STOPP/START analysis of ambulatory geriatric patients attending an internal medicine clinic in Jember, Indonesia

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Abstract

Context: Indonesia is one of countries with staggering number of elderly population. This population is at risk having comorbidities, polypharmacy, inappropriate medication, and adverse drug reactions.

Aims: This study aimed to determine the prevalence of Potentially Inappropriate Medications (PIM) and Potentially Prescription Omissions (PPO) among ambulatory geriatric patients.

Settings and Design: The research was conducted in an internal medicine clinic of a hospital in Jember Regency, East Java, Indonesia using a retrospective, cross-sectional design.

Methods and Material: Data were collected consecutively with a targeted sample size of 96 patients during September 2016. Each patient data was traced back for a minimum of three months period. Analysis of drugs with PIM and PPO was based on criteria of the Screening Tool of Older Person’s Prescription (STOPP) and Screening Tool to Alert to Right Treatment (START) version 2.

Statistical analysis used: Descriptive statistics were used to report the results.

Results: The results showed that a total of 92 PIM events occurred in 64 patients (64 %) and were found more in females (66 %), aged 65 yr to 69 yr (70 %) with glimepiride and pioglitazone as the first and second leading drugs causing PIM events. All eight PPOs were in the form of not giving antihypertensive therapy to hypertensive patients according to the START criteria.

Conclusions: In conclusion, the PIM figures were large, while the PPO was small and narrowed to one problem. Increasing alertness and caution in administering drug therapy will be very necessary to reduce adverse drug reactions in geriatric patients.

Keywords: Ambulatory patient, drug evaluation, elderly, potentially inappropriate medication, potentially prescription omission

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Introduction

Since 2015 Indonesia has seen the growth of ageing population surpassing 7% of total population. It was estimated that in 2017 there were 23,700,000 (9%) elderly people in Indonesia. The number was projected to grow reaching 27,000,000 in 2020, 33,700,000 in 2025, and 48,200,000 in 2035.\[1\] The older people tend to live with multimorbidity, leading them to take more than one drug that commonly known as polypharmacy to control their conditions and to reduce the risk of complications.\[2,3\] Apart from the need to redefine the term, polypharmacy has gained more attention in recent yr as part of patient safety issue.\[4,5\] Polypharmacy may increase the risk of problems related to drug administration that are commonly referred as Drug Related Problems (DRP). One important strategy to prevent DRP, especially in this geriatric population, is to avoid giving inappropriate drugs or Potentially Inappropriate Medication (PIM).\[6\] Several criteria were developed to identify the potential improper use of drugs in geriatrics, including Assessing Care of Vulnerable Elders (ACOVE) indicators\[7,8\], Beers Criteria® 2012\[9\], and the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert Doctors to Right Treatment (START) Criteria.\[10,11\] A total of 114 indicators of the tool are divided into two criteria: The STOPP that consists of 80 important clinical indicators for PIM and the START that comprises 34 indicators for several neglected drugs that are commonly called Potentially Prescription Omission (PPO).\[10,11\] This study aimed to assess the PIM and PPO events among ambulatory geriatric patients in the internal medicine clinic using the STOPP/START criteria.

Materials and Methods

This research was conducted using a retrospective, cross–sectional design. Treatment history of ambulatory patients visiting an internal medicine clinic of a hospital in Jember Regency, East Java, Indonesia during the September 2016 was traced retrospectively from their respective medical records for at least 3 mo. Data collection was between November and December 2016. Data analysis was conducted in the Faculty of Pharmacy, University of Jember, Indonesia.

As the study used only one sample and measure the population proportion, the Lemeshow’s formula below was used.\[12\]
By using $z$ value of 1.96 for 95% confidence interval, the population proportion $p$ of 0.5, and the precision $d$ of 0.1, the minimum sample size $n$ is 96. A consecutive sampling was used to collect data from patients who aged 65 yr or more and had a history of being treated for at least 3 mo before September 2016 as recorded in their medical record. Patients were excluded if their medical record contained unreadable handwriting.

The elderly patients’ medical record numbers, names, and diagnosis were provided by the internal medicine clinic and recorded onto the data collection sheets. Based on this information, patients’ medical records were sought from the respective hospital’s department that stores them. The data sheets for each patient were further completed with more information from the medical records, including initial, sex, birth date, complete diagnosis and comorbidities, laboratory and non–laboratory data, and drug therapy. Using STOPP/START criteria version 2[11], each patient was analyzed to detect problems related to PIM and PPO based on their recorded data. Identified problems were tabulated for further descriptive statistical analysis. Drugs were classified according Anatomical Therapeutic Chemical (ATC) Classification System (https://www.whocc.no/).

The privacy of patient data was protected in this study. Only aggregated or summary data were used for dissemination purposes. Permission to conduct the research was released by the hospital X in Jember, Indonesia (No. 423.4/6880/610/2016).

**Results**

**Patient profile**

During September 2016, a total of 164 geriatric patients visited the internal medicine clinic. A number of 100 patients met the inclusion criteria. The number of male and female patients was equal (50 %) (Table 1). Half patients (50 %) aged 65 yr to 69 yr. There were six types of diagnosis; with the most common diagnosis for both sexes was diabetes, accounted for 40 males and 35 females. While for other diagnosis males were dominant than females, this did not apply for arthritis. No patient
received only one medicine and a third patients (33 %) received four drugs at once, while just more than a quarter (26 %) received three combination drugs.

**Table 1.** Characteristics of elderly patients visiting an internal medicine clinic

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Males, N = 50</th>
<th>Females, N = 50</th>
<th>Total, N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 to 69</td>
<td>28</td>
<td>22</td>
<td>50</td>
</tr>
<tr>
<td>70 to 74</td>
<td>16</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>75 to 79</td>
<td>5</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>≥ 80</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>24</td>
<td>49</td>
</tr>
<tr>
<td>Arthritis</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Gastritis</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td><strong>Number of drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>15</td>
<td>33</td>
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<tr>
<td>5</td>
<td>13</td>
<td>7</td>
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<td>6</td>
<td>9</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Patient treatment profile**

Blood glucose lowering drugs (A10B); drugs for peptic ulcer (A02B); and antiinflammatory and antirheumatic products, nonsteroids (M01B) ranked the first to third largest number of drug classes given to the patients, accounting for 124, 36, 33 uses, respectively (Table 2). Individual drug analysis revealed that glimepiride (n = 56 patients) and acarbose (n = 36 patients) placed the two most commonly prescribed drugs.

**Table 2.** Treatment profile based on ATC grouping

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Class</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A10B</td>
<td>Blood glucose lowering drugs</td>
<td>124</td>
<td>43.8</td>
</tr>
<tr>
<td>A02B</td>
<td>Drugs for peptic ulcer and GORD</td>
<td>36</td>
<td>12.7</td>
</tr>
</tbody>
</table>

(Continued on text page)
Table 2. Continued

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Class</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>M01A</td>
<td>Anti–inflammatory and antirheumatic products, nonsteroids</td>
<td>33</td>
<td>11.7</td>
</tr>
<tr>
<td>C08C</td>
<td>Selective calcium channel blocker</td>
<td>25</td>
<td>8.8</td>
</tr>
<tr>
<td>C09C</td>
<td>Angiotensin II antagonist</td>
<td>21</td>
<td>7.4</td>
</tr>
<tr>
<td>B03B</td>
<td>Vitamin B12 and folic acid</td>
<td>17</td>
<td>6.0</td>
</tr>
<tr>
<td>N05B</td>
<td>Anxiolytic</td>
<td>10</td>
<td>3.5</td>
</tr>
<tr>
<td>M04A</td>
<td>Antigout preparations</td>
<td>9</td>
<td>3.2</td>
</tr>
<tr>
<td>C07A</td>
<td>Beta–blocking agents</td>
<td>8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

ATC: Anatomical Therapeutic Chemical Classification System

**PIM based on STOPP criteria and PPO based on START criteria**

A total of 92 PIM events were detected in 64 patients (64 %) with 38 events occurring in 38 individuals, 50 events in 25 individuals, and 6 events in 2 individuals. By gender, PIM events were found in 62 % males (31/50) and 66 % females (33/50). By age group, the proportion of patients having PIM events decreased across all age groups with the largest proportion (35/50, 70 %) occurring among those aged 65 yr to 69 yr and the smallest proportion (7/15, 47 %) among age group 75 yr to 79 yr. There were nine drugs contributing to PIM events (Figure 1). Glimepiride was accounted for 61 % PIM events (56/92) and pioglitazone 18 % PIM events (17/92).

Compared to PIM events, PPO events were less minimally occurring. In total, there were only eight PPO events that incurred more in men (12 %, 6/50) than women (4 %, 2/50). All events were in the form of the need to provide antihypertensive therapy to patients.

**Figure 1.** The frequency of individual drugs causing PIM based on STOPP criteria.
Discussion

This study aimed to assess possible PIM and PPO events emerging among ambulatory geriatric patients using the second version of STOPP/START Criteria developed by O’Mahony et al.[11] One similar study reported from Jakarta, Indonesia. [13] It was conducted similarly in a geriatric ambulatory patients, but not specifically in a clinic, rather in the whole hospital. Therefore, the PIM and PPO events revealed were different.

In this present study, glimepiride emerged as the most frequent drug related to PIM. This drug is one of second generation of sulphonylureas which is long–acting, commonly used, and widely available globally, including in Indonesia.[14],[15] In the STOPP criteria, glimepiride should not be given to elderly patients because it may cause prolonged hyperglycemia.[11] The drug was recently added also into one of avoided drugs for elderly people in the 2019 Beers Criteria® due to the similar reason of prolonged hypoglycemia with quality of evidence “high” and strength of recommendation “strong”.[9] Despite its adverse effect on blood glucose level, glimepiride may also increase risk of progression to end–stage renal disease and two–fold increase of serum creatinine among patients aged 62 compared to gliclazide, a short acting sulphonylurea.[15] Hypoglycemia may lead to adverse outcomes such as altered mental status, seizures, coma, and death.[15],[16] A paper in 2017 reported of a large cohort study using linked databases in UK showed an increased risk of severe hypoglycemia (adjusted HR 2.83; 95 % CI 1.64 to 4.88) among the initiators of long–acting sulphonylureas, including glyburide or glimepiride, compared to short–acting sulphonylureas such as gliclazide, glipizide, or tolbutamide.[17] That study, although did not exclusively study the elderly people, involved the older adults as well as older people, with mean age (SD) of participants 66.8 (12.2) yr in long–acting sulphonylureas group and 68.4 (12.5) yr in short–acting sulphonylureas group. This suggests the safer short–acting sulphonyureas as alternative for use among the elderly.

This study, pioglitazone was found to be the second most frequent drug causing PIM events. Pioglitazone is a thiazolidindiones acting as peroxisome proliferator–activated receptor gamma agonist and is commonly reserved as second–line
treatment of type 2 diabetes mellitus, especially for patients with insulin resistance.\textsuperscript{18,19} Noted in the START criteria, this drug should be used carefully in heart failure and elderly patients due to increase risk of fracture, bladder cancer, and exacerbation of heart failure.\textsuperscript{10,11} The 2019 Beers Criteria\textsuperscript{®} reorganized recommendations on the use thiazolidinediones among elderly patients with heart failure.\textsuperscript{9} This drug class should be used “with caution” in older adults with asymptomatic heart failure, but should be “avoided” in those with symptomatic heart failure.\textsuperscript{9} Indeed, the clinical use of pioglitazone is not free from safety issues such as weight gain, CHF, bone fractures, macular edema, and bladder cancer.\textsuperscript{20} In regards to the later risk, there has been much debate. A retrospective cohort study reported in 2016 using multiple databases from four different European countries involving 56 337 type 2 diabetes patients initially using pioglitazone matched in the same country to 317 109 type 2 diabetes patients using any antidiabetic agents other than pioglitazone revealed that there was no evidence to link ever use of pioglitazone to bladder cancer risk compared with never use.\textsuperscript{21} However, a systematic review and meta–analysis reported two yr after that multinational retrospective cohort study proved otherwise. Including two RCTs recruiting 9 114 patients and 20 observational studies involving almost 4 846 088 patients; Tang et al.\textsuperscript{22} showed non–significant result of the increased risk of bladder cancer from the RCTs (OR 1.84; 95 § CI 0.99 to 3.42), but significant from the observational studies (OR 1.13; 95 § CI 1.03 to 1.25). Routine monitoring for signs of bladder cancer was then suggested for patients put in long–term and high–dose pioglitazone therapy.

Five non–steroidal anti–inflammatory drugs (NSAIDs), including meloxicam, methampyrone (also known as dipyrone or metamizole), diclofenac sodium, acetosal, and mfenamic acid were found to contribute to PIM events in this study. The STOPP Criteria notes many circumstances that should be reviewed by the presence of NSAIDs as well as COX–2 selective inhibitors in elderly patients.\textsuperscript{10,11} This study, NSAIDs were used in patients with eGFR < 60 mL min\textsuperscript{−1} 1.73 m\textsuperscript{−2} (13 PIM events). NSAIDs and moderate COX–2 selective inhibitor meloxicam were also used in patients with moderate hypertension (4 PIM events). A Canadian community–based cohort involving 10 184 elderly (\geq 66 yr of age) subjects found an increased risk of progression of chronic kidney disease (defined as a decrease in
Pratama et al. (2020): Analysis of ambulatory geriatric. February 2020. Vol. 23 (3A) glomerular filtration rate ≥ 15 mL min⁻¹ 1.73 m⁻²) with OR 1.26 (95 % CI 1.04 to 1.53) among patients with high–dose NSAIDs.[23] Subsequently, in a 2013 meta–analysis that include that Canadian study similar finding was found that only high–dose NSAIDs, but not regular–dose NSAIDs significantly increased the risk of accelerated chronic kidney disease progression.[24] However, if the outcome of interest is acute kidney injury and the dose of NSAIDs was not classified as regular versus high, the baseline risk resulted from NSAIDs exposure appear clearer. Among the elderly in general population the pooled odds ratio of acute kidney injury for current NSAIDs exposure from observational studies was 2.51 (95 % CI 1.52 to 2.68).[25] This study, although to date there has been no systematic review or meta–analysis examining the risk of exacerbation of hypertension due to NSAIDs use among elderly population, it is generally considered that the presence of NSAIDs, but not selective COX–2 inhibitors, may raise blood pressure by 5 mmHg in average.[26] The NSAIDs mechanism of action that can elevate serum aldosteron may lead to sodium retention and therefore hypertension.[26]

In regards to PPO events, this study found eight cases of untreated hypertension with systolic blood pressure > 140 mmHg. Almost all cases were with diabetic co–morbidty. This coexistence increase the risk of cardiovascular disease and mortality as well as disease progression to nephropathy and retinopathy.[27] Recommended blood pressure goals may differ from one professional organisation to another. For example, the 2018 American Diabetes Association, the 2014 Joint National Committee–8, and the 2016 National Heart Foundation Australia recommended a blood pressure goals of < 140/90 mmHg for hypertension with diabetes.[27],[28] First line drugs may be also different from one to another guideline, but usually include monotherapy of ACE–Inhibitors/ARB, thiazide–like diuretic, or dihydropyridine CCB.[27]

In conclusion, this study found a large number of PIM events, but small PPO events based on STOPP/START Criteria among individuals visiting the internal medicine clinic in Jember, East Java, Indonesia.

Acknowledgement

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Pratama et al. (2020): Analysis of ambulatory geriatric. February 2020. Vol. 23 (3A)

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