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# Risk Factors Associated with Major Adverse Cardiovascular Events after Ischemic Stroke: A Linked Registry Study

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**Keywords**
Stroke · Cardiovascular diseases · Epidemiology · Cardiovascular risk factors · Administrative data

**Abstract**

***Introduction:*** Survivors of stroke are at risk of experiencing subsequent major adverse cardiovascular events (MACE). We aimed to determine the incidence of, and risk factors for, MACE after first-ever ischemic stroke, by age group (18–64 years vs. ≥65 years). ***Methods:*** Observational cohort study using patient-level data from the Australian Stroke Clinical Registry (2009–2013), linked with hospital administrative data. We included adults with first-ever ischemic stroke who had no previous acute cardiovascular admissions and followed these patients for 2 years post-discharge, or until the first post-stroke MACE event. A Fine-Gray sub-distribution hazard model, accounting for the competing risk of non-cardiovascular death, was used to determine factors for incident post-stroke MACE. ***Results:*** Among 5,994 patients with a first-ever ischemic stroke (median age 73 years, 45% female), 17% were admitted for MACE within 2 years (129 events per 1,000 person-years). The median time to first post-stroke MACE was 117 days (89 days if aged <65 years vs. 126 days if aged ≥65 years; $p = 0.025$). Among patients aged 18–64 years, receiving intravenous thrombolysis (sub-distribution hazard ratio [SHR] 0.51 [95% CI, 0.28–0.92]) or being discharged to inpatient rehabilitation (SHR

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0.65 [95% CI, 0.46–0.92]) were associated with a reduced incidence of post-stroke MACE. In those aged ≥65 years, being unable to walk on admission (SHR 1.33 [95% CI 1.15–1.54]), and history of smoking (SHR 1.40 [95% CI 1.14–1.71]) or atrial fibrillation (SHR 1.31 [95% CI 1.14–1.51]) were associated with an increased incidence of post-stroke MACE. Acute management in a large hospital (>300 beds) for the initial stroke event was associated with reduced incidence of post-stroke MACE, irrespective of age group. ***Conclusions:*** MACE is common within 2 years of stroke, with most events occurring within the first year. We have identified important factors to consider when designing interventions to prevent MACE after stroke, particularly among those aged <65 years.



## Introduction

Globally, stroke and cardiovascular events are leading causes of mortality and morbidity [1]. Survivors of stroke are at an increased risk of developing new-onset cardiovascular events [2]. Many underlying risk factors and pathophysiology are similar in ischemic heart disease and stroke, with accumulating evidence of shared underlying inflammatory mechanisms mediated by the brain-heart axis [3].

In an observational study of people aged ≥65 years in Canada, incident ischemic stroke was associated with an increased risk of first-ever major adverse cardiovascular events (MACE) within 30 days [4]. However, it is unclear whether this finding was similar in younger survivors of stroke, in whom the incidence of stroke has steadily increased over the past decade [5–7]. In Australia, approximately 1 in 4 strokes occur in adults aged <65 years [8]. The increasing incidence of stroke in this age group may require more targeted interventions to prevent MACE and enable younger survivors of stroke to return to pre-stroke activities, such as employment. Therefore, reliable information concerning the incidence of MACE post-stroke is needed to develop interventions to optimize prevention. We aimed to determine the incidence of, and risk factors for, MACE after first-ever ischemic stroke, by age group (18–64 years vs. ≥65 years).

## Methods

*Study Design and Datasets*

An observational cohort study was conducted using person-level linked data from the Australian Stroke Clinical Registry (AuSCR), as part of the Stroke123 Project [9]. The AuSCR is a collaborative national effort to prospectively monitor acute stroke care and associated patient health outcomes [10]. All patients admitted to participating AuSCR hospitals, between 2009 and 2013, with a clinical diagnosis of stroke or transient ischemic attack (TIA) were included. Overall, 98% of these participants had their data linked with state-wide hospital administrative datasets (2004–2015) and the National Death Index [9]. The final dataset included 15,482 patients from 39 hospitals across 4 Australian states (Queensland, New South Wales, Victoria, and Western Australia).

*Participants*

For the present study, we included patients aged ≥18 years, admitted for an incident ischemic stroke (i.e., no prior stroke documented in the AuSCR), discharged alive, with complete information on age and sex. To enable examination of incident post-stroke MACE, patients with a prior MACE in the 5-year period before their index stroke event were excluded.

*Identification of Outcomes*

The outcome was incident post-stroke MACE identified in hospital administrative data in the 2-year period after first-ever stroke. MACE consisted of either non-fatal acute coronary syndrome (acute myocardial infarction or unstable angina), newly diagnosed heart failure, stroke, TIA, or cardiovascular death (codes provided in online suppl. Methods; for all online suppl. material, see https://doi.org/10.1159/000535872). A sensitivity analysis was also undertaken to confirm whether similar factors were associated with MACE in the first year post-stroke.

*Patient Factors*

Patient characteristics, clinical, and health system factors were obtained from the AuSCR. Ability to walk on admission for ischemic stroke was used as a proxy marker for stroke severity [11]. Socio-economic position was determined using the Index of Relative Socio-Economic Advantage and Disadvantage, based on residential postcodes recorded in the AuSCR [12].

*Clinical Processes of Care*

Clinical factors obtained from the AuSCR included acute processes of care and discharge destination (home, aged care, rehabilitation, and other hospital setting). Patient comorbidities were identified in hospital administrative data using diagnoses in the 5-year period before, and including, the initial stroke event [13]. The Charlson Comorbidity Index was derived to summarize multimorbidity [14, 15].

*Health System Factors*

System factors (e.g., number of beds and location of hospitals) were derived using de-identified hospital-level information provided by the AuSCR office.

*Statistical Analyses*

Patient, clinical, and system characteristics were compared between registrants with and without post-stroke MACE using $\chi^2$ tests (categorical variables) or Wilcoxon Rank-Sum tests (non-parametric continuous variables) within each age group (age <65 vs. ≥65 years). For the calculation of rates, follow-up commenced from the date of hospital discharge and ended at the first occurrence of the outcome (MACE) or a censoring

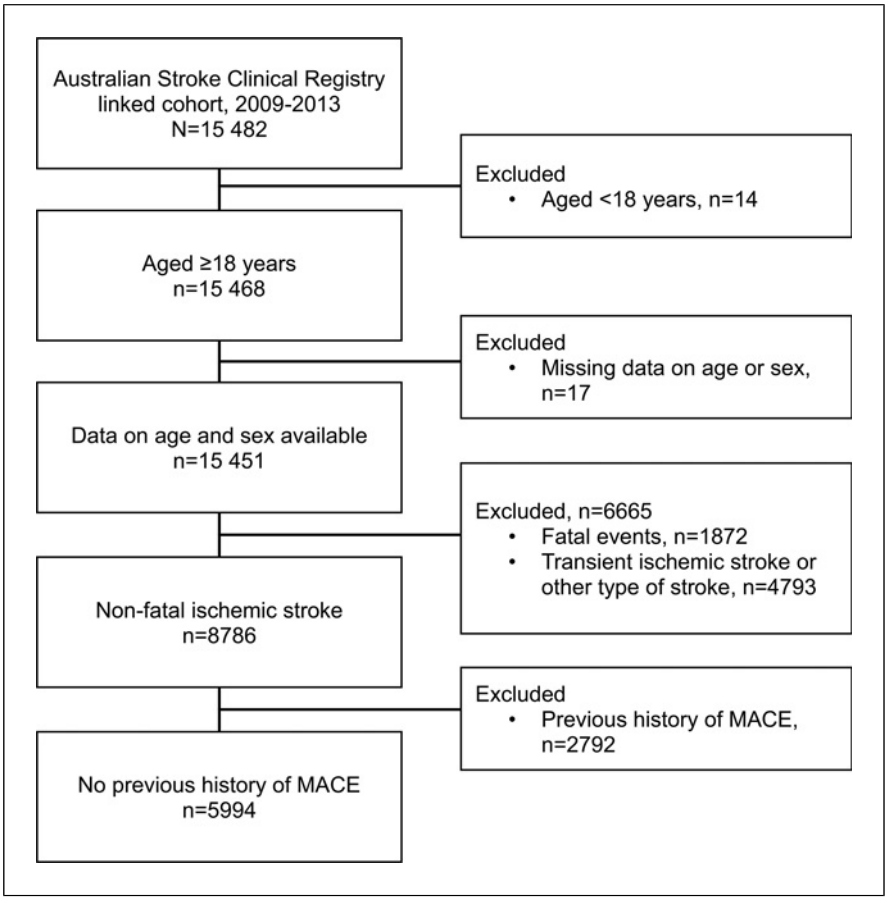


**Fig. 1.** Flow diagram outlining participant inclusion criteria.

event (non-cardiovascular death or end of follow-up at 2 years). Rates of post-stroke MACE were expressed per 1,000 person-years, with corresponding 95% confidence intervals (CIs).

The *stcrprep* package in Stata/SE 17.0 (StataCorp, TX, USA) was used to estimate cumulative incidence functions for incident post-stroke MACE, accounting for non-cardiovascular death as the competing risk [16]. This package was also used to build multivariable models of factors (patient, clinical, system) associated with post-stroke MACE, using the Fine-Gray method [17]. See online supplementary Methods for our variable selection process. Estimates were reported using sub-distribution hazard ratios (SHRs) with corresponding 95% CIs.

## Results

Of the 15,482 AuSCR registrants in the Stroke123 dataset, 5,994 (Fig. 1) were eligible for inclusion (44.8% female, median age of 73 years, 30.2% aged 18–64 years). Characteristics of participants by age (<65 vs. ≥65 years) are shown in Table 1.

Within 2 years following first-ever ischemic stroke, a MACE occurred in 1,011 (17%) participants, representing a rate of 129.3 events per 1,000 person-years. Most events occurred during the first year of follow-up, with the median time to first MACE being 117 days (interquartile range 27–336 days). One in two events were a recurrent stroke/TIA. In participants aged 18–64 years, the median time to incident post-stroke MACE was 37 days sooner compared with those aged ≥65 years (<65 years: 89 days vs. ≥65 years: 126 days; $p = 0.025$). After accounting for the competing risk of non-cardiovascular death, the cumulative incidence of MACE was approximately 20% within 2 years (online suppl. Fig. I).

In the first year post-stroke, incident MACE occurred at a rate 182.3 per 1,000 person-years (95% CI, 168.6–197.3) in those aged ≥65 years compared to 102.4 per 1,000 person-years in those aged 18–64 years (95% CI, 87.7–119.5; Table 2). This risk declined in the second year for both groups but remained greater in survivors of ischemic stroke aged ≥65 years (100.2 events per 1,000 person-years [95% CI, 86.8–115.7]) than in those aged 18–64 years (43.1 events per 1,000 person-years [95% CI, 31.9–58.4]). See online supplementary Tables I, II for unadjusted factors associated with post-stroke MACE.

**Table 1.** Cohort characteristics by age group

| | Overall (*N* = 5,994), *n* (%) | Age <65 years (*N* = 1,810), *n* (%) | Aged ≥65 years (*N* = 4,184), *n* (%) | *p* value |
|---|---|---|---|---|
| Female | 2,683 (44.8) | 626 (34.6) | 2,057 (49.2) | <0.001 |
| Median age, years (IQR) | 73.3 (62.5, 82.1) | 55.9 (47.1, 61.2) | 78.6 (72.2, 84.7) | <0.001 |
| Born in Australia | 3,884 (64.8) | 1,255 (69.3) | 2,629 (62.8) | <0.001 |
| Socio-economic position* | | | | |
| Most disadvantaged | 980 (16.3) | 309 (17.1) | 671 (16.0) | 0.021 |
| Second most disadvantaged | 1,039 (17.3) | 323 (17.8) | 716 (17.1) | |
| Third most disadvantaged | 1,032 (17.2) | 343 (19.0) | 689 (16.5) | |
| Fourth most disadvantaged | 1,160 (19.4) | 342 (18.9) | 818 (19.6) | |
| Least disadvantaged | 1,783 (29.7) | 493 (27.2) | 1,290 (30.8) | |
| Unable to walk on admission | 3,112 (51.9) | 786 (43.4) | 2,326 (55.6) | <0.001 |
| Arrived by ambulance | 3,481 (73.1) | 923 (63.7) | 2,558 (77.2) | <0.001 |
| Transferred from another hospital | 775 (13.0) | 363 (20.1) | 412 (9.9) | <0.001 |
| Provided intravenous thrombolysis | 711 (11.9) | 199 (11.0) | 512 (12.2) | 0.17 |
| Stroke unit care | 5,141 (85.8) | 1,551 (85.7) | 3,590 (85.8) | 0.91 |
| Discharged with antihypertensive agents | 4,146 (69.2) | 1,064 (58.8) | 3,082 (73.7) | <0.001 |
| Received a care plan at discharge if discharged into the community | 1,544 (49.7) | 546 (50.4) | 998 (49.4) | 0.59 |
| Comorbidities | | | | |
| Hypertension | 4,080 (68.1) | 946 (52.3) | 3,134 (74.9) | <0.001 |
| Dyslipidemia | 804 (13.4) | 240 (13.3) | 564 (13.5) | 0.82 |
| Atrial fibrillation | 1,652 (27.6) | 205 (11.3) | 1,447 (34.6) | <0.001 |
| Diabetes mellitus | 987 (16.5) | 243 (13.4) | 744 (17.8) | <0.001 |
| Angina | 660 (11) | 115 (6.4) | 545 (13.0) | <0.001 |
| Smoking | 1,342 (22.4) | 745 (41.2) | 597 (14.3) | <0.001 |
| Obesity | 230 (3.8) | 107 (5.9) | 123 (2.9) | <0.001 |
| Carotid stenosis | 336 (5.6) | 85 (4.7) | 251 (6.0) | 0.044 |
| Cancer | 604 (10.1) | 79 (4.4) | 525 (12.5) | <0.001 |
| Renal disease | 462 (7.7) | 73 (4.0) | 389 (9.3) | <0.001 |
| Chronic pulmonary disease | 333 (5.6) | 65 (3.6) | 268 (6.4) | <0.001 |
| Infection | 1,181 (19.7) | 236 (13.0) | 945 (22.6) | <0.001 |
| Charlson comorbidity index, median (IQR) | 0 (0, 1) | 0 (0, 1) | 0 (0, 2) | <0.001 |
| None (0) | 3,524 (58.8) | 1,308 (72.3) | 2,216 (53.0) | <0.001 |
| Low (1) | 974 (16.2) | 248 (13.7) | 726 (17.4) | |
| Medium (2) | 673 (11.2) | 114 (6.3) | 559 (13.4) | |
| High (3+) | 823 (13.7) | 140 (7.7) | 683 (16.3) | |
| Median length of stay (IQR), days | 6 (3, 10) | 5 (3, 9) | 6 (3, 11) | <0.001 |
| Discharge destination | | | | |
| Home | 2,808 (46.8) | 1,075 (59.4) | 1,733 (41.4) | <0.001 |
| Rehabilitation | 2,055 (34.3) | 497 (27.5) | 1,558 (37.2) | |
| Other | 1,131 (18.9) | 238 (13.1) | 893 (21.3) | |
| Hospital characteristics | | | | |
| Rural hospital | 1,046 (17.5) | 319 (17.6) | 727 (17.4) | 0.82 |
| Teaching hospital | 2,967 (49.5) | 883 (48.8) | 2,084 (49.8) | 0.47 |
| Large hospital (>300 beds) | 4,892 (81.6) | 1,495 (82.6) | 3,397 (81.2) | 0.20 |
| High-volume hospital (350+ annual episodes) | 2,536 (42.3) | 717 (39.6) | 1,819 (43.5) | 0.005 |

IQR, interquartile range; LOS, length of stay. *Measured by Index of Relative Socio-Economic Advantage and Disadvantage.

In the multivariable models, there were multiple factors associated with MACE post-stroke within 2 years (Table 3). Based on the Charlson Comorbidity Index, the risk of post-stroke MACE was greater in patients with a high comorbidity burden than in those with no comorbidity burden. The magnitude of this effect was

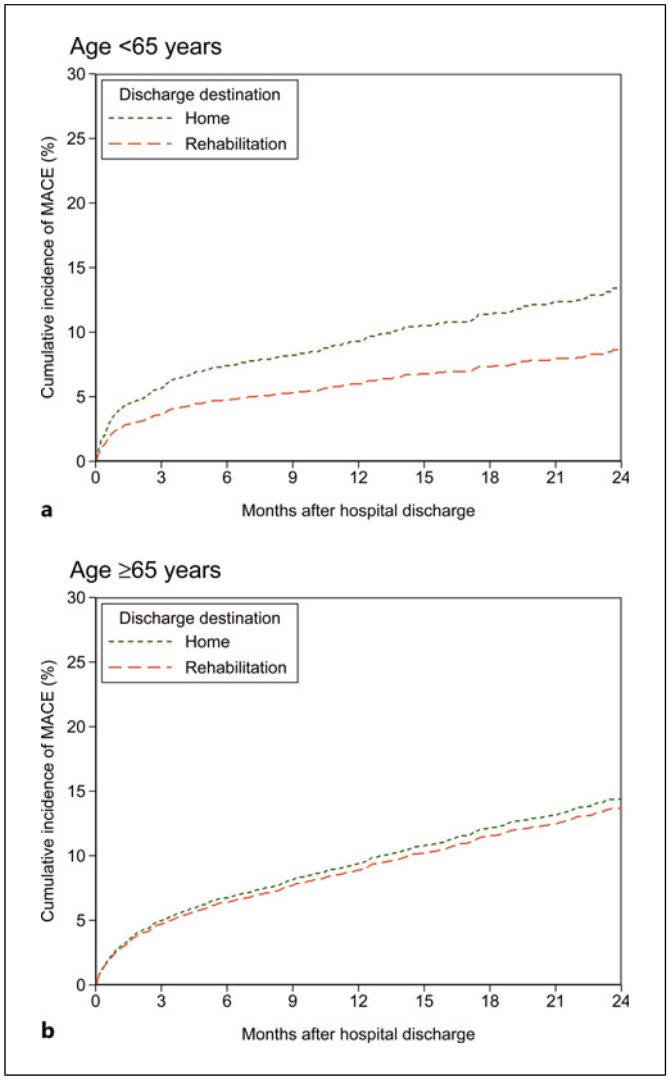


**Fig. 2.** Effect of discharge destination on the cumulative hazard of major adverse cardiovascular events after ischemic stroke by age group. MACE indicates major adverse cardiovascular event.

greater for patients aged 18–64 years (SHR 2.29 [95% CI, 1.56–3.38]) than those aged ≥65 years (SHR 1.48 [95% CI, 1.22–1.78]).

Among patients aged ≥65 years, the incidence of post-stroke MACE was greater in those who experienced a more severe stroke (SHR 1.33 [95% CI, 1.15–1.54]). Having a history of atrial fibrillation (SHR 1.31 [95% CI, 1.14–1.51]) or smoking (SHR 1.40 [95% CI, 1.14–1.71]) was also associated with post-stroke MACE in those aged ≥65 years. An association with age was also observed, whereby each 1-year increase in age was associated with a 4% increased risk of MACE following ischemic stroke ($p < 0.001$).

Patients hospitalized in large facilities (>300 beds) for their initial presentation had a reduced incidence of post-stroke MACE within 2 years in both age groups (18–64 years: SHR 0.69 [95% CI, 0.49–0.96]; ≥65 years: SHR 0.74 [95% CI, 0.62–0.87]). In those aged ≥65 years, being discharged to a destination other than home or rehabilitation was associated with an increased incidence of post-stroke MACE (SHR 1.69 [95% CI, 1.41–2.01]). Whereas, discharge to rehabilitation was associated with reduced post-stroke MACE risk in those aged 18–64 years (SHR 0.65 [95% CI, 0.46–0.92]). This association was attenuated in the cohort aged ≥65 years (SHR 0.93 [95% CI, 0.78–1.11]; Fig. 2). Interestingly, an association was observed specifically in those aged <65 years, whereby provision of intravenous thrombolysis was associated with a reduced risk of post-stroke MACE (SHR 0.51 [95% CI, 0.28–0.92]). There were minimal changes to the multivariable models predicting MACE when follow-up was limited to the first year post-stroke (online suppl. Table III).

## Discussion

In this multicenter, multi-jurisdictional, hospital-based registry study, we provide new evidence on the risk of MACE within 2 years following first-ever ischemic stroke. Of concern, 17% of patients experienced a MACE within 2 years, reinforcing the importance of risk-mitigating strategies in this high-risk population. We further identified disparities in the pattern and magnitude of MACE post-stroke, related to specific patient, clinical, and system-level factors. Increased understanding of these factors is important for optimizing clinical management to reduce the overall burden of preventable cardiovascular diseases.

Similar to an earlier study undertaken in Canada among survivors of stroke aged >65 years, we found increased age and comorbidity burden were associated with increased incident MACE after ischemic stroke [4]. Our study provides additional data to understand this risk beyond 90 days post-stroke and presents novel data for younger survivors of ischemic stroke (aged 18–64 years). This information is important to support the implementation of risk-mitigation strategies in the working-age population. We also identified unique system factors which appeared to reduce the risk of MACE, such as being treated in a large hospital for the initial stroke presentation. This finding may have been attributable to increased resources and specialized staff

**Table 2.** Incidence rates of each individual component of the composite MACE outcome overall and by age group

| Outcome | Overall ($N$ = 5,994) | | Aged <65 years ($N$ = 1,810) | | Aged ≥65 years ($N$ = 4,184) | |
|---|---|---|---|---|---|---|
| | events | rate (95% CI)* | events | rate (95% CI)* | events | rate (95% CI)* |
| MACE | | | | | | |
| Within 12 months | 782 | 157.1 (146.5–168.5) | 161 | 102.4 (87.7–119.5) | 621 | 182.3 (168.6–197.3) |
| Between 13 and 24 months | 229 | 80.6 (70.8–91.8) | 42 | 43.1 (31.9–58.4) | 187 | 100.2 (86.8–115.7) |
| Acute coronary syndrome | | | | | | |
| Within 12 months | 48 | 8.0 (6.1–10.7) | 13 | 7.2 (4.2–12.4) | 35 | 8.4 (6.0–11.7) |
| Between 13 and 24 months | 26 | 4.4 (3.0–6.4) | 7 | 3.9 (1.9–8.2) | 19 | 4.6 (2.9–7.2) |
| Incident heart failure | | | | | | |
| Within 12 months | 66 | 11.1 (8.7–14.1) | 7 | 3.9 (1.8–8.1) | 59 | 14.2 (11.0–18.3) |
| Between 13 and 24 months | 42 | 7.1 (5.3–9.6) | <5 | 2.2 (0.8–5.9) | 38 | 9.3 (6.7–12.7) |
| Recurrent ischemic stroke or TIA | | | | | | |
| Within 12 months | 383 | 66.9 (60.6–74.0) | 123 | 71.9 (60.3–85.8) | 260 | 64.8 (57.4–73.2) |
| Between 13 and 24 months | 122 | 22.0 (18.4–26.3) | 31 | 18.6 (13.1–26.4) | 91 | 23.5 (19.1–28.8) |
| Mortality due to cardiovascular disease | | | | | | |
| Within 12 months | 338 | 59.0 (53.0–65.6) | 21 | 11.7 (7.6–17.9) | 317 | 80.5 (72.1–89.9) |
| Between 13 and 24 months | 118 | 21.0 (17.6–25.2) | 6 | 3.4 (1.5–7.5) | 112 | 29.3 (24.3–35.2) |

CI, confidence interval; MACE, major adverse cardiovascular event; TIA, transient ischemic attack. *Crude rate, per 1,000 person-years, of the first occurrence of the relevant MACE outcome.

**Table 3.** Multivariable backward stepwise competing risk regression of factors associated with the incidence of MACE up to 2 years after stroke by age group

| | Working age (<65 years), $N$ = 1,810 | | Non-working age (≥65 years), $N$ = 4,184 | |
|---|---|---|---|---|
| | SHR (95% CI) | $p$ value | SHR (95% CI) | $p$ value |
| Age, per 1-year increase | 0.99 (0.98–1.01) | 0.28 | 1.04 (1.03–1.05) | <0.001 |
| Female | 0.82 (0.60–1.11) | 0.19 | 1.12 (0.97–1.29) | 0.12 |
| Severe stroke (unable to walk on admission) | 1.33 (0.99–1.79) | 0.06 | 1.33 (1.15–1.54) | <0.001 |
| Provided intravenous thrombolysis | 0.51 (0.28–0.92) | 0.026 | – | – |
| Smoking | – | – | 1.40 (1.14–1.71) | 0.001 |
| Atrial fibrillation | – | – | 1.31 (1.14–1.51) | <0.001 |
| Charlson comorbidity index | | | | |
| None (0) | Ref | | Ref | |
| Low (1) | 1.42 (0.97–2.07) | 0.07 | 1.19 (0.98–1.45) | 0.08 |
| Medium (2) | 0.53 (0.23–1.22) | 0.14 | 1.41 (1.15–1.73) | 0.001 |
| High (3+) | 2.29 (1.56–3.38) | <0.001 | 1.48 (1.22–1.78) | <0.001 |
| Large hospital (>300 beds) | 0.69 (0.49–0.96) | 0.029 | 0.74 (0.62–0.87) | <0.001 |
| Discharge destination | | | | |
| Home | Ref | | Ref | |
| Rehab | 0.65 (0.46–0.92) | 0.015 | 0.93 (0.78–1.11) | 0.42 |
| Other | 0.77 (0.51–1.18) | 0.23 | 1.69 (1.41–2.01) | <0.001 |

CI, confidence interval; SHR, sub-distribution hazard ratio. Dashes (–) used to denote non-significant factors (i.e., $p > 0.05$), which were omitted from the final model.

present at large hospitals to enable the provision of more comprehensive services to support secondary prevention.

Consistent with prior research [18], smoking was associated with an increased risk of MACE within 2 years post-stroke. However, this risk was only significant in

people aged ≥65 years. Potentially, older patients had a greater duration of cumulative damage caused by tobacco which elevated the risk of MACE [19]. It is also important to acknowledge that the prevalence of smoking was significantly lower in people aged 18–64 years (14% vs. 41%; $p < 0.001$), which may have reduced the statistical power to detect a difference in this age group. The greater rate of MACE observed for survivors of ischemic stroke aged ≥65 years (vs. 18–64 years) might also be explained by their increased comorbidity burden, decreased access to post-stroke rehabilitation, and greater stroke severity. Although the risk of incident post-stroke MACE was lower in those aged 18–64 years (vs. ≥65 years), MACE tended to occur earlier post-stroke. This finding might reflect gaps in post-stroke care for younger survivors of stroke, for example, gaps in commencement of stroke secondary prevention medications [20].

People aged <65 years who were discharged to inpatient rehabilitation after first-ever stroke had a reduced 2-year risk of incident MACE. This finding is likely explained by the additional time these patients spent in a healthcare setting, which likely provided additional opportunities for risk factor assessment and optimization of secondary prevention [21]. In the USA, implementation of a modified cardiac rehabilitation for stroke led to improved overall function, improved cardiovascular performance, and decreased all-cause mortality [22]. There is strong international evidence that rehabilitation after stroke is cost-effective, improves long-term recovery, and maximizes health outcomes [23]. Despite this evidence, fewer than half of all Australians access this service post-stroke [24], which often relates to limited availability of publicly funded beds in rehabilitation hospitals, especially in rural and remote regions [25]. It might be beneficial to increase the availability of stroke rehabilitation services in Australia, especially for people of working age who appear to benefit most in terms of MACE prevention.

Other types of post-discharge support programs to improve secondary prevention knowledge and behaviors may also be effective for managing cardiovascular risk after stroke. In the USA, the STROKE-CARD trial was shown to significantly reduce cardiovascular risk following stroke [21]. This program involved systematic screening for post-stroke complications, managing warning signs of imminent cardiovascular events, and providing education to enhance patient-empowerment and knowledge of cardiovascular risk. Other eHealth-enabled trials to improve the delivery of goal-orientated information after stroke may also be effective for reducing cardiovascular events. The ongoing ReCAPS trial [26], involving the delivery of personalized messages for 12 weeks post-stroke, may also help to improve attainment of secondary prevention goals and reduce cardiovascular readmissions.

A strength of this study was the inclusion of a large, comprehensive cohort of patients with stroke from a national registry with linked hospital administrative data from 4 Australian jurisdictions. This enabled analysis of important comorbidities from presentations in the 5-year period preceding the stroke event. However, comorbidities may have been missed if they were inadequately coded or not documented in the medical record. Another strength of the study was the use of registry data to examine a wider range of acute care factors than what is routinely collected in hospital administrative data.

Given the observational study design and the use of retrospectively linked administrative data, there were important factors (e.g., medication use) omitted in our predictive models. We inferred stroke severity from a patient's inability to walk on admission (a validated proxy measure [11]), but acknowledge this measure may be influenced by pre-existing conditions and pre-stroke functional status. Consequently, we cannot discount the possibility of unmeasured confounding. Recent changes in clinical guidelines in Australia, including the availability of mechanical thrombectomy and telerehabilitation, may also limit the generalizability of our findings. We must also acknowledge that participation of hospitals in the AuSCR is voluntary and covered ≈40% of public hospitals during the study period [27]. Consequently, our sample may under-represent episodes from smaller or regional hospitals. Notwithstanding these potential limitations, our results are novel since this is the first time reliable data on the risk of MACE after incident stroke have been described in Australia, including among working-age adults in whom the risk of stroke is increasing.

## Conclusion

In summary, we provide evidence on the risk of MACE after stroke, and describe patient, system, and clinical risk factors associated with these serious events. Increased availability and usage of rehabilitation units for survivors of stroke, particularly those of working age, may represent an important opportunity to reduce the burden of MACE after stroke. Hence, our results open the possibility for further understanding of risk factors to guide comprehensive secondary prevention and continuity of care over the life course following ischemic stroke.

## Acknowledgments

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## 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. Specific approvals for the Stroke123 project were received from data custodians, the Monash University Human Research Ethics Committee (CF13/1303–2013000641), and ethics committees in New South Wales, Western Australia, and Queensland.

## Conflict of Interest Statement

D.A.C. is the current data custodian for the Australian Stroke Clinical Registry (AuSCR). D.A.C., M.F.K., and R.G. are members of the AuSCR Steering or Management Committees. N.E.A. is a member of the AuSCR Research Task Group. N.E.A. and M.F.K. are members of the Research Advisory Committee of the Stroke Foundation. D.A.C. reports receiving educational grants from Amgen Australia, Boehringer Ingelheim, Medtronic, and Bristol Myers Squibb outside the submitted work. M.F.K. reports receiving educational grants from Amgen Australia and GSK outside the submitted work. L.L.D. reports receiving an educational grant from GSK outside of the submitted work. All other authors report no conflicts.

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## Author Contributions

A.S.D., L.L.D., M.T.O., L.K., and M.F.K. conceptualized the study. L.L.D. undertook the data analysis. A.S.D. prepared the first draft of the manuscript. N.E.A., J.K., D.A.C., and M.F.K. were responsible for data acquisition. L.N. provided input into the data analysis. All authors reviewed and edited the manuscript for scientific content and approved the final version.

## Data Availability Statement

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

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