemia without evidence of infarct on MRI were more frequently incompletely investigated compared with their male counterparts. The reasons for this are unclear.

Third, it is possible that women who received a diagnosis of a so-called stroke mimic are at increased risk of adverse vascular events. For example, migraine, especially with aura, and psychosocial stressors have been shown to be associated with increased risk of stroke incidence and recurrence.[22-24] Our sample size was too small to test these hypotheses, but we believe our findings highlight the need for dedicated studies on sex and gender differences in the clinical presentation, diagnosis, and treatment of minor ischemic cerebrovascular events.

Numerous studies have found that women are more likely than men to report nonfocal symptoms when presenting with acute ischemic stroke[2,3,25] and that the presence of nonfocal symptoms is associated with misdiagnosis.[5,13,26] We did not find any substantial sex differences in presenting symptoms, but we observed that women and men who reported focal stroke symptoms, with or without accompanying nonfocal symptoms, were at increased risk of having evidence of acute infarct on MRI and were more likely to receive a diagnosis of TIA or stroke. Contrary to the classic teaching that "nonspecific" or "atypical" symptoms are usually associated with stroke mimics, our findings suggested that nonfocal symptoms were common in minor ischemic cerebrovascular events and that these symptoms should not discourage clinicians from pursuing investigations for cerebral ischemia.

Sex differences in the presentation, diagnosis, and imaging of patients with transient or mild acute neurologic symptoms

have not been extensively studied, but this question is clinically relevant because minor ischemic cerebrovascular events are common, are challenging to diagnose, and represent an important opportunity for stroke prevention.[11,27,28] Whereas most prior studies first identify a cohort of patients who had received a diagnosis of stroke or TIA and then describe sex differences in presenting symptoms or outcomes, we studied a cohort of patients with acute neurologic symptoms who were subsequently thoroughly investigated, and we did not exclude people diagnosed as having stroke mimics.[29,30]

Limitations

Our study nevertheless had some limitations. Patients were recruited from the emergency departments of academic centers, and all patients were referred to the neurology service acutely. Patients without obvious neurologic symptoms may not have been referred to the neurology service and therefore not captured in SpecTRA, which may limit the generalizability of our findings to the population of general emergency departments. Furthermore, we did not collect data on the care of patients after the initial diagnosis, including interventions to optimize vascular risk factors. It is possible that the care of patients who receive a diagnosis of a stroke mimic is different from that of patients who receive a diagnosis of TIA or minor stroke and thus influences subsequent risks of vascular events. Finally, the adjudicators were not blinded to the sex of the patients. Therefore, we cannot exclude any implicit bias in the adjudication process of the final clinical diagnosis, particularly in patients without MRI evidence of acute infarct.

Conclusions

In a cohort of patients with acute transient or mild neurologic symptoms, our findings suggest that women were less likely than men to receive a diagnosis of cerebral ischemia, even when presenting with similar symptoms. However, the risks of subsequent vascular events were similar in women and men, suggesting important missed opportunities for prevention of vascular events.

ARTICLE INFORMATION

Accepted for Publication: February 1, 2019.

Published Online: May 22, 2019. doi:10.1001/jamaneurol.2019.1305

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Statistical analysis: Lesperance, Croteau, Balshaw.
Obtained funding: A. M. Penn, Votova, Coutts.
Administrative, technical, or material support: A. M. Penn, M. Penn, Hegedus, Bilston, Coutts.
Supervision: A. M. Penn, Lesperance, Votova, Coutts.

Conflict of Interest Disclosures: Drs Votova, Bibok, and Hegedus reported receiving grants from Genome Canada, Genome Alberta, Genome British Columbia, and the Heart and Stroke Foundation of Canada during the conduct of the study. Dr Saly reported receiving grants from Genome Canada during the conduct of the study. Dr Klourfeld reported receiving grants from Genome Canada, Genome British Columbia, and the Heart and Stroke Foundation of Canada during the conduct of the study. Mr Hong reported receiving grants from Alberta Innovates Health Solutions during the conduct of the study. Dr Coutts reported receiving grants from Genome Canada during the conduct of the study. No other disclosures were reported.

Funding/Support: Funding for this study was provided by Genome British Columbia, Genome Alberta, and Genome Canada (grant 4125; Dr A. M. Penn).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Meeting Presentation: This paper was presented at the Fifth European Stroke Organization Conference; May 22, 2019; Milan, Italy.

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