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STOPP/START criteria for identifying potentially inappropriately prescribed drugs: Elderly patients with chronic kidney disease

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Elderly patients with chronic kidney disease (CKD) are particularly susceptible to potentially inappropriate prescribing (PIP) due to polypharmacy, altered pharmacokinetics and comorbidities. The aim of this study was to examine the prevalence of PIP and identify factors associated with potentially inappropriately prescribed and missed medications in patients over 65 years of age with CKD. The study was conducted at the Nephrology Clinic of the University Clinical Centre Nis and included 135 participants. PIP was evaluated using the STOPP/START criteria, version 2. The results showed that 32.6% of patients had at least one potentially prescribed omission (PPO), while 40.7% had at least one potentially inappropriately prescribed medication (PIM). PPO was more frequent among older patients, those living alone, and patients with a greater number of comorbidities. The greatest risk for PPO was observed in patients with stable angina pectoris, acute myocardial infarction, osteoporosis, and gout, as well as those treated with spironolactone, aminophylline, digoxin, trimetazidine and iron

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preparations, whereas statins had a protective effect. PIM was more common in patients with lower education levels and in those taking a greater number of medications, particularly digoxin, benzodiazepines, and nonsteroidal anti-inflammatory drugs, while reading drug instructions was associated with a reduced risk of PIM. These findings confirm that the prevalence of PIP is high among elderly patients with CKD and highlight the importance of applying the STOPP/START criteria in routine clinical practice to optimize pharmacotherapy and reduce the risk of adverse outcomes in this vulnerable population.

Key words: elderly patients, chronic kidney disease, potentially inappropriate prescribing, STOPP/START criteria, polypharmacy

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STOPP/START kriterijum za identifikaciju potencijalno neadekvatno propisanih lekova: Stariji pacijenti sa hroničnom bolesti bubrega

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Stariji pacijenti sa hroničnom bubrežnom bolešću (HBB) su posebno podložni potencijalno neadekvatnom propisivanju lekova (PIP) zbog polifarmacije, promenjene farmakokinetika i prisutnih komorbiditeta. Cilj ovog istraživanja bio je da se ispita prevalencija PIP-a i identifikuju faktori povezani sa potencijalno neprikladno propisanim i propuštenim lekovima kod pacijenata starijih od 65 godina sa HBB. Studija je sprovedena na Klinici za nefrologiju Univerzitetskog kliničkog centra Niš i obuhvatila je 135 ispitanika. Za procenu PIP-a korišćeni su STOPP/START kriterijumi, verzija 2. Rezultati su pokazali da je 32,6% pacijenata imalo potencijalno propuštene lekove (PPO), dok je 40,7% imalo makar jedan potencijalno neprikladno propisan lek (PIM). PPO je bio češći kod starijih ispitanika, onih koji žive sami i pacijenata sa većim brojem komorbiditeta. Najveći rizik za PPO imali su oboleli od stabilne angine pektoris, akutnog infarkta mioakrda, osteoporoze i gihta, kao i pacijenti na terapiji spironolaktonom,

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aminofilinom, digoksinom, trimetazidinom i preparatima gvožđa, dok su statini imali protektivni efekat. PIM je bio češći kod pacijenata sa nižim nivoom obrazovanja i onih sa većim brojem lekova, naročito kod onih koji uzimaju digoksin, benzodiazepine i nesteroidne antiinflamatorne lekove, dok je čitanje uputstava o leku smanjivalo rizik od PIM-a. Rezultati studije potvrđuju da je prevalencija PIP-a visoka kod starijih pacijenata sa HBB i naglašavaju značaj primene STOPP/START kriterijuma u kliničkoj praksi radi optimizacije farmakoterapije i smanjenja rizika od neželjenih ishoda.

Ključne reči: stariji pacijenti, hronična bubrežna bolest, potencijalno neadekvatno propisivanje lekova, STOPP/START kriterijumi, polifarmacija

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Introduction

According to the Hippocratic Oath, particularly the principle 'first, do no harm,' every medical intervention should prioritize safety. However, achieving this ideal represents a significant challenge in modern healthcare systems.

Providing optimal care for elderly patients is particularly complex due to their heterogeneity and the lack of robust evidence on drug efficacy, as older adults are frequently excluded from clinical trials (1). Elderly patients with chronic kidney disease (CKD) constitute a particularly vulnerable population. The aging process itself has multiple consequences affecting public health and societal stability. Age-related physiological changes often result in multimorbidity and polypharmacy, which increase the risk of drug-drug interactions, adverse drug reactions (ADRs), hospitalizations, greater healthcare utilization, and higher mortality rates (2–4). Considering that these patients also have impaired renal function -the main excretory organ- prescribing for such a vulnerable group requires considerable expertise.

Potentially inappropriate prescribing (PIP) encompasses prescribing practices that increase the risk of adverse outcomes. This includes the use of an inappropriate drug, incorrect dosage regimen, or the omission of a beneficial drug, all of which may worsen existing conditions or cause new health problems. Elderly CKD patients are at particularly high risk due to their extensive medication use, the need for dose adjustments, and the contraindication of certain drugs (5,6).

One of the most commonly used criteria in Europe for PIP detection is the STOPP (*Screening Tool of Older Persons Potentionally Inappropriate Prescriptions*) and START (*Screening Tool to Alert doctors to the right Treatment*) criteria, first published in Ireland in 2008 (7). The main goal of the STOPP criteria is to minimize the harmfulness of drugs by avoiding potentially inappropriate medication (PIM), while the START criterion aims to minimize therapeutic failure by encouraging the prescription of a drug that is not prescribed even though there is a clear indication (potential prescribing omission - PPO). It has been proven that when these criteria are applied, the ADR in hospitalized patients is significantly reduced within 72 hours (with an absolute risk reduction of 9.3%), and also in the elderly with acute illnesses, the average length of hospital stay is reduced by three days (8).

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Aim

The key objective of this study was to determine the prevalence of potentially inappropriate prescribing among elderly patients with CKD and to identify factors associated with PIP. STOPP and START criteria were applied for PIP detection, Version 2 (9). Patients were categorized into two groups: those with at least one PIP (cases) and those without PIP (controls).

Methods

This observational case-control study was conducted at the Nephrology Clinic, University Clinical Center Niš. Patients aged 65 years and older with CKD were included. Data were collected from medical records and patient questionnaires, which covered sociodemographic data, medical history, hospitalizations, ADRs, lifestyle habits (smoking, alcohol, coffee consumption), comorbidities, and medication use. Patients were also asked whether they read medication instructions or consulted their physicians about ADRs and drug interactions. Laboratory data were extracted from medical records. For patients lacking creatinine clearance (ClCr) values, clearance was estimated using the Cockcroft-Gault formula (10).

Statistical analysis

Data were analyzed using SPSS software (version 21.0; Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequencies. Normality was tested using the Shapiro–Wilk and Kolmogorov–Smirnov tests. The Mann–Whitney U test was used for continuous variables, while the χ^2 or Fisher's exact test was used for categorical variables. Univariate and multivariate logistic regression analyses were applied to identify predictors of potentially inappropriate medication (PIM) and potential prescribing omissions (PPO). Only statistically significant results ($p<0.01$) are presented.

Results

A total of 135 patients over the age of 65 with CKD were included, of which 78 (57.8%) were men and 57 (42.2%) were women. The largest number of patients (56.3%) had the third stage of CKD, 24.4% with the second stage, 11.9% with the fourth stage, 5.2% with initial CKD and 2.2% with the fifth stage of CKD.

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START

In 44 patients (32.6%), the absence of the indicated drug in the prescribed therapy was observed, and the maximum number of indicated and non-prescribed drugs was three, which was recorded in 2 patients (1.5%). It was found that PPO was more common in elderly patients (t=2.731, p<0.01) and in those living alone (χ^2=7.085, p<0.01). Also, the occurrence of PPO was more frequent in patients with a greater number of comorbidities (t=3.631, p<0.001).

Using univariate logistic regression, 21 independent variables were singled out that can play a role in predicting potentially inappropriate prescription of drugs in the examined patients. After including all these variables, a statistically significant multivariate model was obtained (χ^2=120.528, p<0.001) which explains 59.0-82.3% of the variance of the dependent variables (table 1). 11 variables retained their independent prognostic value. With each year of age, the risk of developing PIP increases 1.2 times (p<0.05). Patients with stable angina pectoris have a 52 times higher risk (p<0.05), acute myocardial infarction 118 times higher risk (p<0.05), osteoporosis 279 times higher risk (p<0.001), and gout 20 times higher risk of potentially inappropriate prescribing of drugs (p<0.05). Patients on spironolactone therapy have a 41 times higher risk (p<0.01), aminophylline 34 times (p<0.05), digoxin 38 times (p<0.01), trimetazidine 73 times (p<0.01), and iron preparations 26 times higher risk (p<0.01). In contrast, patients prescribed statins have a significantly lower risk of potentially inappropriate prescribing under START criterion (p<0,001).

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Table 1. Multivariate logistic regression of PPO according to START

	B	*SE*	*Wald*	*P*	*HR*	95% *CI* (*HR*)
Age	0,176	0,087	4,131	**0,042**	**1,193**	**1,006-1,413**
Stable angina pectoris	3,948	1,579	6,241	**0,012**	**51,835**	**2,347-1144,844**
Acute myocardial infarction	4,769	2,164	4,855	**0,028**	**117,758**	**1,694-8188,123**
Osteoporosis	5,6930	1,679	11,241	**0,001**	**278,800**	**10,371-7495,109**
Gout	2,983	1,197	6,206	**0,013**	**19,742**	**1,889-206,315**
Spironolactone	3,703	1,193	9,634	**0,002**	**40,588**	**3,915-420,746**
Aminophylline	3,527	1,38	6,524	**0,011**	**34,022**	**2,272-509,471**
Digoxin	3,642	1,304	7,802	**0,005**	**38,180**	**2,964-491,795**
Trimetazidine	4,285	1,632	6,897	**0,009**	**72,585**	**2,965-1776,850**
Iron preparations	3,160	1,161	7,415	**0,006**	**23,573**	**2,424-229,222**
Statins	-11,689	3,397	11,841	**0,001**	**0,000**	**0,000-0,007**

STOPP

A total of 55 patients (40.7%) had at least one potentially inadequately prescribed drug according to the STOPP, and the maximum number of potentially inadequately prescribed drugs was 3 and that in only one patient (0.7%). PIM was more common in patients with a lower level of education ($Z=2.106$ $p<0.05$), while patients who read drug instructions have a lower risk of having inadequately prescribed medication ($\chi^2=4.490$, $p<0.05$).

PIM was more frequent in patients taking more medications ($t=2.158$, $p<0.05$).

Using univariate logistic regression, 8 independent variables were singled out, which may play a role in predicting potentially inappropriate prescription of drugs in the examined patients. After including all these variables, a statistically significant multivariate model was obtained ($\chi^2=31.012$, $p<0.001$) which explains 20.5-27.7% of the variance of the dependent variables

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(table 2). 5 variables retained their independent prognostic value. Patients who read the drug instructions have a 2.2 times lower risk of potentially inappropriate drug prescribing ($p<0.05$). Gout increases the risk 3.3 times ($p<0.05$). In patients prescribed digoxin, benzodiazepines, or non-steroidal anti-inflammatory drugs, the risk is higher 7.2 times ($p<0.01$), 3.6 times ($p<0.01$), or 3.8 times ($p<0.05$), respectively.

Table 2. Multivariate logistic regression of PIM according to STOPP

	B	***SE***	***Wald***	***P***	***HR***	**95% *CI* (*HR*)**
The patient is reading the drug information leaflet	0,809	0,406	3,964	**0,046**	**2,245**	**1,013-4,976**
Gout	1,207	0,528	5,217	**0,022**	**3,343**	**1,187-9,416**
Digoxin	1,980	0,761	6,768	**0,009**	**7,239**	**1,629-32,166**
Benzodiazepines	1,267	0,429	8,718	**0,003**	**3,550**	**1,531-8,230**
Nonsteroidal anti-inflammatory drugs	1,326	0,632	4,411	**0,036**	**3,768**	**1,093-12,992**

Discussion

Renal failure is common in elderly patients, in whom the risk of drug-related "problems" is particularly high due to reduced excretion and therefore increased plasma levels of drugs and their metabolites (11). The prevalence of PIP varies depending on the geographic region where the study was conducted, the criteria used to assess the adequacy of prescribing, and the study design, while the prevalence of PIP in patients with CKD varies from 13% to 96% (12,13). The results of our study show that the prevalence of PIP was 32.6% according to START and 40.7% according to STOPP, which is slightly higher than the results we published recently, but at that time our subjects were hemodialysis patients, PPO was present in 22%, while PIM was present in 39% of patients (14). Krystina P. and her colleagues in a study (15)

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of PIP in the elderly with CKD determined that half of their respondents had at least one PIP, namely 50% PPO and 54% PIM.

PPO was more common in older patients and in those aged 75-84 years, which is consistent with the results of a study conducted in Turkey (16). The appearance of PPO was also influenced by the way of life, because this phenomenon was more common in those who live alone. It is related to each other, because there can be misunderstandings between elderly patients and doctors due to e.g. cognitive disorders. Elderly people who live alone have no one at home to help them with medicines, to remind them at what time and which medicine they should take, because the elderly can become forgetful with age, they can have tremors that make it difficult for them to dose medicines, they can mix up medicines due to similarities in shape or color.

The occurrence of PPO was more frequent in patients with a greater number of comorbidities, and it is already known that when patients take multiple drugs, it is more likely that they have at least one inappropriate drug or are deprived of a drug that is essential for their condition. The results of our research show that the highest prevalence of prescription failure is in patients with cardiovascular diseases, which is in line with numerous other studies. (17–19).

It is interesting that we did not come across a connection between PPO and the total number of medicines that the patient takes. Otherwise, the average number of comorbidities in our patients was 4.99±2.02, and not a single patient was without comorbidities, while the average number of medications the patients took was 7.13±2.61.

Unlike the START criteria, the number of comorbidities was not important for the occurrence of PIM according to STOPP, but the total number of prescribed drugs was, and the most common were benzodiazepines that were not properly prescribed (long-acting benzodiazepines and with long-acting metabolites > 1 month). And a recent study (20) conducted in Spain came to the same connection, i.e. the total number of drugs taken by the patient was statistically significant for PIM according to the STOPP criterion ($p<0.03$). Numerous studies show that reducing the number of medications the patient takes is associated with a reduction in the risk of PIP (16,21,22).

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Conclusion

CKD has several characteristics that require a special drug dosing regimen: reduced glomerular filtration affects the clearance of many drugs; CKD is most often associated with other comorbidities (diabetes, cardiovascular diseases, anemia...); electrolyte and acid-base disorders, hypoalbuminemia. Therefore, the selection and dosage of drugs in patients with CKD requires special attention. In the elderly with CKD, the presence of many comorbidities, each of which requires special therapy, leads to the possible prescription of a large number of drugs. Some of them may be indicated for one disease, but contraindicated in the presence of another disease or another drug. Therefore, the list of potentially inappropriate drugs may be complex, but necessary to avoid adverse events.

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References

1. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007; 370:173–84.

2. Vrdoljak D, Borovac JA. Medication in the elderly-considerations and therapy prescription guidelines. Acta Med Acad 2015; 44:159–68.

3. Marengoni A, Pasina L, Concoreggi C, Martini G, Brognoli F, Nobili A, et al. Understanding adverse drug reactions in older adults through drug-drug interactions. Eur J Intern Med 2014; 25:843–6.

4. 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; 84:1757–63.

5. Gallieni M, Cancarini G. Drugs in the elderly with chronic kidney disease: beware of potentially inappropriate medications. Nephrol Dial Transplant 2015; 30:342–4.

6. Lüthke N, Scheuch M, Engeßer J, von Rheinbaben S, Hoffmann R, Aymanns S, et al. Potentially inappropriate medication in patients with chronic kidney disease and elderly patients. Clin Nephrol 2022; 98:42–8.

7. 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; 46:72–83.

8. Anrys P, Boland B, Degryse JM, De Lepeleire J, Petrovic M, Marien S, et al. STOPP/START version 2-development of software applications: easier said than done? Age Ageing 2016; 45:590–3.

9. 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; 44:213–8.

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10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41.

11. Long CL, Raebel MA, Price DW, Magid DJ. Compliance with dosing guidelines in patients with chronic kidney disease. Ann Pharmacother 2004; 38:853–8.

12. Molnar AO, Bota S, Jeyakumar N, McArthur E, Battistella M, Garg AX, et al. Potentially inappropriate prescribing in older adults with advanced chronic kidney disease. PLoS One 2020; 15.

13. Tesfaye WH, Castelino RL, Wimmer BC, Zaidi STR. Inappropriate prescribing in chronic kidney disease: A systematic review of prevalence, associated clinical outcomes and impact of interventions. Int J Clin Pract 2017; 71.

14. Ranković GN, Janković SM, Radovanović RV, Jović Z, Pešić G, Pavlović S, et al. Potentially inappropriate prescribing of drugs in elderly patients on chronic hemodialysis treatment. Clin Nephrol 2018; 89:453–60.

15. Parker K, Bull-Engelstad I, Benth JŠ, Aasebø W, von der Lippe N, Reier-Nilsen M, et al. Effectiveness of using STOPP/START criteria to identify potentially inappropriate medication in people aged ≥ 65 years with chronic kidney disease: a randomized clinical trial. Eur J Clin Pharmacol 2019; 75:1503–11.

16. Sayın Z, Sancar M, Özen Y, Okuyan B. Polypharmacy, potentially inappropriate prescribing and medication complexity in Turkish older patients in the community pharmacy setting. Acta Clin Belg 2022; 77:273–9.

17. Rakesh KB, Chowta MN, Shenoy AK, Shastry R, Pai SB. Evaluation of polypharmacy and appropriateness of prescription in geriatric patients: A cross-sectional study at a tertiary care hospital. Indian J Pharmacol 2017; 49:16.

18. Reich O, Rosemann T, Rapold R, Blozik E, Senn O. Potentially inappropriate medication use in older patients in Swiss managed care plans: prevalence, determinants and association with hospitalization. PLoS One 2014; 9.

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19. Ryan C, O'mahony D, Kennedy J, Weedle P, Cottrell E, Heffernan M, et al. Potentially inappropriate prescribing in older residents in Irish nursing homes. Age Ageing 2013; 42:116–20.

20. Gonzalez-Lopez A, Nava-Rebollo A, Chocarro-Martinez A, Andres-Martin B, Santana-Zapatero H, Herrera-Gomez F, et al. Potentially inappropriate prescribing in patients on dialysis using STOPP-START criteria. Nefrología (English Edition); 39:92–4.

21. van der Stelt CAK, Vermeulen Windsant-van den Tweel AMA, Egberts ACG, van den Bemt PMLA, Leendertse AJ, Hermens WAJJ, et al. The Association Between Potentially Inappropriate Prescribing and Medication-Related Hospital Admissions in Older Patients: A Nested Case Control Study. Drug Saf 2016; 39:79–87.

22. 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; 38:360–72.

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