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Efficacy of pharmacists' assessment and intervention based on Screening Tool for Older Persons' Appropriate Prescriptions for Japanese compared with STOPP criteria version 2 in elderly patients with cardiovascular disease

Short running title: Pharmacists' intervention using STOPP-J

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Abstract

Aim:

This study aimed to evaluate the efficacy of pharmacists' assessment and intervention using the Screening Tool for Older Persons' Appropriate Prescriptions for Japanese (STOPP-J) to detect and correct potentially inappropriate medications (PIMs) compared with the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria version 2.

Methods:

A prospective observational study was conducted at a medical unit of Cardiovascular Surgery and Cardiovascular Internal Medicine in Japanese University Hospital involving new inpatients aged ≥ 65 years prescribed ≥ 1 daily medication. Pharmacists detected PIMs based on STOPP-J and STOPP criteria version 2, and corrected them with physicians. The number of patients with PIMs, content and changes in PIMs were compared between both criteria.

Results:

Overall, 230 patients were included (mean age, 75.4 years; 162 males; mean number of medications, 8.3). STOPP-J detected significantly more patients with PIMs than STOPP criteria version 2 [122 (53%) vs. 75 (33%), $p < 0.001$]. The number of PIMs based on STOPP-J was 232, 61 (26%) of which were recommended the physicians to change and 50 (22%) were changed. Meanwhile, the number of PIMs based on STOPP criteria version 2 was 133, 61 (46%) of which were recommended the physicians to change and 54 (41%) were changed. Several medications detected as PIMs using STOPP-J were not detected using STOPP criteria version 2.

Conclusions:

STOPP-J detected significantly more patients with PIMs than STOPP criteria version 2, and pharmacists' assessment and intervention based on STOPP-J were suggested to be effective for detecting and correcting PIMs.

Keywords:

Elderly, Polypharmacy, Potentially inappropriate medications, STOPP criteria version 2, STOPP-J

Introduction

Potentially inappropriate medications (PIMs) comprise prescriptions that include an incorrect dose, frequency and modality of administration, or duration of treatment; are likely to result in clinically significant drug–drug or drug–disease interactions; or have no clear evidence-based clinical indication.[1] The elderly often have multimorbidity and, consequently, are in a state of polypharmacy. Age-related physiological changes in the elderly can lead to changes in the pharmacokinetic and pharmacodynamic properties of medications, resulting in adverse drug reactions.[2] PIMs and polypharmacy in the elderly are a major concern because they are associated with an increase in adverse drug reactions, hospitalizations, healthcare resource utilization, healthcare costs, and mortality.[3-8]

PIMs have been often prescribed in the Japanese elderly and become problems needed to be resolved. A nationwide survey conducted in Japan has reported that 48.4% of study patients were prescribed PIMs based on the 2003 Beers Criteria Japan.[9] To enhance the safety of geriatric pharmacotherapy in Japan, the Japan Geriatrics Society has published the “Guidelines for medical treatment and its safety in the elderly 2005”.[10] The guidelines were completely revised in 2016 based on a systematic review and were renamed the “Screening Tool for Older Persons’ Appropriate Prescriptions for Japanese (STOPP-J)”.[11] STOPP-J includes two lists: “List of drugs to be prescribed with special caution” and “List of drugs to consider starting.” “List of drugs to be prescribed with special caution” shows the drug classes that are likely to cause serious adverse effects in elderly patients along with their indications and recommended usage.[11] “List of drugs to

consider starting" shows potential prescribing omissions (PPOs), and include the drugs that were appeared not to be used much in medical practice, although they were highly beneficial for the elderly.[11] Additionally, STOPP-J provides flowcharts to be followed when changing PIMs.[11] The revised guidelines are expected to reduce the use of PIMs, adverse drug reactions, and negative drug interactions when applied to prescriptions for the elderly, but they have not been sufficiently verified in clinical practice.

Several explicit criteria for screening PIMs have been developed and applied to healthcare settings: The Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP)/Screening Tool to Alert doctors to Right Treatment (START) criteria,[12] the Beers criteria,[13] and the European Union (EU) (7)-PIM list.[14] In particular, a systematic review provided evidence that the use of STOPP/START criteria reduced falls, delirium episodes, hospital stay length, care visits, and medication costs, and overall PIM rates.[15] We had previously reported the prevalence of PIMs in the Japanese elderly and the efficacy of pharmacists' assessment and intervention based on STOPP criteria version 2.[16] However, to the best of our knowledge, there have been no study compared the efficacy of STOPP-J with STOPP criteria version 2 in clinical settings.

This study aimed to evaluate the efficacy of pharmacists' assessment and intervention based on STOPP-J for detecting and correcting PIMs compared with STOPP criteria version 2 in Japanese clinical settings.

Methods

Study design and settings

A prospective observational study was conducted from April to September 2016 on new inpatients at a medical unit of Kobe University Hospital, Japan. The main departments in this unit were Cardiovascular Surgery and Cardiovascular Internal Medicine. The study protocol was approved by the Ethical Committee of Kobe University Hospital (No. 1758).

Pharmacists' assessment and intervention based on STOPP-J and STOPP criteria version 2

The pharmacists' method of detecting and correcting PIMs followed our previously reported method,[16] although identification of PIMs was based on "List of drugs to be prescribed with special caution" in STOPP-J[11] and STOPP criteria version 2.[12] We did not verify PPOs as in the "List of drugs to consider starting" in STOPP-J[11] or START criteria.[12] Three clinical pharmacists were trained to detect and correct PIMs based on these criteria before they participated in the study. One or two of these pharmacists worked daily on weekdays in the subject unit of this study. These pharmacists carefully conducted medication reconciliation, confirmed medical history and laboratory data, and detected PIMs at the time of patient admission. They also considered each patient's intent to change prescriptions and did not recommended a physician to discontinue/change prescriptions without patient's consent. PIMs based on STOPP-J were examined for dose reduction, discontinuation, and switch to alternatives according to the flowchart in STOPP-J.[11] PIMs based

on STOPP criteria version 2 were evaluated for the benefits and risks of discontinuing/changing the medications. If the pharmacists assessed that the benefit of discontinuing/changing the medications outweighed the risks, they recommended a physician to discontinue/change those medications. If there was a risk of withdrawal symptoms or exacerbation of disease by changing the medications and the pharmacists determined it would be difficult to modify the medications during hospitalization, they did not recommend a physician to discontinue/change those medications. The pharmacists and the physicians discussed and finally decided whether to change the PIMs.

Sample size and study subjects

There were no studies to evaluate a prevalence of PIMs based on STOPP-J before starting our study. The proportion of patients with PIMs was 42.1% in our previous study using STOPP criteria version 2,[16] meanwhile 48.4% in Japanese nationwide survey using the 2003 Beers Criteria Japan.[9] Based on these data, assuming that the proportion of patients with PIMs was 40-50% when using STOPP-J, a minimum sample size of 171 was calculated for detecting with 95% confidence interval width and 15% accuracy. This was a descriptive study conducted for a fixed period, and we assumed that 200-250 samples were included during the study period.

Newly admitted patients aged ≥ 65 years who were prescribed at least one daily medication were included in this study. The main subjects of STOPP-J were individuals aged ≥ 75 years and elderly individuals who were not yet 75 years old but who were frail or in need of special care.[11] Because

the targeted subjects of this study were hospitalized patients, and the subjects of STOPP criteria version 2 were individuals aged ≥ 65 years,[12] the targeted age of the subjects in this study was integrated to be ≥ 65 years. PIMs were categorized by pharmacological classes, but those meeting the criterion "Any duplicate drug class prescription" in STOPP criteria version 2 were excluded in order to evaluate the drug classes detected as PIMs. Patient characteristics (age, sex, number of medications, and length of hospitalization), the number of patients with PIMs, PIMs categorized by pharmacological class, and PIMs changed within 14 days after the pharmacists' intervention were compared between patients detected by STOPP-J and STOPP criteria version 2.

Statistical analysis

The statistical significance of the difference in mean values between the two groups was analyzed by Student's t-test if the variances of the two groups were similar. The chi-square test was used for comparison of the proportions of categorical variables between the groups. *P* values < 0.05 were considered to indicate a statistical significance. All statistical analyses were performed using GraphPad Prism 6 (La Jolla, CA, USA).

Results

Patient characteristics

The characteristics of the study population are shown in Table 1. Overall, 230 patients (Cardiovascular Surgery department, n = 201; Cardiovascular Internal Medicine department, n =

29) were included [mean age, 75.4 years; 162 (70%) males; mean number of medications, 8.3; mean length of hospitalization, 16.5 days]. The number of patients prescribed at least one PIM based on each criteria was 122 (53%) for STOPP-J and 75 (33%) for STOPP criteria version 2, and STOPP-J detected significantly more patients with PIMs than STOPP criteria version 2 ($p < 0.001$). There were no significant differences in age, number of medications, and length of hospitalization between patients with PIMs detected by STOPP-J and those with PIMs detected by STOPP criteria version 2.

The prevalence of PIMs based on STOPP-J and STOPP criteria version 2 in the study population are shown in Figure 1. The number of patients with PIMs detected by STOPP-J only was 53 (23%), that detected by STOPP criteria version 2 only was 6 (3%), that detected by both criteria was 69 (30%) and patients without PIMs was 102 (44%).

PIMs detected by STOPP-J and STOPP criteria version 2

The total number of PIMs categorized by pharmacological classes was 234 based on STOPP-J and 104 based on STOPP criteria version 2 (Figure 2). PIMs related to benzodiazepines (including Z-drugs) were most frequent in both criteria; 68 detected by STOPP-J and 66 detected by STOPP criteria version 2. The detected number of PIMs related to non-steroidal anti-inflammatory drugs (NSAIDs) and sulphonylureas was comparable for both criteria. PIMs detected by STOPP-J, but less or not detected by STOPP criteria version 2, were loop diuretics, H2 receptor antagonists, antithrombotic drugs (antiplatelet drugs and anticoagulants), aldosterone antagonists, laxatives

magnesium oxide, α1-receptor blockers, α-glucosidase inhibitors, biguanides, and antimuscarinics/anticholinergics. PIMs detected by STOPP criteria version 2, but not detected by STOPP-J, were verapamil and β-blockers.

Detailed contents of PIMs and that corrected using STOPP-J and STOPP criteria version 2

Detailed contents of PIMs based on STOPP-J and STOPP criteria version 2 and the number of medications changed after the pharmacists' intervention are shown in Tables 2 and 3, respectively. The total number of PIMs defined according to STOPP-J was 232. Of the 232 PIMs, 61 (26%) were recommended to a physician for change and 50 (22%) were discontinued/changed after the pharmacists' intervention. Meanwhile, the total number of PIMs defined according to STOPP criteria version 2 was 133. Of the 133 PIMs, 61 (46%) were recommended to a physician for change and 54 (41%) were discontinued/changed after the pharmacists' intervention. The proportion that accepted the pharmacists' recommendation was 82% based on STOPP-J, and 89% based on STOPP criteria version 2. The most frequent PIMs were related to benzodiazepines in both criteria. Among PIMs detected by STOPP-J frequently, "combined therapy with multiple antithrombotic drugs," "loop diuretics," "aldosterone antagonists," "α1-receptor blockers nonselective for receptor subtypes," and "H2 receptor antagonists" were less recommended for change by the pharmacists, and the proportion of medications changed was less than 25%.

Discussion

To the best of our knowledge, this is the first report to evaluate the effects of STOPP-J on detecting and correcting PIMs compared with STOPP criteria version 2 in the Japanese elderly. In this study, based on STOPP-J, 53% of the elderly were prescribed at least one PIM, and STOPP-J detected more PIMs and more patients with PIMs than STOPP criteria version 2.

We had previously reported that 42.1% of study patients were prescribed at least one PIM based on STOPP criteria version 2 in the observational study.[16] In addition, a prospective observational study conducted at a Japanese primary care clinic had reported that the prevalence of PIMs based on STOPP criteria version 2 was 32.3% of study patients.[17] Meanwhile, a retrospective cohort study conducted in long-term care facilities had reported that patients with PIMs based on Beers Criteria 2012 comprised 37.5% of study patients.[18] STOPP criteria version 2 has been reported to detect more PIMs than Beers Criteria 2012,[19, 20] the EU (7)-PIM list, and the comprehensive protocol.[21] The proportion of patients with PIMs based on STOPP-J in our study was higher than that based on STOPP criteria version 2 and the results of the other study using STOPP criteria version 2[16, 17] and Beers Criteria 2012.[18] These results suggested the efficacy of STOPP-J for detection of PIMs in the Japanese elderly.

In the present study, PIMs related to benzodiazepines, NSAIDs, and sulphonylureas were frequently detected in STOPP-J and STOPP criteria version 2. Our previous study[16] and another Japanese study using STOPP criteria version 2 had also reported that these medications detected as PIMs frequently.[17] In contrast, several medications were detected as PIMs by using STOPP-J, but

not always detected by using STOPP criteria version 2 in this study. Among these medications, H2 receptor antagonists, laxatives magnesium oxide and α-glucosidase inhibitors were not included in STOPP criteria version 2; thus, the detection of these PIMs by STOPP-J was considered meaningful. Meanwhile, loop diuretics, aldosterone antagonists, antithrombotic drugs, α1-receptor blockers, biguanides, and antimuscarinics/anticholinergics were included in STOPP criteria version 2, but many cases did not entirely match the criteria. Many indications in STOPP-J were applicable to all subjects;[11] thus, a wide range of pharmacological classes of PIMs could be detected. However, its wide applicability in STOPP-J may lead to increase the detection of PIMs that do not need to be changed; therefore the flowcharts in STOPP-J should be used when changing PIMs to avoid changing appropriate medications.

The importance of this study was to evaluate the prevalence and correction of PIMs based on STOPP-J and STOPP criteria version 2. In this study, the number of changes in PIMs was comparable between STOPP-J and STOPP criteria version 2. A recent randomized controlled trial (RCT) for evaluating the effectiveness of pharmacist-led educational intervention reported that 43% of patients in the intervention group no longer used the PIMs after 6 months.[22] In our study, most PIMs not changed were not recommended for correction by the pharmacists according to the flowchart in STOPP-J.[11] The reasons why the pharmacists did not recommend changing these PIMs were as follows: prescribed medications were effective and needed to be continued; adjustment of medications was impossible in a short-term hospitalization; alternatives were not available; and/or lack of patient consent to change the medications. Because our study subjects were patients of

cardiovascular surgery and cardiovascular internal medicine, loop diuretics, aldosterone antagonists, antiplatelet drugs, anticoagulants, and antihypertensive drugs were used properly and needed in most patients. The trained pharmacists evaluated the benefits and risks of discontinuing/changing PIMs based on the patients' comorbidity, laboratory data, combined medication and the treatment schedule after hospitalization in this study. Thus, pharmacists' evaluation to minimize the risk of changing PIMs was suggested to be necessary when correcting them. The proportion that accepted the pharmacists' recommendation was more than 80% in this study. Previous RCTs have reported the proportion that accepted the pharmacists' recommendation based on the STOPP criteria[23] was 91%[24] and 82.4%.[25] STOPP-J presented the "recommended usage" and the flowcharts for changing medications together with lists of PIMs, which were helpful for the pharmacists and physicians. A recent systematic review of validated explicit criteria has also indicated the necessity for information on alternative therapies and special use considerations to help clinicians make decisions about drug prescriptions.[26]

Several limitations of this study should be acknowledged. First, it was an observational study conducted in a single medical unit at a Japanese university hospital. Thus, our results may not be generalizable to other care settings or countries. In particular, the study subjects were patients of cardiovascular surgery and cardiovascular internal medicine; thus, the classes and the changing proportion of detected PIMs may have been affected by the patients' characteristics. Second, the target age of our study patients was ≥ 65 years, even though the main subjects of STOPP-J were individuals aged ≥ 75 years and those aged < 75 years who were frail or in need of special care.[11]

Although the reason for the fixed target age of ≥ 65 years in our study was mentioned in the methods, the results may have been different if the subjects were aged ≥ 75 years. Third, we could not verify the clinical outcomes resulting from the correction of PIMs. The meta-analysis of RCTs of medication review in hospitalized patients provided no evidence that medication review reduces mortality or hospital readmissions.[27] In contrast, a recent RCT has reported that a multifaceted pharmacist intervention may reduce the number of emergency department visits and hospital readmissions.[28] This RCT suggested the importance of post-discharge follow-up for hospitalized patients.[28] To improve the clinical outcome of correcting PIMs, post-discharge follow-up and the collaboration with community healthcare systems will be required. Fourth, we could not verify PPOs as in the "List of drugs to consider starting" in STOPP-J[11] or START criteria.[12] The prevalence of PPOs and its impact on clinical outcome should also be examined in a future study in Japan.

In conclusion, the present study reported the efficacy of pharmacists' assessment and intervention based on STOPP-J for detecting and correcting PIMs in Japanese elderly patients with cardiovascular disease. STOPP-J detected significantly more patients with PIMs than STOPP criteria version 2, although the number of changes in PIMs was comparable for both criteria. Pharmacists' intervention using the "List of drugs to be prescribed with special caution" and the flowcharts in STOPP-J could correct PIMs. Further research is needed to verify the change in clinical outcome by correcting PIMs using STOPP-J.

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Disclosure statement

The authors declare no conflict of interest.

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Figure legends

Figure 1 The prevalence of PIMs based on STOPP-J and STOPP criteria version 2 in the study population

Figure 2 Pharmacological classes of PIMs detected by STOPP-J and STOPP criteria version 2

Each bar shows the number of PIMs detected by STOPP-J or STOPP criteria version 2 in each pharmacological class. PIMs corresponded to criterion of which “Any duplicate drug class prescription” in STOPP criteria version 2 were excluded.

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs.

Table 1. Characteristics of study population

		All patients	Patients with PIMs detected by STOPP-J	Patients with PIMs detected by STOPP criteria version 2	*p* value
Total	n (%)	230	122 (53)	75 (33)	$p<0.001$
Male	n (%)	162	88 (54)	57 (35)	
Age, years	Mean ± SD	75.4 ± 6.1	75.8 ± 6.1	76.0 ± 6.0	$p=0.82$
Number of medications	Mean ± SD	8.3 ± 4.2	9.8 ± 4.1	10.8 ± 4.1	$p=0.10$
Length of hospitalization, days	Mean ± SD	16.5 ± 15.3	16.5 ± 15.8	15.7 ± 16.8	$p=0.71$
Departments					
Cardiovascular Surgery	n (%)	201	103 (51)	63 (31)	
Cardiovascular Internal Medicine	n (%)	29	19 (66)	12 (41)	

Abbreviations: SD, standard deviation.

Table 2. Number of PIMs detected by STOPP-J and those changed after pharmacists' intervention

Criteria	Indications (left blank if all subjects are applicable)	Total	Recommended (%)	Changed (%)
Total		232	61 (26)	50 (22)
Hypnotics				
Benzodiazepines		56	24 (43)	20 (36)
Non-benzodiazepine hypnotics		12	8 (67)	7 (58)
Antidepressants				
Tricyclic antidepressants		1	0 (0)	0 (0)
Antithrombotic drugs (antiplatelet drugs, anticoagulants)				
Combined therapy with multiple antithrombotic drugs (antiplatelet drugs, anticoagulants)		18	2 (11)	1 (6)
Digitalis				
Digoxin	Dose >0.125 mg/day	2	2 (100)	0 (0)
Diuretics				
Loop diuretics		39	1 (3)	1 (3)
Aldosterone antagonists		18	0 (0)	0 (0)
α-Blockers				
α1-Receptor blockers nonselective for receptor subtypes		10	1 (10)	1 (10)
H2 receptor antagonists				
H2 receptor antagonists		22	4 (18)	4 (18)
Laxatives				
Laxative magnesium oxide	Decreased kidney function	12	9 (75)	7 (58)
Antidiabetic drugs				
Sulphonylureas		9	0 (0)	0 (0)
Biguanides		5	1 (20)	1 (20)
Thiazolidine derivatives		3	0 (0)	0 (0)
α-glucosidase inhibitors		6	0 (0)	0 (0)
Insulin				

Insulin administration on a sliding scale	1	0 (0)	0 (0)
Overactive bladder medications			
Muscarinic receptor antagonists	5	1 (20)	1 (20)
NSAIDs			
NSAIDs	13	8 (62)	7 (54)

Abbreviations: NSAID, non-steroidal anti-inflammatory drug.

List of drugs includes only PIMs detected during the study period.

Table 3. Number of PIMs detected by STOPP criteria version 2 and those changed after pharmacists' intervention

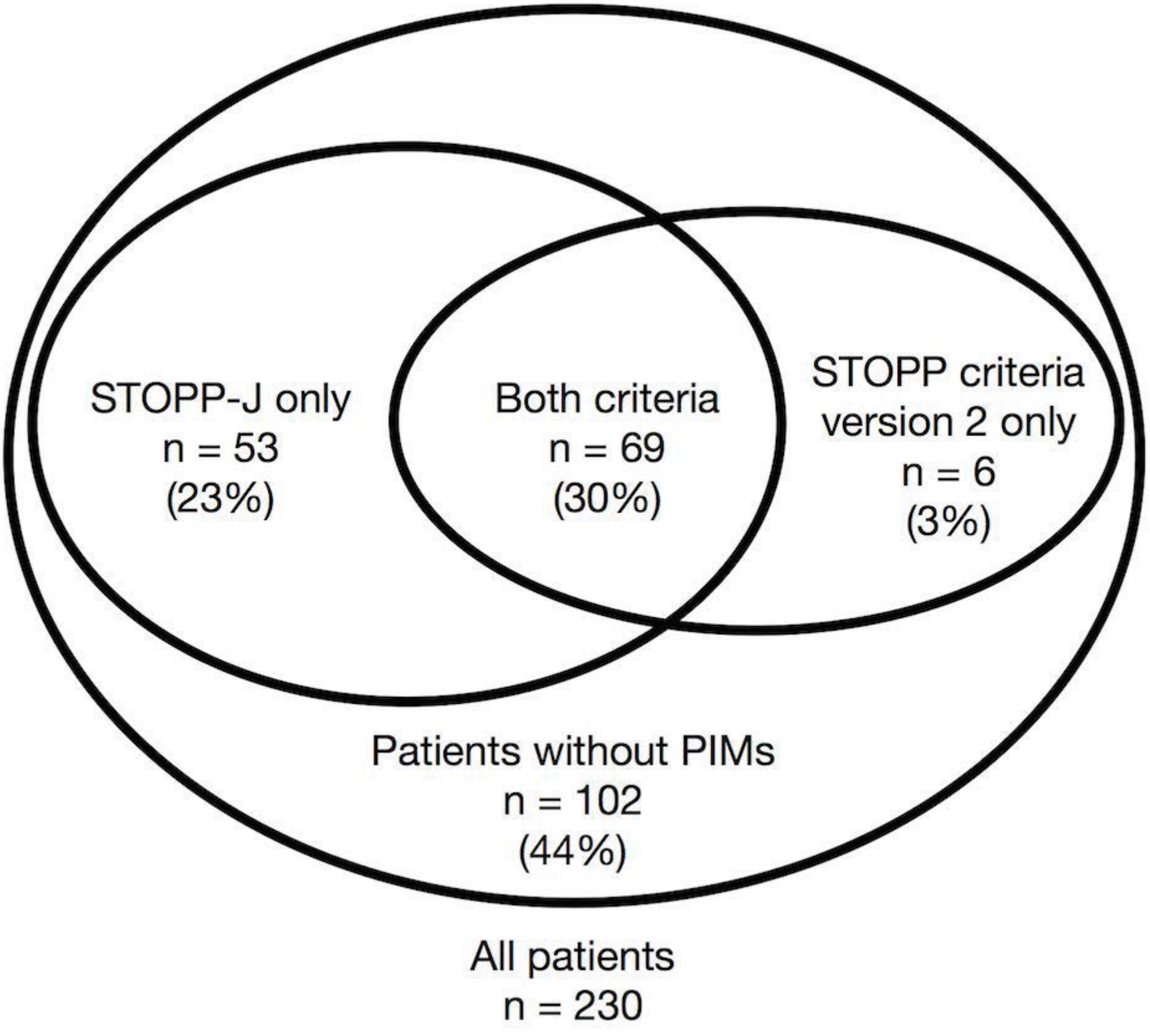
Criteria[a]	Total	Recommended (%)	Changed (%)
Total	133	61 (46)	54 (41)
Drug indication criteria			
Any drug prescribed without an evidence-based clinical indication	2	2 (100)	2 (100)
Any duplicate drug class prescription	20	9 (45)	9 (45)
Cardiovascular system criteria			
β-blocker in combination with verapamil or diltiazem	5	1 (20)	1 (20)
Thiazide diuretic with current significant hypokalemia, hyponatremia, hypercalcemia or with a history of gout	1	0 (0)	0 (0)
ACE inhibitors or angiotensin receptor blockers in patients with hyperkalemia	1	0 (0)	0 (0)
Coagulation system criteria			
Ticlopidine in any circumstances	2	0 (0)	0 (0)
NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	1	0 (0)	0 (0)
Central nervous system criteria			
Benzodiazepines for ≥ 4 weeks[b]	64	29 (45)	25 (39)
Renal system criteria			
NSAIDs if eGFR < 50 mL/min/1.73 m^2	7	6 (86)	5 (71)
Gastrointestinal system criteria			
PPI for uncomplicated peptic ulcer disease or erosive peptic esophagitis at full therapeutic dosage for >8 weeks	1	0 (0)	0 (0)
Musculoskeletal system criteria			
NSAID with established hypertension or heart failure	1	1 (100)	1 (100)
COX-2 selective NSAIDs with concurrent cardiovascular disease	4	4 (100)	4 (100)
Urogenital system criteria			
Selective α-1 blockers in those with symptomatic orthostatic hypotension or micturition syncope	1	1 (100)	1 (100)

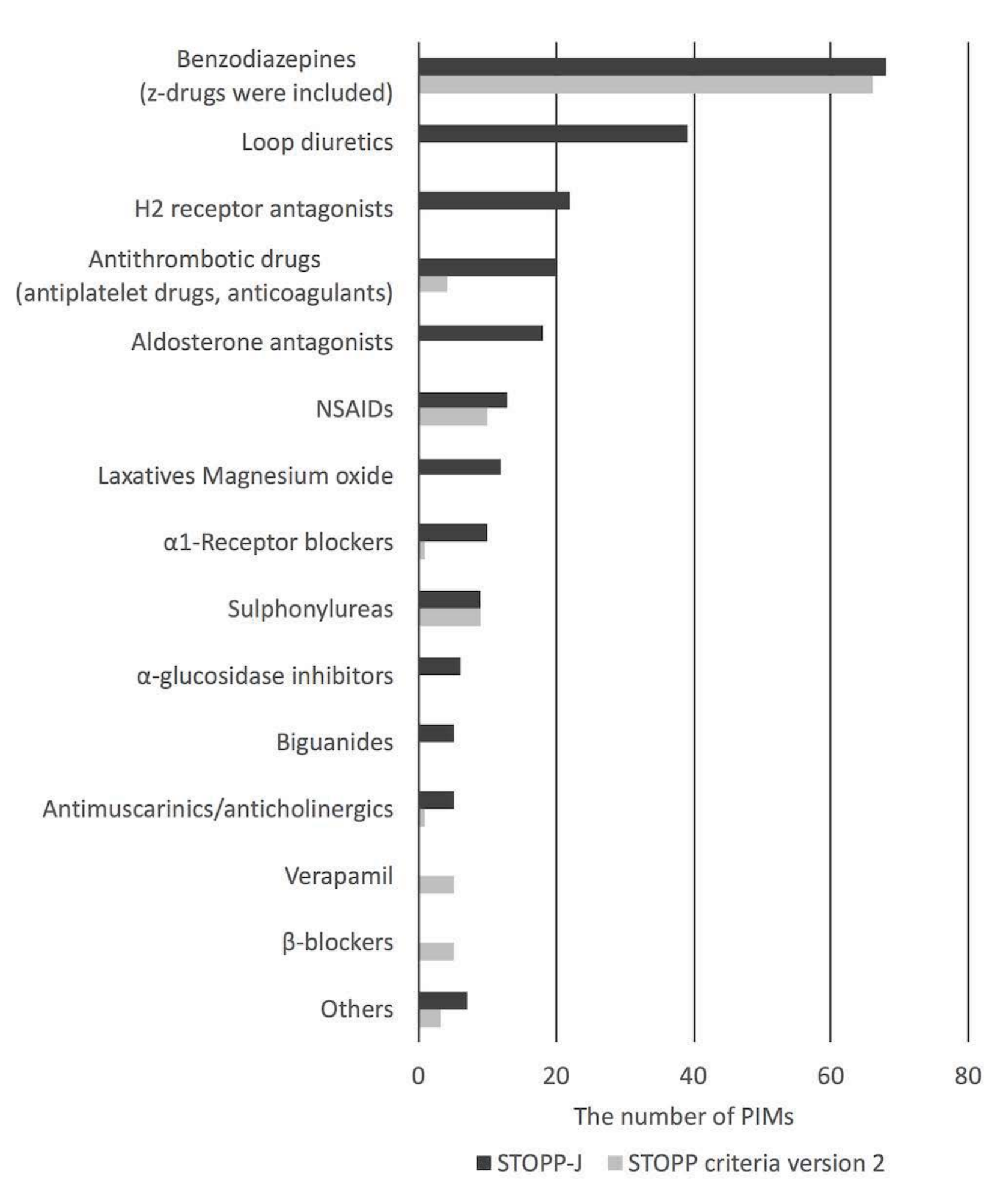
Endocrine system criteria			
Sulphonylureas with a long duration of action with type 2 diabetes mellitus	9	0 (0)	0 (0)
Drugs that predictably increase the risk of falls in older people			
Benzodiazepines	12	8 (67)	6 (50)
Hypnotic Z-drugs	2	0 (0)	0 (0)

Abbreviations: ACE, angiotensin-converting enzyme; PPI, proton-pump inhibitors; NSAID, non-steroidal anti-inflammatory drug; eGFR, estimated glomerular filtration rate; COX-2, cyclooxygenase-2.

[a]Criteria include only PIMs detected during the study period.

[b]The criterion of "Benzodiazepines for ≥4 weeks" included both benzodiazepines and hypnotic Z-drugs.


STOPP-J only
n = 53
(23%)
Both criteria
n = 69
(30%)
STOPP criteria
version 2 only
n = 6
(3%)
Patients without PIMs
n = 102
(44%)
All patients
n = 230


Benzodiazepines
(z-drugs were included)
Loop diuretics
H2 receptor antagonists
Antithrombotic drugs
(antiplatelet drugs, anticoagulants)
Aldosterone antagonists
NSAIDs
Laxatives Magnesium oxide
α1-Receptor blockers
Sulphonylureas
α-glucosidase inhibitors
Biguanides
Antimuscarinics/anticholinergics
Verapamil
β-blockers
Others
0
20
40
60
80
The number of PIMs
STOPP-J
STOPP criteria version 2