Potentially Inappropriate Medication and Associated Factors Among Older Patients with Chronic Coronary Syndrome at Hospital Discharge in Beijing, China

Mei Zhao, Jun-xian Song, Fang-fang Zheng, Lin Huang, Yu-fei Feng

1Department of Pharmacy, Peking University People’s Hospital, Beijing, People’s Republic of China; 2Department of Cardiology, Peking University People’s Hospital, Beijing, People’s Republic of China

*These authors contributed equally to this work

Purpose: Medication therapy is crucial in the management of chronic coronary syndrome (CCS). The use of potentially inappropriate medications (PIMs) contributes to poor outcomes in older patients, making it a major public health concern. However, few studies are available on PIMs use in older Chinese CCS patients. To investigate the frequency of prescribed PIMs at discharge and explore risk factors in older adults with CCS.

Patients and Methods: The cross-sectional study was conducted in a tertiary hospital in China over three months, from 1st October to 31st December, 2019. CCS patients aged over 60 years who were discharged alive were recruited. Information on demographics and medications at discharge was collected. Clinical data including diagnoses, frailty status, New York Heart Association (NYHA) class and age-adjusted Charlson Comorbidity Index (ACCI) were evaluated in each patient. PIMs were identified using the 2019 Beers criteria. Binary logistic regression was performed to recognize variables related to PIMs.

Results: A total of 447 eligible patients with 2947 medications were included. The prevalence of PIMs use was 38%. Medications to be avoided, to be used with caution, and with drug–drug interactions were 38.4%, 48.9% and 12.7% of the PIMs, respectively. Medications with drug–disease/syndrome interactions and those adjusted for kidney function were not identified. The common PIMs were diuretics (37.1%), benzodiazepines and benzodiazepine receptor agonist hypnotics (15.2%), glimepiride (13.1%), and co-prescription of potassium-sparing diuretics and renin-angiotensin system (RAS) inhibitors (9.7%). Individuals with frailty syndrome, polypharmacy, multiple comorbidities, atrial fibrillation, psychiatric disorders and greater NYHA class severity were more likely to receive PIMs.

Conclusion: Prescription of PIMs was a common burden in older adults. A CCS multidisciplinary team is needed to control PIMs, especially in vulnerable older patients.

Keywords: potentially inappropriate medication, Beers criteria, chronic coronary syndrome, older adults, discharge

Introduction

Coronary artery disease (CAD) remains the top cause of death and disability-adjusted life-years (DALYs) worldwide, particularly in elderly individuals.1,2 As a dynamic phase of CAD, chronic coronary syndrome (CCS) may acutely destabilize with poor control.3 A chronic pharmacotherapy to reduce recurrence and provide symptoms relief is responsible for CCS treatment. Due to multimorbidity,
more medications consumption and changes in pharmacokinetics and pharmacodynamics, geriatrics are more prone to inappropriate drug use. As a result, it is necessary to recognize the inappropriate prescriptions in older CCS populations.

The Beers criteria defines potentially inappropriate medications (PIMs) in elderly individuals as drugs that have more risks than benefits or for which better tolerated or safer alternatives are available. The use of Beers-PIMs has been associated with a range of adverse events including falls, fractures, cognitive dysfunction and rehospitalization, along with increased health expenditure. The prevalence of CAD-PIMs in the geriatric population ranged from 20% to 60% in the USA, Sweden and Ethiopia. A study in Taiwan stated that 86.1% of older patients with both heart failure and diabetes were taking PIMs. Given a large proportion of CCS patients with advanced age, the Beers criteria may be valid and efficacious to detect PIMs.

In addition to quantifying PIMs, it is vital to investigate the relevance between individual characteristics and PIMs use to formulate better interventions to reduce PIMs. The burden of PIMs appears high in older adults with chronic polypharmacy and multimorbidity. Frailty syndrome is manifested as a marked vulnerability for more intensive medication intake, multi-morbidities and decreased resistance to PIMs. Tools for cardiac capacity stratification such as the New York Heart Association (NYHA) class, serve as a good prognostic factor in heart failure, lung disease, prescription pattern and quality of life. Moreover, physicians’ awareness of the number of drugs and benefit/risk profiles helps to prescribe fewer PIMs. Presumably, CAD patients taking multiple medications, or experiencing a high prevalence of frailty or transition to frail status, are at the risks of receiving PIMs.

Despite the emerging evidence of PIMs in clinical practice, few studies have examined PIMs in the CCS population. The aims of the present study were to: 1) assess PIMs at hospital discharge; and 2) identify risk factors for the use of PIMs.

Methods
Design
The cross-sectional study was carried out at Peking University People’s Hospital, Beijing, China, from 1 October to 31 December 2019. The hospital is a government-run tertiary teaching and national referral center that was established in 1918. It offers medium- and high-complexity care. The cardiovascular internal medicine ward has more than 130 beds and delivers advanced treatments for various cardiovascular diseases. The study was approved by the ethics committee of Peking University People’s Hospital and conducted in accordance with the Declaration of Helsinki. Written informed consent forms were obtained from patients or their proxy. Anonymity and confidentiality ensured patient names did not appear in the findings. The information of each patient was recorded anonymously and used for research purposes. Only researchers involved in this study had access to patient records.

Participants
Older people for developing countries were defined as aged over 60 years by the World Health Organization. Eligible older CCS patients who were hospitalized for at least 24 hours and alive at discharge were selected. The exclusion criteria were as follows: (1) terminal disease or bed-ridden patients with a short life expectancy; (2) self-discharge or discharge against medical advice, that is, a patient choosing to leave the hospital before the physician recommends to discharge; (3) discharge without medication; (4) transfer to another ward or hospital; and (5) inability to participate in the study. When a patient had multiple admissions during the study period, only the last admission was included.

The sample size was calculated to be 387 patients, with an estimated prevalence of PIMs at 40%, an 95% confidence interval and an α-error of 5%. Convenience sampling was used and 447 subjects were recruited for the final analysis.

Use of PIMs
Data on discharge prescriptions were collected. As-needed medications, eye drops, topical medications and other non oral drugs, herbs, nutritional supplements and over-the-counter drugs were excluded. Quantitative assessment of drug use was recorded. For drugs administered weekly, such as bisphosphonates, the number of medications was calculated on the day of maximum usage. In the case of single-pill fixed-dose combination tablets, such as irbesartan/hydrochlorothiazide, each pharmacologically active substance was counted.

PIMs were evaluated using the 2019 Beers criteria supported by the American Geriatric Society. Five types of criteria were identified: (1) medications that should be...
avoided; (2) medications with drug-disease/syndrome interactions; (3) medications that should be used with caution; (4) medications with clinically important drug-drug interactions, with the severity of interactions was searched through Lexi-Interact (https://www.uptodate.com/drug-interactions), and (5) medications that should be adjusted considering kidney function. The first author manually identified PIMs at the patient level, and then the corresponding author verified all PIMs. All authors discussed any discrepancies until consensus was achieved.

Data Collection
The electronic medical records of 447 patients were reviewed. Demographic information including age, sex and healthcare insurance information was collected.

Clinical data, including length of hospital stay, diagnoses, NYHA class and serum creatine level were all acquired. The NYHA classification subjectively estimates the cardiac capacity based on a patient’s self-report of physical activity and symptoms such as dyspnea. The age-adjusted Charlson Comorbidity Index (ACCI) was summed as the weighted combination of age and comorbidity scores. The ACCI has been widely used to detect the severity of comorbidity burden, and predict mortality in older adults. Clinicians were responsible for NYHA class and ACCI assessment.

If any data were missing or unclear, the pharmacists contacted the principal physicians to collect as much accurate information as possible.

Functional Status
Frailty was assessed with the 5-item FRAIL scale: fatigue, resistance, ambulation, illness and weight loss. Patients meeting at least 3 criteria were regarded as frail (3–5), 1 or 2 criteria as pre-frail and none of these criteria as robust (0).

Statistical Analysis
Numerical variables were examined for normal distribution and expressed as median with interquartile range (IQR) or mean ± SD, and categorical data are expressed as percentage.

Binary logistic regression was conducted to detect the important characteristics associated with the prescription of PIMs. PIMs use was considered as a binary outcome. Age, hospital stay, ACCI, multiple comorbidities and polypharmacy were dichotomized based on their median values. These factors and certain chronic conditions were considered as covariables. The goodness-of-fit was examined with Hosmer-Lemeshow test, such that p > 0.05 indicated a good regression model. The forward stepwise method was used to calculate the odds ratio (OR) and 95% confidence interval (CI) of OR. A two-tailed p < 0.05 was confirmed as statistically significant.

Statistical analysis was performed with SPSS 23.0 software (IBM SPSS statistics for Windows, version 23.0, IBM Corp, Armonk, NY). Tables and figures were drawn with GraphPad Prism 8.0 software (GraphPad Software Inc., La Jolla, CA, USA).

Results
Patient Characteristics
The demographic and clinical characteristics of the 447 inpatients were shown in Table 1. The study comprised 60.0% male and 40.0% female participants. The mean age was 71.5±7.2 years and the ages ranged from 60 to 90 years. The majority of the population was either pre-frail (46.1%) or frail (13.0%). At discharge, angina was the most frequently clinical CCS scenario (n=298, 66.7%), and up to 90% of patients were declared as NYHA class 1 and 2. The presence of approximately 18 chronic conditions was recorded: hypertension, atrial fibrillation, diabetes mellitus, dyslipidemia, atherosclerosis, cerebrovascular disease, thyroid disorder, asthma, chronic obstructive pulmonary disease, cancer, chronic kidney disease, chronic liver disease, osteoarthritis, rheumatoid arthritis, gastrointestinal disease, thromboembolic disease, psychiatric disorder (anxiety/depression/insomnia) and hyperuricemia. Nearly three out of five patients had 5 or more chronic conditions with a range of 0–13. Specifically, hypertension, dyslipidemia, atherosclerosis and type 2 diabetes mellitus were the top four comorbid diseases. The ACCI scores ranged from 2–13, with a median of 5. Thus, patients were classified into 2 groups: low ACCI group (ACCI = 2–4, 49.4%) and high ACCI group (ACCI = 5–13, 50.6%) (Table 1).

PIMs Prescriptions for CCS Patients
The participants had a total of 2947 chronic medications at discharge. The median of discharge medications was 6. 65.5% of the whole cohort were prescribed of 6 or more drugs. Polypharmacy in this study was defined as the concurrent use of ≥ 6 drugs, which was expected to represent a tendency for inappropriate drug use. According to the 2019 Beers criteria, 38% of individuals were taking...
237 inappropriate prescriptions. The proportion of PIMs among discharge medications was 8.0% (237/2947). Overall, among patients with PIMs, 70.0%, 23.5% and 6.5% of patients had one, two or three to five PIMs, respectively. Medications to be avoided, to be used with caution and with clinically important drug-drug interactions were 38.4% (91/237), 48.9% (116/237), and 12.7% (30/237) of PIMs, respectively. Both medications with drug-disease/syndrome interactions and those needed to be adjusted for kidney function were not identified in these participants (Table 2).

| Characteristics | n (%) |
|-----------------|-------|
| Sex             |       |
| Male            | 268 (60.0) |
| Female          | 179 (40.0) |
| Age (mean, SD)  |       |
| 60–64           | 71.5 (7.2) |
| 65–69           | 88 (19.7) |
| 70–74           | 112 (23.1) |
| 75–79           | 102 (22.8) |
| 80–85           | 63 (14.1) |
| 85–90           | 65 (14.5) |
| Functional status |     |
| Robust (0)      | 183 (40.9) |
| Pre-frailty (1–2) | 206 (46.1) |
| Frailty (3–5)   | 58 (13.0) |
| Comorbidities (median, IQR) |       |
| Hypertension    | 341 (76.3) |
| Dyslipidemia    | 307 (68.7) |
| Atherosclerosis | 245 (54.8) |
| Type 2 diabetes mellitus | 179 (40.0) |
| ACCI (median, IQR) |       |
| Low ACCI (2–4)  | 221 (49.4) |
| High ACCI (5–13) | 226 (50.6) |
| Length of stay (median, IQR) |       |
| ≥7 days         | 7 (7–9) |
| NYHA class      |       |
| 1               | 251 (56.2) |
| 2               | 151 (33.8) |
| 3               | 38 (8.5) |
| 4               | 7 (1.5) |

Abbreviations: ACCI, age-adjusted Charlson Comorbidity Index; NYHA, New York Heart Association; IQR, interquartile range.

The most prescribed PIMs was the category of drugs that may exacerbate or induce syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatremia (40.9%). The majority of these drugs were diuretics (n=88), of which 54 patients were prescribed with loop diuretics and 34 were prescribed with hydrochlorothiazide. Benzodiazepines and benzodiazepine receptor agonist hypnotics or Z-drugs (BZD/Z, 15.2%) and long-acting sulfonylureas (glimepiride, 13.1%) were followed. Other frequently observed PIMs were new oral anticoagulant (NOAC, 8.0%) and proton-pump inhibitors (PPIs) > 8 weeks in non-high risk patients (6.3%). Among those with unnecessary use of PPIs, 1 patient received pantoprazole at 40 mg, 1 received omeprazole at 20 mg, and the remaining 13 patients received rabeprazole (10 individuals at 20 mg and 3 individuals at 10 mg). The proportion of PIMs mentioned above were 83.5% among the total exposure to PIMs (Table 3).

Nearly 10% of patients were co-prescribed potassium-sparing diuretics and renin-angiotensin system (RAS) inhibitors, resulting in an elevated risk of hyperkalemia and renal function impairment. The combination of warfarin and amiodarone was considered category D in Lexi-Interact, which signified the regimen modification. A 74-year-old female was taking doxazosin and furosemide dosing 20 mg daily, and there was no identified interaction between them in Lexi-Interact (Table 4).

Factors Associated with PIMs

As shown in Figure 1, the presence of PIMs was associated with pre-frailty and frailty (OR=2.034, CI=1.337–3.095). Patients with polypharmacy, 5 or more chronic
illnesses and high ACCI values nearly doubled the risk to receive PIMs (OR=1.712, CI=1.045–2.805; OR=1.824, CI=1.155–2.882; OR=1.701, CI=1.136–2.547, respectively). Compared with NYHA class 1, increases in NYHA class severity showed higher occurrences of PIMs use (NYHA class 2: OR=2.167, CI=1.365–3.441; NYHA class 3/4: OR=6.405, CI=2.903–14.129). Two chronic conditions that correlated with PIMs were atrial fibrillation (OR=2.332, CI=1.256–4.332) and psychiatric disorders such as depression/anxiety/insomnia (OR=10.437, CI=4.098–26.579).

**Discussion**

To the best of our knowledge, this is the first study to evaluate PIMs using the 2019 Beers criteria in older Chinese patients with CCS. Approximately two-fifths of CCS patients were taking PIMs, and almost half fell into the category of medications to be cautiously used. The result was slightly lower than previous results.\(^{11,13,35}\) This discrepancy may be due to different settings. For instance, those with acute coronary syndrome and cardiovascular diseases without coronary lesions were excluded. Additionally, consistent with studies conducted in Europe and the USA, individuals with a worse health status, an increase in the number of comorbidities, high ACCI score, a greater number of prescribed drugs, poor cardiac function and certain chronic conditions were expected to be in subgroups at an elevated threat to receive PIMs.\(^{36,37}\)

Since the initial publication of the Beers criteria in 1991, country- and region-specific derivations of PIMs criteria have been developed. The 2017 Chinese criteria divide PIMs into high- and low-risk medications along

### Table 3 PIMs That Should Be Avoided and to Be Used with Caution Using the 2019 Beers Criteria

| The 2019 Beers Criteria | n (%) | Rationale |
|-------------------------|-------|-----------|
| **Medications that should be avoided** | 91 (38.4) | |
| Benzodiazepines and Z-drugs | 36 (15.2) | Cognitive impairment, fall, fracture and delirium |
| Long-acting sulfonylureas-glimepiride | 31 (13.1) | Risk of severe prolonged hypoglycemia |
| PPI > 8 weeks in non-high-risk patients | 15 (6.3) | Clostridium difficile infection and fractures |
| Peripheral α-1 blockers for hypertension | 5 (2.1) | Risk of orthostatic hypotension |
| Antidepressants | 2 (0.8) | Risk of anticholinergic effects |
| Digoxin>0.125 mg/d in heart failure | 1 (0.4) | Risk of digitalis |
| Reserpine (>0.1 mg/d) | 1 (0.4) | Orthostatic hypotension and bradycardia |
| **Medications to be used with caution** | 116 (48.9) | |
| NOAC-rivaroxaban and dabigatran | 19 (8.0) | Risk of gastrointestinal bleeding |
| Diuretics-loop diuretics and thiazide | 88 (37.1) | Risk of SIADH or hyponatremia |
| Carbamazepine | 3 (1.3) | |
| Sertraline | 3 (1.3) | |
| Citalopram | 2 (0.8) | |
| Mirtazapine | 1 (0.4) | |

**Table 4** Potentially Clinical Important Drug-Drug Interactions to Be Avoided Using the 2019 Beers Criteria

| Object Drug/Class | Interacting Drug/Class | n (%) | Risk Rationale | Severity |
|-------------------|------------------------|-------|----------------|----------|
| Potassium-sparing diuretics | RAS inhibitors | 23 (9.7) | Hyperkalemia or kidney injury | C\(^b\) |
| CNS-active drugs\(^a\) | ≥2 CNS-active drugs | 3 (1.3) | Fall and fracture | C |
| Warfarin | Amiodarone | 2 (0.8) | Bleeding | D\(^c\) |
| Prednisone | Aspirin | 1 (0.4) | Ulceration and bleeding | C |
| Doxazosin | Furosemide | 1 (0.4) | Urinary incontinence | NA\(^d\) |

**Notes:** \(^a\)CNS-active drugs: antiepileptics, antipsychotics, benzodiazepine, benzodiazepine receptor agonist hypnotics, tricyclic antidepressant and serotonin-reuptake inhibitor; \(^b\)C: monitor therapy; \(^c\)D: consider therapy modification; \(^d\)NA: no interaction.

**Abbreviations:** RAS, renin-angiotensin system; CNS, central nervous system.
with experts’ opinions, and each medication was categorized as A or B with the frequency of use. It is worth noting that, clopidogrel, warfarin and spironolactone as the most commonly prescribed agents in cardiovascular system, are included in the Chinese criteria, but not the Beers criteria (warfarin and spironolactone are considered among the drug-drug interactions). As a generally safe, effective and easy to administer drug, clopidogrel is widely used in China. In this study, 300 patients were on clopidogrel. When clopidogrel was removed, similar PIMs were found between the Chinese criteria and the Beers criteria. In comparison with the PIMs based on Chinese criteria, Beers-defined PIMs engendered more substantial adverse outcomes, such as rehospitalization. One additional consideration is that the Chinese criteria were revised in 2017, and it may need to be updated with new information about currently available drugs. The Beers list that was updated in 2019 demonstrated a more robust evidence of PIMs use in Chinese geriatric inpatients than the 2015 version. Thus, the 2019 Beers criteria seem to be more tangible in clinical practice and offer a more reliable predictor of adverse events.

Consistent with findings in other cardiovascular settings, there was a high prevalence of diuretics as PIMs. Diuretics are mainly expected to alleviate volume overload and hypertension. 4 patients over 70 years receiving hydrochlorothiazide at 12.5 mg were at a stage 2/3 of chronic kidney disease. Guidelines have previously recommended against thiazide use in advanced chronic kidney disease. Thus, it is important to advise physicians to closely monitor electrolyte and creatine during use.

Heavy consumption of BZD/Z is common in older adults. BZD/Z are mainly used for anxiety, insomnia, as well as short-term control of depression. A prospective study reported that a variety of outpatients taking BZD/Z were suffering from cardiovascular diseases. A follow-up testified that having ever used BZD/Z brought about a 65% increase in female cardiovascular mortality in those aged over 50 years. Antidepressants and cognitive behavioral therapy (CBT) have been shown to be efficacious in elderly. Prescribers should take anticholinergic effects, cardiovascular outcomes and treatment options into account when making a decision for elderly CCS patients with psychiatric disorders.

Glimepiride was added to the 2019 Beers list due to severe prolonged hypoglycemia in older adults. Glimepiride is frequently observed as a PIM in older diabetes inpatients. Initial treatment with sulfonylurea monotherapy increased ischemic stroke, cardiovascular death and all-cause mortality. As it is cost-effective and has good glucose lowering potency, glimepiride remains...
competitive. Compared with short-acting sulfonylurea, long-acting had an increased risk of hypoglycemia. A Japanese study has suggested sulfonylurea conversion when HbA1c < 6.3% or 6.7% in older diabetic patients. Patients receiving glimepiride should be educated with regular monitoring of blood glucose and HbA1c.

Other groups of interest were NOAC and PPI. NOAC is preferred for better compliance and a greater clinical benefit. It has been found a lower dose of NOAC might be feasible and safe for Asians. In patients aged over 75 years with NOAC, assessment of bleeding risk using HAS-BLED and creatine level should be implemented in treatment plan. Long-term use of PPI without a clear indication has been common in older adults. A meta-analysis showed that the non-PPI group was associated with less myocardial infarction recurrence than the clopidogrel supplemented with PPI group. Healthcare providers should be prompted to check and reduce needless use of long-term PPI. The co-prescription of RAS inhibitors with potassium-sparing diuretics is more likely to result in acute kidney injury, especially in pre-existing renal dysfunction and poor cardiac function. This concomitant use raises concerns regarding renal toxicity and electrolytes.

Individuals considered as frail or pre-frail often suffer from chronic morbidities and an increased medication burden, and are thus associated with adverse outcomes. Similar to previous results, polypharmacy and multiple chronic conditions were significantly associated with PIMs prescriptions. One possible explanation is that with people aging and progress in disease management, increased prevalence of comorbidities necessitate intensive and simultaneous medication use. A Spanish study indicated that a 14% or 15% increase in PIMs for each additional prescribed drug. The association between atrial fibrillation, psychiatric disorders and PIMs exposure can be largely attributed to the use of NOAC and BZD/Z. In addition, use of PIMs tended to increase with the severity of the NYHA class. Patients with heart failure had a moderate anticholinergic drug burden, which was highlighted in the Beers criteria. Additionally, patients with NYHA class 3/4 bear heavier medication counts, more anxiety and depression and a higher level of cognitive impairment than those with NYHA class 2. The finding implied that deterioration in cardiac function might be associated with some inappropriate prescriptions.

Although it may not be possible to eradicate PIMs, some encouraging directions to reduce PIMs were uncovered in this study. Health education, medication review, polypharmacy optimization and deprescribing, as well as physical exercise and cardiac rehabilitation could be considered for implementation in the management of CCS. Clinical pharmacists in a multidisciplinary team should participate in medication assessments to detect and resolve medication-related problems.

Several limitations should be mentioned. First, as an observational study, it was conducted using a convenience sampling at one center, hence, the prevalence of PIMs may have limited generalizability to the whole CCS population. Despite of this, risk factors associated with PIMs were consistent with previous studies and could provide guidance for future interventions. Second, the absence of assessments of over-the-counter drugs, traditional patent medications and nutritional treatments might have led to an underestimation of PIMs exposure. Third, information in electronic medical records is too limited to evaluate potential prescription omissions (PPOs). Due to the ongoing prevalence of PPOs for those with cardiovascular diseases, further studies on PPOs in CCS are worth exploring.

Conclusions
In older CCS patients, 40% were prescribed PIMs at discharge that should be avoided, to be used with caution or with potential interactions. Frailty syndrome, polypharmacy, more comorbidities and certain chronic illnesses were associated with increased odds of taking PIMs. Furthermore, deterioration in NYHA class were more likely to be prescribed PIMs. A thorough medication review and vigilance in regarding risk factors relevant to PIMs by a multidisciplinary team should be enforced in the treatment of older CCS patients.

Acknowledgments
We would like to thank Liu Hui-Xin for the statistical support for the manuscript. This manuscript has been revised by an English native speaker from the USA.

Author Contributions
ZM and SJ conceived and designed the study. ZF, HL and FY discussed the data and revised the main manuscript. All authors made substantial contributions to the acquisition and interpretation of data, drafted the article and critically revised it for important intellectual content;
References

1. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204–1222.

2. Costantino S, Paneni F, Cosentino F. Ageing, metabolism and cardiovascular disease. *J Physiol*. 2016;594(8):2061–2073. doi:10.1113/JP270538

3. Knuts J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407–477.

4. Koren G, Nordon G, Radinsky K, Shalev V. Clinical pharmacology of old age. *Expert Rev Clin Pharmacol*. 2019;12(8):749–755. doi:10.1080/17512433.2019.1632188

5. American Geriatrics Society. 2019 updated AGS Beers criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694. doi:10.1111/jgs.15767

6. Masumoto S, Sato M, Maeno T, Ichinohe Y, Maeno T. Potentially inappropriate medications with polypharmacy increase the risk of falls in older Japanese patients: 1-Year Prospective Cohort Study. *Geriatr Gerontol Int*. 2018;18(7):1064–1070. doi:10.1111/ggi.13307

7. Bonfiglio V, Umegaki H, Kuzuya M. Potentially inappropriate medications and polypharmacy: a study of older people with mild cognitive impairment and mild dementia. *J Alzheimers Dis*. 2019;71(3):889–897. doi:10.3233/JAD-190284

8. Wang P, Wang Q, Li F, Bian M, Yang K. Relationship between potentially inappropriate medications and the risk of hospital readmission and death in hospitalized older patients. *Clin Interv Aging*. 2019;14:1871–1878. doi:10.2147/CIA.S21849

9. Hyttinen V, Jyrkkä J, Valtonen H. A systematic review of the impact of potentially inappropriate medication on health care utilization and costs among older adults. *Med Care*. 2016;54(10):950–964. doi:10.1097/MLR.0000000000000587

10. Harrison SL, Kouladjian OL, Milte R, et al. Costs of potentially inappropriate medication use in residential aged care facilities. *BMC Geriatr*. 2018;18(1):9. doi:10.1186/s12877-018-0704-8

11. Sheikhi-Taha M, Dimassi H. Potentially inappropriate home medications among older patients with cardiovascular disease admitted to a cardiology service in USA. *BMC Cardiovasc Disord*. 2017;17(1):189. doi:10.1186/s12872-017-0623-1

12. Ivanova I, Elseviers M, Wettermark B, Schmidt MK, Vander SR, Christens T. Electronic assessment of cardiovascular potentially inappropriate medications in an administrative population database. *Basic Clin Pharmacol Toxicol*. 2019;124(1):62–73. doi:10.1111/bcpt.13095

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

14. Lai YR, Yang YS, Tsai ML, et al. Impact of potentially inappropriate medication and continuity of care in a sample of Taiwan elderly patients with diabetes mellitus who have also experienced heart failure. *Geriatr Gerontol Int*. 2016;16(10):1117–1126. doi:10.1111/ggi.12606

15. Madhavan MV, Gersh BJ, Alexander KP, Granger CB, Stone GW. Coronary artery disease in patients ≥80 years of age. *J Am Coll Cardiol*. 2018;71(18):2015–2040. doi:10.1016/j.jacc.2017.12.068

16. Guillot J, Maumus-Robert S, Marceron A, Noize P, Pariante A, Bezin J. The burden of potentially inappropriate medications in chronic polypharmacy. *J Clin Med*. 2020;9(11):3728. doi:10.3390/jcm9113728

17. Maclaglan LC, Maxwell CJ, Gandhi S, et al. Frailty and potentially inappropriate medication use at nursing home transition. *J Am Geriatr Soc*. 2017;65(10):2205–2212. doi:10.1111/jgs.15016

18. Caraballo C, Desai NR, Mulder H, et al. Clinical implications of the New York Heart Association classification. *J Am Heart Assoc*. 2019;8(23):e014240. doi:10.1161/JAHA.119.014240

19. Carbone RG, Paredi P, Menselise A, Bottino G, Puppo F. New York Heart Association class associated with imaging is a prognostic mortality risk predictor in interstitial lung diseases. *Eur Rev Med Pharmacol Sci*. 2020;24(17):9012–9021. doi:10.26355/eurrev_202009_22844

20. Apinarová M, Apinar J, Pamenca J, et al. Prescription and dosage of RAAS inhibitors in patients with chronic heart failure in the FAR NHL registry. *Vitn Lek*. 2019;65(1):13–14. doi:10.36290/vnl.2019.004

21. Schjødt I, Johnsen SP, Strømberg A, Valentin JB, Logstrup BB. Inequalities in heart failure care in a tax-financed universal healthcare system: a Nationwide Population-Based Cohort Study. *ESC Heart Fail*. 2020;7(5):3095–3108. doi:10.1002/ehf2.12938

22. Maliwa MA, van der Heijden GJ, Bots ML, et al. Quality of life and NYHA class 30 years after mechanical aortic valve replacement. *Cardiovasc Surg*. 2003;11(5):381–387. doi:10.1016/S0967-2109(03)00030-9

23. Je K, Felton M, Springer S, Wilson SA, Albert SM. Physician factors associated with polypharmacy and potentially inappropriate medication use. *J Am Board Fam Med*. 2017;30(4):528–536. doi:10.3122/jabfm.2017.04.170121

24. Vrettos I, Voukelatou P, Katsoras A, Theotoka D, Kalliakmanis A. Diseases linked to polypharmacy in elderly patients. *Curr Gerontol Geriatr Res*. 2017;2017:4276047. doi:10.1155/2017/4276047

25. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: a systematic review and meta-analysis. *Int J Cardiol*. 2017;236:283–289. doi:10.1016/j.ijcard.2017.01.013

26. Ma L, Tang Z, Zhang L, Sun F, Li Y, Chan P. Prevalence of frailty and associated factors in the community-dwelling population of China. *J Am Geriatr Soc*. 2018;66(3):559–564. doi:10.1111/jgs.15214

27. Beard JR, Officer A, de Carvalho IA, et al. The world report on ageing and health: a policy framework for healthy ageing. *Lancet*. 2016;387(10033):2145–2154. doi:10.1016/S0140-6736(15)00516-4

28. Alfandre DJ. “I’m going home”: discharges against medical advice. *Mayo Clin Proc*. 2009;84(3):255–260.

29. Morin L, Larocche ML, Texier G, Johnell K. Prevalence of potentially inappropriate medication use in older adults living in nursing homes: a systematic review. *J Am Med Dir Assoc*. 2016;17(9):862.e1–9. doi:10.1016/j.jamda.2016.06.011

30. Abolhassani N, Marques-Vidal P. Polypharmacy, defined as taking five or more drugs, is inadequate in the cardiovascular setting. *J Clin Epidemiol*. 2018;101:1–4. doi:10.1016/j.jclinepi.2018.05.002

31. Keshri S, Aalipour M, Namazi S. A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. *J Res Pharm Pract*. 2016;5(4):257–263. doi:10.4103/2279-042X.192461
32. Lin JX, Huang YQ, Xie JW, et al. Age-adjusted Charlson Comorbidity Index (ACCI) is a significant factor for predicting survival after gastric cancer in patients with gastric cancer. *BMC Surg.* 2019;19(1):53. doi:10.1186/s12893-019-0513-9
33. Chan TC, Luk JK, Chu LW, Chan FH. Validation study of charlson comorbidity index in predicting mortality in Chinese older adults. *Geriatr Gerontol Int.* 2014;14(2):452–457. doi:10.1111/j.1111.13129
34. Morley JE, Malms trom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging.* 2012;16(7):601–608. doi:10.1007/s12603-012-0084-2
35. Kimura T, Ogura F, Kukita Y, et al. Efficacy of pharmacists’ assessment and intervention based on screening tool for older persons’ appropriate prescriptions for Japanese compared with screening tool of older persons’ potentially inappropriate prescriptions criteria version 2 in older patients with cardiovascular disease. *Geriatr Gerontol Int.* 2019;19(11):1101–1107. doi:10.1111/jgg.13773
36. Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol.* 2011;67(11):1175–1188. doi:10.1007/s00228-011-0611-0
37. Muhllack DC, Hoppe LK, Stock C, Haefeli WE, Brenner H, Schöttker B. The associations of geriatric syndromes and other patient characteristics with the current and future use of potentially inappropriate medications in a large Cohort Study. *Eur J Clin Pharmacol.* 2018;74(12):1633–1644. doi:10.1007/s00228-018-2534-1
38. Zhang L, Desai NR, Li J, et al. National quality assessment of early clopidogrel therapy in Chinese patients with acute myocardial infarction (AMI) in 2006 and 2011: insights from the China patient-centered evaluative assessment of cardiac events (PEACE)-retrospective AMI study. *J Am Heart Assoc.* 2015;4(7):e001906. doi:10.1161/JAHA.115.001906
39. Huang Y, Zhang L, Huang X, Liu K, Yu Y, Xiao J. Potentially inappropriate medications in Chinese community-dwelling older adults. *Int J Clin Pharm.* 2020;42(2):598–603. doi:10.1007/s11096-020-00980-y
40. He D, Zhu H, Zhou H, Dong N, Zhang H. Potentially inappropriate medications in Chinese older adults: a comparison of two updated Beers criteria. *Int J Clin Pharm.* 2021;43(1):229–235. doi:10.1007/s11096-020-01139-5
41. Zahwe M, Skouri H, Rachidi S, et al. Potentially inappropriate medications in elderly patients with heart failure: Beers Criteria-Based Study. *Int J Pharm Pract.* 2020;28(6):652–659. doi:10.1111/iipp.12651
42. Sinha AD, Agarwal R. Thiazide diuretics in chronic kidney disease. *J Sleep Res.* 2017;26(6):675–700. doi:10.1111/jsr.12594
43. Sharma R, Chhabra M, Vidyasagar K, Rashid M, Fialova D, Bhagavathula AS. Potentially inappropriate medication use in older hospitalized patients with type 2 diabetes: a Cross-Sectional Study. *Pharmac (Basel).* 2020;8(4):219. doi:10.3390/pharmacy8040219
44. Filion KB, Douros A, Azoulay L, Yin H, Yu OH, Suissa S. Sulfonlureas as initial treatment for type 2 diabetes and the risk of adverse cardiovascular events: a Population-Based Cohort Study. *Br J Clin Pharmacol.* 2019;85(10):2378–2389. doi:10.1111/bcp.14056
45. Douros A, Yin H, Yu O, Filion KB, Azoulay L, Suizza S. Pharmacologic differences of sulfonlureas and the risk of adverse cardiovascular and hypoglycemic events. *Diabetes Care.* 2017;40(11):1506–1513. doi:10.2337/dc17-0595
46. Abe H, Shikuma J, Suwahani H, et al. Assessing hypoglycemia frequency using flash glucose monitoring in older Japanese patients with type 2 diabetes receiving oral hypoglycemic agents. *Geriatr Gerontol Int.* 2019;19(10):1030–1035. doi:10.1111/jgg.13765
47. Zhao et al. Use of benzodiazepines and cardiovascular mortality in non-dependent elderly patients with heart failure. *Hypertension.* 2013;61(2):386–393. doi:10.1161/HJH.0b013e3182a0557-2
48. Chen Q, Zhu S, Liao J, He W. Study of acute kidney injury on 309 elderly hospitalized patients with type 2 diabetes: a Cross-Sectional Study. *Pharmacy (Basel).* 2019;8(4):386–393. doi:10.3390/pharmacy8040219
49. Mafi JN, May FP, Kahn KL, et al. Low-value proton pump inhibitor prescriptions among older adults at a large academic health system. *J Am Geriatr Soc.* 2017;65(12):2600–2604. doi:10.1111/jgs.14177
50. Wang X, Fang L, Liu B, Zheng Y, Zeng J. Real-world comparisons of reduced-dose non-vitamin K antagonist oral anticoagulants versus warfarin in atrial fibrillation: a systematic review and meta-analysis. *Heart Fail Rev.* 2020;25(6):973–983. doi:10.1007/s10741-019-09887-x
51. Bisson A, Angoulvant D, Philippart R, Clementy N, Babuty D, Fauchier L. Non-vitamin K oral anticoagulants for stroke prevention in special populations with atrial fibrillation. *Adm Ther.* 2017;34(6):1283–1290. doi:10.1016/j.admt.2017.0550-7
52. Fournier A. Use of benzodiazepines and cardiovascular mortality in co-morbid older patients at hospital discharge. *Geriatr Gerontol Int.* 2019;19(10):1030–1035. doi:10.1111/jgg.13765
53. Mozaffarian D, Sonnenberg RA, Miro AL, Carvalho RC, Aguiar PM, et al. Potentially inappropriate medications identified by Beers and STOPP criteria in older adults. *Eur J Clin Pharmacol.* 2018;74(11):1475–1484. doi:10.1007/s10028-018-2515-4
54. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res.* 2017;26(6):675–700. doi:10.1111/jsr.12594
63. Sargent L, Flattery M, Shah K, et al. Influence of physiological and psychological factors on cognitive dysfunction in heart failure patients. *Appl Nurs Res*. 2020;56:151375. doi:10.1016/j.apnr.2020.151375

64. Hashimoto R, Fujii K, Shimoji S, et al. Study of pharmacist intervention in polypharmacy among older patients: non-randomized, controlled trial. *Geriatr Gerontol Int*. 2020;20(3):229–237. doi:10.1111/ggi.13850

65. Stuhec M, Bratovic N, Mrhar A. Impact of clinical pharmacist’s interventions on pharmacotherapy management in elderly patients on polypharmacy with mental health problems including quality of life: a Prospective Non-Randomized Study. *Sci Rep*. 2019;9(1):16856. doi:10.1038/s41598-019-53057-w