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ORIGINAL RESEARCH

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

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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,

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more medications consumption and changes in pharmacokinetics and pharmacodynamics, geriatrics are more prone to inappropriate drug use.[4] 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.[5] 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.[6–10] The prevalence of CAD-PIMs in the geriatric population ranged from 20% to 60% in the USA, Sweden and Ethiopia.[11–13] A study in Taiwan stated that 86.1% of older patients with both heart failure and diabetes were taking PIMs.[14] Given a large proportion of CCS patients with advanced age,[15] 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.[16] Frailty syndrome is manifested as a marked vulnerability for more intensive medication intake, multi-morbidities and decreased resistance to PIMs.[17] 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.[18–22] Moreover, physicians' awareness of the number of drugs and benefit/risk profiles helps to prescribe fewer PIMs.[23] Presumably, CAD patients taking multiple medications,[24] or experiencing a high prevalence of frailty or transition to frail status,[25,26] 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.[27] 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;[28] (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%, a 95% confidence interval and an α-error of 5%.[29] 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.[30]

PIMs were evaluated using the 2019 Beers criteria supported by the American Geriatric Society.[5] 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),[31] 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.[32,33] 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.[26] 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).[34]

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

Table 1 Demographic and Clinical Characteristics of the Sample (n=447)

Characteristics	n (%)
Sex	
Male	268 (60.0)
Female	179 (40.0)
Age (mean, SD)	71.5 (7.2)
60–64	88 (19.7)
65–69	112 (25.1)
70–74	102 (22.8)
75–79	63 (14.1)
80–85	65 (14.5)
85–90	17 (3.8)
Functional status	
Robust (0)	183 (40.9)
Pre-frailty (1–2)	206 (46.1)
Frailty (3–5)	58 (13.0)
Comorbidities (median, IQR)	5 (3–6)
Hypertension	341 (76.3)
Dyslipidemia	307 (68.7)
Atherosclerosis	245 (54.8)
Type 2 diabetes mellitus	179 (40.0)
ACCI (median, IQR)	5 (3–6)
Low ACCI (2–4)	221 (49.4)
High ACCI (5–13)	226 (50.6)
Length of stay (median, IQR)	7 (7–9)
≥7 days	247 (55.3)
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.

Table 2 Number of Medications and PIMs at Discharge

	n (%)
Medications at discharge (median, IQR)	6 (5–8)
Range	1–17
Polypharmacy (≥6)	293 (65.5)
Number of patients prescribed with PIMs	170 (38.0)
1 PIM	119 (70.0)
2 PIMs	40 (23.5)
3–5 PIMs	11 (6.5)
Total number of PIMs	237
Medications that should be avoided	91 (38.4)
Medications that should be used with caution	116 (48.9)
Potentially clinical important drug-drug interactions to be avoided	30 (12.7)
Medications with drug-disease/syndrome interactions	0 (0.0)
Medications that should be adjusted along with kidney function	0 (0.0)

Abbreviations: PIMs, potentially inappropriate medications; IQR, interquartile range.

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).

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 by. 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

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 digitalism
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)	

Abbreviations: Z-drugs, benzodiazepine receptor agonist hypnotics; PPI, proton-pump inhibitor; NOAC, new oral anticoagulant; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

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.

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 threaten 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

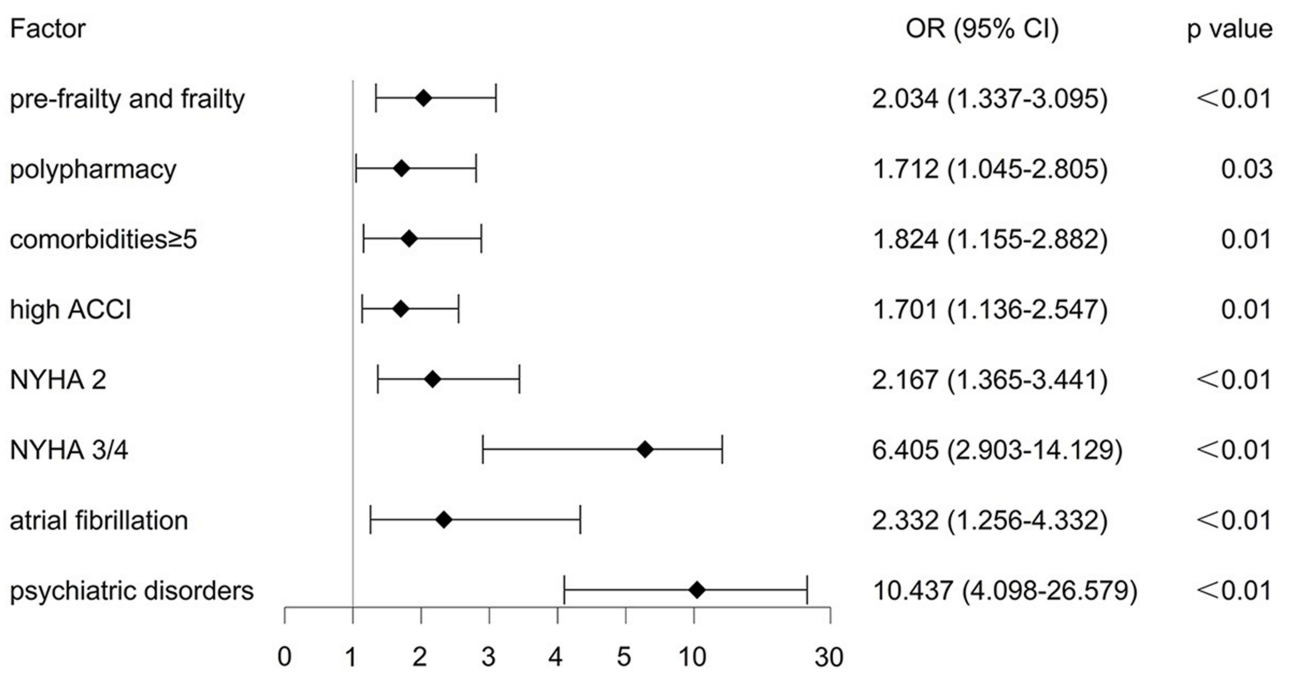

Figure 1 Binary logistic regression of factors associated with PIMs.
Abbreviations: ACCI, age-adjusted Charlson Comorbidity Index; NYHA, New York Heart Association; OR, odds ratio; CI, confidence interval.

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.[38] In this study, 300 patients were on clopidogrel. When clopidogrel was removed, similar PIMs were found between the Chinese criteria and the Beers criteria.[39] In comparison with the PIMs based on Chinese criteria, Beers-defined PIMs engendered more substantial adverse outcomes, such as rehospitalization.[8] 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.[40] 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.[11,41] 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.[42] Thus, it is important to advise physicians to closely monitor electrolyte and creatine during use.[43]

Heavy consumption of BZD/Z is common in older adults.[44] 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.[45] 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.[46] Antidepressants and cognitive behavioral therapy (CBT) have been shown to be efficacious in elderly.[47] 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.[48] Initial treatment with sulfonylurea monotherapy increased ischemic stroke, cardiovascular death and all-cause mortality.[49] 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.[50] A Japanese study has suggested sulfonylurea conversion when HbA1c < 6.3% or 6.7% in older diabetic patients.[51] 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.[52] It has been found a lower dose of NOAC might be feasible and safe for Asians.[53] In patients aged over 75 years with NOAC, assessment of bleeding risk using HAS-BLED and creatine level should be implemented in treatment plan.[54] Long-term use of PPI without a clear indications has been common in older adults.[55] A meta-analysis showed that the non-PPI group was associated with less myocardial infarction recurrence than the clopidogrel supplemented with PPI group.[56] 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.[57,58] 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.[59] Similar to previous results, polypharmacy and multiple chronic conditions were significantly associated with PIMs prescriptions.[7,60,61] 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.[62] 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.[63] 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.[64,65]

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.

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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;

gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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