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Title: Potentially inappropriate prescribing and vulnerability and hospitalization in older community-dwelling patients

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Running title: Potentially inappropriate prescribing and health outcomes in older populations

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Abstract

Background: The predictive validity of existing explicit process measures of potentially inappropriate prescribing (PIP) is not established.

Objective: To determine the association between PIP, and vulnerability and hospital visits in older community-dwelling patients.

Methods: This was a retrospective cohort study of 931 community-dwelling patients aged ≥ 70 years in 15 general practices in Ireland in 2010. PIP was defined by the Beers 2012 criteria and the Screening Tool of Older Person's Potentially Inappropriate Prescriptions (STOPP). Vulnerability was measured by the Vulnerable Elders Survey (score ≥ 3). The number of hospital visits was measured using patients' medical records and self-report for the previous 6 months. Multilevel logistic and Poisson regression was used to examine the association between PIP, and vulnerability and hospital visits after adjusting for patient and practice level covariates, socioeconomic status, comorbidity, number of drug classes, social support, and adherence.

Results: The prevalence of PIP determined by the Beers 2012 and STOPP criteria was 28% ($n = 246$) and 42% ($n = 377$), respectively. Patients with ≥ 2 PIP indicators were almost twice as likely to be classified as vulnerable (Beers adjusted odds ratio [OR] = 1.80; 95% CI = 1.08, 3.01; $P < 0.05$; STOPP adjusted OR = 1.86; 95% CI = 1.13, 3.04; $P < 0.05$). Patients with ≥ 2 STOPP indicators had an increased risk in the expected rate of hospital visits (adjusted incidence rate ratio = 1.32; 95% CI = 1.14, 1.54; $P < 0.01$). The Beers 2012 criteria were not associated with increased hospital visits.

Conclusion: STOPP is a more sensitive measure of PIP than the Beers 2012 criteria and of clinical benefit in primary care settings.

Keywords: Potentially inappropriate prescribing, STOPP, Beers 2012 criteria, vulnerability, functional decline, health care use, older populations

Introduction

Medication-related problems are common in older populations and are associated with significant health and economic consequences, including increased risk of adverse drug events (ADEs) and increased morbidity, mortality, and health care use.¹ However, the selection of appropriate medication in older people is a challenging and complex process. Older people have substantial interindividual variability in their health status and functional capacity, making the generalization of prescribing decisions difficult for clinicians.² Evidence suggests that inappropriate medication use may be a possible cause of adverse health outcomes in older populations, and a number of criteria and screening tools have been developed to measure and assist prescribers in detecting potentially inappropriate prescribing (PIP).¹

Appropriateness of prescribing can be assessed by explicit (criterion-based) or implicit (judgment based) screening tools.² The Beers criteria developed in the United States in 1991 are the most frequently used and validated explicit measure of PIP.³ The criteria were updated and revised in 1997 and in 2003, and most recently in 2012.⁴ The Beers 2012 criteria encompass 53 drugs and drug classes divided into 3 categories; (1) drugs to be avoided in older people independent of diagnoses; (2) drugs to be avoided in older people with certain diseases and syndromes; and (3) drugs to be used with caution in older people.⁴ PIP prevalence rates ranging from 14% to 37% in the United States and Canada and 23% to 43% in Europe have been reported.⁵ In Europe, the Screening Tool of Older Person's Potentially Inappropriate Prescriptions (STOPP) has recently been developed, consisting of 65 indicators of PIP associated with ADEs in older populations.⁶ A systematic review reported prevalence rates ranging from 21% to 79% in the United States, Europe, and Asia.⁷ Implicit process measures of PIP include the medication appropriateness index (MAI), which assesses 10 elements of overall prescribing quality (indication, effectiveness, dose, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration, and cost).⁸ Prevalence rates of 92% and 94% have been reported in the United States and Europe, respectively.^{9,10}

PIP screening tools should optimize prescribing to be of value in clinical practice, but to date, there is no clear evidence that PIP is associated with adverse patient outcomes.⁷ The STOPP criteria but not the Beers criteria have been associated with ADEs in older hospitalized patients.¹ The Beers 2003 criteria accounted for only 3.2% of older people's emergency

department visits for ADEs in a nationally representative sample of older Americans.^{11,12} A modified version of the MAI, created specifically for predicting ADE risk, was found to be associated with self-reported ADEs in veteran primary care clinics but not the standard MAI.¹³

Research to date has predominantly focused on assessing the predictive validity of the Beers 1997 and 2003 criteria, and the criteria have subsequently been revised and expanded.⁴ There has been little assessment to date of the newer PIP measures, and no previous studies have compared the STOPP criteria with the 2012 iteration of the Beers criteria. PIP studies have also largely focused on hospitalized older patients and nursing home patients.¹ The impact of PIP on primary care or community-based patients and whether it is associated with patient-related outcomes has not been explored. The aim of this study was to determine the association between PIP, as defined by the Beers 2012 and STOPP criteria, and vulnerability and hospital visits in an older community-dwelling cohort in Ireland in 2010.

Methods

Study population

This is a retrospective cohort study examining the association between PIP defined by the Beers 2012 and STOPP criteria and patient-related health outcomes (vulnerability, hospital visits) in a cohort of general practice (GP) patients aged ≥ 70 years in 15 practices in the Republic of Ireland in 2010. Details of the study population have been presented previously.¹⁴ Ethical approval was granted by the Royal College of Surgeons in Ireland. All participants gave informed consent before taking part in the study.

Exposure to PIP

Information on patients dispensed medications for the 6 months prior to each patient's date of participation (patient consent and questionnaire completion) was available from the Health Services Executive Primary Care Reimbursement Services (HSE-PCRS) pharmacy claims database. The HSE-PCRS General Medical Services scheme is means tested and provides free health services, including medications, to eligible persons in Ireland. Prescriptions are coded using the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system, and prescriber information, defined daily doses, strength, quantity, method, and unit of administration of each drug dispensed are available.¹⁵ Consent was obtained from participants to link their prescription dispensing information with their questionnaire data and their GP medical record.

Fifty (77%) of the 65 STOPP criteria were applied to all patients dispensed medication for the study period; 49 (94%) of 52 Beers 2012 criteria relating to drugs to avoid were applied. There was insufficient clinical information in some patients' medical records to apply all the

criteria. All the available Beers 2012 and STOPP criteria were included in individual composite indicators that measured the total number of PIP indicators per patient, classified into 3 levels: no indicators, 1 indicator, and ≥ 2 indicators.

Outcomes

A questionnaire evaluating vulnerability, health-related quality of life, and other patient-reported outcomes was sent to each participant with the option to self-complete, complete by phone, or complete in person. The Vulnerable Elders Survey (VES) was developed from research with more than 6000 community-dwelling US Medicare beneficiaries aged ≥ 65 years to identify older people at increased risk of functional decline or death over 2 years.¹⁶ VES measures a number of predictors of functional decline, such as activities of daily living (ADLs), instrumental ADLs (IADLs), and age and self-rated health and is described as a screening tool to identify vulnerability in older people that is not readily identifiable to clinicians. A VES score of ≥ 3 identifies vulnerability.^{16,17} VES has good psychometric properties and predictive validity.^{16,18} The number of hospital visits, including accident and emergency department visits (A&E), inpatient visits, and outpatient visits, for the 6 months prior to the participant's date of consent was measured by patient medical record review and self-report.

Covariates

Covariates included patient age, gender, socioeconomic status, private health insurance, comorbidity, number of different repeat drug classes, social support and social network, medication adherence, practice-level general practitioner (GP) gender and deprivation and have been described previously.¹⁴ Patient socioeconomic status was established by social class and deprivation level.¹⁹ Comorbidity was measured using the Charlson comorbidity

index. The number of different repeat drug classes (first 3 characters of the ATC code, ≥ 3 prescriptions) was calculated using the HSE-PCRS pharmacy claims data for the 6 months prior to the patient's date of interview. Each patient was required to receive at least 3 prescriptions per different drug class. Social support was measured using the Medical Outcomes Social Support Survey (MOS) and the Lubben Social Network Scale (LSNS).^{20,21} The MOS is based on the patient's subjective assessment of affectionate, informational, and physical support. The LSNS is an objective measure of family and friends networks, which asks patients how many people they have contact with and how often. Adherence to medication was measured by; (1) the medication possession ratio using the HSE-PCRS pharmacy claims data and; (2) a self-report measure, the Morisky Medication Adherence Scale.^{22,23}

Data analysis

The overall prevalence of PIP according to the Beers 2012 and STOPP criteria was calculated as a proportion of all eligible patients aged ≥ 70 years in the 15 practices in 2010. The prevalence of the individual Beers 2012 and STOPP criteria was also calculated. Multilevel logistic regression investigated the association between PIP and VES. Multilevel unadjusted and adjusted odds ratios (ORs) with 95% CIs were estimated in a 2 level random intercept logistic model for the following: (1) patient level 1 exposure variable (PIP); (2) patient level 1 covariates (age, gender, socioeconomic status, comorbidity, number of different repeat drug classes, adherence, and social support); and (3) practice level 2 covariates (GP gender and deprivation).

Multilevel Poisson regression investigated the association between PIP and the number of hospital visits (A&E and inpatient and outpatient visits). Incidence rate ratios (IRRs) and 95% CIs were estimated.²⁴ The model was additionally adjusted for patients with private

health insurance and functional decline (VES). Initial data analysis and application of the PIP criteria to the data set was performed using SAS statistical software package version 9.1 (SAS Institute Inc, Cary, NC). Multilevel modeling was performed in STATA version 11.2 (StataCorp, College Station, TX). All the variables and residuals were checked graphically for linearity, normality, heteroskedasticity, and outliers.

Results

Study population

A total of 931 community-dwelling patients took part in the study, of whom 504 (54%) were female and 584 (63%) were ≥ 75 years old (mean age = 78; SD = 5.4; range = 70-98).

Exposure to PIP

The prevalence of PIP in the older cohort was 28% (n = 246), as defined by the Beers 2012 criteria. According to Beers 2012 criteria, 149 patients (18%) were prescribed 1 PIP indicator and 104 patients (12%) were prescribed ≥ 2 PIP indicators. The prevalence of PIP was 42% (n = 377), as defined by all 50 STOPP indicators. Two hundred and fifteen patients (24%) were prescribed 1 PIP indicator and 162 (18%) were prescribed ≥ 2 PIP indicators according to STOPP criteria. Table 1 presents the most common PIP indicators (prevalence $\geq 5\%$) defined by the Beers 2012 and STOPP criteria. Supplementary Tables 1 and 2 present the prevalence of all PIP criteria.

Vulnerability (VES)

A total of 270 patients (30%) were classified as vulnerable according to the VES and at risk for health deterioration. [Table 2](#) shows the number and percentage of patients and the unadjusted and adjusted ORs (95% CI) for patients classified as vulnerable by exposure to PIP, and patient and practice level covariates, in a 2-level random intercept logistic model. The likelihood of vulnerability increased significantly with PIP for both the Beers 2012 and STOPP criteria: 48% to 53% of patients with ≥ 2 PIP indicators were classified as vulnerable, respectively, compared with 25% to 22% of those with none. Patients with ≥ 2 PIP indicators for both the Beers 2012 and STOPP criteria were almost twice as likely to be classified as vulnerable, after adjusting for patient and practice level covariates. Age, female gender,

comorbidity, and the number of different repeat drug classes and social support were also still significantly associated with vulnerability. Patients who were adherent to their medication were also significantly less likely to be vulnerable.

Hospital visits

A total of 246 (27%) patients reported attending hospital once during the study period, 101 (11%) twice, 51 (6%) 3 times, and 87 (10%) ≥ 4 times. The median number of hospital visits was 1 (interquartile range = 0, 2). Table 3 shows the unadjusted and adjusted IRRs (95% CIs) for the number of hospital visits per patient during the 6-month study period by exposure to PIP and by patient and practice level covariates estimated in a 2-level random intercept Poisson model. There was almost a one-third increase in the expected rate of hospital visits for those with ≥ 2 PIP indicators defined by the STOPP criteria, after adjusting for patient and practice level covariates. There was no significant association between the number of hospital visits and the Beers 2012 criteria. The expected number of hospital visits significantly decreased for women and those who were adherent to their medication and significantly increased with comorbidity and the number of drug classes.

Discussion

The overall prevalence of PIP was high in this cohort of community-dwelling older patients. Patients with ≥ 2 PIP indicators, as defined by the Beers 2012 and STOPP criteria, were almost twice as likely to be classified as vulnerable and at risk of health deterioration after adjusting for patient and practice level covariates. Age, female gender, comorbidity, number of different repeat drug classes, social support, and medication adherence were also independently associated with vulnerability. Thirty percent of the cohort was classified as vulnerable, and this prevalence rate is similar to that in a nationally representative sample of American Medicare beneficiaries and Irish community-dwelling older people ≥ 65 years old.^{16,17} Vulnerable older people have 4.2 times the risk of death or functional decline over a 2-year period compared with those who are not vulnerable and are significantly more likely to use hospital services.^{17,18}

No previous research has examined the relationship between PIP and vulnerability in older populations. The association between the Beers 1997 and 2003 criteria and measures of patient functional status, including ADLs and IADLs, have previously been evaluated in community-dwelling and hospitalized older patients, and no significant associations were reported.^{25,26} An association was reported between the Beers 1997 criteria and decreased self-perceived health status in both older American community-dwelling patients and frail home-based patients.^{27,28} The current study applied the Beers 2012 criteria, and there was a high prevalence of potentially inappropriate psychotropic medication use ($\geq 5\%$), which is associated with an increased risk of falls, hip fractures, delirium, and impaired cognition in older people.²⁹ There was also a high prevalence of pain medication use (nonsteroidal anti-inflammatory drugs [NSAIDs] and opiates) according to both the Beers 2012 and STOPP

criteria, and physical therapy for musculoskeletal complaints or simple/compound analgesics may be effective for some older patients rather than long-term NSAID use.³⁰

Patients with ≥ 2 PIP indicators also had an increased rate of hospital visits after adjustment for a number of patient and practice level covariates according to STOPP, but not the Beers 2012 criteria. Studies of American community-dwelling older patients have found minimal association between the Beers 1997 and 2003 criteria and the use of health services, although patients had an increased risk of earlier hospitalization over time.^{26,31} The STOPP criteria have been associated with an increased risk of A&E visits in community-dwelling older people.¹⁴ A prospective study of acutely ill older patients found that ADEs resulting from the STOPP criteria were almost 3 times as likely to be causal or contributory to hospitalization compared with the Beers criteria.¹ Aspirin and NSAIDs have consistently been shown to be associated with preventable hospital admissions and ADEs in older populations, and their prevalence was high ($\geq 5\%$) in the current study.³² Long-term use of proton pump inhibitors in older patients has been associated with accelerated osteoporosis and an increased risk of hip fracture and *Clostridium difficile* hospital infections.³³

This study was conducted across 15 practices in one region in Ireland, and the results may not be generalizable to different regions or to the general older population. In some practices, there was not sufficient clinical information to apply all the PIP criteria, and these criteria were excluded from the study. The STOPP criteria require further modification and refinement to be more easily applicable in primary care settings. The association between PIP and the outcomes vulnerability and hospital visits, needs to be interpreted with caution. This study controlled for a number of covariates associated with functional decline and health service use, but results may be confounded by unknown risk factors. The reasons for A&E and outpatient and inpatient hospital visits are very different, and there may be residual

confounding. Equally, despite the independent associations between PIP and vulnerability, it may be indicative of frailer, isolated, and multimorbid patients prescribed an increased number of medications and more likely to be taking a PIP. Underprescription of medicines that are of benefit to older populations is also an important component of PIP and was not assessed. A high percentage of undertreatment of cardiovascular disease, hyperlipidemia, osteoporosis, chronic obstructive pulmonary disease, depression, and cancer has been reported in older populations and is associated with increased morbidity and health service use.³⁴ These findings will be explored further when following up this cohort and also whether or not the association between PIP, vulnerability, and adverse health outcomes, including hospitalization, persist.

Notwithstanding the limitations, this study is the first to compare the association between PIP, as defined by the Beers 2012 and STOPP criteria, and adverse health outcomes in older community-dwelling populations. The use of patient dispensing data from the national pharmacy claims database (HSE-PCRS) and patients' GP medical records enabled an accurate application of the PIP criteria and assessment of patient comorbidities. The study also controlled for a number of covariates, including morbidity, functional ability, social support, number of drug classes, and medication adherence. There have been important limitations in the methods of previous studies, including no adjustment for important confounders, nonconsideration of drug duration and dose-response relation, and dependence on self-reported medication use and medical conditions on hospital admission.²

Theories of successful ageing have extended beyond the biomedical model of absence of disease and optimization of life expectancy to include more sociopsychological elements such as high social participation and functioning, independence, and life satisfaction.³⁵ The absence of disease is unrealistic for the majority of older people, and there is ample evidence

that many older people consider themselves happy and well, even in the presence of chronic disease.³⁶ The association between PIP and patient vulnerability is an important outcome because social functioning, positive interactions and relationships with others, and continued ability to remain independent and participate in society is a primary concern for older people.³⁷ In the current study, vulnerable patients perceived themselves as having a high need for affectionate, informational, and physical support (MOS), while a high frequency of social contacts with family and/or friends was associated with nonvulnerability (LSNS). The use of the Beers 2012 and STOPP criteria as screening tools in primary care may encourage physicians to consider medications as a possible cause of adverse symptoms and functional decline in older people, thereby avoiding unnecessary and potentially harmful prescribing cascades.

There is some evidence that the STOPP criteria as a process measure of PIP can be linked to adverse health outcomes in older people.^{1,14} This study, alongside previous findings, suggests that the STOPP criteria are more sensitive than the recently updated Beers 2012 criteria at identifying patients at risk of ADEs and hospitalization.^{1,12} Further large-scale prospective studies and randomized controlled trials are needed to assess if routine application of PIP indicators in clinical practice substantially reduces PIP and improves functional ability and health outcomes in older populations. Nonadherence to medication was also associated with vulnerability and hospitalization. PIP screening tools have been criticized for measuring only the pharmacological appropriateness of prescribing, whereas measuring appropriateness in a broader sense might include other areas such as patients' beliefs and preferences concerning treatment.² Engaging older patients in monitoring and managing their medications may improve health outcomes.

Future research should also focus on the development and evaluation of intervention strategies to improve prescribing. Reducing PIP will require an enhancement in methods to regularly assess drug effectiveness, dosage, duration, interactions, adverse symptoms, and adherence.³⁸ Information technology systems and computerized decision supports may provide the infrastructure to monitor prescribing in older patients more effectively in the future.³⁹ Multidisciplinary approaches to prescribing, including use of geriatric medicine services and involvement of pharmacists, have also been shown to improve the quality of care in older populations.⁴⁰

In conclusion, the STOPP and Beers 2012 criteria were associated with vulnerability in older community-dwelling populations, independent of morbidity, number of medications, and other important covariates. The STOPP criteria were also additionally associated with an increased risk of hospitalization. PIP indicators are not meant to replace clinical assessment and judgment but can be used as screening tools to improve the care of vulnerable, older community-based populations. The present study results indicate that the STOPP criteria are important quality indicators for prescribing practice and of clinical benefit in community and primary care settings.

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Declaration of Conflicting Interests

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Authors' Note

CC, FM, TF, KB, and CT planned and designed the study. TF, FM, CC interpreted the STOPP and Beers 2012 criteria and their application to the prescribing database. CC, FM, CT, and KB analyzed the study data. CC drafted the manuscript. FM, KB, CT, and TF critically reviewed and approved the final manuscript. KB is guarantor.

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Table 1: The most prevalent PIP indicators as per Beers 2012 and STOPP criteria

| PIP Indicators with a prevalence \geq 5% | N | % (95% CI) |
|---|------------|---------------------|
| <i>BEERS 2012 CRITERIA</i> | | |
| <i>Central Nervous System</i> | | |
| Benzodiazepines- short, immediate and long acting | 66 | 7.3 (5.6, 9.0) |
| <i>Pain</i> | | |
| Chronic use of non-COX selective NSAIDS | 55 | 6.1 (4.5, 7.6) |
| <i>Drug-Disease Interactions</i> | | |
| Anticonvulsants, antipsychotics, benzodiazepines, non-benzodiazepine hypnotics, TCAs, SSRIs in patients with a history of falls and fractures | 61 | 6.7 (5.1, 8.4) |
| <i>STOPP</i> | | |
| <i>Cardiovascular System</i> | | |
| Calcium channel blockers with chronic constipation† | 63 | 6.9 (6.55, 7.39) |
| Aspirin with a past history of peptic ulcer disease without histamine H2 receptor antagonist or PPI (risk of bleeding) | 58 | 6.4 (6.02, 6.81) |
| <i>Gastrointestinal System</i> | | |
| PPI for peptic ulcer disease at maximum therapeutic dosage for > 8 weeks‡ (dose reduction or earlier discontinuation indicated) | 146 | 16.6 (15.27, 17.03) |
| <i>Musculoskeletal System</i> | | |
| Long-term use of NSAID (i.e. > 3 months) for pain relief (simple analgesics preferable) | 62 | 6.9 (6.44, 7.27) |
| <i>Analgesic Drugs</i> | | |
| Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives (risk of severe constipation) | 43 | 4.8 (4.46, 5.05) |

* PPI=proton pump inhibitor, TCA=tricyclic antidepressant, NSAID=non-steroidal anti-inflammatory drug, SSRI=selective serotonin re-uptake inhibitor

† Prevalence was assessed using patient report of chronic constipation and by GP record.

‡ PPI at maximum therapeutic dose = 40 mg daily omeprazole, pantoprazole and esomeprazole, 30 mg daily lansoprazole and 20 mg daily rabeprazole.

Table 2: Number and percentage of patients and multilevel unadjusted and adjusted odds ratios (95% CI) for patients defined as vulnerable (VES) by exposure to PIP and patient and practice level covariates

| Patient level fixed effects | Total (N) | N (%), Median (IQR) | Unadjusted OR (95% CI) (N=904) | VES | |
|--|-----------|-----------------------------------|--------------------------------|--|-------------------------------------|
| | | | | Adjusted OR Beers 2012 (95% CI) (N=841)* | Adjusted OR STOPP (95% CI) (N=841)* |
| Age † | - | Median (IQR) 80 (75, 85) | 1.14 (1.10, 1.17) ‡ | 1.13 (1.09, 1.17) ‡ | 1.13 (1.09, 1.17) ‡ |
| Gender | | N (%) | | | |
| Male | 415 | 90 (22) | 1 | 1 | 1 |
| Female | 489 | 180 (37) | 2.13 (1.57, 2.89) ‡ | 2.25 (1.54, 3.29) ‡ | 2.20 (1.50, 3.23) ‡ |
| Social Class | | N (%) | | | |
| Unskilled | 342 | 118 (35) | 1 | 1 | 1 |
| Skilled | 562 | 152 (27) | 0.81 (0.59, 1.11) | 0.98 (0.67, 1.43) | 0.96 (0.66, 1.41) |
| Deprivation † | | Median (IQR) 0.87 (1.63, 1.91) | 1.06 (0.99, 1.14) | 1.08 (1.00, 1.17) | 1.07 (0.99, 1.16) |
| Co-morbidity § Charlson weights | | N (%) | | | |
| 0 | 537 | 129 (24) | 1 | 1 | 1 |
| ≥1 | 365 | 141 (39) | 1.87 (1.39, 2.52) ‡ | 1.62 (1.12, 2.34) ‡ | 1.59 (1.09, 2.29) ‡ |
| No. of drug classes | | Median (IQR) 8 (5, 10) | 1.32 (1.25, 1.40) ‡ | 1.32 (1.22, 1.43) ‡ | 1.29 (1.19, 1.40) ‡ |
| MPR § | | N (%) | | | |
| MPR < 50% | 76 | 23 (30) | 1 | 1 | 1 |
| MPR ≥ 50% < 80% | 187 | 42 (22) | 0.64 (0.35, 1.18) | 0.27 (0.13, 0.56) ‡ | 0.25 (0.12, 0.52) ‡ |
| MPR ≥ 80% | 592 | 196 (33) | 1.09 (0.64, 1.86) | 0.42 (0.22, 0.81) ‡ | 0.39 (0.20, 0.75) ‡ |
| Self-report Adherence § | | N (%) | | | |
| Non-Adherent | 332 | 117 (35) | 1 | 1 | 1 |
| Adherent | 553 | 150 (27) | 0.72 (0.53, 0.97) ‡ | 0.63 (0.44, 0.91) ‡ | 0.64 (0.44, 0.93) ‡ |
| Social Support (MOS) § | | N (%) | | | |
| Low social support | 52 | 10 (19) | 1 | 1 | 1 |
| Medium social | 212 | 62 (29) | 1.90 (0.88, 4.10) | 2.91 (1.12, 7.56) ‡ | 2.69 (1.04, 6.94) |

| Patient level fixed effects | Total (N) | N (%), Median (IQR) | Unadjusted OR (95% CI) (N=904) | VES | |
|--|-----------|--|--------------------------------|--|-------------------------------------|
| | | | | Adjusted OR Beers 2012 (95% CI) (N=841)* | Adjusted OR STOPP (95% CI) (N=841)* |
| support | | | | | |
| High social support | 636 | 195 (31) | 2.15 (1.04, 4.45)‡ | 3.57 (1.38, 9.24) ‡ | 3.28 (1.28, 8.42)‡ |
| <i>Social network (LSNS)</i> | - | Median (IQR) 8 (6, 9) | 0.89 (0.83, 0.96) ‡ | 0.83 (0.75, 0.91) ‡ | 0.83 (0.75, 0.91) ‡ |
| <i>PIP Beers 2012 ‡</i> | | N (%) | | | |
| 0 | 641 | 162 (25) | 1 | 1 | - |
| 1 | 159 | 58 (36) | 1.64 (1.14, 2.35)‡ | 1.03 (0.66, 1.62) | - |
| ≥ 2 | 104 | 50 (48) | 4.16 (2.83, 6.10)‡ | 1.80 (1.08, 3.01) ‡ | - |
| <i>PIP STOPP ‡</i> | | N (%) | | | |
| 0 | 527 | 115 (22) | 1 | - | 1 |
| 1 | 215 | 69 (32) | 1.64 (1.14, 2.35)‡ | - | 1.14 (0.74, 1.78) |
| ≥ 2 | 162 | 86 (53) | 4.16 (2.83, 6.10)‡ | - | 1.86 (1.13, 3.04)‡ |
| Practice level fixed effects (N=15) | | | Unadjusted OR (95% CI) | | Adjusted OR (95% CI)** |
| <i>GP Gender</i> | | N (%) | | | |
| Male | 704 | 209 (30) | 1 | 1 | 1 |
| Female | 200 | 61 (31) | 0.98 (0.48, 2.00) | 0.78 (0.45, 1.33) | 0.80 (0.46, 1.41) |
| <i>Deprivation † </i> | - | Median (IQR) 0.15 (1.62, 0.61) | 1.18 (1.03, 1.37)‡ | - | - |

* In the adjusted model, data was missing for 63 (7%) patients, co-morbidity was missing for 2 (0.22%) patients, MPR was missing for 49 (5%) of patients, self-report adherence was missing for 9 (1%) patients, social support was missing for 3 (0.33%) patients; these patients were excluded from the multivariable analysis (N=841).

†Patient age was centred on age 70 (minimum age) e.g. patient age-70. Patient and practice deprivation were centred on their mean value.

‡ z score (p< 0.05).

§In the unadjusted model, co-morbidity was missing for 2 (0.22%) patients, MPR was missing for 49 (5%) patients, self-report adherence was missing for 19 (2%) patients, social support was missing for 4 (0.44%) patients and social network was missing for 2 (0.22%) patients.

|| Practice deprivation excluded from adjusted model due to collinearity with patient deprivation.

Table 3: The median (IQR) and unadjusted and adjusted IRR (95% CI) for the number of hospital visits by exposure to PIP and patient and practice level covariates

| Patient level fixed effects | Median (IQR) | Unadjusted IRR (95% CI) (N=904) | Hospital ≥ 1 | |
|---------------------------------|--------------|---------------------------------|---|--------------------------------------|
| | | | Adjusted IRR Beers 2012 (95% CI) (N=844)* | Adjusted IRR STOPP (95% CI) (N=844)* |
| <i>Age</i> † | - | 1.02 (1.01, 1.03) | 1.00 (0.99, 1.02) | 1.01 (0.99, 1.02) |
| <i>Gender</i> | | | | |
| Male | 1 (0, 2) | 1 | 1 | 1 |
| Female | 0 (0, 1) | 0.71 (0.63, 0.80)‡ | 0.67 (0.56, 0.80) ‡ | 0.67 (0.56, 0.80)‡ |
| <i>Social Class</i> | | | | |
| Unskilled | 1 (0, 2) | 1 | 1 | 1 |
| Skilled | 1 (0, 2) | 1.00 (0.89, 1.13) | 0.93 (0.75, 1.15) | 0.92 (0.75, 1.14) |
| <i>Deprivation</i> † | - | 0.99 (0.96, 1.01) | 0.98 (0.93, 1.03) | 0.98 (0.93, 1.03) |
| <i>Co-morbidity</i> | | | | |
| <i>Charlson weights</i> | | | | |
| 0 | 0 (0, 1) | 1 | 1 | 1 |
| ≥ 1 | 1 (0, 2) | 1.57 (1.38, 1.75)‡ | 1.27 (1.07, 1.51) ‡ | 1.27 (1.07, 1.51)‡ |
| <i>No. of drug classes</i> | - | 1.12 (1.10, 1.15)‡ | 1.11 (1.05, 1.17) ‡ | 1.09 (1.03, 1.16)‡ |
| <i>MPR</i> | | | | |
| MPR < 50% | 1 (0, 2) | 1 | 1 | 1 |
| MPR $\geq 50\% < 80\%$ | 1 (0, 2) | 0.84 (0.67, 1.05) | 0.61 (0.39, 0.95) ‡ | 0.60 (0.38, 0.93)‡ |
| MPR $\geq 80\%$ | 1 (0, 2) | 0.83 (0.68, 1.00) | 0.59 (0.42, 0.81) ‡ | 0.57 (0.41, 0.79)‡ |
| <i>Self-report Adherence</i> | | | | |
| Non-Adherent | 1 (0, 2) | 1 | 1 | 1 |
| Adherent | 0 (0, 1) | 0.62 (0.56, 0.70) | 0.65 (0.49, 0.87) ‡ | 0.65 (0.48, 0.88)‡ |
| <i>Social Support (MOS)</i> | | | | |
| Low social support | 0 (0, 2) | 1 | 1 | 1 |
| Medium social support | 1 (0, 1) | 0.87 (0.66, 1.15) | 0.97 (0.66, 1.43) | 0.96 (0.65, 1.41) |
| High social support | 1 (0, 2) | 1.10 (0.85, 1.42) | 1.19 (0.82, 1.72) | 1.18 (0.81, 1.73) |
| <i>Social Network (LSNS)</i> | - | 0.99 (0.97, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.99, 1.00) |
| <i>Private health insurance</i> | | | | |
| No | 1 (0, 2) | 1 | 1 | 1 |
| Yes | 1 (0, 1) | 0.92 (0.81, 1.05) | 0.97 (0.73, 1.29) | 0.97 (0.72, 1.30) |
| <i>Vulnerability</i> | | | | |

| Patient level fixed effects | Median (IQR) | Unadjusted IRR (95% CI) (N=904) | Hospital ≥1 | |
|--|-----------------|------------------------------------|--|---|
| | | | Adjusted IRR Beers 2012 (95% CI) (N=844)* | Adjusted IRR STOPP (95% CI) (N=844)* |
| No | 0 (0, 1) | 1 | 1 | 1 |
| Yes | 1 (0, 2) | 1.58 (1.40, 1.78)‡ | 1.22 (0.98, 1.51) | 1.20 (0.97, 1.49) |
| PIP Beers 2012 | | | | |
| 0 | 0 (0, 1) | 1 | 1 | - |
| 1 | 1 (0, 2) | 1.42 (1.23, 1.63)‡ | 1.09 (0.89, 1.34) | - |
| ≥ 2 | 1 (0, 3) | 1.79 (1.55, 2.07)‡ | 1.08 (0.85, 1.38) | - |
| PIP STOPP | | | | |
| 0 | 0 (0, 1) | 1 | - | 1 |
| 1 | 1 (0, 2) | 1.42 (1.23, 1.63)‡ | - | 1.18 (0.84, 1.67) |
| ≥ 2 | 1 (0, 3) | 1.79 (1.55, 2.07)‡ | - | 1.32 (1.14, 1.54)‡ |
| Practice level fixed effects (N=15) | | | | |
| Gender | | | | |
| Male | 1 (0, 2) | 1 | | 1 |
| Female | 1 (0, 1) | 0.86 (0.62, 1.18) | 0.97 (0.75, 1.25) | 0.99 (0.76, 1.27) |
| Deprivation †# | - | 1.07 (1.00, 1.15) | - | - |

* In the adjusted model data was missing for 60 (7%) patients, co-morbidity was missing for 2 (0.22%) patients, MPR was missing for 49 (5%) patients and self-report adherence was missing for 9 (1%) patients; these patients were excluded from the multivariable analysis (N=844).

† Patient age was centred on age 70 (minimum age) e.g. patient age-70. Patient and practice deprivation were centred on their mean value.

‡ z score p < 0.05.

|| In the unadjusted model, co-morbidity was missing for 2 (0.22%) patients, MPR was missing for 49 (5%) patients and self-report adherence was missing for 19 (2%) patients

Practice deprivation excluded from adjusted model due to collinearity with patient deprivation.