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Patterns of use and discontinuation of secondary prevention medications after stroke

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Coinvestigator Appendix-http://links.lww.com/WNL/B259

Abstract (250 words)

Objective: To investigate whether certain patient, acute-care, or primary-care factors are associated with medication initiation and discontinuation in the community post-stroke or TIA.

Methods: Retrospective cohort study using prospective data on adult patients with first-ever acute stroke/TIA from the Australian Stroke Clinical Registry (April 2010 to June 2014), linked with nationwide medication dispensing and *Medicare* claims data. Medication users were those with ≥1 dispensing in the year post-discharge. Discontinuation was assessed among medication users and defined as having no medication supply for ≥90 days in the year post-discharge. Multivariable competing risks regression, accounting for death during the observation period, was conducted to investigate factors associated with time to medication discontinuation.

Results: Among 17980 registry patients with stroke/TIA, 91.4% were linked to administrative datasets. Of these, 9817 adults with first-ever stroke/TIA were included (45.4% female, 47.6% aged ≥75 years, and 11.4% intracerebral hemorrhage). While most patients received secondary prevention medications (79.3% antihypertensive, 81.8% antithrombotic, and 82.7% lipid-lowering medication), between one-fifth and one-third discontinued treatment over the subsequent year post-discharge (20.9% antihypertensive, 34.1% antithrombotic, and 28.5% lipid-lowering medications). Prescription at hospital discharge (sub-hazard ratio [SHR]: 0.70; 95% CI: 0.62-0.79), quarterly contact with a primary-care physician (SHR: 0.62; 95% CI: 0.57-0.67), and prescription by a specialist physician (SHR: 0.87; 95% CI: 0.77-0.98) were all inversely associated with antihypertensive discontinuation.

Conclusions: Patterns of use of secondary prevention medications after stroke/TIA are not optimal, with many survivors discontinuing treatment within one-year post-discharge. Improving post-discharge care for patients with stroke/TIA is needed to minimize unwarranted discontinuation.

Introduction

Nearly half of all survivors of stroke experience recurrent cardiovascular events within 10 years, highlighting the importance of strategies to minimize their risk factors post-discharge.[1] It is estimated that a combination of lifestyle changes and use of secondary prevention medications reduces the risk of recurrent cardiovascular events by ~80%.[2] Optimal secondary prevention medications recommended in international clinical guidelines after stroke or TIA include the use of antihypertensive medications for all patients with high blood pressure, as well as antithrombotic and lipid-lowering agents for non-hemorrhagic stroke.[3] A weak recommendation to initiate antihypertensive medications in normotensive patients also exists in Australian guidelines since the benefits of blood pressure lowering were found to extend to all patients irrespective of baseline blood pressure in the PROGRESS trial.[4, 5] However, in a recent study from Australia,[6] approximately one third of patients were discharged from acute-care hospitals without antihypertensive medications, with significant variation between hospitals.

Current evidence on post-stroke use of medications is mainly from the time of hospital discharge or when back in the community, often using self-reported methods.[7] Few authors have published data on the continued use of secondary prevention medications following stroke/TIA based on objective measures such as electronic pharmacy claims data. As patients who discontinue secondary prevention medications are at increased risk of re-hospitalization and death,[8] comprehensive information on the factors influencing use of these medications after stroke is required. Therefore, the aim of this study was to investigate whether certain

patient, acute-care, or primary-care factors are associated with medication initiation or discontinuation in the community post-stroke or TIA.

Methods

Study Design and Population

This retrospective cohort study comprised patients with a clinical diagnosis of stroke or TIA who were registered in the Australian Stroke Clinical Registry (AuSCR) between April 2010 and June 2014. The AuSCR is a collaborative national effort to monitor the quality of acute-care and outcomes of patients with stroke/TIA admitted to participating hospitals.[9] Clinicians from 25 hospitals in Victoria, New South Wales, Queensland, Tasmania, and Western Australia were responsible for prospectively identifying patients for inclusion. For the present study, we included only patients with a first-ever stroke or TIA. Patients aged <18 years, those who opted out, and those who died while in-hospital were excluded.

Data Linkage

In addition to annual linkages of AuSCR records with national death information, data from our cohort were also linked with nationwide medication dispensing data from the Pharmaceutical Benefits Scheme and medical claims data from the Medicare Benefits Schedule (termed *Medicare)*.

The Pharmaceutical Benefits Scheme is a national health scheme funded by the Australian Government that provides all permanent residents of Australia with access to subsidized prescription medications.[10] Details of all prescription medications dispensed within Australia are captured in this database including the date of supply, medication type, strength, and quantity dispensed. There is no record available of prescriptions written but not dispensed, nor of medications supplied in-hospital or over-the-counter without a prescription. However, all medications for secondary prevention of stroke require a prescription in Australia, apart from aspirin which can be purchased either with or without a prescription (over-the-counter).

Use of this database is reported to be reliable and valid for health services research in Australia.[10]

The *Medicare* dataset contains information on all transactional data related to health services subsidized by the Australian Commonwealth Government under the *Medicare* scheme. This includes all visits with physicians, a limited number of visits with allied health professionals, and pathology and imaging services.

Medications for Secondary Prevention

Antihypertensive, antithrombotic, and lipid-lowering medications were identified in medication dispensing data in the year after hospital discharge using World Health Organization Anatomical Therapeutic Chemical codes (Table e-1; doi.org/10.26180/5f0557b0a24a9). As the median length of stay in Australia following acute stroke/TIA is ≈4 days,[11] the date of discharge was imputed from the date of admission in cases where the date of discharge was missing (2% of cases). Medications that were dispensed in a single unit quantity (<0.1% of medications) were excluded since these medications are likely to be administered via non-oral routes (e.g. topically or intravenously). In the absence of data on blood pressure or contraindications, all patients with stroke/TIA were considered eligible to receive antihypertensive medications.[5] Since antithrombotic and lipid-lowering medications are not recommended for patients with intracerebral hemorrhage (ICH), these patients were considered ineligible for these medications.[5] As dosage information was unavailable in our dispensing data, we adopted an approach used in other studies whereby typical daily doses are imputed using the registered product information for each medication .[12, 13] In brief, we deemed that all medications were intended to be taken once daily apart from captopril, propranolol, metoprolol tartrate, labetalol, nifedipine, verapamil, frusemide, gemfibrozil, apixaban, dabigatran, and dipyridamole/aspirin, all of which were considered to be taken twice daily.[12]

Outcomes

a) Medication Initiation

Use of each secondary prevention medication was determined for each patient in the year following discharge from hospital. Medication users were defined as those with a dispensing of medication, greater than a single unit quantity, in the year post-discharge. Use of each secondary prevention medication before admission was based on a history of medication dispensing of the corresponding drug <90 days prior to the date of admission for stroke/TIA.

b) Medication Discontinuation

Medication discontinuation was calculated among users of medications in the subsequent year post-discharge. We defined discontinuation as the absence of a medication dispensing for a period ≥90 days from the expected end date of the final medication supply.[14] We performed sensitivity analyses to determine the effect of either a 60- or 180-day treatment gap to define medication discontinuation. Patients who switched between medications within the same therapeutic class were not considered to have discontinued. For patients with multiple periods of discontinuation, we considered the first date of discontinuation only.

Definitions

Patient factors, such as age, sex, and clinical diagnosis, were obtained from the AuSCR (see table e-2 for definitions of each clinical diagnosis; doi.org/10.26180/5f0557b0a24a9). Severe stroke was defined as being unable to walk on admission, a validated proxy measure for inferring stroke severity.[15] Socioeconomic position was determined using the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD),[16] an area-level indicator based on the patients' post-code of residence. Patients were divided into five strata of IRSAD, with greater IRSAD quintiles indicating lesser relative socioeconomic disadvantage.

Patients were also characterized as long-term concession card holders if ≥90% of scripts in the medication dispensing data were claimed using a concession subsidy.[17]

All acute-care hospital factors, such as clinical processes of care (e.g. management in a stroke unit) and hospital-level characteristics (e.g. size and rurality), were obtained from the AuSCR. As the prescription of antithrombotic and lipid-lowering medications at discharge were not recorded in the AuSCR for the entire study period, only the prescription of antihypertensive medications at discharge from hospital was investigated.

Factors related to primary-care services (termed primary-care factors), such as the regularity and frequency of contact with physicians in the year after hospital discharge, were identified using *Medicare* item codes (Table e-3; doi.org/10.26180/5f0557b0a24a9). Physicians were characterized based on their medical specialty, either as a general practitioner (termed primary-care physician) or specialist physician. Regular primary-care contact was defined as having at least quarterly visits with a primary-care physician following discharge from hospital.[18] In Australia, enhanced models of primary-care are also available for patients with chronic conditions, including stroke. These *Medicare*-funded initiatives include use of chronic disease management plans and multidisciplinary, team-based care, known as team-care arrangements. We investigated the effect of these enhanced models of care on the use and discontinuation of secondary prevention medications after stroke. Using physician-specific prescriber codes in the medication dispensing data, we also explored the effect of having the same primary-care physician prescribe ≥90% of all medications in the year post-discharge.[19]

Standard Protocol Approvals, Registrations, and Patient Consents

Hospitals participating in the registry are required to obtain site-specific ethics approval before commencing data collection. To minimize selection biases, patients are included in the

registry based an opt-out model of consent whereby patients are notified of their automatic inclusion and are provided with information should they wish not to participate. Each year during our study period, between 1%-6% of registrants opted out from the AuSCR.[11] All aspects of this study were approved by ethics committees at Monash University (Approval: #7864) and the Australian Institute of Health and Welfare (Approval: #EO2017/1/346). Additional approvals for the acquisition and linkage of these data were obtained from the AuSCR Research Task Group and the Australian Department of Health.

Statistical Analyses

Descriptive statistics were used to describe patient, acute-care, and primary-care factors according to medication use and discontinuation. In univariable analyses, χ^2 tests were used for categorical variables and Wilcoxon rank-sum tests for non-parametric, continuous variables. Time to commencement of different secondary prevention medication were compared using Wilcoxon signed-rank tests.

In multivariable analyses, multiple logistic regression models were performed to investigate the associations between specific factors and use of each medication after stroke. Models were adjusted for age, sex, socioeconomic position, clinical diagnosis, stroke severity, stroke unit treatment, in-hospital stroke, discharge destination, use of medication prior to admission, regularity of primary-care contacts and year of hospital discharge. These results are presented as odds ratios (ORs) with corresponding 95% CIs. Multivariable competing risks regression was used to investigate time to medication discontinuation, accounting for patients who died during the observation period. For these models, factors from the univariable analysis with a $p<0.1$ were considered eligible for inclusion in the manual step-wise modelling process. These results were presented as sub-distribution hazard ratios (SHRs) with corresponding 95% CIs. All multivariable models were multi-level, to account for hospital-level sampling of

patients. Variables with a variance inflation factor >5 were excluded due to collinearity and an overall condition index of <30 was ensured in final models.[20]

Sensitivity analyses were performed to test the influence of missing data on the final models. Medications dispensed without a government subsidy before 1st July 2012 were not recorded in the medication dispensing dataset. Therefore, a sensitivity analysis in long-term concession card holders and those discharged on or after 1st July 2012 was undertaken. Since aspirin can be purchased over-the-counter without a prescription, we performed additional sensitivity analyses to compare whether our model for discontinuation of antithrombotic medications was similar after the exclusion of aspirin. Sub-group analyses were also undertaken among incident users of each medication to assess whether the final models were similar for those without prior medication use. All analyses were performed using STATA/MP 15.1 for Windows (StataCorp, College Station, USA, 2017).

Data Availability

Due to ethical and legal restrictions, linked administrative data from this study cannot be shared. However, aggregated data outputs and coding that support the findings of this study are available from the corresponding author on reasonable request, following approval from the relevant data custodians.

Results

Of the 17980 patients registered in the AuSCR between 2010 and 2014 (46.1% female, 52.5% aged ≥75 years, 13.6% ICH, and 15.7% TIA), 16434 (91.4%) were successfully linked to medication dispensing and *Medicare* data. After excluding patients who were ineligible (Figure 1), a total of 9817 adults remained who survived their first-ever stroke or TIA. Characteristics of the final cohort were similar to those of the initial cohort (45.4% female, 47.6% aged ≥75 years, 11.4% ICH and 17.1% TIA; Table 1). Within one year, most of the

eligible patients were dispensed medications for secondary prevention of stroke (79.3% antihypertensive, 81.8% antithrombotic, and 82.7% lipid-lowering). The median time to first dispensing of medications after discharge was approximately two weeks for all medications, with longer delays in the commencement of treatment observed for antihypertensive medications than for other agents (Figure 2). Although the proportion of patients who used and discontinued each medication was similar between clinical diagnoses, the median time to medication initiation was shorter for patients with TIA (Table e-4; doi.org/10.26180/5f0557b0a24a9). Unadjusted comparisons of users and non-users are provided in Table e-5 (doi.org/10.26180/5f0557b0a24a9). Patients who were prescribed antihypertensive medications at discharge from hospital were dispensed antihypertensive medications in the community 9 days sooner following discharge than those who were not prescribed antihypertensive medications at discharge (Figure 3). Sex differences in the use of medications were observed following age stratification, whereby younger women with stroke were less likely to receive secondary prevention medications than men of similar age (Table e-6; doi.org/10.26180/5f0557b0a24a9).

Following multivariable adjustment, users of each medication were 14%-36% less likely to be female than male and 16-33% less likely to have suffered a severe stroke (i.e. unable to walk on admission) than a mild stroke (Table 2). Compared to patients with ischemic stroke, those with TIA were less likely to be users of both antithrombotic and lipid-lowering medications. Quarterly contact with a primary-care physician, prescription by a specialist, or receipt of a chronic disease management plan were each associated with increased use of secondary prevention medications.

Medication discontinuation in the year following hospital discharge was most common for antithrombotic medications, with 34.1% of users discontinuing within 1 year (Figure 4). The majority of these patients appeared to discontinue aspirin between 110-120 days post-

discharge, after exhausting a 112-tablet supply of aspirin (Figure e-1; doi.org/10.26180/5f0557b0a24a9). Compared to patients who continued antithrombotic medications, those who discontinued were younger and less commonly a concession card holder (Table e-7; doi.org/10.26180/5f0557b0a24a9). A similar proportion (28.5%) of patients also discontinued lipid-lowering medications, but fewer patients (20.9%) discontinued antihypertensive medications in the year following discharge. Of those who discontinued any secondary prevention medication, the majority did so within 180 days of discharge (57.5%, 60.6%, and 65.6% of patients who discontinued antihypertensive, antithrombotic, and lipid-lowering medication, respectively). In sensitivity analyses, the median time to discontinuation was similar when a 60 or 180-day treatment gap was used to define medication discontinuation (Table e-8; doi.org/10.26180/5f0557b0a24a9). Upon excluding aspirin, similar factors were associated with discontinuation of antithrombotic agents compared to when aspirin was included (Table e-9; doi.org/10.26180/5f0557b0a24a9).

Following multivariable adjustment, patients who discontinued were 11-13% less likely to have been prescribed by a specialist, 27-38% less likely to have had quarterly contact with their primary care physician, and 20-31% less likely to visit the same primary care physician (Table 3). Compared to being discharged to rehabilitation, aged care or other acute care, those who were discharged directly home were more likely to discontinue antithrombotic and lipid-lowering medications. Patients who were discharged from acute care with an antihypertensive medication prescription were less likely to discontinue antihypertensive medications than those discharged without antihypertensive medications. Patients with a history of medication use before admission were 53-55% less likely to discontinue each class of secondary prevention medication. However, when the analyses were restricted to incident users of each medication, similar factors and effect sizes were associated with discontinuation (Table e-10; doi.org/10.26180/5f0557b0a24a9). There were also minimal changes to the final

models for discontinuation when we excluded patients without a concession card or those discharged prior to July 2012 (Table e-11; doi.org/10.26180/5f0557b0a24a9).

Discussion

In this study, we present evidence that approximately one-fifth of patients did not receive antihypertensive, antithrombotic or lipid-lowering medications in the year following stroke/TIA. Of those who received secondary prevention medications, an additional one third of patients discontinued their medications within one year of discharge from hospital. The median time to medication discontinuation was between 4-6 months post-discharge, highlighting the need for careful monitoring of patients and implementation of interventions to improve medication adherence in the first few months following hospital discharge. We identified several factors associated with a greater chance of continued use of secondary prevention medications: provision of medication on hospital discharge, regular contact with a primary-care physician, and specialist physician contact. Independent of differences in age and stroke severity, we found patients who were discharged directly home were more likely to discontinue antithrombotic and lipid-lowering medications, than those discharged to other services such as rehabilitation and aged care. Improved follow-up with patients living in the community in the initial period following hospital discharge may be needed to reduce inappropriate discontinuation of medications after stroke/TIA.

Primary-care factors were strongly associated with both the use and discontinuation of secondary prevention medications after stroke. In particular, regular contact with a primary-care physician was more strongly associated with use of each secondary prevention medications after stroke than increased frequency of primary-care physician contacts in the year following stroke. Increased frequency of primary-care physician contacts may be indicative of poor health or more serious chronic conditions that may increase absolute and relative contraindications for use of secondary prevention medications.[21] More sensitive

measures of primary-care regularity are needed to accurately assess the continuum of primary-care post-stroke. Prescription by the same primary-care physician was associated with a lesser risk of medication discontinuation than patients with multiple primary-care physicians.[22] Patients prescribed by the same primary-care physician may receive more simplified drug regimens and consistent medication advice to promote continued use of medications than patients with multiple primary-care physicians.[23] Further research is ongoing in this area to determine optimum long-term primary care management for patients with stroke living in the community.[24]

We identified several inequalities in the use of secondary prevention medications after stroke. Although differences were not observed by socioeconomic position, we found long-term concession card holders were at a lesser risk of discontinuing medications. Despite Australia having one of the most comprehensive universal healthcare systems in the world,[25] this finding adds to the growing body of literature supporting the notion that cost remains a significant barrier to medication adherence.[26] Reducing copayments for prescription medications may help to prevent medication discontinuation in those with chronic, multimorbid conditions such as stroke.

Consistent with previous research, we provide evidence that a prescription at discharge from hospital is associated with improved long-term medication use.[27] Although in the present study, we could only evaluate the prescription of antihypertensive medications at discharge, this acute-care factor had a strong, negative association with medication discontinuation in our multivariable model. For the first time, we present data to show that patients who are not prescribed antihypertensive medications at discharge take ≈1.5 weeks longer to receive antihypertensive medications in the community than those prescribed at discharge. Delays in the initiation of secondary prevention medications may be problematic, especially in patients with TIA who are at high-risk of ischemic stroke in the weeks following hospital discharge.[28]

It is important that ongoing efforts are made to improve the timeliness at which patients receive secondary prevention medications in the community, if not already provided with these medications at hospital discharge.

Our estimates of medication discontinuation are similar to those reported in earlier studies conducted internationally using a treatment gap of 90 days to define medication discontinuation.[29-32] In contrast to one earlier study conducted in Sweden,[33] women in our cohort were less likely to receive secondary prevention medications after stroke/TIA. This finding is similar to our earlier work in which women with ischemic stroke were 15% less likely to be discharged from acute care with an antihypertensive agent.[6] Our finding that women were less likely to receive each secondary prevention medication may be partly due to the combination of greater burden of comorbidities and frailty associated with the advanced age of women in our cohort, but also raises the possibility of gender inequities in prescribing habits.[34] We also found women were more likely to discontinue lipid-lowering medications than men. This finding is similar to one other study performed in Slovakia,[32] in which women were 31% more likely to discontinue statins in the year after TIA than men. These sex differences in the use of statins may be driven by a combination of advanced age, decreased awareness of cardiovascular risk, and higher risk of statin intolerance in women.[35]

Age was associated with use of medications after stroke and the associations differed according to the type of secondary prevention medication. Younger patients were less likely to receive antihypertensive or antithrombotic medications compared to older patients. Although lifestyle interventions are often an effective first-line strategy for managing risk factors in younger adults, young patients with stroke remain at high-risk of future cardiovascular events.[1] Therefore, pharmacological interventions are needed in conjunction with lifestyle modifications for prevention of recurrent stroke, irrespective of age. In contrast, older patients were less likely to receive lipid-lowering medications after stroke, potentially

because of affordability, side-effects or clinical indications against the use of lipid-lowering medications in patients with limited life expectancy.[5]

We identified a large spike in discontinuation of antithrombotic medications at between 110-120 days post-discharge. Further examination of this finding revealed that the majority of patients who discontinued during this period were prescribed a 112-day supply of low-dose aspirin at discharge from hospital. Since aspirin can be purchased over-the-counter without a prescription in Australia, patients may have obtained refills of aspirin outside of the Pharmaceutical Benefits Scheme that were not captured in our dataset. However, <2.6% of Australians aged ≥65 years who participated in the Australian Longitudinal Study of Ageing reported they obtained aspirin over-the-counter without a prescription.[36] This is likely due to the fact that most older Australians are concession card holders and consequently can obtain prescription aspirin at a heavily discounted price compared to over-the-counter. We also showed that including or excluding aspirin yielded similar factors and effect sizes in our multivariable model for antithrombotic discontinuation, demonstrating the robustness of our findings.

A major strength of this study was the use of medication dispensing data for calculation of medication use and discontinuation, which is a more robust method than relying on self-reported measures.[7] In contrast to studies of prescription patterns, where prescriptions are often never filled, our use of dispensing data provide a more accurate picture of the number of patients with stroke who are treated with secondary prevention medications. Unlike other studies,[29-33] our stroke cohort was prospectively identified by hospital clinicians rather than relying on diagnostic codes recorded in administrative claims data to identify patients with stroke/TIA. Through linkage with the AuSCR, we were able to explore a wider range of stroke-specific factors that are unavailable in administrative claims data alone.

There are several limitations of our study. Firstly, we were unable to verify whether patients actually took the medication they were dispensed. However, medication adherence calculated using medication dispensing data has been shown to closely align with those derived from direct measurement.[37] As the reasons for withholding medications were not available in our data, we could not determine whether medications were withheld due to end-stage disease, contraindications, side-effects, polypharmacy concerns, cognitive decline, surgery, or readmissions. Therefore, we may have underestimated the proportion of patients in whom secondary prevention medications were appropriately withheld or withdrawn. As data on stroke etiology were also unavailable, we were unable to determine the suitability of prescribing antiplatelet vs anticoagulant medications, or lipid lowering therapies which may have been appropriately tailored to a specific cause of stroke. We also could not ascertain whether medication use led to better control of risk factors, such as lower blood pressure or cholesterol levels. While efforts were made to impute standard dosages for secondary prevention of stroke, the strength and dosing are often dependent on individual patient physiology, such as the requirement for regular blood testing to ensure safe dosage of warfarin. In future studies, we will link registry data with patient management systems used by primary-care physicians to provide greater insight into individual dosing regimens and reasons for medications changes or cessation.

Conclusion

The majority of patients receive one or more secondary prevention medications after stroke/TIA, but up to one-third discontinue their medications within one year of discharge from hospital. Provision of medication on hospital discharge, regular primary-care physician contact, and specialist physician contact were associated with greater preventative medication use, and a lesser risk of medication discontinuation. Further research is required to understand why medications are not dispensed, why patients discontinue medications, and

whether withholding evidenced-based medications was a result of appropriate targeting, or a missed opportunity for effective secondary prevention.

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Appendix 1: Authors

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Lachlan L. Dalli, BBiomedSc (Hons)	Stroke and Ageing Research, Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia	Drafting of the manuscript, literature review, analysis of data, and interpretation of the data.
Joosup Kim, PhD	Stroke and Ageing Research, Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia	Interpretation of the data, contribution to data analysis methods, revisions of the manuscript for intellectual content, and supervision of analyses.
Amanda G. Thrift, PhD	Stroke and Ageing Research, Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia	Interpretation of the data, contribution to data analysis methods, revisions of the manuscript for intellectual content.
Nadine E. Andrew, PhD	Peninsula Clinical School, Central Clinical School, Monash University, Frankston, VIC, Australia	Acquisition and linkage of data, acquisition of funding, interpretation of the data, and revisions of the manuscript for intellectual content
Frank M. Sanfilippo, PhD	School of Population and Global Health, The University of Western Australia, Perth,	Interpretation of the data, contribution to data analysis methods, and revisions of the manuscript for intellectual content.

Name	Primary Location	Contributions
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Derrick Lopez, PhD	School of Population and Global Health, The University of Western Australia, Perth, WA, Australia	Interpretation of the data, contribution to data analysis methods, and revisions of the manuscript for intellectual content.
Rohan Grimley, MBBS	Sunshine Coast Clinical School, Griffith University, Birtinya, QLD, Australia	Collection of AuSCR data, interpretation of the data and revisions of the manuscript for intellectual content.
Natasha A. Lannin, PhD	Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC, Australia	Interpretation of the data and revisions of the manuscript for intellectual content
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Table 1: Baseline Demographic and Clinical Characteristics of Cohort

	N=9817
	n (%)
Female	4460 (45.4)
Age, median (Q1, Q3), y	74.2 (63.3, 82.5)
Born in Australia	6362 (64.8)
Socioeconomic position[a]	
Most disadvantaged	1051 (10.9)
Second most disadvantaged	1565 (16.2)
Third most disadvantaged	1918 (19.9)
Fourth most disadvantaged	2194 (22.7)
Least disadvantaged	2933 (30.4)
Concession card holder	6763 (73.8)
Clinical diagnosis	
Intracerebral hemorrhage	1122 (11.4)
Acute ischemic stroke	6684 (68.1)
Transient ischemic attack	1679 (17.1)
Undetermined	324 (3.3)
Unable to walk on admission[b]	4739 (48.3)
Stroke occurred in hospital	455 (4.7)
Year discharged	
2010	840 (8.6)
2011	1608 (16.4)
2012	2419 (24.6)
2013	3195 (32.6)
2014	1755 (17.9)

Patient state	
Australian Capital Territory/New South Wales	2656 (27.4)
Queensland	1664 (17.2)
Tasmania	495 (5.1)
Victoria	4329 (44.7)
Western Australia	534 (5.5)
Length of stay, median (Q1, Q3), days	5 (2, 9)
Discharged to community with care plan[c]	2773 (54.1)
Discharge destination	
Home	4988 (50.8)
Inpatient rehabilitation	2843 (29.0)
Aged care facility	636 (6.5)
Other[d]	1350 (13.8)
Use of medication prior to admission	
Antihypertensive	5798 (59.1)
Antithrombotic	2404 (24.5)
Lipid-Lowering	3709 (37.8)

Q1=25th percentile; Q3=75th percentile.

[a] Determined using Index of Relative Socio-economic Advantage and Disadvantage.

[b] 6-8% missing data.

[c] 4-6% missing data.

[d] Other refers to other acute care, transitional care services, statistical discharges and patients who left against medical advice.

Table 2: Factors Associated with Use of Secondary Prevention Medications After Stroke or TIA

	Adjusted Logistic Regression Models[a]		
	Antihypertensive N=9817	**Antithrombotic N= 8695**	**Lipid-Lowering N= 8695**
	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]
Patient factors			
Female	0.79 (0.70-0.89)	0.86 (0.76-0.97)	0.64 (0.56-0.73)
Age, per 10-year increase	1.16 (1.11-1.21)	1.26 (1.20-1.31)	0.94 (0.90-0.99)
Born in Australia	0.98 (0.86 -1.11)	1.03 (0.90-1.17)	0.96 (0.83-1.11)
Socioeconomic position[b]			
Most disadvantaged	[Reference]	[Reference]	[Reference]
Second most disadvantaged	1.01 (0.80-1.28)	0.92 (0.71-1.17)	1.04 (0.79-1.35)
Third most disadvantaged	1.02 (0.82-1.28)	1.09 (0.85-1.39)	1.08 (0.84-1.40)
Fourth most disadvantaged	0.97 (0.78-1.22)	0.85 (0.67-1.08)	0.97 (0.75-1.25)
Least disadvantaged	0.95 (0.76-1.19)	0.77 (0.61-0.98)	0.94 (0.73-1.22)
Concession card holder	1.09 (0.93-1.27)	2.04 (1.73-2.40)	0.88 (0.73-1.06)
Use of medication prior to admission	7.39 (6.46-8.45)	2.31 (1.94-2.75)	5.73 (4.81-6.82)
Clinical diagnosis			
Intracerebral hemorrhage	[Reference]	…	…
Ischemic stroke	0.98 (0.82-1.17)	[Reference]	[Reference]
Transient ischemic attack	0.74 (0.59-0.94)	0.72 (0.61-0.85)	0.68 (0.57-0.82)
Undetermined	0.55 (0.38-0.82)	0.67 (0.47-0.94)	0.57 (0.40-0.81)
Unable to walk on admission	0.83 (0.73-0.94)	0.84 (0.74-0.97)	0.67 (0.58-0.78)
Stroke occurred while in-hospital	0.67 (0.51-0.87)	0.64 (0.49-0.83)	0.60 (0.46-0.79)
Acute-care factors			
Transfer from another hospital	1.06 (0.88-1.27)	1.12 (0.92-1.38)	0.83 (0.67-1.02)

Received thrombolysis	1.14 (0.91-1.41)	1.12 (0.90-1.38)	1.31 (1.04-1.64)
Treated in a stroke unit	1.03 (0.88-1.21)	1.20 (1.01-1.43)	1.68 (1.41-2.01)
Treated in a rural hospital	0.94 (0.72-1.23)	1.11 (0.75-1.62)	0.87 (0.58-1.31)
Treated in a large hospital (>300 beds)	0.96 (0.70-1.31)	1.03 (0.67-1.58)	0.66 (0.42-1.06)
Length of stay >4 days	0.93 (0.82-1.07)	1.16 (1.01-1.33)	0.80 (0.69-0.93)
Prescribed antihypertensive at discharge	6.62 (5.82-7.55)	…	…
Discharged to community with care plan	1.24 (1.03-1.50)	1.02 (0.84-1.23)	1.16 (0.93-1.43)
Discharge destination			
Home	[Reference]	[Reference]	[Reference]
Inpatient rehabilitation	1.13 (0.96-1.32)	1.32 (1.11-1.56)	0.81 (0.68-0.97)
Aged care facility	0.40 (0.32-0.52)	0.58 (0.45-0.74)	0.25 (0.20-0.32)
Other[c]	0.44 (0.36-0.53)	0.54 (0.44-0.66)	0.35 (0.29-0.43)
Primary-care factors			
Frequency of contacts with primary-care physician, per 5 visit increase	1.25 (1.21-1.31)	1.30 (1.25-1.36)	1.06 (1.03-1.10)
Quarterly contact with primary-care physician	2.90 (2.58-3.25)	2.86 (2.54-3.23)	2.70 (2.38-3.07)
Chronic disease management plan	1.54 (1.33-1.77)	1.23 (1.07-1.42)	1.50 (1.27-1.76)
Team-care arrangement	1.55 (1.33-1.80)	1.13 (0.97-1.32)	1.49 (1.26-1.77)
Medication management review	1.50 (1.16-1.93)	2.28 (1.68-3.09)	1.02 (0.81-1.29)
Same primary-care physician prescribed ≥90% of medications	0.76 (0.67-0.87)	0.57 (0.49-0.65)	0.74 (0.64-0.85)
Prescribed by specialist physician	2.85 (2.42-3.37)	2.73 (2.30-3.25)	1.47 (1.25-1.73)

Abbreviations: Q1=25th percentile; Q3=75th percentile.

[a] Each factor adjusted for age, sex, socioeconomic position, clinical diagnosis, stroke severity, management in a stroke unit, in-hospital stroke, discharge destination, use of medication <90 days prior to admission, quarterly physician contacts and year of hospital discharge. [b] Determined using

Index of Relative Socioeconomic Advantage and Disadvantage[16]. [c] Other refers to other acute care, transitional care services, statistical discharges and patients who left against medical advice.

Table 3: Multivariable Model of Factors Associated with Discontinuation of Secondary Prevention Medications After Stroke or TIA, Among Users of Secondary Prevention Medications

	Multivariable Competing Risks Regression[a]		
	Antihypertensive n= 7782	**Antithrombotic** n= 7105	**Lipid-Lowering** N= 7189
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Patient factors			
Female	0.95 (0.84-1.07)	1.05 (0.95-1.16)	1.19 (1.10-1.29)
Age, per 10-year increase	1.01 (0.95-1.07)	0.85 (0.82-0.88)	0.99 (0.95-1.03)
Concession card holder	0.94 (0.82-1.06)	0.80 (0.72-0.89)	0.62 (0.56-0.68)
Use of medication prior to admission	0.45 (0.40-0.50)	0.47 (0.41-0.55)	0.45 (0.39-0.50)
Clinical diagnosis			
Intracerebral hemorrhage	[Reference]	…	…
Ischemic stroke	1.12 (0.96-1.30)	[Reference]	[Reference]
TIA	1.19 (0.96-1.47)	1.30 (1.12-1.52)	1.27 (1.13-1.44)
Undetermined stroke	1.34 (0.93-1.94)	1.65 (1.37-1.98)	1.07 (0.71-1.61)
Unable to walk on admission	1.10 (0.97-1.24)	1.00 (0.93-1.08)	1.00 (0.90-1.11)
Acute-care factors			
Prescribed antihypertensive at discharge	0.70 (0.62-0.79)	…	…
Discharged directly home	1.06 (0.96-1.17)	1.22 (1.11-1.34)	1.19 (1.06-1.34)
Primary-care factors			
Quarterly contact with primary-care physician	0.62 (0.57-0.67)	0.73 (0.67-0.79)	0.62 (0.57-0.68)
Received chronic disease management plan	0.94 (0.86-1.04)	0.88 (0.77-1.01)	0.88 (0.81-0.96)
Same primary-care physician prescribed	0.80 (0.67-0.96)	0.73 (0.61-0.87)	0.69 (0.62-0.76)

≥90% of medications			
Prescribed by specialist physician	0.87 (0.77-0.98)	0.89 (0.81-0.98)	0.89 (0.81-0.98)

SHR=sub-distribution hazard ratio; CI=confidence interval.

[a] Adjusted for factors shown in each model, as well as year of hospital discharge and death as a competing risk for medication discontinuation.

Figure 1: Flowchart Displaying Final Cohort Selection Process

Abbreviations: AuSCR=Australian Stroke Clinical Registry; PBS=Pharmaceutical Benefits Scheme; ICH=intracerebral hemorrhage; MBS=Medicare Benefits Schedule.

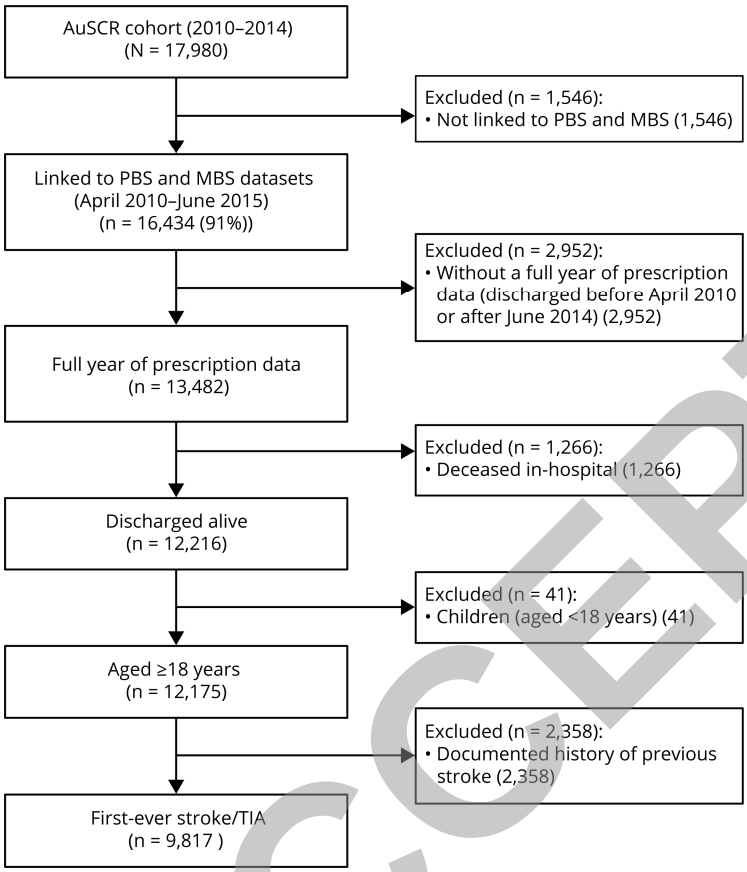


Figure 2: Days to First Dispensing of Secondary Prevention Medication After First-Ever Stroke/TIA

Box-plot diagrams displaying days to first dispensing of antihypertensive (n= 7789 users; median: 16 days; interquartile range [IQR]: 3-39 days), antithrombotic (n= 7112 users; median: 9 days; IQR: 0-35 days) and lipid-lowering (n= 7194 users; median: 8 days; IQR: 0-28 days) medications within one year of discharge following first-ever acute stroke/TIA. Whiskers extend to 1.5-fold the IQR of the upper (75th percentile) and lower (25th percentile) quartiles of box. Wilcoxon Signed-Rank Tests used to compare time to commencement between antihypertensive and antithrombotic (P<0.001), antihypertensive and lipid-lowering (P<0.001), and antithrombotic and lipid-lowering medications (P=0.001).

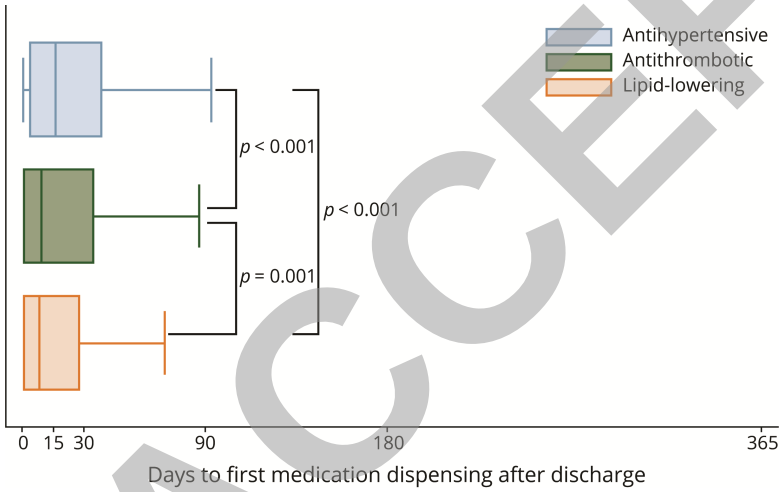


Figure 3: Days to First Dispensing of Antihypertensive Medication Following First-Ever Stroke/TIA, By Prescription of Antihypertensive Medications at Hospital Discharge

Histograms with box-plot overlaid (in red) to depict the median and interquartile range [IQR] of days to first antihypertensive dispensing after discharge between patients who were (n= 6703) and were not (n=3114) recorded as having been prescribed antihypertensive medications at discharge in the Australian Stroke Clinical Registry. Wilcoxon Rank-Sum Tests used to compare data between those who were (median: 14 days; IQR: 2-34) and were not (median: 23 days; IQR: 6-59 days) prescribed antihypertensive medications at discharge (*P*<.001 for comparison).

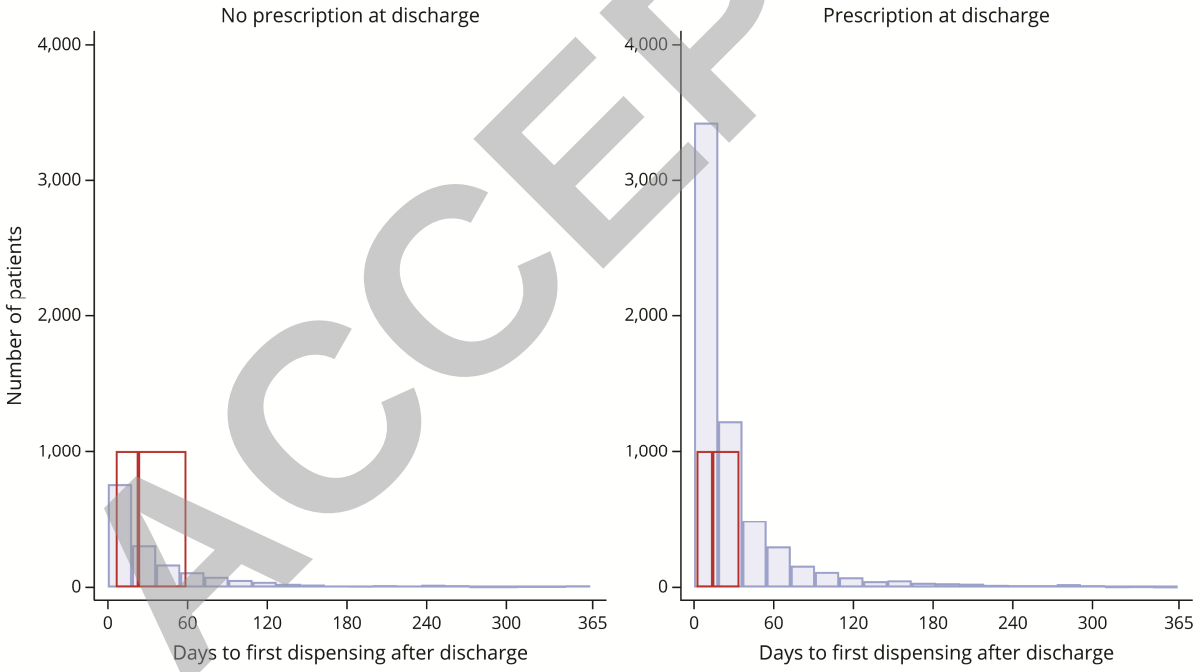
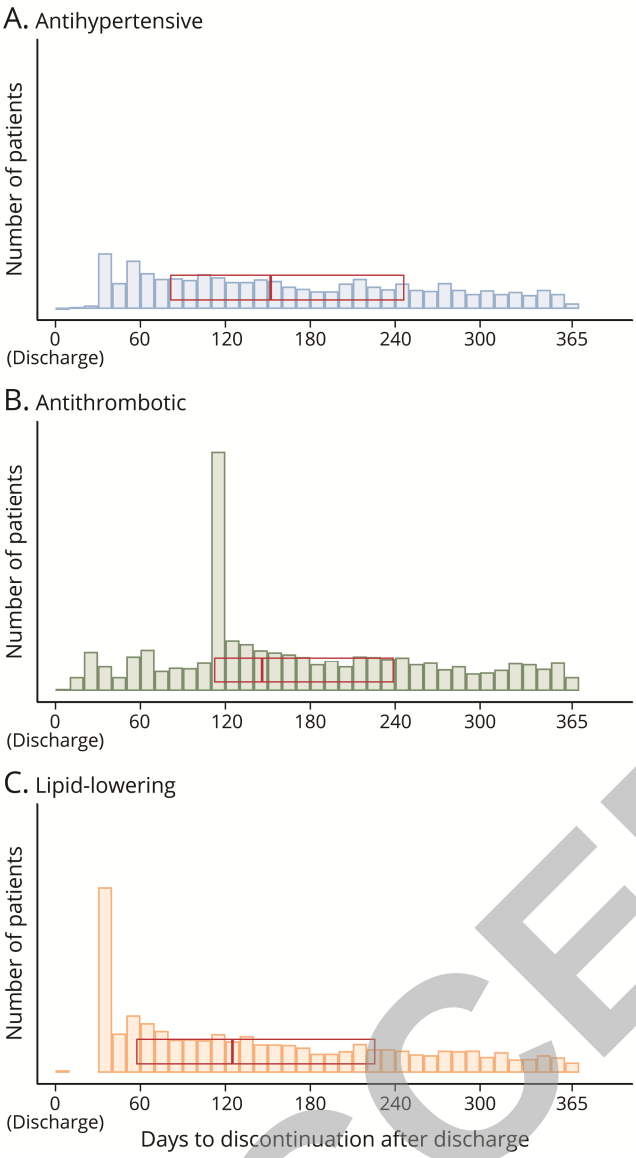


Figure 4: Days to Medication Discontinuation Within One-Year of First-Ever Stroke/TIA, Among Users of Each Secondary Prevention Medication

Each panel consists of histogram displaying distribution of days to discontinuation with box-plot overlaid (in red) to depict the median and interquartile range [IQR]. Top panel (A) represents antihypertensive medications (n=1624 discontinued; median: 152 days; IQR: 81-246.5 days); middle panel (B), antithrombotic (n=2426 discontinued; median: 146 days; IQR: 112-239 days); and, lower panel (C), lipid-lowering medications (n=2053 discontinued; median: 125 days; IQR: 57-226 days).



Patterns of use and discontinuation of secondary prevention medications after stroke

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