Potentially Inappropriate Prescribing and Related Hospital Admissions in Geriatric Patients: A Comparative Analysis between the STOPP and START Criteria Versions 1 and 2.

Short Title: Potentially Inappropriate Prescribing and Related Hospital Admissions in Geriatric Patients

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ABSTRACT

Background: Older persons are at significant risk of drug-related admissions (DRA). We previously demonstrated that 27% of hospitalizations in geriatric patients were associated with potentially inappropriate medicines (PIMs) and/or potential prescribing omissions (PPOs) identified by the Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria version 1 (v_1). The updated STOPP/START criteria version 2 (v_2) comprised a 31% increase in prescribing criteria.

Objectives: As a secondary analysis of our study conducted in 2008, we aimed to compare the prevalence and types of DRA identified by STOPP/START.v_1 and STOPP/START.v_2.

Methods: We applied the STOPP/START.v_2 criteria to a subset of 100 consecutively admitted geriatric patients selected from our original cross-sectional study of 302 patients. A geriatrician and a pharmacist adjudicated whether the identified PIMs and PPOs were related to acute hospitalization. Admissions were defined as DRA if the identified PIM(s) and/or PPO(s) were related to the main cause of admission or played a significant contributory role in the admission.

Results: The median patient age was 83 years and the median number of medications at home was 8. Compared to STOPP/START.v_1, STOPP/START.v_2 not only yielded more instances of inappropriate prescribing but also targeted significantly more PIMs and PPOs associated with preventable DRA (23% versus 40% of all admissions, $P<0.001$). PIMs of fall-risk-increasing drugs and PPOs of musculoskeletal and cardiovascular system drugs were most frequently associated with DRA.

Conclusion: The latter instances of inappropriate prescribing with major clinical relevance warrant particular attention during medication review in older persons.

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KEY POINTS

- More drug-related admissions (DRA) in geriatric patients were associated with potentially inappropriate medicines (PIMs) and/or potential prescribing omissions (PPOs) identified by STOPP/START.v_2 compared to STOPP/START.v_1 (40% versus 23% of all admissions), a significant difference.
- Admissions for falls and fractures associated with PIMs of fall-risk-increasing drugs and/or PPOs of musculoskeletal system drugs were the most common type of DRA.
- STOPP/START.v_2 PIMs and PPOs warrant specific attention during medication review in older persons as they are frequently associated with preventable DRA.

1. INTRODUCTION

Hospitalizations resulting from adverse drug events, so-called drug related hospital admissions (DRA), represent a growing patient safety threat in the older population and are associated with adverse clinical and economic outcomes [1-6]. Up to 75% of DRA are potentially preventable [1, 7, 8]. Several studies, including a study conducted by our research group and published in this journal, demonstrated an association between preventable hospitalizations and inappropriate prescribing [9-12]. Inappropriate prescribing encompasses the prescription of more drugs than are clinically needed (overprescribing), the incorrect prescription of drugs that are needed (misprescribing) and the failure to prescribe drugs that are needed (underprescribing) [13].

In 2008, the first version of the STOPP (Screening Tool of Older People's Prescriptions) and START (Screening Tool to Alert to Right Treatment) criteria were developed as an explicit tool to detect potentially inappropriate medicines (PIMs; over- and misprescribing) and potential prescribing omissions (PPOs; underprescribing) [14]. To incorporate the most recent evidence, the STOPP/START criteria version 1 (v_1) have been updated in 2014 [15]. The updated STOPP criteria version 2 (v_2) include the addition of general implicit criteria targeting prescriptions with an inappropriate indication or inappropriate duration of therapy, a list of drugs to monitor in renal insufficiency and vaccines. The main changes in prescribing recommendations occurred for antiplatelet agents, anticoagulants, cardiovascular system, central nervous system and musculoskeletal system drugs, among others. Several criteria from STOPP/START.v_1 have been removed in STOPP/START.v_2 because of weak or equivocal supporting evidence, including the START.v_1 criteria regarding antiplatelet and statin therapy for primary prevention in diabetes mellitus. Changes in recommendations between STOPP/START.v_1 and STOPP/START.v_2 are provided in the electronic supplementary material S1. The STOPP/START criteria v_2 resulted in 80 STOPP and 34 START criteria compared to 65 STOPP and 22 START criteria in version 1, a 31% increase in prescribing criteria [15].

Not surprisingly, research comparing the two versions of the STOPP/START criteria found increased prevalence rates of inappropriate prescribing events with the updated criteria [16, 17]. Yet no studies have evaluated the potential clinical impact of the STOPP/START.v_2 criteria compared to the STOPP/START.v_1 criteria in terms of their association with DRA. As a secondary analysis of our study conducted in 2008, we aimed to compare the prevalence and types of

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DRA identified by STOPP/START.v_2 and STOPP/START.v_1 in a sub-sample of patients selected from our original study.

2. METHODS

For this comparative analysis, the last one hundred consecutively admitted geriatric patients were selected from the original dataset of 302 patients [9]. For pragmatic reasons only a sub-sample of 100 patients was selected and no a priori sample size calculation was performed. The patients were aged 75 years or older, at risk of functional decline (as defined by an Identification of Seniors at Risk (ISAR) score of ≥ 2/6 [18]), and were acutely admitted to non-geriatric units of a teaching hospital in Brussels, Belgium. In the original study, the patients were included by the inpatient geriatric consultation team, a multi-disciplinary team that aims to improve care for older patients admitted to non-geriatric units according to the principles of comprehensive geriatric assessment [19]. The patients' datasets were compiled based on chart review and patient and/or carer interviews and included demographic, clinical and medication data, prospectively collected by the inpatient geriatric consultation team in 2008. Medication data included prescription and over-the-counter medicines taken daily or 'as needed' just before hospitalization.

A geriatrician with expertise in geriatric pharmacotherapy and a last-year medical student (BB & LEM) reviewed the 100 patient datasets to identify PIMs and PPOs using STOPP/START.v_2. Next, a geriatrician and a pharmacist (BB & ST) with experience in geriatric pharmacotherapy and DRA adjudication independently assessed whether these PIMs and PPOs were related to hospitalization and thus a potential DRA. In case of disagreement, a clinical pharmacist with expertise in geriatric pharmacotherapy and DRA adjudication (OD), was involved to establish consensus. For assessing the link between inappropriate prescribing and hospitalization, the adjudicators reviewed the datasets including demographic data, the patient's comorbidities, the patient's home medications, the main admission diagnoses as documented in the discharge letter and the identified PIMs and PPOs present upon admission. In line with the method used in the original study based on STOPP/START.v_1 and the Hallas definition (Table 1), admissions were defined as preventable DRA if the identified PIM(s) and/or PPO(s) were related to the main cause of admission (e.g. hospitalization for gastro-intestinal bleeding and PIMs of antithrombotic agents and/or PPOs of proton pump inhibitors) or played a significant

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contributory role in the admission (e.g. hospitalization for severe diarrhoea with dehydration and PIMs of diuretics; the diuretics might have worsened dehydration) [9, 20].

Inappropriate prescribing events and DRA related to STOPP/START.v_1 for the 100 patients were extracted from our original study for comparison. Descriptive statistics were used to present the data. The McNemar test was performed in the R software package to compare prevalence rates of DRA between STOPP/START.v_2 and v_1. The ratio v_2/v_1 for DRA detected by STOPP/START.v_2 and v_1 was calculated. For patients who presented with ≥ 1 PIM and/or PPO, the positive predictive value of the STOPP/START.v_2 and v_1 criteria for having a related DRA was calculated. Inter-rater reliability for DRA identification between the geriatrician and the pharmacist was determined for the 100 cases by calculating percentage agreement and agreement corrected for chance (Cohen's kappa).

Ethics approval

The ethics committee from the Cliniques universitaires Saint-Luc (Brussels, Belgium) provided approval for anonymous use of the medical record database (reference number B403201111806).

3. RESULTS

The patient characteristics are presented in Table 2. The median age was 83 years and 62% of patients were female. The 100 patients were prescribed a total of 789 daily medications at home with a median number of 8 medications.

As shown in Table 3, applying STOPP/START.v_2 compared to v_1 resulted in a more than three-fold increase in PIMs and a nearly two-fold increase in PPOs. STOPP.v_2 mainly targeted PIMs of medications prescribed without an indication and compared to STOPP.v_1 pointed at more PIMs of benzodiazepines and Z-drugs. START.v_2 targeted more PPOs of calcium, vitamin D, bisphosphonates, ACE-inhibitors and β-blockers, whereas START.v_1 targeted more PPOs of antiplatelet agents and statins including for primary cardiovascular prevention in diabetic patients (17%) (Table 3).

Overall, inappropriate prescribing events (PIMs and/or PPOs) detected by STOPP/START.v_2 compared to STOPP/START.v_1 were related to hospitalization in respectively 40% and 23% of patients. In other words preventable DRA were listed 1.7 times more often in STOPP/START.v_2 compared to STOPP/START.v_1, a significant difference ($P<0.001$). For patients who presented with ≥ 1 PIM and/or PPO, the positive predictive value of STOPP/START.v_2 for a having a related DRA was 0.41 compared to 0.31 for STOPP/START.v_1 (Table 4). Ninety-one percent of DRA related to STOPP/START.v_1 PIMs or PPOs, were adjudicated as being the main cause of admission, compared 85% of DRA related to STOPP/START.v_2. Likewise, respectively 9% and 15% of DRA related to STOPP/START.v_1 and STOPP/START.v_2 were adjudicated as playing a significant contributory role in the admission. There was substantial agreement between the geriatrician and the pharmacist for DRA identification; 90% agreement, κ = 0.79 (95% confidence interval; 0.66-0.91), P<0.001 [21].

Table 4 summarizes the principal reasons for admission and the related PIMs and PPOs. Both STOPP/START.v_1 and v_2 targeted mostly hospitalizations for PIMs of fall-risk-increasing drugs, PPOs of musculoskeletal system drugs and PPOs of cardiovascular system drugs. However the total number of DRA targeted by the updated criteria has nearly doubled. PIM- and/or PPO-related hospitalizations for falls and fractures were the most common DRA, accounting for 45% of DRA according to STOPP/START.v_2. PPO-related hospitalizations for cardiovascular problems (ischaemic heart disease, heart failure, atrial fibrillation) accounted for 33% of DRA according to STOPP/START.v_2. Unlike STOPP/START.v_1, STOPP/START.v_2 also targeted PIM-related admissions for medications prescribed without an evidence-based indication documented in the medical chart, accounting for 7.5% of DRA. For instance one patient was admitted for acute kidney failure and drug rash with eosinophilia and systemic symptoms (DRESS syndrome) and was prescribed allopurinol without evidence of an indication of clinical gout. Other examples of PIM-related admissions for medications prescribed without an indication included admissions for bleeding events with inappropriate prescriptions of NSAIDs, SSRI's and antiplatelet agents.

4. DISCUSSION

We demonstrated that compared to STOPP/START.v_1, STOPP/START.v_2 not only yields more instances of inappropriate prescribing but also targets significantly more PIMs and PPOs associated with preventable DRA (23% *versus* 40% of admissions; P<0.001). These instances of inappropriate prescribing with major clinical relevance warrant particular attention during medication review in older persons. In particular PIMs of fall-risk-increasing drugs and PPOs of musculoskeletal system drugs (vitamin D, calcium, bisphosphonates) were most frequently associated with DRA.

To our knowledge, this is the first study to compare the association between acute hospitalizations and PIMs and PPOs identified by the STOPP/START criteria v_1 and v_2 in geriatric patients. Previous research investigating the association between hospitalizations and inappropriate prescribing according STOPP.v_1 and/or START.v_1 has reported DRA prevalence rates varying from 11% to 27% of admissions, which is in line with our DRA prevalence rate of 23% based on STOPP/START.v_1 [9-12]. Using the STOPP/START.v_2 criteria in the same 100 patients, we found a high DRA prevalence rate of 40%, suggesting that the updated STOPP/START.v_2 criteria have a significantly better potential for targeting PIMs and PPOs associated with preventable medication-related harm.

For the sake of comparison we applied the STOPP/START.v_2 criteria developed in 2014 to prescribing data from 2008. Therefore one might argue that our PIM prevalence of 87% might be an overestimation, yet it is still in line with the PIM prevalence range of 42-89% reported by previous studies that have applied the STOPP.v_2 criteria in the inpatient setting [22]. Few studies have reported PPO prevalence rates using START.v_2 criteria. Our PPO prevalence of 79% is higher than the 69% and 67% prevalence rates reported by Counter and Wauters and colleagues, conducted respectively in the inpatient setting and community setting [22, 23]. However these studies did not include the complete set of START criteria in their analysis.

This study had a number of limitations. Firstly, the mono-centric study design limits the broader international relevance of our findings. Moreover our sample size was small and cases were not selected at random, only the last 100 consecutive patients were included. However the aim of this secondary analysis was to compare the prevalence and types of DRA identified by STOPP/START.v_1 and STOPP/START.v_2. The cross-sectional study design is well-suited to estimate prevalence rates and can give an indication of the association between inappropriate prescribing and DRA, yet it does not allow for definite conclusions regarding the causal relationship. Whether medication review using the STOPP/START.v_2 criteria is effective in reducing DRA in multi-morbid older persons is currently being investigated in a large-scale multi-centre randomized controlled trial called OPERAM (http://operam-2020.eu).

We did not consider patient preferences, life expectancy, exposure length and time until benefit of medications, which are also essential elements for assessment of appropriateness of prescribing, yet these are often undocumented in medical charts [13, 24, 25]. Hindsight bias is another limitation of retrospective chart review; knowing the outcome and its severity may

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influence the adjudication of causation [26]. Finally, DRA adjudication was based on clinical judgment. We did not use a standardized DRA adjudication approach with causality assessment to be in line with the method used in our original study for the sake of comparison [27]. Nevertheless adjudication was performed by a duo of a geriatrician and a pharmacist, which is a recommended approach for evaluation of adverse drug events and there was substantial agreement for DRA identification between both reviewers [28, 29].

5. CONCLUSION

Compared to STOPP/START.v_1, STOPP/START.v_2 not only yields more instances of inappropriate prescribing but also targets significantly more PIMs and PPOs associated with preventable drug-related admissions. These instances of inappropriate prescribing with major clinical relevance warrant particular attention during medication review in older persons. The results of this small cross-sectional study do not allow for definite conclusions regarding the causal relationship between hospital admissions and inappropriate prescribing events, in particular for potential prescribing omissions, and will need to be investigated further with prospective studies.

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TABLES

Table 1: Adjudication of drug-related admissions (DRA) based on the Hallas definition[20]

DRA – Main reason for admission	The inappropriate prescribing event was related to the primary cause of admission and no other diseases or symptoms contributed significantly to the admission.
DRA – Contributory reason for admission	The inappropriate prescribing event played a substantial role in admission but other factors also contributed significantly.
No DRA	The inappropriate prescribing event played a minor or uncertain role and the patient would have been admitted without occurrence of the inappropriate prescribing event. Other symptoms or circumstances were the reason for admission.

Table 2: Patient characteristics (*n* = 100)

Variable	Value
Age (years; median [P_{25}-P_{75}])	83 [79–86]
Female (*n*)	62
Living alone (*n*)	56
No. of medications per patient (median [P_{25}-P_{75}])	8 [6–9]
ISAR score (median [P_{25}-P_{75}])	3 [3–4]
Geriatric syndromes (*n*)	
Previous falls	52
Dependency in ADL (Katz score ≥ 9/24)	31
Malnutrition	22
Cognitive disorder	16
Most frequent morbidities (*n*)	
Hypertension	74
Atherosclerosis	55
Renal failure (GFR <50 ml/min)	43
Atrial fibrillation	35
Diabetes type 2	26
Osteoporosis	20
Depression	22
Main cause of hospitalization (*n*)	
Cardiovascular problems	57
Fall-related problems	27
Gastro-intestinal problems	9
Miscellaneous	7

Abbreviations: ADL, Activities of Daily Living; GFR, Glomerular Filtration Rate

Table 3: Most frequent PIMs and PPOs detected using the STOPP/START criteria version 1 (v_1) and version 2 (v_2) (*n*=100)

	STOPP v_1	**STOPP v_2**	**START v_1**	**START v_2**
Total *n* of PIMs or PPOs	57	206	101	193
Median [P_{25}-P_{75}]) *n* of PIMs/PPOs per patient	0 [0-1]	2 [1–3]	1 [0–2]	2 [1-3]
N of patients with ≥ 1 PIM or PPO	39	87	57	79
Prevalence most frequent PIMs & PPOs (n)				
Drugs without an indication	-	94	-	-
Drugs beyond the recommended duration	-	10	-	-
Duplicate drug class prescriptions	6	6	-	-
Central nervous system				
Benzodiazepines	19	41	-	-
Z-drugs	-	10	-	-
Musculoskeletal system				
Calcium and/or vitamin D	-	-	14	62
Bisphosphonates	-	-	10	23
Cardiovascular system				
ACE-inhibitors	-	-	9	14
β-blockers	10	2	1	18
Antiplatelet agents	8	3	20	6
Statins	-	-	26	17

Abbreviations: PIM, Potentially Inappropriate Medicine; PPO, Potential Prescribing Omission; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions

Table 4: Prevalence of DRA related to STOPP/START criteria v_1 and v_2 (*n* =100)

		STOPP/ START.v_1	STOPP/ START.v_2	Ratio v_2/v_1
Patients with ≥1 PIM and/or PPO (*n*)		75	97	1.29
Total DRA (PIM- and/or PPO-related) (*n*)		23[a]	40[a,b]	1.74[a]
Positive predictive value[c] (95% confidence interval)		0.31 (0.21-0.42)	0.41 (0.31-0.52)	
Patients with ≥1 PIM (*n*)		39	87	2.23
PIM-related DRA (*n*)		11	23[b]	2.09[b]
Reason for admission	***PIMs identified***			
Fall and/or fracture	Benzodiazepines, Z-drugs, neuroleptics, anticholinergics including tricyclic antidepressants	7	14	
Acute kidney failure	Diuretics, xanthine oxidase inhibitors	0	2	
Bleeding	NSAIDs, SSRIs, antithrombotic agents	1	3	
Heart failure exacerbation	NSAIDs	1	1	
Ischaemic heart disease, peak hypertension	NSAIDs	0	1	
Complete heart block	β-blockers (and hypoglycaemia)	1	0	
Syncope associated with Lewy body dementia	Neuroleptics	1	1	
Syncope associated with swallowing disorder	Z-drugs, neuroleptics	0	1	
Patients with ≥1 PPO (*n*)		57	79	1.39
PPO-related DRA (*n*)		12	22[b]	1.83[b]
Reason for admission	***PPOs identified***			
Fall with fracture	Vitamin D; calcium, bisphosphonates	4	8	
Ischaemic heart disease	ACE-Inhibitors, β-blockers, antithrombotic agents, statins	5	7	
Heart failure	ACE-inhibitors	3	5	
Atrial fibrillation	β-blocker	0	1	
COPD exacerbation	Bronchodilators	0	1	

Abbreviations: DRA, Drug-Related Admission; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; PIM, Potentially Inappropriate Medicine; PPO, Potential Prescribing Omission; SSRI, Selective Serotonin Reuptake Inhibitor; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions

[a]Significant difference (McNemar test, $P<0.001$)

[b]As patients could have several inappropriate prescribing events (PIMs/PPOs) related to the admission, the numbers may not add up to the stated totals. For 5/40 DRA related to STOPP/START.v_2 there were both PIMs and PPOs involved. Therefore the reported v_2/v_1 ratio's for PIM-related admissions (2.09) and PPO-related admissions (1.83) are higher than the overall v_2/v_1 ratio (1.74) for DRA related to PIMs and/or PPOs. The latter ratio represents the main study outcome.

[c] Positive Predictive Value: the number of patients with a DRA related to a PIM and/or PPO divided by the number of patients who had ≥ 1 PIM and/or PPO according to STOPP/START.v_1 or v_2 in our sample.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of interest

The authors (Stefanie Thevelin, Leïla El Mounaouar, Sophie Marien, Benoit Boland, Séverine Henrard, Olivia Dalleur) have no conflicts of interest that are directly relevant to the content of this study.

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REFERENCES

1. Parameswaran Nair N, Chalmers L, Peterson GM, Bereznicki BJ, Castelino RL, Bereznicki LR. Hospitalization in older patients due to adverse drug reactions -the need for a prediction tool. Clinical interventions in aging. 2016;11:497-505.
2. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Carkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018.
3. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc (Wash). 2001;41(2):192-9.
4. Leendertse AJ, Van Den Bemt PM, Poolman JB, Stoker LJ, Egberts AC, Postma MJ. Preventable hospital admissions related to medication (HARM): cost analysis of the HARM study. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(1):34-40.
5. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168(17):1890-6.
6. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365(21):2002-12.
7. Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. International journal for quality in health care : journal of the International Society for Quality in Health Care. 2003;15 Suppl 1:i49-59.
8. Franceschi M, Scarcelli C, Niro V, Seripa D, Pazienza AM, Pepe G, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. Drug Saf. 2008;31(6):545-56.
9. Dalleur O, Spinewine A, Henrard S, Losseau C, Speybroeck N, Boland B. Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. Drugs & aging. 2012;29(10):829-37.
10. 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(11):1013-9.
11. van der Stelt CA, Vermeulen Windsant-van den Tweel AM, Egberts AC, van den Bemt PM, Leendertse AJ, Hermens WA, 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(1):79-87.
12. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing. 2008;37(6):673-9.
13. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet (London, England). 2007;370(9582):173-84.
14. 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(2):72-83.
15. 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 and ageing. 2015;44(2):213-8.
16. Boland B, Guignard B, Dalleur O, P.-O. L. Application of STOPP/START and Beers criteria: compared analysis on identification and relevance of potentially inappropriate prescriptions. European Geriatric Medicine. 2016;7(5):416-23.
17. Blanco-Reina E, Garcia-Merino MR, Ocana-Riola R, Aguilar-Cano L, Valdellos J, Bellido-Estevez I, et al. Assessing Potentially Inappropriate Prescribing in Community-Dwelling Older Patients Using

the Updated Version of STOPP-START Criteria: A Comparison of Profiles and Prevalences with Respect to the Original Version. PLoS One. 2016;11(12):e0167586.

18. McCusker J, Bellavance F, Cardin S, Belzile E, Verdon J. Prediction of hospital utilization among elderly patients during the 6 months after an emergency department visit. Ann Emerg Med. 2000;36(5):438-45.

19. Deschodt M, Braes T, Broos P, Sermon A, Boonen S, Flamaing J, et al. Effect of an inpatient geriatric consultation team on functional outcome, mortality, institutionalization, and readmission rate in older adults with hip fracture: a controlled trial. J Am Geriatr Soc. 2011;59(7):1299-308.

20. Hallas J, Harvald B, Gram LF, Grodum E, Brosen K, Haghfelt T, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med. 1990;228(2):83-90.

21. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005;37(5):360-3.

22. 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(8):1757-63.

23. Wauters M, Elseviers M, Vaes B, Degryse J, Dalleur O, Vander Stichele R, 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(5):1382-92.

24. Lang PO, Petrovic M, Dalleur O, Ferahta M, Benetos A, Boland B. The exercise in applying STOPP/START.v2 in vulnerable very old patients: Towards patient tailored prescribing. European Geriatric Medicine. 2016;7(2):176-9.

25. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Archives of internal medicine. 2006;166(6):605-9.

26. Fischhoff B. Hindsight not equal to foresight: the effect of outcome knowledge on judgment under uncertainty. 1975. Qual Saf Health Care. 2003;12(4):304-11; discussion 11-2.

27. Thevelin S, Spinewine A, Beuscart JB, Boland B, Marien S, Vaillant F, et al. Development of a Standardized Chart Review Method to Identify Drug-Related Hospital Admissions in Older People. Br J Clin Pharmacol. 2018.

28. Phansalkar S, Hoffman JM, Nebeker JR, Hurdle JF. Pharmacists versus nonpharmacists in adverse drug event detection: a meta-analysis and systematic review. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2007;64(8):842-9.

29. van Doormaal JE, Mol PG, van den Bemt PM, Zaal RJ, Egberts AC, Kosterink JG, et al. Reliability of the assessment of preventable adverse drug events in daily clinical practice. Pharmacoepidemiol Drug Saf. 2008;17(7):645-54.

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