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Original Research

Old age, high risk medication, polypharmacy: a 'trilogy' of risks in older patients with atrial fibrillation

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ABSTRACT*
Background: The safety of pharmacotherapy in atrial fibrillation (AF) is compounded by a trilogy of risks old age, high-risk medications (e.g., antithrombotics, antiarrhythmics), polypharmacy due to multiple patient comorbidities. However, to date, scarce study has investigated the use of polypharmacy (including potentially inappropriate medication (PIM)) in AF patients, and how this may contribute to their overall risk of medication misadventure.
Objectives: To review the extent of polypharmacy and PIM use in older patients (65 years or older) with AF.
Methods: Information was extracted from a database characterising a cohort of older AF patients treated in general practice in New South Wales, Australia. Patient characteristics, number and types of drugs, the degree of PIM use were recorded. The predictors for the use of polypharmacy in older AF patients were identified.
Results: Overall, 367 patients (mean age 77.8 years) were reviewed, among which 94.8% used 5 medications or more and over half used 10 medications or more. Cardiovascular agents were most commonly used (98.9%), followed by antithrombotics (90.7%). Among agents deemed PIMs, digoxin (30.2%) was the most frequently used, followed by benzodiazepines (19.6%), and sotalol (9.8%). AF patients using polypharmacy were more likely to have low bleeding risk (OR=10.97), representing those patients in whom high-risk antithrombotics are mostly indicated. Patients with major-polypharmacy (5-9 medications) are more likely to have obstructive pulmonary diseases (OR=2.32), upper gastrointestinal diseases (OR=2.02) and poor physical function (OR=1.04), but less likely to have cognitive impairment (OR=0.27).
Conclusion: Polypharmacy affects oldest AF patients, comprising medications that are indicated for AF, yet regarded as PIMs. Patients with lower risk of bleeding, obstructive pulmonary diseases, upper gastrointestinal diseases and poor physical function are also at higher risk of using higher number of medications. This may lead to an increased risk for medication misadventure due to the concomitant use of polypharmacy and medications for AF.

Keywords: Polypharmacy; Atrial Fibrillation; Drug-Related Side Effects and Adverse Reactions; Aged; Inappropriate Prescribing; Australia

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INTRODUCTION

Atrial fibrillation (AF) is a leading cause of morbidity and mortality. It is associated with a significantly increased risk of stroke, heart failure and dementia.[1] In regard to its management, the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend the use of both antiarrhythmics and antithrombotics.[1,2] Similar recommendations are presented within Australian guidelines.[3] However, despite guidelines, patients with AF present a quandary for health care professionals. First, their age (i.e., being older persons) presents specific challenges in the selection of medicines and associated management, due to age-related physiological changes as well as functional and cognitive impairments.[4] Second, the need to use high-risk medications (e.g., antithrombotics and antiarrhythmics), as indicated by clinical guidelines, increases their risk for medication misadventure (e.g., bleeding, bradyarrhythmias).[1]

However, the risks do not stop here. In fact, patients with AF are exposed to a trilogy of risks, inherent to their overall disease presentation and management. Aside from their advancing age and the use of high-risk medicines, there is an additional risk factor: polypharmacy. A multitude of agents may be prescribed to AF patients for stroke prevention, management of the arrhythmia, treatment of accompanying cardiovascular and stroke risk factors, as well as therapies for other comorbidities. Collectively, these complicate medication management and increase the risk of medication misadventure, manifesting as non-adherence, adverse drug reactions (ADRs), and drug interactions, all of which can lead to poor clinical outcomes.[5] In turn, this complicates health professionals' decision-making, particularly in relation to prescribing anticoagulation for stroke prevention.[6]

International studies have shown that polypharmacy is common in patients with AF[7,8] and in patients using anticoagulants.[3] However, in Australia, little attention has been paid to the degree of polypharmacy in elderly AF patients and how this may contribute to their overall risk of medication misadventure. Therefore, the aim of this study was to characterise AF patients in the Australian primary care setting in terms of this 'trilogy' of risks, and to specifically: 1) describe the extent of use of polypharmacy in older AF patients; 2) determine the degree to which these medications may be potentially inappropriate; 3) identify factors

associated with the use of polypharmacy; and 4) identify factors associated with major polypharmacy versus minor polypharmacy in older AF patients.

METHODS

Ethical approval

Ethics approval was obtained from the participating institutions.[9] Patient data were coded and de-identified prior to analysis.

Design

In this cross-sectional study, information was extracted from a database pertaining to a cohort of AF patients (65 years or older) recruited for a previous study conducted in general practices within metropolitan and regional areas of New South Wales, Australia (detailed description of the study recruitment/data collection methods is reported elsewhere).[9] Patients with a confirmed diagnosis of AF were recruited by their general practitioners (GPs) during routine care.

Data Collection

Purpose-designed data collection instruments were used to extract and record data from medical notes, patient interviews, and a brief patient survey (e.g., medical history, medication use). All collected data were verified by the patients' GPs.

Definitions and Measures

Polypharmacy is most commonly defined as the use of five or more regular medications.[10] For the purposes of this study, polypharmacy was categorised as follows[11]:

- Non-Polypharmacy: four or less medications
- Minor-Polypharmacy: use of five to nine medications
- Major-Polypharmacy: concomitant use of ten or more medications

Diagnoses were coded using the World Health Organization (WHO) International Statistical Classification of Diseases, 10th Revision (ICD-10).[12] CHADS2[13] and CHA2DS2VASc[14] scores 0, 1, 2 or over were classified as low, intermediate and high stroke risk, respectively. HAS-BLED[15] scores 0, 1-2, 3 or over were classified as low, intermediate and high bleeding risk, respectively. HEMORR2HAGES[16] scores 0-1, 2-3, 4 or over were classified as low, intermediate and high bleeding risk, respectively. In this study, CHA2DS2VASc and HAS-BLED were used as they are commonly recommended by international guidelines.[14,15] Although CHA2DS2VASc and HAS-BLED are advocated in more recent European Society of Cardiology guidelines, CHADS2 was additionally used in this study because it is included in Australian local guidelines (e.g., National Prescribing Service guideline (2013)[17], Therapeutic Guidelines (2012)[18]), while HEMORR2HAGES was used because it is recommended by National Clinical Guideline Centre (UK) and American College of Cardiology/American Heart Association guidelines.[16,19] Moreover, since these scoring tools have different sensitivities and specificities, the use of four scores assisted in reducing any false positives and false negatives in the risk assessment. SF-36, a survey, which provides psychometrically-based physical and mental health summary measures and a preference-based health utility index, was also used.[20]

Recorded medications included both over-the-counter and prescription medicines used by patients (as documented in their medication histories), regardless of short-term or long-term use. All medications were classified according to Anatomical Therapeutic Chemical (ATC) classification system.[21] The medications used by patients were then assessed to whether they were 'potentially inappropriate medicines' (PIMs) for older patients, according to two explicit criteria, i.e. Beers criteria 2012[22] and PRISCUS criteria.[23] Both Beers criteria and PRISCUS criteria were selected because of slight variations in defining certain medications as potentially inappropriate based on the dosage (e.g., digoxin).

Statistical Analysis

Computerised data analysis employed SPSS (Statistical Package for the Social Sciences Version.[19] To explore relationships involving continuous variables, ANOVA (parametric distribution) and Kruskal-Wallis (non-parametric distribution) were used. The Chi-square test examined differences in independent proportions. Multivariate logistic regression (Forward Wald) analysis was used to assess the influence of the predictors on polypharmacy. $p<0.1$ was used in multivariate logistic regression. $p<0.05$ was considered statistically significant for all other analysis.

RESULTS

Patient characteristics

The mean age of patients (N=367) was 77.8 years; two-thirds were less than 75 years old. The age categories were based on those used by clinical guidelines for anticoagulant treatment, as well as the apparent distribution of polypharmacy by age in the cohort (Table 1). In terms of their AF history, most (87.5%) patients had AF for at least 1 year, with over half (57.5%) diagnosed as having persistent AF. Most patients were categorised as being at least at intermediate risk of stroke (92.1% by CHADS2 and 100% by CHA2DS2VASc). Over half of the patients (53.4%) were identified to have 'intermediate' or 'high' bleeding risk as per HEMORR2HAGS and 93.9% patients were identified to have 'intermediate' or 'high' as per HAS-BLED scores.

Extent of polypharmacy

Overall, 348 (94.9%) patients were using some degree of polypharmacy, whilst just over half (55.9%; n=205) of the patients were using major-polypharmacy (Table 1). Compared to patients in the non-polypharmacy group (5.1% of patients), those with minor-polypharmacy and major-polypharmacy had more comorbidities ($p<0.01$)

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Table 1. Patient characteristics

Characteristics **N (%) of patients** 367 (100)	**Non-polypharmacy (0-4 drugs)** (% of total) 19 (5.2)	**Minor-polypharmacy (5-9 drugs)** (% of total) 143 (39.0)	**Major-polypharmacy (≥10 drugs)** (% of total) 205 (55.9)	**p-value***
Gender				0.07
male	13 (3.5)	87 (23.7)	103 (28.1)	
female	6 (1.6)	56 (15.3)	102 (27.8)	
Age μ (SD)	75.5 (6.8)	77.5 (6.9)	78.2 (7.1)	0.17
Age group				0.38
≥75 years	9 (2.4)	91 (24.8)	129 (24.6)	
<75 years	10 (2.7)	52 (14.2)	76 (20.7)	
Type of AF				0.56 †
Paroxysmal	5 (1.4)	49 (13.3)	73 (19.9)	
Persistent	12 (3.3)	86 (23.4)	113 (30.8)	
New Onset	1 (0.3)	6 (1.6)	14 (3.8)	
Unknown	1 (0.3)	2 (0.6)	5 (1.4)	
History of AF				0.78
<1 year	3 (0.8)	16 (4.4)	27 (7.4)	
≥ 1 year	16 (4.4)	127 (34.6)	178 (48.5)	
Current Cardiac Rhythm				0.22‡
Normal Sinus Rhythm	2 (0.8)	11 (3.0)	28 (7.6)	
Controlled AF	17 (4.6)	131 (8.4)	177 (48.2)	
Uncontrolled AF	0 (0.0)	1 (0.3)	0 (0.0)	
$CHADS_2$ score§				
Low	4 (1.2)	11 (3.0)	14 (3.8)	0.004
Intermediate	7 (1.9)	53 (14.4)	48 (13.1)	
High	8 (2.4)	77 (20.9)	143 (38.9)	
CHA_2DS_2-VASc score§				
Intermediate	2 (0.6)	6 (1.6)	6 (1.6)	0.24
High	17 (4.6)	137 (37.3)	199 (54.2)	
$HEMORR_2HAGS$ score¶				
Low	14 (3.8)	75 (20.4)	81 (22.1)	0.04
Intermediate	3 (0.8)	65 (17.7)	116 (31.6)	
High	2 (0.6)	3 (0.8)	8 (2.4)	
HAS-BLED score#				
Low	1 (0.3)	2 (0.6)	2 (0.6)	0.51
Intermediate	15 (4.1)	124 (33.8)	177 (48.2)	
High	3 (0.8)	17 (4.6)	26 (7.1)	

* Difference among non-polypharmacy, minor-polypharmacy and major-polypharmacy
† P value: persistent compared with all other
‡ P value: sinus rhythm compared with all other
§ $CHADS_2$ (13) and CHA_2DS_2VASc (14) scores of 0, 1, ≥ 2 were classified as low, intermediate and high stroke risk, respectively.
¶ $HEMORR_2HAGES$ (16) scores of 0-1, 2-3, ≥ 4 were classified as low, intermediate and high bleeding risk, respectively.
# HAS-BLED (15) scores of 0, 1-2, ≥ 3 were classified as low, intermediate and high bleeding risk, respectively.

(Table 2). In terms of major diseases (excluding AF), patients in the major-polypharmacy group had a higher incidence of diabetes (p<0.01), upper gastrointestinal (GI) discomfort (p<0.01), and asthma or chronic obstructive pulmonary disease (p<0.01). Patients in the major-polypharmacy group had a significantly lower SF-36 physical score than those with minor-polypharmacy or non-polypharmacy (p=0.01).

Polypharmacy in AF patients according to 'risk category'

When comparing the use of polypharmacy by stroke risk (per CHADS2), a higher proportion of patients used polypharmacy among those at high risk of stroke, compared to those at low risk of stroke (98.4% vs. 84.6%, p=0.002). When compared by bleeding risk (per HEMORR2HAGS), a higher proportion of patients used polypharmacy among those at intermediate risk of bleeding, compared to those at high risk of bleeding (96.5% vs. 86.2%, p=0.013) (Table 1). When comparing the use of polypharmacy across various risk categories per CHA2DS2VASc and HAS-BLED scores, no significant difference was found.

A number of patients were identified as having specific medication safety issues that might affect a patient's medication management ability and/or put them at a risk of medication misadventure. Among those patients with documented cognitive impairment (n=18), 83.3% had major-polypharmacy and the remainder had minor-polypharmacy. Among all of the patients who reportedly needed assistance with medication management, 46.3% had major-polypharmacy and the remainder had minor-polypharmacy. All patients with poor medication adherence (self-reported) had some degree of polypharmacy; almost three quarters (72.7%) of these patients had major-polypharmacy (Table 2).

Number and types of drugs

Patients with major-polypharmacy used almost two and half times the mean number of medications (mean=2.5, SD=1.0) per diagnosed disease, compared to non-polypharmacy patients (mean=1.1, SD=0.5, P<0.01). Unsurprisingly, drugs

Table 2. Medication safety considerations

Characteristics **N (%) of patients** 367 (100)	**Non-polypharmacy (0-4 drugs)** (% of total) 19 (5.2)	**Minor-polypharmacy (5-9 drugs)** (% of total) 143 (39.0)	**Major-polypharmacy (≥10 drugs)** (% of total) 205 (55.9)	**p-value***
Comorbidities. μ (SD)	4.7 (3.3)	5.0 (2.4)	6.3 (2.4)	<0.01
Number of drugs (both prescription and non-prescription). μ (SD)	3.9 (0.6)	7.4 (1.4)	13.9 (3.4)	<0.01
Prescription drugs μ (SD)	3.47 (0.6)	6.3 (1.5)	12.0 (3.3)	<0.01
Non-prescription drugs (e.g., OTC, supplements). μ (SD)	0.21 (0.4)	1.08 (1.0)	1.9 (1.4)	<0.01
Cognitive impairment	0 (0.0)	3 (0.8)	15 (4.1)	0.07
Visual impairment	0 (0.0)	8 (2.2)	14 (3.8)	0.70
Hearing impairment	2 (0.6)	9 (7.9)	20 (6.2)	0.48
Language barrier	0 (0.0)	1 (0.3)	3 (0.8)	0.71
Mobility impairment	1 (0.3)	4 (1.1)	12 (3.3)	0.34
Residential care facility	0 (0.0)	1 (0.3)	3 (0.8)	0.71
Difficulty access medical care	0 (0.0)	2 (0.6)	1 (0.3)	0.63
Need assistance with medication	4 (1.1)	51 (13.9)	95 (25.9)	0.03
Poor adherence (self-reported)	0 (0.0)	6 (1.6)	16 (4.4)	0.27
Other major diseases				
Chronic heart failure	3 (0.8)	38 (10.3)	51 (13.9)	0.65
Hypertension	12 (3.7)	97 (26.4)	140 (38.1)	0.88
Diabetes	1 (0.3)	37 (10.1)	35 (9.5)	0.03
Prior stroke or TIA	5 (7.5)	27 (7.3)	35 (9.5)	0.52
Coronary heart disease	3 (0.8)	43 (11.7)	64 (16.9)	0.40
Asthma or COPD	4 (1.1)	12 (3.7)	43 (11.7)	<0.01
Arthritis (OA, RA, Psoriasis Arthritis)	3 (0.8)	32 (8.7)	62 (16.9)	0.16
Upper GI discomfort †	3 (0.8)	33 (8.9)	88 (24.0)	<0.01
Renal disease	0 (0.0)	7 (1.9)	9 (2.3)	0.92
Previous fall	0 (0.0)	4 (1.2)	7 (1.2)	1.00
Self-reported Health SF-36 ‡				
Physical. μ (SD)	46.5 (5.9)	45.1 (8.2)	42.4 (7.4)	<0.01
Mental. μ (SD)	58.2 (3.8)	55.4 (7.1)	54.8 (7.4)	0.10

TIA =transient ischaemic attack, COPD =chronic obstructive pulmonary disease, OA =osteoarthritis, RA= rheumatoid arthritis, GI= gastrointestinal, SF-36 =The Short Form (36) Health Survey is a patient-reported survey of patient health.
* Difference between non-polypharmacy, minor-polypharmacy and major-polypharmacy
† Upper GI diseases include gastric ulcer, gastritis, esophagitis/ulcer, duodenal ulcer or gastroesophageal reflux disease
‡ SF-36, a survey, which provides psychometrically-based physical and mental health summary measures and a preference-based health utility index (54). A high score of SF-36 means better health. Physical includes: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning. Mental includes: Role-Emotional, Mental Health

acting on the cardiovascular system, as well as blood and blood forming agents, were the most commonly used medications (Table 3 and 4). Since all patients had at least an intermediate stroke risk (as per CHA2DS2VASc), most were taking warfarin±aspirin (79.8%) and around one in ten were on dabigatran (11.7%). Around one in twenty patients were using aspirin or clopidogrel (6.8%) (Table 5). Among all patients, nearly two-thirds were using beta blockers (59.4%), while around one in ten patients were using sotalol (9.8%) or nondihydropyridine calcium channel blockers (10.3%). Surprisingly, 30.2% patients were using digitalis glycosides (digoxin), despite it not being indicated as a first-line therapy by clinical guidelines (24) and noting that it is identified as a PIM. Among "non-cardiovascular" medications, analgesics (N02) and drugs for acid-related disorders were most commonly used (taken by over half of the patients). Among these, 55.3% of patients were using analgesics in combination with antithrombotics, comprising 137 (37.3%) patients using warfarin concurrently with paracetamol, 32 (8.7%) patients using warfarin concurrently with opioids, and 9 (2.5%) patients using warfarin concurrently with nonsteroidal anti-inflammatory drugs (NSAIDs).

Factors associated with polypharmacy versus non-polypharmacy

Univariate analysis was used to identify the factors associated with polypharmacy (5 medications or more) versus non-polypharmacy. Univariate analysis identified that patients using polypharmacy were more likely to have a higher stroke risk, per CHADS2 (OR=4.40, 95%CI 1.23-15.66, p=0.03 compared with low stroke risk) and a lower bleeding risk, per HEMORR2HAGS (OR=10.97, 95%CI 1.66-72.60, p=0.01 compared with high bleeding risk). In multivariate analysis, only a lower bleeding risk (HEMORR2HAGS) remained a significant predictor of polypharmacy (OR=10.97, 95%CI 1.66-72.60, p=0.01) (Model: Cox&Snell R^2=0.03, Nagelkerke R^2=0.09, 94.8% correctly predicted). CHA2DS2VASc and HAS-BLED were not found to be significantly associated with polypharmacy.

Univariate analysis was used to identify the factors associated with major-polypharmacy versus minor-polypharmacy. Univariate analysis identified that patients using major-polypharmacy were more likely to have higher number of comorbidities (OR=1.28, 95%CI 1.15-1.42, p<0.001), upper gastrointestinal disease (includes gastric ulcer, gastritis, oesophagitis/ulcer, duodenal ulcer or

Table 3. Pharmacotherapy use and potentially inappropriate medicines (PIM): Cardiovascular agents.

Main therapeutic classes and most common subclasses † **N (%) of patients** 367 (100)	**Overall** (% of total) N (%) 367 (100)	**Non-polypharmacy (0-4 drugs)** (% of total) N (%) 19 (5.2)	**Minor-polypharmacy (5-9 drugs)** (% of total) 143 (39.0)	**Major-polypharmacy (≥10 drugs)** (% of total) 205 (55.9)	**p-value***
Blood and blood forming agents (B)	361 (98.4)	19 (5.2)	140 (38.1)	202 (55.0)	<0.01
Antithrombotic agents (B01)	361 (98.4)	19 (5.24)	140 (38.1)	202 (55.0)	<0.01
Vitamin K antagonists (B01AA)	293 (79.8)	14 (3.8)	122 (33.3)	157 (42.8)	<0.01
Direct thrombin inhibitors (dabigatran) (B01AE)	43 (11.7)	3 (0.8)	12 (3.3)	28 (7.6)	<0.01
Platelet aggregation inhibitors (B01AC)	38 (10.4)	2 (0.6)	7 (1.7)	29 (7.9)	<0.01
Cardiovascular system (C)	363 (98.9)	17 (4.6)	142 (38.7)	204 (55.6)	0.01
Lipid modifying agents (C10)	228 (62.1)	10 (2.7)	85 (23.2)	133 (36.2)	0.42
HMG CoA reductase inhibitors (C10AA)	220 (59.9)	9 (2.5)	84 (22.9)	127 (34.1)	0.42
Antihypertensive agents (C02)					
Prazosin‡ (C02CA01)	19 (5.2)	1 (0.3)	9 (2.5)	9 (2.5)	0.73
Methyldopa ‡ (C02AB)	6 (1.6)	0 (0.0)	1 (0.3)	5 (1.4)	0.31
Agents acting on the renin-angiotensin system (C09)	241 (65.7)	10 (2.7)	92 (25.1)	139 (37.9)	0.36
ACE inhibitors, plain (C09AA)	144 (39.2)	1 (0.3)	53 (14.4)	90 (24.5)	<0.01
Angiotensin II antagonists (C09CA)	119 (32.4)	4 (1.1)	47 (12.8)	68 (18.5)	0.56
Calcium channel blockers (C08)	95 (25.9)	5 (1.4)	30 (8.2)	60 (16.3)	0.03
Dihydropyridine derivatives (C08CA)	67 (18.3)	2 (0.6)	17 (4.6)	48 (13.1)	0.02
Benzothiazepine derivatives (diltazem) (C08DB)	17 (4.6)	0 (0.0)	7 (1.9)	10 (2.7)	1.00
Phenylalkylamine derivatives (verapamil) (C08DA)	21 (5.7)	3 (0.8)	6 (1.6)	12 (3.7)	0.12
Diuretics (C03)	162 (44.1)	3 (0.8)	53 (14.4)	106 (28.8)	<0.01
Sulfonamides (C03CA)	140 (38.1)	3 (0.8)	43 (11.7)	94 (25.6)	<0.01
Aldosterone antagonists (spironolactone) (C03DA)	34 (9.3)	0 (0.0)	11 (3.0)	23 (33.5)	0.22
Beta Blocker agents (C07)	218 (59.4)	8 (2.2)	87 (23.7)	123 (3.5)	0.28
Beta blocking agents, non-selective (C07AA)	55 (14.9)	2 (0.6)	26 (7.1)	27 (7.3)	0.40
Sotalol (C07AA07)	30 (9.8)	1 (0.3)	19 (5.2)	16 (4.4)	0.18
Beta blocking agents, selective (C07AB)	154 (41.9)	10 (2.7)	51 (13.9)	93 (25.4)	0.12
Cardiac therapy (C01)	175 (47.7)	10 (2.7)	71 (19.3)	94 (25.6)	0.74
Antiarrhythmics, class III (C01BD) (amiodarone) ¶	29 (7.1)	1 (0.3)	11 (3.0)	17 (4.6)	0.90
Digitalis glycosides (digoxin) § (C01AA)	111 (30.2)	8 (2.2)	30 (8.2)	73 (19.9)	<.0.01
Flecainide ‡ (C01BC04)	8 (2.2)	1 (0.3)	3 (0.8)	4 (1.1)	0.67
Organic nitrates (C01DA)	71 (19,3)	1 (0.3)	17 (4.6)	53 (14.4)	<0.01

NSAID: nonsteroidal anti-inflammatory drugs; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors
* Difference between non-polypharmacy, minor-polypharmacy and major-polypharmacy.
†All medications were classified according to Anatomical Therapeutic Chemical (ATC) classification system.
‡ Potentially inappropriate medicines (PIMs) according to both Beers criteria and PRISCUS criteria
§ Within these 111 patients, 22 patients met Beers criteria for potentially inappropriate use of digoxin (i.e. digoxin >0.125mg/d).
¶ Only included in Beers criteria.

gastroesophageal reflux disease, OR=2.51, 95%CI 1.56-4.04, p<0.001), obstructive pulmonary disease (asthma or chronic obstructive pulmonary disease (COPD), OR=2.89, 95%CI 1.47-5.72, p=0.002), and poor physical function (as measured by SF-36 physical score, OR=1.05, 95%CI 1.02-1.08, p=0.003), but less likely to have cognitive impairment (OR=0.27, 95%CI 0.07-0.96, p=0.04). In multivariate analysis, obstructive pulmonary disease (adjusted OR=2.32, 95%CI 1.14-4.71, p=0.02), upper gastrointestinal disease (adjusted OR=2.02, 95%CI 1.23-3.34, p=0.006), cognitive impairment (adjusted OR=0.27, 95%CI 0.07-0.97, p=0.04), and poor physical function (as measured by SF-36 physical score, adjusted OR=1.04, 95%CI 1.00-1.07, p=0.01) remained significant predictors of major-polypharmacy (Model: Cox&Snell R^2=0.10, Nagelkerke R^2=0.13, 63.5% correctly predicted).

Inappropriate use of medications

Overall, 250 (68%) patients (mean age 77.9 years) were using at least 1 PIM (Table 3 and 4). Among the most frequently identified PIMs (Table 4), four agents were for rhythm and/or rate control: digoxin (30.2%), sotalol (9.8%), amiodarone (7.9%), and flecainide (2.2%). Among those on digoxin, only 24 (21.6%) patients had a documented diagnosis of chronic heart failure, as required by guidelines (24).

The most commonly used “non-AF” PIMs were benzodiazepines (long, short and intermediate acting) (19.1%), followed by spironolactone (9.3%) and tricyclic antidepressants (TCA) (amitriptyline, imipramine) (7.6%).

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Table 4. Pharmacotherapy use and potentially inappropriate medicines (PIM): Non-cardiovascular agents & overall use.

Main therapeutic classes and most common subclasses † **N (%) of patients** 367 (100)	**Overall** (% of total) N (%) 367 (100)	**Non-polypharmacy (0-4 drugs)** (% of total) N (%) 19 (5.2)	**Minor-polypharmacy (5-9 drugs)** (% of total) 143 (39.0)	**Major-polypharmacy (≥10 drugs)** (% of total) 205 (55.9)	**p-value** *
Drugs for acid related disorders (A02)	198 (53.9)	6 (1.6)	55 (14.9)	137 (37.3)	<0.01
Proton pump inhibitor (A02BC)	156 (42.5)	6 (1.6)	43 (11.7)	107 (29.2)	<0.01
Drugs for functional gastrointestinal disorders (A03)					
Metoclopramide¶ (A03FA01)	8 (2.2)	0 (0.0)	2 (0.6)	6 (1.6)	<0.01
Psycholeptics (N05)	73 (19.9)	1 (0.3)	17 (4.6)	55 (14.9)	0.01
Benzodiazepine derivatives (N05CD)	70 (19.1)	1 (0.3)	17 (4.6)	52 (14.2)	0.002
Short and intermediate acting ‡	54 (14.7)	1 (0.3)	14 (3.8)	39 (10.6)	0.02
Long acting ‡	18 (4.9)	0 (0.0)	3 (0.8)	15 (4.1)	0.27
Psychoanaleptics (N06)	70 (19.1)	1 (0.3)	13 (3.5)	56 (15.2)	<0.01
Antidepressant (N06A)	68 (18.5)	1 (0.3)	12 (3.3)	55 (14.9)	<0.01
TCA (N06AA) (amitriptyline, imipramine)	28 (7.6)	1 (0.3)	4 (1.1)	23 (6.2)	<0.01
SSRI (N06AB) (fluoxetine) ‡	24 (6.5)	0 (0.0)	5 (1.6)	19 (5.2)	0.03
Analgesics(N02)	207 (56.4)	5 (1.4)	59 (16.2)	143 (39.0)	<0.01
Anilides (paracetamol) (N02BE)	196 (53.4)	5 (1.4)	56 (16.1)	135 (36.8)	<0.01
Opioids (N02A)	42 (11.4)	0 (0.0)	5 (1.4)	37 (10.1)	<0.01
Corticosteroids, dermatological preparations (D07)	93 (25.3)	5 (1.4)	26 (28.0)	62 (16.9)	0.04
Corticosteroid for systemic use (H02)	27 (7.4)	0 (0.0)	5 (1.4)	22 (6.0)	0.02
Drugs for obstructive airway diseases (R03)	89 (24.3)	5 (1.4)	20 (5.4)	64 (17.4)	<0.01
Selective beta-2-adrenoreceptor agonists (R03AC)	51 (13.9)	4 (1.1)	8 (2.2)	39 (10.6)	<0.01
Corticosteroids inhaler (R03BA)	61 (16.6)	4 (1.1)	14 (3.8)	43 (11.8)	0.02
Drugs used in Diabetes (A10)	62 (16.9)	4 (1.1)	14 (3.8)	44 (12.0)	0.02
Insulin and analogues (A10A)	14 (3.8)	0 (0.0)	3 (0.8)	11 (3.0)	0.19
Blood glucose lowering drugs excl. insulin (A10B)	56 (15.3)	4 (1.1)	13 (3.5)	39 (10.6)	0.03
Anti-inflammatory and anti-rheumatic products (M01)					
Non-selective NSAID (M01AB) (diclofenac¶, ibuprofen¶, naproxen¶, indomethacin‡, piroxiacam‡)	16 (4.3)	0 (0.0)	5 (1.4)	11 (3.0)	0.29
Sex hormones and modulators of the genital system (G03)					
Estrogen with or without progestin¶ (G03CA)	23 (6.3)	1 (0.3)	4 (1.1)	18 (4.9)	0.59
Urologicals (G04)					
Urological spasmolytic agents (G04BD) (oxybutynine, tolterodine, solifenacin) ‡	9 (2.5)	1 (0.3)	1 (0.3)	7 (1.9)	0.16
Use of potentially inappropriate medications (PIMs)					
Overall use of PIMs	250 (68.2)	12 (3.3)	79 (21.5)	159 (43.3)	<0.001
One PIM (mean age =77.9 years)	144 (40.3)	9 (2.5)	56 (15.3)	84 (22.9)	-
Two PIMs(mean age =76.4 years)	68 (18.5)	2 (0.5)	15 (4.1)	51 (13.9)	-
Three PIMs (mean age =77.0 years)	38 (7.6)	1 (0.3)	7 (1.9)	20 (5.4)	-
Four PIMs (mean age =75.8 years).	5 (1.4)	0 (0.0)	1 (0.3)	4 (1.1)	-

NSAID: nonsteroidal anti-inflammatory drugs; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors
* Difference between non-polypharmacy, minor-polypharmacy and major-polypharmacy.
†All medications were classified according to Anatomical Therapeutic Chemical (ATC) classification system.
‡ Potentially inappropriate medicines (PIMs) according to both Beers criteria and PRISCUS criteria
§ Within these 111 patients, 22 patients met Beers criteria for potentially inappropriate use of digoxin (i.e. digoxin >0.125mg/d).
¶ Only included in Beers criteria.

DISCUSSION

Our study presents some initial findings on the use of high-risk medications and polypharmacy, including PIMs, among older AF patients in a primary care setting. The study has identified a high prevalence of polypharmacy in older patients with AF (94.8%). This rate of polypharmacy is higher than reported in a study of older patients (aged 70 or older years, including AF and non-AF patients), treated in the general practice setting in Germany[25] and higher than in an Australian study of older patients (aged 70 years or older) admitted to general medical units in acute care hospitals.[10] Not unexpectedly, the most frequently prescribed medications included cardiovascular agents, consistent with other studies[26], followed by antithrombotics. The significance of this is that these commonly used medications not only contribute to the burden of polypharmacy in AF patients, but they are also regarded to be high risk medicines and, in some cases, PIMs. Since these are guideline-indicated therapies for AF patients[1], this polypharmacy comprising PIMs creates a particularly high-risk situation for patients, further increasing the likelihood of adverse drug reactions and medication misadventure.[27] Regarding the use of aspirin as a monotherapy, evidence-based clinical practice guidelines suggest that aspirin

Table 5. Antithrombotic therapy use stratified according to stroke risk

Stroke risk N (% of total)	**Warfarin** 279 (76.0)	**Warfarin+aspirin** 14 (3.8)	**Dabigatran** 43 (11.7)	**Clopidogrel** 3 (0.8)	**Aspirin** 22 (6.0)	**Nil therapy** 6 (1.6)
$CHADS_2$ score§						
Low	25 (6.8)	1 (0.3)	2 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Intermediate	87 (23.7)	1 (0.3)	14 (3.8)	0 (0.0)	7 (1.9)	1 (0.3)
High	167 (45.5)	12 (3.3)	27 (7.4)	3 (0.8)	14 (3.8)	5 (1.4)
CHA_2DS_2-VASc score§						
Intermediate	11 (3.0)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.00
High	268 (73.0)	21 (5.7)	42 (11.4)	3 (0.8)	21 (5.7)	6 (1.6)

§ CHADS2[13] and CHA2DS2VASc[14] scores of 0, 1, 2 or more were classified as low, intermediate and high stroke risk, respectively.

alone is insufficient to reduce stroke risk. In our study, since the stroke risk in this patient sample was at least intermediate (as per CHA2DS2VASc), the observed use of aspirin monotherapy was potentially not aligned with evidence-based guidelines.[14]

It is important to note that among the most commonly used AF therapies in this study, several (i.e., antiarrhythmics) were identified as PIMs according to Beers criteria or the PRISCUS list. In particular, the use of digoxin was surprisingly high in this study population and consistent with other studies.[28,29] Given that digoxin is no longer recommended as a mainstay therapy, being reserved for those AF patients who have congestive heart failure unresponsive to first-line therapies, this possible overuse in patients with AF raises concerns about the safety and necessity of its use.[28]

Medication safety in AF patients is further compounded when patients require pharmacotherapy for other non-AF conditions. As also reported in earlier studies, a surprisingly high number of patients used analgesics, suggesting that in older patients with AF there is a high prevalence of pain conditions (e.g., arthritis).[30] The concurrent use of analgesics with AF pharmacotherapy may lead to drug interactions and/or GI (gastrointestinal) adverse drug reactions which may increase the risk of bleeding, especially GI bleeding. Noting that the prevalence of NSAIDs use in our study was only 4.3%, much lower than other studies of AF patients[33] and the use of NSAIDs in combination with warfarin only 2.5%, the rate of such interactions might be relatively low. Nevertheless, the episodic nature of pain can complicate AF management, because pain is symptomatic and therefore patients may prioritise analgesic use over AF therapy.[34] However, this study found that the use of paracetamol in combination with warfarin is relatively common. As reported by other studies, the interaction between warfarin and paracetamol is often underestimated, but is important because it can potentiate the anticoagulant effect of warfarin and increase the rate of fatal bleeding 2.7 times (compared to warfarin use alone).[19,20] The mechanism of this interaction is not fully understood but some studies support the hypothesis that paracetamol (or its metabolites) interact with certain enzymes responsible for the synthesis of vitamin K dependent coagulation factors (vitamin K-dependent γ-carboxylase and vitamin K epoxide reductase).[19]

Although proton pump inhibitors (PPIs) are commonly used medications, this study shows that the use of PPIs is higher than that in other studies of general older patients in nursing homes[35] and those admitted to hospitals.[36] The frequent use of PPIs for GI conditions in our study raises concerns that many AF patients may potentially suffer from drug-induced GI adverse drug reactions, since a number of AF pharmacotherapies (e.g., antiarrhythmics, antithrombotics) are reported to cause GI symptoms, including upper GI bleeding. Separate to GI adverse drug reactions, according to the approved product information, acid-minimising/suppressing agents (e.g., omeprazole)[37] may also interact with prescribed AF medications (e.g., warfarin, digoxin), increasing the potential for side effects (e.g. bleeding, arrhythmia) leading to suboptimal clinical outcomes.[38]

In relation to the over-use of therapies, a surprisingly high proportion of patients were found to be taking benzodiazepines in this study, which are recognised as a major cause of adverse drug reactions in the older patients.[39] A previous study pertaining to general older patients (aged >65 years) in the Australian general practice setting reported that 45% of patients using benzodiazepines experienced two to six adverse drug reactions, whilst 15% of patients had seven or more reactions during the study period.[39] Benzodiazepines, as well as other psycholeptics, psychoanaleptics, diuretics, antihypertensive agents, anti-inflammatory and anti-rheumatic products (e.g., NSAIDs) are regarded as PIMs in older persons; many of these may lead to a high risk of falls, and/or increased risk of intracranial bleeding, whilst others can cause GI bleeding, exacerbating the background risks already posed by specific AF therapies.[40]

Regarding the different classifications of bleeding risk assessment, two tools were used: HAS-BLED, which is widely incorporated into international treatment guidelines[1,2], and HEMORR2HAGES, as recommended by National Clinical Guideline Centre (UK) and American College of Cardiology/American Heart Association guidelines.[1,19] Compared with HAS-BLED, HEMORR2HAGES uniquely includes a wider range of risk factors namely: malignancy, anemia, genetic factors, reduced platelet count or function, excessive falls risk, in addition to the common bleeding risk factors (e.g., hypertension, abnormal renal/liver function, stroke, bleeding predisposition, age, alcohol use). HAS-BLED has better sensitivity than HEMORR2HAGES in identifying any clinically relevant bleeding in anticoagulated patients with AF.[41] However, HEMORR2HAGES has a higher diagnostic accuracy due to its higher specificity.[41] The

association between a lower HEMORR2HAGES (but not HAS-BLED) score and polypharmacy may be explained by the wider range of risk factors included in it, although none of the individual risk factors were found to be significantly associated with polypharmacy in this study. In this regard, decision support tools (such as CARAT[42]) can help assess these risk factors when recommending antithrombotic therapy, and therefore maybe useful in identifying the potential for polypharmacy (and therefore any medication safety issues).

This study has identified that patients using polypharmacy are also more likely to have a low risk of bleeding. Given that the decision-making around the use of antithrombotics in AF focuses on weighing the risk of stroke versus the risk of bleeding, in this equation these "low risk" patients (low bleeding risk) are generally deemed to be more eligible for anticoagulants (e.g., warfarin) than patients at a higher bleeding risk. However, these same low-risk patients are also more likely to have polypharmacy (as identified here), thereby increasing the risk of drug-drug interactions, adverse drug reactions and treatment non-adherence. Therefore, in prescribing antithrombotics for AF patients, clinicians must consider both the stroke versus bleeding risks alongside the relevant medication safety considerations (i.e., the implications of polypharmacy), to ensure that in optimising antithrombotic therapy they are not inadvertently putting "low risk" patients at high risk of medication misadventure. Whilst this should not stop the use of antithrombotics, it does reinforce the need for comprehensive patient assessment with regular review and follow-up to monitor for medication misadventure in all patients including those apparently at "low risk".

In this study, patients with major-polypharmacy were more likely to have obstructive pulmonary disease (asthma or COPD), upper gastrointestinal disease and poor physical function (as per SF-36), but less likely to have cognitive impairment. This is consistent with other studies showing that asthma or COPD and gastrointestinal disease[43,44] are associated with excessive polypharmacy (≥10 drugs).[45] Possible reasons include that obstructive pulmonary disease can cause a range of different comorbidities, including heart disease (e.g., heart failure, arrhythmias), chronic kidney disease, cancer, metabolic disease (e.g., osteoporosis, diabetes) and pulmonary embolism.[46] Since patients with upper gastrointestinal disease have a higher risk of gastrointestinal bleeding[38], the association of upper gastrointestinal diseases with major-polypharmacy in patients with AF needs some vigilance; the concomitant use of oral antithrombotics (e.g., dabigatran, aspirin) and NSAIDs in the presence of polypharmacy and gastrointestinal disease may predispose patients to an increased risk of GI haemorrhage and associated morbidity and mortality. Similarly, poor physical function (measured by SF-36), as reported by previous studies was found to be associated with the use of an increased number of medications.[47] Since patients with polypharmacy are at higher risk of adverse reactions[5], it is important to balance the need for multiple medications with patients' desired quality of life. In contrast, cognitive impairment has been shown to be associated with a reduced use of medications.[43,44] This may be due to prescribers' concerns about using multiple medications in those patients, as studies have shown that cognitive impairment may cause lower adherence and communication difficulties, including a decreased ability to report adverse effects.[48,49]

The 'trilogy' of risks in older AF patients warrants specific attention when managing their medication regimens. Services such as Home Medicines Review (HMR)[50] can help to assess the medication regimens of such patients, and have been shown to reduce the use of PIMs.[51] Other services such as MedsCheck (medicines use review) and Diabetes MedsCheck (diabetes medication management) are structured pharmacy services, involving face-to-face consultations between the pharmacist and consumer.[52] These services are designed to enhance the quality use of medicines through patient education, self-management and medication adherence strategies, and may help to reduce the medication misadventure experienced by patients.[53] Some available risk assessment tools, such as CHA2DS2VASc[14] and HAS-BLED[15], can assist in quantifying the stroke or bleeding risk for an individual patient. However, medication management in AF patients requires a more careful balance of risks and benefits to ensure optimal therapy that not only minimises the stroke and bleeding risks, but also reduces the risk for medication misadventure from any cause.

Targeted decision support tools, which systematically assess a patient's medical history, stroke and bleeding risk and which consider pertinent medication safety issues (e.g. polypharmacy, drug-drug interactions), may assist here[42]; these tools can support prescribing as well as facilitate the regular review of medication regimens. Regular medication review services using risk assessment tools may help reduce the risk and optimise medication use. However, there are still some gaps in implementing these tools and services in the medication management of AF patients. Designed for specific contexts (e.g., stroke, bleeding) or certain types of medication (e.g., antithrombotics), these tools (CHA2DS2VASc[14], HAS-BLED[15] and CARAT[42]) alone may not be completely useful in the comprehensive review and management of AF patients' overall medication regimen (as opposed to just their antithrombotic therapy). Also, these tools and services have not yet been evaluated in large-scale studies involving older AF patients. Therefore, given that the use of pharmacotherapy in this specific context (older persons with AF) is complex, further research needs to more comprehensively investigate the risk factors and explore the impact of targeted interventions on managing the 'trilogy' of risks.

In considering the findings of this study, some limitations need to be acknowledged. The retrospective nature of the study, and the limited

number of AF patients in the cohort reviewed, result in relatively wide confidence intervals, requiring that the findings to be interpreted with caution. The logistic regression analysis for the outcome "major-polypharmacy versus minor polypharmacy" has limited prediction value, which means that there may be other risk factors associated with major-polypharmacy which need to be explored in future studies. However, the selection of these patients is representative of older patients with AF encountered in the Australian general practice setting, providing an important insight into the specific challenges of using pharmacotherapy in this patient cohort. Furthermore, although there is uncertainty around the reliability of GPs' medication records as the primary source of medication histories, the medication lists recorded in this study were verified by the GPs. Due to the cross-sectional design of this study, only explicit criteria were used to identify PIMs. Though many of the results of this study confirm the previous findings in the literature, this study is first to demonstrate the relationship between low-bleeding risk and polypharmacy.

CONCLUSIONS

Polypharmacy affects most older AF patients, comprising medications that are indicated for AF, yet regarded as PIMs. Patients with a lower risk of bleeding, obstructive pulmonary disease, upper gastrointestinal disease and poor physical function are significantly more likely to use multiple medications. This may lead to an increased risk of medication misadventure due to the concomitant use of polypharmacy and high-risk medications indicated for AF.

CONFLICT OF INTEREST

None to declare.

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