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a prescription at discharge improve short and long term adherence

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A Prescription at Discharge Improves Long-term Adherence for Secondary Stroke Prevention

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Background: Medication adherence is important for optimal secondary stroke prevention. We evaluated short-term adherence to antihypertensive and lipid-lowering agents after a new ischemic stroke, as predictor of adherence at 1 and 2 years. *Methods:* A 5-year cohort of patients from 11 institutions in the Registry of the Canadian Stroke Network was linked to population-based administrative health records. Patients diagnosed with acute ischemic stroke and discharged home were included. Medication adherence was assessed through documented prescription filling at 7 days, 1 year, and 2 years. *Results:* From 2003 to 2008, 6437 ischemic stroke patients were discharged home from hospital, and 1126 patients filled a prescription for antihypertensive and lipid-lowering agents within 7 days of discharge. Patients provided with a prescription at discharge were more likely to show adherence at 7 days. Adherence at 1 year remains higher in these patients for antihypertensive (93.8% vs. 87.7%; odds ratio [OR], 2.31; 95% confidence interval [CI], 1.69-3.16), lipid-lowering agents (88% vs. 81.6%; OR, 1.77; 95% CI, 1.36-2.32), or both (85.8% vs. 79.9%; OR, 1.72; 95% CI, 1.32-2.25). Findings are similar at 2 years for antihypertensive (92.2% vs. 87.7%; OR, 1.78; 95% CI, 1.3-2.43), lipid-lowering agents (82.6% vs. 79.0%; OR, 1.31; 95% CI, 1.01-1.69), or both (81.1% vs. 77.0%; OR, 1.4; 95% CI, 1.09-1.82). *Conclusions:* Provision of a prescription strengthens adherence at 1 week from discharge for both prior and new users of antihypertensive and lipid-lowering drugs. Medication adherence at 1 week after discharge for acute ischemic stroke predicts adherence for secondary preventive therapies at 1 and 2 years. **Key Words:** Ischemic stroke—stroke prevention—medication—outcomes.

Ischemic stroke accounts for over 970,000 annual hospitalizations in the United States.[1] The projected annual cost of stroke is 85 billion dollars by 2020.[1] Recurrence risk is highest within 3 months after an ischemic stroke: 17% for transient ischemic attacks and 18% for 'minor' ischemic strokes.[2] Implementing adequate secondary prevention is crucial for reducing the incidence or recurrence of cerebrovascular events.[1,3]

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Hypertension and dyslipidemia are important modifiable cerebrovascular risk factors.[1,4] Treatment targets are well established, and previous studies support early initiation and adherence in achieving desired effects.[2,5-9] Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are effective in blood pressure reduction and prevention of recurrent ischemic strokes.[10-12] Early initiation of statins is an important intervention via low-density lipoprotein cholesterol reduction and the associated 17% reduction in stroke risk per decrease in 1 mmol/L of low-density lipoprotein cholesterol.[13,14] Optimal secondary stroke prevention therapy provides an 80% reduction in the risk of recurrent cardiovascular events.[15] However, many patients do not receive the expected benefit of therapy because of suboptimal adherence.[5,6]

Identifying determinants of adherence is thus important to optimize secondary prevention.[6] Different strategies used in ambulatory care suggest better adherence within a structured program and in-hospital initiation of therapy.[5-8,16] However, long-term adherence has not been correlated with short-term adherence after discharge. We investigated the association between adherence at 7 days, 1 year, and 2 years for ischemic stroke patients discharged home.

Methods

Study Design

We conducted a retrospective cohort study among patients with acute ischemic stroke admitted to any of the 11 stroke centers participating in the Registry of the Canadian Stroke Network (RCSN). Patients 66 years of age and older discharged home from hospital for a primary diagnosis of ischemic stroke, between July 1, 2003, and June 30, 2008, were eligible for inclusion. Diagnosis of ischemic stroke for inclusion in the RCSN database was based on clinical assessment supported by neuroimaging, either by computed tomography (CT) or magnetic resonance imaging (MRI). We excluded patients younger than 65 (not eligible for universal provincial drug coverage, n = 2803); having had a stroke after hospital admission for a procedure or pre-existing illness, as an active alternate illness may confound use of a secondary prevention agent, (n = 527); and patients deceased or discharged to palliative care or an assisted living setting (n = 1596).

Data Sources

We linked 6 databases to obtain relevant information for the present study (Fig 1). Under the Ontario Health Insurance Plan, in Ontario, Canada, access to medical care includes full coverage for physician fees, charges associated with emergency department (ED) and clinic visits and hospital admissions, prescription drug coverage for individuals more than 65 years of age, and direct public transport between home and hospital for patients with limited mobility.

Since 2001, the Ontario Stroke System also established 24 Stroke Prevention Clinics, fully funded by the Ontario Ministry of Health and Long-Term Care to ensure early diagnosis, assessment, and management of nondisabling stroke patients.[17] This health care system model allows for a province-wide, comprehensive assessment of stroke patients after discharge.

Through linkage of encrypted unique identifiers in several provincial health care administrative databases (Fig 1), we obtained all information necessary for this study. The index stroke was identified from the RCSN, which also provides a record of the patients' preadmission medications collected at the time of admission. Details regarding the RCSN can be accessed at https://osr.ices.on.ca.[18] It is a clinical database initiated in 2001 with the goal of measuring and monitoring delivery of stroke care, containing records on over 40,000 stroke and transient ischemic attacks patients. Trained neurology nurses collect detailed data for the RCSN through chart abstraction and using custom software, both during and after hospital admission for the index event. Stroke severity was scored on admission using the Canadian Neurological Scale (CNS), which assesses comprehension, level of consciousness, speech and motor function of the face, arm, and leg. It is a simple and validated scale where lower scores indicate greater stroke severity, with good to excellent inter-rater agreement.[19] In this study, stroke severity was categorized a priori as mild (CNS ≥ 8), moderate (5-7), or severe stroke (1-4); a score of 0 was assigned to comatose patients.

Hospital readmissions and ED visits were identified through the Canadian Institute for Health Information and the National Ambulatory Care Reporting System, respectively. The most responsible diagnosis and secondary diagnoses of all hospitalizations are recorded in the Canadian Institute for Health Information's discharge abstract database, using the International Classification of Diseases codes, version 9. Similar data pertaining to ED visits are available through the National Ambulatory Care Reporting System. Demographic data, including date of birth, gender, and date of decease, are provided by the Registered Persons Database. Both in-patient and ambulatory physician services received are identified through the Ontario Health Insurance Plan's billing database. Information on filling of outpatient prescription under the provincial drug plan was obtained through the Ontario Drug Benefit database (ODB). Although the RCSN collects information on medications at discharge, filling of the prescription provided is ascertained through the ODB database. Each prescription supplies medications for up to 3 months, requiring a refill at this maximal interval.

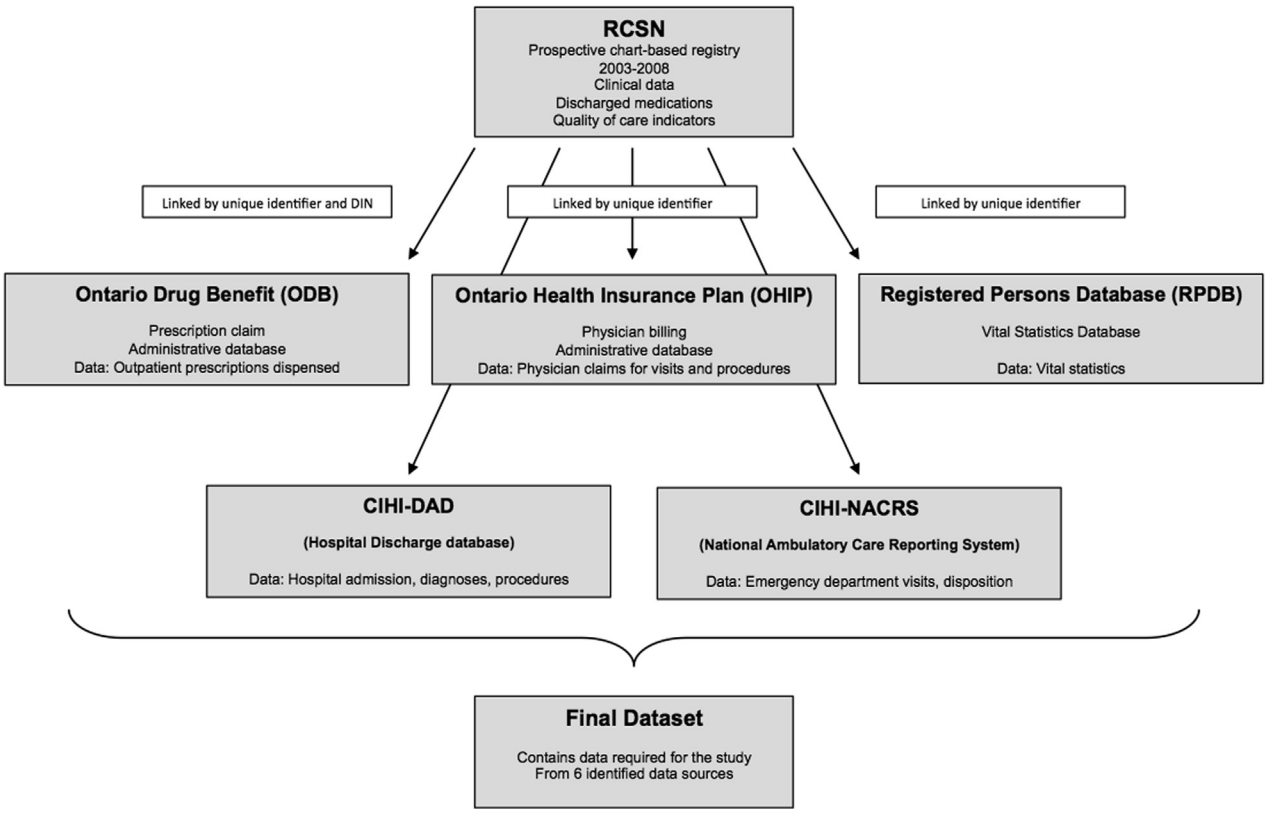

Figure 1. *Data sources. Abbreviations: DIN, Drug identification number; RCSN, Registry of the Canadian Stroke Network; CIHI-DAD, Canadian Institute of Health Information-Discharge Abstract Database; CIHI-NACRS, Canadian Institute of Health Information-National Ambulatory Care Reporting system.*

Exposure and Adherence

Adherence was defined as continued prescription filling after initiation of therapy for patients discharged alive after the index stroke.[5,7] The RCSN records medications at discharge for several stroke prevention strategies. A prescription for antihypertensive or lipid-lowering agents is usually provided by the admitting physician before discharge from hospital. Because the 7-day period to fill a prescription is considered part of the in-patient care, we verified that patients discharged filled these prescriptions within 7 days (before primary care physician follow-up).

Prescription filling was used as a proxy measure of adherence.[6,8,19] Antihypertensive agents assessed in our study include ACEI and ARB, both of which have demonstrated effectiveness as antihypertensive in secondary stroke prevention.[10-12,20-22] Similar adherence rates were demonstrated in prior studies for different statins or antihypertensive agents, including beta-blockers, diuretics, ACEI, and ARB.[6] Lipid-lowering agents include all statins. The ODB database was used to estimate the intended duration of each prescription.

New users were defined as patients not taking the prescribed medication class within 1 month or longer before hospital admission. To determine the effect of in-hospital stroke prevention care, we assessed prescription filling at 7 days after discharge. At each assessment, adherence is compared between patient cohorts with and without prior use of either antihypertensive or lipid-lowering agents (Fig 2).

Outcome Measures

The primary outcome was adherence to combined secondary prevention strategies (eg, both antihypertensive and lipid-lowering therapy) at 1 year. Secondary outcomes included the adherence to either antihypertensive agents, statins or both, at 2 years. We also completed a subgroup analysis to compare adherence to stroke prevention agents between prior and new users.

We measured prior exposure to the prescribed medications. All patients were categorized as "prior users", indicating experience with the prescribed agents; or "new users", if medications are newly initiated during admission or within 7 days of hospital discharge. Other factors reported to influence adherence were included in the analysis: age, comorbidities, clinical presentation, stroke subtype, and severity.[23,24] Patients were categorized into 3 age groups in strata of 10 years: 65-74, 75-84, and more than 85 years of age. Comorbidities were assessed with the Charlson Comorbidity Index, with scores of 0, 1, 2, or 3 and more. Clinical presentation was accounted for as a categorical variable by stroke symptoms (Table 1). Stroke subtype was assessed at the time of discharge, in 6 categories: artery-to-artery, cardioembolic,

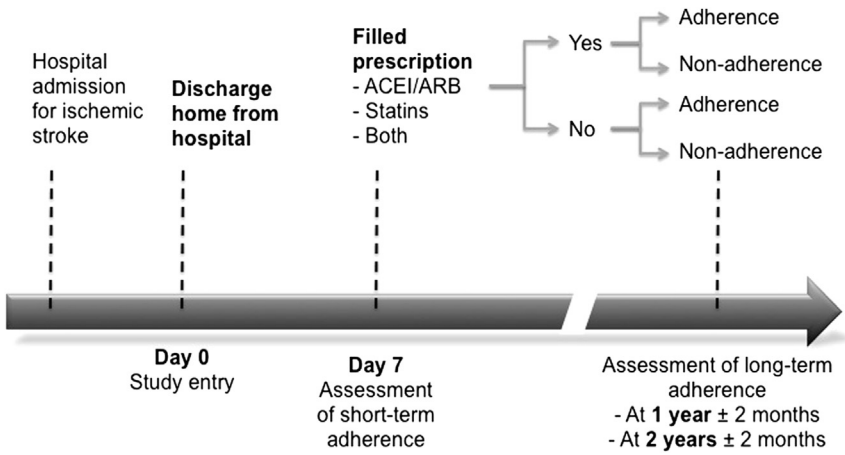

Figure 2. *Exposure and times of outcome measures. Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.*

lacunar, or other identified etiologies. Patients with incomplete work-up or missing data were categorized as "Undetermined", and where an exhaustive work-up failed to identify an etiology as "No etiology".[25] Stroke severity was accounted for by the 4 CNS categories: mild, moderate, severe, or comatose. These data were missing for 100 patients. Further details on variable definition can be found at the RCSN website and elsewhere.[26-28]

Statistical Analysis

Chi-square and Mantel–Haenszel tests were used to compare categoric variables; analysis of variance (ANOVA) or Kruskal–Wallis tests were used to compare mean and median differences for continuous variables. We used logistic regression to estimate the odds ratio (OR) for the association between provision of a prescription at discharge for antihypertensive, statins, or both agents and adherence at 7 days, 1 year, and 2 years. This analysis was performed for prior users, new users, and all patients. The multivariable analysis was adjusted for age, sex, Charlson Comorbidity Index, and stroke severity.

Results

During the 61-month study period, we identified 6347 eligible patients with primary diagnosis of ischemic stroke. The mean age was 78.8 ± 7 years. Most patients were aged 75-84 years (47.6%; 3024), 29.9% (1898) of patients were between 66-74 years, and 22.5% (1425) were more than 85 years of age. (Table 1) From this base cohort, we identified 4581 patients (72.2%) taking antihypertensive agents and 2145 (33.8%) taking statins, before admission.

Overall adherence to combined antihypertensive agents and statins was 85.8% at 1 year (Table 2). It decreases by 4.7% to 81.1%, by 2 years (Table 3). Adherence to antihypertensive agents was 93.8% at 1 year and 92.2% at 2 years. Adherence to statins shows a similarly decreasing trend over time, with 88% at 1 year and 82.6% at 2 years (Tables 2 and 3).

Prior and New Users

Adherence at 1 year was consistently better in all patients using antihypertensive agents or statins before admission. More prior users filling prescription at 7 days for ACEI or ARB refilled their prescription at 1 year (96%; OR, 3.5; 95% confidence interval [CI], 2.4-5.2), when compared with new users (87%; OR, 1.11; 95% CI, .54-2.26). Prior users were more likely to remain adherent at 1-year follow-up (92.3%; OR, 1.64; 95% CI, 1.03-2.61) than new users (85.5%; OR, 3.6; 95% CI, 2.5-5.2). A similar trend was observed at 2 years (Table 3).

Early Adherence and Long-term Adherence

All patients were more likely to demonstrate early adherence if provided a prescription before discharge, regardless of whether they previously used the medication (Table S1 in Appendix). This observation holds true for both antihypertensive and lipid-lowering therapy (Table S1 in Appendix).

Patients showing early adherence demonstrated continued adherence at 1 year to antihypertensive (93.8%; OR, 2.31; $P < .0001$), lipid-lowering (88.0%; OR, 1.77; $P < .0001$), and combined regimens (85.8%; OR, 1.72; $P < .0001$; Table 2). Similar effects are noted when prior users and new users' data are analyzed separately (Table 2).

Likewise, early adherence was associated with adherence at 2 years for antihypertensive (92.2%; OR, 1.78; $P = .0003$), lipid-lowering (82.6%; OR, 1.31; $P = .0394$), or both agents (81.1%; OR, 1.4; $P = .0099$) (Table 3). A trend of tapering ORs is observed, with decreasing difference between prior and new users, from 7 days to 2 years after discharge. Similar effects are observed in subgroup analyses for prior and new users (Table 3).

Table 1. *Characteristics of study patients, 7 days after discharge*

	Prescriptions filled 7 days after discharge					
Variables	Total, N = 6347	Anti-HTN only, N = 1311	Statins only, N = 556	Both, N = 3936	Neither, N = 544	*P* value
Age						
Mean ± SD	78.74 ± 7.19	80.59 ± 7.48	77.18 ± 6.95	78.14 ± 6.86	80.22 ± 7.91	<.001
Median (IQR)	79 (73-84)	81 (75-86)	77 (72-82)	78 (73-83)	80 (74-86)	<.001
Age groups, n						
65-74 y	1898 (29.9)	292 (22.3)	212 (38.1)	1248 (31.7)	146 (26.8)	<.001
75-84 y	3024 (47.6)	617 (47.1)	248 (44.6)	1926 (48.9)	233 (42.8)	
≥85 y	1425 (22.5)	402 (30.7)	96 (17.3)	762 (19.4)	165 (30.3)	
Charlson Comorbidity Index, n						
0	2052 (32.3)	425 (32.4)	214 (38.5)	1215 (30.9)	198 (36.4)	<.001
1	1860 (29.3)	364 (27.8)	193 (34.7)	1144 (29.1)	159 (29.2)	
2	1053 (16.6)	241 (18.4)	54 (9.7)	687 (17.5)	71 (13.1)	
≥3	1382 (21.8)	281 (21.4)	95 (17.1)	890 (22.6)	116 (21.3)	
Comorbidities, n						
Atrial fibrillation	1288 (20.3)	375 (28.6)	60 (10.8)	753 (19.1)	100 (18.4)	<.001
Diabetes	1625 (25.6)	307 (23.4)	107 (19.2)	1126 (28.6)	85 (15.6)	<.001
Hyperlipidemia	2274 (35.8)	175 (13.3)	203 (36.5)	1794 (45.6)	102 (18.8)	<.001
Hypertension	4657 (73.4)	1014 (77.3)	224 (40.3)	3172 (80.6)	247 (45.4)	<.001
Current smoker	804 (12.7)	140 (10.7)	88 (15.8)	500 (12.7)	76 (14.0)	.014
Preadmission medications, n						
Anti-HTN	4581 (72.2)	1065 (81.2)	126 (22.7)	3184 (80.9)	206 (37.9)	<.001
Statins	2145 (33.8)	71 (5.4)	170 (30.6)	1825 (46.4)	79 (14.5)	<.001
Warfarin	723 (11.4)	197 (15.0)	31 (5.6)	449 (11.4)	46 (8.5)	<.001
Aspirin	2368 (37.3)	458 (34.9)	183 (32.9)	1564 (39.7)	163 (30.0)	<.001
Clopidogrel	561 (8.8)	89 (6.8)	41 (7.4)	400 (10.2)	31 (5.7)	<.001
Clinical presentation, n						
Aphasia	2165 (34.1)	471 (35.9)	177 (31.8)	1302 (33.1)	215 (39.5)	-
Brainstem/Cerebellar	1317 (20.7)	258 (19.7)	122 (21.9)	838 (21.3)	99 (18.2)	
Dysarthria	2656 (41.8)	519 (39.6)	247 (44.4)	1,675 (42.6)	215 (39.5)	
Visual field defects	755 (11.9)	162 (12.4)	60 (10.8)	471 (12.0)	62 (11.4)	
Weakness	5240 (82.6)	1060 (80.9)	448 (80.6)	3280 (83.3)	452 (83.1)	
Stroke subtype, n						
Large artery disease	1076 (17.0)	154 (11.7)	111 (20.0)	728 (18.5)	83 (15.3)	<.001
Cardioembolic	1630 (25.7)	425 (32.4)	95 (17.1)	982 (24.9)	128 (23.5)	
Lacunar	1077 (17.0)	179 (13.7)	95 (17.1)	743 (18.9)	60 (11.0)	
Other	155 (2.4)	28 (2.1)	19 (3.4)	79 (2.0)	29 (5.3)	
Undetermined	289 (4.6)	83 (6.3)	16 (2.9)	167 (4.2)	23 (4.2)	
No etiology	2120 (33.4)	442 (33.7)	220 (39.6)	1237 (31.4)	221 (40.6)	
Stroke severity (CNS), n						
Coma	54 (.9)	16 (1.2)	1 (.2)	24 (.6)	13 (2.4)	<.001
Severe	974 (15.3)	227 (17.3)	70 (12.6)	547 (13.9)	130 (23.9)	
Moderate	1114 (17.6)	222 (16.9)	93 (16.7)	704 (17.9)	95 (17.5)	
Mild	4105 (64.7)	815 (62.2)	386 (69.4)	2616 (66.5)	288 (52.9)	
Missing data	100 (1.6)	31 (2.4)	6 (1.1)	45 (1.1)	18 (3.3)	
Admission to stroke unit	4376 (68.9)	788 (60.1)	400 (71.9)	2,852 (72.5)	336 (61.8)	-
Thrombolysis (index stroke)	949 (15.0)	166 (12.7)	82 (14.7)	612 (15.5)	89 (16.4)	-

Abbreviations: Anti-HTN, antihypertensive; CNS, Canadian Neurological Scale; IQR, interquartile range; SD, standard deviation.
Numbers in brackets represents percentages unless otherwise mentioned.

Discussion

The risk of recurrent cardiovascular event can be reduced by over 80% with good adherence to combined secondary stroke prevention strategies.[29] In the present study, we evaluated adherence to combined secondary prevention therapies at 1 year and 2 years after acute stroke, and compared adherence to single antihypertensive or lipid-lowering agents over the same periods. We

Table 2. *Adherence at 1 year, all users*

Prescription filling 7 days after discharge, n (%)		Filling prescription, n (%)*	Not filling prescription, n (%)*	OR (95% CI)†	*P* value
Adherence to ACEI/ARBs (N = 2255)					
Yes	1447 (64.2)	1358 (93.8)	89 (6.2)	2.31 (1.69-3.16)	<.001
No	808 (35.8)	709 (87.7)	99 (12.3)	1.0 (ref)	
Adherence to statins (N = 1969)					
Yes	1317 (66.9)	1159 (88.0)	158 (12.0)	1.77 (1.36-2.32)	<.001
No	652 (33.1)	532 (81.6)	120 (18.4)	1.0 (ref)	
Adherence to ACEI/ARBs and statins (N = 1696)					
Yes	953 (56.2)	818 (85.8)	135 (14.2)	1.72 (1.32-2.25)	<.001
No	743 (43.8)	594 (79.9)	149 (20.1)	1.0 (ref)	

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CI, confidence interval; OR, odds ratio.
*Indicates row percentage.
†Adjusted by age, sex, stroke severity, and Charlson Comorbidity Index. Odds ratios represent likelihood of adherence, based on adherence status 7 days after discharge.

found a 1-year adherence rate of 85.8%, with an additional 4.7% drop by 2 years. Single-agent adherence rates for antihypertensive agents or statins follow a similar trend. Our results further led to 2 observations. First, adherence to combined secondary stroke preventive agents at 7 days after discharge is associated with the provision of a discharge prescription in all users. Second, early adherence predicts adherence at 1 and 2 years.

Previous studies showed lower adherence to secondary stroke prevention medications in noninstitutionalized patients after discharge.[6] These patients have the highest potential benefit from secondary prevention, as they remain functionally independent despite the index stroke. Thus, we focused our study on these patients to identify means to improve adherence.

Although all groups showed a slight decline in adherence over 2 years, overall adherence consistently exceeded 80%, higher than previously reported.[5-7,16] This high adherence may reflect complete funding of these medications for patients over 65 years old and a strong link between in-patient and outpatient care through Ontario's Stroke Prevention Clinics.[17] This observation is also in keeping with previous data demonstrating better adherence after in-hospital initiation of secondary preventive therapies.[7,30] Of note, in our study, prior users consistently showed better adherence to antihypertensive agents, statins, or both, over the 2 years of study. Identification of factors accounting for this difference is beyond the scope of this study.

Other previously recognized factors affecting adherence (patient gender, age, comorbidities, and stroke severity) were adjusted for in our statistical analyses.[6] Discharge disposition reflects the need for support from caregivers and health care providers, which likely also affects adherence.[5,6] Our patients' discharge dispositions were similar across all groups and unlikely to account for differences in adherence observed.

Some limitations deserve discussion. First, the stroke care establishment in Ontario may differ from other regions, although follow-up with a specialist is a common

Table 3. *Adherence at 2 years, all users*

Prescription filling 7 days after discharge, n (%)		Filling prescription, n (%)*	Not filling prescription, n (%)*	OR (95% CI)†	*P* value
Adherence to ACEI/ARBs (N = 2004)					
Yes	1289 (64.3)	1188 (92.2)	101 (7.8)	1.78 (1.3-2.43)	<.001
No	715 (35.7)	628 (87.7)	87 (12.2)	1.0 (ref)	
Adherence to statins (N = 1796)					
Yes	1206 (67.1)	996 (82.6)	210 (17.4)	1.31 (1.01-1.69)	.04
No	590 (32.9)	466 (79.0)	124 (21.0)	1.0 (ref)	
Adherence to ACEI/ARBs and statins (N = 1544)					
Yes	871 (56.4)	706 (81.1)	165 (18.9)	1.4 (1.09-1.82)	.01
No	673 (43.6)	518 (77.0)	155 (23.0)	1.0 (ref)	

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CI, confidence interval; OR, odds ratio.
*Indicates row percentage.
†Adjusted by age, sex, stroke severity, and Charlson Comorbidity Index. Odds ratios represent likelihood of adherence, based on adherence status 7 days after discharge.

component of stroke discharge planning in many tertiary centers.[18,31] Second, our study included patients with good physician access and prescription coverage, and access to health care may differ in other regions. Third, our analysis could not identify reasons for which patients did not fill or refill discharge prescriptions. Fourth, patients discharged to long-term care facilities or under palliative care were excluded, as their adherence depends on other variables in the provision of chronic daily care. Finally, medication adherence was used as an established surrogate for better outcomes from secondary stroke prevention, based on previous studies.[5-8]

Despite the aforementioned limitations, our study includes a comprehensive data collection with near-complete follow-up. Moreover, the analysis was conducted in a province with universal health insurance and drug coverage, eliminating the confounds of access to stroke care and prevention in evaluation of practice-related effects on adherence. Linkage between databases also allows for evaluation of "real world" adherence without use of self-reporting, a method believed to overestimate persistence and adherence rates.[6,7]

In conclusion, clinicians can apply 2 simple interventions that bridge gaps to successful secondary stroke prevention. Routine provision of an updated or new prescription before discharge is an effective strategy to ensure a sustained adherence. Ensuring short-term adherence at discharge improves long-term adherence to secondary stroke prevention therapies. Together, this approach will contribute to reducing the risk of a recurrent cerebrovascular event in stroke survivors.

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Dr Saposnik and Dr Bell, as co-Principal Investigators, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.04.026

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