Neuroepidemiology

Original Paper

Neuroepidemiology 2022;56:365–372
DOI: 10.1159/000526071

Received: June 16, 2022
Accepted: July 5, 2022
Published online: July 21, 2022

Real-World Effectiveness of Lipid-Lowering Medications on Outcomes after Stroke: Potential Implications of the New-User Design

Muideen T. Olaiya[a] Nadine E. Andrew[a, b, f] Lachlan L. Dalli[a] David Ung[a, b] Joosup Kim[a, c] Dominique A. Cadilhac[a, c] Peter Wood[d] Janet May[e] Ben Clissold[a] Monique F. Kilkenny[a, c] on behalf of the PRECISE investigators

[a]Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [b]Peninsula Clinical School, Central Clinical School, Monash University, Frankston, VIC, Australia; [c]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Heidelberg, VIC, Australia; [d]Division of Medicine, Queensland Health, Brisbane, QLD, Australia; [e]Latrobe Regional Hospital, Traralgon West, VIC, Australia; [f]National Centre for Healthy Ageing, Frankston, VIC, Australia

Keywords
Stroke · Secondary prevention · Adherence · Mortality · Outcomes · Bias

Abstract

Introduction: Observational studies are increasingly being used to provide evidence on the real-world effectiveness of medications for preventing vascular diseases, such as stroke. We investigated whether the real-world effectiveness of treatment with lipid-lowering medications after ischemic stroke is affected by prevalent-user bias. ***Methods:*** An observational cohort study of 90-day survivors of ischemic stroke using person-level data from the Australian Stroke Clinical Registry (2012–2016; 45 hospitals) linked to administrative (pharmaceutical, hospital, death) records. The use of, and adherence to (proportion of days covered <80% [poor adherence] vs. ≥80% [good adherence]), lipid-lowering medications within 90 days post-discharge was determined from pharmaceutical records. Users were further classified as prevalent (continuing) or new users, based on dispensing within 90 days prior to stroke. A propensity score-adjusted Cox regression was used to evaluate the effectiveness of lipid-lowering medications on outcomes (all-cause mortality, all-cause and cardiovascular disease readmission) within the subsequent year. Analyses were undertaken using prevalent-user (all users vs. nonusers) and new-user designs (new users vs. nonusers). ***Results:*** Of 11,217 eligible patients (median age 72 years, 42% female), 9,294 (83%) used lipid-lowering medications within 90 days post-discharge, including 5,479 new users. In both prevalent-user and new-user designs, nonusers (vs. users) had significantly greater rates of mortality (hazard ratio [HR] 2.35, 95% CI: 1.89–2.92) or all-cause readmissions (HR 1.22, 95% CI: 1.05–1.40) but not cardiovascular disease readmission. In contrast, associations between having poor (vs. good) adherence on outcomes were stronger among new users than all users. Among new users, having poor adherence was associated with greater rates of mortality (HR 1.48, 95% CI: 1.12–1.96), all-cause readmission (HR 1.14, 95% CI: 1.02–1.27), and cardiovascular disease readmission (HR 1.20, 95% CI: 1.01–1.42). ***Conclusions:*** The real-world effectiveness of treatment with lipid-lowering medications after stroke is attenuated when evaluated based on prevalent-user rather than new-user design. These findings may have implications for designing studies on the real-world effectiveness of secondary prevention medications.

© 2022 The Author(s).
Published by S. Karger AG, Basel

Downloaded from karger.com/ned/article-pdf/56/5/365/3752590/000526071.pdf by Access through James Cook University Library user on 18 November 2026

Karger@karger.com
www.karger.com/ned

Karger
OPEN ACCESS

© 2022 The Author(s).
Published by S. Karger AG, Basel

This is an Open Access article licensed under the Creative Commons Attribution-NonCommercial-4.0 International License (CC BY-NC) (http://www.karger.com/Services/OpenAccessLicense), applicable to the online version of the article only. Usage and distribution for commercial purposes requires written permission.

Correspondence to:
Muideen T. Olaiya, muideen.olaiya@monash.edu

Introduction

Observational studies are increasingly being used to provide evidence on the real-world effectiveness of pharmacological interventions for preventing cardiovascular diseases or stroke [1]. These observational studies often involve comparisons between all users (prevalent/continuing and new users) and nonusers. However, this prevalent-user design may bias the estimation of treatment effects (benefits/harms), as prevalent users tend to tolerate the medication better than new users, and are therefore less susceptible to adverse outcomes [2, 3].

The new-user design is the preferred approach for investigating the effectiveness or safety of medications, especially when using secondary data sources, such as administrative data [3, 4]. This approach involves comparing treatment initiators with similar non-initiators, thereby eliminating the prevalent-user (selection) bias. Confounding at the time of treatment allocation is also minimized by adjusting for pretreatment characteristics [3].

Lipid-lowering agents are strongly recommended for secondary prevention among patients with ischemic stroke [5], based on evidence from clinical trials [6–8], complemented by real-world evidence from observational studies [9–11]. However, it is unclear if effect estimates from these real-world observational studies are affected by the prevalent-user bias. We investigated whether the real-world effectiveness of treatment with lipid-lowering medications after stroke is affected by the prevalent-user bias.

Methods

Study Design, Participants and Setting

This was an observational study of adult patients with a clinical diagnosis of ischemic stroke admitted to one of 45 hospitals that contributed data to the Australian Stroke Clinical Registry (AuSCR) [12] in the states of Victoria and Queensland between 2012 and 2016. Person-level data from the AuSCR were linked to administrative data, as part of the PRECISE project [13]. The present analysis was limited to AuSCR registrants who were aged ≥18 years, hospitalized for ischemic stroke (index event), had no documented stroke in the AuSCR before the index event, and had survived 90 days since hospital discharge after the index event (landmark period).

Data Sources and Linkage

Data were obtained and linked from the AuSCR, Pharmaceutical Benefits Schedule (PBS), Medicare Benefits Schedule (MBS), and Departments of Health of the states of Victoria and Queensland. Details of these programs and the type of data collected are reported in online supplementary Methods and Table I (for all online suppl. material, see www.karger.com/doi/10.1159/000526071).

Exposures

Patients were defined as "users" or "nonusers" based on whether they had at least one dispensing of a lipid-lowering medication during the landmark period (within 90 days of discharge) [14]. Users were further classified as prevalent (continuing) or new users based on whether they were dispensed lipid-lowering medications within 90 days prior to stroke [15, 16]. Dispensing records were obtained from the PBS dataset. Lipid-lowering medications were identified in the PBS dataset using the Anatomical Therapeutic Chemical classification codes (online suppl. Table II).

Adherence among users was calculated using the proportion of days covered (PDC) method [14]. This approach involved determining the proportion of days a patient is covered by, or had access to, medications (numerator) within the 90-day landmark period (denominator). The numerator was adjusted to account for presupply or early refills of the same medication. Patients were assumed to have been prescribed a dose of one tablet of lipid-lowering medications per day, consistent with standard prescribing recommendations [17] and literature [18]. Because of the dispersion of data on PDC and to ensure reliable comparison of findings with literature, adherence was categorized as poor (PDC <80%) or good (PDC ≥80%). Given the limited number of patients (<6) who were dispensed injectables, these medications were excluded.

Outcomes

Outcomes included mortality and hospital readmission in the subsequent year following the landmark period, i.e., 91–455 days post-discharge for ischemic stroke. Readmissions due to CVD were defined as emergency department presentations or inpatient admissions that had ICD-10-AM principal diagnosis codes of I00-I99. Stroke-related readmissions were not specifically investigated due to few cases being identified. To account for single events characterized by multiple admissions, and to prevent over-counting of events, consecutive hospital admissions occurring within a 24 h interval were merged and considered as a single event, whilst retaining the primary diagnosis of the first admission [19, 20]. To minimize bias in calculating rates of readmission due to differences between Australian states in hospital recording requirements for outpatient rehabilitation, chemotherapy, radiotherapy, or dialysis [20, 21], we excluded readmissions for these sessions/procedures.

Covariates

Covariates included patient characteristics, acute care following stroke, and community care within 90 days post-discharge, as described in online supplementary Methods.

Statistical Analysis

Characteristics of patients were summarized and compared using χ^2 tests, *t* test or Wilcoxon rank-sum test, where appropriate. For analyses of the association between the use of lipid-lowering medications and outcomes, nonusers were compared with the reference group of users. To minimize selection bias due to primary nonadherence, i.e., no dispensing of lipid-lowering medication during the landmark period, analyses of medication adherence were restricted to users only, where patients with poor adherence were compared with those with good adherence (reference group) [22].

Downloaded from karger.com/ned/article-pdf/56/5/365/3752590/000526071.pdf by Access through James Cook University Library user on 18 November 2026

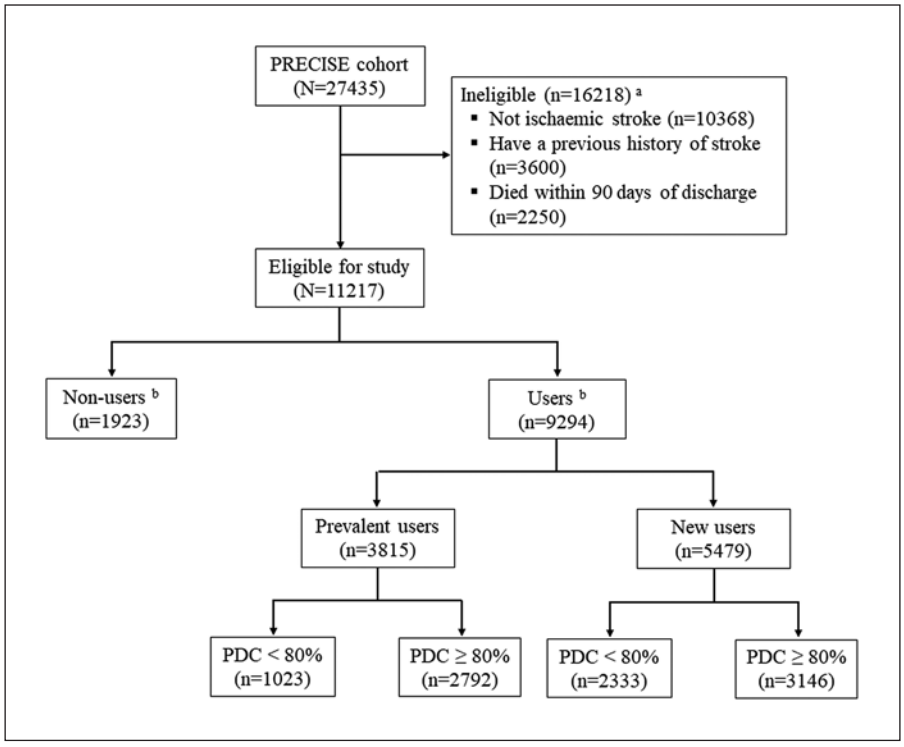

Fig. 1. Flow of participants. TIA, transient ischemic attack; PDC, proportion of days covered. [a]Patients may fulfill more than one exclusion criterion; [b]Use of lipid-lowering medications within 90 days of discharge for the index event.

To estimate cumulative rates of outcomes (per 1,000 person-years), patients were followed after the landmark period until the occurrence of an outcome or 365 days (up until June 2018), whichever occurred first. The landmark analysis ensured an unbiased estimation of time-to-event probabilities in the treatment groups conditional on the group membership of patients during the landmark period [23]. Cox proportional hazards regression were used to model outcomes. For analyses of readmissions, we accounted for multiple readmissions and within-subject correlation of failure times and excluded periods of hospitalization from the time at risk [24]. Potential interactions of covariates, e.g., age, sex, discharge destination, on outcomes were investigated by including the product terms in regression models.

To improve the balance of covariates (i.e., socio-demographics, use of other preventive medications, comorbidities, and acute and community-based care characteristics) between groups, Cox regression models were adjusted for propensity scores, generated using the stabilized inverse probability treatment weights approach [25, 26]. This approach was also used to minimize confounding by indication (e.g., some patients being preferentially prescribed lipid-lowering medication).The propensity score model comprised all covariates that were associated with use/adherence of medications or with outcomes. All analyses, including propensity score models and adjustments, were undertaken using both prevalent-user (comparing all users vs. nonusers) and new-user designs (new users vs. nonusers), in order to investigate the effects of the prevalent-user bias [27]. All analyses were performed using STATA/MP 15.0 for Windows (StataCorp, College Station, USA, 2017). A two-sided $p < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

The PRECISE cohort comprised 17,067 patients with ischemic stroke (median age 74.8 years, 44% female). Of these, 11,217 patients (66%) were eligible for this study (Fig. 1). The median age of patients was 71.9 years, 42% were female, and 83% were users of a lipid-lowering medication (Table 1). Among users, 5,938 (64%) had a good adherence within 90 days of hospital discharge (Table 1). Compared to nonusers, users were older, but less often female or residents of a regional area ($p < 0.05$). By contrast, users were more often dispensed antihypertensive medications within the 90 days prior to the index event, or received care concession benefits in the year prior to the index event (all $p < 0.001$). Users more often had a milder stroke (i.e., able to walk on admission) and fewer comorbidities than nonusers. However, compared to nonusers, users were more often treated in a stroke unit, discharged home, discharged with antihypertensives or with a care plan, treated with a primary care physician management plan, and had more frequent contact with the primary care physician (all $p < 0.05$; Table 1). Our propensity score adjustment, via inverse probability of treatment weighting, improved the balance of covariates between users and nonusers (online suppl. Fig. S1).

Downloaded from karger.com/ned/article-pdf/56/5/365/3752590/000526071.pdf by Access through James Cook University Library user on 18 November 2026

Table 1. Characteristics, acute and community-based care of patients with ischemic stroke by use and adherence to lipid-lowering medications

	Nonusers *N* = 1,923, *n* (%)	Users *N* = 9,294, *n* (%)	*p* value[a]	Level of adherence among users		
				<80% *N* = 3,356, *n* (%)	≥80% *N* = 5,938, *n* (%)	*p* value[b]
Patient characteristics						
Median (IQR) age in years	71.4 (57.1, 82.8)	71.9 (61.9, 80.2)	0.011	69.8 (58.6, 79.0)	72.9 (63.9, 80.8)	<0.001
Female	875 (45.5)	3,842 (41.3)	<0.001	1,347 (40.1)	2,495 (42.0)	0.077
Born in Australia[c]	1,360 (72.3)	6,282 (69.3)	0.011	2,238 (68.3)	4,044 (69.8)	0.135
Live in a regional Australia	653 (34.0)	2,894 (31.1)	0.016	1,055 (31.4)	1,839 (31.0)	0.641
Socioeconomic advantage						
Quintile 1 (least advantage)	411 (21.4)	1,800 (19.4)	0.156	636 (19.0)	1,164 (19.6)	0.645
Quintile 2	281 (14.6)	1,509 (16.2)		541 (16.1)	968 (16.3)	
Quintile 3	411 (21.4)	2,026 (21.8)		759 (22.6)	1,267 (21.4)	
Quintile 4	433 (22.5)	2,150 (23.1)		780 (23.2)	1,370 (23.1)	
Quintile 5 (most advantage)	386 (20.1)	1,803 (19.4)		639 (19.0)	1,164 (19.6)	
Medication use in 90 days prior to stroke						
Lipid-lowering	334 (17.4)	3,815 (41.0)	<0.001	1,023 (30.5)	2,792 (47.0)	<0.001
Antihypertensives	1,022 (53.1)	5,692 (61.2)	<0.001	1,808 (53.9)	3,884 (65.4)	<0.001
Antithrombotics	408 (21.2)	1,970 (21.2)	0.984	564 (16.8)	1,406 (23.7)	<0.001
Received care concession benefits in the year prior to stroke	1,146 (59.6)	6,034 (64.9)	<0.001	1,897 (56.5)	4,137 (69.7)	<0.001
Year admitted for stroke						
2012	168 (8.7)	761 (8.2)	<0.001	267 (8.0)	494 (8.3)	0.025
2013	393 (20.4)	1,505 (16.2)		571 (17.0)	934 (15.7)	
2014	418 (21.7)	2,080 (22.4)		798 (23.8)	1,282 (21.6)	
2015	415 (21.6)	2,211 (23.8)		774 (23.1)	1,437 (24.2)	
2016	529 (27.5)	2,737 (29.4)		946 (28.2)	1,791 (30.2)	
Unable to walk on admission	1,330 (69.2)	5,547 (59.7)	<0.001	2,211 (65.9)	3,336 (56.2)	<0.001
Comorbidities						
Hypertension	1,046 (54.4)	5,391 (58.0)	0.004	1,933 (57.6)	3,458 (58.2)	0.550
Dyslipidemia	80 (4.2)	643 (6.9)	<0.001	256 (7.6)	387 (6.5)	0.043
Atrial fibrillation	637 (33.1)	2,432 (26.2)	<0.001	842 (25.1)	1,590 (26.8)	0.075
Diabetes mellitus	417 (21.7)	2,460 (26.5)	<0.001	860 (25.6)	1,600 (26.9)	0.166
Smoking	960 (49.9)	5,198 (55.9)	<0.001	1,886 (56.2)	3,312 (55.8)	0.694
Obesity	54 (2.8)	254 (2.7)	0.854	113 (3.4)	141 (2.4)	0.005
Cardiovascular disease[d]	625 (32.5)	2,655 (28.6)	0.001	918 (27.4)	1,737 (29.3)	0.052
Cancer	175 (9.1)	704 (7.6)	0.023	223 (6.6)	481 (8.1)	0.011
Liver disease	71 (3.7)	161 (1.7)	<0.001	87 (2.6)	74 (1.2)	<0.001
Renal disease	239 (12.4)	989 (10.6)	0.022	347 (10.3)	642 (10.8)	0.478
Median (IQR) CCI score	2 (1, 3)	2 (0, 3)	<0.001	2 (1, 3)	2 (0, 3)	<0.001
Stroke occurred in hospital	126 (6.6)	343 (3.7)	0.027	140 (4.2)	203 (3.4)	<0.001
Acute care						
Managed in a stroke unit	1,596 (83.0)	8,001 (86.1)	<0.001	2,908 (86.7)	5,093 (85.8)	0.238
Discharge destination						
Home	718 (37.3)	4,776 (51.4)	<0.001	1,374 (40.9)	3,402 (57.3)	<0.001
Rehabilitation	51 (2.7)	111 (1.2)		28 (0.8)	83 (1.4)	
Residential aged care	684 (35.6)	3,096 (33.3)		1,418 (42.3)	1,678 (28.3)	
Other	470 (24.4)	1,311 (14.1)		536 (16.0)	775 (13.1)	
Prescribed antithrombotic agents at discharge	1,054 (54.8)	5,250 (56.5)	0.177	1,913 (57.0)	3,337 (56.2)	0.452
Prescribed antihypertensive agents at discharge	1,112 (57.8)	7,174 (77.2)	<0.001	2,465 (73.5)	4,709 (79.3)	<0.001
Community care at ≤90 days post-discharge						
Median (IQR) contacts with a primary care physician	3 (0, 6)	6 (3, 9)	<0.001	5 (3, 8)	6 (4, 9)	<0.001
Treated with a management plan	139 (7.2)	1,346 (14.5)	<0.001	445 (13.3)	901 (15.2)	0.012
Medications prescribed by specialist physician	[e]	944 (10.2)	[e]	314 (9.4)	630 (10.6)	<0.001

Data are summarized as frequencies and proportions except otherwise stated. IQR, interquartile range (25th percentile, 75th percentile); CCI, Charlson comorbidity index. [a] *p* value of the difference in the distribution of variables between users and nonusers of medications. [b] *p* value of the difference in the distribution of variables based on the level of adherence among medication users. [c] Data are missing for 270 patients (2.4%). [d] Excludes stroke and transient ischemic attack. [e] No dispensing among nonusers.

Downloaded from karger.com/ned/article-pdf/56/5/365/3752590/000526071.pdf by Access through James Cook University Library user on 18 November 2026

Table 2. Associations between use of lipid-lowering medications within 90 days of discharge for ischemic stroke and outcomes in the subsequent year based on the prevalent-user design

	Total	Events	Rate[a]	Unadjusted HR (95% CI)	PS-adjusted HR (95% CI)
All-cause mortality[b]					
Nonuser	1,923	247	139.6	2.11 (1.84, 2.42)	2.35 (1.89, 2.92)
User	9,294	506	56.2	Reference	Reference
PDC <80%	3,356	213	65.9	1.30 (1.14, 1.48)	1.30 (1.14, 1.49)
PDC ≥80%	5,938	293	50.7	Reference	Reference
All-cause readmission					
Nonuser	1,923	2,395	1,385.5	1.16 (1.09, 1.25)	1.22 (1.05, 1.40)
User	9,294	10,233	1,152.3	Reference	Reference
PDC <80%	3,356	3,761	1,182.0	1.02 (0.98, 1.06)	1.05 (0.98, 1.13)
PDC ≥80%	5,938	6,472	1,135.7	Reference	Reference
Readmission for CVD					
Nonuser	1,923	343	198.4	1.03 (0.89, 1.18)[c]	1.25 (0.78, 2.01)[c]
User	9,294	1,617	182.1	Reference	Reference
PDC <80%	3,356	589	185.1	1.02 (0.89, 1.16)	1.04 (0.91, 1.20)
PDC ≥80%	5,938	1,028	180.4	Reference	Reference

HR, hazard ratio; PS, propensity score; CI, confidence interval; CVD, cardiovascular disease including stroke. [a] Rates are expressed per 1,000 person-years. [b] Obtained from Cox proportional hazards regression models. [c] Estimates may be biased by small cell size.

Outcome Analyses Based on Prevalent-User Design (All Users vs. Nonusers)

There were 753 deaths during the 1-year follow-up period (unadjusted cumulative mortality rate 69.9 per 1,000 person-years), including 247 deaths among nonusers (139.6 per 1,000 person-years) and 506 among users (56.2 per 1,000 person-years; Table 2). Users with poor adherence had an overall greater mortality rate than users with good adherence (Table 2). A total of 12,628 all-cause readmissions were identified (cumulative rate 1,190.3 per 1,000 person-years), including 2,395 readmissions for nonusers (1,385.5 per 1,000 person-years) and 10,233 readmissions for users (1,152.3 per 1,000 person-years; Table 2). Similarly, rates of readmissions due to cardiovascular disease (Table 2) or other causes (online suppl. Table III) were greater among users than nonusers. There was no significant difference in rates of readmission between users with poor versus good adherence (Table 2).

In propensity score-adjusted models, compared to users, nonusers had significantly greater rates of mortality (hazard ratio [HR] 2.35, 95% confidence interval [CI] 1.89–2.92) and all-cause readmission (HR 1.22, 95% CI: 1.05–1.40; Table 2). Also, there was a greater, but nonsignificant, rate of readmissions for CVD among nonusers than users in adjusted models (HR 1.25, 95% CI: 0.78–2.01; Table 2). Among users, having poor adherence was associated with greater rates of mortality (HR 1.30, 95% CI: 1.14–1.49), but not readmission (Table 2). There were no significant interactions of use of, or adherence to, medications with covariates in the association with mortality or readmission.

Outcome Analyses Based on New-User Design (New Users vs. Nonusers)

For analyses between users and nonusers, outcomes did not differ between analyses based on the prevalent-user design (Table 3) and those based on the new-user design (Table 2). In contrast, for analyses of poor versus good adherence among users, the magnitude of the association between having poor adherence and outcomes was stronger in analyses based on the new-user design (Table 3). In adjusted models comprising only new users, those with poor adherence had significantly greater rates of mortality (HR 1.48, 95% CI: 1.12–1.96), all-cause readmission (HR 1.14, 95% CI: 1.02–1.27), and readmission for CVD (HR 1.20, 95% CI: 1.01–1.42) than those with a good adherence (Table 3).

Discussion

In this study, we provide data on the real-world effectiveness of treatment with lipid-lowering medications within the first 90 days of discharge after ischemic stroke

Downloaded from karger.com/ned/article-pdf/56/5/365/3752590/000526071.pdf by Access through James Cook University Library user on 18 November 2026

Table 3. Subgroup analysis of associations between use of lipid-lowering medications within 90 days of discharge for ischemic stroke on outcomes based on the new-user design

	Total	Events	Rate[a]	Unadjusted HR (95% CI)	PS-adjusted HR (95% CI)
All-cause mortality[b]					
Nonuser	1,923			3.12 (2.60, 3.73)	2.35 (1.82, 3.02)
New user	5,479	237	44.4	Reference	Reference
PDC <80%	2,333	125	55.3	1.52 (1.17, 1.97)	1.48 (1.12, 1.96)
PDC ≥80%	3,146	112	36.3	Reference	Reference
All-cause readmission					
Nonuser	1,923	2,395	1,385.5	1.38 (1.27, 1.50)	1.23 (1.19, 1.36)
New-user	5,479	5,296	1,002.5	Reference	Reference
PDC <80%	2,333	2,401	1,077.0	1.14 (1.02, 1.26)	1.14 (1.02, 1.27)
PDC ≥80%	3,146	2,895	948.1	Reference	Reference
Readmission for CVD					
Nonuser	1,923	343	198.4	1.28 (1.10, 1.50)	1.14 (0.97, 1.35)[c]
New user	5,479	813	153.9	Reference	Reference
PDC <80%	2,333	375	168.2	1.17 (1.00, 1.38)	1.20 (1.01, 1.42)
PDC ≥80%	3,146	438	143.4	Reference	Reference

HR, hazard ratio; PS, propensity score; CI, confidence interval; CVD, cardiovascular disease including stroke. [a] Rates are expressed per 1,000 person-years. [b] Obtained from Cox proportional hazards regression models. [c] Estimates may be biased by small cell size.

on health outcomes. Compared to users of lipid-lowering medications within the first 90 days of discharge, nonusers had significantly worse survival and greater rates of all-cause readmissions in the subsequent year in both the prevalent-user and new-user design. However, associations of poor adherence with worse survival and greater rates of CVD readmissions were attenuated in the prevalent-user design than the new-user design.

Our results align with those from prior studies on the effectiveness of use of, and adherence to, lipid-lowering medications following discharge after stroke [28, 29]. In a study of 935 young Finnish people (aged <50 years) with first-ever ischemic stroke (1994–2007), followed for a median period of 8 years, nonusers had a 2.6-fold greater rate of mortality, but similar rates of recurrent vascular events than statin users (defined as having ≥2 dispensing) [28]. Similar results were obtained in a study of 2,153 Koreans with acute ischemic stroke and atrial fibrillation [29]. Among 2,274 Taiwanese patients who were new users of statins after acute ischemic stroke or transient ischemic attack, good adherence (i.e., medication possession ratio >80%) over a 12-month period post-event, was associated with lower rates of recurrent nonfatal vascular events after 4.5 years of follow-up (HR = 1.26) [15]. Overall, our findings confirm and expand on these prior findings, broadening generalizability to a wider population of people with ischemic stroke, and providing evidence of more robust associations in a new-user design.

Current findings are different from those from a secondary prevention trial of long-term (median 5 years) treatment with high-dose statin after a recent stroke or transient ischemic attack (n = 4,731 patients) [30]. In that study, treatment with statins was not associated with all-cause mortality but was associated with lower rates of cardiovascular events (HR 0.74) after a median 5 years of follow-up. The difference between findings of this clinical trial and those from studies based on real-world data, including the present study, may be due to the difference in the characteristics of the study population. Given the strict selection criteria in the Swedish trial (i.e., limited to those with low disability and uncontrolled cholesterol levels), and the inclusion of those with hemorrhagic stroke, findings may not be directly comparable to those from studies with diverse eligible stroke cohorts.

Our study expands on earlier research by providing evidence on the greater effectiveness of lipid-lowering medications after stroke using the new-user design. Moreover, our study cohort was identified in the AuSCR through a clinician-assigned diagnosis rather than ICD-10-AM codes. The use of pharmaceutical claims data enabled us to capture dispensing of lipid-lowering and other secondary prevention medications beyond hospital discharge. Our propensity score adjustment approaches

Downloaded from karger.com/ned/article-pdf/56/5/365/3752590/000526071.pdf by Access through James Cook University Library user on 18 November 2026

improved the balance of covariates, thereby minimizing bias due to confounding by indication and enhancing the robustness of our risk estimates.

The main limitation of this study relates to the use of administrative data to indirectly measure adherence to medications. For example, we could not ascertain whether patients actually took the prescribed medications. We were also unable to ascertain whether patients were withheld, or discontinued, lipid-lowering medications for valid clinical reasons (e.g., due to contraindications or side-effects) or the adequacy of management of lipid levels. Similarly, although we adjusted for a large number of covariates, we cannot discount the possibility of unmeasured confounding, such as race/ethnicity. However, these biases would be minimized by our propensity score matching.

In conclusion, we provide real-world evidence on potential implications of not accounting for prevalent-user bias in analyses of the benefits of lipid-lowering medications for preventing adverse outcomes after ischemic stroke. Current findings provide support for the use of a new-user design for evaluating the effectiveness of medication use for secondary prevention after stroke.

Acknowledgments

We thank the PRECISE investigators and staff (N.E.A., M.F.K., J.K., D.A.C., Vijaya Sundararajan, Amanda Thrift, Leonid Churilov, Natasha Lannin, Mark Nelson, Velandai Srikanth, M.T.O., L.L.D., D.U., and Rebecca Barnden) for their advice throughout the development of the PRECISE project. We also acknowledge the staff from the units which undertook the data linkage for this project and each state data collection agency that provided access to these data, including the: Australian Stroke Clinical Registry (which provided the inception cohort for linkage); Victorian Government Department of Health (source of the Victorian Admitted Episodes Dataset (VAED) and Victorian Emergency Minimum Dataset (VEMD), and the Center for Victorian Data Linkage (for provision of Victorian data linkage); Queensland Department of Health, and the Australian Institute of Health and Welfare. Special thanks to the co-investigators and other contributors to the AuSCR, including the AuSCR Steering and Management Committee, site investigators at AuSCR-participating hospitals, and staff at the Florey Institute of Neuroscience and Mental Health, VIC.

Statement of Ethics

Hospitals participating in the registry are required to obtain site-specific ethics approval before commencing data collection. Patients are included in the registry based on an opt-out model of consent, whereby they are notified of their automatic inclusion and provided with the necessary information should they wish not to participate. Approvals for PRECISE and the present sub-study were obtained from Monash University (#12301 and #24748) and the Australian Institute of Health and Welfare Human Research Ethics Committees (EO2018/2/449). Approval for data access was also obtained from the AuSCR Research Task Group.

Conflict of Interest Statement

D.A.C. reports educational grants from Boehringer Ingelhiem, Shire, Ipsen, Amgen, and Medtronic paid to her institution; and is the Data Custodian for AuSCR. A.G.T. is a board member of the Stroke Foundation and prior member of the AuSCR Steering Committee. R.L. is a member of the AuSCR Steering Committee. N.A.L. is a member of the AuSCR Research Task Group. M.F.K. is a member of the AuSCR Management Committee. M.F.K. reports educational grant from Amgen. L.L.D. received compensation from GlaxoSmithKline for consultant services. All other authors report no potential conflicts of interest with respect to the research, authorship or publication of this article.

Funding Sources

The PRECISE project is funded through a National Health Medical Research Council project Grant (#1141848). Analyses and preparation specific to this manuscript was supported by a research grant from Amgen. The following authors receive Research Fellowship support from the NHMRC: A.G.T. (#1042600) and D.A.C. (#1154273). The following authors reported receiving Research Fellowship support from the Heart Foundation of Australia: N.A.L. (#102055) and M.F.K. (#105737). L.L.D. is supported by a Research Training Program scholarship from the Australian Government. Is supported by a Future Leader Fellowship (Award Reference No. 105737) from the National Heart Foundation of Australia. The study funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Author Contributions

M.T.O. conceptualized the study, undertook data analysis and prepared the first draft of the manuscript. N.E.A., J.K., D.A.C. and M.F.K. were responsible for data acquisition. N.E.A., L.L.D., D.U., J.K., D.A.C., P.W., J.M., B.C., and M.F.K. reviewed and edited the manuscript for intellectual content. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

Due to ethical and legal restrictions, patient-level data from this study cannot be shared. However, aggregated data and coding that support the findings of this study are available on reasonable request from the corresponding author.

Downloaded from karger.com/ned/article-pdf/56/5/365/3752590/000526071.pdf by Access through James Cook University Library user on 18 November 2026

References

1 Olaiya MT, Sodhi-Berry N, Dalli LL, Bam K, Thrift AG, Katzenellenbogen JM, et al. The allure of big data to improve stroke outcomes: review of current literature. Curr Neurol Neurosci Rep. 2022;22(3):151–60.
2 Danaei G, Tavakkoli M, Hernán MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. Am J Epidemiol. 2012;175(4):250–62.
3 Prada-Ramallal G, Takkouche B, Figueiras A. Bias in pharmacoepidemiologic studies using secondary health care databases: a scoping review. BMC Med Res Methodol. 2019;19(1):53.
4 Ahern TP. Pharmacoepidemiology in pharmacogenetics. In: Brøsen K, Damkier P, editors. Advances in Pharmacology. Cambridge, MA: Academic Press; 2018. Vol. 83; p. 109–130.
5 Stroke Foundation. Clinical guidelines for stroke management. Melbourne, VIC: Stroke Foundation; 2017.
6 Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549–59.
7 Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393(10170):407–15.
8 Cholesterol Treatment Trialists' (CTT) Collaborators; Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. J Vasc Surg. 2013;57:284.
9 O'Brien EC, Greiner MA, Xian Y, Fonarow GC, Olson DM, Schwamm LH, et al. Clinical effectiveness of statin therapy after ischemic stroke: primary results from the statin therapeutic area of the Patient-centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) study. Circulation. 2015;132(15):1404–13.
10 Asberg S, Henriksson KM, Farahmand B, Asplund K, Norrving B, Appelros P, et al. Ischemic stroke and secondary prevention in clinical practice: a cohort study of 14, 529 patients in the Swedish stroke register. Stroke. 2010;41(7):1338–42.
11 Kim J, Lee HS, Nam CM, Heo JH. Effects of statin intensity and adherence on the long-term prognosis after acute ischemic stroke. Stroke. 2017;48(10):2723–30.
12 Cadilhac DA, Lannin NA, Anderson CS, Levi CR, Faux S, Price C, et al. Protocol and pilot data for establishing the Australian stroke clinical registry. Int J Stroke. 2010;5(3):217–26.
13 Andrew NE, Kim J, Cadilhac DA, Sundararajan V, Thrift AG, Churilov L, et al. Protocol for evaluation of enhanced models of primary care in the management of stroke and other chronic disease (PRECISE): a data linkage healthcare evaluation study. Int J Popul Data Sci. 2019;4(1):1097.
14 Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. Ann Pharmacother. 2009;43(1):36–44.
15 Chen PS, Cheng CL, Kao Yang YH, Li YH. Statin adherence after ischemic stroke or transient ischemic attack is associated with clinical outcome. Circ J. 2016;80(3):731–7.
16 Luijken K, Spekreijse JJ, van Smeden M, Gardarsdottir H, Groenwold RHH. New-user and prevalent-user designs and the definition of study time origin in pharmacoepidemiology: a review of reporting practices. Pharmacoepidemiol Drug Saf. 2021;30(7):960–74.
17 Paquette M, Riou Franca L, Teutsch C, Diener HC, Lu S, Dubner SJ, et al. Persistence with dabigatran therapy at 2 years in patients with atrial fibrillation. J Am Coll Cardiol. 2017;70(13):1573–83.
18 Ung D, Dalli LL, Lopez D, Sanfilippo FM, Kim J, Andrew NE, et al. Assuming one dose per day yields a similar estimate of medication adherence in patients with stroke: an exploratory analysis using linked registry data. Br J Clin Pharmacol. 2021;87(3):1089–97.
19 Gattellari M, Goumas C, Aitken R, Worthington JM. Outcomes for patients with ischaemic stroke and atrial fibrillation: the PRISM study (A Program of Research Informing Stroke Management). Cerebrovasc Dis. 2011;32(4):370–82.
20 Andrew NE, Kilkenny MF, Sundararajan V, Kim J, Faux SG, Thrift AG, et al. Hospital presentations in long-term survivors of stroke: causes and associated factors in a linked data study. Stroke. 2020;51(12):3673–80.
21 Australian Institute of Health and Welfare. Variation in hospital admission policies and practices: Australian hospital statistics. Canberra: Australian Institute of Health and Welfare; 2017.
22 Li X, Cole SR, Westreich D, Brookhart MA. Primary non-adherence and the new-user design. Pharmacoepidemiol Drug Saf. 2018;27(4):361–4.
23 Dafni U. Landmark analysis at the 25-year landmark point. Circ Cardiovasc Qual Outcomes. 2011;4(3):363–71.
24 Westbury LD, Syddall HE, Simmonds SJ, Cooper C, Sayer AA. Identification of risk factors for hospital admission using multiple-failure survival models: a toolkit for researchers. BMC Med Res Methodol. 2016;16:46.
25 Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014;33(7):1242–58.
26 Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health. 2010;13(2):273–7.
27 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003;158(9):915–20.
28 van Dongen MME, Aarnio K, Martinez-Majander N, Pirinen J, Sinisalo J, Lehto M, et al. Use of statins after ischemic stroke in young adults and its association with long-term outcome. Stroke. 2019;50(12):3385–92.
29 Choi KH, Seo WK, Park MS, Kim JT, Chung JW, Bang OY, et al. Effect of statin therapy on outcomes of patients with acute ischemic stroke and atrial fibrillation. J Am Heart Assoc. 2019;8(24):e013941.
30 Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. 2009;8(5):453–63.

Downloaded from karger.com/ned/article-pdf/56/5/365/3752590/000526071.pdf by Access through James Cook University Library user on 18 November 2026