

Antihypertensive Drug Use and Adherence After Stroke

Are There Sex Differences?

Nadia A. Khan, MD, MSc; Lingsong Yun, MSc; Karin Humphries, DSc; Moira Kapral, MD, MSc

Background and Purpose—The majority of stroke fatalities occur in elderly women. We compared prescribing and adherence to antihypertensive therapies shown to reduce fatal and nonfatal stroke recurrence among elderly women and men with acute stroke.

Methods—Using the Registry of the Canadian Stroke Network, we identified all patients ≥ 66 years of age discharged home from 11 tertiary care centers with acute stroke (July 1, 2003, through March 31, 2006) in Ontario, Canada. Stroke cases were linked to the Ontario Drug Benefits Database and evaluated for prescription claims for thiazide diuretic, angiotensin converting enzyme inhibitor, beta blocker, angiotensin receptor blocker, or calcium channel blocker within 1 year of discharge from hospital. One-year adherence was assessed using the proportion of days covered with suboptimal adherence defined as a proportion of days covered < 0.8 .

Results—A total of 3571 patients (51.6% women) ≥ 66 years of age with acute stroke were discharged home, with 87.6% of women and 84.7% of men treated with antihypertensive therapy within 1 year of stroke. Men were more likely than women to be prescribed angiotensin converting enzyme inhibitor monotherapy but just as likely to be prescribed angiotensin converting enzyme inhibitor/diuretic combination. Women were more likely to be prescribed all other classes of antihypertensive therapy. Suboptimal adherence occurred in 32% of patients receiving thiazide diuretics, 25% for angiotensin converting enzyme inhibitors, and 38% for angiotensin converting enzyme inhibitor/diuretic combination. There were no sex differences in adherence to these antihypertensive therapies. Patients who died after stroke had lower adherence to antihypertensive therapy compared with those who survived.

Conclusions—In a cohort of elderly stroke patients, women were generally just as likely or more likely than men to receive antihypertensive prescriptions after stroke. Drug adherence was similarly poor in women and men. (*Stroke*. 2010;41:1445-1449.)

Key Words: antihypertensive ■ sex ■ prescribing ■ stroke

Stroke is one of the leading causes of death among women and men worldwide. In 2002, stroke killed 162 672 people in the United States, 61% of whom were women.¹ Although partly attributable to women's older age at onset of stroke, the reasons underlying the excess stroke death rate in women are not fully understood.

Hypertension is more prevalent among women than men presenting with acute stroke and also connotes a worse prognosis after stroke.^{2,3} Appropriate treatment of hypertension after stroke may therefore have a significant impact on outcomes in women. Robust clinical trial evidence indicates that antihypertensive therapy is one of the most important interventions for reducing long-term cardiovascular mortality and morbidity after stroke.⁴ In particular, diuretic and angiotensin converting enzyme (ACE) inhibitor/diuretic combination therapy is associated with a 28% reduction in fatal and nonfatal stroke among hypertensive and nonhypertensive

patients with previous cerebrovascular disease.⁵ However, these benefits are observed in clinical trials in which adherence rates are considerably higher than in real-world settings. Determining whether there are sex differences in prescribing and adherence to antihypertensive therapies after acute stroke may shed light on the factors contributing to the differences in stroke death rates between women and men.

To date, there are few and conflicting reports on sex differences in the provision of stroke care.⁶⁻⁹ Whereas some studies report that women are less likely to receive antiplatelet therapy,⁶ lipid testing,⁸ and thrombolytic therapy,⁹ other studies indicate that many components of hospital care are equally balanced between women and men.¹⁰ Given that women are more likely to possess risk factors for poor adherence such as depression after stroke and living alone,^{6,11,12} they may be at increased risk for nonadherence to secondary stroke prevention medications.

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In the current study, we evaluate the presence of sex differences in the prescribing of and 1-year adherence to antihypertensive therapies among elderly stroke patients. We evaluated patients with either hemorrhagic or ischemic stroke as well as hypertensive and normotensive patients because all of these subgroups benefit from antihypertensive therapy after stroke. By evaluating elderly patients, we minimize the potential for cost-related barriers to prescribing and adherence because persons >65 years of age have subsidized drug coverage. Understanding medication-taking behavior in this population is an essential component in optimizing the appropriate use of proven secondary preventive therapies and reducing the risk of recurrent fatal and nonfatal stroke.

Methods

Data Sources and Study Population

Using the Registry of the Canadian Stroke Network, we identified all patients admitted to hospital with acute ischemic or hemorrhagic stroke at 11 stroke centers in Ontario, Canada (July 2003 through March 2006). Participating centers, tertiary care institutions with stroke care resources and expertise, represent different geographic regions and account for ≈20% of all stroke admissions for the province. The registry prospectively identifies all consecutive patients presenting to the emergency department or admitted to hospital with a diagnosis of stroke or transient ischemic attack.¹³ Trained research nurses collect data by chart review and interview with hospital care providers. This registry provides detailed baseline information including age, sex, comorbid conditions (including preexisting hypertension, depression, tobacco use, and hyperlipidemia), stroke type, stroke severity based on the validated Canadian Neurological Scale,¹⁴ and baseline systolic and diastolic blood pressure. Inter-rater reliability of these variables in a random sample of patient charts was moderate to excellent (κ 0.6 to 1.0).¹⁵

Prescribing Data

Using unique patient identifiers, stroke patients identified in the registry were linked to the Ontario Drug Benefits Database, which contains information on antihypertensive drug prescriptions, including the quantity and dates of drugs dispensed as well as the number of days supplied from each prescription, for patients ≥65 years of age. Residents may fill prescriptions at any outpatient pharmacy in Ontario with a maximum copayment of \$6.11 (Canadian) for each prescription after a yearly \$100 (Canadian) deductible. Low income seniors have a \$2 (Canadian) maximum copayment with no yearly deductible. Using postal codes, patients in the registry are also linked to data from the 2006 Canada Census to determine median neighborhood income.

For the prescribing analysis, we determined whether patients ≥66 years of age filled a prescription for a diuretic, ACE inhibitor, or ACE inhibitor/diuretic combination before admission for acute stroke, within 3 months and 1 year after discharge from hospital. We also determined prescribing and adherence to angiotensin receptor blockers (ARBs), beta blockers, and calcium channel blockers, antihypertensive agents that have fewer data to support their use in secondary prevention of stroke. Patients were excluded from the main analysis if they were nonresidents of Ontario, if they had been transferred to a rehabilitation or palliative care facility (because drug data for these patients are not captured in the Ontario Drug Benefits Database), or if they had died within 3 months of discharge from hospital. Patients transferred to a rehabilitation facility who were subsequently discharged home were analyzed separately.

Adherence

One-year adherence was assessed for those who filled a prescription for any antihypertensive drug within 3 months of discharge from hospital for acute stroke. We analyzed patients who survived 1 year beyond this 3-month prescribing window to allow for a uniform

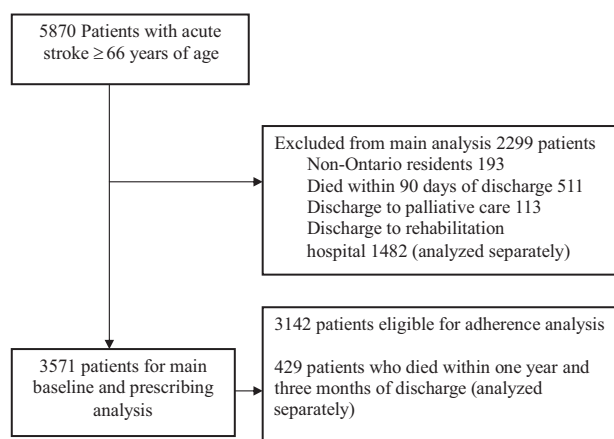


Figure. Patient flow for prescribing and adherence study cohorts.

assessment of adherence. We also separately evaluated adherence among patients who had died during this 1-year period. Adherence was assessed using prescription claims data that highly correlate with home inventory, pill count, as well as serum measures of drug presence.^{16–18} One-year proportion of days covered (PDC) was determined for each patient and each drug class. One year PDC represents the number of days a patient had a medication available during the year divided by 365 days. For patients who had died during this time period, we used survival time since the first prescription fill as the denominator. PDC values were categorized as ≥0.8 to reflect high adherence and <0.8 to reflect suboptimal adherence. PDC values <0.4 indicate low adherence. The PDC cut point of ≥0.8 is associated with improved blood pressure control and reduced mortality relative to other lower levels of adherence among patients with cardiovascular disease.^{19–21}

Statistical Analysis

Differences in baseline characteristics, 1 year prescribing, and levels of adherence according to patient sex were assessed using χ^2 testing for categorical values and *t* tests for continuous variables. Missing data were excluded from the analysis (area level income data were missing in 45 [2.6%] men and 78 [4.2%] women). We used multivariate logistic regression modeling to evaluate the independent effect of patient sex on adherence. We used backward selection modeling with removal of nonsignificant cofactors one by one from the cofactors with largest nonsignificant *P* value. Eventually, only significant cofactors (*P*<0.05) were retained in the final models to give adjusted odds ratios with 95% CIs. Cofactors included variables known to be associated with adherence: age, previous use of antihypertensive agents, comorbid conditions, total number of baseline drugs used, history of depression, and socioeconomic status. Given that severity of stroke may also impact drug adherence, we also considered type of stroke and Canadian Neurological Scale score for each antihypertensive drug class. All assumptions of logistic regression modeling were satisfied. Statistical significance was defined as a 2-tailed *P*<0.05. All analyses were performed using SAS software version 9.1 (SAS Institute Inc).

Results

Baseline Characteristics

There were 5870 patients ≥66 years of age identified with acute stroke, of whom 1482 were discharged to rehabilitation facilities (53% women). After exclusions, there were 3571 patients for the main analysis (Figure). Women were more likely to be older and have a previous diagnosis of hypertension with higher baseline systolic blood pressure, whereas men were more likely to have coexisting vascular disease.

Women were more likely to present with subarachnoid hemorrhage and greater stroke severity compared with men (Table 1).

Prescribing of Antihypertensive Agents

Before admission to hospital for acute stroke, women were more likely than men to be receiving ≥ 1 antihypertensive agent (76% versus 69%; $P < 0.001$). After stroke, 84.7% of men and 87.6% of women received ≥ 1 antihypertensive agent (Table 2). Most patients who received antihypertensive therapy received ≥ 2 antihypertensive agents rather than monotherapy. The most common monotherapy for both sexes was calcium channel blocker. Men were more often prescribed ACE inhibitor monotherapy compared with women. The most common combination antihypertensive regimens were ACE inhibitor and diuretic-based. There was no sex difference in prescribing of ACE inhibitor/diuretic combination, but women were more likely to be prescribed thiazide diuretics, beta blockers, calcium channel blocker, and ARBs relative to men. This prescribing pattern was generally similar among patients discharged to rehabilitation facilities. Patients who died within 1 year of filling their antihypertensive prescription were less likely to be prescribed ACE inhibitor (41.7% versus 50.4%; $P < 0.001$) or ARB (6.3% versus 9.6%; $P = 0.025$) compared with those who survived 1 year. However, there were no sex differences in prescriptions among those who died.

Adherence to Antihypertensive Agents

Among the 3142 patients who survived 1 year from the initial prescribing period, the proportion of patients highly adherent to antihypertensive drugs ranged from 61.8% to 75.8% (Table 3). There were no significant sex differences in adherence to any of the antihypertensive agents, even after adjusting for baseline variables. Similarly, there were no sex differences in adherence in patients discharged to rehabilitation facilities. Adherence was lowest among patients using ACE inhibitor/diuretic combination and indeed was significantly lower for patients using combination antihypertensive therapy in general compared with monotherapy ($P < 0.001$). Adherence was also lower among those with newly initiated antihypertensive therapy after stroke: 58% highly adherent in the diuretic group, 66% for ACE inhibitors, and 67% for beta blockers. In the adjusted analysis, previous use of the medication was a significant predictor of adherence in all models. Greater stroke severity (Canadian Neurological Scale score < 8) was significantly associated with high adherence in the ACE inhibitor and calcium channel blocker models. Factors such as depression, living alone, socioeconomic status, and total number of baseline medications were not significantly associated with adherence.

Adherence was lower among those 429 patients who died within 1 year of stroke compared with those who survived 1 year even when accounting for differences in follow-up time and patient sex (high PDC ≥ 0.8 63% versus 67%; low PDC < 0.4 7.1% versus 4.4%; $P = 0.04$). Low PDC (< 0.4) was also associated with an increased risk of death within 1 year compared with higher PDC levels (odds ratio, 1.75; 95% CI, 1.07 to 2.87; $P = 0.025$). There were no sex differences in

Table 1. Baseline Characteristics According to Patient Sex

Characteristics	Men (n=1729)	Women (n=1842)	P Value
Age group, y n (%)			
66–75	794 (45.9)	607 (32.9)	< 0.001
76–85	762 (44.1)	872 (47.3)	
86+	173 (10.0)	363 (19.7)	
Lives alone n (%)	231 (13.4)	473 (25.7)	< 0.001
Married n (%)	1250 (72.3)	720 (39.1)	< 0.001
Low income n (%)*	675 (40.1)	778 (44.1)	0.07
Comorbid conditions			
Systolic blood pressure mm Hg, mean (SD)	158.21 \pm (29.1)	162.9 \pm (31.0)	0.02
Diastolic blood pressure mm Hg, mean (SD)	82 \pm (15.4)	82.0 \pm (17.2)	0.5
Hypertension n (%)	1130 (65.4)	1319 (71.6)	< 0.001
Atrial fibrillation n (%)	264 (15.3)	351 (19.1)	0.002
Previous myocardial infarctions n (%)	336 (19.4)	220 (11.9)	< 0.001
Previous stroke/transient ischemic attack n (%)	602 (34.8)	589 (32.0)	0.07
Heart failure n (%)	131 (7.6)	168 (9.12)	0.10
Peripheral arterial disease n (%)	150 (8.7)	91 (4.94)	< 0.001
Diabetes n (%)	461 (26.7)	390 (21.2)	0.001
Depression n (%)	25 (1.4)	47 (2.6)	0.02
Chronic kidney disease n (%)	24 (1.4)	7 (0.4)	0.001
Charlson comorbidity index score > 2 n (%)	655 (37.9)	570 (30.9)	< 0.001
Current smoking n (%)	265 (15.3)	159 (8.6)	< 0.001
Stroke characteristics			
Intracranial hemorrhage n (%)	179 (10.3)	177 (9.6)	0.004
Ischemic stroke n (%)	1509 (87.3)	1585 (86.1)	
Subarachnoid hemorrhage n (%)	41 (2.4)	80 (4.3)	
Canadian Neurological Scale score > 8 n (%)	1220 (70.6)	1155 (62.7)	< 0.001
Unconscious n (%)	15 (0.9)	12 (0.6)	0.4
Previous medication use			
≥ 3 Baseline medications prescribed†	621 (35.9)	694 (37.7)	0.1
ACE inhibitor n (%)	536 (31.0)	568 (30.8)	0.9
Thiazide diuretic n (%)	473 (27.4)	697 (37.8)	< 0.001
Calcium channel blocker n (%)	431 (24.9)	513 (27.9)	0.048
Beta blocker n (%)	474 (27.4)	561 (30.5)	0.045
ACE inhibitor and diuretic n (%)	264 (15.3)	414 (22.5)	< 0.001
≥ 1 antihypertensive n (%)	1199 (69.3)	1404 (76.2)	< 0.001
Any ≥ 2 antihypertensives n (%)	781 (45.2)	949 (51.5)	< 0.001

*Low income refers to patient's neighborhood income in the lowest 40th percentile; †includes any prescription medication.

Table 2. Antihypertensive Therapy Medication Prescribing in Men and Women 3 Months and 1 Year After Discharge From Hospital for Acute Stroke n (%)

Antihypertensive	Three Months After Discharge			One Year After Discharge		
	Men	Women	P Value	Men	Women	P Value
ACE inhibitor only	247 (14.3)	181 (9.8)	<0.001	219 (12.7)	145 (7.9)	<0.001
ACE inhibitor+other antihypertensives	671 (38.8)	723 (39.3)	0.8	851 (49.2)	902 (49.0)	0.9
Thiazide diuretic only	51 (2.9)	81 (4.4)	0.02	48 (2.8)	65 (3.5)	0.2
Thiazide diuretic plus other antihypertensives	543 (31.4)	718 (39.0)	<0.001	697 (40.3)	923 (50.1)	<0.001
ACE inhibitor and thiazide diuretic	413 (23.9)	474 (25.7)	0.2	493 (28.5)	556 (30.2)	0.2
Calcium channel blocker only	338 (19.5)	419 (22.7)	0.02	434 (25.1)	525 (28.5)	0.02
Calcium channel blocker plus other antihypertensives	424 (24.5)	522 (28.3)	0.01	553 (32.0)	678 (36.8)	0.002
Beta blockers only	78 (4.5)	72 (3.9)	0.4	67 (3.9)	52 (2.8)	0.08
Beta blocker plus other antihypertensives	477 (27.6)	595 (32.3)	0.002	610 (35.3)	735 (39.9)	0.004
ARB only	23 (1.3)	31 (1.7)	0.4	25 (1.4)	25 (1.4)	0.8
ARB plus other antihypertensives	110 (6.4)	171 (9.3)	0.004	171 (9.9)	250 (13.6)	<0.001
≥1 antihypertensive	1328 (76.8)	1478 (80.2)	0.01	1464 (84.7)	1613 (87.6)	0.01
≥2 antihypertensives	871 (50.4)	1044 (56.7)	<0.001	1062 (61.4)	1268 (68.8)	<0.001

adherence to antihypertensive therapy in patients who died within 1 year of stroke.

Discussion

In this study, women were just as or more likely than men to receive diuretics or ACE inhibitor/diuretic combination, agents shown to reduce morbidity and mortality after stroke. Further, there were no sex differences in adherence to these antihypertensive therapies within 1 year after stroke.

The findings of our prescribing analysis are consistent with other studies.^{7,22} In a study of 10 076 stroke or transient ischemic attack patients, Simpson et al⁷ found that women were more likely than men to be prescribed a thiazide but less likely to be prescribed an ACE inhibitor even after adjustment for age, comorbid conditions, and socioeconomic status. Simpson also found no significant sex differences in the prescribing of ACE inhibitor/diuretic combinations after stroke. Low prescribing of ACE inhibitor among patients who died may signal a missed opportunity for use of evidence-based secondary prevention. However, this underprescribing was similar among women and men.

Nonadherence to antihypertensive therapy after stroke can have a significant impact on prognosis. In our study, ≈25% to 30% of men and women with recent stroke had poor adherence to proven secondary prevention antihypertensive therapy. Low adherence was associated with increased death within 1 year of prescribing antihypertensive therapy after stroke. Our findings differ from several small studies that found high levels of adherence to antihypertensive agents after stroke.^{23,24} However, these studies assessed adherence based on patient self-report, which may be subject to social desirability and recall bias. Further, by only evaluating whether patients were receiving antihypertensive medications at a single point in time (1 year), these studies would miss large gaps in prescribing.

There are several limitations for this study. We used prescription data as a proxy for actual patient adherence. However, prescription data correlate well with other measures of compliance.^{16–18} We were also unable to assess for contraindications, allergies, or intolerances for the antihypertensive agents and thus our prescribing and adherence results are likely conservative. We were also unable to assess level of blood pressure control for the patients. However, previous

Table 3. Unadjusted and Adjusted One-Year Adherence to Antihypertensive Therapy in Men and Women

Antihypertensive	Men PDC ≥0.8	Women PDC ≥0.8	P Value	Adjusted Odds Ratio (95% CI)*	Variables†	P Value
ACE inhibitor n (%)	608 (74.3)	606 (75.8)	0.06	1.02 (0.91, 1.14)	Previous ACE inhibitor, CNS score	0.8
Thiazide diuretic n (%)	354 (68.6)	460 (67.0)	0.8	0.93 (0.82, 1.05)	Previous diuretic	0.3
ACE inhibitor and thiazide diuretic n (%)	225 (61.81)	261 (63.04)	0.4	0.91 (0.76, 1.09)	Previous diuretic/ACE inhibitor	0.3
Calcium channel blocker n (%)	294 (72.6)	367 (76.1)	0.2	1.16 (0.99, 1.37)	Previous CCB, age, stroke type	0.06
Beta blocker n (%)	348 (72.7)	442 (77.1)	0.5	1.12 (0.98, 1.29)	Previous beta blocker	0.1
ARB n (%)	86 (70.5)	132 (72.9)	0.3	1.03 (0.80, 1.34)	Previous ARB	0.8

*Odds ratio and 95% CI for women vs men; †variables included in adjustment after backward selection.

CNS indicates Canadian Neurological Scale; CCB, calcium channel blocker.

studies demonstrate that high levels of adherence are associated with better blood pressure control.^{20,21,25} In addition, because we did not have data on younger patients or those discharged to palliative care, our findings may not be generalized to these groups.

Conclusion

Previous studies identified that women have greater stroke deaths compared with men. However, in our study, elderly women were just as or more likely than men to receive evidence-based antihypertensive therapy. Despite experiencing a devastating event such as stroke, adherence to therapies known to substantially reduce morbidity and mortality after stroke was similarly poor in women and men. Low adherence to antihypertensive therapy was associated with increased risk of death after stroke. Greater efforts are required to improve antihypertensive drug adherence among women and men, including implementation of follow-up programs after stroke, academic detailing, and educational strategies.

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