



# Impact of Pharmaceutical Interventions with STOPP/START and PIM-Check in Older Hospitalized Patients: A Randomized Controlled Trial

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## Abstract

**Introduction** Pharmaceutical interventions can reduce negative outcomes related to potentially inappropriate prescriptions (PIPs).

**Objective** The objective of this study was to compare the impact of interventions on the reduction of PIPs and on different clinical outcomes using two electronic explicit tools.

**Methods** A randomized controlled trial was conducted in patients hospitalized between 2018 and 2019 at the Acute Care for Elders unit at Lausanne University Hospital in Switzerland. A medication review was conducted using PIM-Check in the first arm and STOPP/START in the second arm. Proposed interventions were communicated to the physicians. Clinical outcomes evaluated were incidence of falls, delirium, activities of daily living (ADL), length of stay, number of drugs at discharge and hospital readmission.

**Results** The 123 included patients (60 in the first arm and 63 in the second arm) were  $86.3 \pm 6.6$  years old, had  $3.5 \pm 1.7$  diseases and were treated by  $6.2 \pm 2.7$  drugs at admission. There was a significant decrease in PIPs in each arm, but no significant difference between arms. The deprescription of nervous system drugs was significantly higher with STOPP/START than with PIM-Check (Chi-square  $p = 0.025$ ). ADL scores between home and discharge were significantly higher in the STOPP/START arm than in the PIM-Check arm ( $4.42$  vs  $3.77$ ;  $p = 0.040$ ). The predictors of ADL score improvement were the deprescription of nervous system drugs ( $\beta = 0.423$ ; 95% CI  $0.034$ – $0.812$ ;  $p = 0.033$ ), the use of STOPP/START ( $\beta = 0.798$ , 95% CI  $0.305$ – $1.290$ ;  $p = 0.002$ ) and a shorter length of hospital stay ( $\beta = -0.033$ , 95% CI  $-0.056$  to  $-0.010$ ;  $p = 0.005$ ).

**Conclusions** Although PIM-Check was non-inferior to STOPP/START in reducing the number of PIPs, STOPP/START had a significantly higher impact on ADL. The use of STOPP/START or the deprescription of two nervous system drugs would allow the patient to acquire almost one more basic function of living. On the other hand, a loss of one point on the ADL score was observed per month of hospitalization.

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## 1 Introduction

The aging of the population is associated with multiple chronic pathologies that often lead to use of multiple medicines. The combination of multimorbidity ( $\geq 2$  chronic diseases) [1] and polypharmacy ( $\geq 5$  drugs) [2] increases the complexity of therapeutic management and the prevalence of potentially inappropriate prescriptions (PIPs) [3].

Pharmaceutical interventions, defined as “any activity undertaken by the pharmacist which benefits the patient” [4], can reduce negative health-related outcomes [5, 6] and avoid excess costs [7] related to PIPs. Clinical pharmacists could use explicit tools to support therapeutic optimization,

### Key Points

Two electronic explicit tools, PIM-Check and STOPP/START, significantly reduced potentially inappropriate prescriptions in older inpatients.

The comparison of both tools shows that PIM-Check recommendations may bring a certain complementarity in some areas of pharmacotherapy not covered in the STOPP/START criteria.

A significant improvement of the activity of daily living (ADL) score was achieved by applying the STOPP/START tool for medication review and by the de-prescription of two central nervous systems drugs.

in addition to standard medication review [8]. Explicit tools are “lists of drug-related criteria, which support improvements to the quality of drug therapy and development of interventions” [8], gathered through expert consensus or guidelines.

Many explicit tools have been developed to detect PIPs, of which only two exist in electronic support forms [8] with manual data entry (medications and pathologies) in a web based form. STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment) version 2 criteria [9] is the explicit tool most used in Europe in older patients [10]. It includes 114 criteria: 80 STOPP criteria for drugs to avoid and 34 START criteria for clinically indicated medicines. An electronic form of STOPP/START has been recently made available (<https://synapse-medicine.com/fr/criteres-stopp-synapse-plateforme>). The second tool, PIM-Check (Potentially Inappropriate Medication checklist), is a recent electronic explicit tool (<http://pimcheck.org/>) intended for use in patients in internal medicine [11]. It contains 160 criteria: 74 related to under-prescribing, 36 to over-prescribing, 16 to drug–drug interactions and 34 to other criteria related to drug monitoring, dose adjustment and choice of medication.

Explicit tools have been useful as an aid to the medication revision process to identify PIPs [12], but their clinical benefit and economic impacts have only been shown in a limited number of randomized controlled trials (RCT) [13, 14]. No formal evaluation of the clinical and/or economic impacts of STOPP/STARTv2 or PIM-Check has been performed [8] and there has been no evaluation of the benefit of PIM-Check use in the geriatric population.

The primary objective of this study was to compare the impact of pharmaceutical interventions on the reduction of PIPs using two electronic explicit tools, STOPP/START and PIM-Check. Secondary objectives were to compare the

impact of interventions on the incidence of falls, delirium, activities of daily living (ADL), length of stay (LOS), number of drugs at discharge and hospital readmission between the two study arms.

## 2 Methods

This reporting of the RCT was undertaken in compliance with the Consolidated Standards of Reporting Trials (CONSORT) statement [15, 16].

### 2.1 Trial Design and Participants

A parallel-group RCT (with 1:1 single allocation ratio) was conducted including patients hospitalized between February 2018 and April 2019 in the Acute Care for Elders (ACE) unit at Lausanne University Hospital in Switzerland. Inclusion criteria were the usual admission criteria into the ACE unit: patients aged  $\geq 65$  years with at least one geriatric syndrome (e.g., cognitive impairment, malnutrition, urinary incontinence, history of falls, risk of falling, multiple comorbidities and/or polypharmacy), with acute illnesses and/or exacerbated chronic condition(s) and requiring acute hospitalization. Nearly 90% of the patients are admitted from the emergency department. Exclusion criteria were patients transferred to surgery divisions, intermediate or intensive care units, and patients without informed consent or with a stay  $< 3$  days.

### 2.2 Randomization

Patients' randomization was guided by the random availability of beds in the 28-bed ACE unit. This unit consists of two sub-units, each independently supervised by one attending physician. The first sub-unit has two sectors (A and B) with two medical fellows, and the second sub-unit has two sectors (C and D) with two other medical fellows. One senior geriatrician supervises the entire medical team. The two attending physicians and the four medical fellows change every 3 months in these sub-units. There has been no specific criteria to preferentially admit one patient to one sector or to the other. The first sub-unit (A + B) was considered as the first arm and the second sub-unit (C + D) was considered as the second arm of the RCT. We chose the sub-units rather than patients to restrict pharmaceutical interventions with PIM-Check to the attending physician in charge of one sector of the clinical ward (first arm) and with STOPP/START to the attending physician of the other sector (second arm). This type of randomization ensured a single allocation ratio (1:1), avoided selection bias and minimized contamination of results. The nursing and therapy staff were the same for all

patients hospitalized in the unit regardless of which sub-unit the patient was hospitalized in.

### 2.3 Ethical Approval and Informed Consent

The Canton of Vaud Ethics Committee for Research on Human Beings (CER-VD) of the Swiss Ethical Committees approved the study protocol (N°2017-01972). The clinical trial was registered through the US National Library of Medicine ClinicalTrials.gov (NCT04028583) and the Swiss National Clinical Trials Portal kofam.ch (SNCTP000002784).

Informed consents were obtained from patients or from a therapeutic representative in case of lack of capacity for discernment, as assessed by the physician in charge of the patient.

### 2.4 Interventions

The research pharmacist collected the list of patients admitted to the ACE unit daily. In the first arm, PIM-Check was used as an intervention to optimize pharmacotherapy. In the second arm, STOPP/START was used as the reference gold standard tool. STOPP/START is the most widely used tool in Europe in the geriatric population [10]. No other pharmacists were present in the unit.

For each new patient admitted in the first sub-unit (sector A or B) or the second sub-unit (sector C or D), a medication review was performed by the pharmacist using PIM-Check or STOPP/START, respectively, within 72 hours of the patient's admittance to the unit, using information in the medical records. Recommendations identified by the tools were printed and transmitted to the attending physician in charge of the patient. The latter decided whether to accept these recommendations or not, and implemented prescribing changes if agreed. The decision for each recommendation was documented and the pharmacist verified the implementation of modifications in the electronic patient record. The outpatient physician was informed about all the changes made to the patients' usual therapy regimen.

### 2.5 Blinding

Patients were blinded on the type of intervention (i.e. PIM-Check or STOPP/START), the presence of recommendations or not and the decision of the physicians. Attending physicians in charge of patients were not blinded.

### 2.6 Prescriptions Assessment After Discharge

Following patients' discharge, a medication review was performed, using the gold standard STOPP/START, by the

pharmacist to quantify the reduction of PIPs on (i) records at admission for patients of the first arm and (ii) records at discharge for all patients (first and second arm). In case a problem was detected affecting the safety of a patient, the physician in charge of the patient was informed to evaluate the problem and to contact the outpatient's physician if necessary.

### 2.7 Data, Outcomes and Endpoints

Patients' information relevant to the study were extracted from the computerized patient records and coded. Data was collected using case report forms (CRF) that included baseline characteristics, outcomes and endpoints. The baseline characteristics were information on basal sociodemographic characteristics (e.g. sex, age, body mass index, marital status), lifestyle (e.g. smoking, alcohol intake) and active co-morbidities. The outcomes measured were number and prevalence of PIPs, number of interventions and their acceptance rate, number of prescribed medications (at admission and discharge), number of falls, ADL scores at home (2 weeks before admission) at admission and discharge, delirium during hospitalization (acute confusional state), LOS, short- and long-term re-hospitalization (i.e. within 1 and 3 months after discharge). The primary endpoint was the percentage of PIPs reduction between admission and discharge per arm and the number of PIPs decrease according to the gold standard STOPP/START, and secondary endpoints were (i) the variation in the number of drug prescriptions between admission and discharge and (ii) the ADL scores variation (between home, admission and discharge).

Medications were classified using the Anatomical Therapeutic Chemical (ATC) Classification System of the World Health Organization [17]. The variation in the number of drug prescriptions between admission and discharge was presented as prescribing, no change and deprescribing.

Falls were defined as an event where the person suddenly, involuntarily and unexpectedly comes to rest on the ground or a lower level with or without injury [18]. Falls during hospitalization are documented by nurses after each incident.

Assessment of ADL was based on the ability/inability of the subject to perform the following routine activities: eating, bathing, getting dressed, toileting, transferring and continence. The score reflects the number of activities performed without assistance and ranges from 0 to 6. Higher values represent a better outcome of ADL. ADL scores are routinely evaluated by nurses and documented in computerized patient records. Improving ADL in older patients is an imperative of care for such a vulnerable population and not just a significant outcome.

The Confusion Assessment Method (CAM) is based on four essential features of delirium: (i) acute onset and

fluctuating course, (ii) inattention, (iii) disorganized thinking and (iv) altered level of consciousness. An identification of delirium according to the CAM diagnostic algorithm (positive result) requires the presence of features 1, 2 and either 3 or 4 [19]. The CAM is routinely performed by nurses and documented in computerized patient records.

## 2.8 Personal Data Protection and Anonymization

The personal data of all patients was treated with respect to their privacy and confidentiality in accordance with the regulatory aspects of good clinical practice. Signed informed consents with patient name, date of birth and signature of the patient or the therapeutic representative (a person designated by the patient who is allowed to make medical decisions on behalf of the patient) were kept locked. An identification code (ID) was attributed to each patient formally included and the 'subject identification code list' was kept locked and separated from the informed consents. The CRF were completed with respect of patients' privacy and anonymity. CRF identified patients only by their ID and were kept locked separately from the informed consents and code list. CRF data were securely computerized in software for data analysis. A sample of 10% of CRF was randomly chosen to verify the correct entry of data.

## 2.9 Data Analysis

Descriptive results were stratified per arm for baseline characteristics, active diseases, prescribed drugs at admission and discharge, prevalence of patients with at least one PIP, number of interventions and their acceptance rate. Several comparisons between arms were performed to address the decrease in PIPs as a primary outcome of the non-inferiority trial and different clinical outcomes. They consisted of (i) the percentage of PIPs reduction between admission and discharge per arm and the number of PIPs decrease according to the gold standard STOPP/START, (ii) the number of prescribed, deprescribed or unchanged drugs per arm, (iii) the prevalence of falls and delirium during hospitalization, the ADL scores with their variations (between home, admission and discharge), the LOS and the prevalence of hospital readmission. Finally, predictors of ADL variation between discharge and home were tested using linear regression.

The impact of interventions was analysed on all included patients and was not restricted to patients with accepted interventions, in order to avoid bias of results. The use of the same tool by an attending physician can affect the prescribing practices. A physician may avoid

inappropriate drug prescriptions if many related recommendations have already been accepted for other patients. This will not be the case for the attending physician of the other arm, who may continue to prescribe the same inappropriate drug.

Results are presented in the form of descriptive and comparative analyses. Categorical variables are presented in proportions with percentages; continuous variables are presented in means with standard deviations (SD) or medians with interquartile range. According to the distribution of the variables and their types, Chi-Square Test or Fisher's exact test were used for categorical variables to compare proportions; and Student's *t*-test or non-parametric Wilcoxon-Mann-Whitney U test were used for continuous variables to compare means between arms. Multivariate linear regressions were performed to identify factors potentially affecting clinical outcomes. Dependent variables were the clinical outcomes and independent variables were those giving a *p*-value <0.2 in the bivariate analyses and variables with a potential influence. Conditions of normality, linearity and homoscedasticity were checked for the linear regressions. All analyses were performed with SPSS (Statistical Package for the Social Sciences) version 23. An association was considered significant with a *p*-value <0.05.

## 2.10 Sample Size Calculation

The sample size has been calculated based on the expected prevalence and reduction of PIPs. According to STOPP/START criteria, prevalence of PIPs of 90% has been measured in the same setting of this study (ACE at Lausanne University Hospital in Switzerland) [20]. A reduction of 22% of the prevalence of patients with at least one PIP at discharge after intervention was measured using STOPP criteria in older hospitalized patients in Switzerland [21].

Assuming a non-inferiority of PIM-Check in reducing PIPs compared with STOPP/START, a prevalence of PIPs of 90% and a reduction of 22% (with a maximal tolerated margin difference of 10% between both tools), using a power of 95% and a significance level (alpha, 1-tailed) of 0.05, a sample size of 104 patients (52 in each arm) is required.

## 2.11 Pilot Study Preceding the Trial

A pilot study was conducted after the approval of the ethics committee and before the beginning of the clinical trial in order to properly implement the study in the service. Patients of the pilot study were excluded from the RCT analysis and results.

## 3 Results

### 3.1 Baseline Data

During the study period, 123 patients were randomized to receive pharmaceutical interventions with either the PIM-Check or STOPP/START. Patients were aged 86.3 years ( $SD \pm 6.6$ ), had 3.5 diseases ( $SD \pm 1.7$ ) and were receiving treatment with 6.2 drugs at admission ( $SD \pm 2.7$ ) as means. The majority were female (74.8%), 62.6% were polymedicated (5–9 drugs) and 10.6% were highly polymedicated ( $\geq 10$  drugs). The majority were non-smokers (80.5%), non-alcohol users (84.6%) and living alone (72.4%) (Table 1).

As shown in Table 2, the most prevalent active diseases were hypertension, osteoporosis, kidney failure, dyslipidemia, atrial fibrillation, diabetes mellitus, ischemic heart disease and heart failure. The most common prescribed drugs at admission and discharge according to the ATC classification were for the alimentary tract and metabolism (among which more than half were vitamin D and calcium), cardiovascular system, nervous system, and blood and blood-forming organs (e.g. antithrombotics, antihemorrhagics, antianemic preparations) (Table 2).

In the PIM-Check and STOPP/START arms, 60 and 63 patients were included, respectively. There were no significant differences at baseline between the two arms in terms of sex, age, smokers, alcohol users, living status, marital status, BMI, number of medications, number of diseases and number of hospitalizations in the preceding year. One patient from the second arm died 37 days after admission (89 years, 2 diseases, 3 drugs, BMI 29.7, no PIPs identified according to the tools at admission).

### 3.2 Impact of Interventions on Prescribing Errors

At admission, the prevalence of PIPs was 78.3% in the PIM-Check arm and 56.5% in the STOPP/START arm.

The mean number of PIM-Check interventions/patient was 2.25 ( $n = 135$  interventions) with a 32% acceptance rate ( $n = 43/135$ ) and the mean number of STOPP/START interventions/patient was 0.82 ( $n = 51$  interventions) with a 43% acceptance rate ( $n = 22/51$ ). Thirty percent of the interventions recommended by the tools were deemed pertinent to patients in both arms. Duplicates (same suggestion for intervention identified in more than one criteria; 6% for PIM-Check and 13% for STOPP/START recommendations) and non-pertinent inapplicable suggestions (64% of PIM-Check and 57% of STOPP/START recommendations) were eliminated by the pharmacist before being transmitted to the attending physician in charge of the patient.

The percentage of PIPs decrease (prevalence of patients with a decrease in the number of PIPs between admission

and discharge) was 31% and 34% in PIM-Check and STOPP/START arms, respectively ( $p = 0.825$ ). The comparison of the reduction of PIPs between the two arms was not significant, indicating that PIM-Check is non-inferior to the gold standard STOPP/START.

The mean number of PIPs decrease per patient between admission and discharge, evaluated by the STOPP/START tool as the gold standard, did not reveal any significant differences between the two arms (0.35 and 0.34, respectively,  $p = 0.954$ ) (Table 3).

### 3.3 Number of Prescribed Drugs

At discharge, the prevalence of patients with hyper-polyparmacy (treated with  $\geq 10$  drugs) was higher in the PIM-Check arm than the STOPP/START arm (23.3% vs 8.1%;  $p = 0.049$ ).

PIM-Check detected more prescribing omissions than START. Out of the same number of prescribed drugs at admission (6.23 vs 6.14 drugs/patient), the number of drugs at discharge was higher in the PIM-Check arm than in the STOPP/START arm (7.13 vs 6.56 drugs/patient). The prevalence of patients with an increase in the number of prescribed drugs between admission and discharge was significantly higher in the PIM-Check arm than the STOPP/START arm (45% vs 25.8%;  $p = 0.023$ ) (Table 3).

Table 4 summarizes the prevalence of prescribed, de-prescribed or unchanged drugs per arm according ATC class. The variation in the number of drugs related to nervous system ATC class was different between the two arms, where the number of medications increased in the PIM-Check arm and decreased in the STOPP/START arm. The prevalence of prescribing nervous system drugs was significantly higher in the PIM-Check arm and the prevalence of deprescribing was significantly higher in the STOPP/START arm ( $p = 0.025$ ) (Table 4). For all other classes of drugs, no difference was observed.

The percentage of nervous system drugs was 15% at admission (112/761 drugs) and the prevalence of patients treated by at least one nervous system drug was 54% at admission (67/123 patients). All classes of central nervous system drugs were represented, except anesthetics (N01), and included analgesics (N02,  $n = 11$ ), antiepileptics (N03,  $n = 4$ ), anti-Parkinson drugs (N04,  $n = 15$ ), psycholeptics (N05,  $n = 46$ , e.g. zolpidem in 12 patients), psychoanaleptics (N06,  $n = 35$ , e.g. escitalopram in 10 patients) and other nervous system drugs (N07,  $n = 1$ ).

**Table 1** Sample characteristics at baseline

Baseline characteristics	PIM-Check arm <i>n</i> = 60	STOPP/START arm <i>n</i> = 63	Total <i>N</i> = 123
Sex, <i>n</i> (%)			
Male	14 (23.3%)	17 (27%)	31 (25.2%)
Female	46 (76.7%)	46 (73%)	92 (74.8%)
Age, mean (SD)	87.15 ( $\pm$ 6.44)	85.44 ( $\pm$ 6.76)	86.25 ( $\pm$ 6.63)
Age, <i>n</i> (%)			
69–74	2 (3.3%)	4 (6.3%)	6 (4.9%)
75–84	18 (30%)	19 (30.2%)	37 (30.1%)
85–94	33 (55%)	38 (60.3%)	71 (57.7%)
95–102	7 (11.7%)	2 (3.2%)	9 (7.3%)
BMI, mean (SD)	24.24 ( $\pm$ 5.86)	24.36 ( $\pm$ 6.44)	24.30 ( $\pm$ 6.14)
BMI, <i>n</i> (%)			
Underweight < 18.50	9 (15%)	9 (14.3%)	18 (14.6%)
Normal range 18.50–24.99	32 (53.3%)	31 (49.2%)	63 (51.2%)
Overweight 25.00–29.99	7 (11.7%)	14 (22.2%)	21 (17.1%)
Obese $\geq$ 30.00	12 (20%)	9 (14.3%)	21 (17.1%)
Smoking, <i>n</i> (%)			
Yes	9 (15%)	10 (15.9%)	19 (15.4%)
No	49 (81.7%)	50 (79.4%)	99 (80.5%)
Ex	2 (3.3%)	3 (4.8%)	5 (4.1%)
Alcohol use, <i>n</i> (%)			
Yes	7 (11.7%)	9 (14.3%)	16 (13%)
No	51 (85%)	53 (84.1%)	104 (84.6%)
Previous	2 (3.3%)	1 (1.6%)	3 (2.4%)
Living, <i>n</i> (%)			
Alone (at home)	42 (70%)	47 (74.6%)	89 (72.4%)
With others (at home or in an institution)	18 (30%)	16 (25.4%)	34 (27.6%)
Marital status, <i>n</i> (%)			
Single	8 (13.3%)	9 (14.3%)	17 (13.8%)
Married	13 (21.7%)	15 (23.8%)	28 (22.8%)
Separated	1 (1.7%)	0 (0%)	1 (0.8%)
Widowed	36 (60%)	36 (57.1%)	72 (58.5%)
Divorced	2 (3.3%)	3 (4.8%)	5 (4.1%)
Number of drugs at admission, mean (SD)	6.23 ( $\pm$ 2.66)	6.14 ( $\pm$ 2.79)	6.19 ( $\pm$ 2.72)
Number of drugs at admission, <i>n</i> (%)			
< 5	14 (23.3%)	19 (30.2%)	33 (26.8%)
5–9	39 (65%)	38 (60.3%)	77 (62.6%)
$\geq$ 10	7 (11.7%)	6 (9.5%)	13 (10.6%)
Number of active diseases, mean (SD)	3.42 ( $\pm$ 1.79)	3.49 ( $\pm$ 1.53)	3.46 ( $\pm$ 1.66)
Number of active diseases, <i>n</i> (%)			
< 5	43 (71.7%)	47 (74.6%)	90 (73.2%)
$\geq$ 5	17 (28.3%)	16 (25.4%)	33 (26.8%)
Number of hospitalizations in the last year, <i>n</i>			
No hospitalizations	31 (51.7%)	36 (57.1%)	67 (54.5%)
At least one	29 (48.3%)	27 (42.9%)	56 (45.5%)
Number of hospitalizations in the last year, mean (range)	0.87 (0–5)	0.68 (0–3)	0.77 (0–5)

*BMI* body mass index, *SD* standard deviation

**Table 2** Diseases and treatments

	PIM-Check arm	STOPP/START arm	Total
Most frequent active co-morbidities: <i>n</i> = 123			
Hypertension	43	43	86 (70%)
Osteoporosis	15	26	41 (33%)
Kidney failure	13	24	37 (30%)
Dyslipidemia	12	18	30 (24%)
Atrial fibrillation	16	12	28 (23%)
Diabetes mellitus (type 2)	12	10	22 (18%)
Ischemic heart disease	10	11	21 (17%)
Heart failure	1	17	18 (15%)
Hypothyroidism	7	8	15 (12%)
Other	76	51	127
Total	205	220	425
Drugs classes at admission (according to ATC classification): <i>n</i> = 123			
Alimentary tract and metabolism	123	132	255
Cardiovascular system	112	109	221
Nervous system	58	54	112
Blood and blood-forming organs	47	63	110
Systemic hormonal preparations, excluding sex hormones and insulins	10	11	21
Respiratory system	10	3	13
Musculo-skeletal system	5	7	12
Genito-urinary system and sex hormones	5	4	9
Anti-infectives for systemic use	3	0	3
Antineoplastic and immunomodulating agents	0	3	3
Sensory organs	1	1	2
Total	374	387	761
Drugs classes at discharge (according to ATC classification): <i>n</i> = 122			
Alimentary tract and metabolism	160	159	319
Cardiovascular system	117	102	219
Nervous system	69	51	120
Blood and blood-forming organs	48	66	114
Systemic hormonal preparations, excluding sex hormones and insulins	10	11	21
Respiratory system	11	3	14
Musculo-skeletal system	3	7	10
Genito-urinary system and sex hormones	5	4	9
Anti-infectives for systemic use	2	0	2
Antineoplastic and immunomodulating agents	0	3	3
Sensory organs	3	1	4
Total	428	407	835

### 3.4 Clinical Impact of Interventions

#### 3.4.1 ADL, Falls, Delirium, LOS and Hospital Readmission

The mean ADL score between PIM-Check and STOPP/START arms were, respectively, 4.90 and 4.71 ( $p = 0.483$ ) at home (2 weeks before admission) and 3.11 and 3.24 at admission ( $p = 0.682$ ). The mean ADL score at discharge was significantly lower in the PIM-Check arm than in the STOPP/START arm (3.77 and 4.42, respectively;  $p = 0.040$ )

(Fig. 1 and Table 3). In addition, the mean ADL score decreased significantly more in the PIM-Check arm than in the STOPP/START arm ( $-1.13$  and  $-0.29$ , respectively;  $p = 0.001$ ) between the values at home and at hospital discharge (Table 3).

In the PIM-Check arm, there were significantly more patients with a decrease in ADL mean score (51.7% vs 30.6%) and fewer patients with an increase (6.7% vs 17.7%) or no change (41.7% vs 51.6%) in this score than in the

**Table 3** Potentially inappropriate prescriptions (PIPs) and clinical outcomes

Outcomes	PIM-Check arm <i>n</i> = 60	STOPP/START arm <i>n</i> = 62	<i>p</i> value
<b>A. Potentially inappropriate prescriptions (PIPs)</b>			
1) Prevalence of patients with at least one error			
- Admission	78.3%	%	
- Discharge	63.3%	38.7 %	
2) Mean number of PIPs per patient			
- Admission	2.25 ( <i>n</i> = 135/60)	0.82 ( <i>n</i> = 51/62)	
- Discharge	1.52 ( <i>n</i> = 91/60)	0.48 ( <i>n</i> = 30/62)	
3) Interventions at admission, <i>n</i> (%)			
- Accepted	43 (32%)	22 (43%)	
- Not accepted	92 (68%)	29 (57%)	
4) Percentage of PIPs decrease	31%	34%	0.825
5) Mean number of PIPs decrease per arm according to STOPP/START from admission to discharge	0.35	0.34	0.954
<b>B. Clinical outcomes</b>			
1) Falls during hospitalization, <i>n</i> (%)			> 0.999
- No falls	57 (95%)	59 (95.2%)	
- At least one fall	3 (5%)	3 (4.8%)	
2) Delirium during hospitalization, <i>n</i> (%)			0.677
- CAM –	57 (95%)	60 (96.8%)	
- CAM +	3 (5%)	2 (3.2%)	
3) ADL at home, mean	4.90	4.71	0.483
4) ADL at admission, mean	3.11	3.24	0.682
5) ADL at discharge, mean	3.77	4.42	<b>0.040</b>
6) ADL variation (discharge–admission), mean	+ 0.65	+ 1.18	<b>0.003</b>
7) ADL variation (discharge–home), mean	– 1.13	– 0.29	<b>0.001</b>
8) ADL variation (discharge–home), <i>n</i> (%)			
- Increase	4 (6.7%)	11 (17.7%)	<b>0.031</b>
- No change	25 (41.7%)	32 (51.6%)	
- Decrease	31 (51.7%)	19 (30.6%)	
9) Mean LOS	12.67	14.05	0.478
10) Number of drugs at discharge, mean	7.13	6.56	0.252
11) Number of drugs at discharge, <i>n</i> (%)			<b>0.049</b>
< 5	12 (20%)	11 (17.7%)	
5–9	34 (56.7%)	46 (74.2%)	
≥ 10	14 (23.3%)	5 (8.1%)	
12) Prescribed drugs variation, <i>n</i> (%)			<b>0.023</b>
- Increase	27 (45%)	16 (25.8%)	
- No change	22 (36.7%)	38 (61.3%)	
- Decrease	11 (18.3%)	8 (12.9%)	
13) Mean number of drugs variation (discharge–admission)	+ 0.90	+ 0.37	0.116
14) Hospital readmission during the first month after discharge			0.346
- No readmission	52 (86.7%)	57 (91.9%)	
- One readmission	8 (13.3%)	5 (8.1%)	
15) Hospital readmission during the first 3 months after discharge			0.780
- No readmission	43 (71.7%)	43 (69.4%)	
- At least one readmission	17 (28.3%)	19 (30.6%)	

Bold values correspond to “statistically significant” results (*p* value < 0.05)

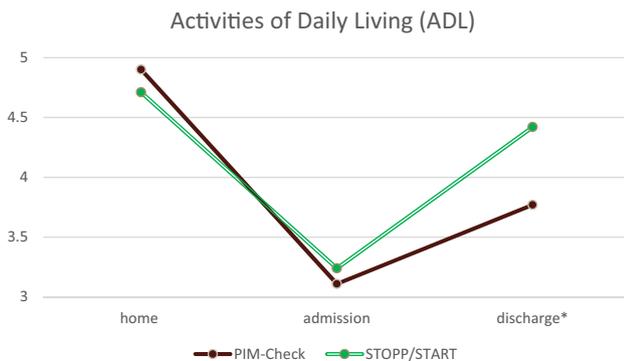
ADL activities of daily living, CAM Confusion Assessment Method, LOS length of stay, SD standard deviation

**Table 4** Drug class variations between admission and discharge

Difference between admission and discharge	<i>p</i> -value	PIM-Check arm <i>n</i> (%)	STOPP/START arm <i>n</i> (%)	Total <i>n</i> (%)
Drugs related to alimentary tract and metabolism ATC class (ATC class A)	0.204			
Prescribing		22 (36.7)	15 (24.2)	37 (30.3)
No change		35 (58.3)	46 (74.2)	81 (66.4)
Deprescribing		3 (5)	1 (1.6)	4 (3.3)
Drugs related to cardiovascular system ATC class (ATC class C)	0.212			
Prescribing		11 (18.3)	5 (8.1)	16 (13.1)
No change		32 (53.3)	40 (64.5)	72 (59)
Deprescribing		17 (28.3)	17 (27.4)	34 (27.9)
Drugs related to nervous system ATC class (ATC class N)	<b>0.025</b>			
Prescribing		<b>16</b> (26.7)	5 (8.1)	21 (17.2)
No change		37 (61.7)	48 (77.4)	85 (69.7)
Deprescribing		7 (11.7)	<b>9</b> (14.5)	16 (13.1)

Bold values correspond to “statistically significant” results ( $p$  value < 0.05)

ATC Anatomical Therapeutic Chemical, *n* (%) number of patients (prevalence)



**Fig. 1** ADL variation between groups. \*Significant difference between STOPP/START and PIM-Check

STOPP/START arm ( $p = 0.031$ ) between home and discharge (Table 3).

No significant differences were found between the two arms in the occurrence of falls and delirium, in LOS and in hospital readmission. The prevalence of falls during hospitalization was the same in the PIM-Check and STOPP/START arms (5% and 4.8%, respectively;  $p > 0.999$ ), equivalent to an incidence of falls of 3.9 and 3.4 falls per 1000 days'

hospitalization, respectively. There was no significant difference in the prevalence of delirium status between arms at discharge (5% and 3.2%, respectively;  $p = 0.677$ ). The mean LOS was the same in both arms (12.67 and 14.05 days, respectively;  $p = 0.478$ ). There was no significant difference in the prevalence of hospital readmission within 3 months after discharge between arms (28.3% and 30.6%, respectively;  $p = 0.780$ ).

### 3.5 Predictors of ADL Improvement

The linear regression conducted to identify factors affecting ADL is presented in Table 5. In the multivariate analysis, the independent predictors of ADL score improvement (increase in the ADL score between home and discharge) were (i) the deprescription of nervous system drugs during hospitalization, (ii) the use of STOPP/START and (iii) a shorter hospital stay. Results of the regression indicate that the deprescription of two nervous system drugs or the use of STOPP/START predicts a similar improvement in the ADL score by almost + 1. The LOS had a negative effect on ADL, indicating a decrease in the ADL score by 1 point per month of hospitalization.

**Table 5** Factors affecting activities of daily living

Dependent variable	Predictors	Beta	Standard error	Confidence interval (95%)	<i>p</i> value
ADL	Deprescribing nervous system drugs	0.423	0.196	0.034–0.812	0.033
	STOPP/START	0.798	0.249	0.305–1.290	0.002
	LOS	– 0.033	0.012	– 0.056 to – 0.010	0.005

ADL activities of daily living, LOS length of stay

## 4 Discussion

This study evaluated the usefulness of new supporting electronic tools in clinical practice and compared the impact of PIM-Check interventions with that of STOPP/START in older patients. This study confirmed that explicit tools reduce the number of PIPs and showed an overall similar impact of PIM-Check compared with STOPP/START in PIPs reduction. Regarding clinical outcomes, a significant association was observed between ADL score and STOPP/START, in addition to the deprescription of central nervous system drugs and length of stay.

A prospective interventional study showed that STOPP/START recommendations, provided to prescribers, decreased PIPs at discharge in older inpatients [22]. Our findings identified a similar mean number of PIPs decrease per patient between both arms using STOPP/START as the reference tool, and a similar percentage of PIPs decrease between arms. The number of interventions at admission was higher in the PIM-Check arm, but with a lower acceptance rate than STOPP/START, which could reflect the more specific recommendations of STOPP/START towards older patients. Yet, the high number of PIM-Check recommendations may bring a certain complementarity in other areas of pharmacotherapy not covered in the STOPP/START criteria [20].

The reduction of PIPs is expected to prevent iatrogenic effects, which is a major issue in the geriatric population. A few studies have shown a clinically relevant impact of the use of such tools in reducing fall [23]. In line with previously reported data prospectively assessing the impact of STOPP/START (version 1) interventions versus standard hospital care in older patients in a larger study population, our study did not detect any positive influence of the intervention on the incidence of falls nor on hospital readmission [14, 24]. One RCT using the FORTA (Fit FOR The Aged) tool or standard care ( $n = 58$  intervention vs  $n = 56$  control) [23] reported a significant positive impact of tool-based interventions on falls (prevalence 3.4% vs 21.4% in the control group with standard of care) in older patients. Yet, our results indicate an association between the use of the STOPP/START tool and the ADL score. The gain of one point on the ADL score by using STOPP/START and the loss of one point per month of hospitalization is clinically relevant. A similar improvement in ADL was also observed with the deprescription of two central nervous system drugs. It is expected that the addition of multiple nervous system drugs, to which older patients are more sensitive, can affect the cognitive abilities of older patients and therefore their daily living. A thorough revision of the indication and the dosage of such drugs should be performed. The loss of ADL is an important health

problem that impacts the quality of life of older adults and the nursing burden of their family. It can be expected that ADL will decrease from home to admission, as a consequence of the acute disease leading to hospitalization. The therapeutic objective of the hospital stay is then to increase the ADL to the baseline value or even to higher scores. We observed that the ADL increased significantly more in the STOPP/START arm than in the PIM-Check, to reach a higher score at discharge. Our results are consistent with a study [25] that detected a significant impact of interventions on ADL ( $n = 202$  intervention vs  $n = 207$  control) using another explicit tool (FORTA) in older patients. A similar improvement is predicted by the deprescription of two central nervous system drugs. So far, factors known to influence the ADL in older patients are sex, age, social activities, individual living habits, psychological status and diseases [26]. To the best of our knowledge, no relation between the use of central nervous system drugs and ADL score has been reported in the literature.

The number of prescribed drugs increased more between admission and discharge in the PIM-Check arm, with a significantly higher prevalence of patients with hyperpolypharmacy at discharge. Although the prescription of clinically indicated medications should not be evaluated as a negative endpoint (e.g. prescription of erythropoietin-stimulating agents in patients with chronic renal failure), the lack of items related to deprescription of drugs that can have a negative effect on geriatric syndromes (e.g. anticholinergics/antimuscarinics) could be a limitation of the sole use of PIM-Check in the geriatric population [4, 27]. As identified in our analysis, the prevalence of deprescription of nervous system drugs was significantly higher with STOPP/START. PIM-Check and STOPP/START generated a substantial number of irrelevant recommendations, including duplicates (6% and 13%, respectively) and non-pertinent inapplicable suggestions (64% and 57%, respectively), which is inherent to the explicit nature of the criteria. Recommendations suggested by such tools need to be filtered by clinical pharmacists prior to being presented to attending physicians.

This study is the first RCT that prospectively compared two explicit tools, and the first that used PIM-Check and/or STOPP/STARTv2 to evaluate several clinical impacts.

This trial confirms the usefulness of such tools in detecting PIPs, but had some limitations. It was a monocentric RCT that did not allow us to determine if our results could be generalizable and, in the absence of a control group (standard of care), this study did not allow us to determine the absolute effects of the explicit tools. The prospective study of the clinical impact of explicit tools requires a large population, which was not reached in our study. The benefit of the reduction of the PIPs can

only be considered a proxy of stronger clinical endpoints. Considering the results on ADL, it should be acknowledged that the correlation with central nervous system drugs was based on a limited number of accepted changes in drug therapy and that some uncontrolled confounders might have contributed to this result. Although it is expected that drug burden and especially central nervous system drugs may strongly affect cognitive abilities in older patients and that length of hospitalization fragilizes patients, these results should be replicated in studies with a larger sample size.

## 5 Conclusion

Pharmaceutical interventions with STOPP/START and PIM-Check reduced the number of PIPs. STOPP/START leads to the deprescription of drugs related to nervous system class in older patients more than PIM-Check. Predictive factors of ADL increase were the deprescription of central nervous system drugs and the use of STOPP/START, which are considered actionable factors that should be considered during medication review. It should be expected that ADL decreases by one point per month of hospitalization.

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## Declarations

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**Conflicts of interest** All authors declare that they have no conflict of interest.

**Ethics approval** The Canton of Vaud Ethics Committee for Research on Human Beings (CER-VD) of the Swiss Ethical Committees approved the study protocol (N°2017-01972).

**Consent to participate** Informed consents were obtained.

**Consent for publication** All authors read and approved the final version for publication.

**Availability of data and material** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

**Code availability** Not applicable.

**Authors' contribution** Study design (AF, AA, PL, CC), data collection and data analysis (AF), drafting of the manuscript (AF), revision of the manuscript (AF, AA, PL, CC).

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