Clinical Implications of Potentially Inappropriate Prescribing According to STOPP/START Version 2 Criteria in Older Polymorbid Patients Discharged From Geriatric and Internal Medicine Wards: A Prospective Observational Multicenter Study

Clinical implications of potentially inappropriate prescribing according to STOPP/START version 2 criteria in older polymorbid patients discharged from geriatric and internal medicine wards: a prospective observational multicenter study.

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Brief summary

Among hospital-discharged older patients, besides comorbidities, unplanned rehospitalization at 6 months is associated with potentially inappropriate medications in home-discharged patients, with number of drugs in long term care facility-discharged patients.

Abstract

Objectives: To evaluate whether STOPP/START v2 potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) are associated with 6-month mortality and unplanned hospitalization in hospital-discharged older patients.

Design: Multicenter prospective cohort observational study

Setting and participants: patients aged ≥65 years consecutively discharged from acute geriatric and internal medicine wards of two university hospitals in North-western Italy

Methods: At discharge, a comprehensive geriatric assessment was performed in each patient, prescribed medications were recorded, and PIMs and PPOs were determined according to STOPP/START v2. Death and unplanned readmissions at 6 months were investigated through telephone interviews; variables associated with outcomes were identified in the overall sample and according to discharge setting (i.e. home vs medium/long-term care facility, MLTCF) through a multivariate logistic regression model.

Results: Among 611 patients (mean age 81.6 years, 48.4% females, 34.2% MLTCF-discharged, mean number of drugs 7.7±3.2), with an inappropriate prescription (IP) prevalence at discharge of 71.7% (PIMs 54.8%, PPOs 47.3%), mortality and unplanned readmission rate were 25.0% and 30.9%. Neither PIMs nor PPOs were associated with overall mortality. A higher number of PIMs was significantly associated with unplanned readmission in the overall sample (OR 1.23, 95%CI 1.03-1.46), and in home-discharged patients (OR 1.38, 95%CI 1.13-1.68). The number of drugs at discharge was associated with readmissions in the overall sample (OR 1.11, 95%CI 1.05-1.18) and in MLTCF-discharged patients (OR 1.27, 95%CI 1.13-1.42). PPOs were not significantly associated with clinical outcomes.

Conclusions and implications: In hospital-discharged polymorbid older patients, 6-month unplanned readmissions were associated with number of PIMs in home-discharged patients

Commento [EB1]: Forse sia per questione di spazio che di rilevanza, mettere l'associazione dicotomica dei PPO all'univariata, come richiesto dal reviewer 1 sarebbe inappropriato?

Commento [MB2]: Non ho trovato questa richiesta da parte di R1

and with number of drugs in MLTCF-discharged patients. This reaffirms the importance of performing a systematic and careful review of medication appropriateness in hospital-discharged older patients.

INTRODUCTION

The growing burden of polypathology is inherently associated with the prescription of complex polytherapies. Polypharmacy and inappropriate prescribing (IP) are well-known risk factors for adverse drug events (ADEs), frequently leading to unfavorable outcomes in older people [1–4]. Balancing the needs to effectively treat multiple diseases and to avoid iatrogenic harm is complex in clinical practice [5,6]. Indeed, under-prescription is tightly linked with over-prescription, since polypharmacy may lead the prescriber to omit potentially beneficial medications [7], leading to increased morbidity and mortality [8].

Different tools have been developed to identify IP and optimize pharmacotherapy in older patients. Despite being the first published and most widely used, the Beers criteria [9] have restricted applicability in Europe and overlook important aspects of IP, such as duplicated prescriptions and potential prescribing omissions (PPOs) [10]. Moreover, potentially inappropriate medications (PIMs) at discharge according to Beers criteria were not associated with short-time re-hospitalization or death [11,12]. To overcome these limitations, a panel of European experts developed the Screening Tool of Older People's Prescriptions and Screening Tool to Alert to Right Treatment (STOPP/START) criteria in 2008 [13], which have been recently updated (STOPP/START v2) [14]. They include a list of conditions in which specific drugs may represent a PIM (STOPP criteria) or a PPO (START criteria).

While IP according to STOPP/START criteria can be regarded as a process measure of medication safety in older patients, it is important to establish its association with adverse outcomes in different clinical settings. Only a few studies have investigated this association so far, mainly retrospectively and focusing on PIMs, with inconsistent results. Indeed, PIMs according to STOPP criteria have been associated with ADEs [15–17] and functional decline [18]. STOPP/START criteria application during hospitalization reduces ADEs [19], and the implementation of an educational program on IP for physicians working in nursing homes,

mainly focused on STOPP/START criteria, reduced the incidence of delirium and falls in a cluster-randomized multicenter trial [*Garcia-Gollarte et al JAMDA 2014*]. However, evidence on the impact of IP on hospitalization and mortality is scant and highly heterogeneous. PIMs identified according to STOPP criteria have been associated with higher morbidity, reduced quality of life and increased emergency department visits and hospital admissions [20–25]. The impact of PPOs has been far less studied; single studies have reported an association with emergency department visits [21] and 4-year mortality [25].

Since there is persistent uncertainty about clinical implications of IP in older medical in-patients, we designed a two-phase prospective observational study to evaluate the prevalence and potential clinical implications (death and unplanned readmissions) of IP according to STOPP/START v2 among hospital-discharged older patients. We have previously reported the results of the cross-sectional analysis [26], demonstrating a high prevalence of both PIMs and PPOs in this population; among other variables, a higher number of drugs at discharge was strongly associated with both PIMs and PPOs, whereas geriatric discharge was protective for both. In this paper, we report the results of the longitudinal part of the study, aimed to investigate the association of IP (including PIMs and PPOs) with overall mortality and unplanned hospital readmission among hospital-discharged older patients.

METHODS

The present study was carried out according to the Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, approved by the local ethics committee, and reported conforming to the Strengthening The Reporting of Observational Studies in Epidemiology statements [27]. Signed informed consent was obtained by patients, or by proxies or caregivers for patients unable to express consent.

Study design, setting and participants

A complete description of the study has been previously published [26]. Briefly, patients aged ≥65 years consecutively discharged between March and June 2017 from three internal medicine and two geriatric wards of two teaching hospitals in North-western Italy were prospectively enrolled. Exclusion criteria were: in-hospital death, lack of informed consent, incomplete data, and previous enrolment. Demographic and clinical variables (age, sex, comorbidities, body weight and serum creatinine at enrolment to estimate glomerular filtration rate according to the Cockcroft–Gault formula), main diagnosis at discharge, discharge setting (home vs medium/long-term care facility, MLTCF), and number of prescribed medications were recorded. Polypharmacy was defined as ≥5 drugs, and excessive polypharmacy as >10 drugs [28]. Comorbidities were grouped according to Cumulative Illness Rating Scale (CIRS) classes; the CIRS-Severity Index (CIRS-SI, the mean score of the first 13 items), and the CIRS-Comorbidity Index (CIRS-CI, the number of items with a score ≥3) were calculated [33]. As outcomes might be affected by disease severity, to better evaluate the impact of exposure as a result of drug–disease or drug–syndrome interaction, only CIRS classes with a score ≥3 were considered in the analysis. A Comprehensive Geriatric Assessment (CGA) was performed in each patient, including evaluation of functional dependence (Katz Index of activities of daily living – ADL [29], and instrumental ADL – IADL [30]), cognitive function (Short Portable Mental Status Questionnaire – SPMSQ [31]) and frailty (CSHA scale [32]). Patients were considered dependent in ADL with ≥3 lost functions, and partially or completely not autonomous in IADL with scores ≤9. Moderate to severe cognitive impairment was identified by SPMSQ scores ≥5. A CSHA score ≥5 identified frail patients, while a score of 9 identified terminally-ill patients, who were excluded from the analysis. In order to capture real-world clinical practice, physicians working in the hospital units involved were not aware about the study.

Exposure: potentially inappropriate medications and potential prescribing omissions

STOPP/START v2 consist of 80 STOPP criteria and 34 START criteria, organized according to physiological system [14]. PIMs at discharge were identified by applying the full list of STOPP v2 criteria. STOPP A category includes two implicit rules: "drugs prescribed without a clinical indication" and "drugs prescribed beyond the recommended duration". Their application was evaluated case-by-case by two investigators, and implicated medications were recorded. PPOs were detected by applying START v2 criteria. Due to the setting of the study, potential indications to acetylcholinesterase inhibitors (START C3), eye drops for open angle glaucoma (START C4) and vaccines (START I) were not assessed. Furthermore, any laxative was considered as fiber supplement (START D2).

Outcome variables

The outcome variables were all-cause mortality and unplanned hospital readmission. Follow up at 6 months ± 6 weeks was carried out between September and December 2017 through telephone interviews with patients or usual caregivers. Missing information was obtained from the hospital's discharge database and register office. Whenever a telephone interview was not possible, or the patient withdrew his consent, the patient was considered as lost at follow-up.

Statistical analysis

Absolute and relative frequencies of dichotomous and categorical variables, and either mean and standard deviation (SD) or median and interquartile range (IQR) of continuous variables were calculated, as appropriate. The univariate association between outcomes and clinical characteristics, and differences among different groups of patients were evaluated using the Chi-square test for dichotomous and categorical variables, and ANOVA or Mann-Whitney test for normally distributed and not normally distributed continuous variables, respectively.

To identify variables independently associated with outcomes, a multivariate logistic regression analysis (stepwise method) was carried out, where PIMs and PPOs (considered as continuous variables), and all significant variables from univariate analysis were entered as independent variables, while death and unplanned readmission were the dependent variables. Potential interactions between presence of renal disease or moderate-severe cognitive impairment and PIMs, PPOs and/or number of drugs at discharge were investigated in multivariate models where the latter resulted significantly associated with outcomes. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Statistical significance was set at *P* value < .05. Statistical analysis was carried out using MedCalc Statistical Software 9.3.7.0 (MedCalc Software BVBA, Ostend, Belgium).

Commento [EB3]: Questa parte di studio abbiamo dovuto farla non con MedCalc ma con Epiinfo, perché l'altro programma non permette di valutarla. Gli OR variano leggermente, quindi non so, ometto di aver usato un software differente?

Commento [MB4]: Io non lo metterei nei metodi, come predefinito, ma solo in discussione direi che, visti i risultati, abbiamo testato le interazioni

RESULTS

Sample characteristics

Of 1.119 patients discharged from the five participating wards during recruitment period, 910 were aged ≥65 years and discharged alive; 34 (3.7%) of them refused to give informed consent. After exclusion of patients for whom complete data were not available (mainly body weight and SPMSQ), the baseline sample included 726 patients; its demographic and clinical characteristics, prevalence of and variables associated with IP have been previously reported [26]. Of patients enrolled at baseline, 49 (6.7%) were terminally-ill and 66 (9.1%) were lost at follow-up (Figure 1), leaving a sample of 611 patients for analysis. There were no significant differences in number and prevalence of PIMs and PPOs between patients lost at follow-up and the study sample (Supplementary Table S1). Table 1 shows the characteristics of study patients (mean age 81.6 years, 48.4% females), who had a high prevalence of functional dependence (71.4% in IADL and 48.7% in ADL), frailty (69.4%), and comorbidities (mean CIRS comorbidity index 4.7±1.6, chronic renal disease in 38.5%, moderate-severe cognitive impairment in 28.5%); 65.8% of patients were discharged at home and 34.2% in MLTCF.

These latter were significantly older, more frequently frail and functionally dependent, and showed a higher comorbidity burden, with higher prevalences of moderate-severe cognitive impairment (46.4% vs 19.2%, p <0.001) and other neurological comorbidities (e.g., history of stroke, seizures, intracranial masses, 29.2% vs 17.2%, p < 0.001, and psychiatric and behavioral diseases, including dementia, 49.8% vs 28.9%, p < 0.001). At discharge, 4,683 prescribed medications were recorded, with a mean of 7.7±3.2 prescribed medications per patient. Overall, 1,036 IPs were recorded, with PIMs being more frequent than PPOs (580 vs 456, respectively). At least one IP was observed in 71.7% of patients; 54.8% and 47.3% of patients had at least one PIM and PPO, respectively, with multiple IP being frequent (Figure 2). A full list of recorded PIMs and PPOs and their prevalence is reported as Supplementary Table S2. Patients discharged with at least one IP showed a higher comorbidity burden, IADL dependence and number of drugs at discharge, compared with patients without IP (Supplementary Table S3).

Variables associated with overall mortality and readmission at follow-up

During a mean follow-up period of 6.3±1.0 months, 153 patients (25.0%) died and 189 (30.9%) experienced at least one unplanned hospital readmission; compared with home-discharged patients, MLTCF-discharged patients showed higher mortality (32.1% vs 21.4%) and a lower readmission rate (24.4% vs 34.3%). All-cause mortality did not differ significantly among patients with and without PIMs (26% vs 23.9%) and with and without PPOs (27.3% vs 23.0%). Among patients with at least one PIM, readmission rate was 35.5%, compared with a 25.4% in those without PIMs (*P* value .009); unplanned re-hospitalizations were also significantly higher in patients with at least one PPO than in patients without (36.7% vs 25.8%, *P* value .005). Similar findings were observed when PIMs and PPOs were considered as continuous variables.

Several variables were significantly associated with study outcomes at univariate analysis and

were included in the multivariate model. Table 2 shows variables independently associated with mortality and unplanned hospital readmission in the overall sample and according to discharge setting. In the overall sample and in each discharge setting, PIMs and PPOs (considered as continuous variables) were not associated with mortality, that was significantly associated with ADL dependence, cognitive impairment, renal and hepatic comorbidity in the overall sample. A higher number of PIMs was independently associated with unplanned hospital readmission (OR 1.23, 95%CI 1.03-1.46), along with a higher number of drugs at discharge (OR 1.11, 95%CI 1.05-1.18) and renal disease, while MLTCF discharge was protective (OR 0.64, 95%CI 0.43-0.95). A higher number of PIMs was independently associated with unplanned readmissions in home-discharged patients (OR 1.38, 95%CI 1.13-1.68), along with renal and cardiac comorbidities. In MLTCF-discharged patients unplanned readmissions were associated with a higher number of drugs at discharge (OR 1.27 95%CI 1.13-1.42) and the presence of neurological comorbidity (not including dementia). PPOs were not found to be independently associated with either outcome in the overall sample and in any subgroup analysis. No significant interaction between specific comorbidities, moderate-severe cognitive impairment, functional dependence and significant exposures was found.

Commento [EB5]: Il reviewer 2 commenta "In each analysis, all variables included in the models and their results should be provided in the table - not only those showing significant p:s!", questo non è possibile per il tipo di modello che abbiamo usato, se vuole possiamo mettere l'univariata come supplementary material, ma sinceramente lo eviterei perché poco informativo, possiamo aggiungere la frase prima in rosso.

DISCUSSION

In this prospective study we have evaluated the association of PIMs and PPOs identified according to STOPP/START v2 in a sample of hospital-discharged older patients, with a high prevalence of IP, poor general health and functional status, and high post-discharge overall mortality and readmission rate (25.0% and 30.9%, respectively). The main findings of this study were: 1) PIMs, PPOs and number of drugs at discharge were not significantly associated with all-cause mortality in the overall study sample and in each discharge setting; 2) a higher number of PIMs was significantly associated with unplanned hospital readmission in the overall study sample (OR 1.23, 95%CI 1.03-1.46) and in home-

249 discharged patients (OR 1.38, 95%CI 1.13-1.68); 3) a higher number of drugs at discharge
250 was associated with unplanned hospital readmission in the overall study sample (OR 1.11,
251 95%CI 1.05-1.18) and in MLTCF-discharged patients (OR 1.27, 95%CI 1.13-1.42).

252 Few studies have investigated the impact of IP according to STOPP/START criteria,
253 mainly retrospectively and focusing on ADEs and related healthcare use [20–25]. In a Belgian
254 prospective study on 503 community-dwellers, PPOs according to START v2 were
255 consistently associated with mortality and hospitalization at 18 months [34]. In a recent study,
256 Fabbietti *et al* have shown that, among inpatients, polypharmacy (i.e. >8 medications), but
257 not PIMs according to both Beers 2015 and STOPP v2, was associated with re-hospitalization
258 at 3 months [23]. In a retrospective study investigating the impact of STOPP/START v2 in an
259 inpatient setting, Counter *et al* have demonstrated that the presence of at least one PIM was
260 associated with repeated readmissions (OR 2.43, 95%CI 1.19-4.98), while the presence of at
261 least one PPO was associated with mortality (OR 1.88, 95%CI 1.20-5.28) [25]. In a prospective
262 study on 1,753 community-dwellers, the prevalence of PIMs and PPOs were 57% and 41.8%,
263 respectively, and higher rates of emergency department visits were observed in those with at
264 least one PIM, or with two or more PPOs [21].

265 At odds with some previous studies [25,34], PIMs and PPOs were not significantly
266 associated with all-cause mortality in both discharge settings. However, the study of Wauters
267 *et al.* included community-dwelling subjects with better health and functional status
268 compared with the patients in our study [34], whereas Counter *et al* retrospectively evaluated
269 259 hospital-discharged patients with scant clinical data and no CGA [25]. In a population of
270 older hospital-discharged patients with high short-term mortality, it is very likely that the
271 burden of comorbidities and poor health status may reduce the impact of inappropriate
272 prescribing on hard outcomes such as mortality and unplanned readmissions. Indeed our
273 findings showed that the most significant predictors of mortality in this population are

cognitive impairment and functional dependence, as well as renal and hepatic comorbidities. In keeping with previous studies [21,25,34], we observed that PIMs were associated with increased hospital readmissions in home-discharged patients. Moreover, when considering the low, although significant, association between PIMs at discharge and unplanned hospital readmission, it should be kept in mind that PIMs were included as continuous variables, highlighting their potentially additional detrimental effect. This association appears to be consistent also when age-specific prognostic indicators, such as those included in a CGA, and polypharmacy, are considered. Therefore, although polypharmacy is strongly associated with IP, it seems not necessarily detrimental *per se*, at least in these patients, unless it includes PIMs. The lack of an association between PIMs and re-hospitalization among MLTCF-discharged patients has several potential explanations, including the daily management of these patients by healthcare professionals, potentially allowing timely therapy adjustments and local management of ADEs. On the other hand, we observed that the number of drugs prescribed at discharge, along with concomitant severe neurologic disease, was associated with increased readmissions in MLTCF-discharged patients. Potential interactions between the presence of renal, cardiac, hepatic disease, moderate-severe cognitive impairment or functional dependence and PIMs, PPOs and/or number of drugs at discharge were specifically investigated but no significant interaction was observed.

Eventually, PPOs were not significantly associated with mortality and unplanned re-hospitalization in the overall sample and in each discharge setting. PPOs should be regarded as a warning against the risk of omitting disease-specific therapies of proven efficacy in older patients. However, in a population of older patients, with severe polymorbidity, poor health status and high prevalence of functional dependence and cognitive impairment, and high short term mortality, it is rather unlikely that omission of disease-specific drugs may have clinical implications in patients with high competing risk of mortality.

The multicenter design of the study, the number of patients enrolled, and the prospective collection of a full set of clinical variables represent in our view the main strengths of our study, since they permitted the application of the entire list of STOPP v2 criteria, excluding only a marginal 2.6% of STOPP/START v2 criteria. Moreover, the systematic evaluation of specific geriatric domains, including frailty, functional and cognitive statuses through CGA bestows clinical robustness to our findings, by reducing the potential bias associated with the complex interplay between polypharmacy, comorbidities and health and functional status. To our knowledge, this methodological approach was not used in most previous studies. Still, some limitations of our study must be addressed, besides those specifically pertaining to the application of partially implicit STOPP v2 criteria and the possible underreporting of significant clinical conditions leading to mislabeling prescriptions as PIMs [26]. First, we could not verify the therapeutic compliance of patients or the subsequent changes made to drug prescription both in the community setting and during subsequent hospitalizations. However, the short follow-up period makes it unlikely that therapeutic changes could have biased our results. Moreover, study outcomes were patient- or caregiver-reported and we could not reliably ascertain the cause of death or readmission for many patients; interviews were standardized and detailed to minimize recall bias. Hence, despite statistically significant associations, we were not able to define whether re-hospitalizations were directly due to IP. Therefore, whether PIMs or number of drugs are causally involved in determining hospital readmissions or act as a surrogate marker of the lack of a careful older patient-centered discharge plan remains a matter of discussion.

CONCLUSIONS AND IMPLICATIONS

This study adds to the body of evidence demonstrating that IP and polypharmacy are frequently observed in hospital-discharged patients and may portend a potentially increased risk of unplanned hospital readmission also in older medical-discharged polymorbid patients.

Commento [EB6]: Reviewer 2: Please provide study questions and hypotheses in the last paragraph.

Commento [EB7]:

Further and larger studies are needed to determine the impact of single PIMs or PPOs on clinical outcomes, while intervention studies will hopefully confirm the clinical benefit of addressing IP.

However, our findings suggest once more the importance of performing a systematic and careful review of medication appropriateness in older in-patients in different clinical settings, the so-called and long praised "geriatrician's salute" [35].

Disclosure statement

All authors declare no potential conflict of interest.

REFERENCES

1. Hamilton HJ, Gallagher PF, O'Mahony D. Inappropriate prescribing and adverse drug events in older people. *BMC Geriatr*. 2009;9:5.
2. Hafner JW, Belknap SM, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. *Ann Emerg Med*. 2002;39:258-267.
3. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365:2002-2012.
4. Sona A, Maggiani G, Astengo M, et al. Determinants of recourse to hospital treatment in the elderly. *Eur J Public Health*. 2012;22:76-80.
5. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *Lancet*. 2007;370:185-191.
6. Steinman MA. Polypharmacy and the balance of medication benefits and risks. *Am J Geriatr Pharmacother*. 2007;5:314-316.
7. Kuijpers MAJ, van Marum RJ, Egberts ACG, Jansen PAF, OLDY (OLd people Drugs & dYsregulations) Study Group. Relationship between polypharmacy and underprescribing. *Br J Clin Pharmacol*. 2008;65:130-133.

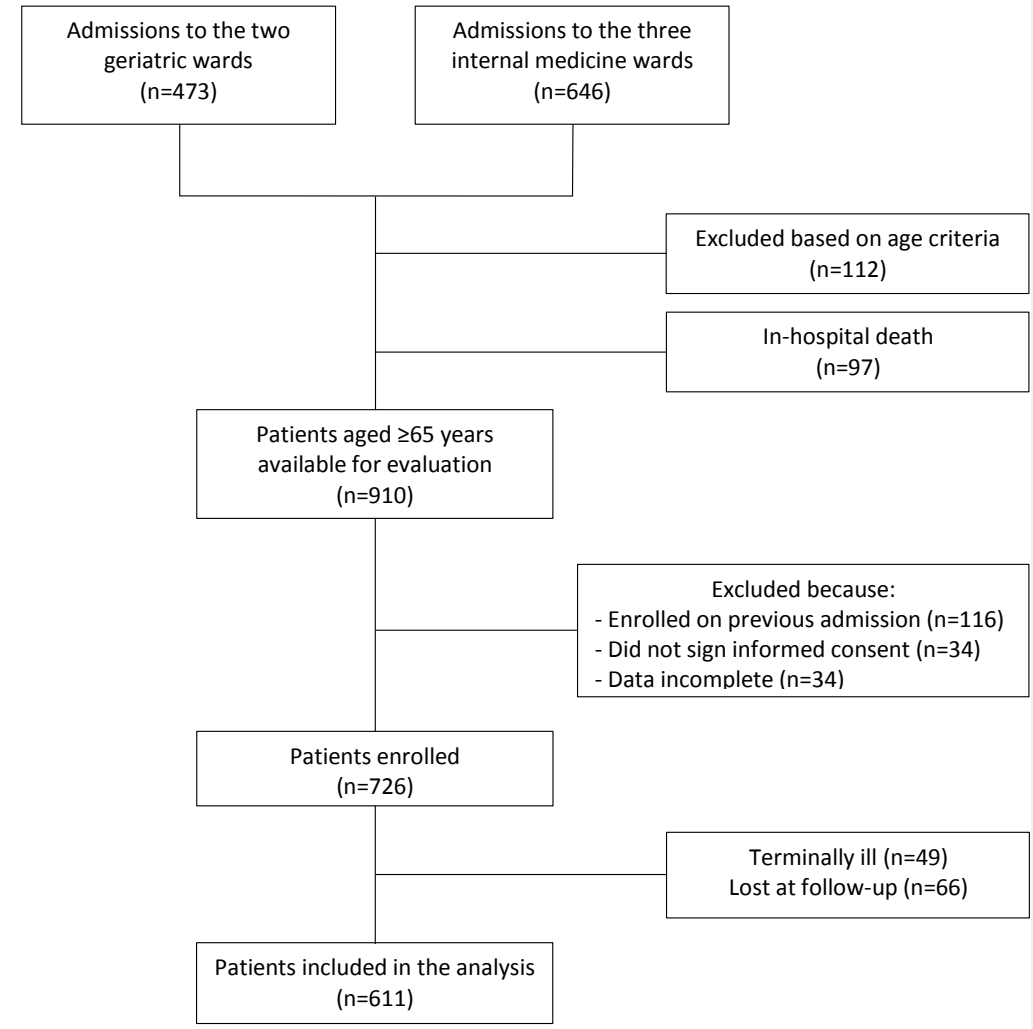
8. Cherubini A, Corsonello A, Lattanzio F. Underprescription of beneficial medicines in older people: causes, consequences and prevention. *Drugs Aging*. 2012;29:463-475.
9. The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2015;63:2227-2246.
10. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet*. 2007;370:173-184.
11. Bo M, Quaranta V, Fonte G, Falcone Y, Carignano G, Cappa G. Prevalence, predictors and clinical impact of potentially inappropriate prescriptions in hospital-discharged older patients: A prospective study. *Geriatr Gerontol Int*. 2018;18:561-568.
12. Pasina L, Djade CD, Tettamanti M, et al. Prevalence of potentially inappropriate medications and risk of adverse clinical outcome in a cohort of hospitalized elderly patients: results from the REPOSI Study. *J Clin Pharm Ther*. 2014;39:511-515.
13. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther*. 2008;46:72-83.
14. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44:213-218.
15. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med*. 2011;171:1013-1019.
16. Onder G, Landi F, Liperoti R, Fialova D, Gambassi G, Bernabei R. Impact of inappropriate drug use among hospitalized older adults. *Eur J Clin Pharmacol*. 2005;61:453-459.

17. Laroche M-L, Charmes J-P, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? *Br J Clin Pharmacol*. 2007;63:177-186.
18. Tosato M, Landi F, Martone AM, et al. Potentially inappropriate drug use among hospitalised older adults: results from the CRIME study. *Age Ageing*. 2014;43:767-773.
19. O'Connor MN, O'Sullivan D, Gallagher PF, Eustace J, Byrne S, O'Mahony D. Prevention of Hospital-Acquired Adverse Drug Reactions in Older People Using Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment Criteria: A Cluster Randomized Controlled Trial. *J Am Geriatr Soc*. 2016;64:1558-1566.
20. Pérez T, Moriarty F, Wallace E, McDowell R, Redmond P, Fahey T. Prevalence of potentially inappropriate prescribing in older people in primary care and its association with hospital admission: longitudinal study. *BMJ*. 2018;363:k4524.
21. Moriarty F, Bennett K, Cahir C, Kenny RA, Fahey T. Potentially inappropriate prescribing according to STOPP and START and adverse outcomes in community-dwelling older people: a prospective cohort study. *Br J Clin Pharmacol*. 2016;82:849-857.
22. Wallace E, McDowell R, Bennett K, Fahey T, Smith SM. Impact of Potentially Inappropriate Prescribing on Adverse Drug Events, Health Related Quality of Life and Emergency Hospital Attendance in Older People Attending General Practice: A Prospective Cohort Study. *J Gerontol A Biol Sci Med Sci*. 2017;72:271-277.
23. Fabbietti P, Di Stefano G, Moresi R, et al. Impact of potentially inappropriate medications and polypharmacy on 3-month readmission among older patients discharged from acute care hospital: a prospective study. *Aging Clin Exp Res*. 2018;30:977-984.

24. van der Stelt C a. K, Vermeulen Windsant-van den Tweel AMA, Egberts ACG, et al. The Association Between Potentially Inappropriate Prescribing and Medication-Related Hospital Admissions in Older Patients: A Nested Case Control Study. *Drug Saf*. 2016;39:79-87.
25. Counter D, Millar JWT, McLay JS. Hospital readmissions, mortality and potentially inappropriate prescribing: a retrospective study of older adults discharged from hospital. *Br J Clin Pharmacol*. 2018;84:1757-1763.
26. Bo M, Gibello M, Brunetti E, et al. Prevalence and predictors of inappropriate prescribing according to the Screening Tool of Older People's Prescriptions and Screening Tool to Alert to Right Treatment version 2 criteria in older patients discharged from geriatric and internal medicine wards: A prospective observational multicenter study. *Geriatr Gerontol Int*. 2019;19:5-11.
27. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-349.
28. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol*. 2012;65:989-995.
29. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914-919.
30. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*. 1969;9:179-186.
31. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23:433-441.

32. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J*. 2005;173:489-495.
33. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. 1968;16:622-626.
34. Wauters M, Elseviers M, Vaes B, et al. Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality, and hospitalization in a cohort of community-dwelling oldest old. *Br J Clin Pharmacol*. 2016;82:1382-1392.
35. Hilmer SN, Gnjidic D. Deprescribing: the emerging evidence for and the practice of the "geriatrician's salute." *Age Ageing*. 2018;47:638-640.

Figure 1



Study flowchart of patient enrolment and follow-up.

457 **Table 1**

458 Main clinical and demographic characteristics of the overall study sample, and stratified

459 according to home or medium/long-term care facility discharge.

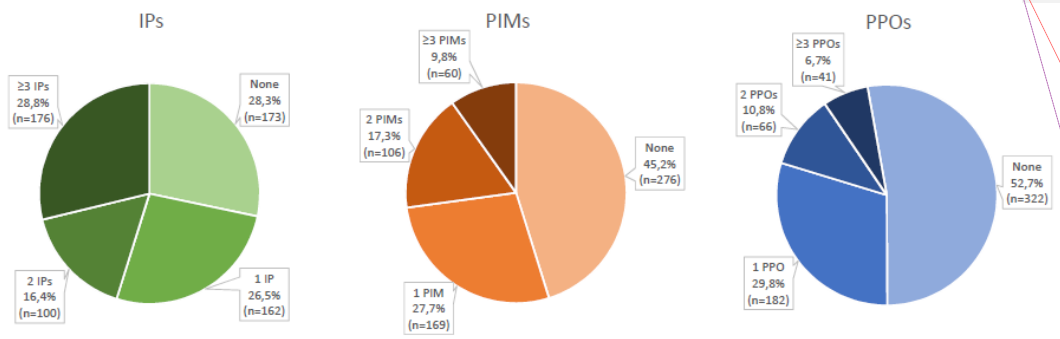
	Overall sample (n=611)	Home discharge (n=402)	MLTCF discharge (n=209)	*p*-value
Age (years), mean ± SD	81.6±7.0	81.0±7.3	82.6±6.6	.008
Female sex, n (%)	296 (48.4)	180 (44.8)	116 (55.5)	.02
Geriatric discharge, n (%)	296 (48.4)	173 (43.0)	123 (58.9)	< .001
Serum creatinine (mg/dl), median (IQR)	0.95 (0.75-1.3)	1.0 (0.79-1.3)	0.86 (0.70-1.2)	< .001
Body weight (kg), median (IQR)	66 (60-74)	68 (60-75)	65 (58-72)	.006
Body weight (kg) for males, median (IQR)	70 (64-76)	70 (65-78)	67 (60-75)	.002
Body weight (kg) for females, median (IQR)	61 (55-70)	62 (55-70)	61 (54-70)	.93
eGFR (ml/min), median (IQR)	50.9 (38.2-65.8)	50.2 (36.5-64.7)	52.2 (40.6-67.5)	.14
Provenience				
Home, n (%)	554 (90.7)	399 (99.3)	155 (74.2)	< .001
MLTCF, n (%)	57 (9.3)	3 (0.75)	54 (25.8)	
Comprehensive geriatric assessment				
ADL dependent, n (%)	287 (47)	159 (39.6)	128 (61.2)	< .001
IADL partially or not autonomous, n (%)	436 (71.4)	249 (61.9)	187 (89.5)	< .001
Moderate-severe cognitive impairment at SPMSQ, n (%)	174 (28.5)	77 (19.2)	97 (46.4)	< .001
Frail according to CSHA, n (%)	424 (69.4)	231 (57.5)	193 (92.3)	< .001
Comorbidities				
CIRS severity index, mean ± SD	1.9±0.3	1.89±0.31	1.87±0.25	.38
CIRS comorbidity index, mean ± SD	4.7±1.6	4.69±1.65	4.73±1.59	.77
Cardiac, n (%)	403 (66)	273 (67.9)	130 (62.2)	.19
Hypertension, n (%)	413 (67.6)	278 (69.2)	135 (64.6)	.29
Vascular and hematological, n (%)	292 (47.8)	189 (47.0)	103 (49.3)	.65
Respiratory, n (%)	237 (38.8)	158 (39.3)	79 (37.8)	.78
Eye, ear, nose, throat, larynx, n (%)	67 (11)	49 (12.2)	18 (8.6)	.23
Upper gastrointestinal tract, n (%)	104 (17.0)	76 (18.9)	28 (13.4)	.11
Lower gastrointestinal tract, n (%)	59 (9.7)	43 (10.7)	16 (7.7)	.29
Hepatic, n (%)	30 (4.9)	21 (5.2)	9 (4.3)	.76
Renal, n (%)	235 (38.5)	171 (42.5)	64 (30.6)	.005
Other genitourinary, n (%)	167 (27.3)	117 (29.1)	50 (23.9)	.21
Musculoskeletal system and skin,	241 (39.4)	141 (35.1)	100 (47.8)	.003

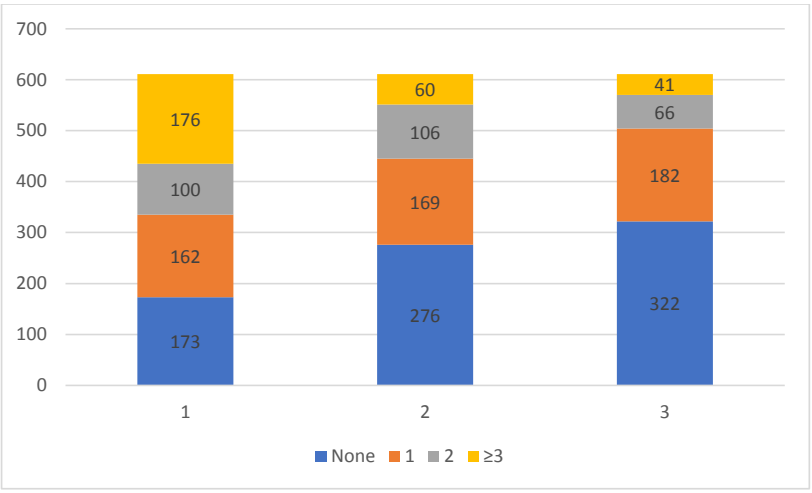
n (%)				
Neurological (not including dementia), n (%)	130 (21.3)	69 (17.2)	61 (29.2)	< .001
Endocrine, metabolic and infective, n (%)	289 (47.3)	195 (48.5)	94 (45)	.46
Psychiatric and behavioral (including dementia), n (%)	220 (36.0)	116 (28.9)	104 (49.8)	< .001
Therapy at discharge				
Number of drugs, mean ± SD	7.7±3.2	7.7±3.2	7.6±3.1	.83
Polypharmacy (≥5 drugs), n (%)	510 (83.5)	337 (83.8)	173 (82.8)	.83
Hyperpolypharmacy (>10 drugs), n (%)	118 (19.3)	77 (19.2)	41 (19.6)	.98
Patients with at least 1 IP, n (%)	438 (71.7)	284 (70.6)	154 (73.7)	.49
IPs per patient, mean ± SD	1.7±1.6	1.6±1.5	1.7±1.8	.11
IPs per patient, median (IQR)	1 (0-3)	1 (0-3)	1 (0-3)	.21
Patients with at least 1 PIM, n (%)	335 (54.8)	217 (54)	118 (56.5)	.62
PIMs per patient, mean ± SD	0.9±1.1	0.9±1.1	0.9±1.2	.72
PIMs per patient, median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	.59
Patients with at least 1 PPO, n (%)	289 (47.3)	184 (45.8)	105 (50.2)	.34
PPOs per patient, mean ± SD	0.7±1	0.7±0.9	0.9±1.2	.03
PPOs per patient, median (IQR)	0 (0-1)	0 (0-1)	1 (0-1)	.16

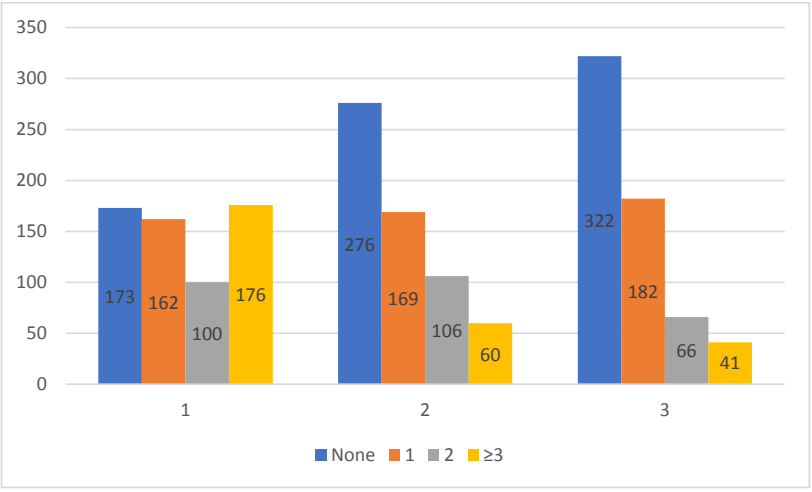
Underlined values indicate statistically significant differences between discharge setting groups.

Abbreviations: ADL =activities of daily living, CIRS = cumulative illness rating scale, CSHA = Canadian Study of Health and Aging, eGFR = estimated glomerular filtration rate, IADL = instrumental activities of daily living, IP = inappropriate prescription, IQR = interquartile range, n= number, MLTCF = medium-long term care facility, PIM = potentially inappropriate medication, PPO = potential prescribing omission, SD = standard deviation, SPMSQ = Short Portable Mental Status Questionnaire

Figure 2







Commento [EB8]: Qui il reviewer 2 vorrebbe in colonne invece che in torta, posto che lo trovo molto meno indicativo, preferisci la versione 1 o 2? (colonne IP/PIMS/PPO)

Commento [MB9]: Come preferisci, direi forse la seconda, è un deficiente, non andiamogli dietro…

Commento [EB10]:

475 Number per patient and prevalence of overall inappropriate prescribing (IP), potentially
476 inappropriate medications (PIMs) and potential prescribing omissions (PPOs) in the overall
477 study sample.
478

Table 2

Variables independently associated with overall mortality and hospital readmission at multivariate analysis in the overall study sample, and according to discharge setting (home vs medium/long-term care facility).

	OR (95% CI)	Coefficient	SE	*p*-value
Overall study sample (n=611)				
Overall mortality				
Female sex	0.64 (0.43-0.95)	-0.4489	0.2074	.03
ADL dependent	2.43 (1.53-3.87)	0.8873	0.2372	< .001
Renal comorbidity	2.52 (1.67-3.78)	0.9231	0.2080	< .001
Hepatic comorbidity	2.59 (1.14-5.84)	0.9500	0.4160	.02
Moderate-severe cognitive impairment at SPMSQ	2.54 (1.59-4.07)	0.9339	0.2399	< .001
Hospital readmission				
Renal comorbidity	1.85 (1.29-2.67)	0.6177	0.1868	< .001
MLTCF discharge	0.64 (0.43-0.95)	-0.4430	0.1995	.03
Number of drugs at discharge	1.11 (1.05-1.18)	0.1063	0.0309	< .001
Number of PIMs	1.23 (1.03-1.46)	0.2048	0.0872	.02
Home-discharged patients (n=402)				
Overall mortality				
Female sex	0.57 (0.34-0.97)	-0.5566	0.2666	.04
ADL dependent	2.24 (1.25-4.00)	0.8050	0.2971	.007
Renal comorbidity	1.84 (1.11-3.06)	0.6096	0.2587	.02
Moderate-severe cognitive impairment at SPMSQ	2.31 (1.21-4.41)	0.8386	0.3291	.01
Hospital readmission				
Cardiac comorbidity	1.68 (1.03-2.74)	0.5168	0.2504	.04
Renal comorbidity	2.38 (1.52-3.71)	0.8651	0.2278	< .001
Number of PIMs	1.38 (1.13-1.68)	0.3216	0.0999	.01
MLTCF-discharged patients (n=209)				
Overall mortality				
Renal comorbidity	4.83 (2.37-9.87)	1.5752	0.3645	< .001
Moderate-severe cognitive impairment at SPMSQ	3.96 (1.97-7.95)	1.3758	0.3558	< .001
Hospital readmission				
Neurological comorbidity	2.37 (1.17-4.81)	0.8642	0.3601	.02
Number of drugs at discharge	1.27 (1.13-1.42)	0.2382	0.0585	< .001

Abbreviations: ADL = activities of daily living, CI = confidence interval, MLTCF = medium-long term care facility, OR = odds ratio, PIM = potentially inappropriate medication, SE = standard error, SPMSQ = Short Portable Mental Status Questionnaire