

# Outcomes for Patients With In-Hospital Stroke: A Multicenter Study From the Australian Stroke Clinical Registry (AuSCR)

Dominique A. Cadilhac, PhD,\*†<sup>1</sup> Monique F. Kilkenny, PhD,\*†<sup>1</sup>  
Natasha A. Lannin, PhD,‡§ Helen M. Dewey, PhD,|| Christopher R. Levi, MBBS,¶  
Kelvin Hill, BAAppSc,\*\* Brenda Grabsch, BSW,† Rohan Grimley, MBBS,\*††  
David Blacker, MBBS,‡‡ Amanda G. Thrift, PhD,\* Sandy Middleton, PhD,§§  
Craig S. Anderson, PhD,|||¶¶ and Geoffrey A. Donnan, MD†,  
On behalf of the Australian Stroke Clinical Registry Consortium

**Background:** The quality of care and outcomes for people who experience stroke whilst in hospital for another condition has not been previously studied in Australia. **Aims:** To explore differences in long-term outcomes among patients with in-hospital events treated in stroke units (SUs) compared to those managed in other hospital wards. **Methods:** Forty-five hospitals participating in the Australian Stroke Clinical Registry between January 2010 and December 2014 contributed data. Survival of all patients with in-hospital stroke to 180 days after stroke and health-related quality of life, using EQ-5D-3L among 73% eligible, were compared using multilevel, multivariable regression models. Models were adjusted for age, sex, index of relative socioeconomic disadvantage, ability to walk, stroke type, transfer from another hospital, and history of stroke. **Results:** Among 20,786 stroke events, 1182 (5.1%) occurred in-hospital (median age 77 years, 49% male). Patients with in-hospital stroke treated in SUs died less often within 30 days (Hazard Ratio 0.56; 95% CI 0.39-0.81) than those not admitted to SUs. Survivors reported similar health-related quality of life between 90 and 180 days compared to those treated in other wards (coefficient = 0.01, 95% CI -0.06-0.09,  $P = .78$ ). Patients managed in SUs more often received recommended management (e.g. swallowing screening). **Conclusion:** The benefits of SU care may extend to patients experiencing in-hospital stroke. Validation, including accounting for potential residual confounding factors, is required.

**Key Words:** Stroke—stroke unit—stroke management—hospitals—outcome  
© 2019 Elsevier Inc. All rights reserved.

From the \*Stroke and Ageing Research, Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Australia; †Stroke Division, the Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg, Victoria, Australia; ‡School of Allied Health (Occupational Therapy), La Trobe University, Heidelberg, Australia; §Occupational Therapy Department, Alfred Health, Prahran, Australia; ||Eastern Health Clinical School, Faculty of Medicine, Nursing and Health Science, Monash University, Box Hill, Australia; ¶Hunter Medical Research Institute, Newcastle, Australia; \*\*Stroke Foundation, Melbourne, Australia; ††Sunshine Coast Clinical School, The University of Queensland, Birtinya, Australia; ‡‡Sir Charles Gairdner Hospital, Perth, Australia; §§Nursing Research Institute, St Vincent's Health Australia (Sydney) and Australian Catholic University, Sydney, Australia; |||George Institute for Global Health, University of Sydney, Sydney, Australia; and ¶¶Neurology Department, Royal Prince Alfred Hospital, Sydney, Australia.

Received May 5, 2018; revision received January 24, 2019; accepted January 25, 2019.

**Grant support:** The following authors received fellowship grants from the National Health and Medical Research Council (NHMRC): DAC (1063761 co-funded Heart Foundation), CRL (1043913), MFK (1109426), AGT (1042600), and CSA (1081356). AuSCR was supported by grants from the NHMRC (1034415), Monash University, Queensland Health, Stroke Foundation, Allergan, Ipsen, and Boehringer Ingelheim.

Address correspondence to Dominique Cadilhac, PhD, School of Clinical Sciences at Monash Health, Monash University, Level 3 Hudson Institute Building, 27-31 Wright Street Clayton VIC 3168, Clayton, Australia. E-mail: [dominique.cadilhac@monash.edu](mailto:dominique.cadilhac@monash.edu).

<sup>1</sup>Contributed equally to this work.

1052-3057/\$ - see front matter

© 2019 Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.01.026>

## Introduction

Given the high prevalence of cardiovascular risk factors among hospitalized patients, stroke can occur in a broad range of patients while they are in hospital receiving management for another condition including major surgery.<sup>1</sup> Stroke unit (SU) care, that includes co-located patients within a hospital receiving specialized, interdisciplinary management can significantly reduce death and disability.<sup>2</sup> Therefore, all patients with stroke should be treated in SUs irrespective of age, stroke severity or type.<sup>3</sup> Approximately, 4%-15% of patients experience a stroke while in hospital for another condition (commonly termed "in-hospital" stroke).<sup>4-6</sup> Compared with patients presenting from the community, patients with in-hospital ischemic strokes have worse outcomes and receive less evidence-based care,<sup>7</sup> with very few treated in SUs.<sup>8</sup> There may be several justifiable reasons why patients with in-hospital stroke are not managed in SUs. However, once their primary condition has stabilized, management in the SU to support rehabilitation from the effects of stroke is important for reducing disability,<sup>7</sup> as well as ensuring commencement of secondary prevention therapies.

To our knowledge, evidence on the long-term outcome of patients with in-hospital stroke is lacking. We aimed to explore whether patients with in-hospital events had better survival and health-related quality of life (HR-QoL) within 180 days if managed in an SU, compared to other wards, and to describe any potential explanatory factors for the associations observed.

## Methods

This was an observational study using data from the Australian Stroke Clinical Registry (AuSCR) obtained from 2010-2014. The AuSCR design has been detailed previously. In brief, the AuSCR is a voluntary, clinical quality registry used in Australian hospitals to capture data on consecutive patients admitted with stroke or transient ischemic attack or events that occur in hospital.<sup>9</sup> The AuSCR commenced in 2009 and was initially funded via research and educational grants, but is now mainly supported by state government grants (since 2012). The majority of hospitals that contribute data to AuSCR are public and located in the eastern (most densely populated) states.<sup>10</sup> Cases are entered prospectively in the AuSCR based on clinical diagnosis of stroke during the admission. Case ascertainment is checked annually using *International Classification of Diseases (ICD)-10* discharge codes obtained from the hospital administrative system and compared to the cases entered in the registry at each hospital (see Supplemental methods).

We included all episodes of ischemic, intracerebral hemorrhage (ICH), and undetermined stroke for the analyses. Transient ischemic attack was excluded. The AuSCR includes a minimum dataset of personal information (e.g. name, address), clinical data, process of care

indicators, and outcomes (see below).<sup>9</sup> Among individuals with multiple episodes of care registered within 90-180 days of an index event, only the first episode was followed up. Annual linkage of AuSCR data to the National Death Index ensures survival status is known for all registrants.

### *Patient Characteristics*

Patient characteristics included age, sex, country of birth, and language spoken at home. The variable "able to walk unaided" is used for assessing stroke severity in AuSCR. It is a global measure of disability that is normally assessed at the time of hospital admission. However, for patients who experience their stroke when already in hospital, this is assessed within the first 24 hours of this event. This simple measure has been validated by Counsell and colleagues (relative risk for 30-day survival 1.63 95% CI 1.15-2.31)<sup>11</sup>; and we have found this variable to be a reliable predictor of independence at time of hospital discharge and for survival.<sup>12,13</sup> Place of residence was used to derive the "index of relative socio-economic advantage and disadvantage" (IRSAD) score for each patient. The scores were divided into quintiles, with quintile 1 representing the most disadvantaged patients. Clinician classification of stroke type (ischemic, ICH, undetermined, as well as whether the event occurred in hospital) and the ICD-10 discharge codes are both collected in AuSCR.<sup>9</sup> For our analyses, if the clinical stroke type was recorded as undetermined it was recoded to ischemic or ICH if the discharge ICD-10 code was not I64. Discharge ICD-10 codes were also used to explore the principle reason for hospital admission among patients experiencing in-hospital stroke, and were also used to develop the Charlson Comorbidity Index<sup>14</sup> for patients where we had information from administrative hospital records.

### *Process of Care Indicators*

All patients with stroke should receive important processes of care for which they are eligible. In AuSCR, four nationally agreed processes of care are collected: admitted to an SU; received intravenous thrombolysis (for ischemic stroke); discharged on an antihypertensive agent; and received a discharge care plan.<sup>9</sup> For a subset of patients from the state of Queensland, four additional processes have been collected since 2012 and are also reported here: time to first mobilization, dysphagia screen, aspirin within 48 hours and being discharged on antiplatelets or antithrombotics if an ischemic event.

### *Outcome Assessment*

We report in-hospital deaths within 7-days, 30-days, 90-days, and 180-days, discharge to home, and length of stay. For the subset of eligible patients who were

followed-up (i.e. within 180 days of admission, first-registered event),<sup>15</sup> HR-QoL was measured using the EuroQol (EQ-5D-3L) questionnaire,<sup>16</sup> and readmissions, recurrent strokes, and the modified Rankin Score (from July 2014) at follow-up were also obtained via self-report. Individual responses for the EQ5D were converted into a utility score using the method reported by Viney and colleagues.<sup>17</sup> This approach was used since it is more responsive for survivors of stroke than using the EQ5D Visual Analogue Scale score, and incorporates deaths and health states considered worse than death (e.g. utility score below zero) as part of the summary measure.<sup>18</sup>

### Statistical Analysis

For patient demographic variables, such as age, sex, and country of birth we only used valid data. Consistent with standard quality of care monitoring practice, when data were missing for process of care indicators we assumed the response was negative to avoid overestimation. Descriptive analyses were used to initially compare the characteristics of patients by the subgroups of interest. Pearson  $\chi^2$  tests were used for categorical variables, and the Kruskal Wallis test was used for the continuous variables.

Models were adjusted for age, sex, IRSAD, ability to walk, type of stroke, transfer from another hospital and documented history of stroke. We included cases transferred as an independent variable since this group differed from nontransferred patients: they were more often male, younger, experienced more severe strokes and intracerebral hemorrhages, and were more common in the in-hospital stroke group (14% versus 4% if not transferred). Regression models were used to investigate differences in outcomes based on whether or not patients with in-hospital stroke received management in an SU.

The primary analysis was run on patients with complete (nonimputed) data. Sensitivity analyses were undertaken using a dataset whereby some variables with >1% missing and unknown responses were recoded as “no” for documented history of previous stroke, or “yes” for “able to walk.” In further sensitivity analyses we also included the Charlson Comorbidity Index in our models. Cox proportional hazards regression analysis was used to calculate differences in the risk of mortality within and up to 7, 30, 90, and 180 days. The analyses using the 30, 90, and 180 day time points excluded those who had died at the previous time point (for example, 30-day analysis excluded deaths at 7 days, and 90 day analysis excluded deaths at 30 days). Differences between HR-QoL utility scores were assessed using median regression to account for the J-shape distribution. In each model, level or cluster was defined as hospital to account for potential residual confounding. All *P* values were two-sided with *P* < .05 considered significant for all analyses. Goodness-of-fit tests including the Pearson Correlation  $\chi^2$  were

undertaken for all our logistic regression models. Where relevant, we have reported pseudo R2 for each model to provide an indication of the potential importance of variables not included in the models on the outcomes of interest, as well as E-values to assess the potential contribution of unmeasured confounding.<sup>19</sup> The analyses were performed using STATA 12.1 (Statcorp, College Station, USA, 2014).

### Ethics and Patient Consent

Ethics approvals were obtained from all participating hospitals; Monash University (CF11/3537-2011001884); and the Australian Institute of Health and Welfare. Consistent with the approach recommended for clinical quality disease registries to reduce selection bias,<sup>20</sup> AuSCR uses an “opt-out” process plus there is a waiver of consent for patients who die in hospital.<sup>9</sup>

### Results

Between 2010 and 2014, 20745 episodes of care were registered in AuSCR for 19,642 individuals from 45 hospitals. Among these episodes, 1182 stroke events (overall 5.1% of total sample) occurred while the patient was in hospital for another condition. Compared with being admitted from the community, patients experiencing in-hospital events were older (median age 77 versus 76 years, *P* < .001); more likely to be female (49% versus 46% *P* = .06); more often born in Australia or identify as having an indigenous background and more likely to be able to walk within 24 hours of stroke onset (38% versus 34%, *P* = .001). Type of stroke was similar between groups (see Supplementary Table e-1). Overall, fewer patients with in-hospital events compared with community-onset events accessed an SU (63% versus community-onset 81%; *P* < .001) (see Supplementary Table e-2). Other differences in receiving processes of care, outcomes and discharge diagnoses between patients with in-hospital events and community-onset events are available in supplementary Tables e-2 to e-5. To our knowledge, none of the patients were treated with mechanical intubation or were treated with mechanical thrombectomy since this treatment was still being assessed in clinical trials and this information was not captured.

Overall, 4389 patients died within 180-days of the index event, and this was more common among those with a stroke that occurred while in hospital for another condition (*P* < .001). Compared with being admitted from the community, patients experiencing in-hospital events were more likely to die within 180 days of stroke (risk adjusted HR: 1.68; 95% CI: 1.49, 1.89; see Supplementary Table e-4).

Among the 1182 registered in-hospital events (median age 77 years, 49% female) from 43 hospitals, demographics, comorbidities and clinical characteristics were similar between those treated and not treated in an SU

(Table 1). Fewer patients with in-hospital stroke treated in an SU had an ICH. Patients with an in-hospital event who were treated in an SU more often received a range of processes of care (e.g. mobilized during admission: 79% SU, 52% other wards and intravenous thrombolysis: 14% SU, 6% other wards; Fig 1) and were more often discharged to rehabilitation (Table 1) compared to those not treated in an SU.

Compared with patients not treated in an SU, there were fewer deaths up to 180-days for patients with in-hospital events treated in an SU. In multivariable analyses, treatment in an SU was associated with a reduced hazard of death at 7 and 30 days after admission when compared to patients not treated in an SU (Table 2). Amongst those who survived to 30 days after admission, there were no further differences in deaths to 90 days after admission between those treated in an SU and those treated in an alternate ward (HR 0.81, 95% CI 0.49-1.32).

Among those who were eligible for follow-up via survey (61% of patients with in-hospital events; median follow-up time: 101 days, Interquartile range: 97, 107 days), self-reported readmission to hospital or recurrent stroke between patients with in-hospital events treated in an SU and patients treated in other wards was similar (Table 3). HR-QoL between 90 and 180 days among patients with in-hospital events treated and not treated in an SU was similar. In a small subanalysis, patients with in-hospital events were more likely to report being independent (mRS 0-2) at 3-6 months follow-up when treated in an SU (21/39; 54%) than those not treated in an SU (1/8; 13%;  $P = .03$ ). Sensitivity analyses indicated that the results derived from our models were robust for example deaths up to 7 days: Original model 0.47 (95%CI 0.28, 0.77) with Charlson Index as a covariate HR: 0.39 (95%CI 0.19, 0.79).

## Discussion

To our knowledge, this is the first comparison of long-term outcomes, in terms of mortality (within 180 days) and HR-QoL (median 101 days), between patients with in-hospital stroke events treated in an SU or in other wards. In this large Australian sample, patients with in-hospital strokes treated in other wards experienced greater early mortality (within 30 days) than patients treated in an SU. Amongst those who survived to 30 days after admission, there was no evidence that treatment in an SU affected survival to 90 or 180 days, although the difference in hazard ratio remained when deaths in the first 7 days were included (data not shown). In those who were followed up between 90 and 180 days after admission, overall HR-QoL was similar between patients treated in an SU and those treated in an alternate ward.

Our study also provides evidence that SU care is associated with increased survival for patients with stroke irrespective of whether the onset was in the community or in hospital.<sup>21</sup> This is most likely explained by evidence of

greater access to evidence-based care as highlighted in the present study, and complementary evidence from studies in the United States and Ireland.<sup>4,8</sup> There is strong evidence for a net benefit of thrombolysis for combined death and dependency, particularly for thrombolysis administered within 3 hours.<sup>22</sup> In the current study, patients managed in an SU were more likely to receive acute care interventions such as thrombolysis and aspirin, and were more often mobilized, received swallow screening, and prescribed prevention medications at discharge. These interventions are most often associated with better outcomes.<sup>23-25</sup>

Strengths of our study include prospective registration of a large number of consecutive patients admitted to a variety of metropolitan and regional areas of Australia. We also explicitly recorded management in SUs in all individuals. In other studies of in-hospital stroke, there has been a reliance on optional reporting of these cases or a derived location of stroke from administrative data.<sup>4</sup> Importantly, the proportion of missing data for in-hospital stroke in our study was less than 2%. Furthermore, random auditing of AuSCR hospital data demonstrated less than 1% discrepancy between auditors on the recording of in-hospital strokes.<sup>10</sup> We had >80% power for our main outcome analyses with 1182 patients with in-hospital stroke (see Supplemental methods).

Limitations of our study include the potential for selection or referral bias. That is, less complex patients or those without competing conditions may have been more often transferred to an SU. We also acknowledge that we had limited or incomplete data on comorbidities. In our study, patients treated in and not in an SU had similar comorbidity profiles, and in a subset of the patients both groups had a median Charlson comorbidity index of 3. Our results indicate a larger survival benefit than what was observed in clinical trials of SU versus general wards<sup>2</sup> and so requires validation. Important predictors of stroke mortality include age, stroke severity, and pre-existing conditions such as atrial fibrillation and diabetes.<sup>26</sup> In a recent paper using the AuSCR data<sup>13</sup> we highlighted the importance of using appropriate risk adjustment variables and methods for comparing mortality outcomes for stroke, especially the need to account for stroke severity. Since the AuSCR contains a pragmatic minimum dataset of variables we were unable to adjust for additional pre-existing co-morbidities and we were unable to describe the type of ward where the patient was managed for patients not admitted to an SU. We acknowledge that having a limited number of variables to include in our models could result in important predictors of outcome being omitted, while too many variables may lead to overfitting (where false-positive predictors are erroneously included in the model), under-fitting, or paradoxical fitting (where a variable with a positive association with the outcome is found to have a negative association).<sup>11</sup> Consistent with observational designs, unmeasured

**Table 1.** Demographic and clinical characteristics of patients with in-hospital events according to treatment in a stroke unit

Characteristics	SU N = 750 n (%)	Non-SU N = 432 n (%)	P value
Female	352/749 (47)	220/428 (51)	.15
Age (in years)			
Less than 65	145/750 (19)	118/428 (28)	.003
65-74	162/750 (22)	91/428 (21)	
75-84	267/750 (36)	118/428 (28)	
85+	176/750 (24)	101/428 (24)	
Median age in years (Q1, Q3)	78 (69, 85)	76 (64, 85)	.024
Australian born	520/750 (69)	299/432 (69)	.97
Indigenous background*	14/741 (2)	13/420 (3)	.19
Previous stroke	197/703 (28)	87/393 (22)	.03
Index of relative socio-economic advantage and disadvantage			
Quintile 1 (most disadvantaged)	139/742 (19)	92/424 (22)	.007
Quintile 2	178/742 (24)	84/424 (20)	
Quintile 3	81/742 (11)	73/424 (17)	
Quintile 4	141/742 (19)	81/424 (19)	
Quintile 5 (most advantaged)	203/742 (27)	94/424 (22)	
Type of stroke			
Intracerebral hemorrhage	98/750 (13)	86/432 (20)	<.001
Ischemic	626/750 (84)	292/432 (68)	
Undetermined stroke	26/750 (4)	54/432 (13)	
Stroke severity			
Able to walk <sup>†</sup>	253/697 (36)	161/383 (42)	.06
Cases with additional administrative data from 2010-2013 <sup>#</sup>	N = 262	N = 192	
Charlson Comorbidity Index (median)	3 (3, 4)	3 (2, 5)	.02
Peripheral vascular disease	4 (2)	13 (5)	.11
Congestive heart failure/myocardial infarct	51 (27)	59 (23)	.32
Renal or Liver disease	29 (15)	36 (14)	.68
Dementia	10 (5)	16 (6)	.68
Chronic pulmonary disease	13 (7)	17 (6)	.91
Cancer	24 (13)	22 (8)	.15
Transfer from another hospital	284/747 (38)	135/428 (32)	.03
Median length of stay (days)	11 (6,20)	13 (6,22)	.26
Died In Hospital	96/730 (13)	109/417 (26)	<.001
Discharge destination			
Home	135/634 (21)	98/308 (32)	<.001
Rehabilitation	292/634 (46)	106/308 (34)	.001
Aged care	44/634 (7)	25/308 (8)	.52

SU, Stroke unit.

\*Identifies as Aboriginal and/or Torres Strait islander; Q1: 25th percentile; Q3: 75th percentile;

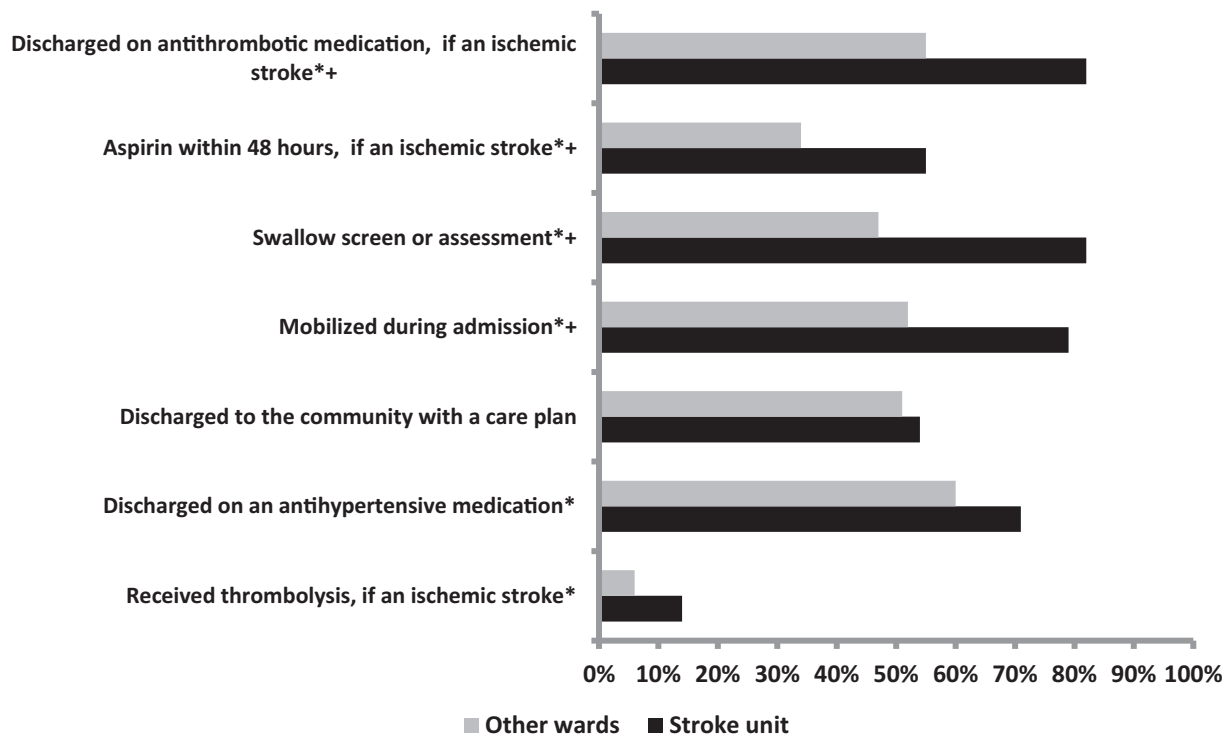
<sup>†</sup>within first 24 hours of stroke onset;

<sup>#</sup>patient-level data linked for AuSCR registrants with hospital administrative records for the index admission from New South Wales, Victoria, Queensland and Western Australia.

confounding is a limitation. The observed estimates could be explained away by an unmeasured confounder associated with both SU care and the outcome if the confounder was of a magnitude equivalent to the E-value estimates generated (from 1.0 to 11.3) above and beyond the measured confounding factors, but a weaker confounding factor could not do so.<sup>19</sup>

It is plausible that patients with multiple conditions (e.g. renal failure) could justifiably not be transferred into the SU as other acute conditions may take priority over stroke management, or because patients may be perceived as less

likely to achieve independence following rehabilitation. However, the benefits of stroke unit care appear to be independent of the co-morbidity profile of patients, and in these circumstances the involvement of the stroke team is still required.<sup>27</sup> It may also be that those transferred to the SU were less often for palliative care where active intervention is minimized, but this remains unclear until our data can be comprehensively linked with administrative records. In complementary cross-sectional data from the 2015 acute national audit (~40 cases per hospital in 112 hospitals),<sup>28</sup> 15% of patients with in-hospital events (23/151) were



**Figure 1.** Processes of care received by patients with in-hospital stroke managed, or not managed, in stroke units. Legend: \*P value < .05; +variables only collected in hospitals located in Queensland.

documented as receiving palliative care at some stage during their acute hospital stay. Only three of these 23 patients (13%) receiving palliative care for in hospital stroke were managed in the SU (unpublished data, Stroke Foundation 2015). These data provide some preliminary evidence that palliative care may be more often undertaken outside the stroke unit among these types of patients.

“Ability to walk” may be considered a crude measure of stroke severity when compared with other popular and validated methods such as the National Institutes of Health Stroke Scale, a direct measure of neurological impairment. However, it is reliable to collect, does not require certification training, and has been validated in

other stroke populations as reliable for predicting stroke outcome.<sup>11,12</sup> In recent validation work by Sim and colleagues the use of simple variables (including ability to walk) performed similarly well to a model that included the NIHSS and age.<sup>29</sup> We have also shown this variable to reliably account for differences in patient case-mix when using the registry data to compare hospital mortality rates.<sup>13</sup> Since 2015 we have also collected the NIHSS in the registry, but missing data remains an issue. To account for potential differences in the severity of comorbidities known to affect this type of stroke,<sup>7</sup> in sensitivity analyses we included the Charlson Comorbidity Index in our models and the results were similar.

**Table 2.** Survival analysis of patients with in-hospital stroke managed and not managed in a stroke unit

Time to death	SU n (%)	Non-SU n (%)	P value	Model*			
				HR	95% CI	P value	E value
Up to 7 days	38/750 (5)	51/432 (12)	<.001	0.47	0.28, 0.77	.003	2.753
8 to 30 days	115/750 (15)	121/432 (28)	<.001	0.56	0.39, 0.81	.002	2.350
31 to 90 days	169/750 (23)	151/432 (35)	<.001	0.81	0.49, 1.32	.396	1.584
91 to 180 days	206/750 (28)	163/432 (38)	<.001	1.11	0.57, 2.16	.757	1.359

CI, confidence interval; HR, hazard ratio; SU, stroke unit (reference category).

\*Model adjusted for age, sex, index of relative socioeconomic disadvantage, ability to walk within first 24 hours of stroke onset, type of stroke, transfer from another hospital and documented history of stroke. 30-day regression excluded deaths up to 7 days, 90-day regression excluded deaths up to 30 days, 180-day regression excluded deaths up to 90 days. The lowest possible E-value is 1,<sup>19</sup> but there are no specific guidelines on the range of E-values. If an E-value is deemed small (residual confounding is a threat) and where it is larger (residual confounding may not be a problem).<sup>30</sup> Therefore, our E-values indicate the minimum strength of association between SU care and the outcome that would be required by an unmeasured confounder to fully explain away each of the SU care and outcome models listed.

**Table 3.** Outcomes at 90-180 day follow-up of patients with in-hospital stroke managed and not managed in a stroke unit

Follow-up	SU n (%)	Non-SU n (%)	P value	Model*				
				OR	95% CI	P value	E-value	Pseudo-R <sup>2</sup>
Readmission	76/305 (25)	30/126 (24)	.81	0.79	0.45, 1.37	.40	1.500	0.040
Recurrent stroke	13/305 (4)	3/126 (2)	.35	5.92	0.74, 47.0	.09	11.317	0.077
<b>EQ-5D-dimensions</b>								
Mobility	155/302 (51)	59/124 (48)	.48	1.24	0.78, 1.99	.36	1.469	0.022
Self-care	156/304 (51)	57/125 (46)	.28	1.16	0.71, 1.92	.55	1.365	0.048
Usual activities	226/304 (74)	94/125 (75)	.85	0.75	0.42, 1.33	.32	1.577	0.057
Pain/discomfort	178/302 (59)	81/125 (65)	.26	0.72	0.44, 1.17	.19	1.637	0.023
Anxiety/depression	165/302 (55)	71/123 (58)	.56	0.99	0.61, 1.61	.98	1.076	0.020
Median VAS (Q1, Q3)	60 (44,80)	60 (50,77)	.62	<b>coefficient</b>	<b>95% CI</b>	<b>P value</b>		
EQ-5D-3L DCE	0.68 (0.45, 0.80)	0.66 (0.45, 0.79)	.99	0.01	-0.06, 0.09	.78	N/A	0.026

CI, confidence interval; OR, odds ratio; Q1, 25th percentile; Q3, 75th percentile; SU, stroke unit (reference category).

\*All models are adjusted for age, sex, index of relative socioeconomic advantage and disadvantage, ability to walk within first 24 hours of stroke onset, type of stroke, transfer from another hospital and documented history of stroke; For assessment of the goodness-of-fit, all  $P > .05$ , indicating that the models were a good fit; EQ-5D-3L, EuroQoL -5 dimension-3 level instrument,<sup>16</sup> VAS, Visual Analogue Scale score of the EQ5D; DCE, discrete choice experiment utilities determined using the method by Viney et al. based on the EQ-5D dimensions.<sup>17</sup> The lowest possible E-Value is 1,<sup>19</sup> but there are no specific guidelines on the range of E-values. If an E-value is deemed small (residual confounding is a threat) and where it is larger (residual confounding may not be a problem).<sup>30</sup> Therefore, our E-values indicate the minimum strength of association between SU care and the outcome that would be required by an unmeasured confounder to fully explain away each of the SU care and outcome models listed. Pseudo R<sup>2</sup> is a statistic that indicates the precision of a logistic regression model and can be used to assess the goodness-of-fit in comparison to another model. That is, where the Pseudo R<sup>2</sup> value is larger it has a better ability to predict the outcome.

Not all cases of in-hospital strokes may have been captured in our dataset. Hospital staffs are responsible for providing data to assess their case ascertainment each year. When we compared the hospitals with incomplete case ascertainment to those with 100% case-ascertainment, we found that the proportion of in-hospital strokes was similar, ranging from 5%-11% for individual hospitals.

In future research we plan to address some of these limitations by enriching the AuSCR data using data linkage techniques to merge hospital admissions and emergency datasets which contain additional information on comorbidities, palliative care, procedure codes and hospital care in an intensive care unit. We will be able to expand the variables available for case-mix adjustment or other features of hospital care without requiring hospital staff to collect more data.

## Conclusion

From this large, multicenter cohort study we observed an association with treatment in an SU and better early (within 30-days) survival for patients experiencing a stroke in hospital compared to their counterparts managed in other types of wards. Although referral bias due to comorbidity or palliation decisions may contribute to the observed differences in outcomes; the benefits of SU care may extend to patients experiencing in-hospital stroke and where feasible, management in an SU should be considered. Future work is required to clarify whether the established benefit of SU care is also applicable to the subgroup of in-hospital stroke not managed in SUs and whether engagement of the stroke service team in their care is of value where transfer is not possible.

**Acknowledgments:** We acknowledge Joyce Lim and Sabrina Small from The George Institute for Global Health (Sydney), and Francis Kung, Karen Moss, Steven Street, Renee Stojanovic, Robin Armstrong, Enna Stroil-Salama, Kate Paice, Kasey Wallis, Adele Gibbs and Alison Dias from AuSCR Office who contributed to AuSCR operations during this study period. Staffs from the Stroke Foundation are acknowledged for their contributions to patient follow-up. We would also like to thank Joosup Kim (Monash University) for assistance with aspects of the data analysis, and the hospital staff for their diligence regarding data collection for AuSCR. Hospital site investigators who provided data between 2010 and 2014 are also acknowledged (see Supplementary material 1: co-investigators). We are grateful to the patients and families who have contributed information.

## Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.jstrokecerebrovasdis.2019.01.026](https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.01.026).

## References

1. Park HJ, Cho HJ, Kim YD, et al. Comparison of the characteristics for in-hospital and out-of-hospital ischaemic strokes. *Eur J Neurol* 2009;16(5):582-588.
2. Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2013;9:CD000197.
3. Farooq MU, Reeves MJ, Gargano J, et al. In-hospital stroke in a statewide stroke registry. *Cerebrovasc Dis* 2008;25(1-2):12-20.
4. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With The Guidelines-Stroke. *Stroke* 2014;45(1):231-238.
5. Fonarow GC, Reeves MJ, Smith EE, et al. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. *Circ Cardiovasc Qual Outcomes* 2010;3(3):291-302.
6. Blacker DJ. In-hospital stroke. *Lancet Neurol* 2003;2(12):741-746.
7. Chen S, Singh RJ, Kamal N, et al. Improving care for acute in-hospital ischemic strokes: a narrative review. *Int J Stroke* 2018. 1747493018790029.
8. Briggs R, McDonagh R, Mahon O, et al. In-hospital stroke: characteristics and outcomes. *Ir Med J* 2015;108(1):24-25.
9. Cadilhac DA, Lannin NA, Anderson CS, et al. Protocol and pilot data for establishing the Australian Stroke Clinical Registry. *Int J Stroke* 2010;5(3):217-226.
10. Cadilhac DA, Lannin NA, Anderson CS, et al. The Australian Stroke Clinical Registry Annual Report 2014. Annual report. Melbourne: The Florey Institute of Neuroscience and Mental Health; 2015 November 2014. Report No.: 1.
11. Counsell C, Dennis M, McDowall M, et al. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. *Stroke* 2002;33(4):1041-1047.
12. Cadilhac D, Kilkenny M, Churilov L, et al. Identification of a reliable subset of process indicators for clinical audit in stroke care: an example from Australia. *Clin Audit* 2010;2:67-77.
13. Cadilhac DA, Kilkenny MF, Levi CR, et al. Risk-adjusted hospital mortality rates for stroke: evidence from the Australian Stroke Clinical Registry (AuSCR). *Med J Aust* 2017;206(8):345-350.
14. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173(6):676-682.
15. Cadilhac DA, Kim J, Lannin NA, et al. Better outcomes for hospitalized patients with TIA when in stroke units: an observational study. *Neurology* 2016;86(22):2042-2048.
16. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199-208.
17. Viney R, Norman R, Brazier J, et al. An Australian discrete choice experiment to value EQ-5D health states. *Health Econ* 2014;23(6):729-742.
18. Golicki D, Niewada M, Karlińska A, et al. Comparing responsiveness of the EQ-5D-5L, EQ-5D-3L and EQ VAS in stroke patients. *Qual Life Res* 2014.



19. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017;167(4):268-274.
20. Clark AM, Jamieson R, Findlay IN. Registries and informed consent. *N Engl J Med* 2004;351(6):612-614. author reply -4.
21. Cadilhac DA, Andrew NE, Lannin NA, et al. Quality of acute care and long-term quality of life and survival: The Australian Stroke Clinical Registry. *Stroke* 2017;48(4):1026-1032.
22. Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014;(7):CD000213.
23. Cadilhac DA, Carter RC, Thrift AG, Dewey HM. Why invest in a national public health program for stroke? An example using Australian data to estimate the potential benefits and cost implications. *Health Policy* 2007;83(2-3):287-294.
24. Lynch E, Hillier S, Cadilhac D. When should physical rehabilitation commence after stroke: a systematic review. *Int J Stroke* 2014;9(4):468-478.
25. Middleton S, McElduff P, Ward J, et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet* 2011;378(9804):1699-1706.
26. Feigin VL, Lawes CM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009;8(4):355-369.
27. Jorgensen HS, Kammergaard LP, Houth J, et al. Who benefits from treatment and rehabilitation in a stroke Unit? A community-based study. *Stroke* 2000;31(2):434-439.
28. National Stroke Foundation. National Stroke Audit Clinical Report: Acute Services. Melbourne: National Stroke Foundation; 2015 December.
29. Sim J, Teece L, Dennis MS, et al. Validation and recalibration of two multivariable prognostic models for survival and independence in acute stroke. *PLoS One* 2016;11(5):e0153527.
30. Ioannidis JPA, Tan YJ, Blum MR. Limitations and misinterpretations of e-values for sensitivity analyses of observational studies. *Ann Intern Med* 2019;170(2):108-111.