

## Research Article

# Evaluation of potentially inappropriate medication use according to the Asian criteria and its impact on hospitalisation outcomes among older outpatients

Kittipak Jenghua<sup>1,2,3,\*</sup>, Sirayut Phatthanasobhon<sup>1,2,3</sup>, Songkot Jaima<sup>4</sup>, Panadda Ngamsom<sup>5</sup>, Duangkamon Poolpun<sup>6</sup>

<sup>1</sup> Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand

<sup>2</sup> Pharmacoepidemiology, Social and Administrative Pharmacy (PSAP) Research Unit, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand

<sup>3</sup> Research on Drug Utilization in Special Populations (RDU-SPEC) Research Unit, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand

<sup>4</sup> Department of Pharmacy, Dokkhamtai Hospital, Phayao Province, Thailand

<sup>5</sup> Pharmacy Department, Chiangkham Hospital, Phayao Province, Thailand

<sup>6</sup> Department of Pharmacy, Buddhachinaraj Hospital, Phitsanulok Province, Thailand

## ABSTRACT

Potentially inappropriate medications (PIMs) are associated with adverse outcomes in older adults. The Asian explicit criteria, compiled from 15 quality-assessed country-specific guidelines, provide a regionally relevant and comprehensive framework for evaluating PIM use. This study investigates the prevalence, predictors, and hospitalisation outcomes of PIM use, as defined by the Asian criteria, among older outpatients in Thailand. A retrospective cohort study was conducted using data on patients aged  $\geq 60$  years who received outpatient care, obtained from the electronic medical records of three public hospitals in Thailand. Outpatient prescriptions from 2023 were analysed to identify PIM use, categorised into disease-independent, disease-specific, and drug–drug interaction (DDI)-based groups. Predictors were examined using multivariable logistic regression, while associations with hospitalisation outcomes in 2024 were assessed using generalised linear models. Among 76,361 older outpatients (mean age:  $69.59 \pm 7.63$  years; 55.66% female), 82.99% received at least one PIM. The prevalence of disease-independent, disease-specific, and DDI-based PIMs was 82.71%, 31.09%, and 10.24%, respectively. Predictors of PIM use included care at lower-level hospitals, female sex, multimorbidity, and polypharmacy, including hyperpolypharmacy. In adjusted analyses, overall PIM use was significantly associated with a 1.17-fold increased risk of all-cause hospitalisation, 1.86-fold for adverse drug event-related hospitalisation, 1.46-fold for in-hospital mortality, and a higher number of admissions. PIM use was widespread among older outpatients and associated with adverse hospitalisation outcomes. The Asian criteria facilitated a comprehensive and context-specific evaluation of PIMs in Asian settings. Integrating these criteria into clinical practice may enhance prescribing safety and help reduce PIM-related risks.

### Keywords:

Potentially inappropriate medication list; Older patients; Explicit criteria; Prevalence; Hospitalisation

## 1. INTRODUCTION

The global ageing population is rising rapidly, with 1.5 billion people projected to be  $\geq 65$  years by 2050, and Asia accounting for a substantial share<sup>1,2</sup>. In Thailand, the proportion of older adults—defined as individuals

aged  $\geq 60$  years—has increased markedly and is expected to exceed 27% by 2030<sup>3</sup>. These demographic shifts are reshaping healthcare needs and call for systems that support chronic disease management and healthy ageing.

Age-related physiological changes affect both pharmacokinetics and pharmacodynamics, making older

### \*Corresponding author:

\* Kittipak Jenghua Email: kittipak.je@up.ac.th



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adults more susceptible to adverse drug events (ADEs) even at standard doses<sup>4</sup>. Multimorbidity is prevalent among older adults and frequently necessitates multiple medications, leading to polypharmacy<sup>5</sup>. An Indian study found that 70.5% of older adults had  $\geq 3$  chronic conditions and 33.7% experienced polypharmacy, with multimorbidity associated with a 2.5-fold higher likelihood of polypharmacy<sup>6</sup>. A recent cohort study further demonstrated that prolonged polypharmacy independently increased the risk of adverse outcomes, including hospitalisation, emergency department visits, and mortality<sup>7</sup>. Managing medications in frail older adults with multimorbidity is complex, especially in primary care where clinicians often lack adequate decision-support for safe prescribing or deprescribing<sup>8</sup>.

To address inappropriate prescribing in older adults, several explicit criteria have been developed to identify potentially inappropriate medications (PIMs), defined as drugs whose risks outweigh their benefits—particularly when safer alternatives exist<sup>9</sup>. The Beers criteria and the Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) are among the most widely used tools<sup>10, 11</sup>. However, most were developed in Western countries, which may differ from other regions in terms of population characteristics, disease prevalence, prescribing practices, and drug availability<sup>10, 12</sup>. For instance, the 2023 Beers update excluded medications no longer used in the United States but still commonly prescribed elsewhere, limiting its global applicability<sup>11</sup>. Additionally, existing tools vary in scope and coverage, underscoring the limitations of relying on a single criterion for universal use<sup>12</sup>. For instance, Bobrova *et al.*<sup>13</sup> demonstrated that integrating the European Union (7)-Potentially Inappropriate Medications (EU(7)-PIM) list and the European FORTA list (EURO-FORTA), can strengthen PIM identification.

In Asia, the integration of multiple national criteria plays a critical role in optimising comprehensive and context-aligned prescribing for older adults across the region. Recently, a systematic review by Chang *et al.*<sup>14</sup> identified 15 Asian country-specific explicit PIM criteria that met quality standards based on the Delphi method, developed in countries including South Korea (four versions), China (two), Japan (two), Taiwan, Singapore, Indonesia, Pakistan, Sri Lanka, Hong Kong, and Thailand. A substantial variation in listed PIMs was observed across the criteria, as reflected in a low average kappa index of 0.230, underscoring the value of cross-national integration of criteria. These criteria were subsequently synthesised into the 2023 Asian criteria, which categorise PIMs into three groups: (1) disease-independent, (2) disease-specific, and (3) drug–drug interaction (DDI)-based. This regionally tailored tool provides a more context-appropriate alternative to Western-derived lists.

PIM use among older outpatients remains high worldwide, with a recent meta-analysis reporting a pooled prevalence of 36.7% globally and 37.2% in Asia<sup>15</sup>. However, reported rates vary across Asian countries depending on the criteria applied and the healthcare setting. In Japan, a study using the STOPP-J criteria reported a 45.5% prevalence among outpatients aged 65–74 years in community pharmacies<sup>16</sup>. In Thailand, a study applying the 2023 Beers criteria found a prevalence of 39.4% in a primary care setting<sup>17</sup>. Several studies have also associated PIM use with adverse outcomes. A UK cohort study using the STOPP criteria found significantly increased risks of hospitalisation, falls, and adverse drug reactions, although not for mortality<sup>18</sup>. In Hong Kong, a prospective study applying the 2023 Beers criteria reported a 1.7-fold increase in hospitalisation risk among PIM users, with higher risk observed in those prescribed multiple PIMs<sup>19</sup>. Despite variations in tools and settings, these findings consistently underscore the negative health impacts of PIM use among older adults.

The continued use of PIMs in clinical practice often reflects real-world barriers. Surveys conducted in both high- and middle-income countries report low awareness and limited use of explicit PIM criteria due to unfamiliarity, time pressures, and lack of integration into clinical workflows<sup>20, 21</sup>. These challenges are particularly pronounced in outpatient settings, where information is often fragmented and follow-up limited. To date, the Asian criteria have not been applied to evaluate PIM use specifically among older outpatients. This study, therefore, aims to determine the prevalence, predictors, and hospitalisation outcomes associated with PIM use, as defined by the Asian criteria, among older outpatients in Thailand.

## 2. MATERIALS AND METHODS

### 2.1. Study design and settings

This multicentre retrospective cohort study assessed the prevalence and predictors of PIM use in 2023 (exposure period) and examined hospitalisation outcomes that occurred during 2024 (outcome period). The study was conducted at three public hospitals in Thailand: a community hospital, a general hospital in Phayao Province, and a tertiary-care hospital in Phitsanulok Province. These hospitals were selected to maximise the coverage of medications listed in the Asian criteria.

### 2.2. Participants

All patients aged  $\geq 60$  years who attended the outpatient departments of the three participating hospitals between 1 January and 31 December 2023

were screened for eligibility. Patients with missing key baseline data or without any outpatient prescription records in 2023 were excluded. All eligible patients were included and subsequently followed through 2024 to assess hospitalisation outcomes.

### 2.3. Definition and classification of PIMs

PIMs were identified using the 2023 Asian explicit criteria, which comprise three groups: (1) disease-independent PIMs; (2) disease-specific PIMs; and (3) DDI-based PIMs<sup>14</sup>. Although the criteria were compiled from 15 country-specific lists with varying levels of consensus, they were used as a single, comprehensive tool without weighting individual items.

A total of 250 medications, extracted from the Asian criteria, were available in at least one participating hospital: 99, 174, and 231 in the community, general, and tertiary-care hospitals, respectively. Among disease-independent PIMs, 67 of 70 drug classes were assessed. Three classes—antiemetics (propranolol), tetracyclic antidepressants (maprotiline), and salicylic acid and derivatives (aspirin [analgesic dose])—were not evaluated due to unavailability across all sites. Of 63 disease-specific conditions, 21 were assessed based on the availability of relevant diagnosis codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Of the 20 clinically significant DDI-based PIM pairs, 19 were evaluated; one pair involving cimetidine and CNS drugs was not assessed due to the absence of cimetidine at all hospitals.

Receipt of these medications was determined from outpatient prescription records using hospital-specific drug codes. Exposure was defined as receipt of at least one PIM from any of the three categories during 2023. Patients who received  $\geq 1$  PIM at any time during this period were classified as PIM users, whereas those who received none were classified as non-users. Exposure status was treated as a fixed binary variable for the 2024 follow-up period.

### 2.4. Data source and collection

Data were retrieved from the electronic medical record (EMR) systems by hospital staff responsible for medical data management. These data were used to construct variables on demographics (sex, age, and health insurance scheme), clinical characteristics (chronic diseases and comorbidity score), and medication-related factors (polypharmacy and hyperpolypharmacy).

All chronic conditions in this study were identified using ICD-10 codes and validated coding algorithms<sup>22, 23</sup>. The comorbidity score, reflecting overall disease burden and mortality risk, was calculated using

the Charlson Comorbidity Index (CCI), based on ICD-10 codes for 19 chronic conditions with weighting applied<sup>24</sup>.

A prescription was defined as the set of systemically administered medications prescribed on the same day across all clinical departments. Prescriptions containing 5–9 or  $\geq 10$  medications were classified as polypharmacy or hyperpolypharmacy, respectively<sup>25</sup>. Patients who received such prescriptions on any day in 2023 were categorised accordingly.

### 2.5. Hospitalisation outcomes

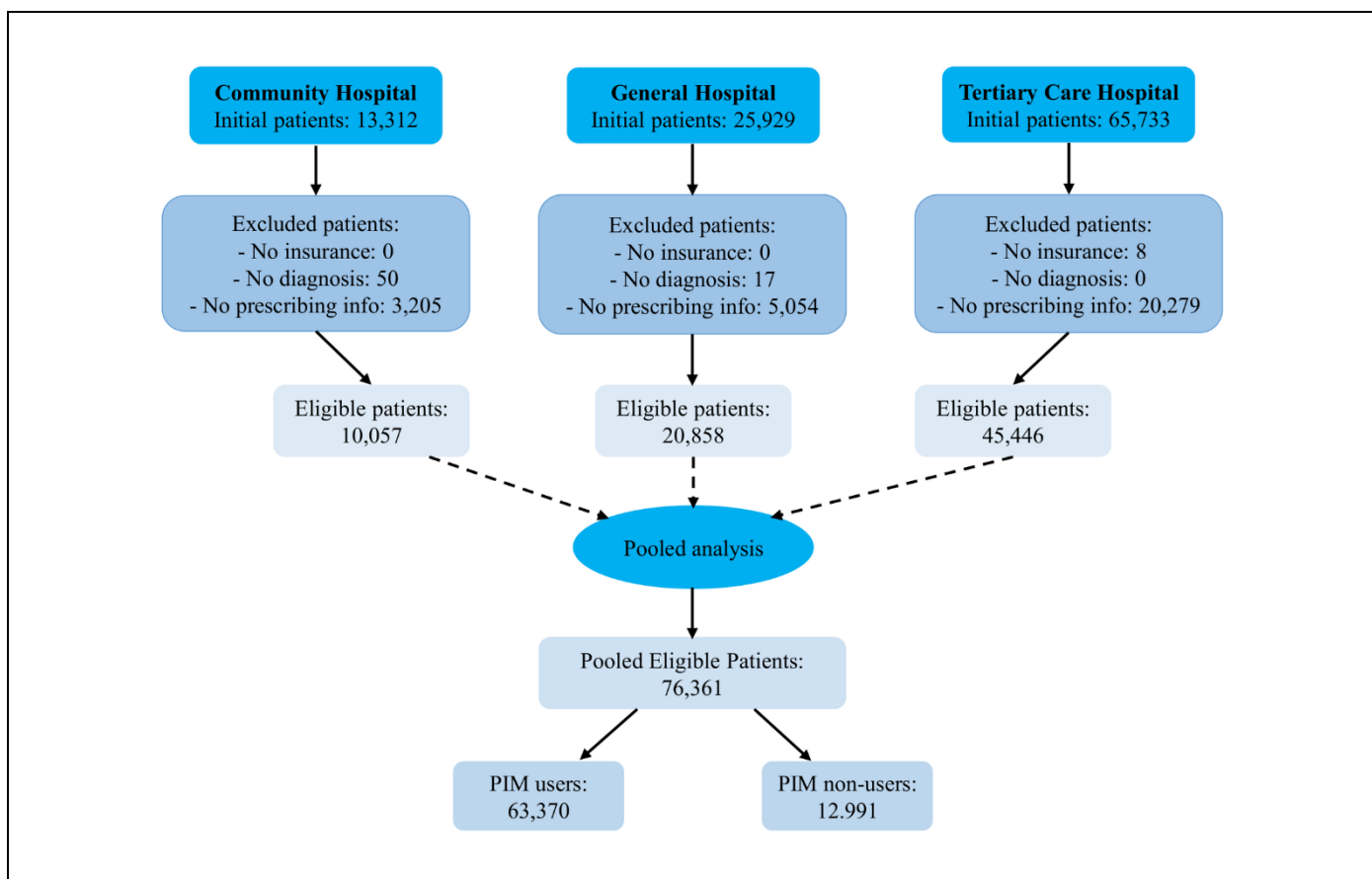
Hospitalisation outcomes were assessed using data on all 2024 admissions retrieved from the EMR systems. The primary outcome was all-cause hospitalisation, defined as the first such admission in 2024 among patients who survived to discharge, while secondary outcomes included the number of hospitalisations, ADE-related hospitalisation, and in-hospital mortality, which could occur during any admission within the follow-up period. ADE-related hospitalisation was identified using ICD-10 codes. The core code set was based on Hohl et al.<sup>26</sup> and expanded with additional codes selected by clinical experts to capture outcomes potentially related to PIMs, such as delirium, gastrointestinal (GI) bleeding, and falls or fractures. The ICD-10 codes used are presented in Supplemental Table S1. In-hospital mortality was determined from discharge status.

### 2.6. Statistical analysis

Data from the three hospitals were combined and summarised using descriptive statistics. Comparisons between PIM users and non-users were performed using inferential statistics. PIM prevalence was reported overall, by PIM type and individual medication. Prevalence was calculated using the most appropriate denominator for each analysis, with further details provided in the results section and figure notes.

Predictors of PIM use were identified using binary logistic regression. Crude and adjusted odds ratios (ORs and aORs) with 95% confidence intervals (CIs) were reported. Variables with P-values  $< 0.20$  in univariable analysis were included in the multivariable model. Backward elimination was applied to retain variables with P-values  $< 0.05$ . Multicollinearity was assessed in the final model using variance inflation factors (VIFs), and variables with VIF  $\geq 5$  were excluded<sup>27</sup>.

Associations between PIM use and binary outcomes (all-cause hospitalisation, ADE-related hospitalisation, and in-hospital mortality) were examined using generalised linear models with a log-link function to estimate adjusted relative risks (aRRs) and 95% CIs. Linear regression was used to estimate adjusted mean differences (aMDs) in the number of hospitalisations.



**Figure 1.** Flow diagram of patient selection and pooled analysis

Subgroup analyses were conducted according to PIM type. All models were adjusted for potential prognostic confounders. The covariate set was defined a priori based on clinical relevance and a conceptual framework, including variables plausibly associated with both PIM exposure and hospitalisation outcomes. These comprised hospital level, age group, sex, the Universal Coverage Scheme (UCS), and comorbidity score. These factors represent established demographic, healthcare-related, and clinical characteristics that may confound the association of interest. Polypharmacy was not included in the main models, as it is closely related to overall PIM exposure and may lie on the causal pathway; including this variable could introduce collinearity and overadjustment, potentially attenuating the estimated effect of PIM use.

All analyses were performed using STATA version 18.0 (StataCorp, College Station, TX, USA). Two-tailed tests were applied, and P-values < 0.05 were considered statistically significant.

### 3. RESULTS

#### 3.1. Patient characteristics

Figure 1 illustrates the patient selection process. Of the 105,974 older patients initially identified, 76,361

were deemed eligible and included in the pooled analysis. Among these, 63,370 (82.99%) were classified as PIM users and 12,991 (17.01%) as non-users.

Table 1 presents the baseline characteristics. The mean age was  $69.59 \pm 7.63$  years, with 76.42% of participants aged 60–75 years, and 55.66% were female. Most patients were covered by the UCS. The median number of chronic conditions was 1 (IQR 0–2), with 17.02% having  $\geq 3$  morbidities. The most common conditions were hypertension (28.68%), diabetes without complications (13.97%), and chronic kidney disease (10.92%). Overall, 40.72% had a CCI  $\geq 1$ . The median number of prescriptions per patient was 3 (IQR 1–5). Polypharmacy and hyperpolypharmacy were present in 55.67% and 15.01% of patients, respectively.

Compared with non-users, PIM users were slightly older (mean age: 69.62 vs 69.46 years), more likely to be female (56.32% vs 52.44%), and more frequently had multimorbidity ( $\geq 3$  conditions: 19.90% vs 2.95%). They also had a higher median number of prescriptions (3 vs 2) and substantially higher rates of polypharmacy (65.59% vs 7.31%).

#### 3.2. Prevalence of PIM use

Among 76,361 older patients, 63,370 (82.99%) received at least one PIM, with the highest prevalence

Table 1. Patient characteristics

Characteristics	Total (n = 76,361)	PIM users (n = 63,370)	PIM non-users (n = 12,991)	P-values
<b>Hospital classification</b>				
Community hospital	10,057 (13.17)	9,055 (14.29)	1,002 (7.71)	< 0.001
General hospital	20,858 (27.31)	17,676 (27.89)	3,182 (24.49)	
Tertiary-care hospital	45,446 (59.51)	36,639 (57.82)	8,807 (67.79)	
<b>Sex</b>				
Male	33,856 (44.34)	27,677 (43.68)	6,179 (47.56)	< 0.001
Female	42,505 (55.66)	35,693 (56.32)	6,812 (52.44)	
<b>Age (year)</b>	69.59 ± 7.63	69.62 ± 7.66	69.46 ± 7.44	0.033
60-75	58,358 (76.42)	48,358 (76.31)	10,000 (76.98)	0.103
≥ 75	18,003 (23.58)	15,012 (23.69)	2,991 (23.02)	
<b>Health insurance schemes</b>				
UCS	53,317 (69.82)	43,751 (69.04)	9,566 (73.64)	< 0.001
CSMBS	20,980 (27.47)	17,859 (28.18)	3,121 (24.02)	
SSS	1,099 (1.44)	935 (1.48)	164 (1.26)	
Others	965 (1.26)	825 (1.30)	140 (1.08)	
<b>Chronic morbidities</b>				
Number of chronic morbidities	1 (0-2)	1 (0-2)	0 (0-1)	< 0.001
Chronic morbidities ≥ 3	12,995 (17.02)	12,612 (19.90)	383 (2.95)	< 0.001
Hypertension	21,902 (28.68)	20,988 (33.12)	914 (7.04)	< 0.001
Diabetes without complications	10,665 (13.97)	10,242 (16.16)	423 (3.26)	< 0.001
Chronic kidney disease, mild to moderate	8,340 (10.92)	8,088 (12.76)	252 (1.94)	< 0.001
Chronic pain	7,796 (10.21)	7,580 (11.96)	216 (1.66)	< 0.001
Cancer, non-metastatic	5,210 (6.82)	4,048 (6.39)	1,162 (8.94)	< 0.001
Lower urinary tract symptoms, benign prostatic hyperplasia	4,458 (5.84)	3,619 (5.71)	839 (6.46)	0.001
Stroke or transient ischemic attack	3,004 (3.93)	2,789 (4.40)	215 (1.65)	< 0.001
Diabetes with complications	2,615 (3.42)	2,387 (3.77)	228 (1.76)	< 0.001
Chronic heart failure	2,441 (3.20)	2,400 (3.79)	41 (0.32)	< 0.001
Liver disease, mild	2,404 (3.15)	1,981 (3.13)	423 (3.26)	0.441
History of falls or fracture	2,354 (3.08)	2,260 (3.57)	94 (0.72)	< 0.001
Chronic pulmonary disease	2,226 (2.92)	2,079 (3.28)	147 (1.13)	< 0.001
Atrial fibrillation	2,167 (2.84)	2,131 (3.36)	36 (0.28)	< 0.001
Chronic kidney disease, severe	1,642 (2.15)	1,542 (2.43)	100 (0.77)	< 0.001
Severe constipation	1,567 (2.05)	1,501 (2.37)	66 (0.51)	< 0.001
Asthma	1,386 (1.82)	1,274 (2.01)	112 (0.86)	< 0.001
AIDS	1,381 (1.81)	1,142 (1.80)	239 (1.84)	0.77
Cirrhosis	1,337 (1.75)	1,141 (1.80)	196 (1.51)	0.021
Rheumatoid arthritis	1,272 (1.67)	1,254 (1.98)	18 (0.14)	< 0.001
Dementia	1,247 (1.63)	1,187 (1.87)	60 (0.46)	< 0.001
Depression	1,217 (1.59)	1,208 (1.91)	9 (0.07)	< 0.001
Myocardial infarction	1,030 (1.35)	1,004 (1.58)	26 (0.20)	< 0.001
Hypothyroidism	1,010 (1.32)	992 (1.57)	18 (0.14)	< 0.001
Chronic viral hepatitis B	718 (0.94)	592 (0.93)	126 (0.97)	0.702
Hemiplegia or paraplegia	627 (0.82)	592 (0.93)	35 (0.27)	< 0.001
Cancer, metastatic	564 (0.74)	511 (0.81)	53 (0.41)	< 0.001
Peptic ulcer disease	517 (0.68)	435 (0.69)	82 (0.63)	0.484
Alcohol misuse	506 (0.66)	476 (0.75)	30 (0.23)	< 0.001

**Table 1.** Patient characteristics (Continued).

Characteristics	Total (n = 76,361)	PIM users (n = 63,370)	PIM non-users (n = 12,991)	P-values
Epilepsy	464 (0.61)	448 (0.71)	16 (0.12)	< 0.001
Peripheral vascular disease	456 (0.60)	423 (0.67)	33 (0.25)	< 0.001
Parkinson's disease	453 (0.59)	414 (0.65)	39 (0.30)	< 0.001
Schizophrenia	368 (0.48)	367 (0.58)	1 (0.01)	< 0.001
Syncope	266 (0.35)	243 (0.38)	23 (0.18)	< 0.001
Liver disease, moderate to severe	211 (0.28)	182 (0.29)	29 (0.22)	0.206
Psoriasis	192 (0.25)	147 (0.23)	45 (0.35)	0.018
Urinary incontinence	169 (0.22)	152 (0.24)	17 (0.13)	0.016
Delirium	165 (0.22)	160 (0.25)	5 (0.04)	< 0.001
Irritable bowel syndrome	115 (0.15)	110 (0.17)	5 (0.04)	< 0.001
Multiple sclerosis	41 (0.05)	30 (0.05)	11 (0.08)	0.094
Inflammatory bowel disease	35 (0.05)	31 (0.05)	4 (0.03)	0.379
HIV infection, no AIDS	8 (0.01)	6 (0.01)	2 (0.02)	0.611
Comorbidity score	0 (0-1)	0 (0-1)	0 (0-0)	< 0.001
Comorbidity score $\geq$ 1	31,097 (40.72)	28,139 (44.40)	2,958 (22.77)	< 0.001
<b>Medication prescriptions</b>				
Number of prescriptions per patient	3 (1-5)	3 (2-5)	2 (1-2)	< 0.001
Polypharmacy	42,513 (55.67)	41,564 (65.59)	949 (7.31)	< 0.001
Hyperpolypharmacy	11,460 (15.01)	11,443 (18.06)	17 (0.13)	< 0.001
Schizophrenia	368 (0.48)	367 (0.58)	1 (0.01)	< 0.001
Syncope	266 (0.35)	243 (0.38)	23 (0.18)	< 0.001
Liver disease, moderate to severe	211 (0.28)	182 (0.29)	29 (0.22)	0.206
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Inflammatory bowel disease	35 (0.05)	31 (0.05)	4 (0.03)	0.379
HIV infection, no AIDS	8 (0.01)	6 (0.01)	2 (0.02)	0.611
Comorbidity score	0 (0-1)	0 (0-1)	0 (0-0)	< 0.001
Comorbidity score $\geq$ 1	31,097 (40.72)	28,139 (44.40)	2,958 (22.77)	< 0.001
<b>Medication prescriptions</b>				
Number of prescriptions per patient	3 (1-5)	3 (2-5)	2 (1-2)	< 0.001
Polypharmacy	42,513 (55.67)	41,564 (65.59)	949 (7.31)	< 0.001
Hyperpolypharmacy	11,460 (15.01)	11,443 (18.06)	17 (0.13)	< 0.001

Age is presented as mean  $\pm$  SD and compared using the independent-sample t-test; the number of chronic morbidities, comorbidity scores, and prescriptions per patient are presented as median (IQR) and compared using the Mann–Whitney U test; categorical variables are presented as n (%) and compared using the chi-squared or Fisher's exact test, as appropriate.

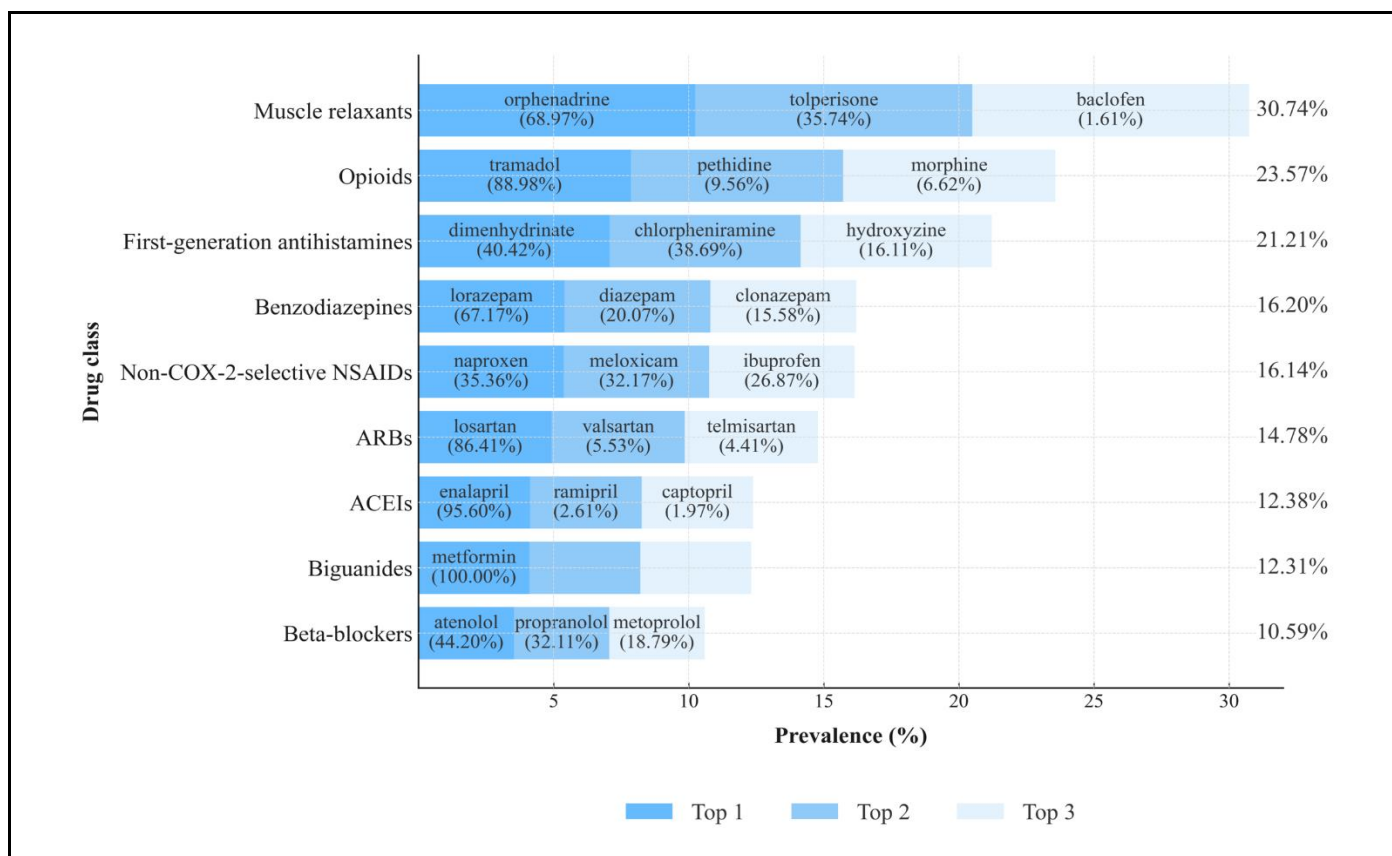
UCS = Universal Coverage Scheme; CSMBS = Civil Servant Medical Benefit Scheme; SSS = Social Security Scheme

observed in the community hospital (90.04%; 9,055/10,057), followed by the general hospital (84.74%; 17,676/20,858) and the tertiary-care hospital (80.62%; 36,639/45,446).

Disease-independent PIMs were prescribed to 63,156 patients (82.71%). Among these patients, paracetamol (acetaminophen) was prescribed most frequently, with a disproportionately high prevalence of 55.11%. Figure 2 presents the drug classes prescribed at a prevalence exceeding 10% (*Note: paracetamol was excluded from the figure to enhance visual clarity due to its dominant prevalence*). The most commonly

prescribed classes were shown to be muscle relaxants (30.74%), with orphenadrine as the principal agent, followed by opioid analgesics (23.57%), mainly tramadol, and first-generation antihistamines (21.21%), primarily dimenhydrinate. Full details are provided in Supplemental Table 2.

Disease-specific PIMs were prescribed to 23,737 patients (31.09%). Figure 3 shows the most common conditions associated with these prescriptions. The highest prevalence was observed in depression (92.03%), with frequent use of benzodiazepines (BZDs) (80.00%), particularly lorazepam; followed by delirium,



**Figure 2.** Prevalence of drug classes and top three drugs among older adults receiving disease-independent PIMs

**Note:** The prevalence for each drug class was calculated by dividing the number of patients who received that specific drug class by the total number of patients who received at least one disease-independent PIM (e.g. 30.74% for muscle relaxants = 19,416/63,156). The prevalence for each drug was calculated by dividing the number of patients who received that specific drug by the number of patients who received the corresponding drug class (e.g. 68.97% for orphenadrine = 13,391/19,416). Bar segment lengths reflect drug ranking (Top 1–3) and do not correspond to actual usage percentages.

**Abbreviations:** NSAIDs = non-steroidal anti-inflammatory drugs; ARBs = angiotensin II receptor blockers; ACEIs = angiotensin-converting enzyme inhibitors.

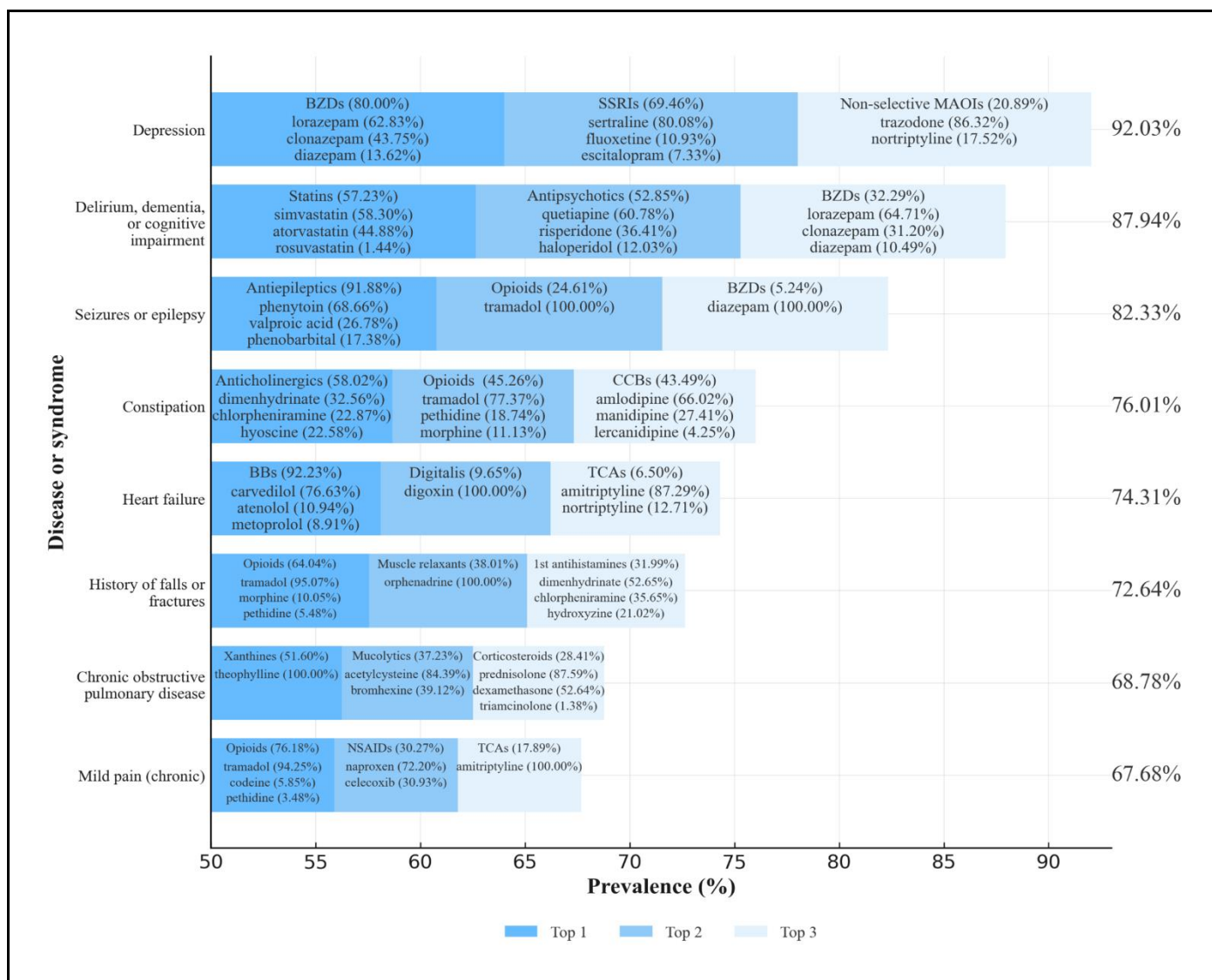
dementia, or cognitive impairment (87.94%) with statins (57.23%), such as simvastatin; and seizures or epilepsy (82.33%) with old-generation antiepileptic drugs (AEDs) (91.88%), mainly phenytoin. Other conditions with high PIM prevalence included constipation (76.01%), treated with anticholinergic agents; heart failure (74.31%) with beta-adrenoceptor antagonists; falls or fractures (72.64%) and mild pain (67.68%) with opioid analgesics; and chronic obstructive pulmonary disease (68.78%) with xanthine derivatives. Additional details are provided in Supplemental Table 3.

DDI-based PIMs were prescribed to 7,823 patients (10.24%). Figure 4 presents five DDI patterns with a prevalence >10%. The most frequent was the combination of BZDs with opioid analgesics (29.34%), primarily lorazepam + tramadol. This was followed by low-dose aspirin combined with clopidogrel, vitamin K antagonists (VKAs), or direct oral anticoagulants (DOACs) (21.48%), most often in combination with clopidogrel. NSAIDs co-administered with anticoagulants or corticosteroids accounted for 19.46%, commonly meloxicam + dexamethasone. Combinations

of multiple anticholinergic agents were identified in 19.14%, mainly amitriptyline + dimenhydrinate. Lastly, aldosterone antagonists combined with potassium-conserving agents were observed in 12.69%, particularly spironolactone + enalapril. Full details are available in Supplemental Table 4.

### 3.3. Predictors of PIM use

Table 2 summarises the univariate and multivariate analyses. Several factors were independently associated with higher odds of PIM use, including receiving care at lower-level hospitals (community: aOR 2.18; general: aOR 1.32, vs tertiary care), female sex (aOR 1.08), and having  $\geq 3$  chronic conditions (aOR 2.01). Among all predictors, increased medication burden demonstrated the strongest associations, with markedly higher odds observed in patients with polypharmacy and hyperpolypharmacy (aORs 16.38 and 18.36, respectively), compared with those prescribed 1–4 medications. In contrast, patients aged  $\geq 75$  years (aOR 0.79) and those covered under the UCS (aOR 0.85) had lower odds of PIM use.



**Figure 3.** Prevalence of drug classes and top three drugs among older adults receiving disease-specific PIMs

**Note:** The prevalence for each disease or syndrome was calculated by dividing the number of patients with a specific disease who received at least one medication identified as a disease-specific PIM for that condition by the total number of patients with that disease (e.g. 92.03% of patients with depression received at least one disease-specific PIM for that condition = 1,120/1,217). The prevalence for each drug class was calculated by dividing the number of patients with the disease who received that specific drug class by the number of patients with the disease who received at least one disease-specific PIM for that condition (e.g. 80.00% received BZDs = 896/1,120). The prevalence for each drug was calculated by dividing the number of patients with the disease who received that specific drug by the number of patients with the disease who received the corresponding drug class (e.g. 62.83% received lorazepam = 563/896). Bar segment lengths reflect ranking order (Top 1–3) and are not proportional to actual usage percentages.

**Abbreviations:** BBs = beta-blockers; BZDs = benzodiazepines; CCBs = calcium channel blockers; MAOIs = monoamine oxidase inhibitors; NSAIDs = non-steroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; 1st antihistamines = first-generation antihistamines.

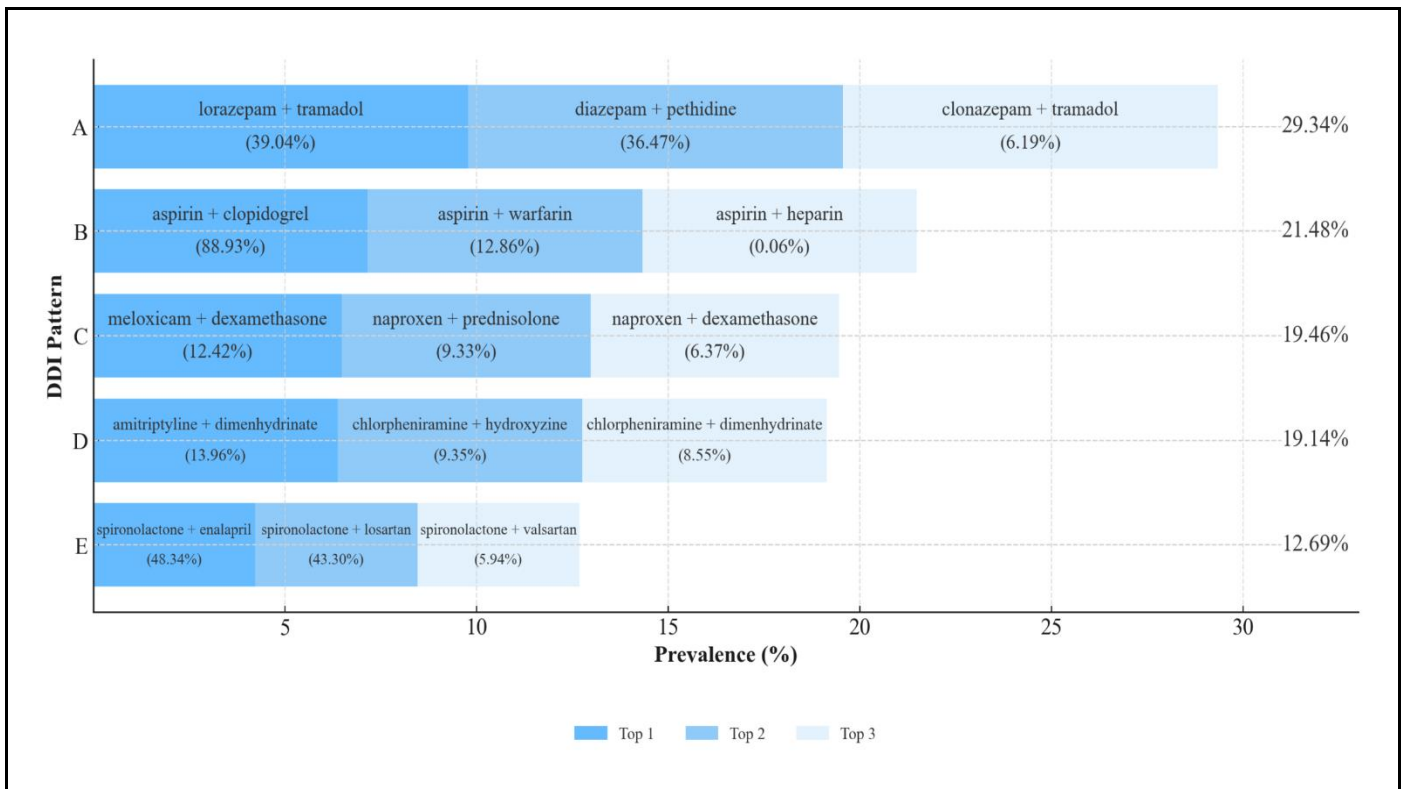
### 3.4. Hospitalisation outcomes of PIM use

All-cause hospitalisation occurred in 14.86% (9,419/63,370) of PIM users, compared with 11.55% (1,501/12,991) of non-users. PIM users also had a higher mean number of hospital admissions ( $1.58 \pm 0.14$  vs  $1.37 \pm 0.27$ ), as well as greater rates of ADE-related hospitalisation (4.31% vs 1.74%) and in-hospital mortality (1.12% vs 0.63%).

Figure 5 presents both crude and adjusted estimates for each outcome by PIM type. After

adjustment for potential confounders, overall PIM use remained significantly associated with increased risks of all-cause hospitalisation (aRR = 1.17), ADE-related hospitalisation (aRR = 1.86), in-hospital mortality (aRR = 1.46), and hospital admission frequency (aMD = 0.11).

When stratified by PIM type, disease-specific and DDI-based PIMs were significantly associated with increased risks across all outcomes. In contrast, disease-independent PIMs were associated only with higher rates of ADE-related hospitalisation and admission frequency,



**Figure 4.** Prevalence of DDI patterns and top 3 DDI sub-patterns among older adults receiving DDI-based PIMs

**Note:** The prevalence for each DDI pattern was calculated by dividing the number of patients who received that specific DDI pattern by the total number of patients who received DDI-based PIMs (e.g., 29.34% received benzodiazepines + opioids = 2,295/7,823). The prevalence for each specific drug combination was calculated by dividing the number of patients who received that specific combination (sub-pattern) by the number of patients who received the corresponding main DDI pattern (e.g., 39.04% received lorazepam + tramadol = 896/2,295). Segment length represents the rank of the top 1–3 sub-patterns and does not reflect actual percentage use.

DDI Patterns A–E represent the following drug combinations:

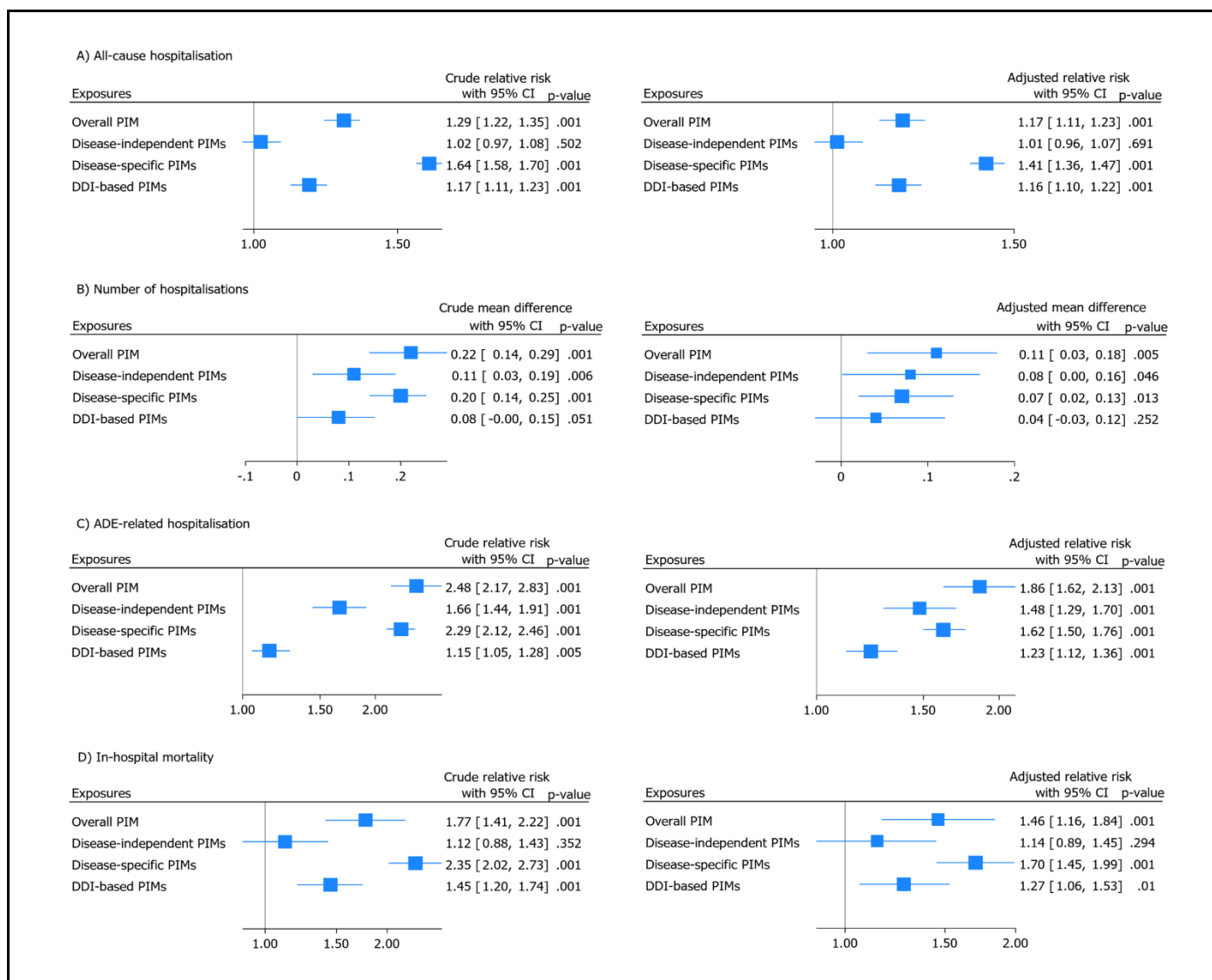
- A = benzodiazepines + opioids;
- B = aspirin + clopidogrel, vitamin K antagonists, or DOACs;
- C = NSAIDs + anticoagulants or corticosteroids;
- D = multiple anticholinergic drugs;
- E = aldosterone antagonists + potassium-conserving agents.

**Table 2.** Crude and adjusted odds ratios for predictors of PIM use among older outpatients

Potential predictors	Crude OR (95% CI), P-value	Adjusted OR (95% CI), P-value
Community hospital	2.17 (2.03-2.33), <0.001	2.18 (2.02-2.35), <0.001
General hospital	1.34 (1.28-1.40), <0.001	1.32 (1.25-1.38), <0.001
Female	1.17 (1.13-1.21), <0.001	1.08 (1.04-1.13), <0.001
Age ≥ 75 years	1.04 (0.99-1.09), 0.103	0.79 (0.75-0.84), <0.001
UCS	0.80 (0.77-0.83), <0.001	0.85 (0.81-0.89), <0.001
≥ 3 chronic morbidities	8.18 (7.38-9.07), <0.001	2.01 (1.80-2.26), <0.001
Comorbidity score ≥1	2.71 (2.59-2.83), <0.001	-
Polypharmacy	24.19 (22.59-25.89), <0.001	16.38 (15.28-17.57), <0.001
Hyperpolypharmacy	168.18 (104.47-270.73), <0.001	18.36 (11.35-29.70), <0.001

Variables with a univariate  $P < 0.20$  were included in the multivariate logistic regression. Backward elimination was applied to retain only those with  $P < 0.05$ . No multicollinearity was detected in the final model (mean VIF = 2.56; all VIFs < 5). The tertiary-care hospital was used as the reference category for hospital level.

UCS: Universal Coverage Scheme



**Figure 5.** Crude and adjusted estimates for hospitalisation outcomes by PIM type.

All models for overall PIM use were adjusted for hospital level, sex, age group, UCS, and CCI, whereas models for PIM subtypes were additionally adjusted for PIM category.

but not with all-cause hospitalisation or in-hospital mortality. These findings underscore the differential impact of each PIM category on hospitalisation outcomes.

## 4. DISCUSSION

This study applied the Asian criteria to evaluate PIM use and its clinical impact among older outpatients. PIMs were highly prevalent, predicted by several factors—most notably polypharmacy—and were associated with adverse hospitalisation outcomes. These findings underscore the need for targeted interventions to support deprescribing in this population.

### 4.1. Prevalence of PIM use

This study identified a high overall prevalence of PIM use among older outpatients, with nearly four

out of five receiving at least one PIM. This rate exceeds previously reported estimates among older outpatients, which have ranged from 27.4% to 54.0%<sup>28-32</sup>. Two primary contextual factors may account for this finding. Firstly, the inclusion of hospitals across different levels of care likely captured a broader spectrum of prescribing practices. A stepwise decline in PIM prevalence was observed from the community hospital (90.04%) to the general hospital (84.74%) and tertiary hospital (80.62%). This trend is consistent with previous studies using the 2023 Beers criteria, which reported prevalence rates of 51.3% at community hospitals in Bahrain<sup>33</sup>, 45.7% at secondary hospitals in Ethiopia<sup>30</sup>, and 32.0% at tertiary hospitals in China<sup>31</sup>. Higher-level hospitals may have greater access to safer therapeutic alternatives and provide better systems of geriatric care. Secondly, the high prevalence may also be attributable to the broader scope of the Asian criteria. Previous studies

have shown that applying different PIM tools to the same population can yield varying prevalence estimates. For example, Eggli et al.<sup>12</sup> applied several PIM tools to a cohort of older adults and reported prevalence rates of 36.0% with the Beers criteria and 33.4% with the Priscus list. Similarly, Endalifer et al.<sup>30</sup> observed differing rates in the same cohort when using the 2023 Beers (45.7%) and STOPP/START version 3 (39.8%) criteria.

Disease-independent PIMs were the most prevalent category, occurring in 82.7% of older outpatients. This rate is substantially higher than those reported for medications to avoid under the Beers criteria (34.5%–57.2%)<sup>17, 19, 29</sup>. Within this category, certain medications demonstrated particularly high prescription rates. Paracetamol was prescribed for over half of the participants, either alone or with orphenadrine. In older adults, reduced hepatic clearance may heighten the risk of toxicity, particularly with prolonged use or concurrent self-medication owing to its wide availability. Orphenadrine has anticholinergic effects that may cause a dry mouth, urinary retention, constipation, and sedation, increasing fall risk; its benefit at typical doses in older adults also remains uncertain<sup>11</sup>. Tramadol can induce or worsen the syndrome of inappropriate antidiuretic hormone secretion and hyponatraemia, particularly during treatment initiation or titration, necessitating serum sodium monitoring<sup>11</sup>. First-generation antihistamines are highly anticholinergic, poorly cleared in older adults, and strongly linked to falls, delirium, and cognitive decline<sup>11</sup>. Supporting these risks, Laird et al.<sup>34</sup> identified first-generation antihistamines (2.9%) as fall-risk-increasing drugs (FRIDs) in aged care homes in Australia. BZDs were prescribed to 16.20% of patients. Similar patterns were noted by Albert et al.<sup>35</sup>, who reported BZDs as the most frequently used PIM class in outpatient care. Despite their therapeutic roles, both short- and long-acting BZDs are discouraged in older adults due to heightened risks of sedation, cognitive impairment, and falls<sup>11</sup>.

In this study, nearly one-third of older outpatients received at least one disease-specific PIM. This rate is substantially higher than previous estimates (3.3%–7.2%) based on the 2023 Beers criteria<sup>17, 30, 32</sup>. This high prevalence likely reflects our evaluation of disease-specific PIMs across 21 conditions. Among the 21 conditions assessed, depression showed the highest PIM prevalence, with BZDs most frequently prescribed. Alsultan et al.<sup>29</sup> reported that 50.98% of older psychiatric outpatients with mood disorders—including depression—received PIMs to avoid, and 84.97% received those to be used with caution, with antidepressants being the most frequently prescribed. In patients with dementia, delirium, cognitive impairment, or a history of falls or fractures, commonly prescribed PIMs included antipsychotics, BZDs, anticholinergics,

and opioids. These patterns are consistent with earlier findings<sup>17, 32</sup>. Among those with a history of falls or fractures, 72.64% received at least one FRID, closely mirroring the 83.2% reported by Laird et al.<sup>34</sup> in Australian aged care facilities using the STOPPFall criteria. Their most common FRIDs included antidepressants, diuretics, opioids, antipsychotics, and BZDs. Similarly, PIMs for heart failure and constipation were frequently observed. Karki et al.<sup>32</sup> found NSAIDs or COX-2 inhibitors in 33.3% and diltiazem in 16.7% of hospitalised older patients with heart failure, while Boateng et al.<sup>18</sup> reported that 1.1% of patients with chronic constipation received drugs known to worsen the condition. Among patients with epilepsy, 91.88% received old-generation antiepileptic drugs (AEDs), which pose increased risks of adverse effects and DDIs. Despite current guidelines recommending newer-generation AEDs, a Thai study still found continued use of sodium valproate and phenytoin, although declining over time<sup>36</sup>. Across conditions, BZDs, anticholinergics, and opioids were repeatedly implicated in multiple PIM categories. These agents are strongly associated with cognitive decline or a risk of falling, yet they remain commonly prescribed<sup>29, 34, 37</sup>. In a nationwide French study, Novais et al.<sup>37</sup> found that 32.8% of older adults were exposed to at least one anticholinergic and sedative (Ac/S) medication, using the 2023 AGS Beers Criteria and REMEDI[e]S tool.

The prevalence of DDI-based PIMs in our study (10.24%) exceeded previous reports, which ranged from 4.1% to 5.93%<sup>17, 30</sup> likely due to variations in prescribing practices and the breadth of DDI criteria applied. The most common DDI involved the concurrent use of BZDs and opioids, a combination that may exacerbate fall risk. Ananchaisarp et al.<sup>17</sup> documented co-prescribing of AEDs with two or more other CNS-active drugs in 1.9% of older adults, raising concerns about the safety of combining multiple CNS depressants. Laird et al.<sup>34</sup> found that 83.2% of aged care residents were exposed to at least one FRID, with over half receiving two or more, including 13.9% prescribed BZDs and 24.1% opioids. Another frequent DDI pattern involved the use of low-dose aspirin with clopidogrel, VKAs, or DOACs, which may increase the risk of GI and intracranial bleeding. Endalifer et al.<sup>30</sup> reported co-prescribing rates of 6.8% for aspirin with warfarin and 0.8% for aspirin with clopidogrel, while Jiang et al.<sup>31</sup> found a 9.44% prevalence for aspirin–clopidogrel use. Combinations of anticholinergic drugs were also common, observed in 19.14% of patients. Novais et al.<sup>37</sup> reported that 32.8% of older French adults were exposed to at least one Ac/S agent, and 7.9% to two or more. To better quantify anticholinergic burden, validated tools such as the Anticholinergic Cognitive Burden (ACB) scale should be employed, as certain medications may exert strong anticholinergic effects even when used alone<sup>38</sup>.

## 4.2. Predictors of PIM use

Previous studies have noted a trend toward higher PIM prevalence at lower-level hospitals<sup>30, 31, 33</sup>. Our study builds on this by identifying hospital level as an independent predictor. Female sex was independently associated with PIM use, consistent with findings from Ethiopia<sup>30</sup>. This may be attributed to sex-specific disease profiles being more frequently treated with PIMs. In contrast to earlier studies reporting a positive association between increasing age and PIM use<sup>30, 31</sup>, our study found that patients aged  $\geq 75$  years were less likely to receive PIMs—possibly reflecting more cautious prescribing practices for this age group in Thailand. UCS coverage was associated with reduced PIM use, potentially due to restricted access to certain PIMs not being included in the National List of Essential Medicines. Multimorbidity emerged as a positive predictor of PIM use, consistent with previous studies<sup>17, 28, 35</sup>. It contributes to the use of multiple medications and increases the risk of inappropriate prescribing. Polypharmacy and hyperpolypharmacy showed the strongest associations with PIM use, consistent with earlier findings<sup>28, 30-32</sup>. Despite its simplicity, the polypharmacy threshold remains useful for identifying patients at risk of PIM use.

## 4.3. Association between PIM use and hospitalisation outcomes

Our study found that PIM use was significantly associated with hospitalisation outcomes, consistent with the findings from Boateng *et al.*<sup>18</sup>, who reported elevated risks of hospitalisation, falls, and ADEs based on the STOPP criteria, though no association with mortality was observed. Similarly, a systematic review by Mekonnen *et al.*<sup>39</sup> found that potentially inappropriate prescribing was linked to ADE-related hospital admissions, functional decline, and ADEs, but not to all-cause mortality or readmission.

In our study, both overall PIM use and each PIM type were significantly associated with an increased risk of ADE-related hospitalisation, with aRRs greater than 1. A recent Thai study of older outpatients found that FRIDs, particularly BZDs, were associated with a 1.35-fold increased risk of falls, reinforcing their role as modifiable contributors to fall-related harm<sup>40</sup>.

Nevertheless, given the observational nature of this study, these findings should be interpreted as associations rather than evidence of causality. PIM use may also reflect underlying clinical complexity, multimorbidity, and medication burden, which are themselves associated with adverse hospitalisation outcomes. Accordingly, PIMs may function, at least in

part, as markers of high-risk patients rather than direct causes of hospitalisation or mortality.

## 4.4. Strengths and limitations

This is the first study to assess PIM use among older outpatients using the Asian criteria, which reflect regionally relevant prescribing practices. It evaluates disease-specific PIMs across 21 conditions, more than previously reported, and includes a wide range of drug classes and clinically important DDIs. The large, multisite sample enhances generalisability, while the inclusion of hospitalisation outcomes provides real-world evidence to inform both clinical practice and policy.

Nonetheless, this study has some limitations. Firstly, its retrospective design and the assessment of PIM exposure and outcomes in separate years may have limited causal inference. Secondly, prescribing variation across the three hospitals may have affected PIM prevalence and outcomes, but inter-hospital differences were not specifically analysed. Thirdly, PIM exposure was treated as a fixed binary variable throughout the follow-up period. This approach does not account for duration, persistence, or changes in exposure over time, which may influence the observed associations. Thirdly, PIM identification was based solely on hospital prescription data and did not consider cumulative dose, medications obtained from external sources, or hospitalisations that may have occurred at other facilities. Finally, residual confounding arising from variables not captured in the available data, such as disease severity, functional status, and frailty, may have influenced both prescribing patterns and hospitalisation outcomes. As a result, the observed associations may not fully reflect the true magnitude of effect.

## 5. CONCLUSIONS

This study found a high prevalence of PIM use among older outpatients based on the Asian criteria, with female sex, polypharmacy, multimorbidity, and hospital level identified as key predictors. PIM use was associated with adverse hospitalisation outcomes, underscoring the need for targeted interventions. The Asian criteria provide a context-specific tool for improving prescribing in Asian settings. In practice, the three PIM categories could be embedded into electronic clinical decision-support systems to enhance medication safety. Disease-independent PIMs may function as a high-risk medication list that triggers alerts when prescribed to older adults. Disease-specific PIMs could be linked to diagnostic codes to generate warnings in patients with high-risk conditions. DDI-based PIMs may be incorporated into automated interaction screening to flag clinically significant drug combinations. These criteria may also support structured outpatient

medication review workflows, particularly for patients with polypharmacy or multimorbidity, thereby helping to reduce PIM use and related risks.

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### Author contribution

Conceptualisation: K.J.; Funding acquisition: K.J.; Methodology: K.J. and S.P.; Software: K.J.; Validation: K.J., S.P., S.J., P.N., and D.P.; Formal analysis: K.J., S.P., S.J., P.N., and D.P.; Investigation: K.J., S.P., S.J., P.N., and D.P.; Resources: K.J.; Data curation: K.J., S.P., S.J., P.N., and D.P.; Writing – original draft preparation: K.J., S.P., S.J., P.N., and D.P.; Writing – review and editing: K.J.; Visualisation: K.J. and S.P.; Supervision: K.J.; Project administration: K.J. All authors have read and agreed to the published version of the manuscript.

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### Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

### Ethics approval

Ethical approvals and data access permissions were obtained prior to data retrieval. Approval was granted by the Human Ethics Committee of the University of Phayao, which covered research conducted at the community hospital (study code: HREC-UP-HSST 1.1/002/68; approval date: 4 October 2024). Additional approvals were obtained from the general hospital (study code: 20/2567; approval date: 22 November 2024) and the tertiary-care hospital (study code: HREC No. 009/2568; approval date: 21 January 2025). All data were anonymised prior to analysis, and no identifiable patient information was collected or stored.

### Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve the writing and clarity of the manuscript. The authors reviewed and edited the output as necessary and accept full responsibility for the content of the final manuscript.

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**Table S1.** ICD-10 Codes for Adverse Drug Events (ADEs)

ICD-10 Code	Definition
<b>Hohl et al. (2013)</b>	
E16	Other disorders of pancreatic internal secretion (e.g. hypoglycemia)
G21	Secondary parkinsonism
G62	Other polyneuropathies
I95	Hypotension
J70	Respiratory conditions due to drugs
K25	Gastric ulcer
L27	Dermatitis due to substances taken internally
L51	Erythema multiforme
M80	Osteoporosis with pathological fracture
T36	Poisoning by systemic antibiotics
T37	Poisoning by other systemic anti-infectives and antiparasitics
T38	Poisoning by hormones and related agents
T39	Poisoning by nonopioid analgesics, antipyretics and antirheumatics
T40	Poisoning by narcotics and psychodysleptics [hallucinogens]
T42	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs
T43	Poisoning by psychotropic drugs, not elsewhere classified
T44	Poisoning by drugs primarily affecting the autonomic nervous system
T45	Poisoning by primarily systemic and haematological agents
T46	Poisoning by agents primarily affecting the cardiovascular system
T50	Poisoning by diuretics and other unspecified drugs
Y40	Drugs, medicaments and biological substances causing adverse effects in therapeutic use
Y57	Other and unspecified drugs and medicaments
<b>Expert-defined extension</b>	
D68	Other coagulation defects
E87	Other disorders of fluid, electrolyte and acid-base balance
F05	Delirium, not induced by alcohol and other psychoactive substances
K92	Other diseases of digestive system (e.g. GI bleeding)
S32	Fracture of lumbar spine and pelvis
S42	Fracture of shoulder and upper arm
S52	Fracture of forearm
S72	Fracture of femur
T88	Other complications of surgical and medical care, not elsewhere classified
W00	Fall on same level involving ice and snow
W01	Fall on same level from slipping, tripping and stumbling
W02	Fall involving ice-skates, skis, roller-skates or skateboards
W03	Other fall on same level due to collision with another person
W04	Fall while being carried or supported by other persons
W05	Fall involving wheelchair
W06	Fall involving bed
W07	Fall involving chair
W08	Fall involving other furniture
W09	Fall involving playground equipment
W10	Fall on and from stairs and steps
W11	Fall on and from ladder
W12	Fall on and from scaffolding
W13	Fall from, out of or through building or structure
W14	Fall from tree
W15	Fall from cliff
W16	Dive or jump into water causing injury other than drowning

**Table S1.** ICD-10 Codes for Adverse Drug Events (ADEs) (Continued).

ICD-10 Code	Definition
W17	Other fall from one level to another
W18	Other slipping, tripping and stumbling and falls
W19	Unspecified fall
Y63	Failure in dosage during surgical and medical care
Y66	Non-administration of surgical and medical care
Y69	Unspecified misadventure during surgical and medical care

**Table S2.** Prevalence of disease-independent PIMs

Gr.	No. of Criteria (X/15)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
<b>Cardiovascular</b>					
1	1	Aldosterone antagonists	2,142 (3.39)	Spironolactone	2,142 (100.00)
2	6	Antiarrhythmic	125 (0.20)	Amiodarone	119 (95.20)
				Flecainide	7 (5.60)
3	1	Vasodilators in cardiac disease	1,422 (2.25)	Isosorbide mononitrate	994 (69.90)
				Isosorbide dinitrate	442 (31.08)
4	9	Central alpha blockers	777 (1.23)	Methyldopa	773 (99.49)
				Rilmenidine	4 (0.51)
				Clonidine	0 (0.00)
				Guanfacine	0 (0.00)
5	1	Arteriolar smooth muscle antihypertensives	2,362 (3.74)	Hydralazine	2,347 (99.36)
				Minoxidil	17 (0.72)
6	9	Digitalis glycoside	475 (0.75)	Digoxin (> 0.125 mg/d)	475 (100.00)
7	8	Peripheral alpha-1 blockers	4,553 (7.21)	Doxazosin	4,480 (98.40)
				Prazosin	76 (1.67)
8	2	Loop diuretics	5,339 (8.45)	Furosemide	5,255 (98.43)
				Indapamide	90 (1.69)
9	3	Potassium sparing diuretics	2,340 (3.71)	Spironolactone	2,142 (91.54)
				Amiloride	205 (8.76)
10	1	Thiazides	1,357 (2.15)	Hydrochlorothiazide	1,357 (100.00)
11	3	Peripheral vasodilators	189 (0.30)	Nicergoline	162 (85.71)
				Pentoxifylline	29 (15.34)
12	1	Lipid modifying agents (Fibrates)	1,201 (1.90)	Gemfibrozil	650 (54.12)
				Fenofibrate	592 (49.29)
13	8	Antithrombotic (antiplatelet)	5,742 (9.09)	Clopidogrel	3,012 (52.46)
				Warfarin	2,497 (43.49)
				Cilostazol	401 (6.98)
				Heparin	21 (0.37)
				Ticagrelor	19 (0.33)
				Fondaparinux	2 (0.03)
				Ticlopidine	1 (0.02)
14	1	Direct thrombin inhibitors	82 (0.13)	Dabigatran	82 (100.00)
15	1	Direct factor Xa inhibitors	42 (0.07)	Rivaroxaban	42 (100.00)
				Apixaban	0 (0.00)
16	7	Calcium channel blocker	371 (0.59)	Diltiazem	174 (46.90)
				Verapamil	136 (36.66)
				Nifedipine (short acting)	61 (16.44)
17	1	Beta blockers	6,690 (10.59)	Atenolol	2,957 (44.20)
				Propranolol	2,148 (32.11)

Table S2. Prevalence of disease-independent PIMs (Continued).

Gr.	No. of Criteria (X/15)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
				Metoprolol	1,257 (18.79)
				Bisoprolol	448 (6.70)
18	2	ACEI	7,821 (12.38)	Enalapril	7,477 (95.60)
				Ramipril	204 (2.61)
				Captopril	154 (1.97)
				Perindopril	47 (0.60)
19	1	ARBs	9,336 (14.78)	Losartan	8,067 (86.41)
				Valsartan	516 (5.53)
				Telmisartan	412 (4.41)
				Azilsartan	403 (4.32)
				Irbesartan	63 (0.67)
				Olmesartan	0 (0.00)
<b>Endocrine</b>					
20	6	Androgens	98 (0.16)	Testosterone	98 (100.00)
				Methyltestosterone	0 (0.00)
21	7	Estrogens only	1 (0.00)	Estradiol	1 (100.00)
				Estriol	0 (0.00)
22	2	Estrogens (including combination)	10 (0.02)	Conjugated estrogens	10 (100.00)
				Hydroxyprogesterone and estrogen	0 (0.00)
				Medroxyprogesterone and estrogen	0 (0.00)
				Norethisterone and estrogen	0 (0.00)
23	12	Sulfonylureas, long-acting	4,780 (7.57)	Glipizide	4,709 (98.51)
				Repaglinide	67 (1.40)
				Glimepiride	16 (0.33)
24	4	Thiazolidinediones	2,508 (3.97)	Pioglitazone	2,508 (100.00)
25	4	Insulin and analogues (Insulin sliding scale)		Insulin regular or insulin aspart alone	0 (0.00)
26	2	Biguanides	7,776 (12.31)	Metformin	7,776 (100.00)
27	1	Alpha-glucosidase inhibitors		Acarbose	0 (0.00)
28	2	SGLT inhibitors	730 (1.16)	Dapagliflozin	554 (75.89)
				Empagliflozin	177 (24.25)
<b>Gastrointestinal</b>					
29	7	H2-receptor antagonists	347 (0.55)	Famotidine	347 (100.00)
				Ranitidine	0 (0.00)
30	1	Antacids	2,584 (4.09)	Aluminium hydroxide	2,584 (100.00)
				Calcium carbonate	0 (0.00)
31	8	Propulsives	1,767 (2.80)	Metoclopramide	1,767 (100.00)
32	3	Synthetic anticholinergic agents in combination with psycholeptics	259 (0.41)	Clidinium + chlordiazepoxide	259 (100.00)
33	6	Antispasmodics	2,674 (4.23)	Hyoscine	1,892 (70.76)
				Dicyclomine (dicycloverine)	803 (30.03)
				Atropine	42 (1.57)
34	2	Antiemetics	Not assessed	Propantheline	Not assessed
<b>Genitourinary</b>					
35	9	Drugs for urinary frequency and incontinence	356 (0.56)	Imidafenacin	275 (77.25)
				Oxybutynin	65 (18.26)
				Solifenacin	26 (7.30)

**Table S2.** Prevalence of disease-independent PIMs (Continued).

Gr.	No. of Criteria (X/15)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
				Tolterodine	0 (0.00)
<b>Systemic hormonal preparations</b>					
36	1	Vasopressin and analogues hormones	17 (0.03)	Desmopressin	17 (100.00)
37	2	Growth hormone		Somatropin and agonists	0 (0.00)
<b>Nervous</b>					
38	8	Antidepressants, selective serotonin reuptake inhibitors (SSRIs)	486 (0.77)	Fluoxetine	467 (96.09)
				Fluvoxamine	20 (4.12)
39	2	Antidepressants, in combination	587 (0.93)	Melitracen and psycholeptics	587 (100.00)
40	3	Antidepressants, tetracyclic	Not assessed	Maprotiline	Not assessed
41	12	Antidepressants, tricyclic	3,288 (5.21)	Amitriptyline	3,203 (97.41)
				Imipramine	92 (2.80)
42	3	Non-selective monoamine reuptake inhibitors	444 (0.70)	Nortriptyline	444 (100.00)
43	1	Psychostimulants		Methylphenidate	0 (0.00)
44	5	Antiparkinsonian agents	603 (0.95)	Trihexyphenidyl (benhexol)	603 (100.00)
45	13	Antipsychotics, first-generation (conventional)	1,182 (1.87)	Flupentixol	589 (49.83)
				Haloperidol	345 (29.19)
				Perphenazine	185 (15.65)
				Chlorpromazine	143 (12.10)
				Fluphenazine	46 (3.89)
				Thioridazine	20 (1.69)
				Trifluoperazine	7 (0.59)
46	9	Antipsychotics, second-generation (atypical)	1,745 (2.76)	Quetiapine	876 (50.20)
				Risperidone	738 (42.29)
				Clozapine	167 (9.57)
				Olanzapine	126 (7.22)
				Lithium	42 (2.41)
				Aripiprazole	19 (1.09)
				Paliperidone	6 (0.34)
				Ziprasidone	2 (0.11)
47	11	Benzodiazepines	10,232 (16.20)	Lorazepam	6,873 (67.17)
				Diazepam	2,054 (20.07)
				Clonazepam	1,594 (15.58)
				Alprazolam	327 (3.20)
				Chlordiazepoxide	259 (2.53)
				Midazolam	102 (1.00)
				Clobazam	2 (0.02)
48	9	Nonbenzodiazepine hypnotics	21 (0.03)	Zolpidem	21 (100.00)
49	2	Barbiturates	78 (0.12)	Phenobarbital	74 (94.87)
				Thiopental	4 (5.13)
50	1	Hypnotics		Dexmedetomidine	0 (0.00)
51	2	Antiepileptics	466 (0.74)	Phenytoin	466 (100.00)
52	1	Acetylcholinesterase inhibitors	392 (0.62)	Donepezil	312 (79.59)
				Galantamine	53 (13.52)
				Rivastigmine	39 (9.95)
<b>Pain medications</b>					
53	10	Non-COX-2-selective nonsteroidal anti-inflammatory drugs (NSAIDs)	10,191 (16.14)	Naproxen	3,604 (35.36)

Table S2. Prevalence of disease-independent PIMs (Continued).

Gr.	No. of Criteria (X/15)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
				Meloxicam	3,278 (32.17)
				Ibuprofen	2,738 (26.87)
				Diclofenac	1,168 (11.46)
				Mefenamic acid	103 (1.01)
				Piroxicam	21 (0.21)
				Indomethacin	7 (0.07)
				Benzydamine	0 (0.00)
54	5	COX-2 selective inhibitors	1,754 (2.78)	Celecoxib	1,308 (74.57)
				Etoricoxib	497 (28.34)
				Parecoxib	2 (0.11)
55	6	Opioids	14,887 (23.57)	Tramadol	13,247 (88.98)
				Pethidine (meperidine)	1,423 (9.56)
				Morphine	986 (6.62)
				Metadone	6 (0.04)
56	2	Salicylic acid and derivatives	Not assessed	Aspirin (analgesic dose)	Not assessed
57	1	Anilides	34,806 (55.11)	Paracetamol	34,806 (100.00)
<b>Respiratory</b>					
58	13	First-generation antihistamines	13,398 (21.21)	Dimenhydrinate	5,416 (40.42)
				Chlorpheniramine	5,184 (38.69)
				Hydroxyzine	2,158 (16.11)
				Brompheniramine	1,283 (9.58)
				Cyproheptadine	921 (6.87)
				Diphenhydramine	264 (1.97)
				Ketotifen	17 (0.13)
59	3	Xanthines	1,377 (2.18)	Theophylline	1,365 (99.13)
				Aminophylline	18 (1.31)
<b>Musculoskeletal</b>					
60	6	Muscle relaxants	19,416 (30.74)	Orphenadrine	13,391 (68.97)
				Tolperisone	6,939 (35.74)
				Baclofen	312 (1.61)
61	1	Antigout preparations	3,467 (5.49)	Colchicine	3,467 (100.00)
62	1	Bisphosphonates	841 (1.33)	Alendronic acid	841 (100.00)
<b>Laxatives</b>					
63	4	Drugs for constipation	4,742 (7.51)	Magnesium oxide	3,411 (71.93)
				Polyethylene glycol electrolyte powder	958 (20.20)
				Sodium phosphate enema	912 (19.23)
				Bisacodyl	597 (12.59)
<b>Corticosteroids</b>					
64	2	Glucocorticoids (systemic use)	5,041 (7.98)	Prednisolone	3,306 (65.58)
				Dexamethasone	2,396 (47.53)
				Triamcinolone	303 (6.01)
				Hydrocortisone	15 (0.30)
				Fludrocortisone acetate	2 (0.04)
				Methylprednisolone	1 (0.02)
				Budesonide	0 (0.00)
<b>Antiinfective agents</b>					
65	3	Antibiotics (systemic use)	674 (1.07)	Clindamycin	656 (97.33)
				Vancomycin	19 (2.82)

**Table S2.** Prevalence of disease-independent PIMs (Continued).

Gr.	No. of Criteria (X/15)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
66	3	Aminoglycoside	19 (0.03)	Amikacin	12 (63.16)
				Gentamicin sulfate	7 (36.84)
<b>Antineoplastic</b>					
67	1	Monoclonal antibodies	48 (0.08)	Rituximab	40 (83.33)
				Bevacizumab	8 (16.67)
68	1	Immunosuppressants	1,156 (1.83)	Methotrexate	933 (80.71)
				Azathioprine	392 (33.91)
				Leflunomide	177 (15.31)
				Etanercept	1 (0.09)
69	1	Antivertigo	1,012 (1.60)	Flunarizine	861 (85.08)
				Cinnarizine	151 (14.92)
70	1	Hormonal preparations	1,644 (2.60)	Levothyroxine	1,644 (100.00)
<b>Overall</b>			<b>63,156 (100.00)</b>		

**Note:**

- **X** represents the number of criteria (out of 15) in which the drug class is identified as a PIM.
- % **Drug Class** was calculated by dividing the number of patients who received each specific drug class by the total number of patients who received at least one disease-independent PIM (e.g. 3.39% for aldosterone antagonists = 2,142/63,156).
- % **Each Drug** was calculated by dividing the number of patients who received a specific drug by the number of patients who received the corresponding drug class (e.g. 100% for spironolactone = 2,142/2,142). Drugs are listed in descending order of frequency within each drug class.
- *Not assessed* indicates that the medication was not available in any of the participating hospitals.

**Table S3.** Prevalence of disease-specific PIMs

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
<b>1. Heart failure</b> 2,441	1	7	Non-COX-2 selective NSAIDs	117 (6.45)	Naproxen	42 (35.90)
					Ibuprofen	39 (33.33)
					Meloxicam	34 (29.06)
					Diclofenac	9 (7.69)
					Mefenamic acid	1 (0.85)
					Indomethacin	0 (0.00)
					Piroxicam	0 (0.00)
	Aspirin (analgesic dose)	Not assessed				
	2	7	COX-2 inhibitors	21 (1.16)	Celecoxib	12 (57.14)
					Etoricoxib	8 (38.10)
					Parecoxib	1 (4.76)
	3	8	Non Dihydropyridine calcium channel blockers	21 (1.16)	Diltiazem	14 (66.67)
					Verapamil	7 (33.33)
	4	7	Thiazolidinediones	63 (3.47)	Pioglitazone	63 (100.00)
5	3	Digitalis	175 (9.65)	Digoxin	175 (100.00)	
6	1	Antiplatelet	15 (0.83)	Cilostazol	15 (100.00)	
7	2	Tricyclic antidepressants	118 (6.50)	Amitriptyline	103 (87.29)	
				Nortriptyline	15 (12.71)	
				Imipramine	0 (0.00)	
8	1	Beta-blockers	1,673 (92.23)	Carvedilol	1,282 (76.63)	
				Atenolol	183 (10.94)	
				Metoprolol	149 (8.91)	

Table S3. Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Propranolol	86 (5.14)
					Bisoprolol	59 (3.53)
					Labetalol	0 (0.00)
	9	1	Anesthetics	0 (0.00)	Propofol	0 (0.00)
	10	2	Phosphodiesterase type 5 inhibitors	10 (0.55)	Sildenafil	10 (100.00)
			<b>Total</b>	<b>1,814 (74.31)</b>		
<b>2. Syncope</b>	1	6	Acetylcholinesterase inhibitors	3 (3.19)	Galantamine	2 (66.67)
266					Donepezil	1 (33.33)
					Rivastigmine	0 (0.00)
	2	5	Alpha-adrenoreceptor antagonists	24 (25.53)	Doxazosin	24 (100.00)
					Prazosin	0 (0.00)
	3	3	Tricyclic antidepressants	12 (12.77)	Amitriptyline	11 (91.67)
					Nortriptyline	1 (8.33)
					Imipramine	0 (0.00)
	4	1	Short to intermediate acting benzodiazepines	55 (58.51)	Lorazepam	43 (78.18)
					Diazepam	7 (12.73)
					Clonazepam	6 (10.91)
					Chlordiazepoxide	3 (5.45)
					Alprazolam	1 (1.82)
					Midazolam	1 (1.82)
					Clobazam	0 (0.00)
	5	2	Antipsychotics	19 (20.21)	Flupentixol	7 (36.84)
					Quetiapine	7 (36.84)
					Risperidone	6 (31.58)
					Haloperidol	2 (10.53)
					Olanzapine	2 (10.53)
					Chlorpromazine	1 (5.26)
					Clozapine	1 (5.26)
					Aripiprazole	0 (0.00)
					Fluphenazine	0 (0.00)
					Lithium	0 (0.00)
					Paliperidone	0 (0.00)
					Perphenazine	0 (0.00)
					Thioridazine	0 (0.00)
					Trifluoperazine	0 (0.00)
					Ziprasidone	0 (0.00)
					Zuclopenthixol	0 (0.00)
	6	1	Centrally acting antihypertensives	2 (2.13)	Methyldopa	2 (100.00)
			<b>Total</b>	<b>94 (35.34)</b>		
<b>3. Hypertension</b>	1	2	Loop diuretics	2,910 (40.39)	Furosemide	2,855 (98.11)
21,902					Indapamide	58 (1.99)
	2	2	Alpha-adrenoreceptor antagonists	2,361 (32.77)	Doxazosin	2,311 (97.88)
					Prazosin	52 (2.20)
	3	1	Nasal decongestants	32 (0.44)	Pseudoephedrine	32 (100.00)

**Table S3.** Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
	4	6	NSAIDs	2,720 (37.75)	Naproxen	887 (32.61)
					Ibuprofen	663 (24.38)
					Meloxicam	654 (24.04)
					Celecoxib	412 (15.15)
					Diclofenac	257 (9.45)
					Etoricoxib	152 (5.59)
					Mefenamic acid	15 (0.55)
					Indomethacin	2 (0.07)
					Piroxicam	2 (0.07)
					Parecoxib	0 (0.00)
					Aspirin (analgesic dose)	Not assessed
	5	1	Potassium sparing diuretics	771 (10.70)	Spironolactone	771 (100.00)
	6	2	Centrally acting antihypertensives	0 (0.00)	Clonidine	0 (0.00)
	7	1	Calcium channel blockers	64 (0.89)	Verapamil	64 (100.00)
			<b>Total</b>	<b>7,205 (32.90)</b>		
<b>4. Cardiovascular disease (acute coronary symptoms)</b>						
1,030	1	3	COX-2 inhibitors	1 (0.18)	Celecoxib	1 (100.00)
					Etoricoxib	0 (0.00)
					Parecoxib	0 (0.00)
	2	1	ACE Inhibitors	350 (63.75)	Enalapril	347 (99.14)
					Ramipril	3 (0.86)
					Captopril	1 (0.29)
					Perindopril	0 (0.00)
	3	1	Nitrates, long term	291 (53.01)	Isosorbide mononitrate	218 (74.91)
					Isosorbide dinitrate	75 (25.77)
	4	1	Androgens	0 (0.00)	Testosterone	0 (0.00)
					Methyltestosterone	0 (0.00)
			<b>Total</b>	<b>549 (53.30)</b>		
<b>5. Atrial fibrillation</b>						
2,167	1	2	Antiplatelet	353 (56.21)	Aspirin (low dose)	289 (81.87)
					Clopidogrel	96 (27.20)
					Cilostazol	16 (4.53)
	2	1	Digitalis	260 (41.40)	Digoxin	260 (100.00)
	3	2	Non Dihydropyridine calcium channel blockers	31 (4.94)	Diltiazem	18 (58.06)
					Verapamil	13 (41.94)
	4	1	Antiarrhythmic	49 (7.80)	Amiodarone	49 (100.00)
			<b>Total</b>	<b>628 (28.98)</b>		
<b>6. Chronic therapy following myocardial infarction</b>						
1,030	1		Nitrates, long-term	291 (48.74)	Isosorbide mononitrate	218 (74.91)
					Isosorbide dinitrate	75 (25.77)
	2		Lipid modifying agents	168 (28.14)	Ezetimibe	148 (88.10)

Table S3. Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Fenofibrate	18 (10.71)
					Gemfibrozil	10 (5.95)
	3		Antiarrhythmic	8 (1.34)	Amiodarone	8 (100.00)
	4		Dihydropyridine antagonists	335 (56.11)	Amlodipine	221 (65.97)
					Manidipine	80 (23.88)
					Lercanidipine	24 (7.16)
					Nifedipine	11 (3.28)
					Felodipine	2 (0.60)
					Nicardipine	2 (0.60)
					Nimodipine	0 (0.00)
			<b>Total</b>	<b>597 (57.96)</b>		
<b>7. Delirium, dementia, or cognitive impairment</b>						
1,377	1	9	Urological spasmolytic	20 (1.65)	Trosipium	18 (90.00)
					Oxybutynin	2 (10.00)
					Solifenacin	0 (0.00)
	2	9	Antihistamines	228 (18.83)	Dimenhydrinate	111 (48.68)
					Chlorpheniramine	49 (21.49)
					Hydroxyzine	46 (20.18)
					Cyproheptadine	36 (15.79)
					Brompheniramine	23 (10.09)
					Ketotifen	1 (0.44)
					Diphenhydramine	0 (0.00)
	3	7	Antiparkinsonism drugs	108 (8.92)	Trihexyphenidyl	108 (100.00)
	4	8	Muscle relaxants	273 (22.54)	Orphenadrine	273 (100.00)
	5	9	Tricyclic antidepressants	71 (5.86)	Amitriptyline	55 (77.46)
					Nortriptyline	15 (21.13)
					Imipramine	2 (2.82)
	6	9	Antipsychotics	640 (52.85)	Quetiapine	389 (60.78)
					Risperidone	233 (36.41)
					Haloperidol	77 (12.03)
					Flupentixol	76 (11.88)
					Clozapine	23 (3.59)
					Perphenazine	18 (2.81)
					Chlorpromazine	11 (1.72)
					Aripiprazole	10 (1.56)
					Olanzapine	4 (0.63)
					Fluphenazine	1 (0.16)
					Thioridazine	1 (0.16)
					Lithium	0 (0.00)
					Paliperidone	0 (0.00)
					Trifluoperazine	0 (0.00)
					Ziprasidone	0 (0.00)
					Zuclopenthixol	0 (0.00)
	7	8	Antispasmodics (intestinal)	55 (4.54)	Hyoscine	32 (58.18)

**Table S3.** Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Dicyclomine	18 (32.73)
					Clidinium-chlordiazepoxide	11 (20.00)
					Atropine	1 (1.82)
	8	3	Psychostimulants	0 (0.00)	Methylphenidate	0 (0.00)
	9	2	Barbiturates	3 (0.25)	Phenobarbital	3 (100.00)
					Thiopental	0 (0.00)
					Amobarbital	0 (0.00)
	10	3	Benzodiazepines	391 (32.29)	Lorazepam	253 (64.71)
					Clonazepam	122 (31.20)
					Diazepam	41 (10.49)
					Alprazolam	19 (4.86)
					Chlordiazepoxide	11 (2.81)
					Midazolam	2 (0.51)
					Clobazam	0 (0.00)
	11	2	Nonbenzodiazepines hypnotics	0 (0.00)	Zolpidem	0 (0.00)
	12	1	Opioids	8 (0.66)	Pethidine	8 (100.00)
	13	1	Corticosteroids	78 (6.44)	Prednisolone	56 (71.79)
					Dexamethasone	27 (34.62)
					Triamcinolone	2 (2.56)
					Fludrocortisone	0 (0.00)
					Hydrocortisone	0 (0.00)
					Methylprednisolone	0 (0.00)
					Budesonide	0 (0.00)
	14	2	Statin	693 (57.23)	Simvastatin	404 (58.30)
					Atorvastatin	311 (44.88)
					Rosuvastatin	10 (1.44)
					Pravastatin	0 (0.00)
	15	2	Iron chelating agents	0 (0.00)	Deferoxamine	0 (0.00)
	16	2	Hormone preparations	1 (0.08)	Testosterone	1 (100.00)
			<b>Total</b>	<b>1,211 (87.94)</b>		
<b>8. History of falls or fractures</b>	1	6	Antipsychotics	116 (6.78)	Risperidone	61 (52.59)
2,354					Quetiapine	37 (31.90)
					Haloperidol	17 (14.66)
					Flupentixol	14 (12.07)
					Clozapine	6 (5.17)
					Perphenazine	6 (5.17)
					Chlorpromazine	4 (3.45)
					Lithium	2 (1.72)
					Aripiprazole	1 (0.86)
					Fluphenazine	0 (0.00)
					Olanzapine	0 (0.00)
					Paliperidone	0 (0.00)
					Thioridazine	0 (0.00)
					Trifluoperazine	0 (0.00)

Table S3. Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Ziprasidone	0 (0.00)
					Zuclophenthixol	0 (0.00)
	2	7	Benzodiazepines	411 (24.04)	Lorazepam	304 (73.97)
					Diazepam	98 (23.84)
					Clonazepam	69 (16.79)
					Alprazolam	9 (2.19)
					Chlordiazepoxide	1 (0.24)
					Clobazam	0 (0.00)
					Midazolam	0 (0.00)
	3	5	Nonbenzodiazepines hypnotics	0 (0.00)	Zolpidem	0 (0.00)
	4	3	Opioids	1,095 (64.04)	Tramadol	1,041 (95.07)
					Morphine	110 (10.05)
					Pethidine	60 (5.48)
					Codeine	27 (2.47)
					Fentanyl	7 (0.64)
					Methadone	0 (0.00)
	5	5	tricyclic Antidepressants	151 (8.83)	Amitriptyline	137 (90.73)
					Nortriptyline	13 (8.61)
					Imipramine	2 (1.32)
	6	2	Antiepileptics	56 (3.27)	Phenytoin	34 (60.71)
					Valproic acid	21 (37.50)
					Phenobarbital	7 (12.50)
					Carbamazepine	3 (5.36)
	7	1	First-generation antihistamines	547 (31.99)	Dimenhydrinate	288 (52.65)
					Chlorpheniramine	195 (35.65)
					Hydroxyzine	115 (21.02)
					Brompheniramine	41 (7.50)
					Cyproheptadine	10 (1.83)
					Diphenhydramine	0 (0.00)
					Ketotifen	0 (0.00)
	8	1	Antispasmodics (intestinal)	80 (4.68)	Hyoscine	71 (88.75)
					Dicyclomine	10 (12.50)
					Atropine	1 (1.25)
					Clidinium-chlordiazepoxide	1 (1.25)
	9	2	Antiparkinsonism drugs	30 (1.75)	Trihexyphenidyl	30 (100.00)
	10	1	Muscle relaxants	650 (38.01)	Orphenadrine	650 (100.00)
	11	1	Alpha-adrenoreceptor antagonists	136 (7.95)	Doxazosin	136 (100.00)
					Prazosin	0 (0.00)
			<b>Total</b>	<b>1,710 (72.64)</b>		
<b>9. Parkinson's disease</b>	1	11	Antipsychotics (except quetiapine and clozapine)	47 (66.20)	Risperidone	20 (42.55)
453					Flupentixol	15 (31.91)

**Table S3.** Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Haloperidol	7 (14.89)
					Aripiprazole	3 (6.38)
					Fluphenazine	3 (6.38)
					Chlorpromazine	1 (2.13)
					Lithium	1 (2.13)
					Olanzapine	1 (2.13)
					Paliperidone	1 (2.13)
					Perphenazine	1 (2.13)
					Thioridazine	0 (0.00)
					Trifluoperazine	0 (0.00)
					Ziprasidone	0 (0.00)
					Zuclophenthixol	0 (0.00)
	2	6	Propulsives	13 (18.31)	Metoclopramide	13 (100.00)
	3	2	MAOI	10 (14.08)	Rasagiline	10 (100.00)
	4	1	Anti-parkinson drugs	10 (14.08)	Bromocriptine	10 (100.00)
			<b>Total</b>	<b>71 (15.67)</b>		
<b>10. Depression</b>	1	4	Centrally acting antihypertensives	10 (0.89)	Methyl dopa	10 (100.00)
1,217	2	1	SSRI	778 (69.46)	Sertraline	623 (80.08)
					Fluoxetine	85 (10.93)
					Escitalopram	57 (7.33)
					Mirtazapine	38 (4.88)
	3	1	SNRI	30 (2.68)	Venlafaxine	28 (93.33)
					Desvenlafaxine	2 (6.67)
	4		Non-selective MAOI	234 (20.89)	Trazodone	202 (86.32)
					Nortriptyline	41 (17.52)
	5	1	Antipsychotics	84 (7.50)	Quetiapine	80 (95.24)
					Aripiprazole	4 (4.76)
					Olanzapine	3 (3.57)
	6	1	Benzodiazepines	896 (80.00)	Lorazepam	563 (62.83)
					Clonazepam	392 (43.75)
					Diazepam	122 (13.62)
					Alprazolam	85 (9.49)
					Chlordiazepoxide	14 (1.56)
					Midazolam	2 (0.22)
					Clobazam	0 (0.00)
			<b>Total</b>	<b>1,120 (92.03)</b>		
<b>11. Seizures or epilepsy</b>	1	5	Antipsychotics	7 (1.83)	Chlorpromazine	5 (71.43)
464					Clozapine	1 (14.29)
					Olanzapine	1 (14.29)
					Thioridazine	0 (0.00)
	2	3	Antidepressants	0 (0.00)	Bupropion	0 (0.00)
	3	1	Opioids	94 (24.61)	Tramadol	94 (100.00)
	4	1	Antiepileptics	351 (91.88)	Phenytoin	241 (68.66)
					Valproic acid	94 (26.78)
					Phenobarbital	61 (17.38)
					Carbamazepine	12 (3.42)

Table S3. Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
	5	1	Benzodiazepines	20 (5.24)	Diazepam	20 (100.00)
					Midazolam	0 (0.00)
	6		Analgesics	2 (0.52)	Pregabalin	2 (100.00)
			<b>Total</b>	<b>382 (82.33)</b>		
<b>12. History of gastric or duodenal ulcers</b>	1	8	antiplatelet	66 (42.04)	Aspirin (low dose)	66 (100.00)
517	2	11	Non-COX-2 selective NSAIDs	52 (33.12)	Naproxen	19 (36.54)
					Meloxicam	18 (34.62)
					Ibuprofen	15 (28.85)
					Diclofenac	4 (7.69)
					Mefenamic acid	2 (3.85)
					Indomethacin	0 (0.00)
					Piroxicam	0 (0.00)
					Aspirin (analgesic dose)	Not assessed
	3	1	Antidepressants	13 (8.28)	Sertraline	11 (84.62)
					Escitalopram	2 (15.38)
					Fluvoxamine	0 (0.00)
	4	3	Corticosteroids	51 (32.48)	Prednisolone	40 (78.43)
					Dexamethasone	16 (31.37)
					Triamcinolone	1 (1.96)
					Fludrocortisone	0 (0.00)
					Hydrocortisone	0 (0.00)
					Methylprednisolone	0 (0.00)
					Budesonide	0 (0.00)
	5	1	H2 receptor antagonists	6 (3.82)	Famotidine	6 (100.00)
					Ranitidine	0 (0.00)
			<b>Total</b>	<b>157 (30.37)</b>		
<b>13. Constipation</b>	1	9	Anticholinergics or antimuscarinics properties	691 (58.02)	Dimenhydrinate	225 (32.56)
1,567					Chlorpheniramine	158 (22.87)
					Hyoscine	156 (22.58)
					Amitriptyline	142 (20.55)
					Hydroxyzine	109 (15.77)
					Risperidone	43 (6.22)
					Brompheniramine	36 (5.21)
					Dicyclomine	28 (4.05)
					Cyproheptadine	24 (3.47)
					Quetiapine	24 (3.47)
					Clidinium-chlordiazepoxide	21 (3.04)
					Flupentixol	17 (2.46)
					Haloperidol	16 (2.32)
					Trospium	15 (2.17)
					Nortriptyline	12 (1.74)
					Olanzapine	5 (0.72)
					Atropine	3 (0.43)

**Table S3.** Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Clozapine	3 (0.43)
					Diphenhydramine	3 (0.43)
					Imipramine	3 (0.43)
					Aripiprazole	2 (0.29)
					Chlorpromazine	2 (0.29)
					Perphenazine	2 (0.29)
					Solifenacin	2 (0.29)
					Oxybutynin	1 (0.14)
					Fluphenazine	0 (0.00)
					Ketotifen	0 (0.00)
					Lithium	0 (0.00)
					Paliperidone	0 (0.00)
					Thioridazine	0 (0.00)
					Trifluoperazine	0 (0.00)
					Ziprasidone	0 (0.00)
					Zuclopenthixol	0 (0.00)
	2	4	Non dihydropyridine calcium channel blockers	6 (0.50)	Verapamil	6 (100.00)
	3	2	Calcium channel blockers:	518 (43.49)	Amlodipine	342 (66.02)
					Manidipine	142 (27.41)
					Lercanidipine	22 (4.25)
					Nifedipine	17 (3.28)
					Verapamil	6 (1.16)
					Diltiazem	3 (0.58)
					Felodipine	3 (0.58)
					Nicardipine	1 (0.19)
					Nimodipine	0 (0.00)
	4	4	Iron preparations	188 (15.79)	Oral iron	188 (100.00)
	5	5	Opioids	539 (45.26)	Tramadol	417 (77.37)
					Pethidine	101 (18.74)
					Morphine	60 (11.13)
					Codeine	23 (4.27)
					Fentanyl	23 (4.27)
					Methadone	1 (0.19)
	6	2	Antacids	165 (13.85)	Aluminium antacids	165 (100.00)
	7	1	Urological spasmolytic	0 (0.00)	Tolterodine	0 (0.00)
	8	1	First-generation antihistamines	178 (14.95)	Chlorpheniramine	158 (88.76)
					Cyproheptadine	24 (13.48)
					Diphenhydramine (oral)	3 (1.69)
	9	1	Antipsychotics	97 (8.14)	Risperidone	43 (44.33)
					Quetiapine	24 (24.74)
					Flupentixol	17 (17.53)
					Haloperidol	16 (16.49)
					Olanzapine	5 (5.15)
					Clozapine	3 (3.09)
					Aripiprazole	2 (2.06)

Table S3. Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Chlorpromazine	1 (1.03)
					Fluphenazine	0 (0.00)
					Lithium	0 (0.00)
					Paliperidone	0 (0.00)
					Thioridazine	0 (0.00)
					Trifluoperazine	0 (0.00)
					Ziprasidone	0 (0.00)
					Zuclophenthixol	0 (0.00)
	10	3	Tricyclic antidepressants	155 (13.01)	Amitriptyline	142 (91.61)
					Nortriptyline	12 (7.74)
					Imipramine	3 (1.94)
			<b>Total</b>	<b>1,191 (76.01)</b>		
<b>14. Chronic kidney disease</b>	1	9	Non-COX-2 selective NSAIDs	544 (13.53)	Naproxen	213 (39.15)
9,468					Ibuprofen	186 (34.19)
					Meloxicam	102 (18.75)
					Diclofenac	79 (14.52)
					Mefenamic acid	7 (1.29)
					Indomethacin	0 (0.00)
					Piroxicam	0 (0.00)
					Aspirin (analgesic dose)	Not assessed
	2	9	COX-2 inhibitors	113 (2.81)	Celecoxib	88 (77.88)
					Etoricoxib	28 (24.78)
					Parecoxib	0 (0.00)
	3	3	Digoxin at a long-term dose greater than 125 µg/day	67 (1.67)	Digoxin	67 (100.00)
	4	3	Direct thrombin inhibitors	7 (0.17)	Dabigatran	7 (100.00)
	5	4	Biguanides	2,259 (56.18)	Metformin	2,259 (100.00)
	6	1	Oral bisphosphonates	38 (0.95)	Alendronate	37 (97.37)
					Risedronate	1 (2.63)
	7	1	Antithrombotic (direct factor Xa inhibitors)	5 (0.12)	Rivaroxaban	5 (100.00)
	8	3	Antigout preparations	1,521 (37.83)	Colchicine	1,521 (100.00)
			<b>Total</b>	<b>4,021 (42.47)</b>		
<b>15. benign prostatic hyperplasia, Lower urinary tract symptoms</b>	1	6	Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence	1,044 (41.20)	Dimenhydrinate	269 (25.77)
4,458					Chlorpheniramine	240 (22.99)
					Hydroxyzine	180 (17.24)
					Amitriptyline	141 (13.51)
					Hyoscine	110 (10.54)
					Brompheniramine	82 (7.85)
					Dicyclomine	66 (6.32)
					Quetiapine	58 (5.56)
					Cyproheptadine	54 (5.17)
					Risperidone	41 (3.93)

**Table S3.** Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Clidinium-chlordiazepoxide	31 (2.97)
					Flupentixol	30 (2.87)
					Nortriptyline	29 (2.78)
					Imipramine	24 (2.30)
					Haloperidol	20 (1.92)
					Chlorpromazine	8 (0.77)
					Atropine	4 (0.38)
					Lithium	3 (0.29)
					Perphenazine	3 (0.29)
					Diphenhydramine	3 (0.29)
					Clozapine	2 (0.19)
					Olanzapine	2 (0.19)
					Thioridazine	1 (0.10)
					Aripiprazole	0 (0.00)
					Fluphenazine	0 (0.00)
					Paliperidone	0 (0.00)
					Trifluoperazine	0 (0.00)
					Ziprasidone	0 (0.00)
					Ketotifen	0 (0.00)
					Zuclopenthixol	0 (0.00)
	2	3	Tricyclic antidepressants	191 (7.54)	Amitriptyline	141 (73.82)
					Nortriptyline	29 (15.18)
					Imipramine	24 (12.57)
	3	3	Antimuscarinic bronchodilators	258 (10.18)	Ipratropium	238 (92.25)
					Tiotropium	125 (48.45)
	4	2	Urological spasmolytic	319 (12.59)	Trospium	283 (88.71)
					Oxybutynin	29 (9.09)
					Solifenacin	23 (7.21)
	5	1	Alpha-adrenoreceptor antagonists	1,702 (67.17)	Doxazosin	1,694 (99.53)
					Prazosin	9 (0.53)
			<b>Total</b>	<b>2,534 (56.84)</b>		
<b>16. Urinary incontinence</b>	1	1	Diuretics	6 (9.38)	Furosemide	6 (100.00)
169					Indapamide	0 (0.00)
	2	3	Alpha-adrenoreceptor antagonists	29 (45.31)	Doxazosin	28 (96.55)
					Prazosin	1 (3.45)
	3	3	Tricyclic antidepressants	20 (31.25)	Amitriptyline	12 (60.00)
					Imipramine	9 (45.00)
					Nortriptyline	1 (5.00)
	4	1	Anticholinergics	21 (32.81)	Hyoscine	16 (76.19)
					Dicyclomine	6 (28.57)
					Mebeverine	2 (9.52)
					Atropine	0 (0.00)
					Glycopyrrolate	0 (0.00)
					Trihexyphenidyl	0 (0.00)
	5	1	Long benzodiazepines	10 (15.63)	Diazepam	7 (70.00)

Table S3. Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
					Chlordiazepoxide	3 (30.00)
					Clorazepate dipotassium	0 (0.00)
	6	1	Estrogens	0 (0.00)	Conjugated estrogens	0 (0.00)
					Estradiol	0 (0.00)
					Estradiol combination	0 (0.00)
<b>Total</b>				<b>64 (37.87)</b>		
<b>17. Bronchial asthma, chronic obstructive pulmonary disease</b>						
	1	8	Beta-blockers	142 (39.34)	Carvedilol	49 (34.51)
1,386					Atenolol	47 (33.10)
					Propranolol	20 (14.08)
					Metoprolol	17 (11.97)
					Bisoprolol	15 (10.56)
					Labetalol	0 (0.00)
	2	2	Benzodiazepines	248 (68.70)	Lorazepam	200 (80.65)
					Clonazepam	44 (17.74)
					Diazepam	24 (9.68)
					Alprazolam	8 (3.23)
					Chlordiazepoxide	4 (1.61)
					Clobazam	0 (0.00)
					Midazolam	0 (0.00)
<b>Total</b>				<b>361 (26.05)</b>		
<b>18. COPD</b>						
	1	5	Xanthines	790 (51.60)	Theophylline (as monotherapy)	790 (100.00)
2,226	2	7	Systemic corticosteroids (instead of inhaled)	435 (28.41)	Prednisolone	381 (87.59)
					Dexamethasone	229 (52.64)
					Triamcinolone	6 (1.38)
					Fludrocortisone	0 (0.00)
					Hydrocortisone	0 (0.00)
					Methylprednisolone	0 (0.00)
					Budesonide	0 (0.00)
	3	6	Beta-blockers	326 (21.29)	Carvedilol	175 (53.68)
					Atenolol	71 (21.78)
					Metoprolol	38 (11.66)
					Propranolol	38 (11.66)
					Bisoprolol	17 (5.21)
					Labetalol	0 (0.00)
	4	1	Mucolytic agents	570 (37.23)	Acetylcysteine	481 (84.39)
					Bromhexine	223 (39.12)
	5	1	Opioid cough suppressants	75 (4.90)	Codeine (cough)	75 (100.00)
	6	4	Benzodiazepines	43 (2.81)	Diazepam	37 (86.05)
					Chlordiazepoxide	5 (11.63)
					Clorazepate	1 (2.33)
	7	2	Beta-blockers	38 (2.48)	Propranolol	38 (100.00)
<b>Total</b>				<b>1,531 (68.78)</b>		

**Table S3.** Prevalence of disease-specific PIMs (Continued).

Diseases or syndromes	Gr.	No. of Sources (X/14)	Drug class	Total for Drug Class n (%)	Drugs	Total for Each Drug n (%)
<b>19. Mild pain (chronic)</b> 7,796	1	5	Opioids	4,019 (76.18)	Tramadol	3,788 (94.25)
					Codeine	235 (5.85)
					Pethidine	140 (3.48)
					Morphine	113 (2.81)
					Fentanyl	26 (0.65)
					Methadone	1 (0.02)
	2	1	Analgesics	423 (8.02)	Pregabalin	423 (100.00)
	3	1	SSRI	10 (0.19)	Venlafaxine	10 (100.00)
	4	1	Antiepileptics	11 (0.21)	Carbamazepine	11 (100.00)
	5	1	Tricyclic antidepressants	944 (17.89)	Amitriptyline	944 (100.00)
	6	1	NSAIDs	1,597 (30.27)	Naproxen	1,153 (72.20)
					Celecoxib	494 (30.93)
	<b>Total</b>				<b>5,276 (67.68)</b>	
<b>20. Diabetes mellitus</b> 12,136	1	5	Beta-blockers	3,440 (85.28)	Carvedilol	1,358 (39.48)
					Atenolol	1,136 (33.02)
					Propranolol	482 (14.01)
					Metoprolol	463 (13.46)
					Bisoprolol	109 (3.17)
					Labetalol	0 (0.00)
	2	6	Corticosteroids (> 1 week without monitoring)	830 (20.58)	Prednisolone	622 (74.94)
					Dexamethasone	302 (36.39)
					Triamcinolone	54 (6.51)
					Hydrocortisone	2 (0.24)
					Fludrocortisone	1 (0.12)
					Methylprednisolone	0 (0.00)
					Budesonide	0 (0.00)
<b>Total</b>				<b>4,034 (33.24)</b>		
<b>21. Impaired liver functions</b> 2,539	1	1	Muscle relaxants	0 (0.00)	Rocuronium	0 (0.00)
	2	1	Analgesics	751 (99.73)	Paracetamol	751 (100.00)
	3	1	Antithrombotic (direct factor Xa inhibitors)	0 (0.00)	Ticagrelor	0 (0.00)
	4	1	Antithrombotic (direct thrombin inhibitors)	3 (0.40)	Dabigatran	3 (100.00)
	5	1	Antithrombotic (direct factor Xa inhibitors)	0 (0.00)	Rivaroxaban	0 (0.00)
<b>Total</b>				<b>753 (29.66)</b>		

**Note:**

- **X** represents the number of criteria (out of 14) in which the drug class is identified as a PIM.
- **% Total** was calculated by dividing the number of patients with a specific disease who received at least one medication identified as a PIM for that disease by the total number of patients with the disease (e.g. 74.31% of patients with heart failure received a disease-specific PIM = 1,814/2,441).
- **% Drug Class** was calculated by dividing the number of patients with the disease who received a specific drug class by the total number of patients with the disease (e.g. 6.45% received non-COX-2 selective NSAIDs = 117/1,814).
- **% Each Drug** was calculated by dividing the number of patients who received a specific drug by the number of patients with the disease who received the corresponding drug class (e.g. 35.90% received naproxen = 42/117). Drugs are listed in descending order of frequency within each drug class.
- *Not assessed* indicates that the medication was not available in any of the participating hospitals.

Table S4. Drug-drug interaction (DDI)-based PIMs

Gr.	No. of Criteria (X/10)	Drug-drug interactions	Total for Drug Combination n (%)
1	5	<b>Aldosterone antagonists + potassium-conserving drugs (ACEIs, ARBs, amiloride, triamterine)</b>	<b>993 (12.69)</b>
		spironolactone + enalapril	480 (48.34)
		spironolactone + losartan	430 (43.30)
		spironolactone + valsartan	59 (5.94)
		spironolactone + azilsartan	8 (0.81)
		spironolactone + ramipril	5 (0.50)
		spironolactone + amiloride	4 (0.40)
		spironolactone + telmisartan	4 (0.40)
		spironolactone + captopril	2 (0.20)
		spironolactone + irbesartan	2 (0.20)
		spironolactone + perindopril	2 (0.20)
2	5	<b>Aspirin + clopidogrel, vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors</b>	<b>1,680 (21.48)</b>
		aspirin + clopidogrel	1,494 (88.93)
		aspirin + warfarin	216 (12.86)
		aspirin + heparin	1 (0.06)
		aspirin + dabigatran	1 (0.06)
3	4	<b>Beta-blockers + verapamil</b>	<b>35 (0.45)</b>
		atenolol + verapamil	10 (28.57)
		carvedilol + verapamil	9 (25.71)
		propranolol + verapamil	9 (25.71)
		metoprolol + verapamil	8 (22.86)
4	4	<b>Antiplatelet agents + vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors</b>	<b>307 (3.92)</b>
		aspirin + warfarin	228 (74.27)
		clopidogrel + warfarin	108 (35.18)
		clopidogrel + dabigatran	7 (2.28)
		aspirin + dabigatran	1 (0.33)
		aspirin + heparin	1 (0.33)
		cilostazol + rivaroxaban	1 (0.33)
		cilostazol + warfarin	1 (0.33)
		cilostazol + dabigatran	1 (0.33)
5	4	<b>Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g., bladder antispasmodics, intestinal antispasmodics, TCAs, and first-generation antihistamines)</b>	<b>1,497 (19.14)</b>
		amitriptyline + dimenhydrinate	209 (13.96)
		chlorpheniramine + hydroxyzine	140 (9.35)
		chlorpheniramine + dimenhydrinate	128 (8.55)
		dimenhydrinate + hydroxyzine	86 (5.74)
		hyoscine + dimenhydrinate	83 (5.54)
		amitriptyline + hydroxyzine	67 (4.48)
		amitriptyline + cyproheptadine	51 (3.41)
		clidinium + dicyclomine	47 (3.14)
		brompheniramine + dimenhydrinate	45 (3.01)
		amitriptyline + chlorpheniramine	42 (2.81)
		chlorpheniramine + diphenhydramine	36 (2.40)
		dicyclomine + amitriptyline	36 (2.40)
		dicyclomine + dimenhydrinate	33 (2.20)

**Table S4.** Drug-drug interaction (DDI)-based PIMs (Continued).

Gr.	No. of Criteria (X/10)	Drug-drug interactions	Total for Drug Combination n (%)
		cyproheptadine + dimenhydrinate	32 (2.14)
		clidinium + hyoscine	26 (1.74)
		brompheniramine + chlorpheniramine	24 (1.60)
		dicyclomine + nortriptyline	23 (1.54)
		brompheniramine + hydroxyzine	20 (1.34)
		amitriptyline + brompheniramine	18 (1.20)
		dicyclomine + hyoscine	18 (1.20)
		dicyclomine + brompheniramine	17 (1.14)
		tropium + imipramine	17 (1.14)
		dicyclomine + cyproheptadine	16 (1.07)
		clidinium + amitriptyline	15 (1.00)
		nortriptyline + dimenhydrinate	15 (1.00)
		amitriptyline + diphenhydramine	14 (0.94)
		cyproheptadine + diphenhydramine	14 (0.94)
		diphenhydramine + hydroxyzine	14 (0.94)
		hyoscine + chlorpheniramine	14 (0.94)
		clidinium + dicyclomine + nortriptyline	13 (0.87)
		hyoscine + cyproheptadine	13 (0.87)
		hyoscine + amitriptyline	12 (0.80)
		nortriptyline + cyproheptadine	12 (0.80)
		clidinium + dimenhydrinate	10 (0.67)
		cyproheptadine + hydroxyzine	10 (0.67)
		chlorpheniramine + cyproheptadine	9 (0.60)
		oxybutynin + tropium	9 (0.60)
		tropium + hydroxyzine	9 (0.60)
		tropium + hyoscine	8 (0.53)
		amitriptyline + dimenhydrinate + hydroxyzine	6 (0.40)
		brompheniramine + cyproheptadine	6 (0.40)
		chlorpheniramine + cyproheptadine + diphenhydramine	6 (0.40)
		chlorpheniramine + dimenhydrinate + hydroxyzine	6 (0.40)
		dicyclomine + chlorpheniramine	6 (0.40)
		dicyclomine + hydroxyzine	6 (0.40)
		hyoscine + hydroxyzine	6 (0.40)
		amitriptyline + chlorpheniramine + dimenhydrinate	5 (0.33)
		chlorpheniramine + diphenhydramine + hydroxyzine	5 (0.33)
		clidinium + nortriptyline	5 (0.33)
		dimenhydrinate + diphenhydramine	5 (0.33)
		clidinium + cyproheptadine	4 (0.27)
		clidinium + dicyclomine + hyoscine	4 (0.27)
		dicyclomine + amitriptyline + dimenhydrinate	4 (0.27)
		dicyclomine + diphenhydramine	4 (0.27)
		hyoscine + nortriptyline	4 (0.27)
		nortriptyline + hydroxyzine	4 (0.27)
		oxybutynin + hyoscine	4 (0.27)
		amitriptyline + brompheniramine + dimenhydrinate	3 (0.20)
		atropine + dimenhydrinate	3 (0.20)
		dicyclomine + nortriptyline + cyproheptadine	3 (0.20)
		hyoscine + brompheniramine	3 (0.20)
		hyoscine + dimenhydrinate + hydroxyzine	3 (0.20)

Table S4. Drug-drug interaction (DDI)-based PIMs (Continued).

Gr.	No. of Criteria (X/10)	Drug-drug interactions	Total for Drug Combination n (%)
		tropium + dimenhydrinate	3 (0.20)
		amitriptyline + brompheniramine + hydroxyzine	2 (0.13)
		amitriptyline + cyproheptadine + dimenhydrinate	2 (0.13)
		amitriptyline + imipramine	2 (0.13)
		amitriptyline + nortriptyline	2 (0.13)
		atropine + hyoscine	2 (0.13)
		brompheniramine + diphenhydramine	2 (0.13)
		clidinium + dicyclomine + dimenhydrinate	2 (0.13)
		dicyclomine + amitriptyline + brompheniramine	2 (0.13)
		dicyclomine + brompheniramine + dimenhydrinate	2 (0.13)
		dicyclomine + cyproheptadine + dimenhydrinate	2 (0.13)
		dicyclomine + hyoscine + cyproheptadine	2 (0.13)
		hyoscine + amitriptyline + dimenhydrinate	2 (0.13)
		nortriptyline + brompheniramine	2 (0.13)
		solifenacin + hydroxyzine	2 (0.13)
		tropium + amitriptyline + hydroxyzine	2 (0.13)
		tropium + chlorpheniramine	2 (0.13)
		tropium + clidinium	2 (0.13)
		tropium + dicyclomine	2 (0.13)
		amitriptyline + brompheniramine + cyproheptadine	1 (0.07)
		amitriptyline + chlorpheniramine + diphenhydramine	1 (0.07)
		amitriptyline + chlorpheniramine + hydroxyzine	1 (0.07)
		brompheniramine + chlorpheniramine + hydroxyzine	1 (0.07)
		brompheniramine + dimenhydrinate + hydroxyzine	1 (0.07)
		chlorpheniramine + cyproheptadine + diphenhydramine + hydroxyzine	1 (0.07)
		chlorpheniramine + dimenhydrinate + diphenhydramine	1 (0.07)
		chlorpheniramine + ketotifen	1 (0.07)
		clidinium + brompheniramine	1 (0.07)
		clidinium + cyproheptadine + dimenhydrinate	1 (0.07)
		clidinium + dicyclomine + amitriptyline	1 (0.07)
		clidinium + dicyclomine + amitriptyline + dimenhydrinate	1 (0.07)
		clidinium + dicyclomine + hyoscine + amitriptyline	1 (0.07)
		clidinium + dicyclomine + hyoscine + brompheniramine + dimenhydrinate	1 (0.07)
		clidinium + dicyclomine + hyoscine + brompheniramine + dimenhydrinate + hydroxyzine	1 (0.07)
		clidinium + hydroxyzine	1 (0.07)
		clidinium + hyoscine + hydroxyzine	1 (0.07)
		clidinium + imipramine	1 (0.07)
		clidinium + nortriptyline + cyproheptadine	1 (0.07)
		cyproheptadine + dimenhydrinate + hydroxyzine	1 (0.07)
		dicyclomine + amitriptyline + chlorpheniramine	1 (0.07)
		dicyclomine + amitriptyline + cyproheptadine	1 (0.07)
		dicyclomine + amitriptyline + cyproheptadine + dimenhydrinate	1 (0.07)
		dicyclomine + amitriptyline + hydroxyzine	1 (0.07)
		dicyclomine + brompheniramine + dimenhydrinate + hydroxyzine	1 (0.07)
		dicyclomine + dimenhydrinate + diphenhydramine	1 (0.07)
		dicyclomine + dimenhydrinate + hydroxyzine	1 (0.07)
		dicyclomine + hyoscine + amitriptyline	1 (0.07)

**Table S4.** Drug-drug interaction (DDI)-based PIMs (Continued).

Gr.	No. of Criteria (X/10)	Drug-drug interactions	Total for Drug Combination n (%)
		dicyclomine + hyoscine + cyproheptadine + dimenhydrinate	1 (0.07)
		dicyclomine + hyoscine + dimenhydrinate	1 (0.07)
		dicyclomine + hyoscine + hydroxyzine	1 (0.07)
		dicyclomine + imipramine	1 (0.07)
		dicyclomine + nortriptyline + brompheniramine	1 (0.07)
		dimenhydrinate + diphenhydramine + hydroxyzine	1 (0.07)
		hyoscine + brompheniramine + dimenhydrinate + hydroxyzine	1 (0.07)
		hyoscine + chlorpheniramine + dimenhydrinate	1 (0.07)
		hyoscine + diphenhydramine	1 (0.07)
		hyoscine + imipramine	1 (0.07)
		imipramine + cyproheptadine	1 (0.07)
		imipramine + hydroxyzine	1 (0.07)
		imipramine + nortriptyline	1 (0.07)
		nortriptyline + chlorpheniramine	1 (0.07)
		nortriptyline + chlorpheniramine + hydroxyzine	1 (0.07)
		oxybutynin + amitriptyline	1 (0.07)
		oxybutynin + amitriptyline + hydroxyzine	1 (0.07)
		oxybutynin + imipramine	1 (0.07)
		oxybutynin + imipramine + chlorpheniramine	1 (0.07)
		Oxybut ynin + imipramine + hydroxyzine	1 (0.07)
		oxybutynin + trospium + amitriptyline + cyproheptadine + hydroxyzine	1 (0.07)
		oxybutynin + trospium + amitriptyline + hydroxyzine	1 (0.07)
		oxybutynin + trospium + hydroxyzine	1 (0.07)
		solifenacin + dimenhydrinate	1 (0.07)
		trospium + amitriptyline	1 (0.07)
		trospium + brompheniramine	1 (0.07)
		trospium + clidinium + dimenhydrinate	1 (0.07)
		trospium + cyproheptadine	1 (0.07)
		trospium + dimenhydrinate + hydroxyzine	1 (0.07)
		trospium + diphenhydramine	1 (0.07)
<b>6</b>	<b>3</b>	<b>Beta-blockers + diltiazem</b>	<b>46 (0.59)</b>
		atenolol + diltiazem	21 (45.65)
		carvedilol + diltiazem	9 (19.57)
		metoprolol + diltiazem	8 (17.39)
		propranolol + diltiazem	5 (10.87)
		bisoprolol + diltiazem	3 (6.52)
<b>7</b>	<b>3</b>	<b>NSAIDs + vitamin K antagonist, direct thrombin inhibitor, factor Xa inhibitors, antiplatelet agent(s) without PPI, corticosteroids without PPI, ACEIs, or ARBs</b>	<b>1,522 (19.46)</b>
		meloxicam + dexamethasone	189 (12.42)
		naproxen + prednisolone	142 (9.33)
		naproxen + dexamethasone	97 (6.37)
		meloxicam + aspirin	96 (6.31)
		meloxicam + losartan	90 (5.91)
		naproxen + triamcinolone	83 (5.45)
		naproxen + enalapril	65 (4.27)
		naproxen + aspirin	60 (3.94)
		celecoxib + losartan	55 (3.61)
		naproxen + losartan	53 (3.48)

Table S4. Drug-drug interaction (DDI)-based PIMs (Continued).

Gr.	No. of Criteria (X/10)	Drug-drug interactions	Total for Drug Combination n (%)
		ibuprofen + prednisolone	52 (3.42)
		ibuprofen + dexamethasone	48 (3.15)
		meloxicam + enalapril	47 (3.09)
		celecoxib + aspirin	46 (3.02)
		meloxicam + azilsartan	43 (2.83)
		ibuprofen + losartan	38 (2.50)
		ibuprofen + enalapril	37 (2.43)
		meloxicam + clopidogrel	36 (2.37)
		diclofenac + prednisolone	34 (2.23)
		celecoxib + dexamethasone	32 (2.10)
		celecoxib + triamcinolone	32 (2.10)
		meloxicam + prednisolone	32 (2.10)
		diclofenac + dexamethasone	31 (2.04)
		diclofenac + enalapril	31 (2.04)
		diclofenac + losartan	31 (2.04)
		celecoxib + valsartan	25 (1.64)
		celecoxib + prednisolone	22 (1.45)
		etoricoxib + losartan	22 (1.45)
		meloxicam + telmisartan	21 (1.38)
		meloxicam + triamcinolone	21 (1.38)
		ibuprofen + aspirin	19 (1.25)
		celecoxib + clopidogrel	18 (1.18)
		diclofenac + aspirin	17 (1.12)
		etoricoxib + azilsartan	16 (1.05)
		celecoxib + azilsartan	15 (0.99)
		celecoxib + enalapril	14 (0.92)
		etoricoxib + aspirin	14 (0.92)
		meloxicam + valsartan	14 (0.92)
		ibuprofen + triamcinolone	11 (0.72)
		ketotifen + prednisolone	9 (0.59)
		naproxen + clopidogrel	9 (0.59)
		celecoxib + telmisartan	8 (0.53)
		etoricoxib + enalapril	7 (0.46)
		naproxen + captopril	7 (0.46)
		etoricoxib + clopidogrel	6 (0.39)
		etoricoxib + telmisartan	6 (0.39)
		etoricoxib + valsartan	6 (0.39)
		etoricoxib + dexamethasone	5 (0.33)
		celecoxib + ramipril	4 (0.26)
		etoricoxib + prednisolone	4 (0.26)
		ibuprofen + captopril	4 (0.26)
		meloxicam + cilostazol	4 (0.26)
		meloxicam + warfarin	4 (0.26)
		naproxen + ramipril	4 (0.26)
		celecoxib + irbesartan	3 (0.20)
		celecoxib + warfarin	3 (0.20)
		diclofenac + triamcinolone	3 (0.20)
		etoricoxib + triamcinolone	3 (0.20)
		ibuprofen + clopidogrel	3 (0.20)

**Table S4.** Drug-drug interaction (DDI)-based PIMs (Continued).

Gr.	No. of Criteria (X/10)	Drug-drug interactions	Total for Drug Combination n (%)
		naproxen + warfarin	3 (0.20)
		celecoxib + captopril	2 (0.13)
		celecoxib + cilostazol	2 (0.13)
		diclofenac + warfarin	2 (0.13)
		naproxen + azilsartan	2 (0.13)
		naproxen + cilostazol	2 (0.13)
		celecoxib + dabigatran	1 (0.07)
		celecoxib + perindopril	1 (0.07)
		diclofenac + captopril	1 (0.07)
		diclofenac + clopidogrel	1 (0.07)
		diclofenac + telmisartan	1 (0.07)
		etoricoxib + cilostazol	1 (0.07)
		etoricoxib + dabigatran	1 (0.07)
		etoricoxib + warfarin	1 (0.07)
		ibuprofen + azilsartan	1 (0.07)
		ibuprofen + perindopril	1 (0.07)
		ibuprofen + telmisartan	1 (0.07)
		ketotifen + dexamethasone	1 (0.07)
		mefenamic acid + aspirin	1 (0.07)
		mefenamic acid + dexamethasone	1 (0.07)
		mefenamic acid + ramipril	1 (0.07)
		meloxicam + ramipril	1 (0.07)
		naproxen + dabigatran	1 (0.07)
		naproxen + irbesartan	1 (0.07)
		naproxen + rivaroxaban	1 (0.07)
		naproxen + telmisartan	1 (0.07)
		naproxen + valsartan	1 (0.07)
		piroxicam + dexamethasone	1 (0.07)
<b>8</b>	<b>2</b>	<b>Acetylcholinesterase inhibitors + beta-blockers, digoxin, diltiazem, or verapamil</b>	<b>38 (0.49)</b>
		donepezil + atenolol	17 (44.74)
		donepezil + carvedilol	5 (13.16)
		donepezil + metoprolol	5 (13.16)
		donepezil + propranolol	3 (7.89)
		galantamine + atenolol	3 (7.89)
		rivastigmine + carvedilol	2 (5.26)
		donepezil + bisoprolol	1 (2.63)
		galantamine + bisoprolol	1 (2.63)
		galantamine + metoprolol	1 (2.63)
		donepezil + digoxin	1 (2.63)
<b>9</b>	<b>2</b>	<b>SSRI + monoamine oxidase inhibitor</b>	<b>3 (0.04)</b>
		escitalopram + rasagiline	3 (100.00)
<b>10</b>	<b>1</b>	<b>Phosphodiesterase type 5 inhibitors + nitrates</b>	<b>0 (0.00)</b>
<b>11</b>	<b>1</b>	<b>Aspirin + dipyridamole or NSAIDs</b>	<b>254 (3.25)</b>
		aspirin + meloxicam	97 (38.19)
		aspirin + naproxen	60 (23.62)
		aspirin + celecoxib	46 (18.11)
		aspirin + ibuprofen	20 (7.87)
		aspirin + diclofenac	17 (6.69)

Table S4. Drug-drug interaction (DDI)-based PIMs (Continued).

Gr.	No. of Criteria (X/10)	Drug-drug interactions	Total for Drug Combination n (%)
		aspirin + etoricoxib	14 (5.51)
		aspirin + mefenamic acid	1 (0.39)
<b>12</b>	<b>1</b>	<b>NSAIDs + loop diuretics, SSRIs, or antihypertensives</b>	<b>196 (2.51)</b>
		naproxen + sertraline	31 (15.82)
		meloxicam + sertraline	22 (11.22)
		meloxicam + fluoxetine	20 (10.20)
		naproxen + furosemide	15 (7.65)
		celecoxib + sertraline	13 (6.63)
		meloxicam + escitalopram	12 (6.12)
		ibuprofen + sertraline	11 (5.61)
		diclofenac + sertraline	10 (5.10)
		meloxicam + furosemide	10 (5.10)
		naproxen + fluoxetine	7 (3.57)
		etoricoxib + fluoxetine	6 (3.06)
		etoricoxib + furosemide	6 (3.06)
		ibuprofen + furosemide	6 (3.06)
		celecoxib + fluoxetine	5 (2.55)
		etoricoxib + sertraline	5 (2.55)
		celecoxib + furosemide	4 (2.04)
		ibuprofen + fluoxetine	4 (2.04)
		diclofenac + furosemide	3 (1.53)
		diclofenac + fluoxetine	2 (1.02)
		naproxen + escitalopram	2 (1.02)
		naproxen + mirtazapine	2 (1.02)
		celecoxib + escitalopram	1 (0.51)
		celecoxib + indapamide	1 (0.51)
		etoricoxib + indapamide	1 (0.51)
		ibuprofen + escitalopram	1 (0.51)
		meloxicam + indapamide	1 (0.51)
		meloxicam + mirtazapine	1 (0.51)
<b>13</b>	<b>1</b>	<b>ACEIs + ARBs</b>	<b>29 (0.37)</b>
		captopril + losartan	16 (55.17)
		enalapril + losartan	8 (27.59)
		enalapril + azilsartan	2 (6.90)
		captopril + azilsartan	1 (3.45)
		captopril + valsartan	1 (3.45)
		perindopril + azilsartan	1 (3.45)
<b>14</b>	<b>1</b>	<b>Warfarin + sulfamethoxazole/trimethoprim, macrolides, quinolones, NSAIDs, cimetidine, metronidazole, or cotrimoxazole</b>	<b>259 (3.31)</b>
		warfarin + aspirin	228 (88.03)
		warfarin + roxithromycin	8 (3.09)
		warfarin + ciprofloxacin	6 (2.32)
		warfarin + celecoxib	4 (1.54)
		warfarin + meloxicam	3 (1.16)
		warfarin + sulfamethoxazole/trimethoprim	3 (1.16)
		warfarin + clarithromycin	2 (0.77)
		warfarin + diclofenac	2 (0.77)
		warfarin + naproxen	2 (0.77)
		warfarin + etoricoxib	1 (0.39)

**Table S4.** Drug-drug interaction (DDI)-based PIMs (Continued).

Gr.	No. of Criteria (X/10)	Drug-drug interactions	Total for Drug Combination n (%)
		warfarin + metronidazole	1 (0.39)
<b>15</b>	<b>1</b>	<b>Benzodiazepines + opioids</b>	<b>2,295 (29.34)</b>
		lorazepam + tramadol	896 (39.04)
		diazepam + pethidine	837 (36.47)
		clonazepam + tramadol	142 (6.19)
		diazepam + morphine	96 (4.18)
		diazepam + tramadol	94 (4.10)
		lorazepam + morphine	91 (3.97)
		midazolam + fentanyl	64 (2.79)
		lorazepam + codeine	60 (2.61)
		clorazepate + tramadol	49 (2.14)
		midazolam + morphine	28 (1.22)
		alprazolam + tramadol	18 (0.78)
		clonazepam + codeine	13 (0.57)
		clorazepate + codeine	13 (0.57)
		chlordiazepoxide + pethidine	11 (0.48)
		chlordiazepoxide + tramadol	11 (0.48)
		lorazepam + fentanyl	9 (0.39)
		alprazolam + codeine	7 (0.31)
		lorazepam + pethidine	7 (0.31)
		clonazepam + morphine	5 (0.22)
		diazepam + fentanyl	3 (0.13)
		alprazolam + morphine	2 (0.09)
		diazepam + codeine	2 (0.09)
		clonazepam + pethidine	1 (0.04)
		clorazepate + morphine	1 (0.04)
		midazolam + pethidine	1 (0.04)
		midazolam + tramadol	1 (0.04)
<b>16</b>	<b>1</b>	<b>Ciprofloxacin + theophylline</b>	<b>15 (0.19)</b>
		ciprofloxacin + theophylline	15 (100.00)
<b>17</b>	<b>1</b>	<b>Phenytoin + sulfamethoxazole/trimethoprim</b>	<b>0 (0.00)</b>
<b>18</b>	<b>1</b>	<b>MAOI + pethidine (Meperidine)</b>	<b>0 (0.00)</b>
<b>19</b>	<b>1</b>	<b>Cimetidine + CNS drugs (TCA, benzodiazepines, and carbamazepine)</b>	<b>Not assessed</b>
<b>20</b>	<b>1</b>	<b>Digoxin + amiodarone, hydrochlorothiazide, diuretics, macrolides antibiotics, or verapamil</b>	<b>333 (4.26)</b>
		digoxin + furosemide	280 (84.08)
		digoxin + spironolactone	158 (47.45)
		digoxin + hydrochlorothiazide	25 (7.51)
		digoxin + amiodarone	4 (1.20)
		digoxin + verapamil	3 (0.90)
		digoxin + roxithromycin	1 (0.30)
		<b>Overall</b>	<b>7,823 (100.00)</b>

**Note:**

- **X** represents the number of criteria (out of 10) in which the drug class is identified as a PIM.

- % **Drug Combination** was calculated by dividing the number of patients who received the main DDI pattern by the total number of patients who received DDI-based PIMs (e.g. 12.69% received aldosterone antagonists + potassium-conserving drugs = 993/7,823).

- % **Specific Drug Combination** was calculated by dividing the number of patients who received a specific drug combination (sub-pattern) by the number of patients with the corresponding main DDI pattern (e.g. 48.34% received spironolactone + enalapril = 480/993). Specific drug combinations are listed in descending order of frequency within each main pattern.

- *Not assessed* indicates that the DDI-based PIM could not be evaluated because cimetidine was not available in any of the participating hospitals.