Evidence-Practice Gaps in Postdischarge Initiation With Oral Anticoagulants in Patients With Atrial Fibrillation

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Background—Oral anticoagulant (OAC) therapy reduces the risk of stroke in people with atrial fibrillation (AF), and is considered best practice; however, there is little Australian evidence around the uptake of OACs in this population.

Methods and Results—We used linked hospital admissions, pharmaceutical dispensing claims, medical services, and mortality data for people in Australia’s 2 most populous states (July 2010 to June 2015). Among OAC-naïve people hospitalized with AF, we estimated initiation of OAC therapy within 30 days of discharge, and persistence with therapy in the first year. We analyzed both outcomes using multivariable Cox regression. In 71 184 people with AF (median age 78 years, 49% female), 22.7% initiated OAC therapy, and persistence with therapy in the first year. We found that OAC therapy was severely underutilized in people hospitalized with AF, even among high-risk individuals. Reasons for this underuse, whether patient, prescriber, or hospital related, should be identified and addressed to reduce stroke-related morbidity and mortality in people with AF. (J Am Heart Assoc. 2019;8:e014287. DOI: 10.1161/JAHA.119.014287.)

Key Words: atrial fibrillation • cardiovascular disease • oral anticoagulants • pharmacoepidemiology • stroke

Atrial fibrillation (AF) increases the risk of stroke nearly 5-fold,1 and AF-related stroke is associated with greater disability and mortality than non-AF stroke.2 Prevalence of AF increases with age, from 5% in people over 55 years to 18% over 85 years;3 in people aged 80 to 89 years, 1 in 4 strokes are attributable to AF.1 Worldwide, the prevalence of AF is increasing,4,5 and in Australia the number of cases is expected to double in the next 20 years.3 Stroke in AF is potentially preventable if people are prescribed oral anticoagulant (OAC) therapy.6 Historically, patients with AF have been treated with warfarin, a vitamin K antagonist; however, warfarin carries an increased risk of bleeding and intracranial hemorrhage that may not be offset by its benefits in some people.7 In the past decade, direct OACs (DOACs) have entered the market and are increasingly being prescribed as an alternative to warfarin. DOACs have similar benefits to warfarin in terms of stroke prevention, but a decreased risk of intracranial haemorrhage,8–10 and are thus a preferred treatment option in AF patients with an increased risk of bleeding.

OAC prescribing in people with AF is considered best practice,11,12 and Australian guidelines recommend that hospitalized patients with AF be discharged on OACs.13 Yet despite their benefits, OACs are commonly underutilized; many studies report poor uptake, even among individuals at high risk of stroke.14,15 Additionally, while compliance is key to the effectiveness of these medicines, nonadherence and discontinuation of OAC therapy are common.14,16–18

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Accompanying Tables S1, S2 and Figures S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014287

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Clinical Perspective

What Is New?

• In this prospective cohort study of 71,184 people naïve to oral anticoagulants, we found that oral anticoagulants were dispensed to 22.7% of people discharged from the hospital with atrial fibrillation.
• Initiation was greatest in people at highest risk of stroke; that is, people with a CHA₂DS₂-VASc score ≥7 (versus 0) (hazard ratio=6.25, 95% CI 5.08–7.69) and with a history of thromboembolism (hazard ratio =2.65, 95% CI 2.49–2.83).
• Initiation was less likely in people with comorbidities such as dementia, cancer, liver disease, and kidney disease.

What Are the Clinical Implications?

• This is the first population-based study in Australia to establish that OACs are severely underutilized in people discharged from the hospital with atrial fibrillation, despite guidelines recommending their use.
• The effectiveness of OACs for stroke prevention is well established and increasing rates of use in high-risk individuals even by a small amount could substantially reduce morbidity and mortality.

While use of OACs has been increasing in Australia since the public subsidy of the DOACs, there are few Australian data describing OAC use in AF patients after hospitalization. Therefore, in this study we used real-world, population-based health data for residents of Australia’s 2 most populous states (New South Wales [NSW] and Victoria) to (1) quantify the rates and predictors of postdischarge initiation of OACs in OAC-naïve patients admitted to the hospital with AF; and (2) describe persistence among people initiating OAC therapy.

Methods

Ethics Approval and Data Access

Ethics approval for this study was given by the Australian Institute of Health and Welfare Human Research Ethics Committee. Because the data were retrospective and did not contain personal identifiers, a waiver of informed consent was granted. Ethics and data approval were obtained for the purposes of conducting this study and do not permit sharing of the data. Details on how to access the data are available from the Australian Institute of Health and Welfare.

Setting

Australia has a publicly funded universal healthcare system, with eligible residents entitled to subsidized access to healthcare services, including prescribed medicines through the Pharmaceutical Benefits Scheme (PBS). Eligible patients pay a copayment towards the cost of their medicines and the government subsidizes the remaining cost. The level of subsidy depends on the patient’s beneficiary status; concessional beneficiaries (people eligible for government entitlements, such as people ≥65 years and low-income earners) pay a lower copayment than general beneficiaries. Once concessional beneficiaries reach the “Safety Net” limit on out-of-pocket payments for PBS-subsidized medicines within a calendar year, they receive their medicines free of charge for the remainder of the year. Additionally, the hospital sector includes a mix of public and private hospitals; public hospitals are primarily managed by the states and territories, while private hospitals are funded through nongovernment sources. In NSW and Victoria, ≈61% of hospital admissions were to public hospitals during the study period.

Data Sources

We used the most contemporary available linked public hospital admitted patient data, pharmaceutical dispensing, medical services, and mortality data from the National Data Linkage Demonstration Project. The National Data Linkage Demonstration Project contains population-level linked data from July 2010 to June 2015 for residents of NSW and Victoria. Data linkage was undertaken by the Australian Institute of Health and Welfare, Oversight of the National Data Linkage Demonstration Project, including approval of project outputs, is by a Steering Committee comprising representatives from Australian Government Department of Health, Australian Institute of Health and Welfare, NSW Ministry of Health, and Department of Health and Human Services Victoria.

The public hospital admitted patient data were drawn from the National Hospital Morbidity Database and contain records of all admissions to public hospitals. The Medicare Benefits Scheme claims extract contains data on all medical services rendered including in- and out-of-hospital general practitioner and specialist visits. Mortality data were derived from the National Death Index data. The PBS claims extract contain records for all medicines subsidized by the PBS; medicines priced below the copayment threshold were not subsidized by the PBS and not captured in our data.

Study Population

Because dispensing of some OACs was not captured in the PBS data for the general population because of their low cost, we restricted the study population to people who were concessional beneficiaries during the entire study period to
ensure that we had complete capture of their PBS dispensing. Approximately 75% of Australians ≥65 years and 15% <65 years are concessional beneficiaries. To ascertain beneficiary status, individuals had to have been dispensed only medicines attracting a concessional subsidy during the study period and have at least 1 dispensing record for any medicine in the 12 months before their index admission. We included all OAC-naïve patients discharged from a public hospital between July 2011 and December 2014, with a diagnosis of AF (International Classification of Diseases, Tenth Revision Australian Modification [ICD-10-AM] code I48.x). The principal diagnosis is primarily responsible for the episode of care, while secondary diagnoses are conditions existing at the time of admission or developing during admission that affect the patient’s care. We included individuals with both a principal and secondary diagnosis of AF in all analyses. Patients were considered to be OAC-naïve if they had no dispensing for an OAC within the 365 days before the index admission date. For patients with multiple eligible hospitalizations, we included their most recent admission only, which we considered the “index admission.” We considered changes in type of care within the hospital (eg, from acute to subacute care), and transfers between hospitals, as continuation of a single admission. We excluded patients who were <18 years, died in-hospital or on the day of discharge, were not residents of NSW or Victoria, and who were funded by the Department of Veterans’ Affairs, because not all dispensings in this population are captured in the PBS data.

Medicines of Interest
We included warfarin and all DOACs (apixaban, dabigatran, and rivaroxaban) publicly subsidized in Australia during the study period. Rivaroxaban was subsidized for prevention of stroke in people with AF in August 2013, and apixaban and dabigatran in September 2013; warfarin was subsidized for all indications for the entire study period.

Sociodemographic and Clinical Characteristics
We extracted the following sociodemographic and clinical information from the index admission: age at discharge, sex, AF diagnosis type (principal or secondary), use of direct-current cardioversion (DCC) (Australian Classification of Health Interventions procedure code 1340000), and length of stay. Direct-current cardioversion is a procedure that restores normal heart rhythm; anticoagulation is recommended for at least 4 weeks after cardioversion. We calculated each person’s risk of stroke using the sexless CHA$_2$DS$_2$-VA score, estimated using ICD-10-AM diagnoses identified in all hospitalizations in the 365 days before the index admission (inclusive), and supplemented using pharmaceutica dispensing information. A full list of ICD-10-AM codes and medicines are in Table S1. We calculated the CHA$_2$DS$_2$-VA score using the following components: age 65 to 74 years (1 point); age ≥75 years (2 points); heart failure (1 point); diabetes mellitus (1 point); stroke or transient ischemic attack (2 points); and vascular disease (1 point). People with a score of 0 are considered at low risk of stroke and do not require OACs, individuals with a score of 1 are deemed to be at moderate risk of stroke and OAC therapy should be considered, and individuals with a score of 2 or more have a high risk of stroke and OACs should always be prescribed in the absence of contraindications.

In addition to conditions included in the CHA$_2$DS$_2$-VA score, we also identified other comorbidities and conditions potentially associated with OAC use in the year before the index admission (inclusive) using both principal and secondary diagnoses, specifically venous thromboembolism, gastrointestinal bleeding, other bleeding conditions (eg, hematuria, hemoptysis), valvular disease, chronic kidney disease, acute kidney injury, liver disease, cancer, chronic obstructive pulmonary disease, dementia, and a history of falls (Table S1).

We quantified dispensing of other medicines within 90 days before the index admission, identified using World Health Organization Anatomical Therapeutic Chemical Classification System codes. These included the following: proton pump inhibitors (A02BC), antiplatelets (B01AC), digoxin (C01AA05), antiarrhythmics (C01B), vasodilators (C01D), diuretics (C03), beta-blockers (C07), dihydropyridine calcium channel blockers (C08 excluding C08D, C10BX03), nondihydropyridine calcium channel blockers (C08D), angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers (C09), lipid-lowering medicines (C10), and nonsteroidal anti-inflammatory drugs (M01A). A full list of medicines is in Table S2. From the Medicare Benefits Scheme data, we identified all professional attendances (eg, general practitioner and specialist visits) in the first 30 days after discharge.

Outcomes
Our primary outcome was OAC dispensing within 30 days of discharge, including the date of discharge. We also calculated persistence with OAC therapy among individuals who initiated OAC therapy within 30 days and discharged before July 1, 2014, to ensure at least 6 months of data capture postdischarge. We considered discontinuation (nonpersistence) as a gap in dispensing of 90 days or more, and only counted the first discontinuation event.

Within 365 days of discharge, we identified the following clinical outcomes among people with at least 1 year of follow-
up: all-cause mortality (within 30 and 365 days), all-cause readmission (within 30 and 365 days), hemorrhagic stroke (ICD-10-AM I60–I62), ischemic stroke (ICD-10-AM I63), and unspecified stroke (ICD-10-AM I64). We identified stroke outcomes in both hospitalization data and mortality data (underlying cause of death only). We expressed stroke outcomes as an incidence rate per 100 person-years, to account for patients who died within 1 year of discharge. We did not stratify outcomes by dispensing of OACs, because we cannot infer a causal relationship without properly accounting for underlying differences in individuals receiving and not receiving treatment.

Statistical Analysis
We compared the distribution of demographic and clinical characteristics by initiation using the $\chi^2$ test (for variables with $\geq 2$ categories) or $t$ test (for dichotomous variables). For the primary outcome of OAC dispensing within 30 days of discharge, we calculated time from discharge to first dispensing, with patients censored at death or 30 days postdischarge, whichever came first. We analyzed time to first dispensing using Cox regression, with the minimum time to dispensing set to 0.1 days. For the secondary outcome of persistence, we restricted this analysis to people who were dispensed an OAC within 30 days only, and who initiated before July 1, 2014. We calculated time to first discontinuation starting from the date of the first dispensing, censored at death, 365 days after discharge, or the end of follow-up, whichever came first. We analyzed the data using Cox regression. For both analyses, we estimated unadjusted (univariate) associations for all variables. We then created multivariable models adjusted for all relevant variables described above, with the exception of comorbidities included in calculation of the CHA2DS2-VA score (specifically prior stroke, hypertension, diabetes mellitus, heart failure, and vascular disease), to avoid overadjustment. While age is also used to calculate the CHA2DS2-VA score, it is crudely categorized and we included a more granular age variable in the model to account for residual confounding.

Sensitivity Analyses
Because our hospitalization data did not include information on admissions to private hospitals, we performed a sensitivity analysis excluding individuals who appeared to have been transferred to a private hospital before discharge; however, we did have data for medicines dispensed when people were private inpatients because the PBS subsidizes all medicines used by private hospital inpatients. Additionally, we also calculated the initiation rate excluding people readmitted to the hospital within 30 days, and persistence excluding people readmitted to the hospital within 365 days.

Results

Cohort Characteristics
We identified 71 184 OAC-naïve people admitted to the hospital with a principal or secondary AF diagnosis between July 1, 2011 and December 31, 2014. The median age at discharge was 78 years (interquartile range, 71–85), and 48.7% were female (Table 1). The median CHA2DS2-VA score was 3 (interquartile range, 2–4); 3.5% (n=2523) were considered at low risk of stroke (CHA2DS2-VA=0), 7.7% (n=5515) were at moderate risk (CHA2DS2-VA=1), and the majority (88.8%; n=63 146) were at high risk (CHA2DS2-VA $\geq$2).

In the 90 days before the index admission, dispensing of other cardiovascular medicines was common, particularly angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (54.7%), lipid-lowering medicines (47.5%), beta-blockers (38.0%), and antiplatelets (26.9%). A minority were dispensed medicines used for rate or rhythm control, such as digoxin (7.0%), nondihydropyridine calcium channel blockers (6.7%), and antiarrhythmics (8.0%). The majority (n=65 212; 91.7%) visited a health practitioner within 30 days of discharge.

Overall, 4.6% died and 15.9% were readmitted within 30 days of discharge, with rates lowest in people with a CHA2DS2-VA score of 0 (1.3% and 13.4%) and highest in people with a score $\geq$7 (11.9% and 21.9%). Among those with a year of follow-up, we observed 2.69 strokes per 100 person-years; this rose from 0.4 per 100 person-years in people with CHA2DS2-VA=0 to 11.6 in people with CHA2DS2-VA $\geq$7 (Figures S1 and S2).

OAC Initiation Within 30 Days of Discharge
Of 71 184 people hospitalized with AF, 16 175 (22.7%) initiated OAC therapy within 30 days of discharge (Table 2). The initiation rate nearly doubled from 17.0% in July to 33.7% in December (Table 2). Because DOACs were subsidized toward the end of the study period (late 2013), the majority of people initiated therapy on warfarin (n=10 935, 67.6%) rather than DOACs. The most common DOAC was rivaroxaban (n=2805, 17.3%) followed by apixaban (n=1829, 11.3%) and dabigatran (n=606, 3.7%). In 2014, 61.7% of people initiated on a DOAC (Figure).

In the univariate (unadjusted) analyses, initiation with an OAC increased with age up until age 75 to 79 years, and then decreased with age. The initiation rate was highest in people aged 75 to 79 years (29.0%) and least in people aged 95 years (3.7%) (Table 2). After adjustment for covariates, there was a
Table 1. Demographic and Clinical Characteristics of Oral Anticoagulant-Naïve Individuals Hospitalized With a Diagnosis of Atrial Fibrillation in New South Wales and Victoria, Australia (July 2011 to December 2014)

| Category                                                                 | n   | %    |
|-------------------------------------------------------------------------|-----|------|
| **N**                                                                  | 71 184 | 100.0 |
| **Age at discharge, y**                                                 |     |      |
| 18–49                                                                   | 1577 | 2.2  |
| 50–54                                                                   | 1027 | 1.4  |
| 55–59                                                                   | 1701 | 2.4  |
| 60–64                                                                   | 3429 | 4.8  |
| 65–69                                                                   | 7660 | 10.8 |
| 70–74                                                                   | 10 598 | 14.9 |
| 75–79                                                                   | 12 840 | 18.0 |
| 80–84                                                                   | 14 103 | 19.8 |
| 85–89                                                                   | 11 223 | 15.8 |
| 90–94                                                                   | 5335 | 7.5  |
| 95+                                                                     | 1691 | 2.4  |
| **Sex**                                                                 |     |      |
| Male                                                                    | 36 483 | 51.3 |
| Female                                                                  | 34 701 | 48.7 |
| **CHA2DS2-VASc score**                                                  |     |      |
| 0                                                                       | 2523 | 3.5  |
| 1                                                                       | 5515 | 7.7  |
| 2                                                                       | 13 592 | 19.1 |
| 3                                                                       | 21 448 | 30.1 |
| 4                                                                       | 15 605 | 21.9 |
| 5                                                                       | 8964 | 12.6 |
| 6                                                                       | 2880 | 4.0  |
| 7                                                                       | 548  | 0.8  |
| 8                                                                       | 109  | 0.2  |
| **Stroke or transient ischemic attack in 1 y before index admission**  |     |      |
| Any                                                                     | 7240 | 10.2 |
| Hemorrhagic stroke                                                      | 782  | 1.1  |
| Ischemic stroke                                                         | 4062 | 5.7  |
| Unspecified stroke                                                      | 1133 | 1.6  |
| Transient ischemic attack                                              | 1575 | 2.2  |
| **Comorbidities in 1 y before index admission**                        |     |      |
| Hypertension                                                            | 52 777 | 74.1 |
| Diabetes mellitus                                                       | 18 172 | 25.5 |
| Heart failure                                                           | 16 616 | 23.3 |
| Vascular disease                                                        | 15 584 | 21.9 |
| Gastrointestinal bleed                                                  | 3614 | 5.1  |
| Other history of bleeding                                               | 4397 | 6.2  |
| Venous thromboembolism                                                 | 2616 | 3.7  |

Table 1. Continued

| Category                                                                 | n   | %    |
|-------------------------------------------------------------------------|-----|------|
| Valvular disease                                                        | 4026 | 5.7  |
| Chronic kidney disease                                                  | 12 874 | 18.1 |
| Acute kidney injury                                                     | 13 375 | 18.8 |
| Liver disease                                                           | 15 63 | 2.2  |
| Cancer                                                                  | 6878 | 9.7  |
| Chronic obstructive pulmonary disease                                   | 7966 | 11.2 |
| Dementia                                                                | 5200 | 7.3  |
| Falls                                                                   | 12 597 | 17.7 |
| **Atrial fibrillation diagnosis type**                                  |     |      |
| Principal diagnosis                                                     | 17 958 | 25.2 |
| Secondary diagnosis                                                     | 53 226 | 74.8 |
| Visit to health practitioner within 30 d of discharge                   | 65 212 | 91.7 |
| **Atrial fibrillation hospitalization in 1 y before index admission**  |     |      |
| 0                                                                       | 35 341 | 49.6 |
| 1                                                                       | 17 140 | 24.1 |
| 2                                                                       | 8474  | 11.9 |
| ≥3                                                                     | 10 229 | 14.4 |
| **Direct current cardioversion during index admission**                | 2086 | 2.9  |
| **Length of index admission**                                           |     |      |
| 1–3 d                                                                  | 17 890 | 25.1 |
| 4–7 d                                                                  | 16 850 | 23.7 |
| 8–18 d                                                                 | 19 687 | 27.7 |
| >18 d                                                                  | 16 757 | 23.5 |
| **Dispensing of other medicines in 90 d before index admission**       |     |      |
| Lipid-lowering medicines                                               | 33 809 | 47.5 |
| Antiplatelets                                                           | 19 122 | 26.9 |
| ACEIs/ARBs                                                              | 38 970 | 54.7 |
| Diuretics                                                               | 34 020 | 30.7 |
| Calcium channel blockers (dihydropyridine)                             | 11 984 | 16.8 |
| Calcium channel blockers (nondihydropyridine)                          | 4766 | 6.7  |
| Beta-blockers                                                          | 22 084 | 31.0 |
| Digoxin                                                                 | 4960  | 7.0  |
| Antiarhythmics (eg, sotalol, amiodarone)                                | 5697  | 8.0  |
| Vasodilators                                                           | 8523  | 12.0 |
| Prescription NSAIDs                                                     | 6956  | 9.8  |
| Proton pump inhibitors                                                  | 30 358 | 42.6 |

ACEIs indicates angiotensin-converting-enzyme inhibitor; ARBs, angiotensin-receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.
Evidence-Practice Gaps in Oral Anticoagulant Use  
Schaffer et al

Figure. People with atrial fibrillation who were dispensed an oral anticoagulant within 30 days of hospital discharge. DOACs were first subsidized in September 2013. DOAC indicates direct oral anticoagulant (apixaban, dabigatran, rivaroxaban).

strong increasing dose–response relationship between the CHA2DS2-VA score and initiation, in people with a score ≥7 having a hazard ratio (HR) of 6.25 (95% CI 5.08–7.70) compared with people with a score of 0. Males were equally likely to initiate compared with females (HR=1.00, 95% CI 0.97–1.03) (Table 3). Initiation was more likely in later time periods after subsidy of DOACs for stroke prevention.

People with other indications for OAC therapy (other than those included in calculation of the CHA2DS2-VA score) were also more likely to initiate OAC therapy, such as venous thromboembolism (HR=2.65, 95% CI 2.49–2.83). People with potential contraindications for OAC therapy or at high risk of adverse events, such as gastrointestinal bleeding (HR=0.62, 95% CI 0.56–0.68), liver disease (HR=0.54, 95% CI 0.46–0.63), dementia (HR=0.44, 95% CI 0.40–0.49), and a history of falls (HR=0.70, 95% CI 0.66–0.74), were less likely to initiate OAC therapy. People with other comorbidities (cancer, chronic obstructive pulmonary disease, kidney disease) and indications of poorer health (longer length of stay, greater number of prior hospitalizations) were also less likely to initiate.

Persistence With OAC Therapy

Among people initiating OAC therapy within 30 days of hospital discharge and who were discharged before July 1, 2014 (n=12 142), we observed that 39.9% discontinued treatment at 1 year;10.7% discontinued after the first dispensing. Male sex, valvular disease, kidney disease, and a greater number of prior hospitalizations were associated with an increased risk of discontinuation (Table 4). People initiating with a DOAC were near half as likely to discontinue compared with those who initiated on warfarin (HR=0.55, 95% CI 0.50–0.60). There was also a dose–response relationship between CHA2DS2-VA score and discontinuation, with people with a score ≥7 least likely to discontinue (HR=0.22, 95% CI 0.14–0.35, compared with a score of 0).

Sensitivity Analyses

Initiation rates with OACs were similar after excluding people who were readmitted within 30 days of discharge (24.1%), who died within 30 days of discharge (23.6%), or who appeared to have been transferred to a private hospital (22.8%). Persistence was similar after excluding people who were readmitted within 1 year of discharge (37.9%).

Discussion

Despite evidence-based recommendations to prescribe OACs for AF postdischarge, we observed very low levels of dispensing in our cohort, even among high-risk individuals, with three quarters of hospitalized patients with a diagnosis of AF not dispensed an OAC within 30 days of discharge. Patterns of uptake did broadly reflect recommendations, with people with a higher CHA2DS2-VA score and other stroke risk factors, such as a history of venous thromboembolism, more likely to be dispensed an OAC. Conversely, people with contraindications for OAC therapy, such as a history of hemorrhagic stroke and gastrointestinal bleeding, as well as poorer health as measured by an increasing number of hospitalizations, cancer, dementia, and a history of falls were less likely to receive therapy. Encouragingly, initiation has been increasing over time with the subsidy of the DOACs.

Our observed rate of initiation was lower than in similar international studies. In a 2006 study of >300 000 patients with AF admitted to the hospital in Québec, Canada, 65% were prescribed warfarin within 1 year.24 Among 109 000 patients hospitalized in Denmark, 44% filled a prescription for an OAC within 90 days of discharge.25 In a 2018 US study of 388 045 patients with incident AF, only 34% had a dispensing for an OAC within 6 months.26 Within Australia, 2 small hospital-based studies found that only 32% to 36% of hospitalized patients with an AF diagnosis did not receive any OAC therapy.14,29 However, in a national Australian study of 2049 people hospitalized with stroke who had a previous diagnosis of AF, only 28% had been taking OACs, and only 33% of people with AF and ischemic stroke were discharged on OACs.30 Additionally, we also saw high rates of discontinuation, with greater persistence in people initiating with DOACs, consistent with previous real-world studies finding generally poor adherence to these medicines.17,18,31–33 As expected, people who received direct-current cardioversion were more likely to discontinue, because OACs may only be required in the short
Table 2. Characteristics of Patients Who Did and Did Not Initiate an Oral Anticoagulant Within 30 Days of Discharge in New South Wales and Victoria, Australia (July 2011 to December 2014)

| Characteristics                                      | Did Not Initiate Within 30 Days, n (%) | Initiated Within 30 Days, n (%) | P Value* |
|------------------------------------------------------|---------------------------------------|--------------------------------|----------|
| N                                                    | 55 009 (100.0)                        | 16 175 (100.0)                 |          |
| Age at discharge, y                                  |                                       |                                |          |
| 18–49                                                | 1361 (2.5)                            | 216 (1.3)                      | <0.001   |
| 50–54                                                | 848 (1.5)                             | 179 (1.1)                      |          |
| 55–59                                                | 1355 (2.5)                            | 346 (2.1)                      |          |
| 60–64                                                | 2647 (4.8)                            | 782 (4.8)                      |          |
| 65–69                                                | 5653 (10.3)                           | 2007 (12.4)                    |          |
| 70–74                                                | 7621 (13.9)                           | 2977 (18.4)                    |          |
| 75–79                                                | 9122 (16.6)                           | 3718 (23.0)                    |          |
| 80–84                                                | 10 641 (19.3)                         | 3462 (21.4)                    |          |
| 85–89                                                | 9284 (16.8)                           | 451 (2.8)                      |          |
| 90–95                                                | 1629 (3.0)                            | 62 (0.4)                       |          |
| 95+                                                  |                                       |                                |          |
| Sex                                                  |                                       |                                |          |
| Male                                                 | 26 698 (48.5)                         | 8003 (49.5)                    | 0.09     |
| Female                                               | 28 311 (51.5)                         | 8172 (50.5)                    |          |
| CHADS2-VAScore                                       |                                       |                                |          |
| 0                                                    | 2201 (4.0)                            | 322 (2.0)                      | <0.001   |
| 1                                                    | 4372 (7.9)                            | 1143 (7.1)                     |          |
| 2                                                    | 10 659 (19.4)                         | 2933 (18.1)                    |          |
| 3                                                    | 16 620 (30.2)                         | 4828 (29.8)                    |          |
| 4                                                    | 12 036 (21.9)                         | 3569 (22.1)                    |          |
| 5                                                    | 6548 (11.9)                           | 2416 (14.9)                    |          |
| 6                                                    | 2080 (3.8)                            | 800 (4.9)                      |          |
| 7                                                    | 413 (0.8)                             | 135 (0.8)                      |          |
| 8                                                    | 80 (0.1)                              | 29 (0.2)                       |          |
| Time period of index admission                       |                                       |                                |          |
| July–December 2011                                   | 7609 (13.8)                           | 1563 (9.7)                     | <0.001   |
| January–June 2012                                    | 7106 (6.9)                            | 1585 (5.1)                     |          |
| July–December 2012                                   | 8112 (8.5)                            | 1872 (6.4)                     |          |
| January–June 2013                                    | 7600 (8.7)                            | 1899 (6.9)                     |          |
| July–December 2013                                   | 8153 (10.2)                           | 2561 (10.1)                    |          |
| January–June 2014                                    | 7356 (10.3)                           | 2789 (12.2)                    |          |
| July–December 2014                                   | 9074 (14.2)                           | 3906 (19.5)                    |          |
| Stroke or transient ischemic attack in 1 y before index admission | | | |
| Any                                                  | 4434 (8.1)                            | 2806 (17.3)                    | <0.001   |
| Hemorrhagic stroke                                   | 632 (1.1)                             | 150 (0.9)                      | 0.02     |
| Ischemic stroke                                      | 2195 (4.0)                            | 1867 (12.1)                    | <0.001   |
| Unspecified                                          | 728 (1.3)                             | 405 (2.5)                      | <0.001   |

*Calculated using χ² test for variables with multiple categories, or t test for variables with 2 categories.
Table 3. Predictors of Oral Anticoagulant Initiation Within 30 Days of Discharge Among Oral Anticoagulant–Naïve Patients in New South Wales and Victoria, Australia (July 2011 to December 2014) Estimated From Cox Proportional Hazards Model (n=71 184)

| Age at discharge, y | Unadjusted Estimates From Univariate Model | Adjusted Estimates From Multivariable Model* |
|--------------------|-------------------------------------------|-------------------------------------------|
|                    | Hazard Ratio 95% CI | Hazard Ratio 95% CI |
| 18–49              | 0.44 0.38–0.50 | 0.81 0.69–0.94 |
| 50–54              | 0.57 0.49–0.66 | 1.01 0.86–1.18 |
| 55–59              | 0.67 0.60–0.75 | 1.16 1.03–1.30 |
| 60–64              | 0.76 0.70–0.82 | 1.27 1.16–1.38 |
| 65–69              | 0.89 0.84–0.94 | 1.07 1.01–1.14 |
| 70–74              | 0.96 0.92–1.01 | 1.19 1.13–1.25 |
| 75–79              | 1.00 Ref | 1.00 Ref |
| 80–84              | 0.83 0.79–0.87 | 0.89 0.85–0.94 |
| 85–89              | 0.58 0.55–0.61 | 0.67 0.63–0.71 |
| 90–95              | 0.27 0.24–0.29 | 0.32 0.29–0.35 |
| 95+                | 0.11 0.09–0.15 | 0.14 0.11–0.18 |

| Sex       | Unadjusted Estimates From Univariate Model | Adjusted Estimates From Multivariable Model* |
|-----------|-------------------------------------------|-------------------------------------------|
|           | Hazard Ratio 95% CI | Hazard Ratio 95% CI |
| Female    | 1.00 Ref | 1.00 Ref |
| Male      | 1.03 1.00–1.07 | 1.00 0.97–1.03 |

| Time period of index admission | Unadjusted Estimates From Univariate Model | Adjusted Estimates From Multivariable Model* |
|-------------------------------|-------------------------------------------|-------------------------------------------|
|                               | Hazard Ratio 95% CI | Hazard Ratio 95% CI |
| July–December 2011            | 1.00 Ref | 1.00 Ref |
| January–June 2012             | 1.07 1.00–1.15 | 1.06 0.99–1.14 |
| July–December 2012             | 1.11 1.03–1.18 | 1.08 1.01–1.16 |
| January–June 2013             | 1.19 1.11–1.27 | 1.16 1.08–1.24 |
| July–December 2013             | 1.44 1.35–1.54 | 1.44 1.35–1.54 |
| January–June 2014             | 1.69 1.59–1.79 | 1.73 1.63–1.84 |
| July–December 2014             | 1.88 1.77–1.99 | 1.96 1.85–2.08 |

| CHA2DS2-VA score | Unadjusted Estimates From Univariate Model | Adjusted Estimates From Multivariable Model* |
|------------------|-------------------------------------------|-------------------------------------------|
|                  | Hazard Ratio 95% CI | Hazard Ratio 95% CI |
| 0                 | 1.00 Ref | 1.00 Ref |
| 1                 | 1.69 1.49–1.91 | 1.61 1.41–1.84 |
| 2                 | 1.78 1.59–2.00 | 2.19 1.92–2.50 |
| 3                 | 1.86 1.66–2.09 | 2.84 2.48–3.25 |
| 4                 | 1.90 1.70–2.13 | 3.43 2.98–3.93 |
| 5                 | 2.30 2.05–2.58 | 4.89 4.24–5.63 |
| 6                 | 2.40 2.11–2.73 | 5.74 4.92–6.70 |
| 7–8               | 2.15 1.78–2.59 | 6.25 5.08–7.70 |

| Comorbidities in 1 y before index admission | Unadjusted Estimates From Univariate Model | Adjusted Estimates From Multivariable Model* |
|--------------------------------------------|-------------------------------------------|-------------------------------------------|
|                                            | Hazard Ratio 95% CI | Hazard Ratio 95% CI |
| Stroke                                     | 2.06 1.98–2.14 | * |
| Hypertension                               | 1.33 1.28–1.38 | * |
| Diabetes mellitus                          | 1.08 1.04–1.11 | * |
| Heart failure                              | 0.97 0.93–1.00 | * |
| Vascular disease                           | 0.86 0.82–0.89 | * |
| Gastrointestinal bleed                     | 0.47 0.42–0.51 | 0.62 0.56–0.68 |

Continued
term in this population. Adherence is key to efficacy of OACs, particularly in those at high risk of stroke, and thus it is reassuring that persistence increased along with the CHA2DS2-VA score. The low rates of initiation in our cohort in comparison to other studies may be partly explained by their relatively poorer health, with higher rates of comorbidities, such as falls, kidney disease, and prior bleeding, and high rates of readmission and mortality within 1 year of discharge. Additionally, the majority of patients had a secondary diagnosis rather than principal diagnosis, meaning that AF was not the main focus of the admission; even so, we still observed low rates of initiation in people with a principal AF diagnosis (36%). Many patients were also already taking other medicines that may be used for stroke prevention, such as antiplatelets. While we did not specifically examine uptake of these medicines after discharge, some patients may have been prescribed antiplatelets instead of OACs, despite the proven efficacy of OACs over antiplatelets. In fact, a large US study found that one third of people at moderate to high risk of stroke were receiving aspirin alone instead of OACs, particularly those with other cardiovascular conditions, such as angina, hypertension, and dyslipidemia.

Table 3. Continued

|                                      | Unadjusted Estimates From Univariate Model | Adjusted Estimates From Multivariable Model* |
|--------------------------------------|------------------------------------------|---------------------------------------------|
|                                      | Hazard Ratio 95% CI                       | Hazard Ratio 95% CI                         |
| Other history of bleeding            | 1.16 1.08–1.26                           | 1.12 1.04–1.20                              |
| Venous thromboembolism               | 2.29 2.13–2.47                           | 2.65 2.49–2.83                              |
| Valvular disease                     | 1.42 1.34–1.51                           | 1.34 1.27–1.43                              |
| Chronic kidney disease               | 0.72 0.69–0.75                           | 0.81 0.76–0.85                              |
| Acute kidney injury                  | 0.65 0.62–0.68                           | 0.81 0.77–0.86                              |
| Liver disease                        | 0.42 0.36–0.49                           | 0.54 0.46–0.63                              |
| Cancer                               | 0.34 0.31–0.37                           | 0.44 0.41–0.48                              |
| COPD                                 | 0.72 0.68–0.75                           | 0.86 0.82–0.91                              |
| Dementia                             | 0.31 0.28–0.34                           | 0.44 0.40–0.49                              |
| Falls                                | 0.47 0.44–0.49                           | 0.70 0.66–0.74                              |
| Atrial fibrillation diagnosis type   |                                         |                                             |
| Principal diagnosis                  | 2.14 2.07–2.21                           | 2.28 2.19–2.36                              |
| Secondary diagnosis                  | 1.00 Ref                                 | 1.00 Ref                                    |
| Atrial fibrillation hospitalization in 1 y before index admission | 0.68 0.65–0.72                           | 0.94 0.89–0.99                              |
| No. hospitalizations in 1 y before index admission | 1.00 Ref                                 | 1.00 Ref                                    |
| 1                                    | 0.75 0.72–0.77                           | 0.80 0.77–0.84                              |
| 2                                    | 0.60 0.57–0.63                           | 0.68 0.64–0.72                              |
| ≥3                                   | 0.42 0.39–0.44                           | 0.52 0.49–0.56                              |
| Direct-current cardioversion during index admission | 2.25 2.08–2.43                           | 1.52 1.42–1.62                              |
| Length of index admission            |                                         |                                             |
| 1–3 d                                | 1.00 Ref                                 | 1.00 Ref                                    |
| 4–7 d                                | 1.12 1.07–1.17                           | 1.48 1.41–1.55                              |
| 8–18 d                               | 0.92 0.89–0.96                           | 1.36 1.29–1.42                              |
| >18 d                                | 0.75 0.72–0.79                           | 1.25 1.18–1.32                              |

COPD indicates chronic obstructive pulmonary disease.

*Model adjusted for all variables in table except for stroke, hypertension, diabetes mellitus, heart failure, and vascular disease because these are included in calculation of the CHA2DS2-VA score.

Strengths and Limitations
This representative, population-based study of >70 000 OAC-naïve AF patients with detailed information on comorbidities and medicine use from multiple data sources is the largest study of postdischarge use of OACs in Australia. In contrast to many studies, we were able to look at the transition from
Table 4. Predictors of Nonpersistence Within 1 Year Among Patients Who Were Dispensed an Oral Anticoagulant Within 30 Days of Discharge in New South Wales and Victoria, Australia (July 2011 to June 2014) Estimated From Cox Proportional Hazards Model (n=12,142)

| Unadjusted Estimates From Univariate Model | Adjusted Estimates From Multivariable Model* |
|-------------------------------------------|---------------------------------------------|
| Hazard Ratio | 95% CI | Hazard Ratio | 95% CI |
| **Age at discharge, y** | | | |
| 18–54 | 0.70 | 0.53–0.94 | 1.10 | 0.91–1.32 |
| 55–64 | 1.01 | 0.84–1.24 | 0.80 | 0.70–0.91 |
| 65–74 | 1.00 | Ref | 1.00 | 0.92–1.07 |
| 75–84 | 0.87 | 0.78–0.97 | 1.00 | Ref |
| 85+ | 0.68 | 0.59–0.77 | 0.89 | 0.81–0.98 |
| **Sex** | | | |
| Female | 1.00 | Ref | 1.00 | Ref |
| Male | 1.20 | 1.13–1.27 | 1.14 | 1.07–1.21 |
| **First oral anticoagulant dispensed** | | | |
| Warfarin | 1.00 | Ref | 1.00 | Ref |
| Direct oral anticoagulant | 0.56 | 0.51–0.61 | 0.55 | 0.50–0.60 |
| **CHA2DS2-VASc score** | | | |
| 0 | 1.00 | Ref | 1.00 | Ref |
| 1 | 0.76 | 0.63–0.93 | 0.76 | 0.62–0.94 |
| 2 | 0.57 | 0.48–0.68 | 0.57 | 0.46–0.70 |
| 3 | 0.51 | 0.42–0.60 | 0.49 | 0.39–0.60 |
| 4 | 0.51 | 0.43–0.61 | 0.46 | 0.37–0.57 |
| 5 | 0.42 | 0.35–0.51 | 0.38 | 0.30–0.47 |
| 6 | 0.39 | 0.31–0.49 | 0.34 | 0.26–0.44 |
| 7–8 | 0.27 | 0.18–0.41 | 0.22 | 0.14–0.35 |
| **Comorbidities in 1 y before index admission** | | | |
| Stroke | 0.58 | 0.53–0.63 | * |
| Hypertension | 0.82 | 0.77–0.88 | * |
| Diabetes mellitus | 0.91 | 0.86–0.98 | * |
| Heart failure | 0.95 | 0.88–1.02 | * |
| Vascular disease | 1.38 | 1.29–1.47 | * |
| Gastrointestinal bleed | 0.98 | 0.81–1.17 | 0.92 | 0.76–1.11 |
| Other bleed | 1.08 | 0.96–1.22 | 1.03 | 0.91–1.17 |
| Venous thromboembolism | 1.16 | 1.04–1.30 | 1.07 | 0.95–1.20 |
| Valvular disease | 1.78 | 1.62–1.95 | 1.57 | 1.43–1.73 |
| Chronic kidney disease | 1.10 | 1.01–1.20 | 1.10 | 0.99–1.21 |
| Acute kidney injury | 1.18 | 1.08–1.28 | 1.12 | 1.01–1.24 |
| Liver disease | 1.00 | 0.73–1.38 | 0.82 | 0.59–1.13 |
| Cancer | 0.98 | 0.83–1.16 | 0.88 | 0.74–1.04 |
| Chronic obstructive pulmonary disease | 0.94 | 0.84–1.05 | 0.90 | 0.81–1.01 |
| Dementia | 0.86 | 0.70–1.06 | 0.95 | 0.77–1.16 |
| Falls | 0.95 | 0.86–1.05 | 1.04 | 0.93–1.16 |

Continued
hospital to community care, using the most contemporary data available. However, our study has several limitations. The PBS dispensing claims capture all subsidized medicines dispensed in the community and private hospitals, but privately prescribed (nonsubsidized) medicines were not captured in our data. In 2011, the most recent year for which data are available, 80% of warfarin was dispensed through the PBS, and we have restricted our study population to concessional beneficiaries who have incentive to have their medicines dispensed through the PBS, because of their less expensive cost as compared with a private prescription. Thus, we are likely capturing the majority of OAC dispensing in our population. We also could not assess primary nonadherence, and some people were likely prescribed OACs but never dispensed the medicines. In a Danish study, primary nonadherence for antithrombotics (including OACs) was 17%. We also did not exclude people with contraindications or who did not have any observed risk factors for stroke. Achieving a 100% dispensing rate is neither feasible nor desirable, as OACs carry an increased risk of hemorrhage and are not recommended in low-risk individuals, or in people with contraindications. Nonetheless, rates of initiation were well below acceptable rates, and we observed nearly 1200 incident strokes in the year after discharge, many of which could have been prevented. Our data are several years old and may not represent current practice. However, even if initiation rates doubled this would be below acceptable standards.

Future work should focus on determining whether this suboptimal use of OACs has persisted in more recent years.

### Conclusions

This is the first study of its size in Australia to look at the journey of patients with AF from admission to the hospital through to discharge to the community. We quantified for the first time that OACs are underused in people with AF discharged from the hospital. The effectiveness of OACs for stroke prevention is well established, and increasing rates of use in high-risk individuals even by a small amount could substantially reduce morbidity and mortality. Further research is needed to elucidate the reasons for underuse and whether they are patient, prescriber, or hospital factors, and how best to improve care in this population.

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### Table 4. Continued

| Diagnosis type                                             | Unadjusted Estimates From Univariate Model | Adjusted Estimates From Multivariable Model* |
|------------------------------------------------------------|-------------------------------------------|--------------------------------------------|
| Diagnosis type                                             | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI |
| Principal diagnosis                                        | 0.99         | 0.93–1.05 | 0.91         | 0.85–0.98 |
| Secondary diagnosis                                        | 1.00         | Ref     | 1.00         | Ref |
| Atrial fibrillation hospitalization in 1 y before index admission | 0.96         | 0.87–1.06 | 0.86         | 0.78–0.98 |
| No. hospitalizations in 1 y before index admission         | 1.00         | Ref     | 1.00         | Ref |
| 0                                                          | 1.09         | 1.02–1.17 | 1.14         | 1.05–1.23 |
| 1                                                          | 1.16         | 1.05–1.28 | 1.22         | 1.09–1.36 |
| 2                                                          | 1.19         | 1.06–1.33 | 1.27         | 1.12–1.44 |
| ≥3                                                         | 1.61         | 1.44–1.79 | 1.47         | 1.31–1.64 |
| Direct-current cardioversion during index admission         | 0.97         | 0.89–1.05 | 0.91         | 0.83–0.98 |
| 1                                                          | 1.14         | 1.05–1.23 | 0.95         | 0.87–1.04 |
| >18 d                                                      | 0.95         | 0.87–1.04 | 0.84         | 0.75–0.94 |

*Model adjusted for all variables in table except for stroke, hypertension, diabetes mellitus, heart failure, and vascular disease because these are included in calculation of the CHA2DS2-VASA score.
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SUPPLEMENTAL MATERIAL
Table S1. List of diagnosis codes and medicines used to define conditions.

| Condition       | ICD-10 codes in hospital diagnosis                                                                 | Medicine dispensings (WHO ATC codes)                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Components of CHA2DS2-VA score                                                                 |                                                                                                      |
| Hypertension    | I10 – Essential (primary) hypertension<br>I11 – Hypertensive heart disease<br>I12 – Hypertensive renal disease<br>I13 – Hypertensive heart and renal disease<br>I15 – Secondary hypertension | Dihydropyridine calcium channel blockers (C08 excluding C08D, C10BX03) (*Note: non-dihydropyridine calcium channel blockers such as diltiazem and verapamil were excluded as they are more commonly used for rate control in this population)<br>ACEIs/ARBs (C09)<br>Thiazide and thiazide-like diuretics (C03A, C03EA01, C03BA11, C03BA04)<br>Moxonidine (C02AC05) |
| Diabetes        | E10 – Type 1 diabetes mellitus<br>E11 – Type 2 diabetes mellitus<br>E12 – Malnutrition-related diabetes mellitus<br>E13 – Other specified diabetes mellitus<br>E14 – Unspecified diabetes mellitus | Drugs used in diabetes (A10)                                                                           |
| Heart failure   | I10.0 – Hypertensive heart disease with (congestive) heart failure<br>I13.0 – Hypertensive heart and renal disease with (congestive) heart failure<br>I13.2 – Hypertensive heart and renal disease with both (congestive) heart failure and renal failure<br>I50 – Heart failure |                                                                                                      |
| Stroke          | *Haemorrhagic*<br>I60 – Subarachnoid haemorrhage<br>I61 – Intracerebral haemorrhage<br>I62 – Other nontraumatic intracranial haemorrhage |                                                                                                      |
|                 | *Ischaemic*                                                                                         |                                                                                                      |
| Code | Description |
|------|-------------|
| I63  | Cerebral infarction |
| I64  | Stroke, not specified as haemorrhagic or infarction |
| I64  | Transient ischaemic attack |
| G45.9| Transient cerebral ischaemic attack, unspecified |

**Vascular disease**

| Code | Description |
|------|-------------|
| I21  | Acute myocardial infarction |
| I22  | Subsequent MI |
| I23  | Certain current complications following AMI |
| I24  | Other acute ischaemic heart diseases |
| I25  | Chronic ischaemic heart disease |
| I70  | Atherosclerosis |
| I71  | Aortic aneurysm and dissection |
| I73  | Other peripheral vascular diseases |

**Comorbidities and risk factors**

**Chronic kidney disease**

| Code | Description |
|------|-------------|
| E10.2| Type 1 diabetes mellitus with renal complications |
| E11.2| Type 2 diabetes mellitus with renal complications |
| E13.2| Other specified diabetes mellitus with renal complications |
| E14.2| Unspecified diabetes mellitus with renal complications |
| I12  | Hypertensive renal disease |
| I13  | Hypertensive heart and renal disease |

| Code | Description |
|------|-------------|
| N08  | Glomerular disorders in diseases classified elsewhere |
| N18  | Chronic kidney disease |
| N19  | Unspecified kidney failure |

**Acute kidney injury**

| Code | Description |
|------|-------------|
| N17  | Acute renal failure |

**Liver disease**

| Code | Description |
|------|-------------|
| B16  | Acute hepatitis B |
| B17  | Other acute viral hepatitis |
| B18  | Chronic viral hepatitis |
| Code  | Condition                                                                 |
|-------|---------------------------------------------------------------------------|
| B19   | Unspecified viral hepatitis                                                |
| K70   | Alcoholic liver disease                                                   |
| K71   | Toxic liver disease                                                       |
| K72   | Hepatic failure, not elsewhere classified                                  |
| K73   | Chronic hepatitis, not elsewhere classified                                |
| K74   | Fibrosis and cirrhosis of the liver                                       |
| K76.0 | Fatty (change of) liver, not elsewhere classified                          |
| K76.2 | Central haemorrhagic necrosis of the liver                                |
| K76.6 | Portal hypertension                                                       |
| K76.7 | Hepatorenal syndrome                                                      |
|       |                                                                           |
| COPD  |                                                                           |
| J40   | Bronchitis, not specified as acute or chronic                             |
| J41   | Simple and mucopurulent chronic bronchitis                                |
| J42   | Unspecified chronic bronchitis                                            |
| J43   | Emphysema                                                                 |
| J44   | Other chronic obstructive pulmonary disease                               |
|       |                                                                           |
| Cancer|                                                                           |
| C00-C97 | Malignant neoplasms                                                       |
|       |                                                                           |
| Dementia and Alzheimer disease |                                                                           |
| F00   | Dementia in Alzheimer disease                                             |
| F01   | Vascular dementia                                                         |
| F02   | Dementia in other disease classified elsewhere                            |
| F03   | Unspecified dementia                                                      |
| G30   | Alzheimer disease                                                         |
|       |                                                                           |
| Venous thromboembolism |                                                                           |
| I26   | Pulmonary embolism                                                        |
| I80   | Phlebitis and thrombophlebitis                                            |
| I82.8 | Embolism and thrombosis of other specified veins                          |
| I82.9 | Embolism and thrombosis of unspecified vein                              |
| O22.3 | Deep phlebothrombosis in pregnancy                                       |
| O22.9 | Venous complication in pregnancy, unspecified                           |
| O87.1 | Deep phlebothrombosis in the puerperium                                  |
|       |                                                                           |
|       | Anti-dementia drugs (N06D)                                                 |
| **Gastrointestinal bleed** | K25.0 – Gastric ulcer, acute with haemorrhage  
K25.2 – Gastric ulcer, acute with both haemorrhage and perforation  
K25.4 – Gastric ulcer, chronic or unspecified with haemorrhage  
K25.6 – Gastric ulcer, chronic or unspecified with both haemorrhage and perforation  
K26.0 – Duodenal ulcer, acute with haemorrhage  
K26.2 – Duodenal ulcer, acute with both haemorrhage and perforation  
K26.4 – Duodenal ulcer, chronic or unspecified with haemorrhage  
K26.6 – Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation  
K27.0 – Peptic ulcer, site unspecified, acute with haemorrhage  
K27.2 – Peptic ulcer, site unspecified, acute with both haemorrhage and perforation  
K27.4 – Peptic ulcer, chronic or unspecified with haemorrhage  
K27.6 – Peptic ulcer, chronic or unspecified with both haemorrhage and perforation  
K28.0 – Gastrojejunal ulcer, site unspecified, acute with haemorrhage  
K28.2 – Gastrojejunal ulcer, site unspecified, acute with both haemorrhage and perforation  
K28.4 – Gastrojejunal ulcer, chronic or unspecified with haemorrhage  
K28.6 – Gastrojejunal ulcer, chronic or unspecified with both haemorrhage and perforation  
K29.0 – Acute haemorrhagic gastritis  
K62.5 – Haemorrhage of anus and rectum  
K92.0 – Haematemesis  
K92.1 – Melaena  
K92.2 – Gastrointestinal haemorrhage, unspecified |  |
| **Other bleeding** | D68.3 – Haemorrhagic disorder due to circulating anticoagulants  
H35.6 – Retinal haemorrhage  
H43.1 – Vitreous haemorrhage  
H45.0 – Vitreous haemorrhage in diseases classified elsewhere |
| Code     | Description                                      |
|----------|--------------------------------------------------|
| K66.1    | Haemoperitoneum                                 |
| M25.0    | Haemarthrosis                                   |
| N02      | Recurrent and persistent haematuria             |
| N93.8    | Other specified abnormal uterine and vaginal bleeding |
| N93.9    | Abnormal uterine and vaginal bleeding, unspecified |
| N95.0    | Postmenopausal bleeding                         |
| R04.1    | Haemorrhage from throat                         |
| R04.2    | Haemoptysis                                     |
| R04.8    | Haemorrhage from other sites in respiratory passage |
| R04.9    | Haemorrhage from respiratory passages, unspecified |
| R31      | Unspecified haematuria                          |
| R58      | Haemorrhage, not elsewhere classified           |

**Valvular disease**

| Code     | Description                                      |
|----------|--------------------------------------------------|
| I05      | Rheumatic mitral valve disease                   |
| I06      | Rheumatic aortic valve disease                   |
| I34      | Nonrheumatic mitral valve disorders              |
| I35      | Nonrheumatic aortic valve disorders              |

**Falls**

| Code     | Description                                      |
|----------|--------------------------------------------------|
| W00-W19  | Falls                                            |
| Medicine class                          | WHO ATC code | Five most commonly dispensed in class                                                                 |
|----------------------------------------|--------------|-------------------------------------------------------------------------------------------------------|
| Proton pump inhibitors                 | A02BC        | Pantoprazole, esomeprazole, omeprazole, rabeprazole, lansoprazole                                   |
| Antiplatelets                          | B01AC        | Aspirin, clopidogrel, clopidogrel + aspirin, dipyridamole + aspirin, ticagrelor                       |
| Digoxin                                | C01AA05      | Digoxin                                                                                               |
| Antiarrhythmics                        | C01B         | Sotalol, amiodarone, flecaainide, disopyramide, lignocaine                                           |
| Vasodilators                           | C01D         | Glyceryl trinitrate, isosorbide mononitrate, nicorandil, perhexilene, isosorbide dinitrate           |
| Diuretics                              | C03          | Frusemide, spironolactone, indapamide, hydrochlorothiazide, amiloride + hydrochlorothiazide          |
| Beta-blockers                          | C07          | Metoprolol tartrate, atenolol, bisoprolol, carvedilol, nebivolol                                     |
| Dihydropyridine calcium channel blockers| C08 (excluding C08D), C10BX03 | Amlodipine, lercanidipine, felodipine                                                                |
| Non-dihydropyridine calcium channel blockers | C08D | Diltiazem, verapamil                                                                                   |
| ACE inhibitors/ARBs                    | C09          | Perindopril, irbesartan, ramipril, candesartan, irbesartan + hydrochlorothiazide                     |
| Lipid-lowering medicines               | C10          | Atorvastatin, rosuvastatin, simvastatin, pravastatin, ezetimibe                                      |
| NSAIDs                                 | M01A         | Meloxicam, celecoxib, diclofenac, indomethacin, naproxeen                                            |
**Figure S1.** All-cause mortality by CHA\textsubscript{2}DS\textsubscript{2}-VA score among people with ≥ 365 days of follow up (n=58 204).

![Figure S1](image)

**Figure S2.** Incidence of stroke by CHA\textsubscript{2}DS\textsubscript{2}-VA score among people with ≥ 365 days of follow up (n=58 204).

![Figure S2](image)