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Article

Potentially inappropriate prescribing among older patients and associated factors: comparison of two versions of STOPP/START criteria

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The study aimed to estimate and compare the prevalence and type of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) between the STOPP/START original (v1) and updated version (v2) among older patients in various settings, as well as associated factors. The study included 440 patients attending a community pharmacy, 200 outpatients and 140 nursing home users. An increase in the prevalence of STOPP v2 (57.9%) compared to v1 (56.2%) was not statistically significant in the total sample and within each setting ($p>0.05$). A decrease in the prevalence of START v1 (55.8%) to v2 (41.2%) was statistically significant ($p<0.001$) in the total sample and within each setting ($p<0.05$). Drug indication (32.9%) and fall-risk medications (32.2%) were most commonly identified for STOPP v2, while cardiovascular system criteria (30.5%) were the most frequently detected for START v2. The number of medications was the strongest predictor for both STOPP v1 and v2, with odds ratio values of 1.35 and 1.34, respectively. Patients' characteristics associated with the occurrence of STOPP and START criteria were identified. According to both STOPP/START versions, the results indicate a substantial rate of potentially inappropriate prescribing among elderly patients. The prevalence of PIMs was slightly higher with the updated version, while the prevalence of PPOs was significantly lower.

Keywords: Geriatrics. Health services for the aged. Potentially inappropriate medication list. Drug utilization. Prevalence.

INTRODUCTION

With growing populations of older people worldwide, appropriate prescribing has become a global healthcare challenge. Multiple factors contribute to the increased vulnerability of the elderly to inappropriate prescribing (Drenth-van Maanen, Wilting, Jansen, 2020; Hill-Taylor *et al*., 2013). Older patients usually have several diagnoses that lead to the use of numerous drugs and polypharmacy (concurrent use of five or more daily medications) (Boland *et al*., 2016). Multimorbidity and polypharmacy are consistently reported as the correlates of drug-related problems, adverse drug reactions and drug-drug interactions in older adults (Zazzara *et al*., 2021). On the other hand, age-related changes in pharmacokinetics and pharmacodynamics further increase the risk of adverse drug reactions and drug-drug interactions (Drenth-van Maanen, Wilting, Jansen, 2020; Zazzara *et al*., 2021). Low adherence to complex therapeutic regimens and physical or cognitive impairment makes geriatric medicine

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even more challenging (Boland *et al*., 2016; Drenth-van Maanen Wilting, Jansen, 2020). Finally, older patients are often excluded from clinical trials, limiting availability and access to appropriate evidence (Curtin, Gallagher, O'Mahony, 2019; Hill-Taylor *et al*., 2013).

In order to detect potentially inappropriate drugs in elderly patients, several explicit tools have been developed (Beers, 1997; Curtin, Gallagher, O'Mahony, 2019; O'Mahony, 2020). One of the widely used criteria, especially in Europe, is the Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START) developed in 2008 (version 1 - v1) (Gallagher *et al*., 2008; O'Mahony *et al*., 2010). This screening tool includes two lists of criteria for elderly patients, organized according to physiological systems. While the STOPP criteria include a list of potentially inappropriate medications (PIMs; over- and misprescribing), the START criteria are oriented towards potential prescribing omissions (PPOs; underprescribing) (Gallagher *et al*., 2008; O'Mahony *et al*., 2015). In 2015, a revision of the STOPP/START screening tool was performed (version 2 - v2), including the removal of outdated and less-relevant criteria and incorporation of new items and categories (O'Mahony, 2020; O'Mahony *et al*., 2015). This updated version consists of 80 STOPP and 34 START criteria, representing an overall 31% increase in criteria compared with the previous version (O'Mahony *et al*., 2015).

Since the introduction of the STOPP/START criteria, highly prevalent inappropriate prescribing among older patients with multiple morbidities has been reported in all clinical settings (Conejos Miquel *et al*., 2010; Gallagher *et al*., 2011a; Garcia-Gollarte *et al*., 2012; Hamilton *et al*., 2011; Hill-Taylor *et al*., 2013; O'Mahony, 2020; Thomas, Thomas, 2019). Importantly, it was shown that identified STOPP criteria were significantly associated with adverse drug events (Hamilton *et al*., 2011). Further investigation of STOPP/START criteria usage as an intervention resulted in significant improvements in prescribing appropriateness (Gallagher *et al*., 2011b). Moreover, the application of this tool resulted in reduced adverse drug reactions, a reduced number of falls, and lower medication costs (Curtin*, Gallagher, O'Mahony,* 2019; Frankenthal *et al*., 2014; O'Connor *et al*., 2016; O'Mahony, 2020). The growing interest in applying this tool is reflected by the two recently conducted multi-centre trials which included electronic STOPP/START criteria as an intervention (SENATOR and OPERAM) (O'Mahony, 2020).

Considering the important properties of the STOPP/START criteria, but also the significant changes made in the updated version, several studies have investigated potential additional benefits. As expected, increased prevalence rates of PIM events were observed with the new version, while it was not always the case with PPOs (Blanco-Reina *et al*., 2016; Blanco-Reina *et al*., 2019; Hudhra *et al*., 2016; Ma *et al*., 2020; Thevelin *et al*., 2019). Furthermore, STOPP/START v2 targeted more PIMs and PPOs associated with preventable drug-related admissions (Thevelin *et al*., 2019) and instances of potential major clinical relevance (Boland *et al*., 2016). Nevertheless, compared analysis among different prescribing practices is still valuable for the future development of the tool. Moreover, it would be interesting to compare the versions simultaneously at different health care settings. Therefore, the objective of this study was to compare the prevalence of PIMs and PPOs between the STOPP/START v1 and v2 criteria list in a population of elderly (≥65 years) recruited from different levels of health care, as well as to assess differences in various settings. Secondary objectives were to investigate the specific prescribing areas that contribute the most to PIMs and PPOs and the factors associated with the presence of STOPP and START criteria using both versions.

METHODS

A multicentric observational study was performed, including three groups of patients to provide a more comprehensive assessment of STOPP/START criteria: (1) chronic patients attending community pharmacies; (2) outpatients; (3) nursing home users. The main inclusion criteria in all the settings were: age ≥65 years; the presence of at least one chronic disease; complete data on medications and comorbidities. The data for community pharmacy patients were collected prospectively after informing the patients about the study and obtaining written consent. A total of 49 community pharmacies in Serbia voluntarily agreed to participate in the recruitment

of patients. The study was part of a large-scale research program coordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM, Council of Europe) for the assessment of patients' involvement in pharmaceutical care (Kovacevic *et al*., 2017b). Data collection on the patients' demographic and clinical characteristics, as well as the complete therapy, including both prescription and non-prescription drugs, was performed using a predefined translated and validated questionnaire. Patients with cognitive impairment (Alzheimer's disease or dementia), illiterate patients, or those receiving palliative care, were excluded from data collection. Since the EDQM study protocol implicated further personal patient-pharmacist consultations, patients who could not leave their home or those with marked frailty were excluded from the study. The data for outpatients were collected retrospectively from medical records of patients treated at the outpatient clinic of the University Clinical Center Niš, which is one of the four University Clinical Centers in Serbia providing high-level services as a tertiary healthcare institution. Finally, the third data source were medical records of subjects from the Gerontology Center Niš in Serbia, which is associated with the hospital. The institution provides primary health care, as well as consultations with specialists from the University Clinical Center Niš. Institutional Ethical Committees approved the study (at the University Clinical Center Niš and the University of Belgrade – Faculty of Pharmacy; ethical approval number 16992/17 and 2718/2). In order to compare older and updated STOPP/START versions, part of our previously identified v2 criteria (Kovacevic *et al*., 2023, unpublished research) were used.

The presence of STOPP/START criteria was identified through patients' data review, using the v1 and v2 criteria list. Four teacher practitioner pharmacists were in charge of the medication review. The presence of each criterion was binary coded (1 – presence, 0 – absence). Due to a lack of specific data about the patients, the following criteria could not be completely evaluated: (i) **STOPP v1 criteria**: Selective serotonin re-uptake inhibitors (SSRIs) with a history of clinically significant hyponatraemia (in the previous 2 months); (ii) **START v1 criteria**: home continuous oxygen with documented chronic type 1 respiratory failure ($pO2 < 8.0$ kPa, $pCO2 < 6.5$ kPa) or type 2 respiratory failure ($pO2 < 8.0$ kPa, $pCO2 > 6.5$ kPa); (iii) **STOPP v2 criteria**: thiazide diuretic with current significant hypokalaemia, hyponatraemia, hypercalcaemia; ACE inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) in patients with hyperkalaemia; aldosterone antagonists with concurrent potassium-conserving drugs (e.g. ACEIs, ARBs, amiloride, triamterene) without monitoring of serum potassium (serum potassium should be monitored regularly, i.e., at least every 6 months); SSRIs with current or recent significant hyponatraemia; benzodiazepines with acute or chronic respiratory failure, i.e., $pO2 < 8.0$ kPa ± $pCO2 > 6.5$ kPa; (iv) **START v2 criteria:** home continuous oxygen with documented chronic hypoxaemia (i.e. $pO2 < 8.0$ kPa or 60 mmHg or $SaO2 < 89\%$); vitamin D supplement in patients with Bone Mineral Density T-scores more than -2.0 in multiple sites; vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is >-1.0 but < 2.5 in multiple sites). Finally, the data for vaccination history regarding the **START v2 list** (seasonal trivalent influenza annually or pneumococcal vaccine at least once after age 65) were not available in any of the patient groups.

Descriptive and statistical analysis was performed using the IBM SPSS Statistics software (version 22, NY, USA). The results are presented as mean ± standard deviation (S.D.) or median with interquartile range [IQR] for quantitative variables and frequency (number of patients, n, %) for categorical variables. The Kolmogorov-Smirnov test revealed non-normal distribution ($p<0.001$) of variables (age, number of medication, comorbidities, STOPP and/or START criteria per patient for both versions). McNemar's test was used to determine the difference in the prevalence (presence) of STOPP/START criteria between v1 and v2. The median number of STOPP/START criteria per patient according to different versions was compared using the Wilcoxon signed-rank test. A p-value <0.05 was considered statistically significant. Patient data such as age, gender, number of medications, and number of comorbidities were tested as independent variables to assess the odds for the presence of STOPP/START criteria. Statistical analysis was performed using binary logistic regression, separately for the occurrence

of each criterion (STOPP v1, STOPP v2, START v1 and START v2), with a selection threshold of 0.1.

RESULTS

The study sample included a total of 780 elderly patients from different levels of health care. Data were obtained for 440 community pharmacy users (56.4%), 200 outpatients (25.6%) and 140 nursing home users (17.9%). The median age was 72 years (range 65-98), while the majority of patients (n=470, 60.3%) were in the youngest-old group (aged 65-74). The female gender was slightly more prevalent with 423 patients (54.2%). The descriptive statistics are summarized in Table I.

TABLE I - Descriptive statistics of patients included in the study

mean ± S.D. number of patients (%)	Total (n=780)	Nursing home (n=140)	Outpatients (n=200)	Community-dwelling (n=440)
Age, years	73.5 ± 6.7	78.9 ± 7.7	72.8 ± 5.7	72.1 ± 5.8
Gender, male	357 (45.8%)	53 (37.9%)	102 (51%)	202 (45.9%)
Number of medications	7.7 ± 2.7	8.9 ± 3.3	6.7 ± 2.8	7.8 ± 2.3
Number of comorbidities	4.3 ± 1.97	3.6 ± 1.3	5.8 ± 2.5	3.9 ± 1.5

S.D. – standard deviation

A total of 6,003 prescriptions were analysed. The median number of medications was 7 (IQR 6-9), whereas a total range of 0-18 medications per patient was observed. Polypharmacy (≥5 medications) was highly prevalent with 91.5% (n=714), and excessive polypharmacy (≥10 medications) was found in 22.7% (n=177) of the total study sample. The median number of comorbidities equalled 4, and 299 (38.3%) patients had 5 or more comorbidities.

Potentially inappropriate prescribing (either overprescribing or underprescribing) was found in 82.6% (n=644) and 73.1% of patients (n=570), according to STOPP/START v1 and v2 criteria, respectively. The decrease of 9.5% was marked as statistically significant. The results are presented in Table II.

TABLE II - Comparison of the prevalence and the number of STOPP/START criteria in the total study sample

	version 1	version 2	p-value [a]
	Number of patients (%)		
At least one STOPP criteria	438 (56.2%)	452 (57.9%)	0.126
Number of STOPP criteria			
median [IQR]	1 [0-1]	1 [0-2]	<0.001 [b]
1	258 (33.1%)	151 (19%)	<0.001
2	120 (15.4%)	77 (9.9%)	<0.001
3	40 (5.1%)	113 (14.5%)	<0.001
4	17 (2.2%)	66 (8.5%)	0.002

TABLE II - Comparison of the prevalence and the number of STOPP/START criteria in the total study sample

	version 1	version 2	p-value [a]
5	2 (0.3%)	26 (3.3%)	0.934
6	0	14 (1.8%)	-
7	1 (0.1%)	4 (0.5%)	0.995
8	0	0	-
9	0	1 (0.1%)	-
At least one START criteria	435 (55.8%)	321 (41.2%)	<0.001
Number of START criteria			
median [IQR]	1 [0-2]	0 [0-1]	<0.001 [b]
1	221 (28.3%)	199 (25.5%)	0.115
2	145 (18.6%)	85 (10.9%)	<0.001
3	45 (5.8%)	28 (3.6%)	0.017
4	19 (2.4%)	6 (0.8%)	0.007
5	4 (0.5%)	3 (0.4%)	1
6	1 (0.1%)	0	-
At least one STOPP or START criterion	644 (82.6%)	570 (73.1%)	<0.001
Both STOPP and START criteria	229 (29.4%)	203 (26%)	<0.001

[a] – p-value obtained by McNemar's test; [b] – p-value obtained by the Wilcoxon signed-rank test; IQR – interquartile range.

The prevalence of STOPP v1 and STOPP v2 criteria was 56.2% (n=438) and 57.9% (n=452), respectively. The observed increase in prevalence was not assigned a statistical significance (p>0.05). Although the median value of STOPP criteria was estimated to 1 in both v1 (mean 0.9) and v2 (mean 1.3), the Wilcoxon test marked the increase in the median number of STOPP criteria per patient as statistically significant (p<0.001).

To further investigate STOPP criteria within specific subpopulations, v1 and v2 percentages were compared within each setting (Figure S1). The observed increase in PIM prevalence when comparing v1 and v2 among community-dwelling patients (53.6% vs. 56.4%) and outpatients (45.5% vs. 49%) was not assigned a statistical significance (p>0.05). The total number of PIMs according to v1 and v2 in outpatients was 128 and 188 (on average 0.64 and 0.94 per patient), respectively; while in community-dwelling patients it was 384 and 572 (on average 0.87 and 1.3 per patient), respectively. Moreover, the difference between the original and new version was not significant among nursing home users, but a slight decrease in prevalence was observed (79.3% vs. 75.7%). The total number of PIMs in this group of patients according to v1 and v2 was 191 and 399, while on average 1.36 and 2.85 PIMs were detected per patient, respectively.

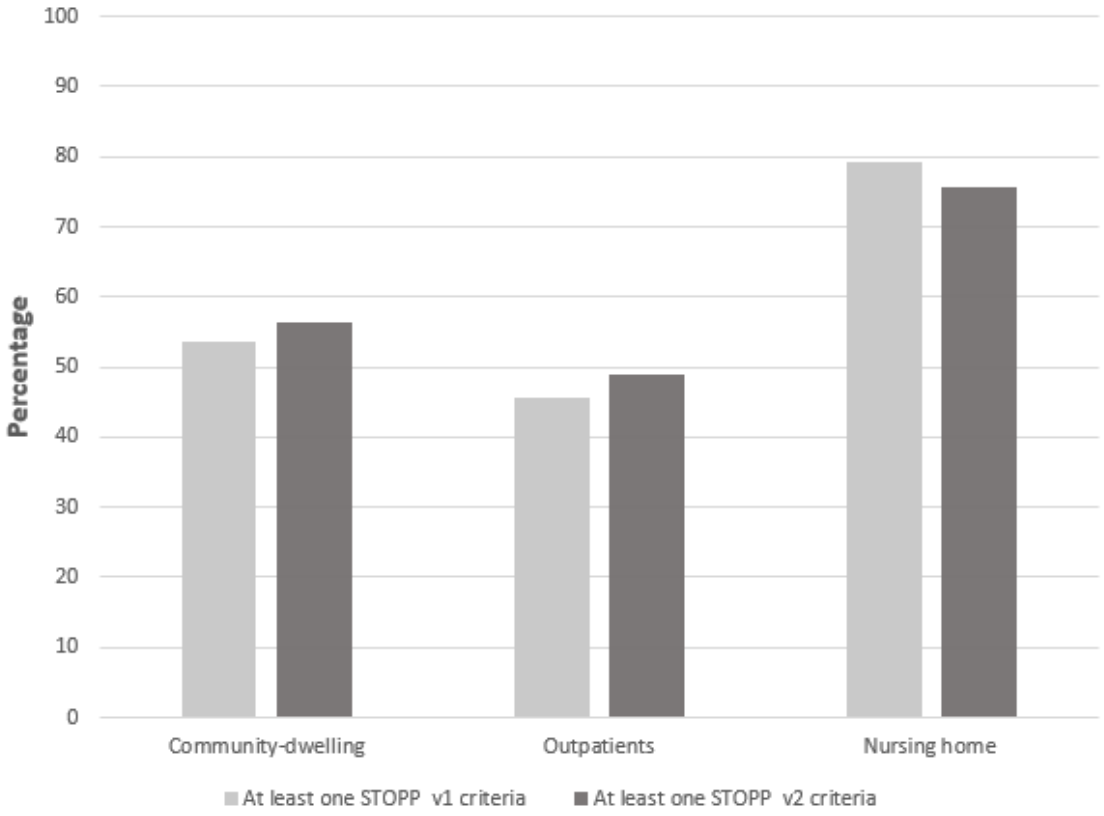

FIGURE S1 - The prevalence of STOPP version 1 (v1) and version 2 (v2) criteria in different settings.

A statistically significant difference in the prevalence of START criteria was observed: START v1 criteria were present in 435 patients (55.8%), whereas START v2 criteria were found in 321 patients (41.2%), $p<0.001$. The decreasing trend in the number of patients across the entire range of START criteria 1-5 was also observed for v2 (Table II). Furthermore, a statistically significant decrease ($p<0.05$) was confirmed for each of the three settings (Figure S2). According to v1 and v2, START criteria were most frequently observed in community-dwelling patients (63.4% vs. 43.4%), followed by outpatients (46.5% vs. 39.5%) and nursing home users (45% vs. 36.4%). The total number of PPOs (average number per patient) according to v1 and v2 was 489 and 299 (1.11 and 0.68) in community-dwelling patients, 177 and 132 (0.89 and 0.66) in outpatients, and 82 and 61 (0.59 and 0.44) in nursing home users, respectively.

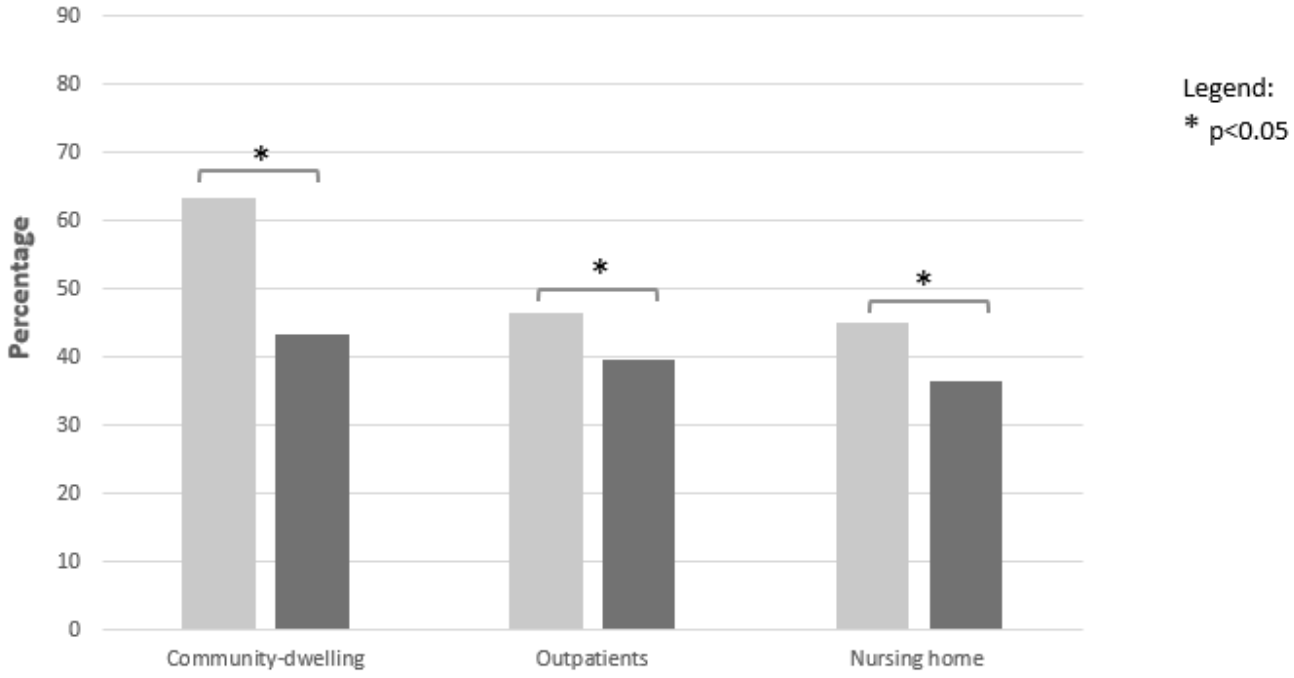

FIGURE S2 - The prevalence of START version 1 (v1) and version 2 (v2) criteria in different settings.

Among the STOPP v1 criteria (Table III), potentially inappropriate overprescribing was the most frequently observed for central nervous system medications (28.5%), followed by the cardiovascular system (16.7%), fall-risk medications (12.6%), and therapeutic duplication (9.9%). According to v2, the highest frequency was determined for the indication/length of therapy in 32.9% of patients, followed by fall-risk medications (32.2%) and the central nervous system (28.7%), whereas the cardiovascular system was ranked fourth (11.3%). Additionally, the prevalence of different STOPP criteria sections was assessed for each setting (Figure S3). The most noticeable difference between v1 and v2 was for fall-risk medications in all settings, particularly among nursing home patients (10% vs. 67.1%). Benzodiazepines were the most frequent drugs involved with PIMs related to falls, and more were targeted by v2 than v1 in the total sample (31.8% vs. 11.7%). Moreover, prolonged use of benzodiazepines (≥ 4 weeks) contributed the most to the PIMs related to the central nervous system (27.95%).

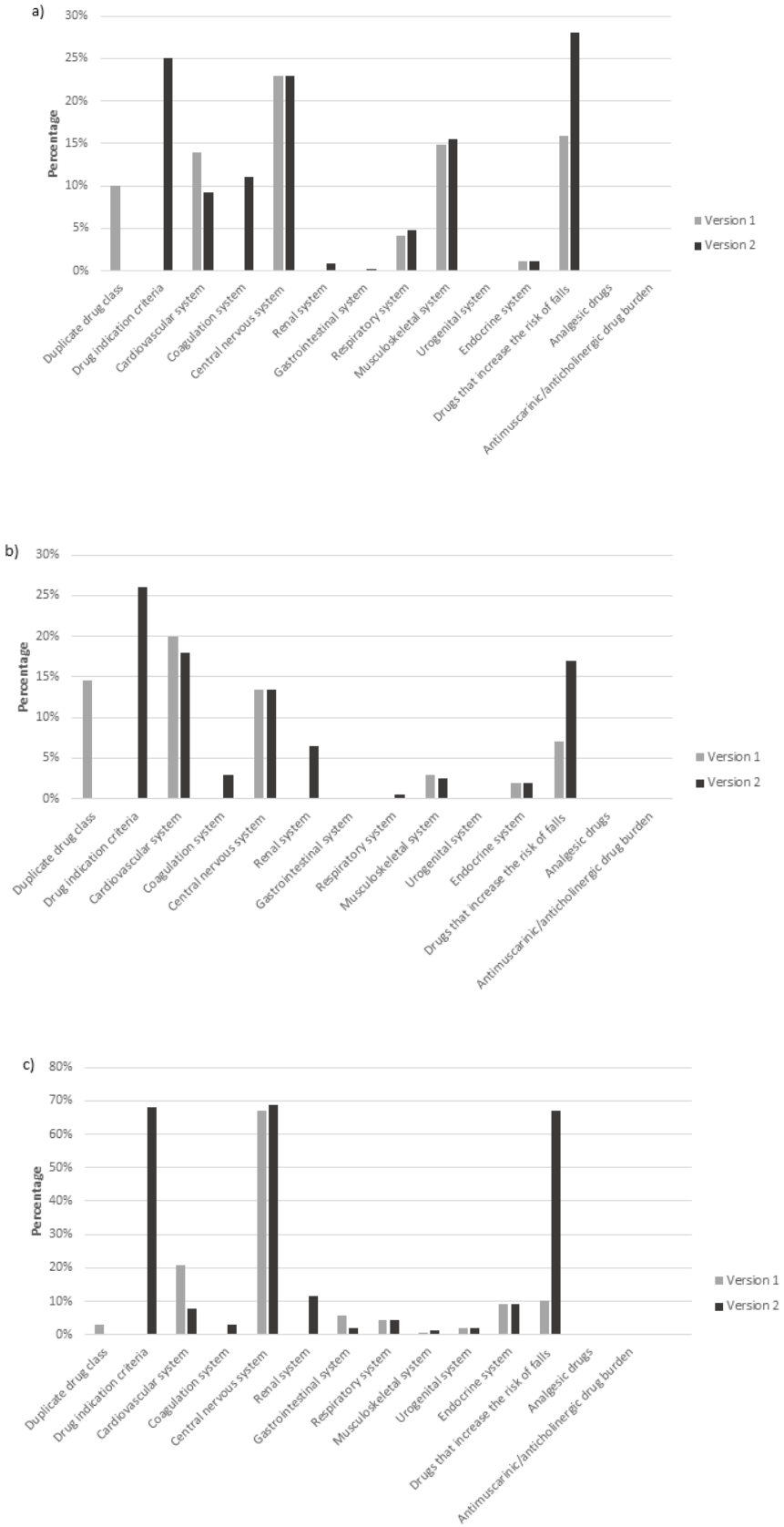

FIGURE S3 - The prevalence of the different STOPP criteria sections in three settings - a) community dwelling, b) outpatients, c) nursing home.

TABLE III - Identified STOPP/START criteria according to the organ systems in the total study sample

	STOPP criteria		START criteria	
	version 1	version 2	version 1	version 2
Number of criteria identified	46 out of 65 (70.8%)	53 out of 80 (66.3%)	19 out of 22 (86.4%)	24 out of 34 (70.6%)
	Number of patients (%)		Number of patients (%)	
Duplicate drug class	77 (9.9%)	-	-	-
Drug indication criteria	-	257 (32.9%)	-	-
Cardiovascular system	130 (16.7%)	88 (11.3%)	230 (29.5%)	238 (30.5%)
Coagulation system	-	59 (7.6%)	-	-
Central nervous system	222 (28.5%)	224 (28.7%)	1 (0.1%)	25 (3.2%)
Renal system	-	33 (4.2%)	-	-
Gastrointestinal system	8 (1%)	4 (0.5%)	12 (1.5%)	4 (0.5%)
Respiratory system	24 (3.1%)	28 (3.6%)	28 (3.6%)	28 (3.6%)
Musculoskeletal system	72 (9.2%)	75 (9.6%)	26 (3.3%)	29 (3.7%)
Urogenital system	3 (0.4%)	3 (0.4%)	-	44 (5.6%)
Endocrine system	22 (2.8%)	22 (2.8%)	239 (30.6%)	0
Drugs that predictably increase the risk of falls in older people	98 (12.6%)	251 (32.2%)	-	-
Analgesic drugs	0	0	-	1 (0.1%)
Antimuscarinic/anticholinergic drug burden	-	0	-	-
Vaccines	-	-	-	n.a.

n.a. – not available

START v1 mainly involved the endocrine system (30.6%), followed by the cardiovascular system (29.5%). In v2, potential underprescribing was most frequently identified for the cardiovascular system (30.5%), whereas the urogenital system was the second most frequent with 5.6% (Table III). START v1 targeted the most PPOs related to statin therapy in diabetes mellitus with a co-existing major cardiovascular factor (24.4%), while lack of antiplatelet therapy in the same clinical situations was ranked third (14.1%). Statin therapy with a documented history of coronary, cerebral, or peripheral vascular disease (20.3%) was ranked first according to v2 and second in v1. Additionally, the prevalence of different START criteria sections was investigated for each setting (Figure S4). The most noticeable difference between v1 and v2 was found for the endocrine system in all settings.

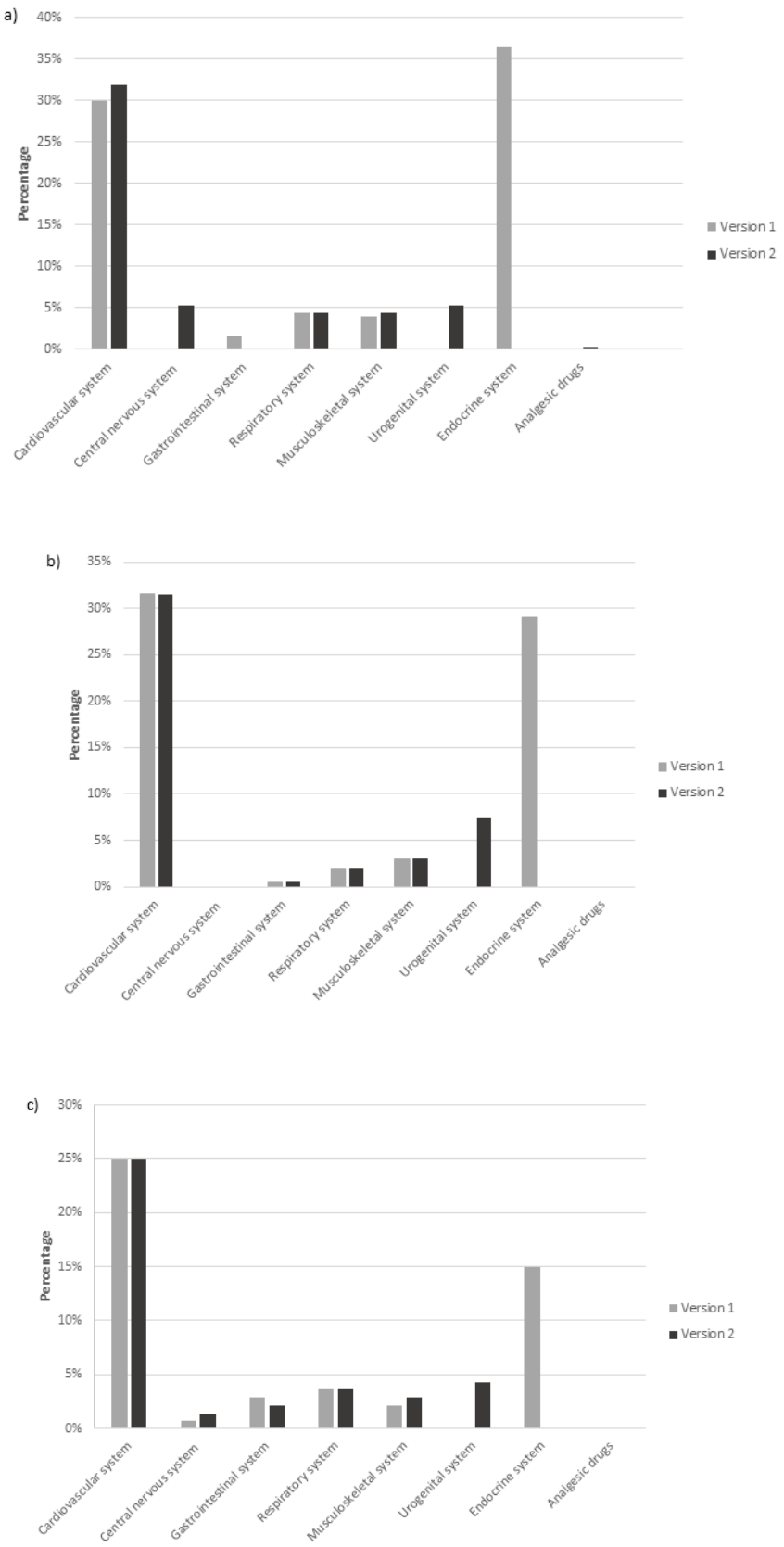

FIGURE S4 - The prevalence of the different START criteria sections in three settings - a) community dwelling, b) outpatients, c) nursing home.

The results on predictive patient variables for the occurrence of potentially inappropriate prescribing are summarized in Table IV. The number of medications was the strongest predictor for both STOPP v1 and STOPP v2 occurrence (odds ratio, OR 1.35 and 1.34, respectively, p<0.001). The number of comorbidities showed a statistically significant association with both START v1 and START v2 criteria (OR 1.11 and 1.26, respectively, p<0.001), but also STOPP v2 (OR 1.13, 95% CI 1.03-1.24). The influence of age was modest, although statistically significant, with a positive predictive impact on STOPP v1 and STOPP v2 criteria and a negative predictive impact on START v1 criteria (OR 0.97). Male patients were more likely to have START v2 criteria (OR 1.62, 95% CI 1.21-2.18), p=0.001.

TABLE IV - Patients' characteristics associated with the STOPP/START criteria in the total study sample

	Age, years	Gender, female	Number of medications	Number of comorbidities
STOPP v1				
OR (95% CI)	**1.04 (1.01-1.06)**	1.28 (0.94-1.74)	**1.35 (1.26-1.45)**	0.98 (0.90-1.07)
p-value	**0.004**	0.115	**<0.001**	0.688
STOPP v2				
OR (95% CI)	**1.06 (1.03-1.08)**	1.28 (0.93-1.75)	**1.34 (1.24-1.44)**	**1.13 (1.03-1.24)**
p-value	**<0.001**	0.130	**<0.001**	**0.012**
START v1				
OR (95% CI)	**0.97 (0.95-0.99)**	1.01 (0.76-1.35)	0.99 (0.94-1.06)	**1.11 (1.02-1.21)**
p-value	**0.011**	0.933	0.973	**0.015**
START v2				
OR (95% CI)	1.00 (0.98-1.03)	**0.62 (0.46-0.83)**	0.99 (0.93-1.05)	**1.26 (1.16-1.38)**
p-value	0.774	**0.001**	0.779	**<0.001**

OR – odds ratio; CI – confidence interval

DISCUSSION

The results of the study indicate a substantial rate of PIMs and PPOs in a cohort of 780 older patients. Interestingly, a statistically significant reduction in prevalence of potentially inappropriate prescribing (either overprescribing or underprescribing) was detected when comparing STOPP/START v1 (82.6%) with v2 (73.1%). Similarly, the prevalence of both STOPP and START criteria was lower in the updated version compared to the first one (Table II). Nevertheless, both versions detected a high frequency of inappropriate prescribing, which indicates the need to optimize therapy in elderly patients across various levels of health care. Even though inappropriate prescribing does not necessarily mean that medical problems will occur, healthcare professionals should be aware of its high prevalence and understand that the implementation of STOPP/START criteria might have a beneficial impact on prescribing quality, clinical and economic burden (Hamilton *et al*., 2011; Hill-Taylor *et al*., 2013; Hill-Taylor *et al*., 2016; O'Mahony *et al*., 2015).

A high prevalence of patients with at least one PIM (57.9%) identified by the STOPP v2 criteria is not surprising, considering the high burden of polypharmacy in older patients. According to a recent systematic

review, average percentages for one or more instances of inappropriate prescribing weighted by study size were 42.8% for community patients and 51.8% for hospitalized patients (Thomas, Thomas, 2019). A wide range of percentages was reported depending on the study design and included population, but in general, higher rates were more common in complex geriatric patients and therapy, and in those living in nursing homes (Anrys *et al*., 2018; Bo *et al*., 2019; Conejos Miquel *et al*., 2010; Counter, Millar, McLay, 2018; Gaubert-Dahan *et al*., 2019; Rogero-Blanco *et al*., 2020; Stojanovic *et al*., 2020; Thomas, Thomas, 2019). Indeed, in our analysis, the highest prevalence was detected for nursing home users (Figure S1).

The observed increase in the prevalence of STOPP v2 criteria when compared with v1 (Table II) was in agreement with previous studies (Blanco-Reina *et al*., 2016; Blanco-Reina *et al*., 2019; Hudhra *et al*., 2016; Ma *et al*., 2020; Thevelin *et al*., 2019), although the difference was not as prominent. In studies performed on community-dwelling patients, the updated version resulted in an approximately twofold increase in prevalence (18.7% vs. 40.4%; 35.4% vs. 66.8%) (Blanco-Reina *et al*., 2016; Blanco-Reina *et al*., 2019). Moreover, the application of v2 resulted in a nearly twofold increase in the prevalence of PIMs (34.5% vs. 63%) (Hudhra *et al*., 2016), or even more (39% vs. 87%) (Thevelin *et al*., 2019) among hospitalized patients. Such a noticeable increase was not observed among Chinese patients between v1 and v2, but the detected difference in PIM use was significant (Ma *et al*., 2020). Such improvements may be due to the significant changes made in the new version, resulting in a 31% increase in the number of criteria. However, an increase in the percentages observed in our study was not statistically significant. Nevertheless, the Wilcoxon test marked the increase in the median number of STOPP criteria per patient as statistically significant (Table II). In line with the whole population, the observed increase in the percentage was not statistically significant when comparing v1 and v2 among community-dwelling patients and outpatients (Figure S1). Surprisingly, although not significant, a slight decrease in prevalence when using v2 was observed among nursing home users. However, the total number of PIMs was higher with the latest version, as well as the average value per patient. Hence, a decrease in PIM prevalence among nursing home users with the new version is probably caused by an overlap between some items, which also contributed to a lower prevalence in the total sample than expected.

Drug indication criteria (lack of drug indication, prolonged treatment duration or therapy duplication) contributed the most to the high frequency of STOPP v2, whereas therapeutic duplications were ranked fourth according to v1 (Table III). Similarly, in some studies based on v2, the most frequently observed PIMs involved drugs related to drug indication criteria (Blanco-Reina *et al*., 2019; Gaubert-Dahan *et al*., 2019; Ma *et al*., 2020; Thevelin *et al*., 2019). Blanco- Reina *et al.* even proposed excluding these criteria during prevalence estimation due to nonspecific items and subjective approach (Blanco-Reina *et al*., 2019). Nevertheless, considering the clinical importance of these items, especially therapy duplication, we included this section in the overall prevalence estimation (Table II), but additionally presented the number of patients with the identified criteria in each section (Table III).

A similar prevalence of PIMs for the central nervous system criteria was recorded between the two versions in the total study sample (Table III), but also within each setting (Figure S3). In contrast, we detected a higher prevalence with the updated version regarding fall-risk medication in the total study sample, and within each setting. It was particularly pronounced among nursing home users (Figure S3). This is important because the PIMs of fall-risk-increasing drugs were most frequently associated with drug-related admissions (Thevelin *et al*., 2019). Consistently to previous findings, benzodiazepines were the most frequent drugs involved with PIMs (Blanco-Reina *et al*., 2019; Bo *et al*., 2019; Ma *et al*., 2020; Stojanovic *et al*., 2020; Thomas, Thomas, 2019; Vezmar Kovacevic *et al*., 2014). Moreover, in our analysis, STOPP v2 targeted more PIMs related to benzodiazepines as fall-risk medications than the first version. Greater caution provided with the updated version is useful, especially considering the overuse of benzodiazepines in Serbia (Kovacevic *et al*., 2017a). It is of particular concern in elderly patients, but deprescribing has been demonstrated to be feasible (Reeve *et al*., 2017). Finally,

the updated version indicated fewer PIMs regarding the cardiovascular system in the total sample (Table III), but also among settings (Figure S3). Indeed, the new version contains fewer criteria in this section, with a new category regarding the coagulation system (O'Mahony *et al*., 2015; O'Mahony *et al*., 2010).

The prevalence of patients with at least one PPO (41.2%) identified by the START v2 criteria (Table II) was between the average percentages weighted by study size for community (35%) and hospitalized patients (64%), according to a recent systematic review (Thomas, Thomas, 2019). Furthermore, the prevalence among patients attending a pharmacy and outpatients was close to individual findings (Buda *et al*., 2020; Rogero-Blanco *et al*., 2020), while we expected a higher rate (Figure S2) for the nursing home population (Anrys *et al*., 2018; Gaubert-Dahan *et al*., 2019; Stojanovic *et al*., 2020). Lack of information regarding vitamin D supplementation in most patients and vaccination history probably contributed to a lower START v2 prevalence. Moreover, the updated version detected a significantly lower prevalence of PPOs than the first version in our analysis (Table II), despite the increase in the number of items. Indeed, in previous studies the updated version mainly targeted more prescribing omissions than original (Boland *et al*., 2016; Ma *et al*., 2020; Thevelin *et al*., 2019). However, the observed decrease was in agreement with one study conducted among community-dwelling residents, where the prevalence of omissions was 34.7% and 21.8% according to START v1 and v2, respectively (Blanco-Reina *et al*., 2016). Further analysis within each subpopulation confirmed a statistically significant reduction of the PPO rate for each of the three settings. According to both versions, omissions were most frequently observed in community-dwelling patients, followed by outpatients and nursing home users (Figure S2).

The high prevalence of cardiovascular criteria (Table III) is in line with previous findings according to both versions (Blanco-Reina *et al*., 2016; Bo *et al*., 2019; Ma *et al*., 2020; Stojanovic *et al*., 2020; Vezmar Kovacevic *et al*., 2014). In addition, the highest prevalence of START v1 observed in the endocrine system, particularly in patients with diabetes mellitus, is consistent with previous studies (Blanco-Reina *et al*., 2016; Projovic *et al*., 2016; Vezmar Kovacevic *et al*., 2014). It is not surprising that new version failed to detect these omissions due to a reduction in the number of criteria for the endocrine system. Specifically, it may be associated with removing aspirin and statin therapy for primary prevention of cardiovascular disease in diabetes mellitus, common items according to v1 in our dataset (O'Mahony *et al*., 2015). In addition to the lack of some information, the withdrawal of these specific items probably contributed to the overall lower prevalence of PPOs in our sample. Similarly, Blanco-Reina et al. detected the most PPOs for the endocrine system using the original version, while it was not the case with v2 (Blanco-Reina *et al*., 2016). Moreover, START v2 usually targeted more PPOs for the cardiovascular than the endocrine section in previous studies (Bo *et al*., 2019; Ma *et al*., 2020).

Due to limited evidence in elderly patients, especially those with diabetes, the prevention of cardiovascular disease is still a challenge. Generally, routine use of aspirin for primary prevention is no longer recommended in older patients, since the benefit does not appear to outweigh the risk (e.g. bleeding) (Montgomery, Miedema, Dodson, 2022). However, statin therapy can be considered for selected patients with elevated risk, taking into account comorbidities, polypharmacy and life expectancy (Montgomery, Miedema, Dodson, 2022). The latest guideline of the American Diabetes Association supports statin therapy in primary prevention for patients aged 40-75 years with diabetes, while for older patients risk-benefit evaluation is recommended (American Diabetes Association Professional Practice Committee, 2022). Undoubtedly, new evidence and recommendations in this field will affect the future development of START criteria.

Factors associated with the criteria in our study were only partly similar between the two versions (Table IV). Previously, predictors of potentially inappropriate prescribing were investigated in numerous studies with diverse designs, populations, and methodology, but usually not simultaneously for both versions of the criteria. Various studies have identified polypharmacy and number of medications as a predictor of PIMs based on the updated or original version of the criteria (Anrys *et al*., 2018; Blanco-Reina *et al*., 2016; Blanco-Reina *et al*., 2019; Bo *et al*., 2019; Buda *et al*., 2020; Counter,

Millar, McLay, 2018; Gallagher *et al*., 2011a; Hill-Taylor *et al*., 2013; Ma *et al*., 2020; Nedin Rankovic *et al*., 2018; Projovic *et al*., 2016; Rogero-Blanco *et al*., 2020; Thomas, Thomas, 2019; Vezmar Kovacevic *et al*., 2014). Similarly, the number of medications was the strongest predictor for both STOPP v1 and STOPP v2 occurrence in our analysis (Table IV). With each increase in the number of medications, the odds for STOPP criteria, irrespective of the version, increase by 34-35% (95% CI 24-45%). Clearly, for patients with many drugs and polypharmacy, overtreatment needs to be considered. While the results were consistent regarding the positive impact of the number of medications on PIMs, there were conflicting reports regarding PPOs. A positive impact of the number of medications was mostly reported (Bo *et al*., 2019; Counter *et al*., 2018; Ma *et al*., 2020), or it was indicated that it had no effect (Vezmar Kovacevic *et al*., 2014). In our analysis, the number of medications was not a significant predictor of v1 or v2 omissions.

The number of comorbidities showed a statistically significant association with both START v1 and START v2 criteria (Table IV). Similarly, a positive influence of the number of comorbidities or comorbidity index was recorded in some studies using either v1 or v2 criteria (Anrys *et al*., 2018; Bo *et al*., 2019; Gallagher *et al*., 2011a; Ma *et al*., 2020; Nedin Rankovic *et al*., 2018), but not in others (Blanco-Reina *et al*., 2019; Counter *et al*., 2018). Interestingly, the number of comorbidities was also a significant predictor for STOPP v2 criteria, but not v1. In addition, higher age and female sex were previously associated with increased odds of inappropriate prescribing (Hill-Taylor *et al*., 2013). Usually, a positive predictive impact of age on STOPP v1 or v2 was recorded, as was the case in our analysis (Table IV), or there was no effect (Buda *et al*., 2020; Counter *et al*., 2018; Hudhra *et al*., 2016; Ma *et al*., 2020). On the other hand, a negative predictive impact on START v1 criteria runs counter to most previous findings based on v1 (Gallagher *et al*., 2011a; Ma *et al*., 2020; Vezmar Kovacevic *et al*., 2014) and v2 (Bo *et al*., 2019). However, in one study omissions were associated with a lower age, which was explained by less need for medical care among the younger elderly, and consequently more opportunity for undertreatment (Pereira *et al*., 2019). Previous studies have shown that women usually experience higher PIM rates (Ma *et al*., 2020; Rogero-Blanco *et al*., 2020). Interestingly, in our analysis, male sex was a significant predictor of START v2 criteria, but not v1 (Table IV).

There are certain limitations to our study. Some of the criteria were not applied in the analysis due to insufficient information from the data sources. The omitted criteria comprise only 2.3%, and 7% of the total number of STOPP/START v1 and v2, implying that the results of the updated version were more exposed. In addition, the methodology of data collection differed among the settings, leading to diverse availability of information. Specifically, only the data for community-dwelling patients were collected prospectively, including even details about over-the-counter medications. Finally, we did not assess the outcomes and costs resulting from PIMs and PPOs detected by the two versions of STOPP/START criteria, and this requires further investigation.

In conclusion, the results of this study indicate a substantial rate of potentially inappropriate prescribing according to both STOPP/START versions. Although a slight increase in PIM prevalence was observed in the total study sample with the updated version, the difference was not as prominent as in the previous comparative analyses. Nevertheless, the updated version detected a noticeably higher prevalence of PIMs related to fall-risk-increasing drugs, previously associated with drug-related admissions (Thevelin et al., 2019), in each healthcare setting. The strongest predictor for both STOPP v1 and v2 was the number of medications. More surprisingly, the prevalence of PPOs significantly decreased with the updated version. Among the tested variables, only the number of comorbidities was a significant predictor for inappropriate omissions using both criteria. Simultaneous assessment in three healthcare settings enabled the confirmation of findings obtained in the total study sample, indicating only a minor possibility for a different pattern among healthcare levels. All of this indicates that there is a need for therapy optimization in elderly patients regardless of the level of health care, especially in those with polypharmacy and multimorbidity.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2022. Diabetes care. 2022;45(Suppl 1):S144-S174.

Anrys PMS, Strauven GC, Foulon V, Degryse JM, Henrard S, Spinewine A. Potentially inappropriate prescribing in Belgian nursing homes: prevalence and associated factors. J Am Med Dir Assoc. 2018;19(10):884-890.

Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med. 1997;157(14):1531-1536.

Blanco-Reina E, Garcia-Merino MR, Ocana-Riola R, Aguilar-Cano L, Valdellos J, Bellido-Estevez I, et al. Assessing potentially inappropriate prescribing in community-dwelling older patients using the updated version of STOPP-START criteria: a comparison of profiles and prevalences with respect to the original version. PLoS One. 2016;11(12):e0167586.

Blanco-Reina E, Valdellos J, Aguilar-Cano L, Garcia-Merino MR, Ocana-Riola R, Ariza-Zafra G, et al. 2015 Beers criteria and STOPP v2 for detecting potentially inappropriate medication in community-dwelling older people: prevalence, profile, and risk factors. Eur J Clin Pharmacol. 2019;75(10):1459-1466.

Bo M, Gibello M, Brunetti E, Boietti E, Sappa M, Falcone Y, et al. Prevalence and predictors of inappropriate prescribing according to the Screening Tool of Older People's Prescriptions and Screening Tool to Alert to Right Treatment version 2 criteria in older patients discharged from geriatric and internal medicine wards: a prospective observational multicenter study. Geriatr Gerontol Int. 2019;19(1):5-11.

Boland B, Guignard B, Dalleur O, Langgh PO. Application of STOPP/START and Beers criteria: compared analysis on identification and relevance of potentially inappropriate prescriptions. Eur Geriatr Med. 2016;7(5):416-423.

Buda V, Prelipcean A, Andor M, Dehelean L, Dalleur O, Buda S, et al. Potentially inappropriate prescriptions in ambulatory elderly patients living in rural areas of Romania using STOPP/START (version 2) criteria. Clin Interv Aging. 2020;15:407-417.

Conejos Miquel MD, Sanchez Cuervo M, Delgado Silveira E, Sevilla Machuca I, Gonzalez-Blazquez S, Montero Errasquin B, et al. Potentially inappropriate drug prescription in older subjects across health care settings. Eur Geriatr Med. 2010;1(1):9-14.

Counter D, Millar JWT, McLay JS. Hospital readmissions, mortality and potentially inappropriate prescribing: a retrospective study of older adults discharged from hospital. Br J Clin Pharmacol. 2018;84(8):1757-1763.

Curtin D, Gallagher PF, O'Mahony D. Explicit criteria as clinical tools to minimize inappropriate medication use and its consequences. Ther Adv Drug Saf. 2019;10:2042098619829431.

Drenth-van Maanen AC, Wilting I, Jansen PAF. Prescribing medicines to older people-How to consider the impact of ageing on human organ and body functions. Br J Clin Pharmacol. 2020;86(10):1921-1930.

Frankenthal D, Lerman Y, Kalendaryev E, Lerman Y. Intervention with the Screening Tool of Older Persons potentially inappropriate Prescriptions/Screening Tool to Alert doctors to Right Treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical trial. J Am Geriatr Soc. 2014;62(9):1658-1665.

Gallagher P, Lang PO, Cherubini A, Topinkova E, Cruz-Jentoft A, Montero Errasquin B, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. Eur J Clin Pharmacol. 2011a;67(11):1175-1188.

Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72-83.

Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther. 2011b;89(6):845-854.

Garcia-Gollarte F, Baleriola-Julvez J, Ferrero-Lopez I, Cruz-Jentoft AJ. Inappropriate drug prescription at nursing home admission. J Am Med Dir Assoc. 2012;13(1):83.e9-15.

Gaubert-Dahan ML, Sebouai A, Tourid W, Fauvelle F, Aikpa R, Bonnet-Zamponi D. The impact of medication review with version 2 STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria in a French nursing home: a 3-month follow-up study. Ther Adv Drug Saf. 2019;10:2042098619855535.

Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med. 2011;171(11):1013-1019.

Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. J Clin Pharm Ther. 2013;38(5):360-372.

Hill-Taylor B, Walsh KA, Stewart S, Hayden J, Byrne S, Sketris IS. Effectiveness of the STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/ Screening Tool to Alert doctors to the Right Treatment) criteria: systematic review and meta-analysis of randomized controlled studies. J Clin Pharm Ther. 2016;41(2):158-169.

Hudhra K, Beci E, Petrela E, Xhafaj D, Garcia-Caballos M, Bueno-Cavanillas A. Prevalence and factors associated with potentially inappropriate prescriptions among older patients at hospital discharge. J Eval Clin Pract. 2016;22(5):707-713.

Kovacevic SV, Miljkovic B, Culafic M, Kovacevic M, Golubovic B, Jovanovic M, et al. Evaluation of drug-related problems in older polypharmacy primary care patients. J Eval Clin Pract. 2017a;23(4):860-865.

Kovacevic SV, Miljkovic B, Vucicevic K, Culafic M, Kovacevic M, Golubovic B, et al. Elderly polypharmacy patients' needs and concerns regarding medication assessed using the structured patient-pharmacist consultation model. Patient Educ Couns. 2017b;100(9):1714-1719.

Ma Z, Tong Y, Zhang C, Liu L. Potentially inappropriate medications and potentially prescribing omissions in Chinese older patients: comparison of two versions of STOPP/START. J Clin Pharm Ther. 2020;45(6):1405-1413.

Montgomery S, Miedema MD, Dodson JA. Aspirin and statin therapy for primary prevention of cardiovascular disease in older adults. Heart. 2022;108(14):1090-1097.

Nedin Rankovic G, Jankovic SM, Velickovic Radovanovic R, Jovic Z, Pesic G, Pavlovic S, et al. Potentially inappropriate prescribing of drugs in elderly patients on chronic hemodialysis treatment. Clin Nephrol. 2018;89(6):453-460.

O'Connor MN, O'Sullivan D, Gallagher PF, Eustace J, Byrne S, O'Mahony D. Prevention of hospital-acquired adverse drug reactions in older people using Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment criteria: a cluster randomized controlled trial. J Am Geriatr Soc. 2016; 64(8): 1558-1566.

O'Mahony D. STOPP/START criteria for potentially inappropriate medications/potential prescribing omissions in older people: origin and progress. Expert Rev Clin Pharmacol. 2020;13(1):15-22.

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): 213-218.

O'Mahony D, Gallagher P, Ryan C, Byrne S, Hamilton H, Barry P, et al. STOPP & START criteria: a new approach to detecting potentially inappropriate prescribing in old age. Eur Geriatr Med. 2010;1(1):45-51.

Pereira TFF, de Sa Soares A, Trevisol DJ, Schuelter-Trevisol F. Assessing the overall medication use by elderly people in a Brazilian hospital using the start/stopp criteria version 2. Braz J Pharm Sci. 2019;55:e17739.

Projovic I, Vukadinovic D, Milovanovic O, Jurisevic M, Pavlovic R, Jacovic S, et al. Risk factors for potentially inappropriate prescribing to older patients in primary care. Eur J Clin Pharmacol. 2016;72(1):93-107.

Reeve E, Ong M, Wu A, Jansen J, Petrovic M, Gnjidic D. A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people. Eur J Clin Pharmacol. 2017;73(8):927-935.

Rogero-Blanco E, Lopez-Rodriguez JA, Sanz-Cuesta T, Aza-Pascual-Salcedo M, Bujalance-Zafra MJ, Cura-Gonzalez I, et al. Use of an electronic clinical decision support system in primary care to assess inappropriate polypharmacy in young seniors with multimorbidity: observational, descriptive, cross-sectional study. JMIR Med Inform. 2020;8(3):e14130.

Stojanovic M, Vukovic M, Jovanovic M, Dimitrijevic S, Radenkovic M. GheOP(3) S tool and START/STOPP criteria version 2 for screening of potentially inappropriate medications and omissions in nursing home residents. J Eval Clin Pract. 2020;26(1):158-164.

Thevelin S, Mounaouar LE, Marien S, Boland B, Henrard S, Dalleur O. Potentially inappropriate prescribing and related hospital admissions in geriatric patients: a comparative analysis between the STOPP and START criteria versions 1 and 2. Drugs Aging. 2019;36(5):453-459.

Thomas RE, Thomas BC. A systematic review of studies of the STOPP/START 2015 and American geriatric society Beers 2015 criteria in patients ≥ 65 years. Curr Aging Sci. 2019;12(2):121-154.

Vezmar Kovacevic S, Simisic M, Stojkov Rudinski S, Culafic M, Vucicevic K, Prostran M, et al. Potentially inappropriate prescribing in older primary care patients. PLoS One. 2014;9(4):e95536.

Zazzara MB, Palmer K, Vetrano DL, Carfi A, Onder G. Adverse drug reactions in older adults: a narrative review of the literature. Eur Geriatr Med. 2021;12(3):463-473.

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