Potentially inappropriate prescribing of cardiovascular system and antiplatelet/anticoagulant drugs among elderly patients: a Korean population-based national study

Jongyeon Kim¹, Euna Han², Hee-Jin Hwang³, Hyeonseok Cho², Young-Sang Kim⁴, Hyejin Chun⁴, Jinkwon Kim⁵, Yon Chul Park⁶, Hye-Young Kang²,✉

¹. Department of Pharmaceutical Medicine and Regulatory Sciences, Colleges of Medicine and Pharmacy, Yonsei University, Incheon, South Korea; 2. College of Pharmacy, Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon, South Korea; 3. Department of Family Medicine, Catholic Kwandong University International St. Mary’s Hospital, Incheon, South Korea; 4. Department of Family Medicine, CHA Bundang Medical Center, CHA University, Seongnam, South Korea; 5. Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, South Korea; 6. Department of Family Medicine, Wonju Severance Christian Hospital, Wonju, South Korea

✉ Correspondence to: hykang2@yonsei.ac.kr or hykang0712@gmail.com

https://doi.org/10.11909/j.issn.1671-5411.2021.05.010

ABSTRACT

OBJECTIVES To investigate the prevalence of potentially inappropriate prescribing (PIP) for cardiovascular system (CVS) and antiplatelet/anticoagulant (AP/AC) drugs among Korean elderly patients, using the Screening Tool of Older Persons’ Prescriptions (STOPP) criteria version 2 and to identify the risk factors related to PIP.

METHODS The 2016 National Aged Patient Sample data, comprising National Health Insurance claim records for a random sample of 20% of patients aged ≥ 65 years, were used to calculate PIP prevalence of outpatient prescriptions. For criteria including drug-disease interactions, PIP prevalence per indication was estimated.

RESULTS Among 1,274,148 elderly patients and 27,062,307 outpatient prescription claims, 100,085 patients (7.85%) and 341,664 claims (1.27%) had one or more PIP. The most frequent PIP was “non-steroidal anti-inflammatory drug with concurrent antiplatelet agent (s) without proton-pump inhibitor prophylaxis” in the claim-level (0.97%) and patient-level (6.33%) analyses. “Beta-blocker with bradycardia” (16.47% of claims) and “angiotensin receptor blockers in patients with hyperkalaemia” (23.89% of claims) showed the highest PIP prevalence per indication. Logistic regression analysis revealed that, among the patient and health care provider characteristics, female, older age, more severe comorbidities, polypharmacy, higher level of healthcare organization, and specialty of prescriber were significantly associated with a higher risk of PIP.

CONCLUSIONS Our findings of a high prevalence of PIP for CVS and AP/AC drugs among the elderly suggest that an effective strategy is urgently needed to improve the prescription practices of these drugs.

In Korea, the proportion of the elderly population aged 65 or older increased to 14.3% in 2018.[¹] Because of pharmacokinetic and pharmacodynamic changes and multiple morbidities, elderly patients are more likely to experience adverse drug events.[²,³] The risk of adverse drug events is even greater if medications classified as being inappropriate for the elderly are prescribed.

Cardiovascular and cerebrovascular diseases are highly prevalent in the elderly population.[⁴,⁵] In cases of hypertension and dyslipidemia, proper medications and good management can prevent cardiovascular complications. Otherwise, acute cardiovascular disease can develop, leading to hospitalization and death.[⁶,⁷] Anticoagulants and antiplatelet drugs are prescribed for the prevention and treatment of cardiovascular events such as heart attack, pulmonary embolism, or stroke in patients at risk of thrombosis or thromboembolism.[⁸,⁹] Therefore, prescribing the proper medications is critical...
to improve the quality of life of elderly patients and to prevent unnecessary health care expenditures.

As a basis for improving the appropriateness of medications, it is necessary to determine whether pharmaceutical treatments are provided at an appropriate level and, in cases of inappropriate use, identify any inappropriate prescribing that could indicate an emerging problem. Although several studies have applied the Screening Tool of Older Persons’ Prescriptions/Screening Tool of Alert To Right Treatment (STOPP/START) criteria to investigate the prevalence of potentially inappropriate prescribing (PIP) for the elderly, a detailed analysis of PIP for the cardiovascular and antiplatelet/anticoagulant (AP/AS) sections of the STOPP criteria using a nationwide database has not been conducted. Therefore, we investigated the prevalence of PIP among elderly in Korea receiving cardiovascular system (CVS) and AP/AS drugs using the STOPP criteria. With the aim of improving adequate medication use, predictors of PIP were also identified.

MATERIALS AND METHODS

Data Source

This study used the 2016 Health Insurance Review and Assessment Service-National Aged Patient Sample data (HIRA-APS-2016-0058), which are cross-sectional data consisting of insurance claim records for a random sample of 20% of patients aged ≥ 65 years enrolled in the National Health Insurance (NHI) or public assistant Medical Aid (MA) in 2016. The research protocol was approved by the Institutional Review Board of Yonsei University (IRB No. 7001988-201808-HR-432-01E). The need for informed consent from the study population was waived by the board.

Study Subjects

Patients aged 65 years or older who had received at least one outpatient prescription in 2016 were included in the study. We excluded the beneficiaries of the Veteran’s relief program. As there are discrepancies in the severity of illness and drug utilization patterns between inpatients and outpatients, we focused on only outpatient prescriptions. Patients treated in long-term care facilities were excluded because their main treatments are inpatient services. Finally, 1,274,148 patients with 27,062,307 prescription claim records for outpatient services were selected for inclusion (Figure 1).

Selecting Criteria

Among the 13 sections of the STOPP criteria version 2, CVS (section B) and AP/AC drugs (section C) were selected for our analysis. The CVS and AP/AC drug sections initially contained 13 and 11 criteria, respectively. The following three steps were conducted to select the criteria that were appropriate for the analysis.

First, two independent reviewers (JK and HYK) assessed whether PIP could be determined for a criterion solely based on the information in 1-year insurance claim records. We excluded five criteria because they required detailed clinical information such as lab test results, which are not available in the claims data. In addition, four other criteria were excluded because they required information on the long-term disease or medication history of the patient. Finally, four criteria required both detailed clinical information and the long-term history of the patient, so they were excluded. As a result, 6 of the 13 criteria in the CVS and 5 of the 11 criteria in the AP/AC drugs section were retained after this step (Table 1).

Next, criteria that included two or more drugs or diseases were subdivided. For example, the criteria...
Table 1: Selection of criteria from the cardiovascular system and antiplatelet/anticoagulant drugs sections in the Screening Tool of Older Persons’ Prescriptions (STOPP) criteria suitable for the analysis using 1-year insurance claims data.

| STOPP criteria                                                                 | Reviewer 1 | Reviewer 2 | Inclusion |
|--------------------------------------------------------------------------------|-------------|-------------|-----------|
| Digoxin for heart failure with normal systolic ventricular function’ (no clear evidence of benefit). | No          | No          | No        |
| Verapamil or diltiazem with New York Heart Association Class III or IV heart failure’ (may worsen heart failure). | No          | No          | No        |
| Beta-blocker in combination with verapamil or diltiazem (risk of heart block). | Yes         | Yes         | Yes       |
| Beta-blocker with bradycardia (< 50/min), type II heart block’ or complete heart block’ (risk of complete heart block, asystole). | Yes*        | Yes*        | Yes*      |
| Amiodarone as first-line” antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil, or diltiazem). | No          | No          | No        |
| Loop diuretic as first-line” treatment for hypertension (safer, more effective alternatives available). | No          | No          | No        |
| Loop diuretic for dependent ankle edema’ without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome, or renal failure (leg elevation and / or compression hosiery usually more appropriate). | Yes         | No          | No        |
| Thiazide diuretic with current significant hypokalemia (i.e., serum K+ < 3.0 mmol/L), hyponatremia (i.e., serum Na+ < 130 mmol/L), hypercalcemia (i.e., corrected serum calcium > 2.65 mmol/L), or a history of gout (hypokalemia, hyponatremia, hypercalcemia, and gout can be precipitated by thiazide diuretic). | No          | No          | No        |
| Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence). | Yes         | Yes         | Yes       |
| Centrally acting antihypertensives (e.g., methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally active antihypertensives are generally less well tolerated by older people than younger people). | No          | No          | No        |
| Angiotensin-Converting Enzyme inhibitors or angiotensin receptor blockers in patients with hyperkalemia. | Yes         | Yes         | Yes       |
| Aldosterone antagonists (e.g., spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g., Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalemia i.e., > 6.0 mmol/L – serum K should be monitored regularly, i.e., at least every 6 months). | Yes         | Yes         | Yes       |
| Phosphodiesterase type-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) in severe heart failure characterized by hypotension, i.e., systolic BP < 90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse). | Yes*        | Yes*        | Yes*      |
| Long-term aspirin at doses greater than 160 mg per day (increased risk of bleeding, no evidence for increased efficacy). | No          | No          | No        |
| Aspirin with a past history” of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer). | No          | No          | No        |
| Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors, or factor Xa inhibitors with concurrent significant bleeding risk, i.e., uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding (high risk of bleeding). | No          | No          | No        |
| Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has had a coronary stent(s) inserted in the previous 12 months” or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy). | No          | No          | No        |
| Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin). | Yes         | Yes         | Yes       |
| Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors in patients with stable coronary, cerebrovascular, or peripheral arterial disease’ (no added benefit from dual therapy). | Yes*        | Yes*        | Yes*      |
| Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence, and fewer side-effects). | Yes         | Yes         | Yes       |
| Vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors for first’ deep venous thrombosis without continuing provoking risk factors (e.g., thrombophilia) for > 6 months” (no proven added benefit). | No          | No          | No        |

*Reviewer 1, **Reviewer 2, ¶Inclusion
terion “Beta-blocker in combination with verapamil or diltiazem” was subdivided into two criteria, one for each drug. As a result, a total of 19 criteria were included: 8 criteria in the CVS and 11 criteria in the AP/AC section.

Because the STOPP criteria were developed in a foreign country, we evaluated the local adoptability of the criteria. Three family medicine clinicians and one neurology clinician independently assessed whether the criteria were applicable to clinical practice in Korea. If at least two of the four clinicians agreed on inclusion, we included the criterion. All the criteria selected in the previous steps attained a consensus among the 4 clinicians for inclusion. Therefore, 8 criteria in the CVS and 11 criteria in the AP/AC section were included in the final analysis.

Diseases included in the criteria were identified based on the diagnosis codes of International Classification of Diseases, 10th revision (ICD-10 code): bradycardia (ICD-10 code: R00.1), hypertension (I10, I11, I12, I13, and I15), urinary incontinence (F98.0, N39.3, N39.4, and R32), hyperkalemia (E87.5), angina (I20, I24.0, I24.8, and I24.9), chronic atrial fibrillation (I48.2), and stable angina (I20.8). If the diagnosis codes were included in claim records, we considered the disease to be present.

Data Analysis

Prevalence of PIP

PIP prevalence was investigated at the claim- and patient-levels. Each PIP was defined as follows:

Claim-level overall PIP prevalence rate (%) = (overall PIP_Claim / Tot_Num_Claim) × 100

Where, overall PIP_Claim = number of outpatient prescription claim records satisfying one or more of the 19 criteria.

Patient-level overall PIP prevalence rate (%) = (overall PIP_Pat / Tot_Num_Pat) × 100

Where, overall PIP_Pat = number of patients with outpatient prescription claim records satisfying one or more of the 19 criteria

Tot_Num_Claim = total number of outpatient prescription claim records

Patient-level overall PIP prevalence rate (%) = (overall PIP_Pat / Tot_Num_Pat) × 100

Where, overall PIP_Pat = number of patients with outpatient prescription claim records satisfying one or more of the 19 criteria

Tot_Num_Pat = total number of patients having at least one claim record for outpatient prescription

Patient-level PIP prevalence rate (%) = (PIP_Claim_i / Tot_Num_Claim) × 100

Where, PIP_Claim_i = number of outpatient prescription claim records satisfying the criterion “i”

Patient-level PIP prevalence rate (%) = (PIP_Pat_i / Tot_Num_Pat) × 100

Where, PIP_Pat_i = number of patients with outpatient prescription claim records satisfying the criterion “i”

For criteria indicating drug-disease interactions such as “Beta-blocker with bradycardia,” PIP prevalence per indication was investigated in both the claim- and patient-level analyses as follows.

Claim-level PIP prevalence rate per indication (%) = (PIP_Claim_i / Tot_Num_Claim_Diag_i) × 100

Where, Tot_Num_Claim_Diag_i = total number of outpatient prescription claim records with diagnosis included in the criterion “i”

Patient-level PIP prevalence rate per indication (%) = (PIP_Pat_i / Tot_Num_Pat_Diag_i) × 100

Where, Tot_Num_Pat_Diag_i = total number of patients with outpatient prescription claim records with diagnosis included in the criterion “i”

Predictors of PIP

Selected patient and prescriber characteristics available in claims data were included as potential predictors of PIP, such as sex, age, severity of comorbid conditions, and type of national health se-
Table 2  Characteristics of the study subjects and their health insurance claim records.

| Variable                                  | Category            | Number of patients (%) | Number of claims (%) |
|-------------------------------------------|---------------------|------------------------|----------------------|
| Sex                                       | Male                | 535,100 (42.00%)       | 10,876,270 (40.19%)  |
|                                           | Female              | 739,048 (58.00%)       | 16,186,037 (59.81%)  |
| Age, yrs                                  | 73.70 ± 6.56, mean ± SD |
|                                           | 65–74               | 763,716 (59.94%)       | 15,136,631 (55.93%)  |
|                                           | 75–84               | 419,001 (32.88%)       | 10,175,796 (37.60%)  |
|                                           | ≥85                 | 91,431 (7.18%)         | 1,749,880 (6.47%)    |
| Types of National Health Security         | National Health Insurance | 1,187,380 (93.19%)   | 24,678,478 (91.19%)  |
|                                           | Medical aid         | 86,768 (6.81%)         | 2,383,829 (8.81%)    |
| Charlson Comorbidity Index                | 2.01 ± 1.90, mean ± SD |
|                                           | 0                   | 297,620 (23.36%)       | 3,674,019 (13.58%)   |
|                                           | 1                   | 314,988 (24.72%)       | 5,835,419 (21.56%)   |
|                                           | 2                   | 251,671 (19.75%)       | 5,716,726 (21.12%)   |
|                                           | ≥3                  | 409,869 (32.18%)       | 11,836,143 (43.74%)  |
| No. of prescriptions per patient for a year| 1−10                | 345,424 (27.11%)       | –                    |
|                                           | 11−20               | 404,743 (31.77%)       | –                    |
|                                           | 21–30               | 253,174 (19.87%)       | –                    |
|                                           | 31–40               | 132,293 (10.38%)       | –                    |
|                                           | ≥41                 | 138,514 (10.81%)       | –                    |
| No. of active ingredients                 | 3.68 ± 2.04, mean ± SD |
|                                           | 1−4                 | –                      | 19,000,721 (70.21%)  |
|                                           | 5−9                 | –                      | 7,656,252 (28.29%)   |
|                                           | ≥10                 | 405,334 (1.5%)         | –                    |
| Type of health care organization          | Tertiary-care hospital | 1,286,860 (4.76%)   | –                    |
|                                           | General hospital    | 2,654,526 (9.81%)      | –                    |
|                                           | Hospital            | –                      | –                    |
|                                           | Clinic and public health organization | 1,598,736 (5.91%) | –                    |
|                                           | 21,522,185 (79.53%) |
| Medical specialty of prescribers          | Internal medicine   | 11,156,108 (41.22%)    | –                    |
|                                           | Neurology           | 909,838 (3.36%)        | –                    |
|                                           | Surgery             | 5,977,377 (22.09%)     | –                    |
|                                           | Family medicine     | 1,000,955 (3.70%)      | –                    |
|                                           | Others              | 8,018,029 (29.63%)     | –                    |
| Region of health care organization        | Seoul               | 5,040,010 (18.62%)     | –                    |
|                                           | Busan               | 2,184,134 (8.07%)      | –                    |
|                                           | Incheon             | 1,222,580 (4.52%)      | –                    |
|                                           | Daegu               | 1,526,189 (5.64%)      | –                    |
|                                           | Gwangju             | 784,886 (2.90%)        | –                    |
|                                           | Daejeon/Chungcheong/Sejong | 3,202,432 (11.83%)   | –                    |
|                                           | Ulsan/Gyeongsang    | 3,931,561 (14.53%)     | –                    |
|                                           | Gyeonggi            | 4,733,979 (17.49%)     | –                    |
|                                           | Gangwon             | 919,128 (3.40%)        | –                    |
|                                           | Jeonla/Jeju         | 3,517,408 (12.99%)     | –                    |

*Includes surgery, orthopedic surgery, neurosurgery, thoracic and cardiovascular surgery, and plastic surgery.
Table 3  PIP prevalence according to the cardiovascular system and antiplatelet/anticoagulant drugs sections of the Screening Tool of Older Persons’ Prescriptions (STOPP) criteria in Korea in 2016.

| PIP criteria                                                                 | Claim-level analysis | Patient-level analysis |
|------------------------------------------------------------------------------|----------------------|------------------------|
|                                                                               | No. of PIP claims | Individual PIP prevalence (%) | PIP prevalence per indication (%) | No. of PIP patients | Individual PIP prevalence (%) | PIP prevalence per indication (%) |
| Beta-blocker in combination with verapamil                                   | 2,229               | 0.01                     | –                                  | 485                   | 0.04                     | –                                  |
| Beta-blocker in combination with diltiazem                                   | 34,062              | 0.13                     | –                                  | 7,213                 | 0.57                     | –                                  |
| Beta-blocker with bradycardia                                                | 628                 | < 0.01                   | 16.47                              | 222                   | 0.02                     | 15.82                              |
| Loop diuretic for treatment of hypertension with concurrent urinary incontinence | 1,986               | 0.01                     | 1.40                               | 438                   | 0.03                     | 1.24                               |
| Angiotensin-Converting Enzyme (ACE) inhibitors in patients with hyperkalemia | 854                 | < 0.01                   | 2.28                               | 244                   | 0.02                     | 2.82                               |
| Angiotensin receptor blockers (ARB) in patients with hyperkalemia            | 8,950               | 0.03                     | 23.89                              | 2,249                 | 0.18                     | 25.97                              |
| Aldosterone antagonists (e.g., spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g., ACE inhibitors, ARBs, amiloride, triamterene) without monitoring of serum potassium | 22,866              | 0.08                     | –                                  | 8,306                 | 0.65                     | –                                  |
| Phosphodiesterase type-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) in concurrent nitrate therapy for angina | 2                   | < 0.01                   | < 0.01                             | 1                     | < 0.01                   | < 0.01                             |
| Aspirin in combination with vitamin K antagonist in patients with chronic atrial fibrillation | 241                 | < 0.01                   | 1.71                               | 62                    | < 0.01                   | 1.82                               |
| Aspirin in combination with direct thrombin inhibitor in patients with chronic atrial fibrillation | 60                  | < 0.01                   | 0.42                               | 22                    | < 0.01                   | 0.64                               |
| Aspirin in combination with factor Xa inhibitors in patients with chronic atrial fibrillation | 213                 | < 0.01                   | 1.51                               | 64                    | 0.01                     | 1.87                               |
| Antiplatelet agents with vitamin K antagonist in patients with stable angina | 646                 | < 0.01                   | 0.67                               | 201                   | 0.02                     | 0.90                               |
| Antiplatelet agents with direct thrombin inhibitor in patients with stable angina | 66                  | < 0.01                   | 0.07                               | 29                    | < 0.01                   | 0.13                               |
| Antiplatelet agents with factor Xa inhibitors in patients with stable angina | 308                 | < 0.01                   | 0.32                               | 122                   | 0.01                     | 0.55                               |
| Ticlopidine in any circumstances                                             | 5,186               | 0.02                     | –                                  | 959                   | 0.08                     | –                                  |
| Nonsteroidal anti-inflammatory drug (NSAID) and vitamin K antagonist in combination | 2,044               | 0.01                     | –                                  | 694                   | 0.05                     | –                                  |
| NSAID and direct thrombin inhibitor in combination                            | 550                 | < 0.01                   | –                                  | 206                   | 0.02                     | –                                  |
| NSAID and factor Xa inhibitors in combination                                | 1,598               | 0.01                     | –                                  | 645                   | 0.05                     | –                                  |
| NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis           | 263,449             | 0.97                     | –                                  | 80,590                | 6.33                     | –                                  |

*Claim-level PIP prevalence rate (%) = (number of prescription claim records satisfying the criterion “i”/total number of prescription claim records) × 100; **claim-level PIP prevalence rate per indication (%) = (number of prescription claim records satisfying the criterion “i”/total number of prescription claim records with a diagnosis included in the criterion “i”) × 100; †patient-level PIP prevalence rate (%) = (Number of patients with prescription claim records satisfying the criterion “i”/total number of patients having at least one claim record for prescription) × 100 ; ‡patient-level PIP prevalence rate per indication (%) = (Number of patients with prescription claim records satisfying the criterion “i”/total number of patients with prescription claim records with diagnosis included in the criterion “i”) × 100.

The severity of the comorbidities was measured using the Charlson Comorbidity Index (CCI) [10], with a higher score indicating a more severe comorbid condition. Prescriber characteristics included type and geographic location of the healthcare organization, and...
type of medical specialty of prescribers. In addition, the number of active ingredients in a prescription was included to assess the degree of polypharmacy. Based on preliminary studies, “polypharmacy” and “excessive polypharmacy” were defined according to whether the prescription had 5–9 or ≥10 different active ingredients, respectively (Table 2).\(^1\)\(^-\)\(^14\)

To identify the patient and prescriber characteristics that were associated with PIP, a multivariate logistic regression analysis was conducted with claim records as the units of analysis. If a claim satisfied one or more of the final 19 criteria, the dependent variable was coded as “1.” More than one claim could be affiliated with the same patient. If the same patient is repeatedly measured, the estimated regression coefficients could be biased because of the within-subject correlation. To avoid this problem, a generalized estimating equation (GEE) for the regression model was used.\(^15\) The statistical results were analyzed using the SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Among the 1,274,148 study subjects, 100,085 patients (7.85\%) received at least one PIP based on eight criteria in the CVS and 11 criteria in the AP/AC drugs. Among the 27,062,307 prescription claim records for outpatient services, 341,664 claims (1.27\%) included one or more PIP. The most prevalent PIP was criterion 19, “NSAID with concurrent antiplatelet agent(s) without proton-pump inhibitor (PPI) prophylaxis” in both the claim-level (0.97\%) and patient-level (6.33\%) analyses (Table 3).

“PIP prevalence per indication” was calculated for the 11 criteria including drug-disease interactions. In the claim-level analysis, criterion 3 “Beta-blocker with bradycardia” (16.47\%) and criterion 6 “Angiotensin receptor blockers (ARBs) in patients with hyperkalaemia” (23.89\%) were found to have the highest prevalence. The same pattern was found in the patient-level analysis, as the highest prevalence were criterion 3 (15.82\%) and criterion 6 (25.97\%) (Table 3).

The multivariate logistic regression analysis results for overall PIP prevalence (i.e., PIP for any of the 19 criteria) showed that females (odds ratio (OR) = 1.32, 95\% confidence interval (CI): 1.29–1.35) and MA beneficiaries (OR = 1.08, 95\% CI: 1.04–1.11) were more likely to have PIP than their counterparts (Table 4). The likelihood of PIP increased with increase in patient age (OR = 1.26 for those aged 75 to 84 years and 1.50 for those above 85 years), number of active ingredients per prescription (OR = 8.66 for 5–9 ingredients and 44.48 for ≥ 10 ingredients), CCI value (OR = 1.39 for CCI of 1, 1.61 for 2, and 1.61 for ≥ 3), and level of the health care organization (OR = 1.21 for hospitals, 1.56 for general hospitals, and 1.93 for tertiary-care hospitals).

Additional logistic regression analyses were performed on criterion 3 and criterion 6, respectively, which showed the highest PIP prevalence per indication. For each of “bradycardia (criterion 3)” and “hyperkalaemia (criterion 6)” patient group, multivariate logistic regression analysis was conducted to examine the factors associated with PIP occurrence (Table 4). For criterion 3, the number of active ingredients per prescription (OR = 2.21 for 5–9 ingredients and 3.50 for ≥ 10 ingredients) and the level of the health care organization (OR = 1.58 for hospitals, 3.03 for general hospitals, and 4.96 for tertiary-care hospitals) had significantly positive associations with PIP. Interestingly, for criterion 6, the risk of PIP significantly decreased as the patient age increased (OR = 0.85 for those aged 75 to 84 and 0.83 for those above 85). The number of active ingredients per prescription had a positive association with PIP for criterion 6 (OR = 3.75 for 5–9 ingredients and 5.58 for ≥ 10 ingredients).

DISCUSSION

In this study, we investigated the prevalence of PIP for CVS and AP/AC drugs prescribed for elderly outpatients in Korea in 2016, using the nationally representative NHI claims data. In both the claim- and patient-level analyses, among the 19 criteria, criterion 19, “NSAID with concurrent antiplatelet agent without PPI prophylaxis” was found to have the highest PIP prevalence (0.98\% and 6.33\%). NSAIDs are known to increase the risk of vascular bleeding and gastric mucosal injury. Because upper gastrointestinal bleeding is a particularly critical issue in the elderly, preventative strategies such as PPI prophylaxis should be considered in clinical practice.\(^16\)
Table 4  Generalized estimated equations logistic regression analysis results for factors associated with potentially inappropriate prescribing (PIP) claims.

| Variables                        | Adjusted OR (95% CI) | PIP for one or more of the 19 criteria | PIP for Criterion 3 | PIP for Criterion 6 |
|----------------------------------|----------------------|---------------------------------------|---------------------|---------------------|
| Sex                              |                      |                                       |                     |                     |
| Male (reference)                 |                      |                                       |                     |                     |
| Female                           | 1.32 (1.29–1.35) *   | 1.06 (0.75–1.51)                      | 0.91 (0.80–1.03)    |                     |
| Age, yrs                         |                      |                                       |                     |                     |
| 65–74 (reference)                |                      |                                       |                     |                     |
| 75–84                            | 1.26 (1.24–1.29) *   | 0.87 (0.62–1.24)                      | 0.85 (0.77–0.94)    |                     |
| ≥ 85                             | 1.50 (1.46–1.56) *   | 1.20 (0.66–2.18)                      | 0.83 (0.92–0.99)    |                     |
| National Health Security         |                      |                                       |                     |                     |
| National Health Insurance (reference) |                 |                                       |                     |                     |
| Medical Aid                      | 1.08 (1.04–1.11) *   | 0.75 (0.43–1.30)                      | 0.86 (0.72–1.03)    |                     |
| No. of active ingredients        |                      |                                       |                     |                     |
| 1–4 (reference)                  |                      |                                       |                     |                     |
| 5–9                              | 8.66 (8.50–8.82) *   | 2.21 (1.62–3.03)                      | 3.75 (3.29–4.28)    |                     |
| ≥ 10                             | 44.48 (43.35–45.64) * | 3.50 (1.66–7.37)                      | 5.58 (4.81–6.47)    |                     |
| Charlson Comorbidity Index       |                      |                                       |                     |                     |
| 0 (reference)                    |                      |                                       |                     |                     |
| 1                                | 1.39 (1.33–1.45) *   | 0.71 (0.31–1.60)                      | 0.90 (0.46–1.73)    |                     |
| 2                                | 1.61 (1.54–1.67) *   | 1.18 (0.56–2.46)                      | 0.95 (0.52–1.74)    |                     |
| ≥ 3                              | 1.61 (1.55–1.67) *   | 1.51 (0.79–2.89)                      | 0.79 (0.44–1.14)    |                     |
| Type of health care organization |                      |                                       |                     |                     |
| Clinic/Public health organization (reference) |         |                                       |                     |                     |
| Hospital                         | 1.21 (1.18–1.25) *   | 1.58 (0.86–2.93)                      | 0.68 (0.44–1.04)    |                     |
| General hospital                 | 1.56 (1.52–1.59) *   | 3.03 (1.65–5.57)                      | 0.94 (0.71–1.23)    |                     |
| Tertiary care hospital           | 1.93 (1.89–1.98) *   | 4.96 (2.61–9.42)                      | 0.96 (0.74–1.24)    |                     |
| Specialty of prescriber          |                      |                                       |                     |                     |
| Internal medicine (reference)    |                      |                                       |                     |                     |
| Neurology                        | 1.22 (1.18–1.26) *   | 1.83 (0.42–7.95)                      | 0.73 (0.44–1.19)    |                     |
| Surgery                          | 1.02 (1.00–1.04) *   | 1.19 (0.88–1.61)                      | 0.76 (0.58–1.01)    |                     |
| Family medicine                  | 0.96 (0.92–0.99) *   | 0.58 (0.09–3.56)                      | 0.77 (0.47–1.26)    |                     |
| Others                           | 0.27 (0.26–0.28) *   | 0.74 (0.48–1.14)                      | 0.47 (0.26–0.84)    |                     |
| Region of health care organization |                    |                                       |                     |                     |
| Seoul (reference)                |                      |                                       |                     |                     |
| Busan                            | 0.95 (0.91–0.99) *   | 0.72 (0.29–1.80)                      | 0.77 (0.60–0.99)    |                     |
| Incheon                          | 0.98 (0.93–1.03)     | 1.40 (0.70–2.80)                      | 0.76 (0.58–1.00)    |                     |
| Daegu                            | 0.91 (0.88–0.95) *   | 1.36 (0.66–2.81)                      | 0.88 (0.67–1.15)    |                     |
| Gwangju                          | 1.15 (1.09–1.21) *   | 0.24 (0.02–2.23)                      | 1.06 (0.73–1.54)    |                     |
| Daejeon/Chungcheong/Sejong       | 1.00 (0.97–1.04)     | 1.36 (0.74–2.49)                      | 0.80 (0.64–1.01)    |                     |
| Ulsan/Gyeongsang                 | 0.99 (0.96–1.03)     | 1.23 (0.67–2.27)                      | 1.08 (0.84–1.37)    |                     |
| Gyeonggi                         | 1.00 (0.97–1.03)     | 0.71 (0.39–1.29)                      | 0.74 (0.61–0.90)    |                     |
| Gangwon                          | 1.07 (1.02–1.13) *   | 1.68 (0.65–4.35)                      | 1.16 (0.83–1.60)    |                     |
| Jeonla/Jeju                      | 1.19 (1.15–1.23) *   | 0.69 (0.36–1.33)                      | 0.64 (0.50–0.81)    |                     |

*P < 0.05; **: Criteria 3: claims including beta–blocker in patients with bradycardia; | Criteria 6: claims including angiotensin receptor blockers in patients with hyperkalemia; includes surgery, orthopedic surgery, neurosurgery, thoracic and cardiovascular surgery, and plastic surgery.

http://www.jgc301.com; jgc@jgc301.com
PIP prevalence per indication was investigated for the 11 criteria including drug-disease interactions. Criterion 3, “beta-blocker with bradycardia (16.47%),” and criterion 6, “ARBs in patients with hyperkalaemia (23.89%)” were found to have considerably higher PIP prevalence than the other criteria. Because of the limited clinical information available in insurance claims data, it is difficult to determine whether beta-blockers or ARBs were prescribed to patients who already had bradycardia or hyperkalemia before medication or whether adverse events occurred after taking these drugs. Even if the symptoms of bradycardia or hyperkalemia were adverse events that occurred following medication, the medication could be continued without interruption according to the decision of the prescribers, as cardiovascular and cerebrovascular diseases are chronic diseases requiring long-term and close monitoring. If the benefits of sustained drug therapy are thought to outweigh the risk of damage from an adverse event or if the adverse events are controlled quickly, medications for chronic diseases could likely be continued with close monitoring. Thus, the results found for criteria 3 and 6 could reflect this situation.

To identify the risk factors related to PIP, a multivariate logistic regression analysis was conducted. Among the potential risk factors related to PIP, the number of active ingredients included in a prescription had the highest odds ratio. Several studies have shown that PIP and polypharmacy were significantly correlated. Polypharmacy often occurs in elderly patients because they have multiple comorbidities, but it also could be the result of prescribing drugs that are not necessarily required. Polypharmacy is considered a major problem in older patients, leading to adverse drug events, poor medication compliance, and higher medication costs.

As observed in other studies, females were vulnerable to have PIP than males. As age or CCI value increased, the likelihood of PIP increased. These tendencies have also been reported in earlier studies. These results might be due to the greater number of medications that patients receive as their age or severity of illness increase. Our results indicated that the higher the level of health care organization, the higher the possibility of PIP. In general, PIP prevalence in hospitals is lower than that in clinics owing to superior expertise of the medical staff and monitoring system. However, in this study, PIP prevalence was investigated with a focus on cardiovascular and cerebrovascular diseases. These are chronic diseases that can have a high severity and progress to a life-threatening condition. Patients visiting higher-level healthcare organizations tend to have a more severe illness. If the severity of the illness is high, symptom control may be favored over the consideration of adverse effects, which may lead to a higher PIP prevalence in higher-level medical institutions. In this study, neurologists were associated with the highest PIP prevalence for CVS and AC/AP drugs. A possible reason for the low PIP prevalence for drugs prescribed by other medical specialty clinicians is their low prescribing rate for CVS and AP/AC drugs. Thus, different results are expected for the PIP prevalence for other classes of medications.

Notably, the likelihood of PIP for criterion 6 decreased as age increased. Hyperkalemia is more likely to occur in patients with diseases such as renal failure, metabolic acidosis, insulin deficiency, and reduced aldosterone secretion. As older patients have decreased renal function and a greater possibility of having various chronic diseases, their risk of hyperkalemia also increases. Therefore, it can be assumed that elderly patients may be more closely monitored during their follow-up for adverse events, and this close monitoring can help avoid ARB prescribing in patients with hyperkalemia.

To improve the appropriateness of prescribing, whether a drug is essential for treatment should be checked before prescribing. In addition, all healthcare professionals, including physicians and pharmacists, can help reduce inappropriate prescriptions by cooperating in their respective fields of expertise. Moreover, the drug utilization review (DUR) system for elderly patients should be continuously updated and managed.

This study had several limitations. First, four Korean clinician panels reviewed each criterion to determine whether the criteria were suitable for clinical application in Korea. Because all the clinician panel members were working for health care institutions located in the capital city area, their
opinions may not reflect non-urban areas in Korea. Second, because only the criteria that could be analyzed using 1-year insurance claims data were selected, not all the criteria included for CVS and AP/AC drugs in the STOPP criteria could be analyzed. Third, because the dataset was based on insurance claims data, the drugs not covered by the insurance could not be evaluated. This could have resulted in underestimation of the actual PIP prevalence. Lastly, as insurance claims data do not contain detailed clinical information, it was not possible to account for situations when medicines were inevitably used as the benefits of using the drugs outweighed the risk of adverse events.

Our study investigated the PIP associated with the CVS and AP/AC sections of the STOPP criteria version 2 and identified patient and prescriber characteristics associated with PIP. This study’s strengths include that it has nationwide representativeness and was conducted using the latest updated version of the STOPP criteria. As cardiovascular and cerebrovascular diseases are chronic diseases with high severity, careful attention and targeted interventions are necessary to reduce PIP prevalence. There is also a need for clinical and policy efforts to improve appropriate prescribing practices for the elderly population.

REFERENCES

[1] Statistics Korea S. 2019 Statistics on the aged. 2019.
[2] Hill-Taylor B, Sketris I, Hayden J, et al. 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: 360–372.
[3] Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 2004; 57: 6–14.
[4] National Health Insurance Service, Health Insurance Review & Assessment Service. 2018 National Health Insurance Statistical Yearbook. 2019.
[5] Korea Institute for Health and Social Affairs. Survey of the Living Conditions of the Elderly in Korea. 2017.
[6] Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016; 387: 957–967.
[7] Korea Academy of Medical Sciences, Korea Centers for Disease Control & Prevention. Evidence-based Guideline for Hypertension in Primary Care. 2018.
[8] Atherosclerosis CoCPGotKSoLa. Korean Guidelines for the Management of Dyslipidemia 4th Ed. 2018.
[9] Sime G, Armstrong C, Barker D, et al. Management of dental patients taking anticoagulants or antiplatelet drugs. Scottish Dental Clinical Effectiveness Programme 2015: 1–40.
[10] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–383.
[11] Herr M, Grondin H, Sanchez S, et al. Polypharmacy and potentially inappropriate medications: a cross-sectional analysis among 451 nursing homes in France. Eur J Clin Pharmacol 2017; 73: 601–608.
[12] Moriarty F, Hardy C, Bennett K, et al. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: a repeated cross-sectional study. BMj open 2015: 5.
[13] O’Dwyer M, Peklar J, McCallion P, et al. Factors associated with polypharmacy and excessive polypharmacy in older people with intellectual disability differ from the general population: a cross-sectional observational nationwide study. BMJ open 2016: 6.
[14] Haider SI, Johnell K, Weitoft GR, et al. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. J Am Geriatr Soc 2009; 57: 62–69.
[15] Ballinger GA. Using generalized estimating equations for longitudinal data analysis. Organizational Research Methods 2004; 7: 127–150.
[16] Zuilo A, Hassan C, Campo SM, Morini S. Bleeding peptic ulcer in the elderly: risk factors and prevention strategies. Drugs & Aging 2007; 24: 815–828.
[17] Ko DT, Hebert PR, Coffey CS, et al. Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. Arch Intern Med 2004; 164: 1389–1394.
[18] Cho H, Choi J, Kim YS, et al. Prevalence and predictors of potentially inappropriate prescribing of central nervous system and psychotropic drugs among elderly patients: A national population study in Korea. Arch Gerontol Geriatr 2018; 74: 1–8.
[19] Hwang HJ, Kim SH, Lee KS. Potentially Inappropriate Medications in the Elderly in Korean Long-Term Care Facilities. Drugs Real World Outcomes 2015; 2: 355–361.
[20] Kim A, Kim H, Rhee S. Risk Factors of Potentially Inappropriate Medications and Cost by Polypharmacy among Elderly Patients of a Community Pharmacy near a Top Tier General Hospital. Korean J Clin Pharm 2015; 25: 159–165.
[21] Kim DS, Huh S, Lee S. Potentially inappropriate medication use at ambulatory care visits by elderly patients covered by National Health Insurance in Korea. Int J Clin Pharmacol Ther 2015; 53: 819–27.
[22] Lim YJ, Kim HY, Choi J, et al. Potentially Inappropriate Medications by Beers Criteria in Older Outpatients: Prevalence and Risk Factors. Korean J Fam Med 2016; 37: 329–333.
[23] Nam YS, Han JS, Kim JY, et al. Prescription of potentially inappropriate medication in Korean older adults based on 2012 Beers Criteria: a cross-sectional population based study. BMC Geriatr 2016; 16: 118.
Hudhra K, Garcia-Caballos M, Casado-Fernandez E, et al. Polypharmacy and potentially inappropriate prescriptions identified by Beers and STOPP criteria in co-morbid older patients at hospital discharge. *J Eval Clin Pract* 2016; 22: 189–193.

Bae MK, Lee IH, Yoon JH. Assessment of potentially inappropriate medication use in Korean elderly patients with chronic heart failure. *Korean J Clin Pharm* 2014; 24: 115–25.

Seo MK, Bae MK, Lee IH, Jeon S, Yoon JH. Assessment of potentially inappropriate medication use in Korean elderly patients with Parkinson’s disease. *Korean J Clin Pharm* 2015; 25: 254.

Allon M, Dansby L, Shanklin N. Glucose modulation of the disposal of an acute potassium load in patients with end-stage renal disease. *Am J Med* 1993; 94: 475–482.

Aronson PS, Giebisch G. Effects of pH on potassium: new explanations for old observations. *J Am Soc Nephrol* 2011; 22: 1981–1989.

Chang AR, Sang Y, Leddy J, et al. Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Health System. *Hypertension (Dallas, Tex : 1979)* 2016; 67: 1181–1188.

Please cite this article as: Kim J, Han E, Hwang HJ, Cho H, Kim Y, Chun H, Kim J, Park YC, Kang HY. Potentially inappropriate prescribing of cardiovascular system and antiplatelet/anticoagulant drugs among elderly patients: a Korean population-based national study. *J Geriatr Cardiol* 2021; 18(5): 327–337. DOI: 10.11909/j.issn.1671-5411.2021.05.010