

Prevention of Hospital-Acquired Adverse Drug Reactions in Older People Using Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment Criteria: A Cluster Randomized Controlled Trial

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OBJECTIVES: To determine whether use of the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria reduces incident hospital-acquired adverse drug reactions (ADRs), 28-day medication costs, and median length of hospital stay in older adults admitted with acute illness.

DESIGN: Single-blind cluster randomized controlled trial (RCT) of unselected older adults hospitalized over a 13-month period.

SETTING: Tertiary referral hospital in southern Ireland.

PARTICIPANTS: Consecutively admitted individuals aged 65 and older (N = 732).

INTERVENTION: Single time point presentation to attending physicians of potentially inappropriate medications according to the STOPP/START criteria.

MEASUREMENTS: The primary outcome was the proportion of participants experiencing one or more ADRs during the index hospitalization. Secondary outcomes were median length of stay (LOS) and 28-day total medication cost.

RESULTS: One or more ADRs occurred in 78 of the 372 control participants (21.0%; median age 78, interquartile range (IQR) 72–84) and in 42 of the 360 intervention participants (11.7%; median age 80, IQR 73–85) (absolute risk reduction = 9.3%, number needed to treat = 11). The median LOS in the hospital was 8 days (IQR 4–14 days) in both groups. At discharge, median medication cost was significantly lower in the intervention group (€73.16, IQR €38.68–121.72) than in the control group (€90.62, IQR

€49.38–162.53) (Wilcoxon rank test Z statistic = -3.274 , $P < .001$).

CONCLUSION: Application of STOPP/START criteria resulted in significant reductions in ADR incidence and medication costs in acutely ill older adults but did not affect median LOS. *J Am Geriatr Soc* 2016.

Key words: adverse drug reaction; prevention; elderly; STOPP/START criteria

Adverse drug reactions (ADRs) are closely associated with inappropriate prescribing and polypharmacy in older people.^{1–4} The Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria have been designed and validated for the purpose of highlighting potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) in older people.⁵ The fundamental aim of the STOPP criteria is to minimize medication-related adversity by highlighting and avoiding PIMs. The complementary aim of the START criteria is to minimize avoidable therapeutic failures by highlighting PPOs and encouraging appropriate prescriptions if they are absent for no sound clinical reason.⁵ A recent single-center randomized controlled trial (RCT) showed that application of the STOPP/START criteria in older hospitalized adults significantly improves medication appropriateness, an effect that was sustained to the end of a 6-month posthospitalization follow-up period.⁶

Pharmacoepidemiologists agree that ADRs in general and ADRs in older people in particular are a serious and growing public health problem.^{7,8} Hospital-acquired ADRs are clinically and economically significant because of the causal association between ADRs and serious adverse outcomes, principally avoidable hospitalizations, and mortality.^{9,10} Hospitalization in older adults resulting from

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adverse medications is a growing problem for which solutions are not yet clear. Recent data from the Dutch Hospital Admissions Related to Medication study indicate clear causative associations between medication-related hospitalization and a cluster of risk factors in older adults (dementia, multimorbidity, nursing home residence, impaired renal function, nonadherence to pharmacotherapy, polypharmacy).¹¹

Four previous RCTs testing various interventions to improve prescribing in older adults showed statistically significant reductions in serious ADRs,¹² drug-related hospital readmissions,¹³ adverse drug events,¹⁴ and drug-related emergency department attendances or readmissions,¹⁵ but there are no published clinical trials that have used PIM or PPO criteria as an intervention for the purpose of ADR prevention in these high-risk older adults.^{10,16}

Given the link between inappropriate prescribing and ADRs^{17,18} and the previous study demonstrating the efficacy of the use of the STOPP/START criteria as an interventional tool for enhancing medication appropriateness,⁶ it was hypothesized that the STOPP/START criteria could also be used to attenuate incident ADRs in older adults hospitalized with acute illness. To address this hypothesis, a RCT was designed to compare the rate of hospital-acquired ADRs in acutely ill older adults who received standard pharmaceutical care and with the rate of those whose medications were adjusted according to the STOPP/START criteria. Therefore, the principal focus of the present study was to examine the effect of the use of the STOPP/START criteria as an intervention for minimizing hospital-acquired incident ADRs (ADRs that were identified between randomization after admission and the endpoint assessment before discharge) in older adults hospitalized with acute illness.

METHODS

Participant Recruitment

Between May 2011 and May 2012, acutely ill individuals aged 65 and older admitted to Cork University Hospital (CUH), an 810-bed tertiary referral center whose direct catchment population is approximately 650,000, were screened. The hospital is the largest of a network of five acute care hospitals in the Munster region of southern Ireland. The profile of acute admissions of older adults to each of these five hospitals was similar, so there was no selection bias when conducting a study of acutely ill older adults referred to CUH, other than the fact that CUH is the only hospital in the region with specialist neurosurgery services.

Exclusion criteria were age younger than 65; admission directly to the intensive therapy unit; admission under the care of a specialist in geriatric medicine, old age psychiatry, clinical pharmacology, or palliative medicine (specialists with expertise in geriatric pharmacotherapy) or attendance at one of these specialist services within the previous 12 months as an inpatient or outpatient; terminal illness; likelihood of discharge within 48 hours of admission (on the basis of documented expected date of discharge by an attending doctor in the case records); and refusal to participate in the trial.

Details of all adults admitted through the emergency department (ED) were routinely recorded in an admission log book (name, date of birth, medical record number, principal reason for admission, admitting attending consultant physician or surgeon, and if the individual had moved from the ED, the ward to which he or she had been transferred). Each morning, the primary researcher (MNO) received a photocopy of the list of acute admissions in the previous 24 hours and, from this list, identified older adults who were potentially suitable for recruitment into the trial using the defined inclusion and exclusion criteria.

Individuals who were screened and recruited into the trial received one of two pharmaceutical care management packages: usual medical and pharmacist inpatient care (control group) or usual medical and pharmacist inpatient care plus application of STOPP/START criteria to their medication list at a single time point within 48 hours of admission (intervention group). Usual pharmacist care consisted of full medication reconciliation, surveillance of prescription order sheets (independent of medical prescribers) with specific written advice attached to the prescription order sheets in the event of unclear drug prescription names, use of brand names rather than generic names, incorrect dose or dose interval, and incorrect prescription duration.

A cluster enrollment design was used based on the attending consultant or consultant group in circumstances in which a group of subspecialists functioned as a single integrated service. Two lists of attending consultants were generated such that the combined rates of ADRs in these groups were known to be comparable from an ADR assessment study completed shortly before the initiation of the present clinical trial.¹⁹ Having finalized the composition of the lists, one list of specialist consultants was assigned as the intervention arm of the study and the other list of specialist consultants as the control arm.

The control cluster consisted of enrolled individuals admitted to eight specialty teams (general surgery, gastroenterology, infectious diseases, respiratory medicine, renal medicine, cardiology, neurology). There were 13 attending consultants in the control cluster. The intervention cluster consisted of individuals admitted to six specialty services within the hospital (orthopedics, endocrinology, respiratory medicine, renal medicine, cardiology, radiation oncology). The intervention cluster had 14 attending consultants. Although respiratory medicine, renal medicine, and cardiology were represented in both clusters, no attending consultant had patients in both clusters. During the previous observational study of 513 individuals consecutively hospitalized with acute illness,¹⁹ 47 of 195 participants (24.1%) in the control cluster and 48 of 209 (22.9%) in the intervention cluster experienced ADRs.

To avoid potentially biased selection of subjects into either arm of the study, the primary researcher (MNO) approached prospective trial participants in the order of their admission to the hospital to assess their eligibility for the trial. The cluster RCT design was chosen for two reasons, namely that the intervention could not be double-blinded (because of its nature) and the need to avoid a possible "training effect" in clinicians attending intervention and control participants (where the learning of several

of the more commonly deployed STOPP/START criteria in intervention participants might be unwittingly applied in control participants, thereby risking trial contamination).

The primary researcher obtained the following details in an interview with each recruited participant (or principal caregiver where necessary): age, sex, full list of current medications including drug allergies and intolerances, full list of current and previous diagnoses, cognitive status (Abbreviated Mental Test score), and activity of daily living status before hospitalization. In all cases, the medication list that the participant or caregiver supplied was cross-referenced with the participant's case records and his or her community pharmacist with the participant's consent. All participant details, including medication lists, were obtained after study enrollment.

All eligible individuals were identified from the acute admissions log book held in the ED. Individuals were enrolled in the study within 48 hours of their presentation to the hospital with acute illness after all newly admitted individuals from the ED admissions register had been screened, beginning with the first individual admitted after 8 a.m. on the previous day. Because of resource limitations, the primary researcher screened no more than four new individuals each day for trial enrollment. An information leaflet was distributed to all potential prospective trial participants explaining the rationale of the trial, its aims, and the implications of trial participation. In the case of individuals with cognitive impairment or communication difficulties of such severity as to make it impossible for the primary researcher to explain the details of the clinical trial in a valid way, the trial information leaflet was offered to the participant's next of kin or nominated caregiver. Written informed consent for participation in the trial was obtained from all participants capable of giving such consent; in the case of participants who were unable to give valid consent, consent was sought from their next of kin or nominated caregiver. The research ethics committee of the local teaching hospitals network approved the trial. The trial was registered with the National Institutes of Health in the United States (www.clinicaltrials.gov; trial number NCT01467050).

Intervention

The primary researcher applied the intervention at a single time point within 48 hours of admission to the hospital in a single-blinded design. This involved deployment of STOPP/START criteria once only in each intervention group participant on the basis of the diagnoses documented in their case records and the list of prescribed drugs and doses at the time of enrollment in the study. The primary researcher immediately notified the participant's attending registrar (senior resident) or specialist consultant of the presence of STOPP/START-defined PIMs and PPOs and answered any clarifying questions that the attending medical staff had relating to recommended medication changes. Within 24 hours of applying STOPP/START criteria, the primary researcher placed a printed report in the participant's case record, reinforcing the oral recommendations based on the specific criteria that applied in each case. The final decision regarding acceptance or rejection of STOPP and START criteria

recommendations lay with the participant's attending senior medical staff.

Outcome Measures

The primary outcome measure in this trial was incident hospital-acquired ADRs during the index hospitalization. For the purposes of this study, hospital-acquired ADRs were defined as those occurring after admission to hospital up to Day 7 to 10 or discharge, whichever came first. ADRs that required immediate dose adjustment or drug discontinuation (immediate or gradual, as required) or reversal of drug effect with appropriate treatment or antidote (e.g., vitamin K for bleeding with warfarin), resulted in severe physiological instability requiring intensive monitoring with or without therapy, or resulted in death were included. The primary researcher judged whether an ADR had occurred on the basis of the clinical event or observation meeting the World Health Organization (WHO) definition of an ADR (a response to a drug that is noxious and unintended and occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease or for the modifications of physiological function);²⁰ the clinical event or observation meeting the WHO Uppsala Monitoring Centre criteria for probable or definite ADR²¹ (clinical effects consistent with the known side-effect profile of the drug according to British National Formulary data,²² a clear temporal relationship between the suspected ADR symptoms and initiation of drug, and other causes of the adverse clinical symptoms and signs being excluded or highly unlikely); affected individuals with one or more symptoms or signs defined according to a trigger list of the most-common clinical phenomena representing ADRs (Table 1) identified from a recent study¹⁹ or the symptoms or signs that the participant experienced representing a well-known and consistently recognized adverse effect of the drug if not included in the trigger list; and corroboration of the clinical event or observation by a second researcher who was blinded to the randomization group of the participant, applying the WHO Uppsala Monitoring Centre criteria for ADR causality assessment in an identical way to the primary researcher.

ADR avoidability was defined using previously developed criteria.²³ ADRs were classified as moderate if they caused a hospital stay of more than 24 hours beyond the expected date of discharge, caused significant deterioration of vital signs (blood pressure, heart rate, oxygen saturation, core temperature), or required specific corrective interventions beyond discontinuation of the offending drug. ADRs were classified as severe if they directly caused death or permanent disability, necessitated admission to a high-dependency unit or intensive therapy unit, or required urgent administration of a specific antidote or other specific intervention to counteract the direct adverse effects of the drug causing the ADR.

Secondary outcome measures included median length of hospital stay (LOS) and median 28-day cost of participants' prescription drugs. The reasons for extrapolated 28-day medication costs as the preferred measure of medication cost, as opposed to daily medication cost or hospitalization medication cost, were the wide variation in LOS in both participant groups and in day-by-day number of

Table 1. Trigger List of Adverse Drug Reactions (ADRs)

Trigger Symptom or Clinical Phenomenon	Medicines Commonly Associated with Specific ADRs Identified According to Trigger Symptom or Clinical Phenomenon
Falls (≥ 1 falls after enrollment)	Benzodiazepines, hypnotics, neuroleptics, opioids
Acute kidney injury (estimated glomerular filtration rate reduced by 50% or a doubling of serum creatinine concentration or urine output ≤ 0.5 mL/kg per hour for 12 hours)	NSAIDs, diuretics, ACE-Is, angiotensin receptor blockers
Significant electrolyte derangement (serum sodium <130 or >150 mmol/L, serum potassium <3.0 or >5.5 mmol/L, corrected serum calcium >2.6 mmol/L)	NSAIDs, diuretics, ACE-Is, angiotensin receptor blockers
Symptomatic orthostatic hypotension (reduction in systolic blood pressure > 20 mmHg or diastolic blood pressure >10 mmHg from supine to erect posture)	Vasodilators
Presyncope or syncope (transient disturbed level of consciousness and postural tone of rapid onset, short duration, and rapid recovery due to global cerebral hypoperfusion, usually resulting from systemic hypotension)	Beta-blockers, digoxin, verapamil, diltiazem
Major constipation (requiring daily laxatives)	Opioids
Bleeding (causing a drop in hemoglobin concentration of > 2 g/dL or cessation of antiplatelet or anticoagulant therapy or requiring blood transfusion or requiring prescription of an antidote (e.g., vitamin K for warfarin reversal))	Antiplatelet agents, anticoagulants
Dyspepsia (subjective persistent upper gastrointestinal symptoms relieved by acid-reducing medication)	NSAIDs
Diarrhea (≥ 3 Bristol Type 6 or 7 stools in 24 hours)	Antibiotics
Movement disorders (Parkinsonism, ataxia, myoclonus)	Benzodiazepines, hypnotics, neuroleptics, opioids

NSAID = nonsteroidal anti-inflammatory drug; ACE-I = angiotensin-converting enzyme inhibitor.

medications and because 28 days is the standard unit of cost that the Health Services Executive in Ireland uses for calculation of reimbursement of prescription costs to older adults.

Statistical Analysis

Based on an in-hospital ADR incidence estimate of 25% obtained from previous data,¹⁹ with an anticipated reduction in ADR incidence to 18% from applying the STOPP/START intervention, a sample size was calculated of 356 participants per group to deliver 80% power to detect a statistically significant difference in ADR incidence between the groups at the 95% confidence level.

Medians and interquartile ranges (IQRs) were determined for nonparametric data and means and standard deviations (SDs) for parametric data. The chi-square statistic was used to compare baseline categorical variable data of the control and intervention groups; with continuous variables, the Student *t*-test was used in the case of normally distributed data and the Wilcoxon rank sum test in the case of nonparametric data comparisons. The Mann-Whitney U-test and the Kruskal-Wallis test were used to determine the independence of two or more nonparametric variables, respectively. To control for imbalance in baseline covariates between the intervention and control groups, an adjusted logistic regression model was developed of the ADR event rate adjusted for variables reported in Table 2. The absolute risk reduction (ARR) and number needed to treat (NNT = 100/ARR to the nearest whole number) were calculated from the proportions of either group experiencing nontrivial ADRs (primary outcome). A Type 1 error rate of 0.05 was used in all statistical

Table 2. Baseline Characteristics of Study Population

Characteristic	Control, n = 372	Intervention, n = 360	P-Value
Age, median (IQR)	78 (72–84)	80 (73–85)	.10
Male, n (%)	187 (50.3)	130 (36.1)	.001
Abbreviated Mental Test score (range 0–10), median (IQR)	10 (8–10)	10 (8–10)	.10
Charlson Comorbidity Index, median (IQR)	2 (1–3)	2 (1–3)	.08
Barthel Index (range 0–20), median (IQR)	18 (13–20)	18 (15–20)	.59
Nursing home residents, n (%)	36 (9.6)	51 (14.1)	.08
Heart failure, n (%)	69 (18.5)	60 (16.7)	.57
Liver failure, n (%)	20 (5.4)	9 (2.5)	.07
Estimated glomerular filtration rate <60 mL/min per 1.73 m ² , n (%)	160 (43.0)	133 (36.9)	.11

IQR = interquartile range.

analyses. All statistical analyses were performed using PASW version 18 statistical software for Windows (SPSS Inc., Chicago, IL).

RESULTS

One thousand forty-two unselected older adults admitted to the hospital with acute illness were screened for enrollment in the trial; 310 were excluded because of expected LOS <48 hours (n = 110), failure to meet inclusion criteria (n = 172), diagnosis of terminal illness (n = 6), and refusal

to participate in the trial ($n = 20$). Table 2 illustrates the demographic and clinical details of the control and intervention groups. Individuals included in the trial had a wide variety of presenting illnesses; supplemental online Appendix A summarizes the principal admission diagnoses in the control and intervention groups (Table S1). A minority of participants (<10%) presented with more than one acute problem (e.g., fall-related fracture and delirium). Table 3 describes the pattern of prescribed drugs use in the two groups at enrollment in the trial.

Seven hundred thirty-two individuals were randomized to the intervention ($n = 360$) or the control ($n = 372$) group; Figure 1 shows a schematic description of the trial process. There were 20 in-hospital deaths of enrolled participants—11 in the intervention group and nine in the control group. The data were analyzed on the basis of intention to treat, such that no enrolled participants' data were excluded. The baseline characteristics of the enrolled population of participants are illustrated in Table 2. The only significant difference between the groups' demographic and clinical characteristics was sex mix (significantly more men in the control group than in the intervention group (50.2% vs 36.1%, $P = .009$). The significantly higher proportion of men in the intervention group was in part due to the clustering of vascular surgery in the intervention group, vascular surgery having a higher proportion of hospitalized men than women.

The median number of daily prescription drugs was similar in both groups (control: 8, IQR 6–11; intervention: 9, IQR 6–11; $P = .71$) (Table 4). In addition, the proportions of participants taking five drugs or fewer per day, six to 10 drugs per day, and 11 or more drugs per day were not significantly different between the groups, and the proportion of participants taking one or more STOPP medications in the control group (42.5%) at baseline was not significantly different from that in the intervention group (48.9%).

With the application of the STOPP/START criteria to the medication lists of the intervention group participants, 451 recommendations were made in 233 participants (64.7%) (292 STOPP criteria recommendations, 159

START criteria recommendations). The attending doctors accepted and implemented 237 of the STOPP recommendations (81.2%) and 139 (87.4%) of the START recommendations.

Primary Outcome Measure

Forty-five ADRs occurred in 42 of the 360 intervention group participants (11.7%); these were definitely avoidable in 31 participants and possibly avoidable in 14 participants according to previously developed criteria.⁽²³⁾ Forty-two of the 45 ADRs (93.3%) in the intervention participants were classified as moderate or severe. Eighty-nine ADRs occurred in 78 of the 372 control group participants (21.0%), 85 of which were definitely or possibly avoidable and 71 of which (79.8%) were classified as moderate or severe. The details of all STOPP criteria-defined PIMs and START criteria-defined PPOs are illustrated in supplemental online Appendix A (Table S2). Table 3 shows the most frequently recorded ADRs and the associated drug classes in the control and intervention groups.

Using univariate logistic regression, the odds of the occurrence of an ADR in the intervention group was half that of the control group (odds ratio (OR) = 0.50, 95% confidence interval (CI) = 0.33–0.75; $P = .001$). The association remained significant and was not attenuated with simultaneous adjustment for the variables shown in Table 2 (adjusted OR (aOR) = 0.48, 95% CI = 0.31–0.79; $P = .001$). Of the covariates examined, significant associations were present only for Barthel Index activity of daily living score (aOR = 0.94 per unit change, $P = .01$) and presence of heart failure (aOR = 2.04, $P = .004$); the association with age fell short of significance (aOR = 1.03, $P = .07$).

The risk of ADRs in the intervention group was lower than that in the control group (absolute risk reduction (ARR) = 9.3 percentage points; 21.0% minus 11.7%), indicating a NNT with the STOPP/START intervention of 11 individuals to prevent one individual having an ADR. ADRs occurred at an overall rate of 12.5% in the

Table 3. Drugs and Drug Classes and Associated Adverse Drug Reactions (ADRs)

Drug Class	Adverse Drug Reactions	Control, n = 89 ADRs ^a	Intervention, n = 45 ADRs ^b
Opioids	Delirium, falls, constipation	19	7
Diuretics	Acute kidney injury, electrolyte disturbance	14	8
Antihypertensive medications (excluding ACE-Is, ARBs)	Symptomatic orthostatic hypotension, symptomatic bradycardia	10	8
Benzodiazepines	Falls, sedation, cognitive decline	12	4
ACE-Is, ARBs	Acute kidney injury, hyperkalemia	8	5
Antibiotics	<i>Clostridium difficile</i> diarrhea, vancomycin-resistant enterococci, gentamicin-induced acute kidney injury	4	4
Anticoagulants	Bleeding requiring transfusion with or without hemostasis intervention	8	5
Nonsteroidal anti-inflammatory drugs	Acute kidney injury, gastrointestinal bleeding	8	3
Antiplatelets	Gastrointestinal bleeding	6	1

^an = 78 participants.

^bn = 42 participants.

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

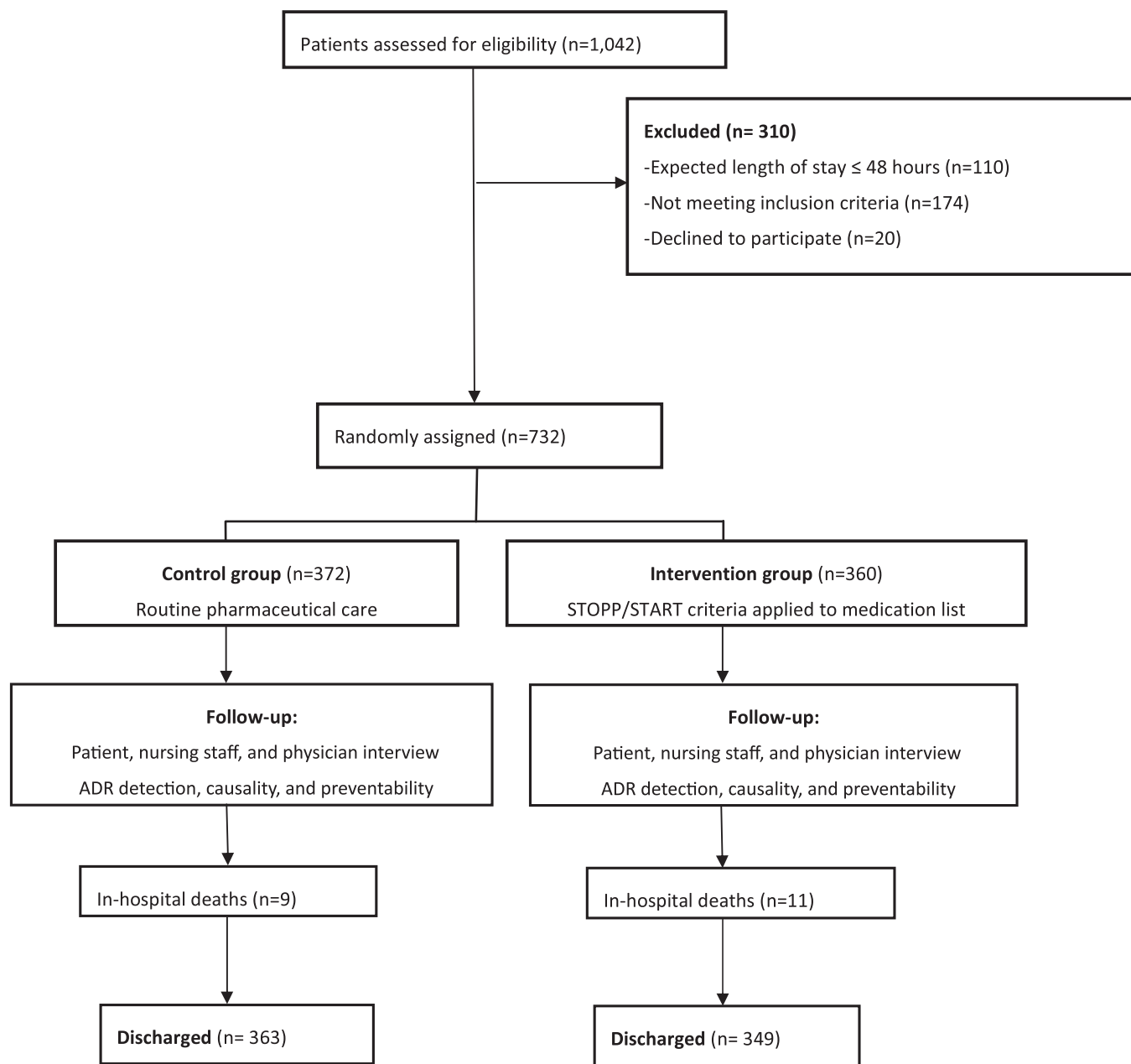


Figure 1. Trial profile. ADR = adverse drug reaction.

intervention group (45 ADRs in 360 participants) and 23.9% in the control group (89 ADRs in 372 participants) (ARR = 11.4 percentage points for ADR occurrence associated with the STOPP/START intervention), with a NNT of nine to prevent one ADR (as distinct from one individual experiencing an ADR, because some participants had more than one ADR during the index admission). Table 5 summarizes these statistics.

Fifty-one of the 89 ADRs (57.3%) that control group participants experienced and 15 of the 45 ADRs (33.3%) that intervention group participants experienced were listed in the STOPP/START criteria ($P < .001$).

Secondary Outcome Measures

Median LOS in both groups was 8 days (IQR 4–14 days) (no significant difference). Not surprisingly, participants

who experienced an ADR had a significantly longer median (10 days, IQR 6–17 days) than those who did not (7 days, IQR 4–14 days) ($P < .001$).

There was no significant difference in the extrapolated median 28-day cost of participants' prescription drugs between the control (€69.11, IQR €36.51–130.00) and intervention (€71.99, IQR €36.06–120.05) groups on admission to hospital ($P = .46$), although the extrapolated median 28-day cost of participants' prescription drugs at discharge was significantly lower in the intervention (€73.16, IQR €38.68–121.72) than the control (€90.62, IQR €49.38–162.53) group (Wilcoxon rank test Z statistic = -3.274 , $P < .001$). The change in median monthly medication cost from admission to discharge was significant in the intervention group (Wilcoxon rank test Z statistic = -2.290 , $P = .02$) and highly significant in the control group (Wilcoxon rank test Z statistic = -3.274 , $P < .001$).

participants and researchers were blinded to the group randomization of each participant and the end points being assessed by a blinded assessor. Similarly, the intervention participants' attending doctors could not be blinded to their randomization group, because they had to decide whether to accept or reject individual STOPP/START criteria recommendations. Nevertheless, every effort was made to minimize observer bias in the primary researcher in the matter of ADR ascertainment; only putative ADRs that met the definition of an ADR described above and that a second blinded researcher confirmed as probable or definite ADRs were accepted as incident ADRs. Also, incident ADRs were defined on the basis of the trigger list of representative clinical events, reducing observer bias. A third limitation is the lack of data on effect on quality of life in the randomization of participant populations; this was not included in the original trial design. A fourth limitation is the lack of hospitalization cost data as an outcome measure, which was beyond the scope of the study.

The cluster randomization resulted in a statistically significant sex imbalance between the control and intervention groups (significantly fewer women in the control group (49.7%) than in the intervention group (63.9%)). Although sex imbalance in any RCT is not desirable, there is no evidence to indicate that sex had a significant influence on the prevalence rates of PIMs, PPOs, or incident ADRs in the present study. Previous studies have shown that women experience higher rates of PIMs and ADRs than men.^{32–34} Given the higher proportion of women in the intervention group, one would have expected higher rates of ADRs in the intervention group if the null hypothesis were true (i.e., the application of the STOPP/START criteria as an intervention has no significant effect on ADR incidence in older adults in the hospital with acute unselected illness). The results show the opposite: a significantly higher rate of ADRs in the control group, which had a significantly smaller proportion of women. Therefore, it is unlikely that the sex imbalance between the groups had a significant influence on the primary outcome results. Although some studies of ADR incidence in hospitalized elderly adults indicate that older age and female sex significantly predispose to ADRs,^{34,35} a recent large-scale retrospective study indicated that multimorbidity and severity of illness, rather than older age and sex, are the principal predisposing factors for ADRs in older adults.³⁶ The groups in the present study were well balanced in terms of multimorbidity, as indicated by the same median Charlson Comorbidity Index score in the two groups.

In summary, this single-center, cluster-randomized clinical trial shows that the application of the STOPP/START criteria as an early single time-point intervention in older people hospitalized with acute, unselected illness results in significantly lower ADR incidence and extrapolated median monthly medication costs than standard pharmaceutical care. Given these findings, routine application of the STOPP/START criteria offers clinically significant ADR prevention benefit to older hospitalized adults, with a favorable NNT of nine to prevent one nontrivial ADR. The second iteration of the STOPP/START criteria³⁷ contains 114 criteria (vs 87 criteria in the first iteration). The new STOPP/START criteria offer a wider range of ADR prevention opportunities to prescribers than the first

iteration, although this remains to be proven in a clinical trial. STOPP/START version 2 will also be the central component of a novel software engine called SENATOR³⁸ designed specifically for prevention of ADRs in older adults that will be tested in a randomized clinical trial in six hospital centers in Europe starting in 2016.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and determined that the authors have no financial or any other kind of personal conflicts with this paper. Stephen Byrne and Denis O'Mahony have part ownership in a patent, "A Prescription Decision Support System" (based on STOPP/START prescribing rules); the patent was registered with the European Patent Office (Munich); Patent No. 11757950.8–1952. They are involved with two European Commission-funded grants that involve clinical trials in which there is computerized deployment of the STOPP/START criteria as part of an intervention designed to optimize pharmacotherapy in older adults. The first EC grant is called "Development and clinical trials of a new Software Engine for the Assessment & Optimization of drug and non-drug Therapy in Older persons [SENATOR]," grant agreement 305930, awarded under the Seventh Framework Programme (FP7). Prof. O'Mahony is coordinator of the SENATOR project. The second EC-funded project is called "OPERAM: OPTimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly." OPERAM is funded under the Horizon 2020 programme (PHC 17–2014). The OPERAM trial is based on another software intervention called Screening Tool to Reduce Inappropriate Prescribing, which uses STOPP/START rules to assess the pharmacotherapy of older people. Joseph Eustace and Paul Gallagher are work package leaders in the SENATOR project.

Author Contributions: O'Connor: participant recruitment, data collection, data analysis, coauthor of manuscript. O'Sullivan: ADR assessment as a blinded ADR rater, control patient recruitment. Gallagher: co-supervision of primary researcher, data analysis, coauthor of manuscript. Eustace: trial design, data analysis, coauthor of manuscript. Byrne: co-supervision of primary researcher, trial design, data analysis, coauthor of manuscript. O'Mahony: codesign of clinical trial, co-supervision of primary researcher, coauthor of the manuscript.

Sponsor's Role: The Health Research Board had no influence on protocol design, conduct of the trial, or data analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Diagnostic profiles of the control and intervention groups.

Table S2. Frequency of potentially inappropriate prescriptions in the intervention group.

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