Treatment with Multiple Therapeutic Classes of Medication Is Associated with Survival after Stroke

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Keywords
Medication · Adherence · Population register · Stroke · Secondary prevention

Abstract

Introduction: Treatment with several therapeutic classes of medication is recommended for secondary prevention of stroke. We analyzed the associations between the number of classes of prevention medications supplied within 90 days after discharge for ischemic stroke (IS)/transient ischemic attack (TIA) and survival. Methods: This is a retrospective cohort study of adults with first-ever IS/TIA (2010–2014) from the Australian Stroke Clinical Registry individually linked with data from national pharmaceutical and Medicare claims. Exposure was the number of classes of recommended medications, i.e., blood pressure-lowering, antithrombotic, or lipid-lowering agents, supplied to patients within 90 days after discharge for IS/TIA. The longitudinal association between the number of classes of medications and survival was evaluated with Cox proportional hazards regression models using the landmark approach. A landmark date of 90 days after hospital discharge was used to separate exposure and outcome periods, and only patients who survived until this date were included. Results: Of 8,429 patients (43% female, median age 74 years, 80% IS), 607 (7%) died in the year following 90 days after discharge. Overall, 56% of patients were supplied all 3 classes of medications, 28% 2 classes of medications, 11% 1 class of medications, and 5% no class of medications. Compared to patients supplied all 3 medication classes, adjusted hazard ratios for all-cause mortality ranged from 1.43 (95% confidence interval [CI]: 1.18–1.72) in those supplied 2 medication classes to 2.04 (95% CI: 1.44–2.88) in those supplied with no medication class. Discussion/Conclusion: Treatment with all 3 classes of guideline-recommended medications within 90 days after discharge was as-
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Introduction

Globally, stroke is a leading cause of death and adult disability [1]. Reducing the risk of subsequent vascular events, including recurrent stroke, is a major focus to improve survival rates after stroke [2]. Effective pharmacological management and control of modifiable risk factors could reduce the risk of these secondary vascular events by up to 80% over a 10-year period following stroke [3]. Proven strategies to improve survival in people with stroke include pharmacological and lifestyle interventions [4]. The best-practice pharmacological intervention for secondary prevention of stroke includes the use of medications from 3 main therapeutic classes, i.e., blood pressure (BP)-lowering, antithrombotic, and lipid-lowering medications [4].

Real-world data are important for generating evidence on the clinical effectiveness of pharmacological interventions to optimize outcomes in people with vascular diseases, such as stroke [5–10]. Most prior studies regarding the effectiveness of pharmacological intervention on outcomes after stroke or transient ischemic attack (TIA) based on real-world data have been limited to medications for 1 or 2 risk factors [9–11]. We determined the associations between the number of classes of medications supplied within 90 days after discharge for first-ever ischemic stroke (IS) or TIA and survival.

Materials and Methods

Study Design, Setting, and Patients

This is a retrospective cohort study of patients admitted for IS/TIA (April 2010–June 2014) from 25 hospitals located in Queensland, Victoria, New South Wales, Tasmania, and Western Australia [12]. For this analysis, we defined our cohort as those aged ≥18 years who were clinically diagnosed with first-ever IS/TIA. Patients with intracerebral hemorrhage or undetermined stroke type were excluded as all 3 therapeutic classes are not recommended for these patients. Our cohort was also limited to patients who were discharged to their usual residence, rehabilitation, or aged care, to minimize the inclusion of patients undergoing palliative care or further acute care. We used a landmark approach [13], whereby those who did not survive the period of exposure to treatment were excluded, i.e., 90 days after discharge for IS/TIA. These methods prevent immortal-time bias, whereby patients who were censored early due to death had a reduced chance of receiving treatment.

Data Sources

More than 95% of registrants were successfully linked from the following sources [14].

Australian Stroke Clinical Registry

This national stroke registry is used to prospectively monitor the quality of care and outcomes of patients with stroke or TIA in hospitals that voluntarily participate (the majority are public hospitals). Data collected in the AuSCR include patient characteristics, nationally prioritized quality of care indicators (i.e., assessment and treatment recommendations in clinical practice guidelines), and outcomes after stroke [15]. Mortality outcomes are obtained by the AuSCR through annual data linkage to the National Death Index, which is a registry of deaths held by the Australian Institute of Health and Welfare.

In Australia, we have a universal health care system with government-funded schemes for access to subsidized prescription medications and medical practitioner/specialist consultations [16]. This study involves analyses of administrative data obtained from these schemes, as outlined below.

Pharmaceutical Benefits Scheme

Data from this source contain details of all subsidized prescription medications that were dispensed to Australian permanent residents. Before July 2012, records only existed for dispensed medications where the patient co-payment was less than the actual medication cost, i.e., a subsidy was provided by the Australian Government. In previous analyses, we reported that the majority of patients (92%) were either discharged after July 2012 or accessed heavily subsidized medications with a healthcare concession card during the 90-day period following their index stroke event [17]. We also showed that excluding these patients had minimal changes to our results on medication utilization.

Medicare Benefits Scheme

This dataset contains information on all transactional claims data on various health services subsidized by the Australian Commonwealth Government, e.g., visits to physicians (including specialists and primary care physicians), pathology and imaging services, and limited visits to allied health professionals under subsidized schemes.

Exposure Assessment

In Australia, BP-lowering, lipid-lowering, and antithrombotic medications are recommended for secondary prevention of stroke in the clinical guidelines. For this study, we included BP-lowering agents (renin-angiotensin system inhibitors, calcium channel blockers, and thiazide diuretics), lipid-lowering agents (statins), and antithrombotic agents (warfarin, dabigatran, rivaroxaban, apixaban, and clopidogrel), either as single agents or combination products [4]. These recommended classes of medications are similar to those in the American Heart Association stroke guidelines [18]. Exposure was defined as the number of therapeutic classes supplied to a patient within 90 days of hospital discharge from the following: BP-lowering agents, lipid-lowering agents, and antithrombotic agents [4]. Medications were identified in Pharmaceutical Benefits Scheme data using World Health Organization Anatomical Therapeutic Chemical Classification codes (see online suppl. Table 1 for specific codes used; see www.karger.com/doi/10.1159/000520823

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Medications comprising both BP- and lipid-lowering (combination) agents were considered belonging to both therapeutic classes.

**Health Outcomes**
Mortality outcomes comprised those from all-causes or cardiovascular diseases (CVD, including stroke), in the subsequent 1-year period (i.e., between 91 and 455 days after discharge).

**Covariates**
Details of patient and acute care factors were obtained from the AuSCR, medication use in the previous 90 days from the Pharmaceutical Benefit Scheme, and community-based care after discharge from the Medicare dataset. The socioeconomic position of patients was derived using the postcode-based Index of Relative Advantage and Disadvantage [19] classified into predetermined quintiles with higher quintiles indicating greater socioeconomic advantage. Inability to walk on admission was used as a marker of stroke severity as this proxy measure has been validated for use in large cohorts of patients with stroke [20]. Receipt of healthcare concession benefits was defined as having ≥90% of pharmaceutical claims made using a subsidy concession card [17]. Contacts with primary care physicians were determined using specific item Medicare Benefits Scheme codes (see online suppl. Table 2 for details). Prescription by a specialist physician was identified from the pharmaceutical claims data using codes on the medical specialty of the prescribing doctor.

**Data Analysis**
Data were summarized by the number of therapeutic classes supplied to patients using χ² tests for categorical data and Wilcoxon rank sum tests for nonparametric continuous data. The longitudinal association between the number of classes of medications supplied within 90 days after discharge and all-cause mortality was evaluated with Cox proportional hazards regression. For cardiovascular mortality, a competing risks model was used to account for deaths from noncardiovascular causes.

All regression models were adjusted for factors known to be associated with the exposure and outcomes (p < 0.10), including sociodemographic (age and sex) and clinical (stroke type and discharge destination) characteristics. Models were also evaluated for correlations between patients within individual hospitals and tested for interactions of the exposure variable with covariates. Missing data were handled in multivariable models using case-wise deletion. All analyses were undertaken using STATA/MP 16.0 for Windows (StataCorp, College Station, TX, USA, 2019).

**Results**

**Patient Characteristics**
A total of 8,429 patients were included in this analysis (online suppl. Fig. 1). The median age was 74 years, 43% were female, and 80% had an IS. Overall, 56% of patients were supplied all 3 classes of medications, 28% 2 classes of medications, 11% 1 class of medications, and 5% no class of medications (Fig. 1). Missing data ranged from 0 to 2% for all variables in our study, with the exception of “unable to walk on admission” and “discharged to community with care plans” where missing data ranged from 4 to 8% (Table 1).

Apart from sex, country of birth, and location and size of the treating hospital, the distribution of patient factors, acute care factors, and community care factors differed.
### Table 1. Patient factors, acute care factors, and community-based care received by increasing number of classes of medications supplied

| Classes of preventative medication supplied within 90 days, n | \( P_{\text{trend}} \) |
|---------------------------------------------------------------|-----------------|
| 0 \( (N = 439) \)                                             |                 |
| 1 \( (N = 921) \)                                             |                 |
| 2 \( (N = 2,378) \)                                           |                 |
| 3* \( (N = 4,691) \)                                          |                 |

| \( n \) (%) | \( n \) (%) | \( n \) (%) | \( n \) (%) |
|-------------|-------------|-------------|-------------|

**Patient factors**

- **Age, median (Q1, Q3), yr***
  - 0: 64.9 (51.8, 77.1)
  - 1: 64.1 (52.6, 78.6)
  - 2: 71.3 (60.6, 81.9)
  - 3*: 75.5 (66.9, 82.4)

- **Female***
  - 0: 195 (44.4)
  - 1: 398 (43.2)
  - 2: 1,042 (43.8)
  - 3*: 2,114 (45.1)

- **Born in Australia***
  - 0: 279 (63.6)
  - 1: 606 (65.8)
  - 2: 1,514 (63.7)
  - 3*: 2,947 (62.8)

**Socioeconomic position**

- **Most disadvantaged***
  - 0: 44 (10.4)
  - 1: 78 (8.6)
  - 2: 238 (10.3)
  - 3*: 514 (11.2)

- **Second most disadvantaged***
  - 0: 74 (17.4)
  - 1: 103 (11.4)
  - 2: 326 (14.1)
  - 3*: 759 (16.5)

- **Third most disadvantaged***
  - 0: 72 (16.9)
  - 1: 174 (19.2)
  - 2: 426 (18.4)
  - 3*: 966 (21.0)

- **Fourth most disadvantaged***
  - 0: 91 (21.4)
  - 1: 208 (23.0)
  - 2: 557 (24.0)
  - 3*: 1,066 (23.2)

- **Least disadvantaged***
  - 0: 144 (33.9)
  - 1: 343 (37.9)
  - 2: 839 (35.3)
  - 3*: 2,639 (56.3)

**Receive care concession benefits***

- 0: 257 (58.5)
- 1: 430 (46.7)
- 2: 1,568 (65.9)
- 3*: 3,778 (80.5)

**Previous medication use***

- **Blood pressure-lowering***
  - 0: 186 (42.4)
  - 1: 295 (32.0)
  - 2: 1,303 (54.8)
  - 3*: 3,634 (77.5)

- **Antithrombotic***
  - 0: 130 (29.6)
  - 1: 157 (17.1)
  - 2: 709 (29.8)
  - 3*: 1,960 (41.8)

- **Lipid-lowering***
  - 0: 145 (33.0)
  - 1: 199 (21.6)
  - 2: 839 (35.3)
  - 3*: 2,639 (56.3)

**Type of stroke***

- **Acute ischemic stroke***
  - 0: 355 (80.9)
  - 1: 680 (73.8)
  - 2: 1,781 (74.9)
  - 3*: 3,739 (79.7)

- **Transient ischemic attack***
  - 0: 84 (19.1)
  - 1: 241 (26.2)
  - 2: 597 (25.1)
  - 3*: 952 (20.3)

**Unable to walk on admission***

- 0: 250 (57.0)
- 1: 392 (42.6)
- 2: 1,035 (43.5)
- 3*: 2,069 (44.1)

**Year of admission***

- 2010, \( N = 648 \)
  - 0: 48 (10.9)
  - 1: 123 (13.4)
  - 2: 182 (7.7)
  - 3*: 295 (6.3)

- 2011, \( N = 1,200 \)
  - 0: 84 (19.1)
  - 1: 195 (21.2)
  - 2: 352 (14.8)
  - 3*: 569 (12.1)

- 2012, \( N = 1,743 \)
  - 0: 104 (23.7)
  - 1: 190 (20.6)
  - 2: 492 (20.7)
  - 3*: 957 (20.4)

- 2013, \( N = 2,238 \)
  - 0: 90 (20.5)
  - 1: 205 (22.3)
  - 2: 648 (27.3)
  - 3*: 1,295 (27.6)

- 2014, \( N = 2,600 \)
  - 0: 113 (25.7)
  - 1: 208 (22.6)
  - 2: 704 (29.6)
  - 3*: 1,575 (33.6)

**Acute care factors**

- **Transfer from another hospital***
  - 0: 72 (16.5)
  - 1: 98 (10.7)
  - 2: 230 (9.7)
  - 3*: 387 (8.3)

- **Received thrombolysis (if ischemic stroke)***
  - 0: 57 (16.2)
  - 1: 109 (16.1)
  - 2: 206 (11.6)
  - 3*: 494 (13.3)

- **Treated in a stroke unit***
  - 0: 365 (83.1)
  - 1: 755 (82.0)
  - 2: 1,995 (83.9)
  - 3*: 4,035 (86.0)

- **Treated in a rural hospital***
  - 0: 66 (15.0)
  - 1: 136 (14.8)
  - 2: 382 (16.1)
  - 3*: 750 (16.0)

- **Treated in a large hospital (>300 beds)***
  - 0: 393 (89.5)
  - 1: 829 (90.0)
  - 2: 2,128 (89.5)
  - 3*: 4,155 (88.9)

- **Length of stay, median (Q1, Q3), days***
  - 0: 7 (3, 15)
  - 1: 4 (2, 8)
  - 2: 4 (2, 8)
  - 3*: 4 (2, 7)

- **Prescribed antihypertensive at discharge***
  - 0: 186 (42.5)
  - 1: 419 (45.5)
  - 2: 1,512 (63.6)
  - 3*: 4,031 (86.0)

- **Discharged to community with care plan***
  - 0: 217 (49.4)
  - 1: 229 (24.9)
  - 2: 691 (29.1)
  - 3*: 1,597 (34.0)

- **Discharge destination***
  - 0: 217 (49.4)
  - 1: 229 (24.9)
  - 2: 691 (29.1)
  - 3*: 1,597 (34.0)

- **Home***
  - 0: 203 (46.2)
  - 1: 618 (67.1)
  - 2: 1,557 (65.5)
  - 3*: 2,858 (60.9)

- **Rehabilitation***
  - 0: 217 (49.4)
  - 1: 229 (24.9)
  - 2: 691 (29.1)
  - 3*: 1,597 (34.0)

- **Residential aged care***
  - 0: 19 (4.3)
  - 1: 74 (8.0)
  - 2: 130 (5.5)
  - 3*: 236 (5.0)

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with each increasing number of classes of medication supplied (Table 1). Specifically, patients who were supplied all classes of medications were more often older and had greater socioeconomic disadvantage than those supplied with fewer classes of medication (both \( p < 0.05 \)). Similarly, patients supplied all classes of medications more often used these medications prior to stroke/TIA, received better acute care, had more frequent contact with primary care physicians, or had medications prescribed by a specialist physician, than those supplied fewer medications.

**Survival Analyses**

Overall, there were 607 all-cause deaths, including 429 CVD deaths, over 8,089 person-years of follow-up. In univariable models, survival in the subsequent 1-year period significantly improved with each increasing number of classes of medication supplied, regardless of the cause of death (Fig. 2). In multivariable models, each additional class of secondary prevention medication had additive benefits on survival (Table 2). Compared with patients who were supplied all 3 classes of medication, adjusted hazard ratios (aHRs) for mortality ranged from 1.43 (95% confidence interval [CI] 1.18–1.72) in those who were supplied 2 classes of medications to 2.04 (95% CI: 1.44–2.88) in those supplied no prevention medication (Table 2). Results were similar for CVD mortality with aHRs ranging from 1.49 (95% CI: 1.20–1.86) in those supplied 2 classes of medications to 2.13 (95% CI: 1.41–3.19) in those supplied no prevention medication. There was no

**Fig. 2.** Cumulative hazard of mortality by the number of classes of medications.
significant interaction of any of the covariates with the number of classes of medications supplied in the association with mortality.

**Discussion**

We provide evidence that treatment with incrementally more therapeutic classes of guideline-recommended secondary prevention medications was associated with better long-term outcomes in a large cohort of people with IS or TIA. Specifically, we found evidence of the association between using multiple therapeutic classes of prevention medication and survival, with lower rates of all-cause and CVD mortality at 1 year for those supplied 2 or 3 medications within 90 days of discharge compared to those who received one or no class of medication.

To our knowledge, our study is the first to report the real-world association between exposure to multiple classes of recommended prevention medications after discharge for stroke/TIA and survival. In a similar study conducted in frail adults (aged ≥65 years) who initiated prevention medications within 14 days after acute myocardial infarction, those prescribed 3 or 4 medication classes had a 26% reduced risk of mortality at 90 days after the acute event than those prescribed 1 medication class [5]. Our findings also accord with those from the secondary analysis of data from a clinical trial of patients with noncardioembolic stroke. In that study, treatment with more categories of prevention medications had additive benefits on survival from all-cause and CVD mortality [21].

Previous studies of outcomes of pharmacological treatment after a stroke/TIA using real-world data have largely been focused on 1 risk factor (i.e., one class of recommended medications), a measure often assessed at discharge from acute care [9–11]. We previously reported that patients with stroke/TIA provided BP-lowering medications at discharge had a reduced risk of mortality within 180 days (HR 0.78) than those not provided BP-lowering medications [11]. Similarly, in 2 separate studies from the USA, a lower 2-year mortality was observed in patients with IS who were provided with antithrombotic (HR 0.72) [9] and lipid-lowering (HR 0.84) medications at discharge than those not provided these medications [10].

Strengths of this study include the large sample size, the inclusion of patients with a clinical diagnosis of stroke and TIA, and the systematic collection of data on prescription of medications and outcomes. Our data on medications included the majority of secondary prevention medications recommended in the Australian clinical guidelines [4]. However, there were no data on prescription medications supplied in hospital or over-the-counter (e.g., aspirin).

The limitations of these analyses relate mainly to bias inherent in a voluntary registry. Specifically, because of lack of data on comorbidities, contraindications, and side effects, we were unable to exclude patients who were withheld medications due to valid contraindications. Our findings may also be affected by nonadjustment for unmeasured confounders, such as comorbidities. Due to the use of pharmaceutical claims data, we were unable to verify whether patients actually took the dispensed medica-

| Classes of medication | Deaths, n | Rate* (Rate per 1,000 person-years) | Unadjusted HR (95% CI) | Adjusted HR (95% CI)† |
|-----------------------|-----------|-----------------------------------|------------------------|----------------------|
| All-cause mortality (N = 8,135) |           |                                   |                        |                      |
| 0                     | 38        | 96.5                              | 1.42 (1.01–1.99)       | 2.04 (1.44, 2.88)    |
| 1                     | 77        | 90.5                              | 1.33 (1.04–1.71)       | 1.78 (1.38, 2.29)    |
| 2                     | 185       | 84.8                              | 1.25 (1.04–1.50)       | 1.43 (1.18, 1.72)    |
| 3                     | 297       | 67.8                              | Ref                    | Ref                  |
| Cardiovascular disease mortality (N = 8,135) |           |                                    |                        |                      |
| 0                     | 28        | 71.1                              | 1.47 (0.99–2.18)       | 2.13 (1.41, 3.19)** |
| 1                     | 53        | 62.3                              | 1.29 (0.95–1.74)       | 1.68 (1.24, 2.27)** |
| 2                     | 137       | 62.8                              | 1.30 (1.05–1.61)       | 1.49 (1.20, 1.86)** |
| 3                     | 211       | 48.2                              | Ref                    | Ref                  |

HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack. * Rate per 1,000 person-years. † Adjusted for sociodemographics (age, sex, and socioeconomic position), clinical characteristics (stroke type and discharge destination), year of admission, and frequency of visits with primary care physicians 1 year. ** Subdistribution hazard ratio.
tions and whether this led to improved control of risk factors. Our findings should be interpreted in the context that there may have been changes in patterns of use of secondary prevention medications, e.g., the availability of newer oral anticoagulant agents has resulted in increased uptake of anticoagulant medications in preference to warfarin. However, both warfarin and new oral anticoagulants were captured in the broad category of anti-thrombotic agents for these analyses. Linkages with general practice data are underway to provide important insights into the treatment provided by general practitioners for the management of IS/TIA and the appropriateness of patients not being prescribed guideline-recommended medications after IS/TIA.

Our findings have important implications for the long-term management of IS/TIA and support the need to ensure all patients with IS or TIA are supplied with all 3 therapeutic classes of secondary prevention medications. Future research is needed to understand the reasons for patients not being supplied these recommended medications and whether there are subgroups of patients where prescription of recommended medications is less beneficial.

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Statement of Ethics

Human Research Ethics Committee approvals were obtained from Monash University (2017-7864 and 2018-12405) and the AIHW (EO2017-1-346). Approvals were received from the AuSCR Research Task Group, the AuSCR Steering Committee, and the Queensland Public Health Act. The AuSCR holds approval for collecting data via an opt-out model of consent, with a waiver of consent for those who died in the hospital.

Conflict of Interest Statement

Prof. Cadilhac reports funding from Boehringer Ingelheim, Shire, Ipsen, Amgen, and Medtronic paid to her institution and is the Data Custodian for the AuSCR. Prof. Thirt reports board membership of the Stroke Foundation and prior membership of the AuSCR Steering Committee. A/Prof. Kilkenny, Prof. Dewey, and A/Prof. Grimley report membership of the AuSCR Management Committee. All other authors report no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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Author Contributions

M.F.K., M.T.O., L.L.D., J.K., and N.E.A. contributed to conception and/or design; M.F.K., M.T.O., and L.L.D. contributed to data analysis; M.F.K., M.T.O., L.L.D., J.K., and N.E.A. contributed to drafting the manuscript; all authors contributed to critical review of the manuscript. All authors read and approved the final version of the manuscript.

Data Availability Statement

Because of 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.

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