Assuming one dose per day yields a similar estimate of medication adherence in patients with stroke: an exploratory analysis using linked registry data

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What is already known about this subject

- Pharmacy claims databases are frequently used to investigate medication use and adherence in many disease conditions.
- For databases without information on the prescribed daily dose, such as the Australian Pharmaceutical Benefits Scheme, it is unclear whether using the World Health Organisation's defined daily doses (DDD) or assuming one dose per day (1DD) to estimate adherence produces similar results to dosages determined using pharmaco-epidemiological methods. One such metric is prescribed daily dose (PDD_{75}), which is based on the 75^{th} percentile of medication refill time for each patient.

What this study adds

- Antihypertensive medications were predominantly dispensed to patients with stroke at a rate which reflected 1DD.
- 1DD yielded similar medication adherence as PDD_{75} dosage estimates derived from the dispensing patterns of each patient.
- The DDD resulted in modest but significant differences in adherence compared to these methods.

Abstract (250 words)

Purpose: Prescribed daily dose (PDD), the number of doses prescribed to be taken per day, is used to calculate medication adherence using pharmacy claims data. PDD can be substituted by (1) 1 dose per day (1DD), (2) an estimate based on the 75th percentile of days taken by patients to refill a script (PDD_{75}) or (3) the World Health Organisation's defined daily dose (DDD). We aimed to compare these approaches for estimating the duration covered by medications and whether this affects calculated 1-year adherence to antihypertensive medications post-stroke.

Methods: We conducted a retrospective review of prospective cohort data from the ongoing Australian Stroke Clinical Registry linked with pharmacy claims data. Adherence was calculated as the proportion of days covered (PDC) for 1DD, PDD_{75}, and DDD. Differences were assessed using Wilcoxon rank-sum tests.

Results: Among 12628 eligible patients with stroke, 10057 (80%) were prescribed antihypertensive medications in the year after hospital discharge (78.2% aged ≥65 years, 45.2% female). Overall, the 75th percentile of patient time until next medication refill was 39 days. The greatest variations in dose regimens, estimated using person- and dose-level refill times, were for beta blockers (11.4% taking 2 tablets/day). There were comparable levels of adherence between 1DD and the PDD_{75} (median PDC 91.0% versus 91.2%; P=0.70), but adherence was slightly higher using DDD (92.3%; both P<0.001). However, this would represent a clinically non-significant difference.

Conclusion: Adherence to antihypertensive medications shows similar estimates across standard measures of dosage in patients during the first year after an acute stroke.

Introduction:

Adherence to prevention medications following stroke is essential for reducing the risk of recurrent events [1], but monitoring adherence to medications is not straightforward when using routinely collected administrative observational data where dosing information is not available.[2] The non-intrusive and population-wide coverage of pharmacy claims data makes it an increasingly popular method of objectively estimating adherence to medications compared with conventional self-reported measures. Other objective measures include counting pills and the use of electronic medication packaging devices, enabling one to monitor each time a pill is removed and assume it has been ingested.[2] In addition to providing comprehensive information on dispensing patterns over time, pharmacy claims data also reflect real-world practice at a whole population level, without responder burden and biases.[3] However, data elements and how these are collected can be inconsistent between countries and administrative PBS claims data in Australia lack actual prescribed daily dose (PDD) information. While there is no feasible gold standard for determining adherence to medications, one of the most widely used metrics is the proportion of days covered (PDC), i.e. the percentage of days with access to medication in a defined period.[4-6]

In Australia, the Pharmaceutical Benefits Scheme (PBS) provides all permanent residents access to subsidised prescription medicines. The PBS database includes details of all medications dispensed, including their type, strength and quantity, and although primarily collected for billing purposes, can facilitate pharmaco-epidemiological research.[7] However, the quantity of medication(s) taken per day or the prescribed daily dose (PDD), are not recorded.[8] Without such information, it is not possible to determine the actual duration of exposure to each medication or assess whether therapeutic adherence is actually being achieved. As most PBS quantities are intended for 1-month supply, one potential solution used within some studies is to assume a PDD of one dose per day (1DD).[9,10] Another is to rely on a

defined daily dose (DDD), as published by the World Health Organisation (WHO).[11] Yet, both of these approaches lack accuracy to account for potential differences in dosage due to the strength of products and do not account for differences in prescribing practices within and across regions, prescribing indication, severity of condition, or specific characteristics of the patient group.[12] Consequently, there can be imprecision in the estimates of medication adherence.[7]

A commonly used metric is to calculate the time taken for patients to refill scripts and estimate dosages by the application of the 75th percentile of refill times for each patient (PDD_{75}).[13-20] However, as shown in a recent study that included a measure of the PDD based on the 80th percentile of the time taken until the next refill of various antihypertensive classes in patients with heart failure,[21] there may be substantial differences between PDC and 1DD estimates. Systematic evaluation of different dosage estimations for determining adherence to medications after stroke is lacking. We aimed to compare the 1DD, PDD and PDD_{75} metrics for estimating duration covered by medications and assess whether this affects 1-year adherence to antihypertensive treatment among survivors of stroke in Australia.

Methods

Study design

This was a retrospective review of prospective data from the ongoing Australian Stroke Clinical Registry (AuSCR) linked to PBS data. The AuSCR is a national clinical registry designed to routinely monitor the quality of care during acute hospital admission for patients with a clinical diagnosis of acute stroke or transient ischaemic attack (TIA) against their health outcomes at 90 to 180 days after hospital discharge.[22] To reduce sampling bias, an opt-out model of consent is used, with only 1-6% of registrants excluded from the AuSCR each year.[23] Annual

linkages of the AuSCR registrants with the Australian National Death Index enable ascertainment of deaths beyond the 90-180 day follow-up period.

This study comprised adult patients who were registered in the AuSCR following an acute stroke or TIA, occurring between April 2010 and June 2014, and were linked to the PBS dataset.[7] All medications listed on the PBS schedule have an associated PBS 'item code' that identifies the medications' form and strength, as well as a 7-character Anatomical Therapeutic Chemical (ATC) classification code to identify medications irrespective of strength.[11] Antihypertensive medications most relevant to secondary stroke prevention include diuretics (ATC code C03), beta blockers (C07), calcium channel blockers (C08), and agents acting on the renin-angiotensin system (C09). Medications provided at discharge from hospital are recorded in the PBS, except for public hospitals in New South Wales and the Australian Capital Territory where patients are typically discharged with a supply of medication for a maximum of one week.[24] Furthermore, medications purchased 'over-the-counter' or during a hospital stay are not recorded in the PBS. Prior to July 2012, prescription medications costing less than the patient co-payment threshold were paid in full by the patient and were not recorded in the PBS as no government subsidy was received. From July 2012, it has been mandatory for all dispensed prescriptions medications to be recorded in the PBS. Although only medications that attracted a government subsidy were included in the PBS prior to July 2012, it is likely that many patients would have qualified for a healthcare (pension) concession card to receive subsidised medications as most patients with acute stroke are aged ≥65 years.[23]

We included patients who were dispensed at least one antihypertensive medication during the year following hospital discharge. Patients were excluded from analyses if they died during hospitalisation or were discharged before 1 April 2010 or after 30 June 2014, as linked PBS data were unavailable at these times. As part of a sensitivity analysis, we excluded patients who

were discharged prior to July 2012 to investigate whether the co-payment threshold affected our findings.

Variables

Data related to demographics, type of stroke, date of hospital discharge, and discharge destination were obtained from the AuSCR dataset. Severity of stroke was determined according to an ability to walk on admission, a validated proxy measure.[25] Socioeconomic status was derived from the postcode of residence using the Index of Relative Socioeconomic Advantage and Disadvantage.[26] The date of hospital admission was substituted for those patients with missing date of hospital discharge (2%).

Patient-level data on adherence to antihypertensive medications in the year after hospital discharge were determined using the PDC method. This involved calculating the overall proportion of days in a patient observation period where there was access to a supply of medication, with various estimates for PDD (Figure 1). Patients were observed from their date of hospital discharge until the end of the observation period of 365 days or date of death, if earlier. The number of days covered is equal to the quantity of medication dispensed within the observation period divided by the estimate for PDD.[9] We also accounted for instances of pre-supply, stockpiling and early death (Supplemental Figure I). In Australia, patients can obtain refills of the same medications in advance of their current supply being exhausted or receive multiple repeat dispensings on a single occasion. These two approaches can lead to stockpiling over an extended period before a refill being recorded, a process which complicates estimates of medication adherence.[7] To address this, we assumed that patients would exhaust their current supply before initiating the next supply of the same medication. Specifically, where multiple dispensing of the same drug overlapped for a patient, we extended the period of drug coverage such that each overlapping drug supply commenced the day after the previous drug

supply had concluded. As suggested by Arnet et al,[8] carryover was granted for patients who switched between different strengths of the same medication class (e.g. carvedilol 12.5mg to 25mg), but was not for therapeutic switches (e.g. atenolol to carvedilol). As the PBS does not include any indication for the PDD, we used the following three approaches to calculating dose: (1) 1DD was applied to all secondary prevention medications (e.g. a 30-tablet supply of 50mg atenolol was assumed to result in 30 days covered in the observation period); (2) the WHO's DDD was applied to all medications of the same ATC code, irrespective of differences in strength (e.g. 75mg/day would apply to a 30-tablet supply of 50mg atenolol over 20 days), combination therapies were assigned a fixed 1 DDD based on WHO guidelines for ATC classification and DDD assignment[11]; and (3) the PDD_{75} was derived from the 75th percentile of number of days between consecutive dispensing of specific PBS item codes, which uniquely identify specific medications, and their strength, pack size and form of delivery (Table 1). This 75^{th} percentile represents the number of days in which individuals would return 75% of the time for a refill of the same item code. The PDD_{75} was calculated for each dispensing as being equal to the quantity dispensed divided by the population 75^{th} percentile of time until refill for the corresponding item code. This would yield whole integers of dosage for capsules, but tablets could be dispensed at a half per day or greater. We used a PDC of ≥80% to define medication adherence in our cohort.[27]

Statistical analysis

Descriptive statistics were used to describe the overall baseline characteristics of the cohort. Wilcoxon rank-sum tests were used to compare the median PDCs between each assumption of dosage. A two-sided $P<0.05$ was considered statistically significant. All analyses were performed using StataMP 15.0 (StataCorp, Texas).[27]

Ethics and data availability

This study was approved by the ethics committees at Monash University (7864) and Australian Institute of Health and Welfare (EO2017/1/346). Additional approvals for data linkage were obtained from the AuSCR Research Task Group and Australian Department of Health. Medication and strength-level data relating to dosages are available in Supplemental Table I.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

Results

Of 17980 AuSCR registrants discharged between 2010 and 2014, 95% were linked to PBS data. After excluding those ineligible (Figure 2), the final cohort comprised 12628 patients (74.4% aged ≥65 years, 45.1% female, 49.6% unable to walk on admission; Table 2). There were 10,057 (80%) who were dispensed antihypertensive medication in the year after stroke (78.2% aged ≥65 years, 45.2% female, 48.8% unable to walk on admission). The most commonly prescribed classes of antihypertensive medications were angiotensin-converting enzyme inhibitors (50.0%), beta blockers (45.5%), calcium channel blockers (33.8%) and diuretics (29.0%). For the 152,982 antihypertensive medications dispensed, the 75th percentile of patients' time until next refill was 39 days (25th percentile, 25 days; median 30 days).

Most dispensed antihypertensive medications had a PDD_{75} of 1 dose per day (Table 3), and most were tablets (96.7%). Variations in the time until next refill were observed both within and between each class of antihypertensive medication (Supplemental Table I), being greatest for beta blockers (11.4% with 2 tablets/day) and diuretics (6.4% with 0.5 tablets/day). An

example representation of the estimated PDD_{75} for beta blockers is provided in Supplemental Figure II.

Most (70.6%) patients were adherent (PDC ≥80%) to antihypertensive medications using the PDD_{75}, with the greatest adherence for medications acting on the renin-angiotensin system and worst for diuretics (Table 4). There were no significant differences in adherence to any antihypertensive medication between the PDD_{75} and 1DD (median PDC 91.0% versus 91.2%; P=0.70), but adherence was slightly higher using the DDD (92.3%; both P<0.001). However, this would represent a clinically non-significant difference. DDD-based PDC estimates tended to be inflated for each class of antihypertensive, except beta blockers and diuretics. These PDC estimates were significantly different from those calculated using either the PDD_{75} or 1DD.

After excluding patients, as part of a sensitivity analysis, who were either discharged before July 2012 (as PBS data is incomplete for medicines below the co-payment threshold) or not long-term concession card holders, 91.7% of the cohort remained (Supplemental Table II) and adherence remained similar overall and across each class of antihypertensive.

Discussion

In our evaluation of the different approaches to estimating medication adherence using Australian PBS data, we found that the simple 1DD approach was comparable to the more complex PDD_{75} in the first year in those who survived their hospitalisation for stroke, except for beta blockers. However, the WHO's DDD approach tended to overestimate the PDC.[28] There are strengths and weaknesses to each approach. For the PDD_{75} metric, the data-driven approach provides wide coverage, efficient and flexible data on alternate dosage from the conventional 1DD (see Table 5 for more details).

Our finding of beta blockers being provided in many different doses was similar to the findings of a study of Alzheimer's disease, a population with similar characteristics to survivors of

stroke in that they tend to be older adults with a high proportion of polypharmacy.[29] In the prior study, where benzodiazepine temazepam was commonly prescribed at either 0.5 or 1 tablet per day, the authors concluded that assumptions over a fixed dose (e.g. 1 tablet per day) required further validation. Our findings are also consistent with a South Australian study of users of antihypertensive therapy in 2007,[17] where the 75th percentile of time for most medications was 35 days. These findings support the current intended duration of 1-month supply prescriptions for chronic conditions in the PBS, as fixed-dose combination therapies are predominately provided in pack sizes of 28 or 30, or of 60 if medications are taken twice daily.[10,18]

The proportion of those adherent to each class of antihypertensive medication may have differed due to factors such as the side effects or differences in comorbidities, which lead to contraindications to the drug. The findings from the present study will form the basis of future research involving these data for estimation of medication adherence and investigations of the factors associated with greater adherence, such as age, type of stroke and socio-economic status. Strengths of our study include the ability to capture all medication dispensing for secondary prevention from a large registry and data on time of death reduced the overall observation time where this was the reason for drug cessation. There are, however, several limitations such as the inferences that were made over the dose and duration of medication without supporting prescribing information from general practitioner or specialist records, or against pill counts. Additionally, being dispensed a medication does not imply that this medication was consumed by the patient.

In summary, our study has provided evidence that compared with the best assessment of exposure periods (PDD_{75}), the simpler approach of using 1DD to calculate the PDC provides similar results. Although the WHO's DDD produced significantly different PDCs for all antihypertensive agents used for patients with a recent stroke, 1DD is an equally valid metric

for calculating the PDC in an Australian population. The application of 1DD for determining medication adherence using PBS dispensing data produced similar estimates for antihypertensive medications, except for beta blockers. The PDD_{75} had the advantage of detecting variations in dosage for beta blockers and may be a more precise metric for this class of antihypertensive, in the absence of data on actual PDD information (gold standard).

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Contributors

All authors contributed to the interpretation of the data and critical revisions of the manuscript for intellectual content. D.U. was also responsible for drafting the manuscript and alongside L.D. performed the statistical analysis and literature review. A.G.T and M.F.K were responsible for the initial conceptualization and design of this study. N.E.A, D.A.C. and M.F.K acquired project funding to facilitate acquisition and linkage of data. All authors approved the manuscript for submission.

Conflict of Interest

D.A. Cadilhac is the current Data Custodian for the AuSCR. D.A. Cadilhac. A.G. Thrift, C.S. Anderson, and M.F. Kilkenny are members of the AuSCR Steering or Management Committees. A.G. Thrift is a member of the Board of the Stroke Foundation. D.A. Cadilhac reported receiving restricted grants from Boehringer Ingelheim, Ipsen, Medtronic and Shire outside the submitted work.

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Table 1. Process for determining the population-level 75th percentile of time between consecutive refills for each Pharmaceutical Benefits Scheme (PBS) item code and prescribed daily dose (PDD_{75}).

Step:	
1	Within a patient's 1-year dispensing history, determine the number of days between consecutive refills of the same PBS item code. All PBS item codes uniquely identify a specific combination of a medication, its form, strength and pack size.[a] For example, item code '01946K' identifies ramipril dispensed as a pack of 30 tablets with a strength of 5mg.
2	For each item code, calculate the 75th percentile of the distribution of time until next dispensing date for each person and the population.
3	For each person and item code, divide the quantity of medication by the 75th percentile of refill pattern to calculate dose per day. Assign an approximate individual PDD_{75}: • ≈ 0.5 if dose/day = 0.375 – 0.749 (for tablets) • ≈ 1 if dose/day = 0.375 – 1.499 (for capsules) • ≈ 1 if dose/day = 0.750 – 1.499 (tablets) • ≈ 2 if dose/day = 1.500 – 2.499 (tablets/capsules) • ≈ 3 if dose/day = 2.500 – 3.499 (tablets/capsules) • ≈ n if dose/day = (n-1).500 – n.499 (tablets/capsules) For each item code, individuals who had <5 dispensings for that item code are assigned the population's PDD_{75} instead.

[a] If an identifier similar to the PBS item code is not available, then consider using the 7-character Anatomical Therapeutic Chemical (ATC) code, which would identify the drug being dispensed.

Table 2. Characteristics of final cohort of patients with stroke/TIA dispensed antihypertensive medications in the year following discharge.

	All antihypertensive medication users **N= 10057** **n (%)**
Female	4546 (45.2)
Age	
<65	2187 (21.8)
65-74	2497 (24.8)
75-84	3372 (33.5)
85+	1999 (19.9)
Type of stroke	
Intracerebral haemorrhage	1046 (10.4)
Ischaemic stroke	6917 (68.8)
Transient Ischaemic Attack	1778 (17.7)
Undetermined stroke	309 (3.1)
Severe stroke (unable to walk on admission)	4909 (48.8)
Previous history of stroke	2011 (21.2)
Socioeconomic position[a]	
Most disadvantaged	1053 (10.6)
Second most disadvantaged	1610 (16.3)
Third most disadvantaged	1989 (20.1)
Fourth most disadvantaged	2223 (22.4)
Least disadvantaged	3030 (30.6)
Year of admission	
2010	824 (8.2)
2011	1571 (15.6)
2012	2592 (25.8)
2013	3344 (33.3)
2014	1726 (17.2)
Discharge destination	
Home	5065 (50.3)
Rehabilitation	3143 (31.3)
Aged care	668 (6.6)
Other	1181 (11.7)
Class of antihypertensive medication dispensed[b]	
Any agent acting on RAS	8363 (83.2)
ACE inhibitor, plain	5027 (50.0)
ACE inhibitor, combination	803 (8.0)
ARB, plain	2803 (27.9)
ARB, combination	1391 (13.8)
Beta blocker	4574 (45.5)
Calcium channel blocker	3394 (33.8)
Diuretic	2913 (29.0)

RAS, renin-angiotensin system; ACE, angiotensin-converting enzyme; and ARB, angiotensin II receptor blocker.

[a] Determined using Index of Relative Socioeconomic Advantage and Disadvantage.

[b] Due to co-administration of multiple antihypertensive medications, patients can be included in multiple medication groups.

Table 3. Estimated prescribed daily doses based on 75th percentile of the days until next dispensing (PDD_{75}).

	Total medication users	Total medications dispensed	Dose per day[a]		
			0.5 units	1 unit	2 units
Class of antihypertensive	$N_{patients}$	$N_{scripts}$	%	%	%
Overall	10057	152982	0.7	96.9	2.4
Agents acting on RAS	8363	84401	0.1	99.8	0.1
ACE inhibitor, plain	5027	43291	<0.1	99.8	0.2
ACE inhibitor, combination	803	6142	<0.1	99.9	0.1
ARB, plain	2803	23529	0.4	99.6	0.0
ARB, combination	1391	11439	0.1	99.9	0.0
Beta blocker	4574	29779	0.9	87.6	11.4
Calcium channel blocker	3394	27771	<0.1	99.3	0.7
Diuretic	2913	11031	6.4	93.6	0.0

RAS, renin–angiotensin system; ACE, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blocker.

[a] Based on 75th percentile of individual patient's time until next dispensing.

[b] Due to co-administration of multiple antihypertensive medications, patients can be included in multiple medication groups.

Table 4. Adherence to antihypertensive medications within 1 year after stroke, based on three different metrics of dosage, by overall and class use.

		PDC summary statistics (%)					
Class of antihypertensive	Adherent[a]	min	Q_1	median	Q_3	max	*P*-Value[b]
Any antihypertensive (N=10057)[c]							
1DD	70.8%	0.3	75.6	91.2	97.0	100	0.700
PDD_{75}	70.6%	0.3	75.3	91.0	97.0	100	<0.001
DDD	71.9%	0.3	75.6	92.3	98.1	100	<0.001
Agents acting on RAS (N=8363)							
1DD	62.6%	0.3	64.9	87.1	95.1	100	0.998
PDD_{75}	62.6%	0.3	64.9	87.3	95.1	100	<0.001
DDD	65.9%	0.3	65.5	90.4	96.7	100	<0.001
Beta blocker (N=4574)							
1DD	51.1%	0.3	52.6	80.8	93.2	100	0.061
PDD_{75}	49.7%	0.3	51.0	79.5	92.6	100	<0.001
DDD	42.3%	0.3	41.6	71.0	91.8	100	<0.001
Calcium channel blocker (N=3394)							
1DD	46.5%	0.3	38.4	76.4	92.3	100	0.874
PDD_{75}	46.3%	0.3	38.4	76.4	92.3	100	<0.001
DDD	52.9%	0.3	43.8	82.7	94.7	100	<0.001
Diuretic (N=2913)							
1DD	36.1%	0.3	34.0	67.1	85.8	100	0.322
PDD_{75}	37.0%	0.3	36.4	68.4	86.3	100	<0.001
DDD	32.8%	0.3	28.2	60.3	84.9	100	<0.001

PDC, the proportion of days covered (measure of medication adherence); Q_1, 25th percentile; Q_3, 75th percentile; 1DD, 1 dose per day; PDD_{75}, prescribed daily dose determined using the 75th percentile of the population's time until next dispensing for the same medication, strength and form; DDD, defined daily dose based on work by the World Health Organisation; RAS, renin–angiotensin system.

[a] Being adherent was classified as having a PDC ≥80% within 1 year after stroke.

[b] *P*-Values were derived using Wilcoxon rank-sum tests and signify comparison between median PDC of the current and subsequent row, within each class of antihypertensive. The DDD of each class was compared with 1DD.

[c] Users of at least one of the following antihypertensive classes: agents acting on RAS, beta blocker, calcium channel blocker and diuretic.

Table 5. Strengths and weaknesses of different approaches for estimating duration on medications for the determination of medication adherence when prescribed daily dosage information is missing from a dataset.[7,10,29]

Dosage estimation	Strengths	Weaknesses
All		• Do not differentiate between loading doses or maintenance doses
1DD	• Simple to implement • Found to be appropriate for most antihypertensive drug classes[a]	• May not provide a suitable estimate for beta blockers and other drugs with significant variation in prescribed daily dose • Does not consider disease severity or acute treatments, which may require higher or lower dosages
PDD_{75}	• Data-driven approach based on dispensing patterns for both individuals and the cohort • Discerns when medications appear to be predominately not taken at 1DD	• May slightly overestimate adherence • Estimates are specific to dispensing patterns and rules in the examined population, which could have limited generalisability to other countries
DDD	• Simple to implement	• Estimate is based on an average of international dosages in adults • May not be accurate due to the characteristics of those in the cohort being examined (e.g. age and severity of disease) • May not reflect prescribed dose in Australia • Usually missing for combination medications • Inaccurate for variable-dose drugs

1DD, 1 dose per day; PDD_{75}, prescribed daily dose determined using the 75^{th} percentile of the population's time until next dispensing for the same medication, strength and form; DDD, defined daily dose based on work by the World Health Organisation.

[a] Antihypertensive classes were agents acting on the renin–angiotensin system, calcium channel blockers and diuretics.

Figure 1. Example calculation of medication adherence within 1-year, using the proportion of days covered (PDC) approach, for 10 dispensings of 30 tablets with an estimated prescribed daily dose of 1 dose per day (1DD). 'Days covered' also accounted for overlapping periods (stockpiling) within a class of antihypertensive and death (Supplemental Figure I), which are not depicted here.

t_1, 1st dispensing; t_n, last dispensing; DDD, defined daily dose; PDD_{75}, prescribed daily dose based on the 75th percentile of medication refill time for each patient; PDD, prescribed daily dose (estimate based on (1) 1DD, (2) PDD_{75} or (3) DDD).

Figure 2. Flow diagram of cohort selection from the Australian Stroke Clinical Registry (AuSCR).

$$Days\ covered = \sum_{t_1}^{t_n} \frac{Quantity\ of\ medication}{Estimate\ of\ PDD}$$
$$= \sum_{t_1}^{t_{10}} \frac{30}{1}$$
$$= 300$$

$$PDC = \frac{Days\ covered}{Observation\ period} \times 100\%$$
$$= \frac{300\ days}{360\ days} \times 100\%$$
$$= 83.3\%$$

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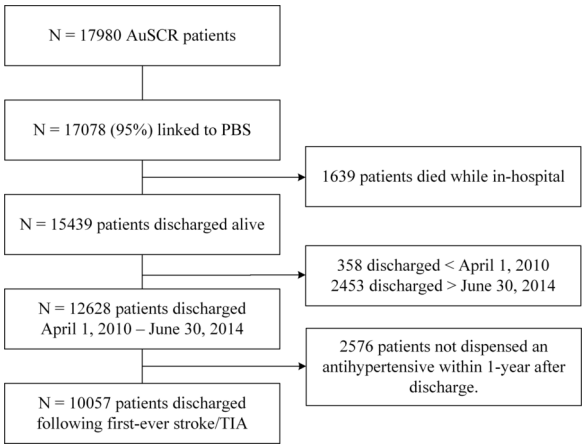

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