Analysis of Potentially Inappropriate Prescriptions (PIP) Based on STOPP/START Criteria in Geriatric Patients with Cardiovascular Disorders at Hasan Sadikin Hospital, Bandung, West Java, Indonesia

Fathurrahmi,[1] Gofarana Wilar,[2] Jutti Levita,[2] Rina Winarni[3]

[1]Master Program in Clinical Pharmacy, Faculty of Pharmacy, Padjadjaran University, West Java, Indonesia 45363
[2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Padjadjaran University, West Java, Indonesia 45363
[3]Hasan Sadikin Hospital, Bandung, West Java, Indonesia

Abstract

The geriatric population in Indonesia is increasing rapidly every year. The large number of drugs consumed by geriatric patients results in potentially inappropriate prescriptions (PIP) in the form of mis-prescribing drugs (potentially inappropriate medicines or PIM) and under-prescribing drugs (potentially prescription omission or PPO). In Indonesia, especially in Bandung, there is limited research on PIP in geriatric patients with cardiovascular disorders (CVDs), while other studies only conducted PIM in generally geriatric patients. This study aims to identify PIP and factors that influence PIM and PPO based on STOPP/START criteria and the relationship between the incidence of PIM and kidney function in geriatric in-patients with CVDs at Hasan Sadikin Hospital, Bandung, West Java, Indonesia. The present retrospective study was cross-sectionally conducted from January to December 2022. The Chi-square tests were carried out to determine factors that were significantly related to PIM and PPO. Of the 192 patients, 33.4% patients experienced PIM with the most being NSAIDs with eGFR <30 mL/min/1.73 m2 (36%). As many as 35% of patients experienced PPO with the most frequent PPO not being given angiotensin-converting enzyme inhibitor (ACEi) in patients with systolic heart failure (41.8%). Factors that were significantly associated with PIM were comorbid kidney dysfunctions (OR 5; 95% CI: 2.367-10.342), and no factors were found that were significantly associated with PPO. Taking everything into consideration, it was found that PIM and PPO were common in hospitalized geriatric patients with CVDs. Kidney dysfunctions are a risk factor for PIM. These findings suggest that it is important to evaluate prescribing for geriatric patients during hospitalization using STOPP/START criteria to reduce the prevalence of PIP. Optimizing prescribing to reduce PIP may provide improvement health outcomes and decrease adverse drug reaction (ADR) risk.

Keywords*:* angiotensin-converting enzyme inhibitor; cardiovascular disorders; potentially inappropriate medicines; potentially inappropriate prescriptions; potentially prescription omission

Introduction

The global geriatric population is predicted to elevate from 9.3% in 2020 to approximately 16.0% in 2050 due to the tendency of a longer life expectancy.[1] Similarly in Indonesia, the geriatric population is expected to rapidly arise. It was reported that in 2020 the geriatric population in Indonesia reached an alarming rate of 9.92%, whereas in 2021 the population aged 65 years or more attained 10% in West Java.[2,3]

People with longer life expectancy often suffer from multimorbidity due to progressive homeostasis disorders related to the decrease of physiological function, pharmacokinetics, and pharmacodynamics.[4] Multimorbidity is linked with an increased risk of death, ailment, dysfunction of the organ, low quality of life (QoL), and adverse drug events (ADEs), which eventually implicates polypharmacy (the simultaneous use of five or more medicines by a patient to alleviate his numerous diseases.[5]

Polypharmacy in elderly patients often causes the escalation of PIP and unsafe prescribing. On that account, amending drug prescribing for elderly patients is crucial to ensure medication safety.[6] A useful strategy to identify PIP and to impede prescribing errors in multimorbid geriatric patients is by routinely applying STOPP/START (screening tool for older people's prescriptions/screening tool to alert doctors to the right treatment) criteria.[7] STOPP/START is an accurate, decent, and comprehensive screening tool that authorizes the physician to evaluate the prescription drugs of an elderly patient on his coexistent diagnoses.[8] STOPP criteria are designed to detect and identify PIM, whereas START criteria are focused on PPO.[7]

The occurrence of at least 1 PIM was found in 51% of 101 patients, while that of at least 1 PPO was found in 74% of 147 patients.

The most common PIM was the treatment of aspirin in patients with no history of coronary, cerebral, or peripheral arterial disease. The most common PPO was not prescribing HMG-CoA inhibitors to patients with coronary, cerebral, or peripheral vascular disease.[9] Additionally, it was reported that an incidence of at least 1 PIM occurred at a range of 36.9 to 51.0%, whereas at least 1 PPO varied between 36.9 and 44.6% in a total of 249 older patients. The most common PIM was the use of proton pump inhibitors while the most common PPO was the omission of vitamin D supplements, thus a considerable observation is required by actively de-prescribing medicines that are not beneficial and starting advantageous medications.[10] PIPs and PIMs were persistent in elderly patients at hospital discharge and were linked with worsened re-hospitalizations and dependence on the activity of daily living 3 months after discharge.[11]

Several studies of PIM prescription were reported in Indonesia. A study conducted at Dr. H. Abdul Moeloek Hospital Lampung, Indonesia in 2018, described that the most PIM (25.81%) was the use of statins in older patients with coronary heart disease and cerebral vascular disease. There was a notable correlation between the occurrence of PIM and comorbidities.[12] Recently, the Indonesian version of STOPP (STOPP_INA) was developed using modified transcultural adaptation guidelines from the American Academy of Orthopedic Surgeons. The expert panel had agreed on a list of 81 criteria for adaptation of STOPP version 2 which was currently being evaluated clinically on hospitalized geriatric patients.[13]

Another study evaluated the STOPP/START to improve the Adapted Medication Appropriateness Index (MAI), the risk of ADRs, and the length of stay (LOS) in the Geriatric Inpatient Ward, Sanglah General

Hospital, Bali, Indonesia, concluded that the use of STOPP/START had improved medication appropriateness and reduced ADR risk and LOS.[14] However, these studies only identify PIM use which is not comprehensive in assessing both PIM and PPO and their associated factors.

Taking everything into consideration, our work aims to analyze PIP based on STOPP/START criteria in geriatric patients with CVD at Hasan Sadikin Hospital, Bandung, West Java, Indonesia.

Methods
The protocol of the study was approved by the Research Ethics Committee of Universitas Padjadjaran Bandung, Indonesia, with the approval document number 830/UN6.KEP/EC/2022. The study has been granted permission by Hasan Sadikin Hospital Bandung with the document number LB.02.01/X.2.2.1/18741/2022. The data of inpatients were taken from the medical records from January to December 2022.

The design of the study was an observational cross-sectional retrospective. Data were collected at the Geriatric Ward, Hasan Sadikin Hospital Bandung, West Java, Indonesia. The inclusion criteria were the medical record number, name of the patient, age, gender, date of hospital admission and discharge, patients who were diagnosed with CVD according to the ICD 10, having comorbidities, name of multiple medications and duration of therapy, and laboratory data.

The exclusion criteria were patients with incomplete medical records, patients who underwent hemodialysis, and patients with >5 comorbidities. The screening tools to detect and identify potentially PIM and PPO were the STOPP/START version 2. This tool was published in 2015 with comprises 65 STOPP criteria and 22 START criteria. The criteria are a consensus of 19 geriatrics pharmacotherapy experts based on published studies and have been validated using the Delphi method. The STOPP and START criteria are arranged according to the body for ease of use and rapid application by clinicians which are used to assess treatment in the group over 65 years by looking at the risks and benefits.[8]

Data were collected on a Microsoft Excel in percentage (%). Variables were age, gender, comorbidities, LOS, and number of medications. Chi-square was applied to identify PIM and PPO in three age groups (65- 74, 75-84, and $\geq$ 85 years old), gender, comorbidities, number of medications (< 5 and $\geq$ 5 drugs), and LOS (< 5 days and $\geq$ 5 days). Variables with a P value $\leq$ 0.25 were further analyzed using the Multivariable Binary Logistic Regression and data were presented as odds ratios (ORs) and CI 95% with a P value of < 0.05 as significantly different. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) 25 for Windows.

Results and Discussion
The medical records of 261 geriatric inpatients (age > 65 years old) were initially collected in this study, however, only 192 data fulfilled the inclusion criteria (tabulated in Table 1). The retrospective data from the medical records of the 192 included geriatric inpatients revealed the occurrence of PIP at 134 (69.9%). Overall, there were 180 incidences of PIP, of which 89 (49.4%) were PIM and 91 (50.6%) were PPO. According to the STOPP criteria, 64 (33.4%) patients experienced at least 1 PIM, while following START criteria, 51 (26.6%) patients experienced at least 1 PPO. The details are presented in Table 2. The occurrence of PIP in geriatric inpatients based on the STOPP/START criteria is presented in Table 3.

The main findings of the present study in geriatric inpatients at Hasan Sadikin Hospital Bandung are (1) the incidence of PIP in geriatric inpatients was high (69.9%), of which 49.4% were PIM and 50.6% were PPO; (2) the most prescribed PIMs were NSAIDs to patients with an eGFR <50 ml/minute/1.73 m2 (36.0%), followed by the combination of NSAIDs with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis (25.8%); (3) factors affecting PIM were hypertension (P = 0.209), diabetes mellitus (P = 0.022), kidney dysfunction (P = 0.000), infectious disease (P = 0.196), osteoarthritis (P = 0.217), cancer (P = 0.078), liver dysfunction (P = 0.217), LOS (P = 0.152), and the number of medications (P = 0.206); (4) factors affecting PPO were hyperlipidemia (P = 0.074), respiratory disorders (P = 0.137), and infectious disease (P = 0.086), presented in Table 4. Variables with a P value ≤ 0.25 were further analyzed using the Multivariable Binary Logistic Regression and data were presented as odds ratios (ORs) and CI 95% with a P value of < 0.05 as significantly different in Table 5; and (5) a significant correlation between comorbidity and the incidence of PIM, in particular, kidney dysfunction was the main factor affecting PIM.

Studies of PIP in Indonesia are very limited. In fact, we found less than ten studies on PIM in Indonesia. To the best our knowledge, this is the first study conducted in Indonesia among geriatric patients with cardiovascular disorders at RSUP dr. Hasan Sadikin Bandung that identify comprehensively both PIM and PPO using the STOPP/START criteria version 2. Most patients found in this study were in the 65-74 year age group (79.2%). This research only included patients with cardiovascular disorders. More than a quarter of STOPP criteria are related to the cardiovascular system, possibly increasing the probability of identifying a greater number of cases satisfying the STOPP criteria. A total of 89 instances of PIM were identified and the three most frequent PIM were NSAIDs to patients with an eGFR <50 ml/minute/1.73 m² (36.0%), other NSAIDs were combined with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis (25,8%), and aspirin plus clopidogrel were prescribed to prevent the occurrence of secondary stroke (6,9%). These PIMs are related the renal system, the cardiovascular system, and antiplatelet/ anticoagulant drugs, respectively.

The three most common PPO were related to the cardiovascular system: ACEi in patients with chronic heart failure (38; 41,8%), beta-blockers for ischemic heart disease (22; 24,1%), and statin for coronary/cerebral/ peripheral vascular diseases (13; 14,3%). In comparison to our results, the study conducted at the hospital in Lampung, Indonesia, described that the PIM (25.81%) was in the use of statins in older patients with coronary heart disease and cerebral vascular disease. The authors also confirmed that there was a notable correlation between the occurrence of PIM and comorbidities.[12]

The retrospective observational study conducted at primary healthcare facilities in Karawang, Indonesia, reported a high prevalence of PIM (52.2%) in older patients, with the most prescribed PIM were chlorpheniramine, mefenamic acid, ibuprofen, and nifedipine.[15] The other study conducted on 91 older outpatients at a hospital in Jakarta, described the PIM as 1.9% of a total of 560 drugs which were benzodiazepines, anticholinergics, antipsychotics, and glimepiride.[16] The prevalence of PIM at a regional public hospital in Banjarmasin was 63.1%.[17]

Table 1. Characteristic of the geriatric inpatients
at Hasan Sadikin Hospital Bandung

Characteristics	Number (n)	(%)
Age (years old)		
65-74	152	79.2
75-84	37	19.3
≥ 85	3	1.6
Gender		
Male	136	70.8
Female	56	29.2
Comorbidities		
Hypertension	117	61.0
Kidney dysfunction	63	33.0
Diabetes mellitus	52	27.0
Respiratory disorders	36	19.0
Hyperlipidemia	28	15.0
Electrolyte imbalance	28	15.0
Infectious disease	16	8.3
Gastrointestinal disorders	15	8.0
Nervous system disorders	9	5.0
Hematology disorders	7	4.0
Cancer	6	3.0
Osteoarthritis	3	1.6
Liver dysfunction	3	1.6
Number of medications		
≥ 5 medications	180	93.8
< 5 medications	12	6.3
Length of stay		
≥ 5 days	103	53.6
< 5 days	89	46.4

Table 2. Geriatric inpatients at Hasan Sadikin Hospital
Bandung that were categorized by STOPP/START

Number of criteria per patient	STOPP		START	
	Number (n)	%	Number (n)	%
1	47	24.5	51	26.6
2	9	4.7	17	8.9
3	8	4.2	2	1.0
Total	64	33.4	70	36.5

STOPP (screening tool for older people's prescriptions); START (screening tool to alert doctors to the right treatment)

A cross-sectional study using the medical records of geriatric patients at the tertiary hospitals in Chengdu, China, from 2016-2018 reported an increase in the incidence of PIM from 71.17% in 2016 to 73.39% in 2018. The common prescribed PIMs in inpatients were diuretics, benzodiazepines, NSAIDs, antipsychotics, and selective serotonin reuptake inhibitors.[18] Another high incidence of PIP was also reported in Korea. According to the STOPP criteria, most potential inappropriate prescribing was of cardiovascular medications (37,9%) and based on START criteria, the CVDs drugs also comprised most of the PPO (37%).[19] Similarly with our study, the most prescribed PIM and PPO were NSAID and cardiovascular medication. A cross-sectional study conducted at the university hospital in Sao Paulo, Brazil, announced that PIMs were received by 32 (13,9%) of 230 patients and PPOs were received by 90 (39,1%) patients. The most common PPOs were the absence of ACEi in patients with chronic heart failure (13%).[20]

Another study in Ethiopian geriatrics patients hospitalized with cardiovascular disorders also reported underuse of ACEi among hospitalized chronic heart failure (14,5%).[21] These study similar with our study showed a higher prevalence of this PPO (41,8%) because the physicians, depending on the patient's prognosis, did not consider the prescription of ACEi to be appropriate.

In the present study, almost all patients (91,6%) had comorbidities. Hypertension (61%), kidney dysfunction (33%), and diabetes mellitus (27%) were the three most frequent disease identified. In this study, kidney dysfunction diagnose was independently associated with PIM and those patients diagnosed with that comorbidity had a 4,95-fold increased risk of taking PIM than their counterparts. Most of patients received more than 5 medications in this study but failed to achieve statistical significance. In fact, concurrent use of 5 or more medicines is reported as a risk factor for a significant increase in PIM prescription.[22] Age, gender, and length of stay were not correlated with both PIM and PPO even in the binary regression analysis in our study. This could be attributed to the small sample size employed in the present study.

Our study demonstrated that the most prescribed PIMs were NSAIDs to patients with an eGFR <50 ml/minute/1.73 m^2 (36.0%). NSAIDs work by reversibly blocking the activity of both isoforms of cyclooxygenases, thus altering the production of prostaglandins in numerous tissues. NSAIDs were reported for their adverse effects on the kidney, gastrointestinal tract, and cardiovascular system. Numerous studies confirmed that NSAIDs have been linked with an elevated risk of acute kidney injury.[23]

Table 3. The occurrence of PIP in geriatric inpatients at Hasan Sadikin Hospital Bandung based on the STOPP/START criteria

PIP incidence	Number (n)	%
PIM	**89**	**49.4**
Digoxin was prescribed to a patient suffering heart failure with a normal function of the systolic ventricle	1	1.1
Loop diuretic was used to treat swollen ankles without clinical/biochemical/radiological evidence of heart failure, liver failure, kidney failure, or nephrotic syndrome	1	1.1
Loop diuretic was prescribed as the first-line medication for hypertensive patients	5	5.6
Thiazide diuretics were prescribed to a patient with hypokalemia (serum K^+ < 3.0 mmol/l), hyponatremia (serum Na^+ < 130 mmol/l), hypercalcemia (corrected serum Ca^{2+} > 2.65 mmol/l)	1	1.1
Aldosterone antagonists (such as spironolactone and eplerenone) were combined with ACEi, ARB, amiloride, or triamterene, without monitoring the levels of serum potassium	1	1.1
ACEi or ARB were prescribed to patients with hyperkalemia.	3	3.4
Beta-blockers were prescribed to patients with bradycardia (< 50 beats/minute), heart block type II, or complete heart block	3	3.4
Aspirin was prescribed in combination with vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors in patients with chronic atrium fibrillation	4	4.5
Aspirin plus clopidogrel were prescribed to prevent the occurrence of secondary stroke	15	6.9
Other NSAIDs were combined with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis	23	25.8
NSAIDs were prescribed to patients with an eGFR <50 ml/minute/1.73 m^2	32	36.0
PPO	**91**	**50.6**
Vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors were prescribed to patients with chronic atrium fibrillation	2	2.2
Antiplatelets (aspirin or clopidogrel or prasugrel or ticagrelor) were prescribed to patients with coronary/cerebral/peripheral vascular diseases	6	6.6
Antihypertensive medications were prescribed to patients with persistent SBP >160 mmHg and/or DBP >90 mmHg; or to diabetic patients with SBP >140 mmHg and/or DBP > 90 mmHg	4	4.4
Statins were prescribed to patients with coronary/cerebral/peripheral vascular diseases except for patients > 85 years old	13	14.3
ACEi was prescribed to patients with systolic heart failure and/or coronary arterial disorders	38	41.8
Beta-blockers for ischemic heart disease	22	24.1
Beta-blockers for persistent systolic heart failure	4	4.4
L-DOPA or dopamine agonists for patients with idiopathic Parkinson's disease	2	2.2
Total PIP	**180**	**100**

ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; DBP: diastolic blood pressure; L-DOPA: L-dihydroxyphenylalanine or levodopa; NSAIDs: non-steroid anti-inflammatory drugs; PIM: potentially inappropriate medicines; PIP: potentially inappropriate prescription; PPO: potentially prescription omission; SBP: systolic blood pressure;

Table 4. Statistical Analysis of the Variables Affecting PIM and PPO Occurrence in Geriatric Inpatients with Cardiovascular Disorders

Variable	PIM (N = 64)	Not PIM (N = 128)	P-Value	PPO (N = 70)	Not PPO (N = 122)	P-Value
Age (years old)						
65-74	49	103	0.811	58	94	0.338
75-84	14	23		12	25	
≥ 85	1	2		0	3	
Gender						
Male	17	39	0.575	21	35	0.847
Female	47	89		49	87	
Comorbidities						
Hypertension	43	74	0.209*	40	77	0.414
Diabetes mellitus	24	28	0.022*	22	30	0.305
Hyperlipidemia	7	21	0.311	6	22	0.074*
Respiratory disorders	11	25	0.695	17	19	0.137*
Kidney dysfunction	36	27	0.000*	26	37	0.333
Gastrointestinal disorders	4	11	0.568	5	10	0.793
Infectious disease	3	13	0.196*	9	7	0.086*
Hematology disorders	2	5	0.785	3	4	0.720
Osteoarthritis	2	1	0.217*	1	2	0.910
Cancer	0	6	0.078*	1	5	0.306
Nervous system disorders	3	6	1.000	2	7	0.363
Electrolyte imbalance	11	17	0.470	11	17	0.737
Liver dysfunction	0	3	0.217*	1	2	0.910
Length of stay						
≥ 5 days	39	64	0.152	66	114	0.300
< 5 days	25	64		4	8	
Number of medications						
≥ 5 medications	62	118	0.206*	41	62	0.816
< 5 medications	2	10		29	60	

* indicates the variable may affect PIM or PPO (P < 0.25); PIM: potentially inappropriate medicines; PPO: potentially prescription omission

Table 5. The Multivariable Binary Logistic Regression of Factors Affecting PIM Occurrence in Geriatric Inpatients with Cardiovascular Disorders

Variable	P value	OR	CI 95%
Comorbidities			
Hypertension	0.266	1.50	0.735-3.062
Diabetes mellitus	0.118	1.81	0.861-3.797
Kidney dysfunction	0.000*	4.95	2.367-10.342*
Infectious disease	0.128	0.34	0.083-1.368
Osteoarthritis	0.211	5.18	0.394-67.993
Cancer	0.999	N/A	N/A
Number of medications	0.166	3.26	0.613-17.298

International consensus guidelines recommend circumventing NSAIDs in patients with an eGFR value of less than 30 ml/minute/1.73 m². [24] A cohort study on 187 patients in Sweden, of whom 105 were using NSAIDs and 82 bought NSAIDs over the counter, described that 42% of those purchasing NSAIDs over the counter revealed an eGFR < 60 ml/minute/1.73 m². The study suggested that geriatrics were oblivious to the risks associated with NSAIDs, which include the risk of kidney injury. [25]

A cross-sectional study on adult patients with chronic kidney damage at the Main Alexandria University Hospital in Egypt concluded that drugs, e.g., diuretics or renin-angiotensin-aldosterone system inhibitors, that may demonstrate drug-drug interaction with NSAIDs, was reported in 36%. NSAIDs were suggested to be used with caution among chronic kidney damage patients. [26]

Another observed PIM was a combination of NSAIDs with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis, which was recorded at 25.8%. A combination of aspirin with clopidogrel (6.9%) was found in prescription to prevent the occurrence of secondary stroke.

The combination of NSAIDs with an antithrombotic given to elderly patients could escalate the risk for adverse events, such as concurrent bleeding. As reported in a retrospective cross-sectional, single-center study on 156 geriatric hospitalized patients at the Gondar University Hospital, Ethiopia, an inappropriate prescribing of antithrombotic therapy was observed. [27] It was clearly understood that there are numerous physiological changes and a continuous decline of organ function in elderly patients, e.g., a decrease in muscle mass and total water, in accordance with an increase in fat ratio, which may lead to the pharmacokinetics of drugs. A diminishing of the liver and kidney function may cause a slower metabolism and excretion process of drugs, thus, elevating the occurrence of toxicity. [28-30]

Conclusion

Our observational cross-sectional retrospective study conducted at the Geriatric Ward, Hasan Sadikin Hospital in Bandung, West Java, Indonesia, by employing STOPP/START criteria, confirmed that the incidence of potentially PIP in geriatric inpatients was high. The most prescribed PIMs were non-steroid anti-inflammatory drugs (NSAIDs) to patients with an eGFR <50 ml/minute/1.73 m², followed by the combination of NSAIDs with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis. There is a significant correlation between comorbidity and the incidence of PIM.

These findings suggest the importance of evaluating the prescriptions for geriatric patients during hospitalization to reduce the incidence of potentially inappropriate prescriptions. This research require future studies whether STOPP/START criteria application improved health outcomes and decrased cost.

Conflict of Interest

None declare

References

1. United Nations Department of Economic and Social Affairs, Population Division (2020). *World Population Ageing 2020 Highlights: Living arrangements of older persons* (ST/ESA/SER.A/451).

2. Statistics Indonesia Statistics of Aging Population. 2020. Available online: *https://www.bps.go.id/publication/2020/12/21/0fc023221965624a644c1111/statistik-penduduk-lanjut-usia-2020.html* (accessed on 09 September 2023)

3. Statistics Indonesia. Statistics of Aging Population 2021. Available at *https://www.bps.go.id/publication/2021/12/21/c3fd9f27372f6ddcf7462006/statistik-penduduk-lanjut-usia-2021.html* [accessed on September 2023].

4. MacMahon, S.; Calverley, P.; Chaturvedi, N.; Chen, Z.; Corner, L.; Davies, M.; Ezzati, M.; Guthrie, B.; Hanson, K.; Jha, V.; et al. *Multimorbidity: a priority for global health research*. The academy of medical researcher. 2018.

5. Salive, M.E. Multimorbidity in Older Adults. *Epidemiological Reviews*. 2013; 35:75-83. https://doi.org/10.1093/epirev/mxs009

6. Rochon, P. A.; Petrovic, M.; Cherubini, A.; Onder, G.; O'Mahony, D.; Sternberg, S.A.; Stall, N.M.; Gurwitz, J.H. Polypharmacy, inappropriate prescribing, and deprescribing in older people: through a sex and gender lens. *The Lancet Healthy Longevity*. 2021;2(5):e290–e300. https://doi.org/10/1016/S2666-7568(21)00054-4

7. Lavan, A.H.; Gallagher, P.F.; O'Mahony, D. Methods to reduce prescribing errors in elderly patients with multimorbidity. *Clinical Interventions in Aging*. 2016; 11:857–866. https://doi.org/10.2147/CIA.S80280

8. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. Gallagher. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age and Ageing*. 2015; 44(2):213-218. https://doi.org/10.1093/ageing/afu145

9. Manias, E.; Kusljic, S.; Lam, D.L. Use of the Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert doctors to the Right Treatment (START) in hospitalised older people. A*ustralian Journal on Ageing*. 2015; 34(4):252-258. https://doi.org/10.1111/ajag.12186

10. Manias, E.; Maier, A.; Krishnamurthy, G. Inappropriate medication use in hospitalised oldest old patients across transitions of care. *Aging Clinical and Experimental Research*. 2019; 31(11):1661–1673. https://doi.org/10.1007/s40520-018-01114-1

11. Mekonnen, A.; Redley, B.; Crawford, K.; Jones, S.; de Courten, B.; Manias, E. Associations between hyper-polypharmacy and potentially inappropriate prescribing with clinical and functional outcomes in older adults. *Expert Opinion on Drug Safety*. 2022; 21(7):985-994. http://doi.org/10.1080/14740338.2022.2044786

12. Julaiha, S.; Riyanto, R.; Pardilawati, C.Y. Factors related to the occurrence of potentially inappropriate medication (PIM) based on the STOPP/START criteria in geriatric patients with cardiovascular diseases. *Jurnal Kesehatan*. 2021;14(2):156-167. https://doi.org/10.26630/jkm.v14i2.3011

13. Fauziyah, S.; Andrajati, R.; Sartika, R.A.D.; Radji, M. Adaptation and validation of the Screening Tool of Older People's Prescriptions instrument for the Indonesian population. Journal of Research in Pharmacy Practice. *Journal of Research in Pharmacy*

Practice. 2020;9(1):24-29. https://doi.org/10.4103/jrpp.JRPP_19_106

14. Herawati, F.; Maharjana, I.B.N.; Kuswardhani, T.; Susilo, A.P. STOPP-START medication review: A non-rando randomized trial in an Indonesian tertiary hospital to improve medication appropriateness and to reduce the length of stay of older adults. *Hospital Pharmacy*. 2021;56(6):668-677. https://doi.org/10.1177/0018578720942227

15. Abdulah, R.; Insani, W.N.; Destiani, D.P.; Rohmaniasari, N.; Mohenathas, N.D.; Barliana, M.I. Polypharmacy leads to increased prevalence of potentially inappropriate medication in the Indonesian geriatric population visiting primary care facilities. *Therapeutics and Clinical Risk Management*. 2018;14:1591-1597. https://doi.org/10.2147%2FTCRM.S170475

16. Rusdi, N.; Komariah, D.; Wulandari, N. and Roosheroe, A. *Identification of Potentially Inappropriate Prescribing in Outpatient Geriatric using STOPP/START Criteria at X Hospital Jakarta*. Proceedings of the 1st Muhammadiyah International Conference on Health and Pharmaceutical Development; 2018 Agustus 11; Jakarta: Universitas Prof. Dr. Hamka; 2018.

17. Wulansari, A.; Wiedyaningsih, C.; Probosuseno. Potentially Inappropriate Medication (PIM) in Geriatric Hospitalized Patients at Dr. H. Moch. Ansari Saleh Regional Public Hospital Banjarmasin. *Majalah Farmasi*. 2023;19(1):91-98. https://doi.org/10.22146/farmaseutik.v19i1.70420

18. Tian, F.; Liao, S.; Chen, Z.; Xu, T. The prevalence and risk factors of potentially inappropriate medication use in older Chinese inpatients with multimorbidity and polypharmacy: a cross-sectional study. *Annals of translational medicine*. 2021;9(18):1483. https://doi.org/10.21037/atm-21-4238

19. Lee, S. J., Cho, S. W., Lee, Y. J., Choi, J. H., Ga, H., Kim, Y. H., Woo, S. Y., jung, W. S., & Han, D. Y. Survey of Potentially Inappropriate Prescription Using STOPP/START Criteria in Inha University Hospital. *Korean Journal of Survey of Family Medicine*. 2013;34(5):319-326. https://doi.org/10.4082/kjfm.2013.34.5.319

20. Mori AL, Carvalho RC, Aguiar PM, et al. Potentially inappropriate prescribing and associated factors in elderly patients at hospital discharge in Brazil: a cross-sectional study. International *Journal of Clinical Pharmacy*. 2017;39(2):386-393. https://doi.org/10.1007/s11096-017-0433-7

21. Abegaz TM, Birru EM, Mekonnen GB. Potentially inappropriate prescribing in Ethiopian geriatrics hospitalized with cardiovascular disorders using STOPP/START criteria. *PloS One*. 2018; 13(5):e0195949. https://doi.org/10.1371/journal.pone.0195949

22. Teka F, teklay G, Ayalew E, Kassa TT. Prevalence of potentially inappropriate medications in Ayder referral hospital, Tigray region, Northen Ethiopia: prospective study. *Journal of Drug Delivery and Therapeutics*. 2016;6(6):16-21. https://doi.org/10.22270/jddt.v6i6.1238

23. Guthrie, B. Can NSAIDs be used safely for analgesia in patients with CKD? *Kidney*. 360. 2020;1(11): 1189-1191. https://doi.org/10.34067%2FKID.0005112020

24. KDIGO 2012. Kidney Disease: Improving Global Outcomes (KDIGO). clinical practice guideline for the evaluation and management of chronic kidney disease. Available at: *https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf* [accessed on September 2023].

25. Modig, S.; Elmståhl, S. Kidney function and use of nonsteroidal anti-inflammatory drugs among elderly people: a cross-sectional study on potential hazards

for an at-risk population. Internatiional *Journal of Clinical Pharmacy*. 2018;40(4):870-877. https://doi.org/10.1007%2Fs11096-018-0598-8

26. Abd ElHafeez, S.; Hegazy, R.; Naga, Y. Wahdan, I.; Sallam, S. Non-steroidal anti-inflammatory drugs among chronic kidney disease patients: an epidemiological study. *The Journal of The Egyptian Public Health Association*. 2019;94(1):8. https://doi.org/10.1186/s42506-018-0005-2

27. Getachew, H.; Bhagavathula, A.S.; Abebe, T.B.; Belachew, S.A. Inappropriate prescribing of antithrombotic therapy in Ethiopian elderly population using updated 2015 STOPP/START criteria: a cross-sectional study. *Clinical Intervention in Aging.* 2016; 11: 819–827. https://doi.org/10.2147/CIA.S107394

28. Young, F.; Maguire, S. Physiology of ageing. Anaesthesia. *Intensive Care Medicine*. 2019;20(12):735-738. https://doi.org/10.1016/j.mpaic.2019.10.006

29. Sipos, M.; Farcas, A.; Leucuta, D.C.; Bulik, N.B.; Huruba, M.; Dumitrascu, D.; Mogosan, C. Prevalence and Risk Factors Associated with Potentially Inappropriate Prescribing According to STOPP-2 Criteria among Discharged Older Patients-An Observational Retrospective Study. *Pharmaceuticals*, 2023;16(6):852. https://doi.org/10.3390/ph16060852

30. Thürmann P.A. Pharmacodynamics and pharmacokinetics in older adults. *Current Opinion in Anaesthesiology*. 2020;33(1):109-113. https://doi.org/10.1097/aco.0000000000000814