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SYSTEMATIC REVIEW

Potentially inappropriate prescribing in multimorbid and polymedicated older adultswith AF: A Systematic Review and Meta-Analysis

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Abstract

Aim Polypharmacy in multimorbid older patients with atrial fibrillation (AF) is a risk factor for potentially inappropriate prescribing (PIP). We aimed to systematically assess the evidence on the prevalence of PIP and its impact on adverse health outcomes in this patient group.

Methods A systematic search of the published peer-reviewed literature describing the prevalence of PIP and/or its association with adverse health outcomes in multimorbid (AF plus one comorbidity) and polymedicated (≥ 2 drugs) adults ≥ 65 years was done up to March 2023. A meta-analysis of the prevalence of PIP of (direct) oral anticoagulants ((D)OACs) was conducted using a random-effects model. Leave-one-out analysis was performed with R (version 4.2.2) and RStudio (version 2022.12.0+353).

Results Of the 12 studies included, only one reported on the prevalence of overall PIP (65%). The meta-analysis of 10 studies assessing PIP of (D)OACs produced a pooled prevalence [95% confidence interval (CI)] of 35% [30–40%], with significant heterogeneity between the included studies (I^2 95%). No statistically significant association was reported in three studies between PIP of (D)OACs, cardiovascular (CV) and all-cause mortality, hospital readmission, CV hospitalisation and stroke. Reported associations between PIP and major bleeding differed, with one study demonstrating a significant association (odds ratio 2.17; 95% CI 1.14–4.12) and the other study not showing such association.

Conclusion This systematic review highlights the scarce evidence regarding the prevalence of PIP and its association with adverse health outcomes in multimorbid older adults with AF. Large, prospective and better-designed studies are needed.

Key Points

PIP is a concern in older adults with AF due to multimorbidity, polypharmacy and age-related pharmacokinetic and pharmacodynamic changes.

Current research on PIP in older adults with AF predominantly focuses on PIP of (D)OACs, despite the complex health profile and polypharmacy in this population.

This study highlights the need for further research to comprehensively evaluate PIP and its association with adverse health outcomes in multimorbid and polymedicated older adults with AF.

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1 Introduction

Atrial fibrillation (AF) is the most common sustained arrythmia. In 2019, 59.7 million people globally suffered from AF [1], and its prevalence is estimated to reach 62.5 million cases worldwide by 2050 [2]. AF's prevalence increases with age [2–5]. Globally the prevalence of AF among adults aged 65–74 years was 4.31%, and among adults aged 75 years or older, it was 8.82% [6]. AF is associated with an increased risk of stroke, bleeding, mortality and results in high and increasing healthcare costs [5, 7]. The most prevalent comorbidities in AF patients are heart failure, hypertension, myocardial infarction, diabetes mellitus, hyperlipidaemia, chronic obstructive pulmonary disease and chronic kidney disease [8–12]. Multimorbidity (i.e., the co-occurrence of two or more (chronic) diseases in the same individual) is common in adults (≥ 18 years) with AF with prevalence ranging from 64 to 98%

[10, 12–14]. Among adults with AF aged 65 years or older, multimorbidity ranges from 38.7% (≥ 75 years) to 98% [11, 13, 15]. Indeed, multimorbidity is associated with a higher risk of adverse outcomes, but is paradoxically inversely related to evidence-based treatments such as oral anticoagulation for stroke prevention [12, 16].

Because of multimorbidity and related polypharmacy, in addition to age-related pharmacokinetic and pharmacodynamic changes, older patients with AF are prone to potentially inappropriate prescribing (PIP) [17–20]. PIP can be a result of overprescribing, misprescribing and underprescribing [21].

Overprescribing refers to the use of medications for which a clear clinical indication does not exist. Misprescribing pertains to the use that involves an incorrect dose, frequency, modality of administration or duration of treatment [21]. Additionally, misprescribing also includes prescribing medications that pose more risk than benefit to the patient, particularly if there are safer alternatives [17–20]. Underprescribing refers to the omission of potentially beneficial medications that are clinically indicated for treatment or prevention of a disease [21]. PIP has been associated with adverse drug reactions events (ADE), hospitalisation, increased healthcare costs, morbidity and death [17, 22–26]. Early detection and discontinuation of PIP could prevent ADE and may improve geriatric care and patients' health-related quality of life [17, 24].

In addition to clinical guidelines providing evidence-based recommendations for pharmaceutical management, both implicit and explicit tools are available to evaluate the quality of prescribing in clinical practice and research. Explicit tools (e.g., 2019 Beers criteria [27] and Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria, version 2 [28]) consist of predefined criteria that determine potentially inappropriate medications in specific medical situations [27–30]. On the other hand, implicit tools [e.g., Medication Appropriateness Index (MAI [31])] are quality indicators that rely on an overall evaluation by a healthcare professional and focus on the patient's individual clinical profile rather than solely on medications or diseases [27–31].

Nonetheless, there is limited knowledge on the prevalence and association with PIP in older multimorbid patients with AF, since vulnerable geriatric patients with AF are mostly underrepresented or excluded from randomized controlled trials (RCT) [13, 32–35]. The aim of the present systematic review was to assess the prevalence of overall PIP and its association with adverse health outcomes in multimorbid and polymedicated older adults with AF.

2 Methodology

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 guidelines [36]. The study protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42021283474) [37].

2.1 Search Strategy

A systematic search of the published peer-reviewed literature was conducted up to March 2023 according to the PRESS checklist 2015 [38] (Supplementary file 1). MEDLINE using the PubMed Interface, EMBASE using the Embase.com interface and Web of Science were searched using keywords related to PIP and AF. Details of the full search strategy for each database are presented in Supplementary file 2. There was no restriction by year of publication. Additional screening of the reference list of the included studies was done.

2.2 Eligibility Criteria

Articles describing the prevalence of PIP (outcome 1) and/or its association with adverse health outcomes (outcome 2) in multimorbid polymedicated older adults (≥ 65 years) with AF were included. The quality of prescribing should have been determined by clinical guidelines, summary of product characteristics (SmPC) and/or explicit or implicit tools. The defined adverse health outcomes were: cardiovascular (CV) hospitalisation, hospital readmissions (hospitalisation within 30 days after previous hospital discharge), emergency department (ED) visits, all-cause and/or CV mortality, major bleeding (bleeding that is clinically significant and/or requires medical intervention), intracranial and/or gastrointestinal bleeding, stroke or ADE (anaemia, falls, delirium).

Multimorbidity was defined as AF with at least one other chronic comorbidity [39]. If the mean or median number of diseases was not described, the presence of comorbidity was deduced from clinical risk scores, namely the "Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex" (CHA_2DS_2-VASc) score, "Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke/Transient ischemic attack" ($CHADS_2$) score, "Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol" (HASBLED) score and the Charlson Comorbidity Index (CCI). To be considered as comorbidity, the minimum scores needed to be CHA_2DS_2-VASc > 3, $CHADS_2$ > 1, HASBLED > 5, CCI ≥ 1. These thresholds were established in a conservative manner to ensure

that the study population had at least one comorbidity (e.g., CHA_2DS_2-VASc assigns one point for female sex and two points for age ≥ 75 years; a mean or median CHA_2DS_2-VASc > 3 is required to ensure a study population with at least one comorbidity).

Although the concurrent use of at least five medications is commonly accepted as polypharmacy, there is still a lack of consensus regarding its definition. To be inclusive, we employed the minimum numeric definition of polypharmacy, which involves the concurrent use of two or more medications [40, 41]. Conference abstracts; case reports; editorials; full-text articles in languages other than English, French or Dutch; cohorts of patients younger than 65 years; and study groups receiving an intervention that temporarily altered drug prescription practices (e.g., percutaneous coronary intervention) were excluded. Finally, matched case-control studies were not considered when assessing the prevalence of PIP, because the study design was not able to provide accurate estimates of prevalence and would induce biased results. However, matched case-control studies were considered when assessing the association between PIP and adverse health outcomes (Table 1).

2.3 Study Selection

After removing duplicates, two reviewers (CA and DV) independently screened the titles and abstracts in Rayyan [42], blinded to each other's decisions, and the interrater reliability was measured with Cohen's kappa [43]. Next, the two reviewers (CA and DV) independently screened the full texts in Rayyan according to the eligibility criteria. Disagreements were resolved via consensus between the two reviewers or arbitration by a third senior author (DDS or MP). Reasons for exclusion of full-text articles were recorded (Fig. 1). The systematic search strategy was updated according to the methodology reported by Bramer et al. [44].

2.4 Data Extraction, Assessment and Synthesis

Data of the study methodology (first author, year, study period, study design, study setting, country, sample size and medication review tool), patient characteristics [sex, age, number of diseases, number of drugs, risk scores (CHA_2DS_2-VASc, HAS-BLED, $CHADS_2$)], outcomes of interest (total and specific prevalence of PIP and measures of association between PIP and adverse health outcomes) were extracted by two reviewers (CA and SA) independently. When both admission and discharge prevalence of PIP were reported, only the prevalence at admission was extracted. Discrepancies were resolved by consensus.

2.5 Quality Assessment

Quality of the included papers and risk of bias were determined independently by two reviewers (CA and SA), using the QualSyst Assessment Tool for quantitative studies [45]. The checklist consists of 14 criteria and a scoring system

Table 1 Inclusion and exclusion criteria for the systematic review

	Inclusion criteria	Exclusion criteria
Population	Age: ≥ 65 years	
Population	Polypharmacy: ≥ 2 drugs	
Population	Multimorbidity: AF and ≥ 1 chronic comorbidity	
Outcome(s)	Prevalence of PIP and/or association between PIP and adverse health outcomes[a]	
Methodology	Use of medication review tool (clinical guidelines, SmPC, explicit or implicit tools)	
Article type	Peer-reviewed research manuscript Review	Conference abstracts, case reports, editorials
Study design	Randomised controlled trial Longitudinal observational study Cross-sectional study Case-control study Meta-analysis Systematic review Evidence-based review	Interventions that temporarily alter drug prescription practices; matched case-control study for the outcome "Prevalence of PIP"
Language	English, French, Dutch	

(a) The adverse health outcomes were defined as: cardiovascular (CV) hospitalisation, hospital readmissions (hospitalisation within 30 days after previous hospital discharge), emergency department (ED) visits, all-cause and/or CV mortality, major bleeding (bleeding that is clinically significant and/or requires medical intervention), intracranial and/or gastrointestinal bleeding, stroke/systemic embolism, ischemic stroke or adverse drug reactions events (ADE: anaemia, falls, delirium)

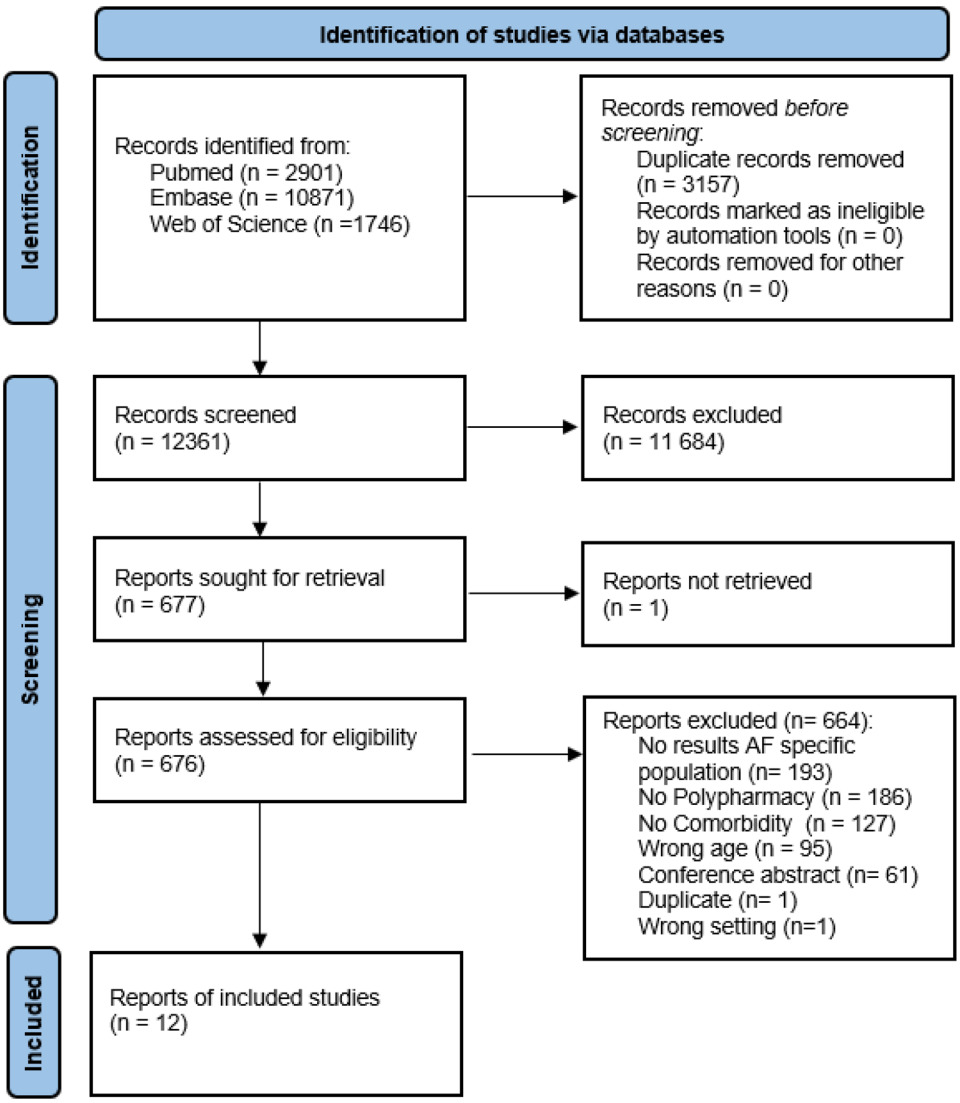

Fig. 1 PRISMA flow diagram. An overview of the literature search and study selection. Some studies were excluded for multiple reasons

("yes" = 2, "partial =1", "no = 0" and "not applicable"). A summary score was calculated for each paper by summing the total score and dividing it by the total possible score, expressed as %. The articles were not excluded from the review on the basis of quality scores alone. Instead, a more comprehensive approach was used, which considered both the quality assessment and results of sensitivity analysis (leave-one-out analysis) [46].

2.6 Statistical Analysis

R (version 4.2.2) and RStudio (version 2022.12.0+353) were used to conduct a meta-analysis of the prevalence of PIP. The proportions were logit transformed prior to analysis. A random-effects model (based on the DerSimonian and Laird estimator [47]) was used, and the proportions were pooled using the inverse variance method. The test for heterogeneity (Q), the estimate of between-study variance (τ^2) and the estimate for the proportion of the observed variability that reflects the between-study variance (I^2) were reported. Leave-one-out analysis was performed, and the leave-one-out diagnostic variables, as outlined in Supplementary file 3, were assessed. The risk of publication bias was assessed through funnel plot asymmetry and Peter's regression test [48]. A two-sided p-value of < 0.05 was considered to indicate statistical significance. Subgroup analyses were not feasible, since the prerequisite minimum number (10) of studies per subgroup was not met [49]. Similarly, meta-analysis of the adverse health outcomes was not performed due to the combination of limited studies included, variation in study design, investigated drug {[direct] oral anticoagulants, [(D) OACs]} and differing type of PIP (misprescribing and/or potentially inappropriate dosing) involved.

3 Results

3.1 Search Results

The search strategy resulted in 15,518 abstracts. After duplicates removal, 12,361 articles were screened based on title and abstract, resulting in 677 included records. There was a good inter-rater agreement for title and abstract screening between the two reviewers (Cohen's kappa = 0.70). Full-text screening resulted in the inclusion of 12 articles (Fig. 1) [50–61]. One article described a matched case-control study to evaluate PIP of (D)OACs, and its association with bleeding [58]. Although the study was excluded from our overall PIP prevalence estimation due to its study design, it was included for the assessment of PIP's association with adverse health outcomes [58]. No eligible articles were additionally identified upon screening the reference list of the included studies.

3.2 Quality Assessment

In all studies except one ($n = 11$), there was insufficient information regarding subject characteristics, results, or sample size justification [50–58, 60, 61]. Most studies ($n = 6$) either did not describe characteristics of the subgroups or neglected to provide a comprehensive characterization of the total population [51, 53, 54, 56, 57, 60]. One study did not provide subject characteristics, nor did it refer to any linked original study ($n = 1$) [56]. Moreover, results were only reported for a specific subgroup, or the outcomes were not quantitatively described ($n = 6$) [50–52, 56, 57, 60] (Supplementary file 2).

3.3 Characteristics of the Included Studies

The included articles were all peer-reviewed research manuscripts. All studies except one [59], focused on a study population characterized by AF. The majority of the studies ($n = 7$) [51–54, 56, 57, 59] were conducted in Europe with study periods spanning from 2003 to 2019 (Table 2). All studies, except for two randomised controlled trials (RCT) [51, 59], were observational ($n = 10$), and the majority were predominantly conducted in hospital settings ($n = 8$) [51, 53, 54, 56–59, 61]. Most of the studies ($n = 7$) used clinical guidelines to assess PIP [51–54, 56–58]. SmPC ($n = 5$) [50–53, 61] and explicit screening tools ($n = 4$) [51, 53, 59, 60] were used to a lesser extent. Implicit screening tools ($n = 1$) were the least often used [59].

The proportion of women in the study populations varied between 43 and 69% (Table 3). The mean (standard deviation) age of participants ranged from 77.1 (7.9) to 90.6 (3.3) years. Only three articles reported the mean or median number of chronic diseases (5–5.8) [52, 56, 60]. The mean or median number of medications ranged from 5 to 13. The mean/median CHA_2DS_2-VASc score across studies ranged between 4 to 5.

3.4 Appropriateness of Prescribing

The studies were primarily focused on the appropriateness of prescribing of (D)OACs, except for the study by Wang et al. [60] describing the overall quality of prescribing in multimorbid polymedicated older adults with AF (Table 4) [60]. They described a prevalence of PIP of 68.4%, with digoxin (30%), benzodiazepines (20%) and antiarrhythmics (8%) most often misprescribed; the prevalence of PIP related to (D)OACs was not reported [60].

The prevalence of PIP of (D)OACs ranged from 8.9 to 56.5% (Table 4) [50–57, 59, 61]. Three studies assessed underprescribing of (D)OACs with a prevalence range of 13.8–39.3% [54, 57, 59]. Four studies reported misprescribing of (D)OACs with a prevalence range of 8.9–56.3% [51, 53, 56, 57]. Additionally, five studies specifically addressed potentially inappropriate dosing of (D)OACs, which falls under the category of misprescribing, with a prevalence ranging from 12.5 to 34.5% [50, 52, 54, 55, 61]. Finally, none of the studies described overprescribing.

3.5 Meta-Analysis of PIP

A meta-analysis of the studies assessing PIP of (D)OACs ($n = 10$) was conducted (Fig. 2). The meta-analysis with a random-effects model and inverse variance method produced a pooled prevalence of 35.2% (95% CI 30.5–40.1%). According to the τ^2 (0.101), I^2 (95%) and Q-statistic (199, $p < 0.0001$), there was significant heterogeneity between studies. The leave-one-out analysis (Supplementary file 3) indicated that the studies by Marcucci et al. [56] and Franchi et al. [53] had the greatest impact on the original summary proportion, as depicted by the reference line. The leave-one-out diagnostic variables (Supplementary file 3) confirmed that these two studies met the criteria of influential studies. To assess the impact of these studies, a sensitivity analysis was performed by removing them from the prevalence estimation. The resulting pooled estimate was reduced to 30.0% (95% CI 27.6–32.6%) with significant heterogeneity remaining ($\tau^2 = 0.020$, $I^2 = 82\%$ and Q-statistic = 40; $p < 0.0001$). The number of studies included in the funnel plot was limited ($n = 10$), yet visually some asymmetry could be identified (Supplementary file3). According to Peter's regression test there is however no statistically significant asymmetry ($p = 0.06$).

Table 2 Descriptive data of the included articles

Author	Year	Study period	Study design	Setting	Sample size	Country	Medication review tool	Quality score
Spinewine, A [59]	2007	2003–2004	RCT	Acute geriatric department	84[a]	Belgium	MAI [62], Beers criteria [63, 64], ACOVE criteria [65]	89% (25/28)
Marcucci, M [56]	2010	2008	Cohort (retrospective)	Internal medicine departments	247	Italy	ACCP 2008 [66]	70% (14/20)
Mazzone, A [57]	2016	2012–2014	Cohort (retrospective)	Acute geriatric department	305	Italy	ESC guidelines 2012 [67], AHA/ACC/HRS guidelines 2014 [68]	75% (15/20)
Wang, Y [60]	2016	2010	Cross-sectional	Community dwelling	348[b]	Australia	Beers criteria 2012 [69], PRISCUS criteria [70]	70% (14/20)
Franchi, C [53]	2018	2016–2017	Cohort (retrospective)	Internal medicine and geriatric department	328[c]	Italy	Beers criteria 2015 [71], ESC guidelines 2016 [72], EPAR—SmPC [73]	90% (18/20)
Antoniazzi, S [51]	2019	2017–2018	RCT	Internal medicine and geriatrics department	246[c]	Italy	Beers criteria 2015 [71], ESC guidelines 2016 [72], EPAR—SmPC [73]	75% (15/20)
Akao, M [50]	2020	2016–2018	Cohort (prospective)	Community dwelling	32,713	Japan	SmPC[d]	80% (16/20)
Capiau, A [52]	2021	2017–2018	Cross-sectional	Community dwelling	654	Belgium	EPAR—SmPC[1], EHRA Practical guide 2015[2] [74]	85% (17/20)
Hupfer, M [54]	2021	2018	Cohort (retrospective)	Geriatric department	407	Germany	ESC guidelines 2016 [72]	90% (18/20)
Jackson, L [55]	2021	2013-2016	Cohort (prospective)	Outpatient clinic	1134	U.S.A.	FDA labelling[d]	95% (19/20)
Raccah, BH [58]	2021	2015-2017	Matched case-control	All hospital departments	509	Israel	PCNE Classification scheme for Drug-Related Problems [75], ESC guidelines 2020 [76], EHRA 2018 [77]	77% (17/22)
Li, R [61]	2022	2013-2019	Cross-sectional	All hospital departments	1882	Australia	SmPC [78–80]	90% (18/20)

Prevalence of PIP was determined by (1) SmPC and by (2) EHRA separately in the study by Capiau et al. [52]. American College of Chest Physicians (ACCP) Practice guidelines of the, *ACOVE* Assessing Care of Vulnerable Elders, *AHA/ACC/HRS* American Heart Association/American College of Cardiology/Heart Rhythm Society, *EHRA* European Heart Rhythm Association, *EPAR*—SmPC European Public Assessment Report—Summary of Product Characteristics, *ESC* European Society of Cardiology, *FDA* Food and Drug Administration labelling, *MAI* Medication Appropriateness Index, *PCNE* Pharmaceutical Care Network Europe, *RCT* randomised controlled trial, *USA* United States of America

[a]This represents the number of AF patients in the study population

[b]We extracted the descriptive data of the polypharmacy subpopulation

[c]The study provided descriptive data and study sample characteristics for the total study populations and not the subgroups relevant for the current review

[d]No reference was provided

Table 3 Study sample characteristics of the included articles

Author	Year	Gender (% female)	Age	Mean/median diseases	Mean/median medications	CHA_2DS_2-VASc	HAS-BLED	$CHADS_2$
Spinewine, A [59]	2007	60/90 (66.7%)[a]	81.9 (6.2)[a]	CCI ≥ 1	7.3 (3.3)[a]	NA	NA	NA
Marcucci, M [56]	2010	120/247 (48.6%)	81.3 (7.5)	5.2 (2.3)[a]	4.9 (2.9)[a]	NA	NA	≥ 2 (75.9%)
Mazzone, A [57]	2016	183/305 (60%)	83[c]	CHA_2DS_2-VASc > 3	5[b]	4 [3–5][b]	1[b]	NA
Wang, Y [60]	2016	158/348 (45.4%)[b]	77.9[b,c]	5.8[b,c]	5.8[c,b]	≥ 2 (336/348) 96.6%	≥ 3 (43/348) 12.4%	≥ 2 (220/348) 63%
Franchi, C [53]	2018	167/328 (50.9%)[d]	83 [78–87][d]	CHA_2DS_2-VASc > 3[d]	7 [5–9]	5 [4–6][d]	3 [2–4][d]	NA
Antoniazzi, S [51]	2019	134/246 (54.5%)[d]	81.4 (6.8)[d]	CHA_2DS_2-VASc > 3[d]	≥5[d]	5 [4–6][d]	2 [2, 3][d]	NA
Akao, M [50]	2020	13,993/32,713 (42.8%)	81.5 (4.8)	CHA_2DS_2-VASc > 3	6.6 (3.2)	4.5 (1.4)	1.9 (0.9)	2.9 (1.2)
Capiau, A [52]	2021	293/654 (44.8%)	77.1 (7.9)	5 [4–6]	8 [6–10]	4 [3–5]	NA	NA
Hupfer, M [54]	2021	280/407 (68.8%)	90.6 (3.3)	CHA_2DS_2-VASc > 3	8.7[b]	4.7 (1.5)	2.2 (0.7)	2.4 (1.1)
Jackson, L [55]	2021	708/1134 (62.4%)	82 [78–86]	CHA_2DS_2-VASc > 3	≥ 2	4 [4, 5]	≥ 2 (62.4%)	NA
Raccah, BH [58]	2021	247/509 (48.5%)	80 [74–86]	CHA_2DS_2-VASc > 3	9 [7–11]	5 [4–6]	2 [1–3]	NA
Li, R [61]	2022	930/1882 (49.4%)	80 [72–86]	$CHADS_2$ > 1	13 [9–16]	4 [3–5]	2 [1, 2]	2 [1–3]

Data are presented as proportion, mean (standard deviation) or median [interquartile range]. *NA Not available*

[a]Descriptive data is given for total population but not for AF-specific subpopulation

[b]The weighted mean [81]/weighted median [82] of the total population was calculated because the data was only reported for the subgroups

[c]We extracted the descriptive data of the polypharmacy subpopulation

[d]The study provided descriptive data and study sample characteristics for the total study population and not the polypharmacy subpopulation

3.6 Association Between PIP and Adverse Health Outcomes

Three studies assessed the association between misprescribing or specifically potentially inappropriate dosing on adverse health outcomes (CV hospitalisation, hospital readmission, all-cause mortality, CV mortality, major bleeding and stroke; Table 5) [51, 55, 58]. In the RCT conducted by Antoniazzi et al. (2019) which included 213 participants with a 6-month post-discharge follow-up, the association between PIP of (D)OACs and all-cause mortality [odds ratio (OR) 1.17; 95% CI 0.64–2.17] and hospital readmission (OR 0.96; 95% CI 0.52–1.75) was not statistically significant. The analysis was adjusted for age, sex, history of falls, body mass index (BMI), aspartate aminotransferase (AST) and alcohol consumption [51]. Similarly, in the cohort study ($n = 1134$) with a 2-year follow-up conducted by Jackson et al. (2021), no statistically significant difference was found in the unadjusted risk of CV hospitalisation [relative risk (RR) 1.02; 95% 0.83–1.26], stroke (RR 0.60; 95% CI 0.22–1.63), all-cause mortality (RR 1.10; 95% CI 0.75–1.62), CV mortality (RR 1.02; 95% CI 0.54–1.93) and major bleeding (RR 1.54; 95% CI 0.93–2.55) between adults with potentially inappropriate versus appropriate dosing of (D)OACs [55]. Contrarily, Raccah et al. (2021) reported a two-fold higher odds of having a major bleeding for adults with misprescribing versus appropriate prescribing of (D)OACs (OR 2.17; 95% CI 1.14–4.12) in a matched case-control study [58]. This study matched each case ($n = 64$) with up to 25 controls ($n = 445$) based on the duration of treatment with (D)OACs, the number of chronic medications and the follow-up time. The follow-up duration of the study varied for each patient and was determined by their individual length of hospitalisation. The analysis was adjusted for age, sex, type of (D)OACs and concomitant use of amiodarone [58]. These studies differed in terms of their study design, sample size and findings.

Table 4 The prevalence of PIP (misprescribing, potentially inappropriate dosing and underprescribing) across included studies

Author	Year	Prevalence of PIP	Prevalence of misprescribing/potentially inappropriate dosing	Types of misprescribing/potentially inappropriate dosing	Prevalence of underprescribing	Types of underprescribing
Spinewine, A [59]	2007	33/84 (39.3%)[a]	NA	NA	33/84 (39.3%)[a]	Anticoagulant and aspirin ($n = 84$): 33/84 (39.3%)[a]
Marcucci, M [56]	2010	138/245 (56.3%)[b]	138/245 (56.3%)[b]	Antithrombotic drugs ($n = 245$): 138/245 (56.3%)[b]	NA	NA
Mazzone, A [57]	2016	98/305 (32.1%)	27/305 (8.9%)	Contraindication OACs and (D)OACs ($n = 305$): 27/305 (8.9%)	71/305 (23.3%)	OACs and (D)OACs ($n = 305$): 71/305 (23.3%)
Wang, Y [60]	2016	238/348 (68.4%)[c]	238/348 (68.4%)[c]	$n = 348$[c] Antihypertensives 24/348 (6.90%): Antiarrhythmics 28/348 (8%): Digoxin 103/348 (29.60%): Flecainidine 7/348 (2%): GI drugs metoclopramide 8/348 (0.23%): Benzodiazepines 69/348 (19.83%): SSRI fluoxetine 24/348 (6.9%): NSAID 16/348 (4.60%): Estrogen 22/348 (6.32%): Urologicals 8/348 (2.30%)	NA	NA
Franchi, C [53]	2018	139/246 (56.5%)[c]	139/246 (56.5%)[c]	OACs (warfarin + acenocoumarol) and (D)OACs ($n = 246$): 139/246 (56.5%)[c]	NA	NA
Antoniazzi, S [51]	2019	72/201 (35.8%)[c]	72/201 (35.8%)[c]	OACs (warfarin + acenocoumarol) and (D)OACs ($n = 201$): 72/201 (35.8%)[c]	NA	NA

Table 4 (continued)

Author	Year	Prevalence of PIP	Prevalence of misprescribing/potentially inappropriate dosing	Types of misprescribing/potentially inappropriate dosing	Prevalence of underprescribing	Types of underprescribing
Akao, M [50]	2020	5024/17,641[d] (28.5%)	5024/17,641[d] (28.5%)	Apixaban (n = 6601): 2244/6601 (34%) - 389/6601 (5.9%) off-label dose, 198/6601 (3.0%) overdose, 1657/6601 (25.1%) underdose Rivaroxaban (n = 5202): 1675/5202 (32.2%) - 16 /5202 (0.3%) off-label dose, 291/5202 (5.6%) overdose, 1368/5202 (26.3%) underdose Edoxaban (n = 4036): 860/4036 (21.3%) - 214/4036 (5.3%) off-label dose, 93/4036 (2.3%) overdose, 553/4036 (13.7%) underdose Dabigatran (n = 1802): 245/1802 (13.6%) - 245/1802 (13.6%) off-label dose, 0/1802 (0%) overdose, 0/1802 (0%) underdose	NA	NA
Capiau, A [52]	2021	120/654 (18.3%)	120/654 (18.3%)[1]	(D)OACs (n = 654): 51/654 (7.8%) overdose, 64/654 (9.8%) underdose, 5/654 (0.8%) contraindicated Inappropriate dosing[e]: - Apixaban (14.5%) - Rivaroxaban (18.7%) - Edoxaban (6.7%) - Dabigatran (25.3%)	NA	NA
		153/654 (23.4%)	153/654 (23.4%)[2]	(D)OACs (n = 654): - 98/654 (15%) overdose - 50/654 (7.6%) underdose - 5/654 (0.8%) contraindicated	NA	NA
Hupfer, M [54]	2021	107/407 (26.3%)	51/407 (12.5%)	(D)OACs (n = 407): 49/407 (12%) underdose 2/407 (0.5%) contraindicated	56/407 (13.8%)	(D)OACs and OACs (n = 407): 56/407 (13.8%)

Table 4 (continued)

Author	Year	Prevalence of PIP	Prevalence of misprescribing/potentially inappropriate dosing	Types of misprescribing/potentially inappropriate dosing	Prevalence of underprescribing	Types of underprescribing
Jackson, L [55]	2021	391/1134 (34.5%)	391/1134 (34.5%)	(D)OACs (n = 1134): 221/1134 (19.5%) overdose, 170/1134 (15%) underdose (D)OACs inappropriate dosing (n = 1134): - Apixaban (n = 612): 202/612 (33%); 95%CI [29.0–36.4] - Rivaroxaban (n = 462): 170/462 (37%); 95%CI [32.8–41.6] - Edoxaban (n = 9): 7/9 (78%); 95%CI [50.6–100.0]) - Dabigatran (n = 51): 12/51 (24%); 95%CI [11.9–35.2]	NA	NA
Li, R [61]	2022	544/1882 (28.9%)	544/1882 (28.9%)	(D)OACs (n = 1882): 62/1882 (3.3%) overdose, 426/1885 (22.6%) underdose, 54/1882 (2.9%) contraindicated and 2/1882 (0.1%) incorrectly dosed - Apixaban (n =1288) 364/1288 (28.3%): - 33/1288 (2.6%) overdose, 295/1288 (22.9%) underdose, 36/1288 (2.8%) contraindicated and 0/1288 (0%) incorrectly dosed - Rivaroxaban (n = 495) 169/495 (34.1%): - 27/495 (5.5%) overdose, 124/495 (25.1%) underdose, 17/ 495 (3.4%) contraindicated and 1/495 (0.2%) incorrectly dosed - Dabigatran (n = 99) 11/99 (11.1%): - 2/99 (2%) overdose, 7/99 (7.1%) underdose, 1/99 (1%) contraindicated and 1/99 (1%) incorrectly dosed	NA	NA

[a]We extracted the prevalence of PIP of the AF subpopulation

[b]There are two patients with missing data on therapy

[c]We extracted the prevalence of PIP of the polypharmacy subpopulation

[d]The study used the subpopulation receiving (D)OACs as the denominator

[e]No ratio or total population (n) is given. The study prevalence was determined by (1) SmPC and by (2) EHRA separately in the study by Capiau et al. [52]

NA not available

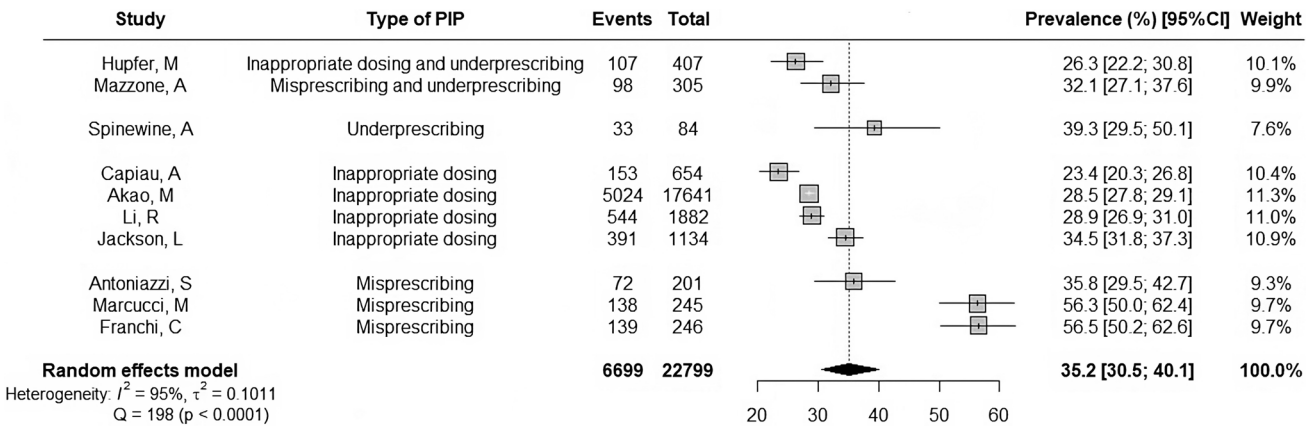

Fig. 2 Meta-analysis on the prevalence of PIP of (D)OACs. Hupfer et al. (2021) [54] assessed underprescribing and potentially inappropriate dosing, while Mazzone et al. (2016) [57] assessed underprescribing and misprescribing. Their total prevalence of PIP was used in the meta-analysis. For the study by Capiau et al. (2021), the prevalence of PIP assessed by the EHRA guidelines were used for the meta-analysis [52]. The EHRA guidelines are more sensitive than the SmPC by considering additional risk factors requiring dose reduction [52]

4 Discussion

The present systematic review aimed to assess the prevalence of PIP and its association with adverse health outcomes in multimorbid and polymedicated older adults with AF. Our principal findings are as follows: (i) the included studies were mostly observational with the majority conducted in hospital settings; (ii) the studies were primarily focused on PIP of (D)OACs, with the prevalence ranging from 8.9 to 56.5%; (iii) the meta-analysis of the studies assessing PIP of (D)OACs resulted in a pooled prevalence of 35.2% (95% CI 30.5–40.1%); and (iv) no statistical significant association was found between PIP and adverse health outcomes except for major bleeding.

Only the study by Wang et al. (2016) [60] assessed PIP considering all prescribed medications, reporting a prevalence of 68% of PIP, while the remaining studies focused solely on PIP of (D)OACs, which resulted in a pooled prevalence of 35%. Since the first approval of (D)OACs by the Food and Drug Administration in 2010 and the European Medicine Agency in 2011, there has been a gradual increase in the prescription of (D)OACs over vitamin K antagonists in AF [84–86]. A similar trend is noticeable in the literature. Initially, studies conducted before 2014 mainly reported PIP of OACs [56, 59], whereas studies performed after 2014 predominantly assessed misprescribing and specifically potentially inappropriate dosing of (D)OACs [50–55, 57, 61]. This transition might reflect the increasing preference for (D)OACs due to their preserved benefit–risk profile and practical advantages compared with vitamin K antagonists. Additionally, the prevalence of underprescribing decreased over time. This decrease in prevalence may also be attributed to the larger sample sizes in more recent studies, which provide better representativeness. The included studies did not assess overprescribing of (D)OACs. This is consistent with the prevalent concerns, primarily driven by physician's apprehension arising from the perceived bleeding risk [87–89].

Current research in multimorbid older adults with AF is predominantly focused on PIP of (D)OACs, despite their complex health profiles and polypharmacy. This is also reflected in the medication review tools used. Clinical guidelines providing recommendations on the management of AF and specifically the use of (D)OAC and SmPC were most often used ($n = 10$). Four studies [51, 53, 59, 60] applied explicit or implicit screening tools to describe only PIP of (D)OACs, even though these screening tools allow the assessment of overall PIP. By applying such screening tools to assess medication lists and consequently other drug classes than (D)OACs only, a comprehensive overview of PIP could have been obtained, which is essential in a population characterized by polypharmacy and potential drug-related problems and drug–drug and drug–disease interactions. In non-multimorbid older adults with AF, PIP would be restricted to the medical treatment of AF alone, consequently they would probably have minimal risk of potential drug–drug and/or drug–disease interactions.

The meta-analysis on PIP of (D)OACs demonstrated significant heterogeneity between studies, which is common in meta-analyses of prevalence data [90]. The prevalence of PIP of (D)OACs ranged from 8.9 to 56.5%. The pooled prevalence was 35.2%. Subgroup analyses to identify plausible causes of heterogeneity were not feasible, since the required minimum number of studies per subgroup was not met. The generally small sample size of the studies, study setting (community dwelling versus hospital setting), study

Table 5 The association between potentially inappropriate dosing or misprescribing on adverse health outcomes

Author	Year	Type of PIP	Study design	Follow-up period	Follow-up sample size	Covariates	CV hospitalisation	All-cause and CV mortality	Major bleeding	Stroke	Hospital readmission
Antoniazzi, S [51]	2019	Misprescribing of (D)OACs	RCT	6 months post-discharge follow-up	213 (82 misprescribed)	Age, sex, history of falls, BMI, AST and alcohol consumption	NA	All-cause mortality OR: 1.17, [0.64–2.17][a,b]	NA	NA	OR: 0.96, [0.52–1.75][a,b]
Jackson, LR [55]	2021	Potentially inappropriate dosing of (D)OACs	Cohort (prospective)	Every 6 months up to two years follow-up	1134 (391 potentially inappropriately dosed)	Unadjusted	RR[b]: 1.02, [0.83-1.26]	All-cause mortality RR[b]: 1.10, [0.75–1.62] CV mortality RR[b]: 1.02, [0.54–1.93]	RR[b]: 1.54, [0.93–2.55]	RR[b]: 0.60, [0.22–1.63]	NA
Raccah, BH [58]	2021	Misprescribing and/or dosing of (D)OACs	Matched case-control study[c]	Length of hospitalisation	Cases: 64 (21 misprescribed) Controls: 445 (147 misprescribed)	Age, sex, type of (D)OACs and concomitant use of amiodarone	NA	NA	OR: 2.17, [1.14–4.12]	NA	NA

[a]RR is calculated based on the reported incidence rate [83]

[b]The study provided the events for the total study population and not the polypharmacy subgroup

[c]Each case was matched based on number of chronic drugs, the treatment duration of (D)OACs and the follow-up time. Each individual case was paired with a maximum of 25 control subjects.

AST aspartate aminotransferase, *BMI* body mass index, *CV* cardiovascular, *(D)OACs* (direct) oral anticoagulants, *NA* not available, *OR* odds ratio, *RCT* randomised controlled trial, *RR* relative risk

population (age ranges, gender distribution) and medication review tool used (clinical guidelines/SmPC versus explicit/implicit screening tools) might have contributed to this significant heterogeneity. The assessment of quality identified inadequate and inconsistent reporting of descriptive variables, results and sample size justification, indicating a possible risk of bias. Despite the small number of studies (n = 10), some asymmetry was visually observed in the funnel plot. It should be noted that the funnel plot and corresponding statistical tests were originally designed for comparative studies and speculate that studies with positive results may be published more frequently than those with negative results. Assessment of potential publication bias may not be appropriate for prevalence studies. However, a more appropriate approach by adjusting the study's precision measure to the inverse sample size was conducted [91, 92].

Moreover, the leave-one-out sensitivity analysis resulted in the identification of two dominant studies [Marcucci et al. (2010) [56] and Franchi et al. (2018) [53]] with a similar prevalence of respectively 56.3% and 56.5%. The removal of the two studies reduced the heterogeneity, but it remained statistically significant. The two studies [Marcucci et al. (2010) [56] and Franchi et al. (2018) [53]] were conducted in internal medicine wards in Italy and had a similar sample size, with 245 and 246 patients, respectively. Marcucci's study was conducted in 2008 and used the ACCP 2008 guidelines, while Franchi's study was conducted between 2016–2017 and employed an explicit screening tool (Beers 2015), ESC 2016 guidelines and the SmPC. Both studies specifically assessed misprescribing. Based on their characteristics, it is not possible to determine the cause of their influential profile compared with the other studies. We suppose that the outcome (i.e., PIP) might not be specific enough, as it encompasses several sub-outcomes (i.e., misprescribing/potentially inappropriate dosing and underprescribing).

None of the included studies provided a comprehensive view of the overall quality of prescribing in multimorbid and polymedicated older AF patients, and its association with adverse health outcomes. However, some studies (n = 3) looked at the association between PIP (misprescribing or potentially inappropriate dosing) of (D)OACs and adverse health outcomes. Reported results on the association between PIP and major bleeding differed, with one study [58] demonstrating a significant association (OR 2.17, 95%CI 1.14–4.12) and the other study [55] showing no such association. There was no statistically significant association with other assessed adverse outcomes (CV hospitalisation, hospital readmission, all-cause and CV mortality). The authors reported the lack of long-term follow-up, insufficient sample size and low event rates as plausible explanations for a lack of association with the adverse health outcomes [51, 55]. Due to the limited number of studies reporting on these associations, no meta-analysis could be performed. Although there are numerous other studies on PIP of (D)OACs in older adults with AF [93–96], they were not included in this review primarily because data on polypharmacy and multimorbidity were not reported. These two characteristics should be incorporated in research on PIP in older adults with AF, as they are typical features of the population and risk factors for PIP.

4.1 Limitations

To date, this is the first systematic review and meta-analysis of studies assessing PIP and its association with adverse health outcomes in multimorbid and polymedicated older adults with AF. The study evaluated all types of PIP by using multiple electronic databases without limiting to specific medication review tools. Good practices were applied on the search strategy as well as the reporting of the systematic review.

A limiting feature of the systematic review is the broadly defined comorbidity (AF plus at least one chronic comorbidity) and polypharmacy (concurrent use of two or more drugs), which might possibly cause an inaccurate estimation of the prevalence of PIP. Additionally, the use of risk scores as surrogate for comorbidity reduces the accuracy of the study population's actual comorbidity burden. Moreover, studies were excluded because they did not quantitatively report the study populations' comorbidity and polypharmacy burden. This may have induced a restriction bias and may limit the external validity of this review. Due to the limited number of studies, subgroup analyses as well as a meta-analysis for the adverse health outcomes could not be performed. Finally, our conclusions regarding the prevalence and association between PIP and adverse health outcomes are limited to (D)OACs.

4.2 Clinical implications

Multimorbidity and polypharmacy are facets to 'clinical complexity' in AF patients [8, 97]. The systematic review highlighted that no study presents a comprehensive assessment of PIP in this clinically complex patient population. However, conducting such an assessment could help identify the most frequently potentially inappropriately prescribed medications and integrate improvements into patient care.

Integrated multidisciplinary care is considered essential for providing optimal and patient-tailored care, especially among older patients with multiple coexisting health problems [98, 99]. Recently an integrated, multidisciplinary and holistic care approach, the atrial fibrillation better care

pathway ('ABC') for AF patients has been developed to streamline integrated care [100]. It is based on three concepts (A) anticoagulation/Avoid stroke drugs, (B) better symptom management and (C) cardiovascular risk factors and comorbidities management [100]. Such an approach should be implemented since the adherence to a holistic or integrated care approach has been associated with improved clinical outcomes [15, 97, 101–103]. In the multimorbidity subgroup of the Mobile Health Technology for Improved Screening and Optimized Integrated Care in Atrial Fibrillation (mAFA-II) cluster randomised trial the integrated care approach significantly reduced clinical adverse events compared with usual care [104], which lead to its recommendation in guidelines [105]. Further large, prospective studies in multimorbid and polymedicated older adults with AF are needed to (1) assess the appropriateness of overall drug prescribing and (2) assess the impact of potentially inappropriate prescribing on patient-related outcomes. This might improve the therapeutic management of the patients in alignment with the need of an integrated multidisciplinary approach to treat multimorbid polymedicated older adults with AF [98, 99].

4.3 Emerged knowledge gaps

Current research is predominantly focused on PIP of (D) OACs, yet evidence on its impact on adverse health outcomes is limited. Additionally, there is no comprehensive view of PIP in multimorbid and polymedicated older adults with AF. Moreover, polypharmacy and comorbidity burden are prevalent characteristics in older adults with AF and known risk factors for PIP, yet they are often not reported or incorporated in the assessment of PIP prevalence. Future studies should take the abovementioned gaps in literature into consideration, and are being addressed in the EU-funded AFFIRMO programme [106].

5 Conclusion

This systematic review assessed the prevalence of potentially inappropriate prescribing and its association with adverse health outcomes in multimorbid and polymedicated older adults with AF. One study described 68% prevalence of PIP for all prescribed medications. PIP of (D)OACs specifically had a pooled prevalence of 35% in multimorbid and polymedicated older adults with AF. A statistically significant association was found between PIP of (D)OACs and major bleeding events. This review highlights the need for further research to assess the prevalence of PIP across all prescribed medications, and to assess the impact of PIP on adverse health outcomes in multimorbid older adults with AF.

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Declarations

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Conflict of Interest MG declares that he received a research grant from the Research Foundation Flanders (project number 11C0820N). Additionally, he declares payment to his institution for giving lectures to IPSA, a non-profit organisation. LL declares payment to her institution for giving lectures to IPSA, a non-profit organisation, and Chiesi Farmaceutici S.p.A and provides consulting services to AstraZeneca. Additionally she is a member of the European Respiratory Society and the Belgian Respiratory Society. GYHL declares consultancy and speaker fees from BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. MP declares that he is the President-elect of the European Geriatric Medicine Society. CA, DV, SA, LD, CD, AC-L, DDB, DLV and DDS declare no conflict of interest that might be relevant to this manuscript.

Data Availability Statement All data generated or analysed during this study are included in this published article (and its supplementary information files).

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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Authors' Contributions CA: Study concept and design, drafting, analysis, methodology, screening of abstracts and full texts, data extraction and quality assessment. DV: Screening of abstract and full text, methodology, reviewing and validation. SA: Data-extraction, quality assessment, reviewing and validation. MG: Methodology, analysis, reviewing and validation. LD: Study concept and design, reviewing and validation. CD: Study concept and design, reviewing and validation. AC-L: Study concept and design, reviewing and validation. LL: Methodology, reviewing and validation. DDB: Methodology, analysis, reviewing and validation. GL: Study concept and design, reviewing and validation. DLV: Study concept and design, methodology, supervision, reviewing and validation. DDS: Study concept and design, methodology, supervision, visualization, reviewing and validation. MP: Study concept and design, methodology, supervision, reviewing and validation. All authors read and approved the manuscript.

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