Factors associated to potentially inappropriate prescribing in older patients according to STOPP/START criteria: MoPIM multicentre cohort study

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Abstract

Objectives: The objectives of the present analyses are to estimate the frequency of potentially inappropriate prescribing (PIP) at admission according to STOPP/START criteria version 2 in older patients hospitalised due to chronic disease exacerbation as well as to identify risk factors associated to the most frequent active principles as potentially inappropriate medications (PIMs).

Methods: A multicentre, prospective cohort study including older patients (≥65) hospitalized due to chronic disease exacerbation at the internal medicine or geriatric services of 5 hospitals in Spain between September 2016 and December 2018 was conducted. Demographic and clinical data was collected, and a medication review process using STOPP/START criteria version 2 was performed, considering both PIMs and potential prescribing omissions (PPOs). Primary outcome was defined as the presence of any most frequent principles as PIMs, and secondary outcomes were the frequency of any PIM and PPO. Descriptive and bivariate analyses were conducted on all outcomes and multilevel logistic regression analysis, stratified by participating centre, was performed on the primary outcome.

Results: A total of 740 patients were included (mean age 84.1, 53.2% females), 93.8% of them presenting polypharmacy, with a median of 10 chronic prescriptions. Among all, 603 (81.5%) patients presented at least one PIP, 542 (73.2%) any PIM and 263 (35.5%) any PPO. Drugs prescribed without an evidence-based clinical indication were the most frequent PIM (33.8% of patients); vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia was the most frequent PPO (10.3%). The most frequent active principles as PIMs were proton pump inhibitors (PPIs) and benzodiazepines (BZDs), present in 345 (46.6%) patients. This outcome was found significantly associated with age, polypharmacy and essential tremor in an explanatory model with 71% AUC.

Conclusions: PIMs at admission are highly prevalent in these patients, especially those involving PPIs or BZDs, which affected almost half of the patients. Therefore, these drugs may be considered as the starting point for medication review and deprescription.

Trial registration number: NCT02830425
Background
Older patients with multiple morbidities and medication requirements pose a challenge to the prescribing physicians. In addition to possible drug-drug or drug-disease interactions, these patients present age-related physiological changes in drug pharmacokinetics and pharmacodynamics, as well as other factors that can influence prescription such as cognitive impairment, functional difficulties or geriatric syndromes [1, 2].

Considering this, the term potentially inappropriate prescribing (PIP) is being widely used to describe a range of situations in which prescribing should be revised, particularly in geriatric patients. PIP includes potentially inappropriate medication (PIM) which, together with polypharmacy, are well-known risk factors for adverse drug events [3, 4], and also includes potential prescribing omissions (PPO), which increase the probability of not taking essential medication [5, 6].

There are several tools to identify and evaluate PIP [7]. Among all, the explicit criteria STOPP/START (Screening Tool of Older Person’s potentially inappropriate Prescriptions / Screening Tool to Alert doctors to Right Treatment) [8], which includes PIMs and PPOs, were the first European criteria and are currently the most used and validated in European elderly people [9]. After the 1st version, containing 84 criteria, a 2nd version with 114 criteria was later developed, expanding the explicit criteria as well as incorporating three implicit criteria [10].

In recent years, many studies have been published using these criteria to assess prescription adequacy in different settings, such as primary care, socio-health centres, nursing homes and hospitals [7, 11–14]. Additionally, several studies have identified factors associated with the number or presence of PIM or PPO, such as polypharmacy, number of morbidities or age, as well as associated PIM or PPO to clinical outcomes such as hospitalization or mortality [15–17].

However, to the best of our knowledge, there are currently no studies evaluating PIP and its associated factors in a cohort of older patients admitted to hospital due to chronic condition exacerbation. This constitutes an especially vulnerable and complex group of patients that come from the community but end up hospitalized, and may present avoidable, inappropriate prescriptions at admission. Moreover, despite the high prevalence of multimorbidity in older patients, there are no studies evaluating a comprehensive list of chronic conditions as possible risk factors for PIP nor any studies focusing on the most frequent active principles as PIMs, which would be really helpful to develop more efficient strategies.

Thus, the objectives of the present analyses are to estimate the frequency of PIMs and PPOs at admission according to STOPP/START criteria (2nd version) and to identify risk factors associated to the most frequent active principles as PIMs, evaluating sociodemographic, clinical and pharmacological variables in older patients admitted to hospital because of an exacerbation of their chronic conditions. These analyses are part of a larger study, named MoPIM (Morbidity, Potentially Inappropriate Medication), with various objectives related to multimorbidity, PIP and adverse drug reactions in these patients.

Methods
Design and setting
A multicentre, prospective cohort study including older patients hospitalized at the internal medicine or geriatric services at five general teaching hospitals in three different regions of Spain between September 2016 and December 2018 was conducted. The detailed protocol was previously published [18].

For the purposes of this study, older patients (≥65 years old) admitted because of an exacerbation of their chronic pathology were included. Patients referred to home hospitalization, admitted because of an acute process, or with a fatal outcome expected at admission were not included.

No written informed consent was deemed necessary for this study, according to the independent ethics committee.

Data acquisition and variables
The following sociodemographic and clinical data was retrieved by the clinical team responsible for the patient: patient’s code, centre, date of birth, sex, functional status just before entering the hospital (Barthel Index) [19], household (alone, with relatives or other people, in a nursing home) and existence of any contact with healthcare services (primary care, emergencies, hospital admission, outpatient care, home care) in the 3 months prior to hospitalization due to exacerbation of any chronic disease. Chronic active conditions were recorded from a consensual list of 64 conditions, which included risk factors and all chronic diseases of the Charlson Comorbidity Index [20].
Regarding pharmacological variables, the number of chronic medications in the electronic prescription at the time of admission and the STOPP/START criteria detected upon admission, with the active principle involved, were collected by the pharmacist of the team. This medication review process is routinely conducted in all participating centres. Medication was only considered chronic if prescribed at least 3 months before admission, and creams, ointments, healing material and over-the-counter medicines were not considered. Active principles were considered individually when registering STOPP/START criteria, regardless of the administered drug combinations.

Sampling and analysis
The estimated sample of 800 patients (see protocol [18]) could not be reached due to organizational reasons in one of the participating centres. Patients included were proportionally distributed to the annual volume of hospitalizations at the internal medicine and/or geriatric services of each centre.

For the purposes of the analyses, age was categorized as 65-74, 75-89, or >89 years and the number of chronic conditions was categorized as 1-7, 8-13 or 14-22. These categorizations were established by using the cutpredi() R function [21], which provides the optimal cut-off points for categorization of quantitative variables based on the relationship between these variables and the outcome (presence of any of the most frequent active principles as PIMs). The Updated Charlson Comorbidity Index [22] was calculated, adjusted by age and categorized by terciles (2-6, 7-8 and 9-14). Barthel Index was categorized as independency (100 points), minimal dependency (60-95), moderate dependency (40-55), severe dependency (20-35) and complete dependency (<20) [23].

Some chronic conditions were grouped according to clinical criteria, as in Baré et al. [24] Eventually, 50 chronic conditions were analysed.

Polypharmacy was defined as the chronic consumption of five or more drugs [25]. On top of that, another categorisation was defined at 10 drugs and patients were therefore classified as presenting ‘oligopharmacy’ (<5 drugs), ‘moderate polypharmacy’ (5-9 drugs), and ‘excess polypharmacy’ (>10 drugs).

All STOPP/START criteria were assessed, except for START criteria 1 (vaccines), due to difficulties of some centres in accessing the information (not registered in the electronic prescription). Regarding the implicit criterion STOPP A1 and given its high frequency, it was divided into the following categories according to the active principle involved: proton pump inhibitors (PPIs), hypolipidemics, analgesics, aspirin, antihypertensives and others.

Descriptive analyses were performed for all variables. Bivariate analyses were conducted to assess possible associations between sociodemographic/clinical variables and PIP related outcomes (any PIM, any PPO, any most frequent active principles as PIMs) by the chi-square test.

Multilevel logistic regression analysis was performed on the primary outcome (presence of any most frequent active principles as PIMs). Hospital centre was set as a level (random effect) in order to account the possibility that in each hospital location, the prescriptive practices of all professionals in each area may be different and lead to some variability in PIP. Explanatory variables (fixed effect) were chosen if \( p < 0.05 \) in the bivariate analysis. The final model was determined by a stepwise algorithm, with a minimal Akaike Information Criteria value, and its Area Under the Curve (AUC) was calculated.

All analyses were performed with R (R Foundation for Statistical Computing, Vienna, v3.6.0).

Results

Description of sociodemographic and clinical data
A consecutive sample of 740 patients aged ≥65 years was obtained, with a mean age of 84.1 years (SD±7.0) and a 53.2% of females. Sociodemographic and clinical variables are summarised in Table 1. The median number of chronic conditions was 8 (interquartile range (IQR) 6-11), ranging from 1 to 22, and the number of chronic prescriptions ranged from 0 to 28, with a median of 10 (IQR 7-13). Most (93.8%) patients presented polypharmacy; precisely, 259 (35%) patients had moderate polypharmacy, and 435 (58.8%) displayed excessive polypharmacy.

Potentially inappropriate prescribing
At least one PIP was reported in 603 (81.5%, 95% confidence interval (CI) 78.5-84.1) patients. The number of PIPs ranged from 0 to 8, with a median of 2 (IQR 1-3).

Regarding PIMs, 542 (73.2%, 95% CI 69.9-76.3) patients presented polypharmacy; precisely, 259 (35%) patients had moderate polypharmacy, and 435 (58.8%) displayed excessive polypharmacy.

Drugs prescribed without an evidence-based clinical indication were the most frequent PIM (STOPP criterion A1, in 33.8% of patients, many of them having multiple PIMs in this criterion, and accounting for 25.7% of the total number of PIMs). Detailed information of the active principles registered within this criterion can be found in Supp. Table 1. Most frequent PIMs are represented in Figure 1A, relative to the total of patients, and all PIMs detected are shown in Supp. Table 2, relative to the total number of PIMs. Regarding the type of
Table 1 Descriptive and bivariate (chi-square test) statistics of sociodemographic and clinical data related to the presence of any PIP, PIM, PPO and most frequent active principles as PIMs (proton pump inhibitors or benzodiazepines), according to STOPP/START criteria. N, % and 95% Confidence Intervals (95% CI) are shown, as well as chi-square p-value.

| Sociodemographic and clinical variables | Total | Any STOPP PIM | Any START PPO | Any most frequent active principles as PIMs (PPI/ BZD) |
|----------------------------------------|-------|--------------|---------------|--------------------------------------------------|
|                                        | N (%) | 95% CI       | p-value       | N (%) 95% CI          | p-value | N (%) 95% CI          | p-value |
| Total                                  | 740 (100) | 542 (73.2) | 69.9‑76.3       | 263 (35.5) 32.2‑39.1 | 0.001   | 345 (46.6) | 43.1‑50.2 | -               |
| Age                                    |       |              |               |                     |         |                     |         |
| 65‑74                                  | 81 (10.9) | 52 (64.2) | 53.3‑73.8       | 13 (16.1) 96.25      | 0.018   | 26 (32.1) | 22.9‑42.9 | 0.018 |
| 75‑89                                  | 495 (66.9) | 374 (75.6) | 71.6‑79.1       | 186 (37.6) 33.4‑41.9 | 0.039   | 243 (49.1) | 44.7‑53.5 | -               |
| >89                                    | 164 (22.2) | 116 (70.7) | 63.4‑77.2       | 64 (39.0) 31.9‑46.7 | 0.039   | 76 (46.3) | 38.9‑54   | -               |
| Sex                                     |       |              |               |                     |         |                     |         |
| Female                                 | 394 (53.2) | 303 (77.0) | 72.5‑80.8       | 142 (36) 31.5‑40.9 | 0.016   | 194 (49.2) | 44.3‑54.2 | 0.128 |
| Male                                   | 346 (46.8) | 239 (69.1) | 64.7‑73.7       | 121 (35) 30.1‑40.1 | 0.039   | 151 (43.6) | 38.5‑48.9 | -               |
| Barthel Index                           |       |              |               |                     |         |                     |         |
| < 20                                   | 90 (12.2) | 64 (71.1) | 61.7‑79.5       | 24 (26.7) 18.6‑36.6 | 0.001   | 39 (43.3) | 33.6‑53.6 < 0.001 |
| 20‑35                                  | 76 (10.3) | 64 (84.2) | 74.4‑90.7       | 31 (40.8) 30.4‑52 | 0.039   | 42 (55.3) | 44.1‑65.9 | -               |
| 40‑55                                  | 124 (16.8) | 99 (79.5) | 66.7‑81.8       | 43 (34.7) 26.9‑43.4 | 0.039   | 63 (50.8) | 42.1‑59.4 | -               |
| 60‑95                                  | 294 (39.7) | 225 (76.5) | 71.4‑81         | 123 (41.8) 36.3‑47.5 | 0.039   | 152 (51.7) | 46.7‑57.4 | -               |
| 100                                    | 156 (21.1) | 96 (61.5) | 53.7‑68.8       | 42 (26.9) 206.3‑44   | 0.039   | 49 (31.4) | 246.9‑39.1 | -               |
| uCCI                                    |       |              |               |                     |         |                     |         |
| 2‑6                                    | 280 (37.8) | 202 (72.1) | 66.6‑77.1       | 86 (30.7) 25.6‑36.3 | 0.007   | 128 (45.7) | 40.5‑51.6 | 0.546 |
| 7‑8                                    | 279 (37.7) | 211 (75.6) | 70.3‑80.3       | 119 (42.6) 37.4‑48.5 | 0.039   | 80 (44.2) | 37.2‑51.5 | -               |
| 9‑14                                   | 181 (24.5) | 129 (71.3) | 64.3‑77.4       | 58 (32) 25.7‑39.2 | 0.039   | 137 (49.1) | 43.3‑54.9 | -               |
| Household                               |       |              |               |                     |         |                     |         |
| With relatives / other people           | 523 (70.7) | 381 (72.9) | 68.9‑76.5       | 183 (35) 31.9‑42.9 | 0.459   | 60 (49.2) | 40.5‑57.9 | 0.532 |
| Nursing home                           | 95 (12.8) | 73 (76.8) | 67.4‑84.2       | 31 (32.6) 24.2‑46.2 | 0.039   | 48 (50.5) | 40.6‑60.4 | -               |
| Alone                                   | 122 (16.5) | 88 (72.1) | 63.6‑79.3       | 49 (40.2) 31.9‑49 | 0.039   | 237 (45.3) | 41.1‑49.6 | -               |
| Prior exacerbation                      |       |              |               |                     |         |                     |         |
| No                                     | 225 (30.4) | 163 (72.4) | 66.3‑77.9       | 80 (35.6) 29.6‑42.2 | 0.995   | 99 (44.2) | 37.7‑50.5 | 0.345 |
| Yes (total)                            | 515 (69.6) | 379 (73.6) | 69.6‑77.2       | 183 (35.5) 31.5‑39.8 | 246 (47.8) | 43.5‑52.1 | -               |
| Emergency care                          | 342 (46.2) | 251 (73.4) | 68.5‑77.8       | 128 (37.4) 32.5‑42.7 | 0.32    | 170 (49.7) | 44.4‑55   | 0.119 |
| Moderate polypharmacy (5‑9)             | 259 (35.0) | 177 (68.3) | 62.4‑73.7       | 98 (37.8) 32.1‑43.9 | 0.039   | 106 (40.9) | 35.1‑47   | -               |
| Excessive polypharmacy (10+)            | 438 (58.8) | 349 (80.2) | 76.2‑83.7       | 146 (33.6) 293.3‑81 | 0.25    | 229 (52.6) | 47.9‑57.3 | -               |
| N° chronic conditions                   |       |              |               |                     |         |                     |         |
| 1‑7                                    | 303 (41.0) | 200 (66.0) | 60.5‑71.1       | 102 (33.7) 28.6‑39.2 | 0.657   | 124 (40.9) | 35.5‑46.5 < 0.001 |
| 8‑13                                   | 374 (50.5) | 288 (77.0) | 72.5‑81         | 137 (36.6) 31.9‑41.6 | 0.657   | 45 (71.4) | 59.3‑81.1 | -               |
| 14‑22                                  | 63 (8.5) | 54 (85.8) | 75.9‑92.3       | 24 (38.1) 27.1‑50.4 | 0.657   | 176 (47.1) | 42.1‑52.1 | -               |

PIP: potentially inappropriate prescribing. PIM: potentially inappropriate medication. PPO: potential prescribing omission. PPI: proton pump inhibitor. BZD: benzodiazepine. uCCI: updated Charlson Comorbidity Index.
active principle involved, PIMs related to PPIs (STOPP criteria A1 or F2) were present in 22.6% of the patients. Benzodiazepines (BZDs) for ≥ 4 weeks (STOPP criterion D5) was the second most frequent PIM, found in 31.8% of the patients. And the presence of any PIMs related to BZDs (STOPP criteria D5, G5, K1 or A1 involving BZDs) was found in 32.3%, with a high redundancy between these criteria.

Therefore, the most frequent active principles as PIMs were PPIs and BZDs, with 345 (46.6%) patients having at least one related PIM.

Regarding PPOs, at least one was identified in 263 (35.5%, 95% CI 32.2-39.1) patients, ranging from 0 to 4, with a median number of 0 (IQR 0-1). In total, 188 (25.4%) patients had 1 PPO, 62 (8.4%) had 2, 11 (1.5%) had 3, and 2 (0.3%) had 4 PPOs. The most frequent

![Fig. 1](image-url) % of patients presenting the following STOPP/START criteria. A: Potentially inappropriate medications (PIMs) found in most patients according to STOPP criteria (present in >2% of the patients). Subcategories of criterion A1 are shown in mild grey. B: Potential prescribing omissions (PPOs) found in most patients according to START criteria (present in >1% of the patients).
PPOs relative to the total of patients are summarized in Figure 1B, starting with vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (START criterion E5, 10.3%), followed by laxatives in patients receiving opioids regularly (H2, 6.8%), beta-blockers with stable systolic heart failure (A8, 5.3%) and ACE inhibitors with systolic heart failure and/or documented coronary artery disease (A6, 5.1%). All PPOs detected are shown in Supp. Table 3, relative to the total number of PPOs.

Factors associated to PIP
Next, we performed a bivariate analysis to uncover the potential relationship of sociodemographic and clinical variables with the prevalence of any PIM, any PPO and any most frequent active principles as PIMs (any PPI/BZD) (Tables 1 and 2).

All the significant variables obtained in the bivariate analysis of the outcome of any PPI/BZD as PIMs were included in a stepwise selection algorithm in order to build a multilevel logistic regression model. This explanatory model (Table 3) obtained a 71% AUC (95% CI 67.4-74.7) and showed contribution of age, polypharmacy, essential tremor and previous fractures excluding hip (not significant but necessary for optimal model). Remarkably, excessively polymedicated patients (>10 drugs) and those suffering from essential tremor were at least twice or trice more likely to have any PPI/BZD as PIMs, respectively (95% CI odds ratio lower limits >2 and >3).

Discussion
Our study found a high proportion of older patients with an elevated rate of multimorbidity and moderate functional impairment, a high prevalence of polypharmacy (93.8%) (much higher than reported for the general Spanish population [26]), and a very high prevalence of excessive polypharmacy (58.8%). These findings are consistent with the inclusion of older patients admitted to hospital due to chronic disease exacerbation.

Regarding PIP, up to 81.5% of the patients met at least one criterion, mainly due to a high prevalence of PIMs (73.2%) instead of PPOs (35.5%). The prevalence of PIMs differs from the estimates of a recent systematic review in which 42.8% of the patients in the community presented at least a PIM, whereas the prevalence of PPOs is very similar [27]. It is plausible that patients in our cohort present a higher prevalence of PIMs due to their polypharmacy, multimorbidity, functional impairment and uncontrolled chronic problems. Besides, another factor could be the application of the STOPP/START criteria version 2, owing to STOPP criteria A (implicit), which may increase PIM detection but could be a possible source of variability too.

An important finding of this study is that the most frequent active principles as PIMs, which were PPIs and BZDs, were present in almost half (46.6%) of the patients, suggesting that actions focused on deprescribing these medications may have a large impact on reducing PIP and, therefore, undesired negative outcomes. Remarkably, many other studies have previously found either BZDs alone [28–30] or together with PPIs [4, 12, 31–33] among the most frequent PIMs.

With respect to PPIs, which are widely prescribed in Spain [34], they were classified as PIMs in 167 patients. PPIs may be related to adverse outcomes, such as fractures [35], hypomagnesaemia [36–39], recurrent C. difficile infection [40, 41], dementia [42, 43], community-acquired pneumonia [44], or severe COVID-19 infection [45–47]. Remarkably, in 160 (95.8%) patients, PPI prescription was assigned to implicit STOPP criterion A1. This situation may explain why other studies did not find a similar prevalence of PPIs as PIMs, since the pharmacists’ judgement becomes more relevant in implicit criteria.

The rest of active principles belonging to STOPP criterion A1 (which was indeed the most frequent PIM) were highly diverse, highlighting the need of more explicit criteria to avoid subjectivity in the screening, maybe at the expense of suppressing criteria about less frequent situations, not to end up with an excessively long list.

Regarding BZDs, they are highly prescribed among older adults in Spain and their use has been increasing lately [48, 49]; however, its prescribing has been found significantly in excess of what the evidence would suggest is appropriate [50]. In fact, BZDs are associated with negative outcomes such as dependence, falls and fractures, cognitive decline or sleep disturbances [51].

Among the registered PPOs, vitamin D in older people who are experiencing falls or osteopenia was not expected to be the most frequent, but this could be partially explained by the strong levels of sun radiation in Spain. Furthermore, we encountered a high rate of patients not taking laxatives when consuming opioids, which could suppose a risk for constipation. The over-the-counter use of these drugs and/or herbal products (due to lack of prize reimbursement in Spain) may be a potential reason for this.

The bivariate analyses showed a significant association of the defined PIP outcomes with some sociodemographic and clinical variables such as age, polypharmacy and number of chronic conditions, which have been previously associated with the presence of PIM and PPO [31, 33, 52, 53]. Regarding specific chronic conditions, a large
| Variable                                      | Any STOPP PIM | Any START PPO | Any most frequent active principles as PIMs (PPI/ BZD) |
|----------------------------------------------|---------------|---------------|--------------------------------------------------------|
| Amputation                                   | No            | 530 73.2 0.873| 257 35.5 0.869                                         |
|                                              | Yes           | 12 75        | 6 37.5                                                 |
| Anaemia                                      | No            | 285 70.2 0.039| 148 36.5 0.567                                         |
|                                              | Yes           | 257 76.9     | 115 34.4                                               |
| Asthma                                       | No            | 477 72.5 0.191| 235 35.7 0.780                                         |
|                                              | Yes           | 65 79.3      | 28 34.1                                                |
| Cardiac arrhythmia                           | No            | 218 68.8 0.017| 107 33.8 0.379                                         |
|                                              | Yes           | 324 76.6     | 156 36.9                                               |
| Cerebrovascular disease (including hemiplegia)| No            | 397 71.9 0.164| 200 36.2 0.501                                         |
|                                              | Yes           | 145 77.1     | 63 33.5                                                |
| Chronic obstructive pulmonary disease        | No            | 334 71.5 0.166| 168 36 0.747                                          |
|                                              | Yes           | 208 76.2     | 95 34.8                                                |
| Chronic gastritis or gastro-oesophageal reflux| No           | 472 73.1 0.774| 219 33.9 0.015                                         |
|                                              | Yes           | 70 74.5      | 44 46.8                                                |
| Chronic renal insufficiency                  | No            | 303 72.1 0.439| 143 34 0.331                                          |
|                                              | Yes           | 239 74.7     | 120 37.5                                               |
| Chronic thyroid disease                      | No            | 435 71.9 0.081| 210 34.7 0.318                                         |
|                                              | Yes           | 107 79.3     | 53 39.3                                                |
| Degenerative arthropathy                     | No            | 244 68.7 0.008| 105 29.6 0.001                                         |
|                                              | Yes           | 298 77.4     | 158 41                                                  |
| Dementia                                     | No            | 416 74.2 0.322| 196 34.9 0.544                                         |
|                                              | Yes           | 126 70.4     | 67 37.4                                                |
| Diabetes with complication                   | No            | 442 72.8 0.576| 221 36.4 0.292                                         |
|                                              | Yes           | 100 75.2     | 42 31.6                                                |
| Diabetes without complication                | No            | 394 73.1 0.884| 186 34.5 0.337                                         |
|                                              | Yes           | 148 73.6     | 77 38.3                                                |
| Drug-related conditions                      | No            | 491 73 0.577 | 241 35.8 0.628                                         |
|                                              | Yes           | 51 76.1      | 22 32.8                                                |
| Dyslipidaemia                                | No            | 268 70.5 0.086| 143 37.6 0.222                                         |
|                                              | Yes           | 274 76.1     | 120 33.3                                               |
| Essential tremor                             | No            | 534 73.1 0.286| 258 35.3 0.207                                         |
|                                              | Yes           | 8 88.9       | 5 55.6                                                 |
| Fibromyalgia                                 | No            | 536 73.2 0.91 | 260 35.5 0.907                                         |
|                                              | Yes           | 6 75         | 3 37.5                                                 |
| Gallstones (previous hepatic colic)          | No            | 482 72.9 0.565| 226 34.2 0.026                                         |
|                                              | Yes           | 60 75.9      | 37 46.8                                                |
| Gout                                         | No            | 443 73.5 0.774| 213 35.3 0.796                                         |
|                                              | Yes           | 99 72.3      | 50 36.5                                                |
| Haematologic disorders                       | No            | 517 73.4 0.598| 246 34.9 0.133                                         |
|                                              | Yes           | 25 69.4      | 17 47.2                                                |
| Heart failure                                | No            | 208 70 0.106 | 101 34 0.475                                           |
|                                              | Yes           | 334 75.4     | 162 36.6                                               |
| Hypertension                                 | No            | 90 65.7 0.027| 42 30.7 0.186                                          |
|                                              | Yes           | 452 75       | 221 36.7                                               |
| Inflammatory osteoarticular disease          | No            | 509 73.7 0.335| 237 34.3 0.008                                         |
|                                              | Yes           | 33 67.3      | 26 53.1                                                |
| Variable                                                        | Any STOPP PIM | Any START PPO | Any most frequent active principles as PIMs (PPI/ BZD) |
|----------------------------------------------------------------|--------------|---------------|-----------------------------------------------------|
|                                                                 | N  %         | p-value       | N  %         | p-value       | N  %         | p-value       |
| Irritable bowel syndrome                                       | No           | 531 72.8 0.043 | 258 35.4 0.489 | 338 46.4 0.254 |
|                                                               | Yes          | 11 100 5 45.5 | 7 63.6 1 25 | | | |
| Ischaemic heart disease without infarction                     | No           | 451 72.7 0.484 | 223 36 0.581 | 278 44.8 0.027 |
|                                                               | Yes          | 91 75.8 40 33.3 | 67 55.8 1 25 | | | |
| Migraine                                                       | No           | 541 73.5 0.029 | 262 35.6 0.659 | 344 46.7 0.385 |
|                                                               | Yes          | 1 25 1 25 | 1 25 | | | |
| Mild liver disease (incl. chronic hepatitis B or C)            | No           | 516 72.9 0.296 | 248 35 0.171 | 327 46.2 0.264 |
|                                                               | Yes          | 26 81.2 15 46.9 | 18 56.2 | | | |
| Moderate or severe liver disease                               | No           | 534 74.1 0.002 | 259 35.9 0.181 | 342 47.4 0.006 |
|                                                               | Yes          | 8 42.1 4 21.1 | 3 15.8 | | | |
| Myocardial infarction                                          | No           | 459 73 0.693 | 231 36.7 0.109 | 287 45.6 0.197 |
|                                                               | Yes          | 83 74.8 32 28.8 | 58 52.3 | | | |
| Neoplasia                                                      | No           | 469 74.6 0.054 | 224 35.6 0.923 | 295 46.9 0.718 |
|                                                               | Yes          | 73 65.8 39 35.1 50 45 | | | | |
| Neurologic disorder of the central nervous system              | No           | 521 73.6 0.32 | 254 35.9 0.37 | 328 46.3 0.451 |
|                                                               | Yes          | 21 65.6 9 28.1 17 53.1 | | | | |
| Non-ischaemic heart disease                                    | No           | 366 72.9 0.765 | 182 36.3 0.555 | 228 45.4 0.341 |
|                                                               | Yes          | 176 73.9 81 34 | 117 49.2 | | | |
| Non-schizophrenic mental disorders                             | No           | 532 73.1 0.426 | 257 35.3 0.291 | 341 46.8 0.352 |
|                                                               | Yes          | 10 83.3 6 50 | 4 33.3 | | | |
| Obesity                                                       | No           | 387 70.7 0.01 | 192 35.1 0.674 | 253 46.3 0.735 |
|                                                               | Yes          | 155 80.3 71 36.8 92 47.7 | | | | |
| Osteoporosis                                                   | No           | 458 71.9 0.04 | 219 34.4 0.101 | 289 45.4 0.089 |
|                                                               | Yes          | 84 81.6 44 42.7 56 54.4 | | | | |
| Pancreas disease                                               | No           | 532 72.9 0.054 | 259 35.5 0.767 | 338 46.3 0.136 |
|                                                               | Yes          | 10 100 4 40 | 7 70 | | | |
| Parkinson's disease                                            | No           | 517 73.2 0.969 | 252 35.7 0.691 | 327 46.3 0.45 |
|                                                               | Yes          | 25 73.5 11 32.4 | 18 52.9 | | | |
| Peptic ulcer disease                                           | No           | 509 73.3 0.812 | 245 35.3 0.599 | 325 46.8 0.659 |
|                                                               | Yes          | 33 71.7 18 39.1 20 43.5 | | | | |
| Peripheral neuropathy or neuritis                             | No           | 494 72.8 0.316 | 243 35.8 0.639 | 312 45.9 0.222 |
|                                                               | Yes          | 48 78.7 20 32.8 33 54.1 | | | | |
| Peripheral vascular disease                                    | No           | 461 72.6 0.330 | 232 36.5 0.164 | 295 46.5 0.825 |
|                                                               | Yes          | 81 77.1 31 29.5 | 50 47.6 | | | |
| Post-traumatic stress disorder                                 | No           | 540 73.3 0.797 | 261 35.4 0.259 | 344 46.7 0.644 |
|                                                               | Yes          | 2 66.7 2 66.7 | 1 33.3 | | | |
| Previous fractures (not hip)                                   | No           | 430 71.5 0.03 | 207 34.4 0.194 | 268 44.6 0.021 |
|                                                               | Yes          | 112 80.6 56 40.3 77 55.4 | | | | |
| Previous hip fracture                                          | No           | 488 72.5 0.154 | 231 34.3 0.028 | 312 46.4 0.651 |
|                                                               | Yes          | 54 80.6 32 47.8 | 33 49.3 | | | |
| Rheumatologic disease                                          | No           | 522 73.7 0.16 | 255 36 0.203 | 332 46.9 0.487 |
|                                                               | Yes          | 20 62.5 8 25 | 13 40.6 | | | |
| Schizophrenia                                                  | No           | 540 73.3 0.797 | 262 35.5 0.936 | 343 46.5 0.486 |
|                                                               | Yes          | 2 66.7 1 33.3 2 66.7 | | | | |
| Sleep apnoea                                                   | No           | 486 72.1 0.026 | 244 36.2 0.230 | 305 45.3 0.017 |
|                                                               | Yes          | 56 84.8 19 28.8 40 60.6 | | | | |
| Tuberculosis                                                   | No           | 536 73.3 0.654 | 260 35.6 0.889 | 340 46.5 0.589 |
number showed an association, such as anaemia, degenerative arthropathy, sleep apnoea, inflammatory osteoarticular disease and previous hip fracture, among many others.

Finally, when modelling the presence of any PPI/BZD as PIMs, we found out the important role of age and polypharmacy, as expected, but also of two chronic conditions: essential tremor and previous fractures (excluding hip). Although these are not highly prevalent conditions, they have a role in the outcome. In fact, there is increasing evidence of a relationship between PPIs and fractures [35], which, together with the association of BZDs to falls and fractures [51], urges to review both PPIs and BZDs prescribing in these patients. Furthermore, the use of BZDs to treat essential tremor has shown a limited effectiveness [54].

Remarkably, the use of a multilevel logistic regression analysis provides more reliable results compared to conventional regression analyses. The latter consider that records of individual patients are independent of records of other patients. However, this assumption may not hold true in multicentre studies; for instance, different geographical areas may have variability in prescribing tendencies and patient profiles. Therefore, multilevel analyses, which allow to analyse data with a hierarchical structure, are appropriate to take these potential effects into account.

Previous, similar studies have been conducted aiming to find associations between chronic conditions and PIP outcomes. However, most have considered only a few comorbidities or risk factors, such as hypertension, dyslipidaemia, osteoporosis, diabetes or COPD [55, 56] and not a large, comprehensive list. Our findings highlight the need of a wider consideration of chronic conditions to incorporate to regression models, in order to detect subtler yet important associations. Regression models including chronic conditions can be useful to stratify patients according to their associated risk of presenting PIPs and, consequently, to identify which patients require a medication review priority.

**Clinical implications**

Our results show how older patients admitted to hospital because of chronic conditions exacerbation present a higher prevalence of PIM compared to other cohorts from the community. Even though this study was carried out in a hospital setting, the medication review was performed the day of admission and, consequently, these were previous prescriptions originated from any facility in the whole healthcare system.

Patients with a larger number of chronic conditions have a higher probability of presenting any PIM or any of the most frequent active principles as PIMs (PPI/BZD). With these results, medication review could be more focused on these specific situations and drugs, given that

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### Table 2 (continued)

| Variable                  | Any STOPP PIM |      | Any START PPO |      | Any most frequent active principles as PIMs (PPI/BZD) |      |
|---------------------------|---------------|------|---------------|------|------------------------------------------------------|------|
|                           | N  | %   | p-value      | N  | %   | p-value      | N  | %   | p-value      |
| Urinary tract stones      | No            | 530 | 73 | 0.287 | 259 | 35.7 | 0.582 | 340 | 46.8 | 0.409 |
|                           | Yes           | 12  | 85.7 | 4  | 28.6 | 5 | 35.7 | 5 | 35.7 |
| Varicose veins            | No            | 421 | 73.1 | 0.86 | 199 | 34.5 | 0.291 | 261 | 45.3 | 0.181 |
|                           | Yes           | 121 | 73.8 | 64 | 39 | 84 | 51.2 |
| Vertigo                  | No            | 483 | 72.9 | 0.479 | 237 | 35.7 | 0.731 | 302 | 45.6 | 0.087 |
|                           | Yes           | 59  | 76.6 | 26 | 33.8 | 43 | 55.8 |

*P<0.05 was considered statistically significant and highlighted in bold. PIP: potentially inappropriate prescribing. PIM: potentially inappropriate medication. PPO: potential prescribing omission. PPI: proton pump inhibitor. BZD: benzodiazepine.

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### Table 3 Multilevel logistic regression model on the outcome of the presence of any most frequent active principles as PIMs (PPI or BZD)

| Variable                  | Any most frequent active principles as PIMs (PPI/BZD) OR (95% CI) |
|---------------------------|---------------------------------------------------------------|
| Age 65-74  | Reference                                                                 |
| Age 75-89 | 1.75 (1.01, 3.09)                                                     |
| Age 90+   | 1.96 (1.05, 3.73)                                                     |
| Oligopharmacy  (0-4) | Reference                                                                 |
| Moderate polypharmacy (5-9) | 3.03 (1.42, 7.01)                                                   |
| Excessive polypharmacy (10+) | 5.12 (2.43, 11.77)                                                   |
| Essential tremor | 19.21 (3.11, 374.95)                                                   |
| Previous fractures (not hip) | 1.43 (0.94, 2.16)                                                   |

PIM: potentially inappropriate medication. OR: odds ratio. CI: confidence interval. PPI: proton pump inhibitor. BZD: benzodiazepine.
it may not always be possible to conduct a medication review in all patients.

Interestingly, Barthel Index was also associated to PIP outcomes, but not in an increasing or decreasing tendency. In all three analysed outcomes (any PIM, any PPO, any PPI/BZD), independent patients or totally dependent ones (100 or <20 Barthel Index) presented the lowest prevalence of inappropriate prescription, whereas the group with highest prevalence of inappropriate prescription was that of severely dependent patients (20-35 Barthel Index). It is therefore possible that the patients at the “extremes” have less PIP because there are more actions directed to medication review in these cases.

These results highlight the need of a thorough medication review in which the hospital pharmacists are integrated within the multidisciplinary geriatric team. With this approach, clinical practice quality could be improved.

Strengths and limitations
The strengths of this study are its multicentre, prospective design in a hospital setting covering different regions of Spain, a team of trained pharmacists integrated in multidisciplinary teams with geriatricians or internal medicine practitioners [57] already familiar with the STOPP/START screening tool, as well as the assurance of high quality and thoroughness in all the gathered clinical and pharmacological data. The study sample size has enough power to estimate the prevalence of PIP, PIM and PPO and is proportional to the volume of admissions of each hospital. Furthermore, the use of a large, comprehensive list of chronic conditions as possible factors associated with PIP as well as an outcome variable that focuses on the presence of the most common misprescriptions are the most powerful strengths of this work.

However, this study also presents some limitations. The application of STOPP/START criteria by different centres and professionals may have induced some biases, especially in those implicit criteria. For this reason, each participating hospital was set as a first level in the multilevel logistic regression model. Moreover, the lack of data on vaccines may affect the prevalence of PPOs. Nonetheless, vaccination is entirely different than the rest of PPOs and therefore the outcome variable excluding vaccines is still clinically and pharmacologically coherent.

Conclusions
The findings of the study confirm that there is a high prevalence of PIP at admission in older, hospitalized patients due to chronic disease exacerbation mainly by the inappropriate prescription of PPIs or BZDs. These drugs have been associated to a set of different chronic conditions as well as age and polypharmacy, giving a starting point for medication review and deprescription. Thus, our study identified a patient profile with higher risk of PIP towards which these actions should be focused. Finally, our results highlight the essentiality of multidisciplinary teams in the clinical management of these patients.

Abbreviations
PIP: Potentially inappropriate prescribing; PIM: Potentially inappropriate medication; PPO: Potentially prescribing omission; BZD: Benzodiazepine; PPI: Proton pump inhibitor; AUC: Area under the curve; IQR: interquartile range; CI: confidence interval.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12877-021-02715-8.

Acknowledgements
The authors acknowledge the dedication and support of the entire MoPIM research group, listed by institution: Parc Taulí University Hospital: Marisa Báre (Institutional Committee for the Improvement of Clinical Practice Adequacy), REDISSEC, Susana Herranz (Acute care Geriatric Unit; REDISSEC), Rosa Jordana (Department of Internal Medicine), Maria Queralt Gorgas (Pharmacy Department, REDISSEC), Sara Ortonobes (Pharmacy Department). Marina Lleal (Institutional Committee for the Improvement of Clinical Practice Adequacy), Celia Corral-Vazquez (Fundación Parc Taulí, REDISSEC), Hospital del Mar Medical Research Institute-IMIM: Elisabet de Jaime (Geriatrics Department), Olivia Fernandez (Pharmacy Department), Maria Sala (Department of Epidemiology and Evaluation, REDISSEC), Miguel Angel Marquez, Marta Arellano, Carlos Clemente and Olga Sabartés (Department of Geriatrics), Núria Carballo and Marta de Antonio (Pharmacy Department), Hospital de Galdakao: Rafael Estrada (Department of Internal Medicine), Maria Olatz Ibarra (Pharmacy Department), Complejo Hospitalario Universitario de Canarias: Candelaria Martin (Department of Internal Medicine), Gloria Julia Nazco (Pharmacy Department), Rubén Hernández (Department of Internal Medicine).

Authors’ contributions
MB conceived and supervised the study, discussed the results, and revised several manuscript versions. ML performed the analysis of the results, participated in the discussion of the results and drafted the manuscript. SO, DF, and NC, participated in medication review, discussion of results and revision of several manuscript versions. MQG helped in the study protocol conception, discussed the results and approved the final version. EdJ and SH participated in patient inclusion, medication review, discussion of the results and revision of the final manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by grants from Instituto de Salud Carlos III-FEDER [PI15/00552] and by the Network for Research into Healthcare in Chronic Diseases, REDISSEC (RD16/0001/0002). These funding bodies had no role in the design of the study, nor in the collection, analysis and interpretation of data nor in writing the manuscript.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and approved by the clinical research ethics committees of each centre; Comité de Investigación Clínica del Parc Taulí [ID: 20166570] and Comité de Ética de Investigación del Hospital Universitario de Canarias [ID: MBM-MOC-2016-01 (2016-56)]. No written informed consent was deemed necessary for this study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Received: 7 October 2021 Accepted: 10 December 2021

Published online: 11 January 2022

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