European Journal of Clinical Pharmacology (2019) 75:1503–1511
https://doi.org/10.1007/s00228-019-02727-9

CLINICAL TRIAL

Effectiveness of using STOPP/START criteria to identify potentially inappropriate medication in people aged ≥ 65 years with chronic kidney disease: a randomized clinical trial

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Received: 13 April 2019 / Accepted: 17 July 2019 / Published online: 29 July 2019

Abstract

Purpose Polypharmacy and inappropriate prescribing are common in elderly with chronic kidney disease (CKD). This study identified potentially inappropriate prescriptions (PIPs) and potential prescribing omissions (PPOs) using the Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert doctors to the Right Treatment (START) criteria in elderly with advanced CKD and determined the effect of a medication review on medication adherence and health-related quality of life (HRQoL).

Methods The intervention consisted of a medication review using STOPP/START criteria with a recommendation to a nephrologist or similar review without a recommendation. End points were prevalence of PIP and PPO, medication adherence, and HRQoL. Group differences in outcomes were assessed using a generalized linear mixed model. The trial was registered under www.clinicaltrial.gov (ID: NCT02424786).

Results We randomized 180 patients with advanced CKD (mean age 77 years, 23% female). The prevalence of PIPs and PPOs in the intervention group was 54% and 50%, respectively. The odds of PPOs were lower in the intervention than the control group (OR 0.42, 95% CI 0.19–0.92, $p = 0.032$), while there was no intergroup difference in the number of PIPs (OR 0.57, CI 0.27–1.20, $p = 0.14$). There was no difference in changes in medication adherence or HRQoL from baseline to 6 months between the groups.

Conclusions The intervention with the STOPP/START criteria identified a high prevalence of inappropriate medications in the elderly with advanced CKD and reduced the number of PPOs. However, there was no detectable impact of the intervention on medication adherence or HRQoL.

Keywords Polypharmacy · Chronic kidney disease · Medication adherence · Elderly · Inappropriate medication

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-019-02727-9) contains supplementary material, which is available to authorized users.

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Introduction

Polypharmacy is common in patients with advanced chronic kidney disease (CKD). Patients with CKD at stages 2 to 5 take an average of 8 different medications, while dialysis patients typically take 10 to 12 different medications [1, 2]. Polypharmacy is associated with adverse drug events (ADEs) and inappropriate medications [3, 4], that is, medications whose risks outweigh their benefits. Inappropriate medications are associated with morbidity, mortality, ADEs, and higher costs [5, 6].

Specialized instruments such as the Screening Tool of Older Persons' Prescriptions (STOPP), the Screening Tool to Alert doctors to Right Treatment (START), and Beers Criteria may be used to detect potentially inappropriate medication (PIM) [7, 8]. The STOPP/START criteria are used worldwide, whereas the Beers Criteria are widely used in the USA,

Australia, and Asia [9]. The STOPP criteria aim to identify potentially inappropriate prescriptions (PIPs), whereas the START criteria identify potential prescribing omissions (PPOs). PIPs include any prescription without a clear clinical indication, dosage, and duration inappropriate for clinical use (overprescribing) or prescribing a medication with an adverse risk-benefit profile when safer alternatives are available (misprescribing). PPOs define any medication that is not prescribed despite having a clear clinical indication (underprescribing) [10].

A recent meta-analysis assessed the effectiveness of applying the STOPP/START criteria in general hospital facilities, nursing homes, or frail elderly included only four randomized trials [11]. Those authors concluded that the use of these criteria was associated with reductions in inappropriate prescriptions, falls, delirium episodes, hospital length of stay, and medication costs, but no improvement was observed in health-related quality of life (HRQoL) or mortality [11]. The effectiveness of using the STOPP/START criteria to detect inappropriate medications in older adults with advanced CKD has not been reported previously.

The present randomized clinical trial used the STOPP/START criteria to identify PIPs and PPOs in patients aged ≥ 65 years with CKD at stage 5 treated either conservatively or with dialysis. For the assessment of medication adherence and its change, we used the eight-item Morisky Medication Adherence Scale (MMAS-8), which has also been used in many previous studies [12]. HRQoL was assessed with the SF-12, which is commonly used in geriatric patients and patients with CKD [13, 14]. We hypothesized that the use of STOPP/START criteria would identify inappropriate medications and lead to improved medication adherence, and this would be associated with improved HRQoL. The primary objectives were to identify any differences in the numbers of PIPs and PPOs and in medication adherence between the intervention and control groups after 6 months of follow-up. The secondary objectives were to determine differences between the groups in the average number of medications and HRQoL scores over the 6-month follow-up.

Materials and methods

Study design and population

This clinical trial had a single-blind, multicenter, parallel-group randomized design. Patients were included from three nephrology centers (Akershus University Hospital; Oslo University Hospital, Ullevål; and Vestre Viken Hospital Trust, Drammen) from July 2015 to January 2017. All patients aged ≥ 65 years with CKD at stage 5 (estimated glomerular filtration rate < 15 ml/min/1.73 m^2, as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation) who were either treated conservatively or with peritoneal dialysis (PD) or hemodialysis (HD) were asked to participate. Patients in the three hospitals were identified from local registers of patients receiving HD or PD, or from the list of patients with CKD scheduled for outpatient visits. We excluded patients with a severe-to-moderate reduction in cognitive function (Mini Mental State Examination–Norwegian Revision (MMSE-NR) score of < 23 before or during the study) [15], severe hearing or visual impairment, or inadequate knowledge of the Norwegian language.

The National Committee for Medical and Health Research Ethics (South/East) and the Akershus University Hospital data protection officer approved the study. The study was conducted in accordance with the Declaration of Helsinki. The patients were given information both orally and in writing, and written consents were obtained. The trial was registered at www.clinicaltrial.gov (ID: NCT02424786).

Baseline data collection

All of the included patients participated in a semi-structured interview prior to randomization. The interviewer asked closed- and open-ended questions, and no audio recording for transcription was made during the interview. Information was collected on medications that included over-the-counter medication, administration mode, side effects, concomitant diseases, accidental falls, and specific symptoms such as vertigo, obstipation, pruritus, or dyspepsia. An accidental fall was defined as "any event in which a person inadvertently or intentionally comes to rest on the ground or another lower level" during the previous 3 months [16]. Falls that occurred after the HD sessions were considered as adverse events.

At the end of the interview, each patient was given questionnaires about HRQoL and medication adherence, which were to be answered at home and returned in postage-prepaid envelopes. Non-respondents received one reminder by telephone.

The Charlson Comorbidity Index (CCI) was calculated at baseline based on information in the medical record of a subject and supplementary information obtained during the interview. This index consists of an aggregate of 19 comorbidities that are weighted and summarized into a single number. The CCI is an accurate predictor of the 2-year mortality in patients with CKD [17, 18].

Randomization and intervention

All patients were randomly assigned at a ratio of 1:1 to the intervention and control groups using random numbers generated by a computer program, with the allocations stored in sealed numbered envelopes. The investigators and physicians were blinded to group allocation until the first interview was

completed, while all of the subjects remained blinded throughout the project.

The intervention consisted of a medication review by one investigator, a nephrologist (KP), who used the STOPP/START criteria to identify possible inappropriate medications. In case of an identified inappropriateness, a follow-up recommendation was written in the electronic medical record to inform the attending physician. These recommendations comprised simple statements explaining why this medication was identified as inappropriate. The attending nephrologists were free to decide whether or not they would comply with the recommendations and revise a patient's current medication list. For the control group, the same investigator performed an identical medication review using the STOPP/START criteria, but no notes were entered into the medical record.

Follow-up data collection

After 6 months, the same investigator carried out a second round of semi-structured interviews with all of the participants using similar questions as in the baseline interview about all medications, administration mode, possible side effects, and information about changes in medications. The same data as at baseline were registered, which also included new comorbidities and the number of hospitalization during the previous 6 months. Each participant was given the same questionnaires about HRQoL and medication adherence to be completed at home and returned by mail.

Outcome measurements

Screening tool to identify potentially inappropriate prescriptions and potential prescribing omissions

The STOPP/START version 2 criteria consist of 80 STOPP and 34 START criteria and have been validated using the Delphi consensus method [19]. The STOPP/START criteria are grouped according to organ systems (e.g., cardiovascular system and musculoskeletal system) to facilitate easy and rapid medication reviews. For each criterion, the tool contains a brief explanation of why a medication or a combination of medicines is considered appropriate or potentially inappropriate.

Medication adherence

The eight-item Morisky Medication Adherence Scale (MMAS-8) is a self-reported and validated questionnaire on the adherence to medication whose total score ranges from 0 (non-adherent) to 8 (adherent) [20–22]. Seven items have a "yes/no" response, and the eighth is scored from 1 to 4. For further analysis of data, medication adherence was dichotomized into non-adherent (MMAS-8 score < 6) and adherent (MMAS-8 score ≥ 6) [23].

Health-related quality of life

We used the 12-item Short-Form Health Survey (SF-12) to assess the patients' HRQoL, which is part of the Kidney Disease Quality of Life Instrument. The SF-12 is self-administered and has been validated in various patient groups, including CKD [24]. The physical and mental health statuses were aggregated into two summary scores in this study: the physical component summary (PCS) score and the mental component summary (MCS) score [25].

Trial end points

The primary end points were the reduction in PIPs and PPOs and the improvement of medication adherence during the 6-month observation period. The secondary end points were the change in the number of medications and PCS and MCS scores.

Statistical analysis

Patient characteristics were described as number (percentage), mean ± SD, or median (minimum–maximum) values, as appropriate. Baseline characteristics were compared between respondents and non-respondents using the independent-samples t test for continuous variables or the χ^2 test or Fisher's exact test for categorical variables.

The differences between the intervention and control group at follow-up were assessed using a linear mixed model for the continuous outcomes (number of medications and PCS and MCS scores), while a generalized linear mixed model was applied to estimate the dichotomous outcomes (medication adherence: adherent versus non-adherent), PIPs according to STOPP criteria (none versus ≥ 1), and PPOs according to START criteria (none versus ≥ 1). The models contained fixed effects for measurement time point (baseline or 6-month follow-up) and the interaction between the time point and group (intervention or control). The interaction term in such a model quantifies differences between groups at follow-up adjusted for the baseline values. Random effects for patients were included. The models were estimated for cases with observations available at baseline. For sensitivity analyses, we conducted complete-case analysis using longitudinal analysis of covariance for the continuous outcomes (fixed effects for the group and baseline values) and binary logistic regression analysis for the dichotomous outcomes (fixed effects for the group).

Prior to the inclusion of patients, we estimated that to detect a difference of 0.5 standard deviations (SDs) in medication adherence score between the groups with a statistical power

of 80% at a significance level of 5%, the study would need a sample size of 63 subjects in each group.

The analyses were performed with STATA (version 15.1, StataCorp, College Station, TX, USA) or SAS (version 9.4, SAS Institute, Cary, NC, USA). All tests were two-sided, and results with p values below 0.05 were considered statistically significant.

Results

Study population

We recruited and randomized 180 patients from 319 eligible patients (Fig. 1). In total, 11% of the patients included at baseline were lost to follow-up due to death and 17% due to no response or incomplete questionnaires. This group was defined as non-respondents ($n = 50$). Respondents and non-respondents had the same baseline characteristics except for the latter having a lower MMSE-NR score ($p = 0.025$) and more hospitalizations during the follow-up period ($p = 0.014$).

The baseline characteristics did not differ between the allocated groups (Table 1).

Identification of potentially inappropriate medications

Among the 180 included patients, 265 inappropriate medications (PIPs and PPOs) according to the STOPP/START criteria were found at baseline (Supplementary Table 1). The most common PIPs were proton-pump inhibitors, benzodiazepines, and first-generation antihistamines, while the most common PPOs were angiotensin-converting enzyme (ACE) inhibitor, statins, and vitamin D. The prevalence of PIPs at baseline was 54% in the intervention group and 55% in the control group; the corresponding prevalence rates of PPOs were 50% and 56%, respectively.

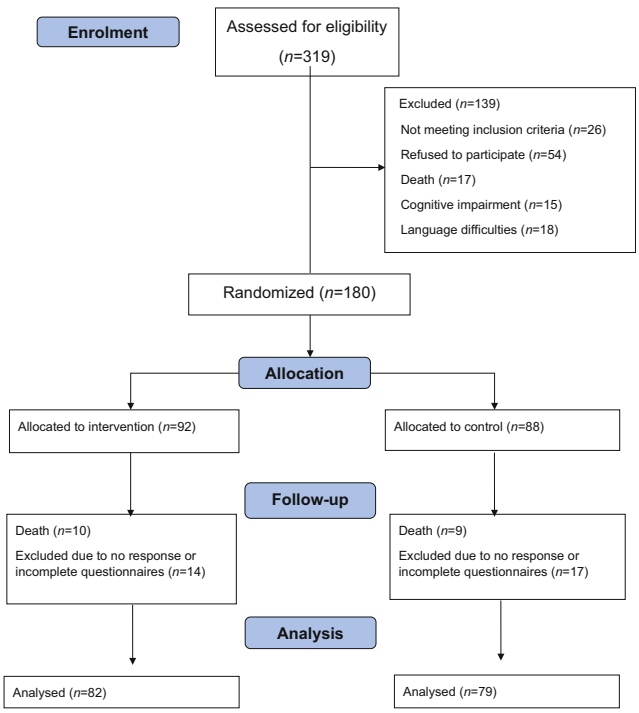

Fig. 1 Flow chart of study inclusion

Outcomes of the intervention

Primary outcomes

The number of patients with one or more PIPs decreased in the intervention group whereas it remained almost the same in the control group (Supplementary Table 2). The probability of PIPs did not differ between the intervention and control groups at follow-up, whereas that of PPOs was lower in the intervention group than the control group (odds ratio (OR) = 0.42, 95% confidence interval (CI) = 0.19–0.92, $p = 0.032$) (Table 2). In the control group, we identified no severe PIPs or PPOs. After 6 months, there was no difference between the groups in medication adherence (Table 2).

Secondary outcomes

There was no significant intergroup difference in the average number of medications or HRQoL score at follow-up (Table 3).

Sensitivity analysis

The sensitivity analyses confirmed the above-mentioned results. There were no intergroup differences in the average number of medications, PCS and MCS scores, medication adherence, or PIPs. The probability of PPOs remained lower in the intervention group than the control group ($n = 161$; OR = 0.46, 95% CI = 0.24–0.87, $p = 0.017$).

Discussion

Using the STOPP/START criteria to screen medication in patients with advanced CKD revealed a high prevalence of PIMs and a reduction in PPOs during the 6-month follow-up period in this study. However, the intervention did not lead to improvements in the number of PIPs, medication adherence, average number of medications, or HRQoL scores. We are not aware of any previous study that has assessed the use of STOPP/START criteria in older people with advanced CKD.

The number of PPOs was the only variable that was reduced in the present study. This contrasts with previous reports of improvements in both PIPs and PPOs after similar

Table 1 Characteristics of the populations ($n = 180$) in the two study groups

	Intervention ($n = 92$)		Control ($n = 88$)	
Sex, female	23	(25)	23	(26)
Age, years	76.0 ± 6.6		76.0 ± 7.6	
Geriatric features				
Mini-Mental State Examination Norwegian Revision score	28	(23–30)	28	(24–30)
Polypharmacy (> 5 drugs)	87	(95)	86	(98)
Living alone	31	(34)	36	(41)
≥ 1 fall within 3 months prior to inclusion	14	(15)	10	(11)
Symptoms				
Vertigo	25	(27)	20	(23)
Obstipation	22	(24)	22	(25)
Pruritus	46	(50)	32	(36)
Dyspepsia	13	(14)	8	(9)
Most frequent comorbidities				
Hypertension	77	(85)	67	(76)
Coronary disease	34	(39)	37	(42)
Malignancy	28	(31)	31	(35)
Diabetes mellitus	30	(34)	22	(25)
Atrial fibrillation	11	(12)	14	(16)
Charlson Comorbidity Index ≥4	61	(66)	62	(70)
Nephrological treatment				
Hemodialysis	46	(43)	41	(47)
Peritoneal dialysis	11	(12)	9	(10)
Conservative treatment	35	(38)	38	(43)

Data are number (percentage), mean ± SD, or median (minimum–maximum) values

interventions using the STOPP/START criteria [11]. Our literature search did not reveal other randomized trials evaluating the effect of using the STOPP/START criteria on clinical outcomes in older people with advanced CKD. The lower impact in the present study compared to previous studies may have been due to the implementation of suggested medication changes being left entirely to the judgment of the attending physician, differences in populations and settings, or the length of the follow-up period. A relatively short follow-up was chosen in this study because of an expected high mortality rate in our older cohort [26], and this was also used in previous randomized controlled trials [11].

The prevalence of PIMs in the present cohort as detected with the STOPP/START version 2 criteria was lower than that in a recent survey of HD patients using the same criteria [27], but similar to those in previous descriptive studies using the STOPP/START version 1 criteria [28, 29]. The differences in the prevalence of PIMs between studies may be caused by differences in the populations, medication practice or traditions, or the use of different versions of the STOPP/START criteria, which also makes interstudy comparisons more difficult.

The PIMs identified in the present study were almost identical to those reported in general geriatric or HD populations [27, 28, 30]. In both arms of the present study, more than 50% of the participants had omissions of recommended preventive medications or medications with documented therapeutic effects in advanced CKD. Such underprescribing is common in older people with or without CKD, such as in treatments for primary or secondary cardiovascular prevention with a beta-blocker after acute myocardial infarction, or statins and vitamin D in CKD [31–34]. This issue is complicated by current guidelines for lipid management in CKD stratifying statin treatment according to the stage of CKD [35].

The present study identified ACE inhibitor as the most common medication omission by applying the START criteria. Patients with CKD are regarded as a high-risk group for cardiovascular events; however, ACE inhibitors are often neglected in this patient group [36–38]. ACE inhibitors are cardio-protective, reduce vascular morbidity and mortality, and slow the progression of renal failure directly and indirectly by meticulous blood pressure control [36, 37]. However, the use of ACE inhibitors in advanced CKD is complicated by risks of side effects, such as hyperkalemia, metabolic acidosis,

Table 2 Differences in primary outcomes between the intervention group and the control group (reference) from a generalized linear mixed model

	n	Odds ratio[a] (95% CI)	*p*
Potentially inappropriate prescriptions according to STOPP criteria (none versus ≥ 1)	180	0.57 (0.27 to 1.20)	0.14
Potentially inappropriate omissions according to START criteria (none versus ≥ 1)	180	0.42 (0.19 to 0.92)	0.032
Medication adherence (adherent versus non-adherent)	157	1.17 (0.41 to 3.39)	0.77

[a] Overall intervention effect over time, or difference between groups at follow-up, with no adjustment for baseline, *CI* confidence interval

and a possibility of further decline of GFR. Therefore, in some patients, nephrologists may justify omission of an ACE inhibitor.

Underprescribing may be attributed to an intention to avoid polypharmacy, lack of knowledge or limited evidence for use of the drugs, or because older people with advanced CKD are regularly excluded from clinical trials [39].

The intervention in the present study did not improve medication adherence. The adherence was high at both baseline and the 6-month follow-up, which supports previous reports of high medication adherence in older patients [40, 41]. This lack of response may therefore be explained by the high medication adherence at baseline, a ceiling effect of the instrument used for assessment or the definition used for high adherence excluding a large proportion of patients from further possible improvements. The findings are in line with those of a pharmacist-led intervention in community-dwelling older people [42].

The lack of improvement in HRQoL in the present study cannot be compared with similar interventions in patients with CKD, as this is the first study in advanced CKD [42]. However, the HRQoL scores of our population were low, and in accordance with those found in other patients with advanced CKD [43, 44].

Only a few previous trials have investigated the changes in the number of medications in cohorts of older people. Our finding of no effect on the average number of medications is in line with that of another randomized trial [45] but contrasts with observations made in patients with dementia and the residents of nursing homes [9, 46].

The present study was a multicenter, randomized, clinical trial with older patients with advanced CKD and a high vulnerability due to polypharmacy and impaired kidney function. The population included in this study is likely to be representative of this patient population in Norway. As the study was randomized, it by design adjusted for both observable and non-observable covariates.

Some other challenges in this study should be noted. When calculating the sample size, we used the medication adherence score as the outcome; however, we had no figures from comparable studies in the literature about the size of effect to be expected. Furthermore, the ceiling effect of the instrument may also have limited the possible improvement, possibly contributing to an underestimation of the number of patients needed to detect a statistical significance. The study had a high proportion of missing data for the outcomes, and it would not be feasible to impute these missing values. We used a generalized linear mixed model to include all patients with available baseline data. Complete-case analyses were performed as sensitivity analyses to assess the robustness of the results and whether the assumptions made in the analyses were valid [47]. Non-respondents had lower MMSE-NR scores and higher hospitalization rates than the respondents, suggesting that the latter were healthier and less frail.

A medication review according to STOPP/START was performed in control patients, but not entered into the

Table 3 Differences in secondary outcomes between the intervention group and the control group (reference) from a linear mixed model

	n	Coefficient[a] (95% CI)	*p*
Number of medications	180	0.40 (− 0.29 to 1.09)	0.26
Quality of life, SF-12			
Physical component summary score	148	1.04 (− 1.89 to 3.98)	0.48
Mental component summary score	148	1.39 (− 1.27 to 4.06)	0.30

[a] Regression coefficient represents overall intervention effect over time, or difference between groups at follow-up, with adjustment for baseline, *CI* confidence interval

medical records. If *severe inappropriateness* would have been detected among the controls, this might have represented an ethical dilemma. During the course of this study, however, we did not identify severe inappropriateness in this group. In case of severe inappropriateness, recommendations would have been written in the electronic medical record or the issue would have been discussed directly with the attending nephrologist, which we think would be in agreement with the general principles of the declaration of Helsinki.

The attending physicians who were responsible for implementing medication changes in the study did follow patients in both the intervention and control groups. It is therefore possible that there was a learning effect from the recommendations for medication changes in the intervention group, which may have benefited the control group, that is, a spill-over effect. This effect may have contributed to underestimations of the differences between the intervention and control groups.

The STOPP/START criteria were developed with a primary focus on the medication for older patients generally and not for specific disease populations. The findings obtained when applying the STOPP/START criteria therefore enable comparisons between different patient categories; however, it might not be feasible to apply the criteria in all settings. A limitation of the present study was that the validity and clinical relevance of these criteria in patients with advanced CKD have not yet been documented. Therefore, the decision of implementing the recommendations was left to the judgment of the attending nephrologist. In general, little is known about the clinical relevance of PIPs or PPOs, as detected using the STOPP/START criteria, at an individual level [48]. However, a recent study of the elderly with hip fracture showed that one in two PIM is clinically relevant at the individual level [49].

Each administered medication should ideally be appropriate, evidence-based, and safe, independent of the specific diseases or age of the patient. The use of a simple screening tool such as the STOPP/START criteria can facilitate a dialog between those involved in the prescribing, dispensing, and administrating medications and the affected patients, and in theory, should help to improve the appropriateness of medication regimens. Finding feasible and effective ways to benefit from such processes and documenting their impact on medication adherence and ultimately the HRQoL of patients require further research.

In conclusion, in this study, an intervention based on the STOPP/START criteria detected PIMs and reduced the number of PPOs, but it did not lead to a reduction in the number of PIPs or improvements in medication adherence or HRQoL.

Acknowledgments The use of the Morisky Medication Adherence Scale (© MMAS) is protected by US copyright laws. Permission for use is required. A license agreement is available from Donald E. Morisky at dmorisky@gmail.com or MMAS Research LLC 14725 NE 20th ST. Bellevue, WA 98007.

Authors' contributions K.P. and K.S. designed the study with support from the other authors. K.P., M.R.N., I.B.E., W.A., and N.v.d.L. participated in screening, recruitment, and data collection. K.S., J.Š.B., and K.P. analyzed the data. K.P. drafted the manuscript with support from K.S. All of the authors contributed to data interpretation, critically reviewed the manuscript, and approved its final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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