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ORIGINAL ARTICLE

Trends over time and risk factors in inappropriate prescribing in older adults with multimorbidity and polypharmacy: a longitudinal secondary analysis of the OPERAM trial

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Summary

BACKGROUND AND AIM OF THE STUDY: Polypharmacy is common among older adults and associated with potentially inappropriate medications and potential prescribing omissions, which together constitute potentially inappropriate prescriptions, contributing to adverse outcomes and increased healthcare costs. Longitudinal data on potentially inappropriate prescriptions and differences across living environments are limited. Our aim was to analyse patterns and determinants of potentially inappropriate prescriptions in multimorbid, older adults across different living environments and their trends over 12 months.

METHODS: We used data from the control group (n = 1045) of the multi-country OPERAM trial (December 2015 – October 2018), a cluster-randomised controlled trial including older adults aged ≥70 years with ≥3 chronic conditions and ≥5 medications, which tested a software intervention to improve prescribing in these patients. The control group received pharmaceutical care in accordance with usual care. STOPP/START criteria were applied to detect potentially inappropriate prescriptions at hospital admission, discharge, and at 2-, 6- and 12-month follow-up. The outcomes were a priori defined as the prevalence of potentially inappropriate prescriptions at hospital admission, differences in potentially inappropriate prescriptions between living settings (nursing home versus community-dwelling) and number of medications (polypharmacy [5–9 medications] versus hyperpolypharmacy [≥10 medications]), changes in potentially inappropriate prescriptions over the 12-month follow-up and factors associated with potentially inappropriate prescriptions. Analyses included descriptive statistics and multivariable regression.

RESULTS: At admission, 664 (63.5%) patients had ≥1 potentially inappropriate medication and 754 (72.1%) had ≥1 potential prescribing omission. Potentially inappropriate prescriptions at admission were most strongly associated with hyperpolypharmacy (potentially inappropriate medication: incidence rate ratio [IRR] 1.54, 95% CI 1.35–1.76) and cognitive impairment (potentially inappropriate medication: IRR 1.44, 95% CI 1.16–1.79), and were also significantly associated with female sex, number of comorbidities, fall history, nursing home residency and older age. Although overall prevalence remained stable over 12 months, substantial individual-level changes occurred, with many

patients experiencing increases or decreases in the number of potentially inappropriate medications or potential prescribing omissions, alongside notable shifts in specific potentially inappropriate medications/potential prescribing omissions. An increasing number of potentially inappropriate prescriptions over time was mostly associated with hyperpolypharmacy (potential prescribing omission: OR 1.71, 95% CI 1.20–2.42 at 12 months) and nursing home residency (potentially inappropriate medication: OR 1.94, 95% CI 1.12–3.36 at 12 months), while significant associations were found for fall history and number of comorbidities.

CONCLUSION: Potentially inappropriate prescriptions remain highly prevalent in multimorbid, older adults and do not clearly improve over time. Frequent changes at patient level and dynamic shifts in specific potentially inappropriate medications/potential prescribing omissions over time underscore the need for individualised, continuous medication reviews addressing both over- and underprescribing. Factors associated with increasing potentially inappropriate prescriptions over time may serve as indicators of high-risk patients and highlight the need for targeted interventions and further research.

Study registration: This study is based on data from the OPERAM trial, which was registered at ClinicalTrials.gov (NCT02986425).

Introduction

Polypharmacy, commonly defined as the use of five or more long-term medications, is a growing issue among older adults. Its prevalence is increasing, due to rising multimorbidity associated with population ageing and the implementation of disease-specific guidelines that are mostly not developed for multimorbid older adults [1–4]. While polypharmacy in older people can be appropriate, it is consistently associated with prescribing of potentially inappropriate medications [5–7]. Potentially inappropriate medications are defined as medications for which the risk of an adverse event outweighs their clinical benefit or which are prescribed without a clinical indication [8]. Widely known tools to identify potentially inappropriate medications include the American Geriatrics Society (AGS) Beers Criteria and the STOPP (Screening Tool of Older Person's Prescriptions) criteria [9, 10]. In addition to increased risk of potentially inappropriate medications, polypharmacy also increases the likelihood of potential prescribing omissions, where clinically indicated medications are not prescribed [11, 12]. Potential prescribing omissions can be assessed using START (Screening Tool to Alert doctors to Right Treatment) criteria. Developed in Europe, STOPP/START criteria are validated instruments endorsed by several national guidelines and are widely used to improve prescribing quality in older adults [10]. Potentially inappropriate medications and potential prescribing omissions, which can be grouped together as potentially inappropriate prescriptions are important to detect as they may contribute to adverse health outcomes, such as adverse drug events, falls, cognitive decline and functional impairment [10, 13]. These issues lead to higher healthcare utilisation and costs [14–16]. Use of STOPP/START criteria may be effective in improving prescribing quality and reducing falls, hospital length of stay, healthcare visits and medication costs [17]. Although these criteria were initially developed for community-dwelling older adults, recent research has shown that they can also help detect potentially inappropriate prescriptions in institutionalised and hospitalised patients [18, 19]. Previous research studies have largely focused on the prevalence of potentially inappropriate prescriptions in older adults, often within specific groups or settings, or patients with specific diseases (e.g. patients with Alzheimer's disease, community-dwelling patients or nursing home residents) and these studies were mostly cross-sectional [20, 21]. Although several studies have examined temporal trends, most have employed repeated cross-sectional designs and focused on overall prevalence [14, 22–27]. However, little is known about longitudinal changes in potentially inappropriate prescriptions within the same patient population of multimorbid older adults with polypharmacy, and about how individual potentially inappropriate medications and potential prescribing omissions differ across care settings and evolve over time. To address these knowledge gaps, we studied patterns of potentially inappropriate prescriptions in older multimorbid adults with polypharmacy across four European countries over a prospective 12-month period. Using data from the multi-country OPERAM trial ("OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older adults"), we compared the prevalence and types of potentially inappropriate prescriptions across predefined patient subgroups by living environment (community-dwelling versus nursing home) and medication burden (polypharmacy versus hyperpolypharmacy) at hospital admission, examined associated patient characteristics, assessed longitudinal changes over time and explored factors associated with these changes [28].

Methods

Study design and setting

This study employed a longitudinal, exploratory design using data from the OPERAM trial (ClinicalTrials.gov NCT02986425). OPERAM was a multi-country, partially blinded cluster-randomised controlled trial, which investigated the effects of hospital pharmacotherapy optimisation on drug-related hospital admissions in multimorbid (≥3 chronic conditions), older (≥70 years) adults with polypharmacy (≥5 chronic medications). It compared a structured pharmacotherapy optimisation intervention performed by a doctor and a pharmacist, with the support of a clinical decision software system (STRIPA), to usual care [29, 30]. Patients were recruited in medical and surgical wards of four European tertiary-care hospitals (Bern, Brussels, Cork, Utrecht).

Ethical approval

OPERAM was approved by the independent research ethics committees at each site (lead ethics committee: Cantonal Ethics Committee Bern, Switzerland: ID 2016-01200; Medical Research Ethics Committee Utrecht, Netherlands: ID 15-522/D; Comité d'Éthique Hospitalo-Facultaire Saint-Luc-UCL: 2016/20JUL/347–Belgian registration No: B403201629175; Cork University Teaching Hospitals Clinical Ethics Committee, Cork, Republic of Ireland: ID ECM 4 (o) 07/02/17), with Swissmedic as the responsible regulatory authority.

Study population and sample size

For this analysis, we included all 1045 patients who had been randomised to the OPERAM control group and were receiving medication-related care as delivered at that time at the four participating hospitals. Focusing on the combined control group allowed us to examine real-world prescribing practices and outcomes without the influence of the systematic pharmacotherapy optimisation intervention, which influenced prescribing practices in the intervention group [28–30].

Data collection

We used data collected during the OPERAM trial at multiple time points: hospital admission, discharge, and 2-, 6- and 12-month post-discharge follow-up. Participants were enrolled between December 2016 and October 2018, and follow-up assessments were conducted via telephone interviews by blinded researchers. The START criteria (v2) were used to detect potential prescribing omissions and the STOPP criteria (v2) to detect potentially inappropriate medications [10]. The present study could assess 30 of the 34 START criteria and 63 of the 80 STOPP criteria; the remaining criteria require laboratory and clinical data that were not available and they were therefore excluded. A detailed list of the included and excluded criteria is provided in tables S1–S3 in the appendix. The assessment of potentially inappropriate medications and potential prescribing omissions was conducted using an R statistical package developed specifically for the OPERAM trial in collaboration with UCLouvain, Belgium and the University of Ioannina, Greece (available at https://github.com/agapiospanos/StartStopp) [31, 32].

Outcomes

The study outcomes were a priori defined as the prevalence of potentially inappropriate prescriptions at hospital admission, differences in potentially inappropriate prescriptions between living settings (nursing home versus community-dwelling) and number of medications (polypharmacy [5–9 medications] versus hyperpolypharmacy [≥10 medications]), changes in potentially inappropriate prescriptions over the 12-month follow-up and factors associated with potentially inappropriate prescriptions.

Data analysis

Baseline characteristics were summarised using descriptive statistics. Normality for each variable was assessed using visual inspection of histograms and the Shapiro–Wilk test, which indicated non-normal data distribution; therefore, continuous variables were reported as medians with interquartile ranges (IQR) and categorical variables as absolute frequencies with percentages.

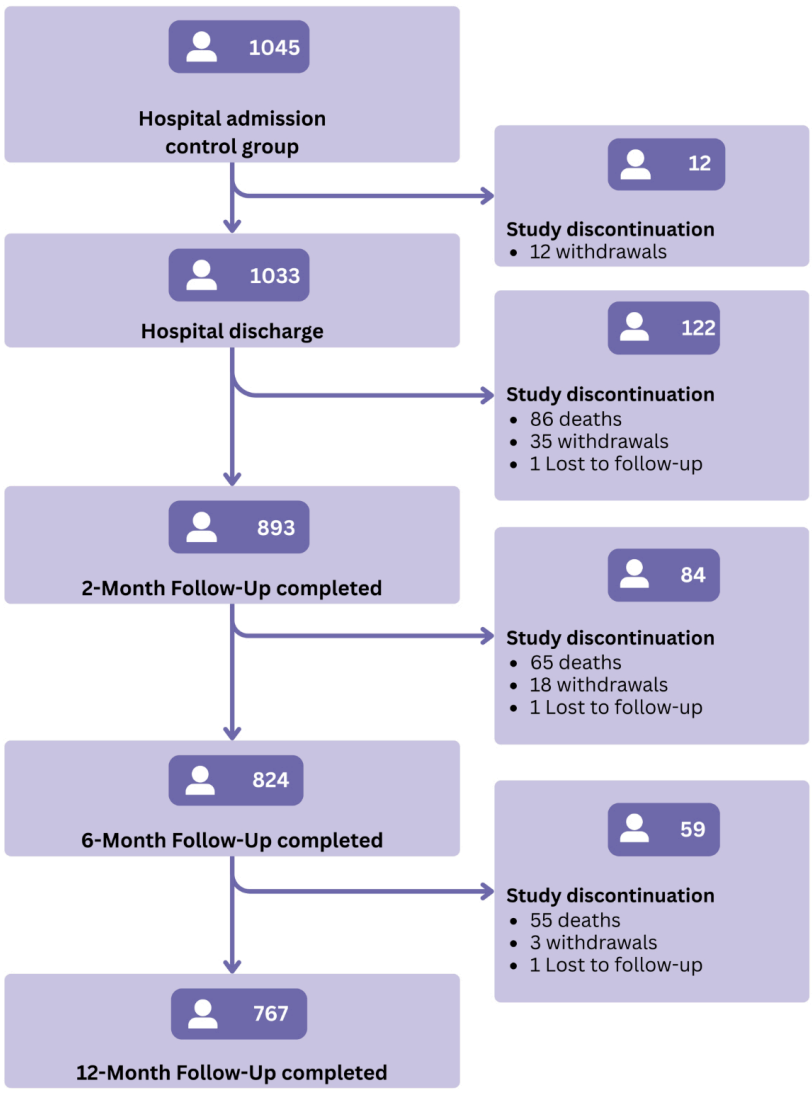
First, we described and compared the median number and prevalence of potentially inappropriate prescriptions at admission between living settings (nursing home versus community-dwelling) and number of medications (polypharmacy [5–9 medications] versus hyperpolypharmacy [≥10 medications]) using Mann–Whitney U tests and Pearson's chi-squared tests, as appropriate.

Additionally, the prevalence of the ten most frequent potentially inappropriate medications and potential prescribing omissions at admission was compared across these subgroups by calculating the percentage of patients meeting each criterion.

Second, we performed multivariable negative binomial regressions to identify patient characteristics associated with the number of potentially inappropriate medications and potential prescribing omissions at admission. Independent variables were selected based on previously published peer-reviewed literature and included nursing home residency (yes/no), age group (70–74, 75–84, ≥85 years), cognitive impairment (yes/no), history of fall within the past year (yes/no), sex (male/female), hyperpolypharmacy (≥10 medications, yes/no) and the number of comorbidities (continuous) [7, 33–35]. To test for non-linearity, the association between the number of comorbidities and the outcome was assessed using quadratic and fractional polynomial terms, with model fit compared by log-likelihood and deviance. Results are reported as incidence rate ratios (IRRs) with 95% confidence intervals.

Third, we investigated changes in potentially inappropriate prescriptions over the 12-month follow-up period. We calculated, for each patient, whether the number of potentially inappropriate medications and potential prescribing omissions increased, decreased or did not change between admission and discharge, and 2-month, 6-month and 12-month follow-up. Individual changes were derived as the within-patient difference in total counts of potentially inappropriate prescriptions between admission and subsequent assessments, and patients were categorised into one of three groups for potentially inappropriate medications and potential prescribing omissions separately: increase, decrease or no change. We further calculated the proportion of patients with at least one potentially inappropriate medication or potential prescribing omission at the respective follow-ups and assessed changes from admission using McNemar's tests. This part of the analysis included only participants who completed the respective follow-ups (discharge n = 1033; 2-month n = 893; 6-month n = 824; 12-month n = 767; figure 1). Furthermore, we examined changes in the prevalence of the ten most frequent potentially inappropriate medications and potential prescribing omissions over time, calculating relative differences and using McNemar's tests.

Figure 1: Flowchart of participants in the control group of the OPERAM trial from index hospital admission to 12-month follow-up.



Finally, we conducted multivariable logistic regression analyses using the same independent variables as in the admission model to identify factors associated with any increase or decrease in the number of potentially inappropriate medications and potential prescribing omissions from admission to discharge and to the 12-month follow-up. Outcomes were modelled as binary (increase versus no increase and decrease versus no decrease). Results are reported as odds ratios (ORs) with 95% confidence intervals. Missing data for covariates of the regression models were minimal (<1% for all variables) and were handled by complete-case analysis (n = 1037 for admission; n = 1030 for discharge; n = 766 for 12-month models). As a sensitivity analysis, we additionally performed multinomial logistic regression to simultaneously estimate factors associated with increases and decreases in potentially inappropriate prescriptions, using "no change" as the reference category, and conducted Fine-Gray competing risk regression models to account for death as a competing event when assessing time to first increase or decrease in potentially inappropriate prescriptions within 12 months. All statistical analyses were conducted using Stata version 16 (StataCorp®, College Station, TX, USA) and R version 4.1.2 (Free Software Foundation, Inc., Boston, MA, USA). Within R, we used the packages *dplyr* (1.1.4; MIT), *tidyr* (1.3.1; MIT), *openxlsx* (4.2.7; MIT), *haven* (2.5.5; GPL-3), *readr* (2.1.5; MIT) and *stringr* (1.5.1; MIT) (all from CRAN). For table export in Stata, we employed the user-written package *estout/esttab* (SSC; GPL). All analyses were considered exploratory and results are presented descriptively, with 95% CIs reported where appropriate.

Results

Flow of participants

A total of 1045 patients were included at hospital admission. Follow-up data were available for 1033/1045 (98.9%) patients at hospital discharge, 893/1045 (85.4%) at 2-month follow-up, 824/1045 (78.8%) at 6 months and 767/1045 (73.4%) at 12 months (figure 1). The majority of drop-outs (206/277 [74%]) were due to death.

Baseline characteristics

The median age of patients was 79 years (IQR 74–84) and 453 patients (43.3%) were female. The median number of comorbidities was 10 (IQR 8–15) and the median number of prescribed daily long-term medications was 9 (IQR 7–12); hyperpolypharmacy was observed in 47.3% of patients. A total of 114 patients (11.0%) resided in a nursing home prior to admission. The nursing home residents were older than community-dwelling patients (median 82 [IQR 77–87] versus 78 [IQR 74–84] years). A total of 39.0% of patients had experienced at least one fall in the year preceding admission. At admission, 88.3% of patients had at least one potentially inappropriate prescription. Specifically, 63.5% had at least one potentially inappropriate medication and 72.1% had at least one potential prescribing omission (table 1).

Table 1: Baseline characteristics and overall prevalence of potentially inappropriate medications/potential prescribing omissions at hospital admission among multimorbid older adults with polypharmacy.

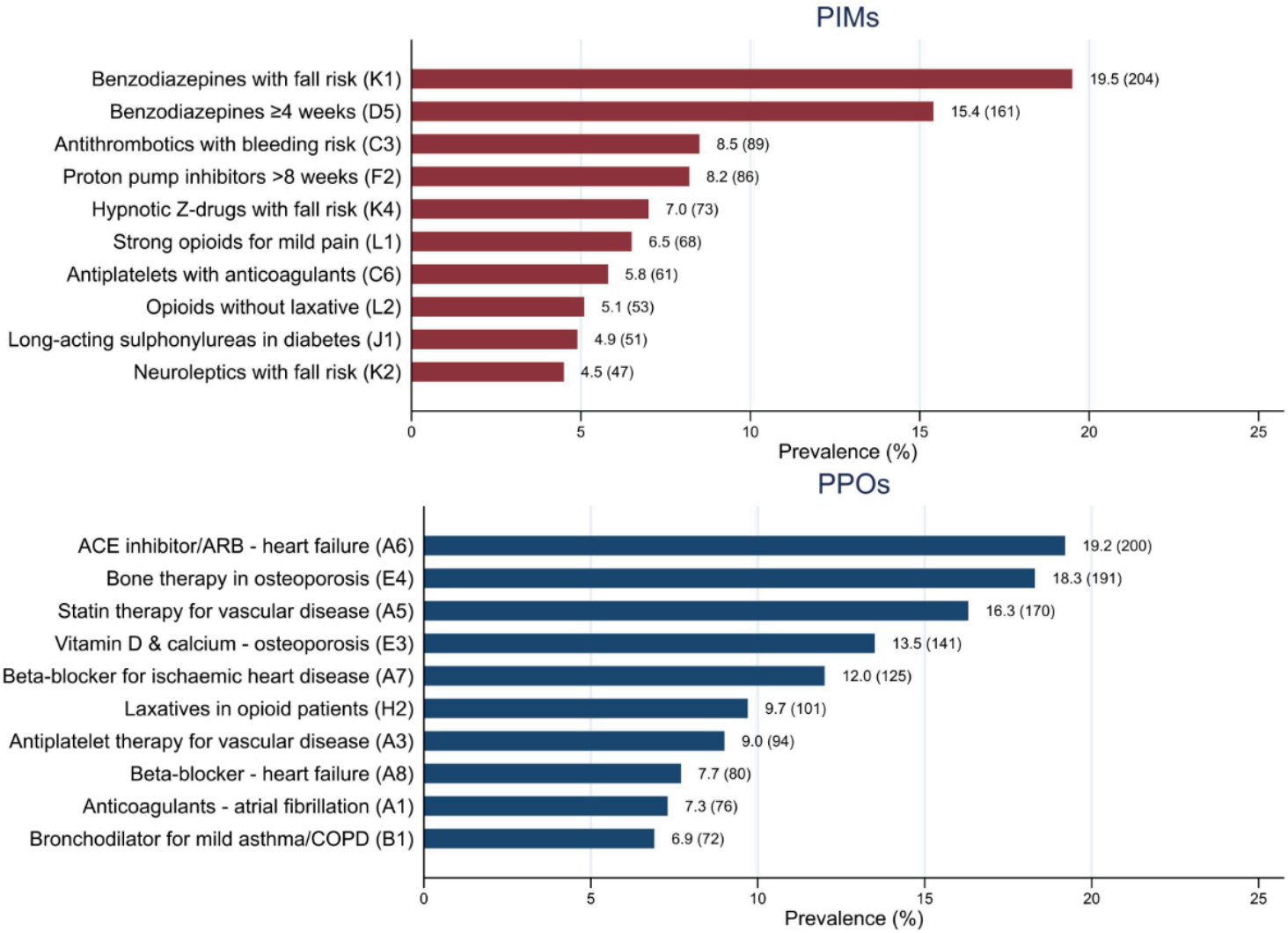
Variable	Values (n = 1045)
Age (years), median (IQR)	79 (74–84)
Female, n (%)	453 (43.3%)
Patients per trial site, n (%)	
... Bern, Switzerland	376 (36.0%)
... Cork, Republic of Ireland	208 (19.9%)
... Louvain, Belgium	238 (22.8%)
... Utrecht, Netherlands	223 (21.3%)
Nº of comorbidities[a], median (IQR)	10 (8–15)
... Bern, Switzerland	15 (11–22)
... Cork, Republic of Ireland	9 (7–11.5)
... Louvain, Belgium	10 (7–14)
... Utrecht, Netherlands	8 (6–10)
Nº of drugs[b], median (IQR)	9 (7–12)
... Bern, Switzerland	10 (7–13)
... Cork, Republic of Ireland	9 (7–12)
... Louvain, Belgium	8 (6–10)
... Utrecht, Netherlands	10 (8–14)
Patients with hyperpolypharmacy[c] (≥10 medications), n (%)	494 (47.3%)
Living in nursing home (in the last 6 months before the index admission)[d], n (%)	114 (11.0%)
Any fall in the year preceding index admission[e], n (%)	405 (39.0%)
Cognitive impairment[f] (e.g. dementia), n (%)	80 (7.7%)
Patients with ≥1 PIM or PPO[g], n (%)	923 (88.3%)
Patients with ≥1 PIM[g], n (%)	664 (63.5%)
Patients with ≥1 PPO[g], n (%)	754 (72.1%)
Nº of PIMs or PPOs per patient[g], median (IQR)	2 (1–4)
Nº of PIMs per patient[g], median (IQR)	1 (0–2)
Nº of PPOs per patient[g], median (IQR)	1 (0–2)

Missing data: [a] n = 1 (0.1%), [b] n = 1 (0.1%), [c] n = 1 (0.1%), [d] n = 5 (0.5%), [e] n = 7 (0.7%), [f] n = 1 (0.1%), [g] n = 1 (0.1%).
Abbreviations: IQR: interquartile range; PIM: potentially inappropriate medication; PPO: potential prescribing omission.

The two most common potentially inappropriate medications were the use of benzodiazepines in patients with risk of falling and long-term benzodiazepine use. The two most frequent potential prescribing omissions were the omission of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients with heart failure and non-prescription of bone-pro-

tective therapy in patients with osteoporosis (figure 2, table S4). The prevalence of all potentially inappropriate medications and potential prescribing omissions is presented in tables S1 and S2 in the appendix.

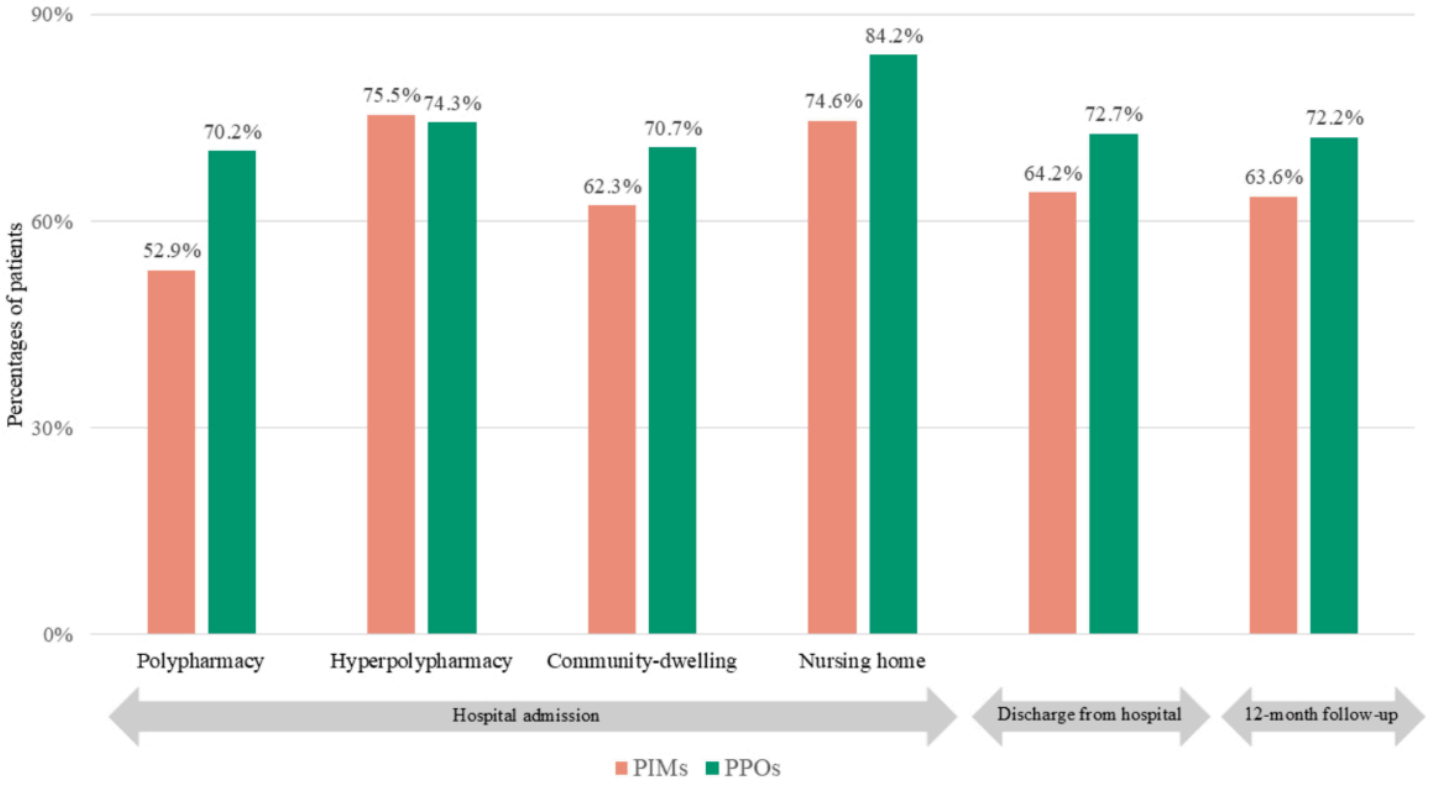
Figure 2 : Prevalence of the ten most frequent potentially inappropriate medications and potential prescribing omissions at admission. Values represent the percentage of patients meeting each criterion, with absolute numbers shown in brackets. Labels such as "Benzodiazepines with fall risk (K1)" refer to the corresponding STOPP/START criterion, where "K1" indicates the specific criterion number as defined in the validated STOPP/START version [10]. Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; PIM: potentially inappropriate medication; PPO: potential prescribing omission.



Comparison by living environment

At admission, nursing home residents had a higher prevalence of potentially inappropriate prescriptions compared to community-dwelling patients (figure 3, tables S5 and S6). The greatest difference in potentially inappropriate medication prevalence was observed in the prolonged use of proton-pump inhibitors (figure S1 in the appendix). Among potential prescribing omissions, the greatest difference concerned the potential omission of statin therapy despite known cardiovascular disease (figure S2).

Figure 3: Percentages of patients with at least one potentially inappropriate medication or potential prescribing omission. Values represent percentages of patients with at least one potentially inappropriate medication or potential prescribing omission. Polypharmacy is defined as the use of 5–9 long-term medications; hyperpolypharmacy as the use of ≥10 long-term medications. Abbreviations: PIM: potentially inappropriate medication; PPO: potential prescribing omission.



Comparison by polypharmacy versus hyperpolypharmacy

Patients with hyperpolypharmacy had a higher prevalence of potentially inappropriate medications than those with polypharmacy. Conversely, the prevalence of potential prescribing omissions was not significantly different between the groups (figure 3, tables S5 and S6). The largest difference in potentially inappropriate medications was observed for prevalence of benzodiazepines in patients with risk of falling (figure S1). Among potential prescribing omissions, the greatest difference was found in the omission of laxatives in patients receiving opioid therapy (figure S2).

Factors associated with potentially inappropriate prescriptions at admission

Multivariable negative binomial regression analysis showed that hyperpolypharmacy, female sex and cognitive impairment were associated with a higher number of potentially inappropriate medications, while nursing home residency, older age, a history of falls, female sex and each additional comorbidity were associated with a higher number of potential prescribing omissions. In contrast, hyperpolypharmacy was associated with fewer potential prescribing omissions (table 2). No evidence of non-linearity was observed for the number of comorbidities. Neither the quadratic nor the fractional polynomial terms improved model fit; thus, a linear specification was retained in the final models.

Table 2: Negative binomial regression of the number of potentially inappropriate medications and potential prescribing omissions at hospital admission (n = 1037).

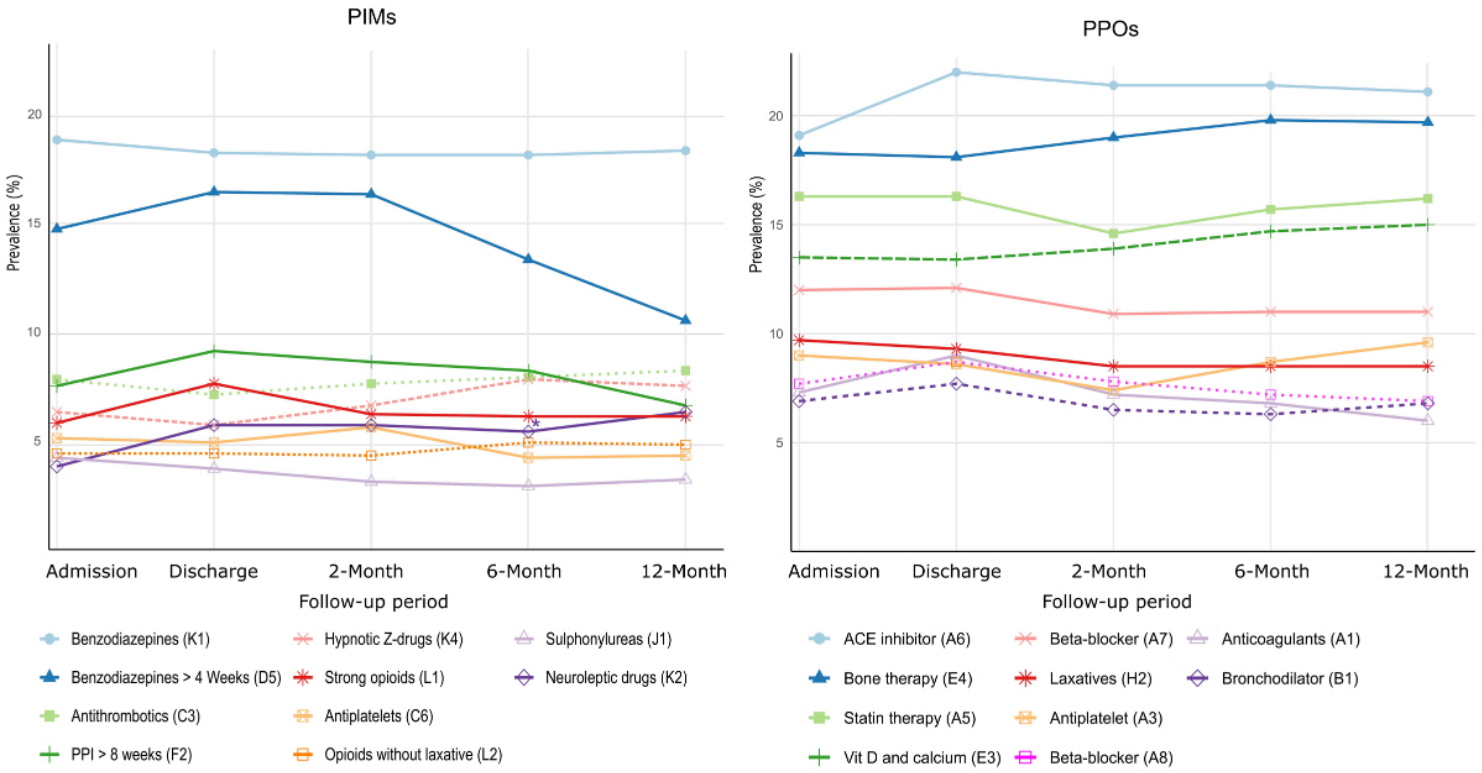
Variable		Number of PIMs		Number of PPOs	
		IRR	**95% CI**	**IRR**	**95% CI**
Nursing home residency		1.08	0.89, 1.31	1.18	1.00, 1.39
Hyperpolypharmacy (≥10 medications)		1.54	1.35, 1.76	0.89	0.79, 1.00
Cognitive impairment		1.44	1.16, 1.79	0.96	0.79, 1.16
Age group	70–74	Reference		Reference	
	75–84	1.02	0.88, 1.19	1.17	1.02, 1.34
	≥85	0.95	0.79, 1.13	1.33	1.14, 1.55
Any fall(s) in the last year		1.09	0.96, 1.24	1.22	1.09, 1.36
Number of comorbidities		1.00	0.99, 1.01	1.03	1.03, 1.04
Sex	Male	Reference		Reference	
	Female	1.19	1.05, 1.35	1.14	1.02, 1.27

Abbreviations: CI: confidence interval; IRR: incidence rate ratio; PIM: potentially inappropriate medication; PPO: potential prescribing omission.
Continuous variables (number of comorbidities) were modelled per one-unit increase; IRRs indicate the relative change in potentially inappropriate medications or potential prescribing omissions per additional comorbidity. Analyses were based on complete cases (n = 1037/1045 for admission). Missing values for covariates were minimal: nursing home residency: n = 5 (0.5%), hyperpolypharmacy: n = 1 (0.1%), cognitive impairment: n = 1 (0.1%), falls in the last year: n = 7 (0.7%), number of comorbidities: n = 1 (0.1%), age group and sex: n = 0.

Changes in potentially inappropriate prescriptions over time

During the index hospitalisation and the 12-month follow-up period, the overall prevalence of potentially inappropriate medications and potential prescribing omissions remained generally stable (table S6). However, analyses of individual patient data indicated variation over time, with many patients experiencing either an increase or a decrease in their number of potentially inappropriate medications or potential prescribing omissions over time (figure S3). The prevalence of specific potentially inappropriate medications and potential prescribing omissions changed substantially over time (figure 4).

Figure 4: Longitudinal trends of the ten most frequent potentially inappropriate medications and potential prescribing omissions. Values represent percentages of patients meeting each criterion. Labels such as "Benzodiazepines (K1)" refer to the corresponding STOPP/START criterion, where "K1" indicates the specific criterion number as defined in the validated STOPP/START version [10]. Abbreviations: ACE: angiotensin-converting enzyme; PIM: potentially inappropriate medication; PPI: proton-pump inhibitor; PPO: potential prescribing omission.



Regarding potentially inappropriate medications, the prevalence of neuroleptic drugs in patients with a history of falls increased over time with a relative increase of 55.6% from admission to 12 months. Conversely, the prevalence of long-term benzodiazepine use initially rose from admission to discharge but then declined at 12 months leading to a relative reduction of 27.3%.

Among potential prescribing omissions, the prevalence of omitted vitamin D and calcium supplementation in patients with osteoporosis showed the largest relative increase from admission to 12-month follow-up. In contrast, the greatest relative decrease was observed for the omission of anticoagulation in patients with atrial fibrillation. Additionally, the omission of ACE inhibitors in patients with heart failure increased from admission to discharge and remained elevated at 12 months.

Factors associated with changes in potentially inappropriate prescriptions over time

Multivariable logistic regression identified several patient characteristics associated with changes in potentially inappropriate prescriptions over time (tables 3 and 4).

Table 3: Multivariable logistic regression of increase and decrease in potentially inappropriate medications and potential prescribing omissions from admission to discharge (n = 1030). Binary outcomes reflect whether patients had an increase or decrease in the total number of potentially inappropriate medications or potential prescribing omissions compared to admission.

Admission to discharge		Increase in PIMs		Decrease in PIMs		Increase in PPOs		Decrease in PPOs	
Variable		**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Nursing home residency		1.26	0.76, 2.09	1.12	0.67, 1.87	1.37	0.85, 2.22	1.31	0.77, 2.24
Hyperpolypharmacy (≥10 medications)		0.58	0.42, 0.82	1.82	1.27, 2.61	1.52	1.09, 2.12	0.46	0.32, 0.67
Cognitive impairment		1.01	0.56, 1.82	1.55	0.88, 2.72	1.53	0.89, 2.63	0.81	0.42, 1.56
Age group	70–74	Reference		Reference		Reference		Reference	
	75–84	0.96	0.66, 1.39	1.04	0.67, 1.59	0.76	0.52, 1.10	1.71	1.10, 2.67
	≥85	0.88	0.56, 1.38	1.62	1.00, 2.61	0.92	0.59, 1.44	1.61	0.96, 2.69
Any fall(s) in the last year		1.55	1.12, 2.15	1.22	0.86, 1.73	1.19	0.85, 1.65	1.54	1.08, 2.18
Number of comorbidities		1.01	0.99, 1.03	1.02	1.00, 1.05	1.02	1.00, 1.04	1.01	0.98, 1.04
Sex	Male	Reference		Reference		Reference		Reference	
	Female	1.24	0.90, 1.70	0.99	0.70, 1.41	0.75	0.54, 1.04	1.33	0.94, 1.88

Abbreviations: CI: confidence interval; IRR: incidence rate ratio; OR: odds ratio; PIM: potentially inappropriate medication; PPO: potential prescribing omission.
Continuous variables (number of comorbidities) were modelled per one-unit increase; ORs indicate the relative change in potentially inappropriate medications or potential prescribing omissions per additional comorbidity. Analyses were based on complete cases (n = 1030/1045 for discharge). Missing values for covariates were minimal: nursing home residency: n = 5 (0.5%), hyperpolypharmacy: n = 1 (0.1%), cognitive impairment: n = 1 (0.1%), falls in the last year: n = 7 (0.7%), number of comorbidities: n = 1 (0.1%), age group and sex: n = 0.

Table 4: Multivariable logistic regression of increase and decrease in potentially inappropriate medications and potential prescribing omissions from admission to 12-month follow-up (n = 766). Binary outcomes reflect whether patients had an increase or decrease in the number of potentially inappropriate medications or potential prescribing omissions compared to admission.

Admission to 12-month follow-up		Increase in PIMs		Decrease in PIMs		Increase in PPOs		Decrease in PPOs	
Variable		**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Nursing home residency		1.94	1.12, 3.36	1.73	0.99, 3.01	1.01	0.56, 1.82	1.40	0.77, 2.56
Hyperpolypharmacy(≥10 medications)		0.83	0.58, 1.20	1.93	1.36, 2.75	1.71	1.20, 2.42	0.51	0.35, 0.74
Cognitive impairment		1.50	0.83, 2.72	0.94	0.49, 1.80	1.26	0.68, 2.34	0.63	0.31, 1.28
Age group	70–74	Reference		Reference		Reference		Reference	
	75–84	1.22	0.81, 1.85	1.23	0.83, 1.84	0.99	0.67, 1.46	1.37	0.91, 2.07
	≥85	1.13	0.67, 1.89	0.94	0.55, 1.58	0.81	0.48, 1.35	1.11	0.65, 1.89
Any fall(s) in the last year		1.10	0.76, 1.58	1.01	0.71, 1.45	0.81	0.56, 1.16	1.52	1.06, 2.18
Number of comorbidities		1.02	0.99, 1.05	1.00	0.97, 1.02	1.03	1.01, 1.06	1.00	0.97, 1.03
Sex	Male	Reference		Reference		Reference		Reference	
	Female	1.40	0.99, 1.99	1.40	0.99, 1.98	1.23	0.87, 1.74	1.16	0.82, 1.66

Abbreviations: CI: confidence interval; OR: odds ratio; PIM: potentially inappropriate medication; PPO: potential prescribing omission.
Continuous variables (number of comorbidities) were modelled per one-unit increase; ORs indicate the relative change in potentially inappropriate medications or potential prescribing omissions per additional comorbidity. Analyses were based on complete cases (n = 766/1045 for 12-month follow-up). Missing values for covariates were minimal: nursing home residency: n = 5 (0.5%), hyperpolypharmacy: n = 1 (0.1%), cognitive impairment: n = 1 (0.1%), falls in the last year: n = 7 (0.7%), number of comorbidities: n = 1 (0.1%), age group and sex: n = 0.

Nursing home residency was associated with an increase in potentially inappropriate medications at 12 months. Hyperpolypharmacy was associated with an increase in potential prescribing omissions and a decrease in potentially inappropriate medications at both discharge and 12 months. Patients aged 75–84 years were more likely to experience a decrease in potential prescribing omissions during hospitalisation compared to those aged 70–74 years. A history of falls was associated with a decrease in potential prescribing omissions at discharge and at 12 months, but also an increase in potentially inappropriate medications at discharge. A higher number of comorbidities was associated with an increase in potential prescribing omissions at 12 months. The multinomial sensi-

tivity analyses showed consistent results, with stronger associations for nursing home residency and female sex, and slightly weaker effects for hyperpolypharmacy (table S7). Similarly, the results of the Fine-Gray competing risk regression were consistent with those of the logistic regression, showing slightly attenuated effect estimates for nursing home residency and hyperpolypharmacy after accounting for death as a competing event and event timing (table S8).

Discussion

Main findings

This study provides a comprehensive analysis of the prevalence, changes and determinants of potentially inappropriate prescriptions in older, multimorbid adults with polypharmacy across four European countries. At hospital admission, 88.3% of patients had at least one potentially inappropriate medication or potential prescribing omission, indicating that potentially inappropriate prescriptions in this at-risk population are highly prevalent, especially in older adults with hyperpolypharmacy (52.9% of whom had at least one potentially inappropriate medication and 70.2% at least one potential prescribing omission) and those living in nursing homes (74.6% with at least one potentially inappropriate medication; 84.2% with at least one potential prescribing omission). Moreover, our analyses indicated variability in the total number of potentially inappropriate prescriptions per patient over the 12-month follow-up period, although the overall prevalence remained consistently high.

High prevalence of potentially inappropriate prescriptions

The high prevalence of potentially inappropriate prescriptions observed in our study aligns with existing literature and is most probably a consequence of the older age, medication burden and multimorbidity of our study population. A previous systematic review reported potentially inappropriate medication and potential prescribing omission prevalence rates of 51.8% and 64.0%, respectively, in hospitalised patients aged ≥65 years [19]. The even higher prevalence of potentially inappropriate medications and potential prescribing omissions identified in the present study are consistent with findings from studies involving more-comparable populations [5, 14, 36]. The most frequent potential prescribing omissions were omissions of ACE inhibitors or ARBs in patients with heart failure and of bone anti-resorptive therapy in osteoporosis; benzodiazepines were the most common potentially inappropriate medications, consistent with previous findings [19, 26].

Comparison between different subgroups

Nursing home residents had a higher prevalence of potentially inappropriate medications and potential prescribing omissions compared to community-dwelling patients, and, as expected, hyperpolypharmacy was associated with more potentially inappropriate medications, reflecting established associations reported in the literature [5–7, 18, 33, 34, 37, 38]. In addition to frailty and multimorbidity, the higher prevalence of potentially inappropriate prescriptions in nursing home residents may also be partly explained by the fact that they were older than community-dwelling patients in our study population.

The most pronounced difference in potential prescribing omission prevalence between nursing home and community-dwelling patients was observed for statin omission in patients with cardiovascular disease. The high rate of statin omissions in this population may reflect rational prescribing in frail patients, based on poor life expectancy and individualised risk-benefit assessments. However, our dataset did not allow us to draw conclusions regarding the clinical rationale relating to possible decisions to deprescribe or whether inappropriate prescription omission may have resulted in technical potential prescribing omissions.

Regarding potentially inappropriate medications, the greatest difference was found in the prolonged use of proton-pump inhibitors, highlighting the high prevalence of non-evidence-based proton-pump inhibitor prescriptions in nursing homes [39]. This may reflect lack of systematic medication review in nursing homes, where medications initially prescribed for a specific indication may not be reassessed or discontinued after the recommended duration.

Determinants of potentially inappropriate prescriptions

Our analysis identified several factors associated with the number of potentially inappropriate prescriptions at admission and their increase or decrease over time. Nursing home residency was associated with a higher potential prescribing omission prevalence at admission and increasing po-

tentially inappropriate medications over time, consistent with previous research reporting high and even rising rates of potentially inappropriate prescriptions in nursing homes [18, 40]. Patients with cognitive impairment were at higher risk for potentially inappropriate medications at admission likely due to the frequent use of centrally acting drugs in this population [6, 33, 41]. A history of falls was also associated with more potential prescribing omissions at hospital admission, possibly driven by underuse of osteoprotective medications – a frequent omission also highlighted in our study. While the literature indicates that a higher number of potentially inappropriate medications is linked to an increased risk of falls, it remains unclear whether a history of falls itself is a risk factor for potentially inappropriate prescriptions [13, 42].

Hyperpolypharmacy being associated with more potentially inappropriate medications and fewer potential prescribing omissions at admission, reinforces the well-established and complex relationship between hyperpolypharmacy and potentially inappropriate prescriptions [25, 33, 43, 44]. While the observed association between hyperpolypharmacy and potentially inappropriate medication reduction over time likely reflects deprescribing efforts in patients with high medication burden, the association with increasing potential prescribing omissions over time, consistent with previous evidence, raises concern [45, 46]. These findings suggest that efforts to reduce inappropriate medications may inadvertently lead to prescription omissions, strengthening the argument for routine medication reviews addressing both over- and underprescribing, particularly in patients with hyperpolypharmacy.

Female sex was associated with higher prevalences of both potentially inappropriate medications and potential prescribing omissions, consistent with prior evidence attributing this to a multifactorial interplay of biological, clinical and sociocultural factors, including higher psychotropic drug use among women than men [6, 7, 34, 46–50]. Older age and a greater number of comorbidities were linked to a greater number of potential prescribing omissions at hospital admission, which is consistent with previous research [33, 34, 46, 51]. In older and multimorbid patients, clinical guidelines may be difficult to implement in full, leading to omissions that are not technically inappropriate but might represent pragmatic clinical prioritisation, aiming to avoid drug-drug and drug-disease interactions [3].

Changes in potentially inappropriate prescriptions over time but no clear trend

Evidence on longitudinal trends in potentially inappropriate prescriptions is mixed. Some studies report rising prevalences of potentially inappropriate prescriptions over time, others find little or no change, consistent with our findings [14, 22, 23, 25, 45, 46, 52–55]. Hospitalisation has been recognised as an opportunity to improve potentially inappropriate prescriptions, particularly in the context of structured interventions [27, 56]. However, in our study, which evaluated standard of care, no consistent improvement in potentially inappropriate prescriptions was observed.

Our findings show that while the overall prevalence of potentially inappropriate prescriptions appears stable over time, this masks potentially individual-level variability, with many patients experiencing increases or decreases in potentially inappropriate medications and potential prescribing omissions. However, identifying which specific potentially inappropriate prescriptions changed per patient was beyond the scope of this study and should be addressed in future research. Moreover, specific potentially inappropriate medications and potential prescribing omissions fluctuated considerably. Notably, the omission of ACE inhibitors or ARBs in patients with systolic heart failure increased over time. This may be partly attributable to new diagnoses made during hospitalisation, where initiation of treatment was deferred due to acute clinical circumstances – such as hypotension or renal impairment – and subsequently not initiated or restarted in the outpatient setting. In contrast, inappropriate benzodiazepine use declined over the same period, likely reflecting increased awareness of their classification as potentially inappropriate medications and growing efforts to promote medication optimisation in older adults – a trend also observed in the literature [25, 53, 55, 57].

Interestingly, despite the decline in benzodiazepine use, a converse increase in prevalence of neuroleptic drug prescriptions was observed over the follow-up period. These opposing trends may suggest a compensatory shift in prescribing patterns, a phenomenon previously described in the literature [58, 59]. Such medication substitution effects highlight the need for deprescribing strategies that address medication classes comprehensively.

Our findings suggest that static prevalence rates may not adequately reflect the dynamic and complex nature of prescribing in older patients. As different potentially inappropriate medications and potential prescribing omissions vary in their clinical relevance, shifts in their type and composition over time could have more meaningful implications for patient outcomes than the

overall prevalence would suggest. These observations support the value of individualised, longitudinal medication reviews – particularly in patients at higher risk – focusing on the most clinically relevant potentially inappropriate medications and potential prescribing omissions. Future research may benefit from incorporating patient-level trajectories and criterion-specific patterns alongside cross-sectional assessments.

Strengths and limitations

This study has several strengths. Firstly, the use of a large, multi-country dataset encompassing four European countries enhances the generalisability of the findings. Data collection was prospective, standardised and nearly complete, contributing to high methodological quality. Furthermore, the broad inclusion criteria support the external validity of our findings. Secondly, the 12-month follow-up of the same patient sample enabled a rare assessment of prescribing trends over time, capturing fluctuations in potentially inappropriate prescriptions. Thirdly, the inclusion of both community-dwelling and nursing home residents offers valuable insight into setting-specific prescribing practices.

Some study limitations should also be acknowledged. Firstly, given the exploratory nature of this study and the large number of comparisons, statistical significance should be interpreted cautiously and all analyses were descriptive and hypothesis-generating. Secondly, not all STOPP/START criteria could be applied due to incomplete clinical or laboratory data. Thirdly, as changes in potentially inappropriate medications and potential prescribing omissions over time were analysed as binary outcomes in the regression model, the analyses did not capture the full spectrum or magnitude of change, although this was explored in sensitivity analyses using multinomial logistic regression, which showed similar results. In addition, we did not assess which specific potentially inappropriate prescriptions were newly identified or discontinued between time points, nor did we perform item-level transition analyses that would depict such criterion-level changes. Finally, individual prescribing decisions based on clinical judgment or patient preferences could not be assessed, as such contextual information was not captured in the dataset.

Conclusion

Potentially inappropriate prescriptions are common among older, multimorbid adults with polypharmacy and the overall prevalence remains largely unchanged over a 12-month follow-up interval. This apparent stability conceals potential dynamic shifts at an individual patient level and in specific potentially inappropriate medications and potential prescribing omissions, which likely vary in clinical relevance and impact. The substantial burden of potentially inappropriate prescriptions underscores the need for continuous, structured medication reviews in multimorbid older people exposed to polypharmacy. Such reviews should address both over- and underprescribing. Targeting high-risk groups – such as nursing home residents, individuals with hyperpolypharmacy, advanced age or cognitive impairment – and focusing on the most variable and clinically relevant potentially inappropriate prescriptions may enhance intervention effectiveness. Future research should move beyond aggregate prevalence metrics and explore longitudinal, patient-level trajectories of key potentially inappropriate medications and potential prescribing omissions to identify modifiable targets and inform more precise, individualised interventions that improve prescribing quality.

Data sharing statement

Data are available from the corresponding author upon reasonable request. Data will be made available for scientific purposes for researchers whose proposed use of the data has been approved by the OPERAM publication committee. The analytical code used for this study is available from the corresponding author upon reasonable request.

Acknowledgments

Author contributions: Katharina Tabea Jungo and Nicolas Rodondi conceived the project. Jonathan Huschka and Carole E. Aubert conducted the project, and analysed and interpreted the data. Jonathan Huschka wrote the first draft of the manuscript. Carole E. Aubert closely supervised manuscript writing. All authors critically revised the manuscript and have approved its final version for publication.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Table S1: Prevalence of included PIMs at admission (n=1045)

Criteria description	n (%)
B Cardiovascular	
B1 Digoxin for heart failure with preserved systolic ventricular function	1 (0.1%)
B2 Verapamil or diltiazem with NYHA Class III or IV heart failure	9 (0.9%)
B3 Beta-blocker in combination with verapamil or diltiazem	9 (0.9%)
B5 Amiodarone as first-line antiarrhythmic therapy	39 (3.7%)
B6 Loop diuretic as treatment for hypertension	12 (1.2%)
B7 Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	7 (0.7%)
B9 Loop diuretic for treatment of hypertension with urinary incontinence	6 (0.6%)
B10 Centrally-acting antihypertensives	14 (1.3%)
B13 Phosphodiesterase type-5 inhibitors in severe heart failure characterized by hypotension or concurrent daily nitrate therapy for angina	2 (0.2%)
C Coagulation	
C1 Long-term aspirin at doses greater than 160 mg/day	2 (0.2%)
C2 Aspirin with a past history of peptic ulcer disease without concomitant PPI	2 (0.2%)
C3 Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk	89 (8.5%)
C4 Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	5 (0.5%)
C5 Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation	5 (0.5%)
C6 Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease	61 (5.8%)
C7 Ticlopidine in any circumstances	1 (0.1%)
C8 Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months	1 (0.1%)
C9 Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months	12 (1.2%)
C10 NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	17 (1.6%)
C11 NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis	9 (0.9%)
D Central nervous system	
D1 Tricyclic antidepressants with dementia, untreated narrow angle glaucoma, cardiac conduction abnormalities, prostatism, Sjogren's illness or previous urinary retention	7 (0.7%)

D2 Tricyclic antidepressants as first-line antidepressant treatment	3 (0.3%)
D3 Neuroleptics with moderate-marked anticholinergic effects with history of prostatism or previous urinary retention	0 (0%)
D5 Benzodiazepines for ≥ 4 weeks	161 (15.4%)
D6 Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism	2 (0.2%)
D7 Anticholinergics to treat extra-pyramidal side-effects of neuroleptic medications	0 (0%)
D8 Medications with anticholinergic effects in patients with delirium or dementia	26 (2.5%)
D9 Antipsychotics in patients with behavioural and psychological symptoms of dementia unless symptoms are severe and not medical treatments have failed	13 (1.2%)
D10 Neuroleptics as hypnotics	1 (0.1%)
D12 Phenothiazines with exception of chloorpromazin for hiccoughs and levopromazine in palliative care	4 (0.4%)
D13 Levodopa or dopamine agonists for benign essential tremor	1 (0.1%)
D14 First-generation antihistamines	14 (1.3%)
F Gastrointestinal	
F1 Metoclopramide with Parkinsonism	1 (0.1%)
F2 PPI for peptic ulcer disease or oesophagitis with exception of barrett's oesophagus at full therapeutic dosage for > 8 weeks	86 (8.2%)
F3 Drugs likely to cause or worsen constipation in patients with chronic constipation	14 (1.3%)
F4 Iron preparations with regulated release or oral elemental iron doses greater than 200 mg daily	0 (0%)
G Respiratory	
G1 Theophylline as monotherapy for COPD	1 (0.1%)
G2 Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD or asthma	15 (1.4%)
G3 Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with untreated narrow angle glaucoma or bladder outflow obstruction	15 (1.4%)
H Musculoskeletal	
H1 NSAID other than COX-2-selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	4 (0.4%)
H2 NSAID with moderate-severe hypertension or heart failure	45 (4.3%)
H3 Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried	8 (0.8%)
H4 Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis	2 (0.2%)
H5 Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis	15 (1.4%)
H6 Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor	8 (0.8%)
H7 COX-2 selective NSAIDs and diclofenac with concurrent cardiovascular disease	4 (0.4%)
H8 NSAID with concurrent corticosteroids without PPI	1 (0.1%)

H9 Oral bisphosphonates in patients with a history of upper gastrointestinal disease or in patients who stay in bed	10 (1.0%)
I Urogenital	
I1 Anticholinergics for neurogenic bladder with concurrent dementia, chronic cognitive impairment, narrow-angle glaucoma or chronic prostatism	5 (0.5%)
I2 Selective alpha-1 blockers in those with daily incontinence, symptomatic orthostatic hypotension, micturition syncope or urinary catheter in situ > 2months	6 (0.6%)
J Endocrine	
J1 Sulphonylureas with a long duration of action and active metabolites with type 2 diabetes mellitus	51 (4.9%)
J2 Thiazolidenediones in patients with documented heart failure	0 (0%)
J3 Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes	0 (0%)
J4 Oestrogens with a history of breast cancer or venous thromboembolism	1 (0.1%)
J5 Oral oestrogens without progestogen in patients with intact uterus	13 (1.2%)
J6 Androgens in the absence of primary or secondary hypogonadism	2 (0.2%)
K Falls	
K1 Benzodiazepines with history or risk of falling	204 (19.5%)
K2 Neuroleptic drugs with history or risk of falling	47 (4.5%)
K3 Drugs with orthostatic hypotension	14 (1.3%)
K4 Hypnotic Z-drugs with history or risk of falling	73 (7.0%)
L Analgetic	
L1 Use of oral or transdermal strong opioids as first line therapy for mild pain	68 (6.5%)
L2 Use of regular opioids without concomitant laxative	53 (5.1%)
M Antimuscarinic/anticholinergic	
M1 Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties	5 (0.5%)
Total	1306

Legend: Values represent number of patients meeting each criterion (percentages of patients)

Abbreviations: ACE: Angiotensin-converting enzyme, NSAID: Non-steroidal anti-inflammatory drugs, NYHA: New York Heart Association, PIM: Potentially inappropriate medication, PPI: Proton pump inhibitor, SSRI: Selective serotonin re-uptake inhibitor

Table S2: Prevalence of included PPOs at admission (n=1045)

Criteria description	n (%)
A Cardiovascular	
A1 Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation (with exception of men 65-75 years without cardiovascular comorbidity)	76 (7.3%)
A2 Antiplatelet agents in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated or not wanted	36 (3.4%)
A3 Acetyl salicylic acid or carbasalate calcium, clopidogrel, prasugrel or ticagrelor with a documented history of coronary, cerebral or peripheral vascular disease and sinus rhythm in patient not treated with Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	94 (9.0%)
A5 Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease or high cardiovascular risk	170 (16.3%)
A6 ACE inhibitor (or angiotensin receptor blocker in case of side effects ACE inhibitor) with systolic heart failure and/or coronary artery disease	200 (19.1%)
A7 Beta-blocker with ischaemic heart disease or stable angina pectoris	125 (12.0%)
A8 Appropriate beta-blocker with stable systolic heart failure	80 (7.7%)
B Respiratory	
B1 Inhaled beta 2 agonist or antimuscarinic bronchodilator for mild to moderate asthma or COPD	72 (6.9%)
B2 Inhaled corticosteroid for COPD, where repeated exacerbations despite long-working bronchodilator	11 (1.1%)
C Central Nervous System	
C1 L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability	2 (0.2%)
C2 Non-TCA antidepressant drug in the presence of moderate-severe depressive symptoms	25 (2.4%)
C3 Acetylcholinesterase inhibitor for mild or moderate Alzheimer's dementia or Lewy Body dementia	3 (0.3%)
C4 Topical prostaglandin, prostaminde or beta-blocker for primary open-angle glaucoma	2 (0.2%)
C5 SSRI's (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning	10 (1.0%)
C6 Dopamine agonist for severe restless legs syndrome with unacceptable suffering despite non-medical treatment, once iron deficiency and severe renal failure have been excluded	11 (1.1%)
D Gastrointestinal	
D1 Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation	12 (1.2%)
D2 Fibre supplement for chronic diverticulosis with constipation	2 (0.2%)
E Musculoskeletal	
E1 DMARD with active, disabling rheumatoid disease (> 4 weeks)	25 (2.4%)
E2 Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy (> 3 months) if dose ≥ 7.5 mg daily prednisone (or equivalent)	60 (5.7%)

E3 Vitamin D and calcium supplement in patients with osteoporosis	141 (13.5%)
E4 Bone anti-resorptive or anabolic therapy in patients with documented osteoporosis, where no contraindication exists	191 (18.3%)
E5 Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia	54 (5.2%)
E6 Xanthine-oxidase inhibitors with a history of recurrent episodes of gout or gout tophi	29 (2.8%)
E7 Folic acid supplement in patients taking methotrexate	2 (0.2%)
F Endocrine	
F1 ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease	3 (0.3%)
G Urogenital	
G1/G2 Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary / 5-Alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary or can be postponed	62 (5.9%)
G3 Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis	0 (0.0%)
Analgetics	
H1 High-potency opioids (exception methadone) in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective	2 (0.2%)
H2 Laxatives in patients receiving opioids	101 (9.7%)
Total	1601

Legend: Values represent number of patients meeting each criterion (percentages of patients)

Abbrevations: ACE: Angiotensin-converting enzyme, DMARD: Disease-modifying anti-rheumatic drug, NSAID: Non-steroidal anti-inflammatory drugs, PPI: Proton pump inhibitor, PPO: Potential prescribing omission, SNRI: Selective serotonin and noradrenalin reuptake inhibitor, SSRI: Selective serotonin re-uptake inhibitor, T-score: Bone mineral density T-score

Table S3: STOPP/START criteria not applied due to unavailable data

STOPP Criteria
A1 Any drug prescribed without an evidence-based clinical indication.
A2 Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
A3 Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants
B4. Beta blocker with symptomatic bradycardia (< 50/min), type II heart block or complete heart block
B8 Thiazide diuretic with current significant hypokalaemia (i.e. serum potassium< 3.0 mmol/l), hyponatraemia (i.e. serum sodium < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout
B11. ACE inhibitors or angiotensin receptor blockers in patients with hyperkalaemia.
B12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium
D4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum sodium < 130 mmol/l
D11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil
E1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m2
E2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m2
E3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2
E4. NSAID's if eGFR < 50 ml/min/1.73m2
E5. Colchicine if eGFR < 10 ml/min/1.73m2
E6. Metformin if eGFR < 30 ml/min/1.73m2
G4. Benzodiazepines with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa
L3. Long-acting opioids without short-acting opioids for break-through pain
START Criteria
A4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently > 90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.
B3. Home continuous oxygen with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%).
I1 Seasonal trivalent influenza vaccine annually
I2 Pneumococcal vaccine at least once after age 65 according to national guidelines

Abbrevations: ACE: Angiotensin-converting enzyme, eGFR: Estimated glomerular filtration rate, NSAID: Non-steroidal anti-inflammatory drugs, SSRI: Selective serotonin re-uptake inhibitors

Table S4: Frequency of the ten most common PIMs and PPOs at admission (n=1045)

Criteria description	n (%)
PIMs	
K1 Benzodiazepines with history or risk of falling	204 (19.5%)
D5 Benzodiazepines for ≥ 4 weeks	161 (15.4%)
C3 Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk	89 (8.5%)
F2 PPI for peptic ulcer disease or oesophagitis with exception of Barrett's oesophagus at full therapeutic dosage for > 8 weeks	86 (8.2%)
K4 Hypnotic Z-drugs with history or risk of falling	73 (7.0%)
L1 Use of oral or transdermal strong opioids as first line therapy for mild pain	68 (6.5%)
C6 Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease	61 (5.8%)
L2 Use of regular opioids without concomitant laxative	53 (5.1%)
J1 Sulphonylureas with a long duration of action and active metabolites with type 2 diabetes mellitus	51 (4.9%)
K2 Neuroleptic drugs with history or risk of falling	47 (4.5%)
PPOs	
A6 ACE inhibitor (or angiotensin receptor blocker in case of side effects ACE inhibitor) with systolic heart failure and/or coronary artery disease	200 (19.2%)
E4 Bone anti-resorptive or anabolic therapy in patients with documented osteoporosis, where no contraindication exists	191 (18.3%)
A5 Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease or high cardiovascular risk	170 (16.3%)
E3 Vitamin D and calcium supplement in patients with osteoporosis	141 (13.5%)
A7 Beta-blocker with ischaemic heart disease or stable angina pectoris	125 (12.0%)
H2 Laxatives in patients receiving opioids	101 (9.7%)
A3 Acetyl salicylic acid or carbasalate calcium, clopidogrel, prasugrel or ticagrelor with a	94 (9.0%)

documented history of coronary, cerebral or peripheral vascular disease and sinus rhythm in patient not treated with Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	
A8 Appropriate beta-blocker with stable systolic heart failure	80 (7.7%)
A1 Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation (with exception of men 65-75 years without cardiovascular comorbidity)	76 (7.3%)
B1 Inhaled beta 2 agonist or antimuscarinic bronchodilator for mild to moderate asthma or COPD	72 (6.9%)

Legend: Values represent number of patients meeting each criterion (percentages of patients)

Abbrevations: ACE: Angiotensin-converting enzyme, PIM: Potentially inappropriate medication, PPI: Proton pump inhibitor, PPO: Potential prescribing omission

Table S5: PIMs and PPOs by living environment and number of medications

	PIMs **Median (IQR)**	**PPOs** **Median (IQR)**
Living environment		
Community-dwelling	1 (0-2)	1 (0-2)
Nursing home	1 (0-2)	2 (1-3)
Number of medications		
Polypharmacy (5-9 medications)	1 (0-2)	1(0-2)
Hyperpolypharmacy (≥ 10 medications)	2 (1-3)	1 (0-2)

Legend: Comparison of median values of PIMs and PPOs between different subgroups.

Abbreviations: PIM: Potentially inappropriate medication, PPO: Potential prescribing omission, IQR: Interquartile range

Table S6: Prevalence of PIMs and PPOs

	PIMs % (n)	PPOs % (n)
Living environment		
Community-dwelling	62.3% (577)	70.7% (648)
Nursing home	74.6% (85)	84.2% (96)
Number of medications		
Polypharmacy (5-9 medications)	52.9% (291)	70.2% (386)
Hyperpolypharmacy (≥ 10 medications)	75.5% (373)	74.3% (367)
Timepoints		
Admission (n=1045)	63.5% (664)	72.1% (753)
Discharge (n=1033)	64.2% (663)	72.7% (751)
2- month follow-up (n=893)	63.9% (571)	71.0% (634)
6-month follow-up (n=824)	64.4% (530)	71.5% (589)
12-month follow-up (n=767)	63.6% (488)	72.2% (554)

Legend: Values represent percentage of patients with at least one PIM or PPO. Absolute numbers are shown in parentheses.

Abbrevations: PIM: Potentially inappropriate medication, PPO: Potential prescribing omission

Table S7: Multinomial regression analyses of factors associated with changes in PIMs and PPOs from hospital admission to discharge and to 12-month follow-up

A: Admission to discharge (n=1030)		**Increase in PIMs**		**Decrease in PIMs**		**Increase in PPOs**		**Decrease in PPOs**	
Variables		**RRR**	**95% CI**	**RRR**	**95% CI**	**RRR**	**95% CI**	**RRR**	**95% CI**
Nursing home residency		1.32	0.78, 2.22	1.20	0.70, 2.05	1.48	0.91,2.42	1.46	0.84, 2.54
Hyperpolypharmacy (≥ 10 medications)		0.64	0.45, 0.91	1.65	1.14, 2.39	1.33	0.95, 1.88	0.50	0.34, 0.72
Cognitive impairment		1.15	0.62, 2.14	1.61	0.89, 2.92	1.50	0.87, 2.59	0.91	0.46, 1.80
Age group	70-74	Reference		Reference		Reference		Reference	
	75-84	0.96	0.65, 1.41	1.03	0.66, 1.59	0.82	0.56, 1.21	1.64	1.05, 2.57
	≥ 85	0.96	0.60, 1.54	1.60	0.98, 2.62	1.00	0.64, 1.58	1.61	0.94, 2.74
Any fall(s) in the last year		1.64	1.17, 2.31	1.36	0.95, 1.95	1.30	0.93, 1.82	1.63	1.13, 2.35
Number of comorbidities		1.02	0.99, 1.04	1.03	1.00,1.05	1.02	1.00, 1.04	1.01	0.99, 1.04
Sex	male	Reference		Reference		Reference		Reference	
	female	1.25	0.89, 1.74	1.04	0.73, 1.49	0.78	0.56. 1.10	1.26	0.89, 1.79
B: Admission to 12-month follow-up (n=766)		**Increase in PIMs**		**Decrease in PIMs**		**Increase in PPOs**		**Decrease in PPOs**	
Variables		**RRR**	**95% CI**	**RRR**	**95% CI**	**RRR**	**95% CI**	**RRR**	**95% CI**
Nursing home residency		3.09	1.63, 5.88	2.85	1.45, 5.60	1.13	0.60, 2.13	1.46	0.78, 2.76
Hyperpolypharmacy (≥ 10 medications)		1.04	0.71, 1.52	1.95	1.34, 2.83	1.46	1.01, 2.10	0.57	0.38, 0.84
Cognitive impairment		1.57	0.82, 3.00	1.14	0.55, 2.33	1.12	0.58, 2.18	0.65	0.32, 1.33
Age group	70-74	Reference		Reference		Reference		Reference	
	75-84	1.33	0.86, 2.06	1.34	0.87, 2.04	1.09	0.72, 1.63	1.40	0.91, 2.15
	≥ 85	1.10	0.64, 1.88	0.95	0.55, 1.65	0.81	0.48, 1.39	1.04	0.60, 1.82
Any fall(s) in the last year		1.11	0.76, 1.64	1.05	0.72, 1.53	0.90	0.62, 1.31	1.47	1.00, 2.15

Number of comorbidities		1.02	1.00, 1.05	1.01	0.98, 1.03	1.03	1.01, 1.06	1.01	0.98, 1.05
Sex	male	Reference		Reference		Reference		Reference	
	female	1.64	1.13, 2.37	1.63	1.33, 2.35	1.32	0.92, 1.89	1.26	0.87, 1.83

Legend:
(A) Multinominal logistic regression of increase and decrease in PIMs and PPOs from admission to discharge.
(B) Multinominal logistic regression of increase and decrease in PIMs and PPOs from admission to 12-month follow-up.
Outcomes were categorized as increase, decrease, or no change (reference).
Continuous variables (number of comorbidities) were modelled per one-unit increase; RRRs indicate the relative change in PIMs or PPOs per additional comorbidity.
Analyses were based on complete cases (n = 1,030/1,045 for discharge, n = 766/1,045 for 12-month follow-up). Missing values for covariates were minimal: nursing home residency: n = 5 (0.5 %), hyperpolypharmacy: n = 1 (0.1 %), cognitive impairment: n = 1 (0.1 %), falls in the last year: n = 7 (0.7 %), number of comorbidities: n = 1 (0.1 %), age group and sex: n = 0 (0 %).
Abbreviations: RRR: Relative risk ratio, CI: Confidence interval, PIM: Potentially inappropriate medication, PPO: Potential prescribing omission

Table S8: Fine-Gray competing risk regression of factors associated with time to first increase or decrease in PIPs within 12 months, accounting for death as a competing event

Admission to 12-month follow-up (n=1030)		**Increase in PIMs**		**Decrease in PIMs**		**Increase in PPOs**		**Decrease in PPOs**	
Variables		**sHR**	**95% CI**	**sHR**	**95% CI**	**Variables**	**sHR**	**95% CI**	**sHR**
Nursing home residency		1.40	1.03, 1.89	1.16	0.83, 1.62	1.20	0.87, 1.64	1.16	0.78, 1.71
Hyperpolypharmacy (≥ 10 medications)		0.69	0.55, 0.85	1.58	1.25, 2.00	1.52	1.23, 1.89	0.56	0.43, 0.73
Cognitive impairment		1.26	0.88, 1.79	1.16	0.76, 1.77	1.22	0.84, 1.75	0.77	0.47, 1.26
Age group	70-74	Reference		Reference		Reference		Reference	
	75-84	1.01	0.78, 1.30	1.06	0.81, 1.39	0.92	0.72, 1.17	1.19	0.88, 1.59
	≥ 85	0.96	0.71, 1.30	1.25	0.91, 1.72	0.90	0.66, 1.22	1.11	0.78, 1.59
Any fall(s) in the last year		1.25	1.00, 1.55	1.13	0.90, 1.43	1.07	0.86, 1.32	1.35	1.05, 1.74
Number of comorbidities		1.01	1.00, 1.03	1.01	0.99, 1.02	1.01	1.00, 1.02	1.01	0.99, 1.03
Sex	male	Reference		Reference		Reference		Reference	
	female	1.21	0.98, 1.50	1.12	0.90, 1.41	0.92	0.74, 1.13	1.32	1.04, 1.69

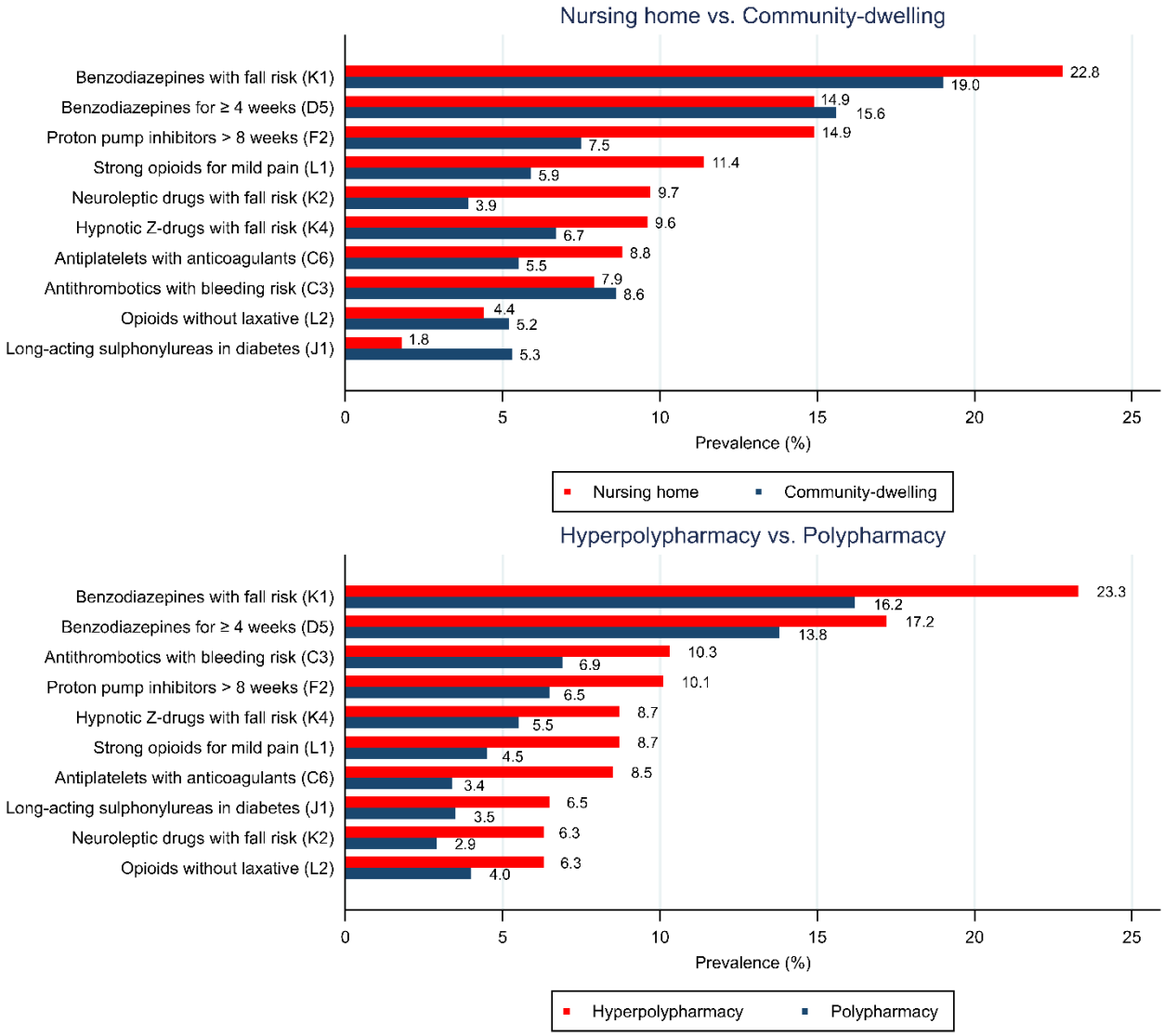
Legend:

Fine-Gray competing risk regression analyses of factors associated with the time to first increase or decrease in PIMs and PPOs within 12 months after hospital admission. Each outcome (PIM increase, PIM decrease, PPO increase, PPO decrease) was modelled separately, with death considered as a competing event. Analyses were based on complete cases (n = 1,030/1,045). 12 patients were excluded due to missing follow-up data across all time points, and an additional 3 patients were excluded due to missing covariate data. Continuous variables (number of comorbidities) were modelled per one-unit increase; subdistribution hazard ratios (sHRs) indicate the relative change in the subdistribution hazard of experiencing a PIM/PPO increase or decrease per additional comorbidity.

Missing values for covariates were minimal: nursing home residency: n = 5 (0.5 %), hyperpolypharmacy: n = 1 (0.1 %), cognitive impairment: n = 1 (0.1 %), falls in the last year: n = 7 (0.7 %), number of comorbidities: n = 1 (0.1 %), age group and sex: n = 0 (0 %).

Abbreviations: sHR: Subdistribution hazard ratio, CI: Confidence interval, PIM: Potentially inappropriate medication, PPO: Potential prescribing omission

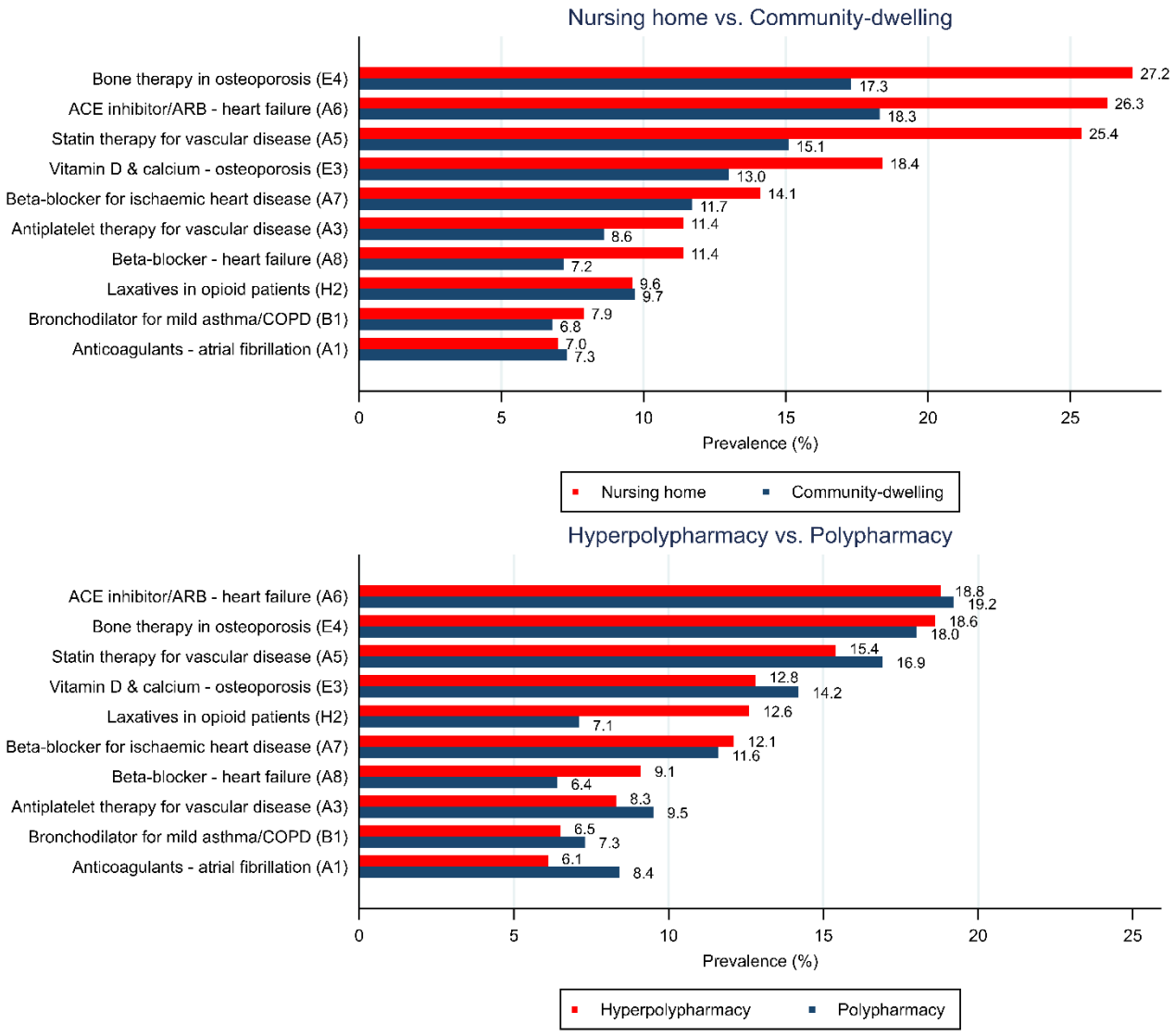
Figure S1: Prevalence of the ten most frequent PIMs by living environment and medication burden



Legend: Values represent percentages of patients meeting each criterion. Labels such as "Benzodiazepines with fall risk (K1)" refer to the corresponding STOPP/START criteria, where "K1" indicates the specific criterion number as defined in the validated STOPP/START version [1].

Abbreviation: PIM: Potentially inappropriate medication

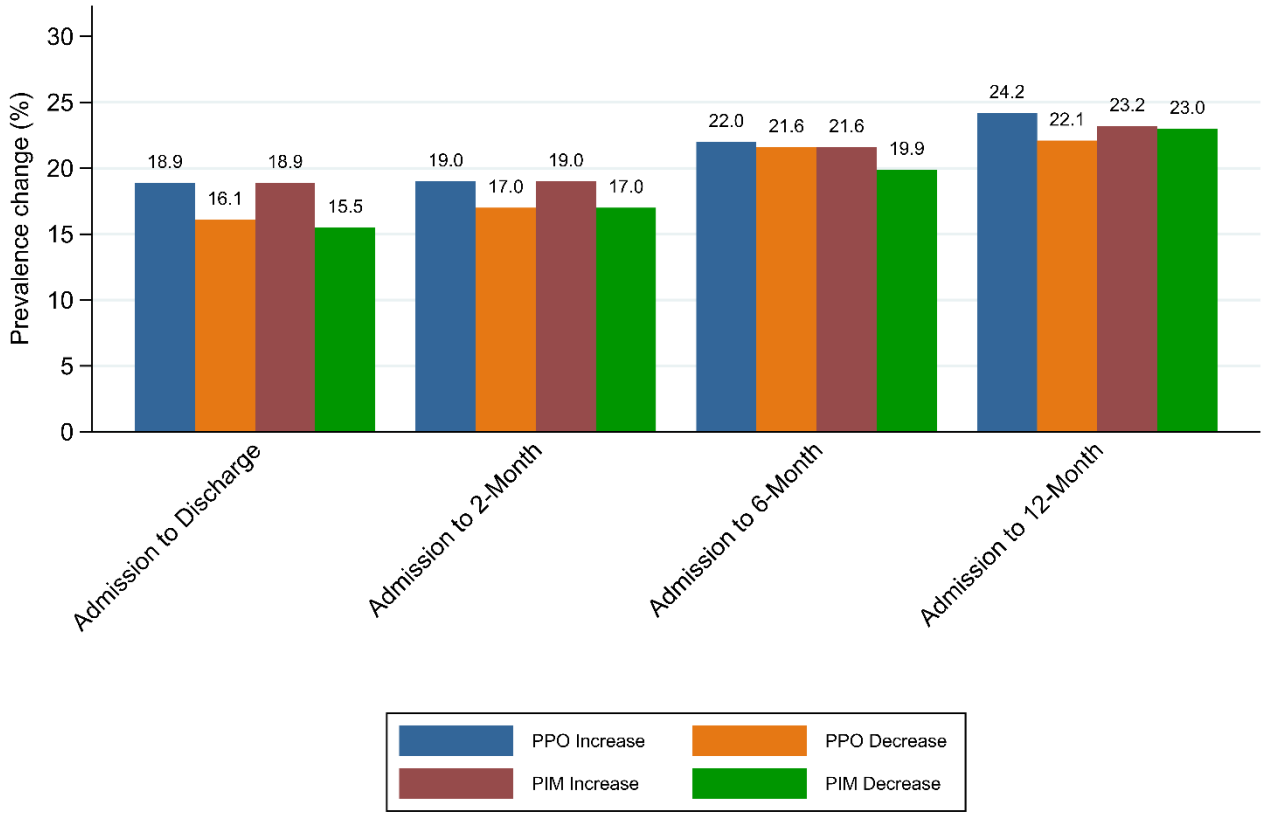
Figure S2: Prevalence of the ten most frequent PPOs by living environment and medication burden



Legend: Values represent percentages of patients meeting each criterion. Labels such as "ACE inhibitor/ARB – heart failure (A6)" refer to the corresponding STOPP/START criteria, where "A6" indicates the specific criterion number as defined in the validated STOPP/START version [1].

Abbreviations: ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, PPO: Potential prescribing omission

Figure S3: Proportion of patients with an increase or decrease in the total number of PIMs and PPOs over time



Legend: Proportion of patients showing an increase or decrease in PIMs or PPOs at follow-up time points, relative to hospital admission.

Abbrevations: PIM: Potentially inappropriate medication, PPO: Potential prescribing omission

References (Appendix)

1. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44:(2):213-8; https://doi.org/10.1093/ageing/afu145