LESS IS MORE

Potentially Inappropriate Medications Defined by STOPP Criteria and the Risk of Adverse Drug Events in Older Hospitalized Patients

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Background: Previous studies have not demonstrated a consistent association between potentially inappropriate medicines (PIMs) in older patients as defined by Beers criteria and avoidable adverse drug events (ADEs). This study aimed to assess whether PIMs defined by new STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria are significantly associated with ADEs in older people with acute illness.

Methods: We prospectively studied 600 consecutive patients 65 years or older who were admitted with acute illness to a university teaching hospital over a 4-month interval. Potentially inappropriate medicines were defined by both Beers and STOPP criteria. Adverse drug events were defined by World Health Organization–Uppsala Monitoring Centre criteria and verified by a local expert consensus panel, which also assessed whether ADEs were causal or contributory to current hospitalization. Hallas criteria defined ADE avoidability. We compared the proportions of patients taking Beers criteria PIMs and STOPP criteria PIMs with avoidable ADEs that were causal or contributory to admission.

Results: A total of 329 ADEs were detected in 158 of 600 patients (26.3%); 219 of 329 ADEs (66.6%) were considered causal or contributory to admission. Of the 219 ADEs, 151 (68.9%) considered causal or contributory to admission were avoidable or potentially avoidable. After adjusting for age, sex, comorbidity, dementia, baseline activities of daily living function, and number of medications, the likelihood of a serious avoidable ADE increased significantly when STOPP PIMs were prescribed (odds ratio, 1.847; 95% confidence interval [CI], 1.506-2.264; $P<.001$); prescription of Beers criteria PIMs did not significantly increase ADE risk (odds ratio, 1.276; 95% CI, 0.945-1.722; $P=.11$).

Conclusion: STOPP criteria PIMs, unlike Beers criteria PIMs, are significantly associated with avoidable ADEs in older people that cause or contribute to urgent hospitalization.

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INAPPROPRIATE MEDICATION USE IS highly prevalent among older people, particularly those presenting to a hospital with acute illness.[1,2] Certain drugs are considered inappropriate or potentially inappropriate in old age because of the higher risk of intolerance related to adverse pharmacodynamics or pharmacokinetics or drug-disease interactions. These observations have formed the basis for various sets of criteria for potentially inappropriate medication in older people, the best known of which is Beers criteria.[3-5] Beers criteria were developed in the United States and first published in 1991[3] and subsequently revised in 1997[6] and most recently in 2003.[5]

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The 2003 iteration of Beers criteria consists of 2 lists of drugs to be avoided in older people (1) independent of diagnosis and (2) considering diagnosis. Beers criteria explicitly caution prescribers to avoid certain drugs (independent of diagnosis) in all older people and to avoid other drugs in some older people with certain medical conditions because of poor risk to benefit ratio and consequently increased risk of adverse drug events (ADEs). One would

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therefore reasonably expect a significant association between potentially inappropriate medications (PIMs) and ADEs. However, 2 recent large-scale retrospective studies that specifically examined the association between Beers criteria PIMs and the incidence of ADEs[1,7] found no statistically significant association. An Italian study of 1756 older patients admitted to a geriatric unit found that 4.4% of hospitalizations were related to ADEs that

were definitely or possibly avoidable.[8] Of those patients whose hospitalization resulted from potentially avoidable ADEs, one-fifth (<1% of all admissions) had received an inappropriate medication or a drug not indicated for the diagnosed disease. A US-based study using the 2003 iteration of Beers criteria showed no significant causal link between Beers criteria PIMs and ADEs[9] identified from emergency department visits by very large numbers of older patients (n=177 504).

In contrast to these negative study findings, other studies have found a significant association between PIMs and ADEs. A study of 550 older people attending an outpatient clinic in Taiwan found that those taking Beers criteria PIMs had a relative risk of adverse drug reactions more than 15 times that of persons who were not taking Beers criteria PIMs.[10] A smaller-scale Brazilian study of 186 older people[11] found that prescription of a Beers criteria PIM increased the risk of an adverse drug reaction by a factor of 2.3. A recent study of Medicare beneficiaries found that the risk of ADEs was doubled by inappropriate medication use,[12] although the definition of inappropriate medication was not confined to Beers criteria PIMs.

Most studies to date examining the association between PIMs and ADEs have also been limited by their retrospective design and restricted use of the limited "independent of diagnosis" subset of Beers criteria, whose transferability had been questioned because of the inclusion of many medications that are not available outside the United States. The lack of a reproducible, statistically significant association between Beers criteria PIMs and ADEs in these studies is also counterintuitive. If the purpose of defining criteria for PIMs is to highlight the inherent increased risk of ADEs, one would expect a significant and consistent association between Beers criteria PIMs and ADEs. The lack of a consistent association suggests that Beers criteria may be inadequate in their inclusion of drugs linked to the common ADEs seen in older people. Because of these perceived deficiencies of Beers criteria, our research group recently devised and validated a new set of PIM criteria in older people, called STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions).[13,14] STOPP criteria are based on commonly encountered PIMs and are listed according to physiological systems, as is the case with most drug formularies. They include 65 instances of more common and more important PIMs that predispose to ADEs in older people. The inter-rater reliability of STOPP has been established, as well as its performance in languages other than English, in a recent study involving 6 comparable teaching hospital centers in Europe.[15] The essential differences between STOPP criteria and Beers criteria are as follows:

1. STOPP criteria are organized according to physiological systems, whereas Beers criteria are not.
2. STOPP criteria deal with drugs that are currently in widespread use; Beers criteria include several drugs that are no longer available in most European countries, eg, trimethobenzamide, carisoprodol, clidinium-chlordiazepoxide, guanadrel, oxaprozin, and ethacrynic acid.
3. STOPP criteria place special emphasis on potential adverse drug-drug interactions and duplicate drug class prescription, whereas Beers criteria do not.
4. STOPP criteria contain several common instances of potentially inappropriate prescribing that are not mentioned in Beers criteria.[13,14]

STOPP criteria and Beers criteria have several areas of overlap. Both sets of criteria emphasize the higher risk of adverse drug reactions and events in older people with use of long-acting benzodiazepines, tricyclic antidepressants, anticholinergic drugs, and non–cyclooxygenase 2–selective nonsteroidal anti-inflammatory drugs. Both sets of criteria also focus on several common potential adverse drug-disease interactions in older people.

The incidence of STOPP-listed PIMs in older people presenting to a hospital with acute illness is approximately 35%.[2] A recent study of acutely ill older patients showed that ADEs resulting from STOPP criteria PIMs were almost twice as likely to be causal or contributory to hospitalization as ADEs resulting from Beers 2003 criteria.[2] However, the identification of ADEs in that study was based on trained clinical judgment as opposed to strict causality and avoidability criteria.

The aims of the present study were to (1) compare the prevalence of ADEs associated with the PIMs listed by STOPP criteria and Beers criteria, (2) compare STOPP criteria and Beers criteria in terms of their association with avoidable ADEs that cause or contribute to urgent hospital admission, and (3) determine whether ADEs identified by an expert consensus panel are significantly and independently associated with PIMs defined by STOPP criteria and Beers criteria.

METHODS

Ethical approval was sought and obtained by the local research ethics committee. We collected data prospectively on 600 consecutive unselected patients 65 years or older with acute illness at the point of hospital admission. Patients were admitted to a variety of medical and surgical services throughout the hospital. However, all data were collected within the first 24 hours of admission in the emergency department in more than 90% of cases, before patients were transferred to the various appropriate specialist departments. We recorded details of current and previous medical diagnoses, comorbidity burden (Charlson Comorbidity Index score), presence or absence of chronic cognitive impairment, current regular prescription medicines, current blood pressure, hematological and biochemical profiles, electrocardiograph results, and history of drug allergy or intolerance. Nonprescription (over-the-counter [OTC]) medication intake was not recorded because OTC drugs are tightly controlled in Ireland compared with other countries, and consequently, OTC drug use in Ireland is not considered an important cause of ADEs (except in cases of overdose). Activities of daily living (ADL) function was measured using the Barthel Index score.[16] Details were obtained from current hospital records as well as from patient and caregiver interviews. When necessary, patients' primary care physicians and community pharmacists were contacted for essential details.

Detection of PIMs was based on patients' medications at the point of hospital admission, prior to any modifications made by the admitting team. STOPP criteria and Beers criteria were then applied to the combined patient clinical profile and juxtaposed medica-

Table 1. Baseline Characteristics of Patients With and Without ADEs on Admission to Hospital

Variable	No. (%)		Test Statistic For Difference Between Groups	*P* Value
	Patients With at Least 1 ADE	Patients With No ADE		
Age, y				
Median (IQR)	79 (73-84)	77 (72-83)	Mann-Whitney = 31545.00	.07
65-74	48 (30.4)	159 (36)		
75-84	77 (48.7)	195 (44.1)	χ^2_2=1.658	.44
≥85	33 (20.9)	88 (19.9)		
Sex			χ^2_1=4.698	.03
Female	106 (67.1)	253 (57.2)		
Male	52 (32.9)	189 (42.8)		
Place of residence			χ^2_2=21.680	<.001
Home	125 (79.1)	408 (92.3)		
Nursing home	25 (15.8)	29 (6.6)		
Sheltered accommodation	8 (5.1)	5 (1.1)		
Functional level			χ^2=19.677	<.001
Independent in ADLs	86 (54.4)	325 (73.5)		
Needs help with ≥1 ADL	72 (45.6)	117 (26.5)		
Falls			χ^2_1=22.560	<.001
≥1 Fall in 3 mo before admission	125 (79.1)	256 (57.9)		
No falls in 3 mo before admission	33 (20.9)	186 (42.1)		
Hospitalization			χ^2_8=6.104	.64
≥1 In previous year	71 (44.9)	186 (42.1)		
None in previous year	87 (55.1)	256 (57.9)		

Abbreviation: ADEs, adverse drug events; ADLs, activities of daily living; IQR, interquartile range.

tion list, and instances of PIMs were recorded, ie, PIMs that were related to preadmission medications only and did not include prescribed medications during the index hospital admission. Adverse drug events were only included if they occurred after PIM exposure and before hospital management began, ie, ADEs pertaining only to preadmission prescription medications were identified and not those occurring during the hospitalization. An ADE was defined as any noxious, unintended, and undesired effect of a drug, excluding therapeutic failures, intentional or accidental poisoning, and drug abuse.[17] All suspected ADEs were individually analyzed by a panel of 4 experts in geriatric pharmacotherapy (2 physicians [D.O'M. and P.G.] and 2 pharmacists [S.B. and C.R.]) affiliated with the Schools of Medicine and Pharmacy at University College Cork, Cork, Ireland. World Health Organization–Uppsala Monitoring Centre (WHO-UMC) criteria[18] were used to define ADEs, and a consensus agreement of at least 3 of the 4 experts was used to define whether ADEs were (1) causal or contributory to hospital admission or (2) incidental findings detected and not related to the cause of admission. Adverse drug event avoidability was assessed using Hallas criteria.[19] The panel convened weekly in a group forum, discussed each case in detail, and checked reference sources such as the British National Formulary and reputable pharmacology texts. Individual panel members voted on whether the ADE was causal or contributory to admission and whether the ADE met individual Hallas criteria. The panelists were not asked to apply STOPP or Beers criteria to the clinical and prescription information—only to comment on the presence of ADEs and whether they judged the ADE as being (1) causal or contributory to admission and (2) avoidable (using Hallas criteria). All of the criteria, both considering diagnosis and dependent on diagnosis, in the latest iteration of Beers criteria[5] were applied to the preadmission clinical and prescription data. Variables were dichotomously coded, ie, a patient had at least 1 potentially inappropriate prescription according to *all* of Beers criteria or had no inappropriate prescriptions.

The proportions of definitely avoidable or potentially avoidable ADEs detected by STOPP criteria and Beers criteria were calculated to determine any significant difference in the ability of the 2 sets of PIM criteria to detect (predict) clinically relevant ADEs, as determined by expert consensus agreement. These proportions were compared using the χ^2 test. We used multiple logistic regression analysis to determine whether ADEs were independently associated with PIMs as defined by STOPP criteria and Beers criteria. Only 1 logistic regression model was constructed to examine the influence of age, sex, number of medications, burden of comorbidity, cognitive impairment, presence of 1 or more STOPP criteria PIMs, and presence of 1 or more Beers criteria PIMs on the presence of ADEs at the time of admission. SPSS version 15 (SPSS Inc, Chicago, Illinois) was used to process all statistical data.

RESULTS

Details of age, sex, place of residence, functional status, recent falls, and recent hospitalization are presented in **Table 1**. The median age of the entire group of 600 patients was 77 years (interquartile range [IQR], 72-83 years) and 241 patients (40.2%) were male. Of the patients, 48.0% had a Charlson Comorbidity Index score of 2 or higher, and 19.5% of patients had a history of chronic cognitive impairment. A total of 4523 medications were prescribed for the 600 patients (median number, 7 per patient [range, 1-27; IQR, 5-10]); 34.0% of patients were prescribed 5 or fewer daily regular prescription drugs, 46.0% were prescribed 6 to 10 daily drugs, and 20.0% were prescribed more than 10 daily medications. According to STOPP criteria, 610 PIMs were identified in 337 patients (56.2% of all patients). With Beers criteria, 235 PIMs were identified in 173 patients (28.8% of all patients).

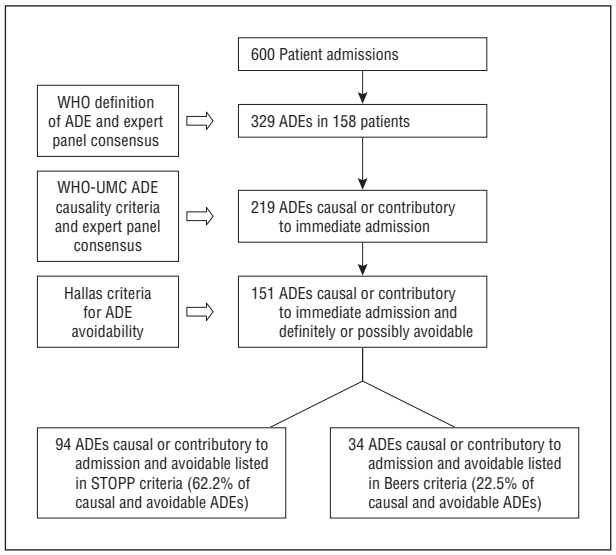

Figure. Flow chart showing how 600 consecutively hospitalized older patients were classified according to the ADEs identified. The chart shows whether ADEs were causal or contributory to admission (WHO-UMC criteria plus expert panel consensus) and whether ADEs were avoidable or possibly avoidable (Hallas criteria). ADEs indicates adverse drug events; STOPP, Screening Tool of Older Persons' potentially inappropriate Prescriptions; WHO, World Health Organization; and WHO-UMC, World Health Organization–Uppsala Monitoring Centre.

Table 2. Most Commonly Prescribed Potentially Inappropriate Medications (PIMs) as per STOPP Criteria[a]

STOPP Criteria PIMs	No.[b]
Proton pump inhibitors for uncomplicated peptic ulcer disease at full therapeutic dosage for >8 wk	128
Aspirin with no history of coronary, cerebral, or peripheral vascular symptoms or occlusive arterial events	66
Benzodiazepines in patients who have had ≥1 fall in the past 3 mo	56
Duplicate drug class prescriptions	56
Long-term (>1 mo), long-acting benzodiazepines or benzodiazepines with long-acting metabolites	48
Loop diuretic as first-line monotherapy for hypertension	24
Long-term use of nonsteroidal anti-inflammatory drugs (>3 mo) for relief of mild joint pain in osteoarthritis	19
Long-term opiates in those with recurrent falls (≥1 fall in past 3 mo)	18
Neuroleptic drugs in those with recurrent falls (≥1 fall in past 3 mo)	16
Long-term opiates in those with recurrent falls (≥1 fall in past 3 mo)	14

Abbreviation: STOPP, Screening Tool of Older Persons' potentially inappropriate Prescriptions.
[a]A total of 610 STOPP criteria PIMs were prescribed to the 600 patients studied.
[b]The number of PIM instances.

Table 3. Most Commonly Prescribed Potentially Inappropriate Medications (PIMs) as per Beers Criteria[a]

Beers Criteria PIMs	No.[b]
Short- to intermediate-acting benzodiazepines and tricyclic antidepressants (imipramine hydrochloride, doxepin hydrochloride, and amitriptyline hydrochloride) in patients with a history of syncope or falls	35
Long-term benzodiazepines or sympatholytics (methyldopa, reserpine, and guanethidine) in patients with depression	26
Long-acting benzodiazepines (chlordiazepoxide, chlordiazepoxide-amitriptyline, diazepam, quazepam, halazepam, and chlorazepate)	25
Doxazosin mesylate	24
Flurazepam hydrochloride	18
Prescription of amitriptyline, chlordiazepoxide-amitriptyline and perphenazine-amitriptyline	18
Short-acting benzodiazepines: doses greater than lorazepam, 3 mg; oxazepam, 60 mg; alprazolam, 2 mg; temazepam, 15 mg; triazolam 0.25mg	13
Prescription of calcium channel blockers, anticholinergics, tricyclic antidepressants (imipramine, doxepin, and amitriptyline) in patients with constipation	11
Prescription of aspirin, nonsteroidal anti-inflammatories, dipyridamole, clopidogrel or ticlopidine hydrochloride in patients with blood-clotting disorders or receiving anticoagulant therapy	10
Amiodarone	8

[a]A total of 235 Beers criteria PIMs were prescribed among the 600 patients studied.
[b]The number of PIM instances.

The breakdown of the study data is illustrated in the **Figure**. A total of 329 ADEs were identified in 158 of the 600 patients (26.3%). Of the 329 ADEs, 36 (10.9%) were judged by consensus agreement to have been the principal cause of the index hospitalization. These 36 ADEs occurred in 36 patients, ie, 6.0% of the total patient population. The consensus panel judged 183 of the 329 ADEs (55.6%) to have been a clinically significant contributory factor to the index hospital admission, as distinct from being the undisputed prime cause. Thus, 219 of 329 ADEs (66.6%) were either causal or significantly contributory to admission in the 158 patients (26.3%) judged by consensus panel agreement to have experienced a clinically significant ADE. Of the 329 ADEs identified by expert panel consensus, 170 (51.7%) involved STOPP criteria PIMs compared with 67 ADEs (20.4%) related to Beers criteria PIMs ($P<.01$), ie, clinically significant ADEs were listed in STOPP criteria 2.54 times more often than in Beers criteria. **Table 2** gives the most commonly prescribed PIMs as per STOPP criteria; **Table 3** gives the equivalent list as per Beers criteria.

Of the 329 ADEs, 235 (71.4%) were classified as avoidable or potentially avoidable according to Hallas criteria. Of these 235 avoidable or potentially avoidable ADEs, 159 (67.7%) involved STOPP criteria PIMs; 67 avoidable or potentially avoidable ADEs (28.5%) involved Beers criteria PIMs, with a significant difference of $P<.001$. Of the total of 329 ADEs, 219 were judged causal or contributory to hospital admission, and of these 219 ADEs, 108 were definitely avoidable and 43 were possibly avoidable, ie, 151 ADEs that were causal or contributory to hospital admission were simultaneously definitely or possibly avoidable according to Hallas criteria. Of these 151 definitely or possibly avoidable ADEs, 94 (62.2%) were listed in STOPP criteria. By comparison, 34 of the 151 definitely or possibly avoidable ADEs that were causal or contributory to admission (22.5%) were listed in Beers criteria, with a significant difference of $P<.001$, ie, definitely or possibly avoidable ADEs relevant to the index admission were listed 2.76 times more frequently in STOPP criteria than in Beers criteria (**Table 4**). **Table 5** gives the

Table 4. Comparison of STOPP Criteria and Beers Criteria in Terms of Total ADEs Identified and Total ADEs Deemed Avoidable (Hallas Criteria)[a]

	STOPP Criteria	Beers Criteria
No. of ADEs of the 329 ADEs identified by expert consensus panel and simultaneously listed in PIM criteria	170[b]	67
No. of consensus panel–identified ADEs deemed avoidable or potentially avoidable (n=235) and simultaneously identified by PIM criteria	159[b]	67
No. of consensus panel–identified ADEs deemed causal or contributory to index hospital admission and simultaneously avoidable or potentially avoidable (n=151) identified by PIM criteria	94[b]	34

Abbreviations: ADEs, adverse drug events; PIM, potentially inappropriate medicine; STOPP, Screening Tool of Older Persons' potentially inappropriate Prescriptions.

[a] The expert panel identified 329 ADEs in 158 of the 600 patients (26.3%), independent of STOPP criteria and Beers criteria. Of the 329 ADEs, 235 were judged to be avoidable or potentially avoidable.

[b] Significant difference (χ^2 test, $P<.001$).

Table 5. Most Common ADEs That Were Classified as Causal or Contributory to Admission and Possibly or Definitely Avoidable as per Hallas Criteria

		No. (%)		
ADE	No. (%)	Attributed to STOPP Criteria PIMs	Attributed to Beers Criteria PIMs	ADEs Appearing Both in STOPP and Beers Criteria
Fall(s) while receiving benzodiazepines	24 (15.9)	24 (100)	22 (91.7)	22 (91.7)
Symptomatic orthostasis while receiving antihypertensives	17 (11.3)	15 (88.2)	1 (5.9)	1 (5.9)
Falls while receiving opiates	10 (6.6)	10 (100)	0	0
Hyponatremia while receiving diuretics	10 (6.6)	0	0	0
Constipation while receiving opiates	6 (4.0)	6 (100)	0	0
Falls while receiving sedative hypnotics	6 (4.0)	0	0	0
Acute kidney injury while receiving diuretics	6 (4.0)	3 (50)	0	0
Symptomatic orthostasis while receiving diuretics	5 (3.3)	5 (100)	0	0
Falls on neuroleptics	5 (3.3)	5 (100)	1 (20)	0
NSAID-related gastritis/peptic ulcer disease	4 (2.6)	3 (75)	1 (25)	1 (25)
Bradycardia while receiving β-blockers	4 (2.6)	0	0	0

Abbreviations: ADEs, adverse drug events; NSAID, nonsteroidal anti-inflammatory drug; PIMs, potentially inappropriate medicines; STOPP, Screening Tool of Older Persons' potentially inappropriate Prescriptions.

most common ADEs that were judged causal or contributory to the index hospitalization and simultaneously definitely or possibly avoidable.

After adjusting for age, sex, comorbidity, chronic cognitive impairment, baseline ADL function, and number of medications, the likelihood of an ADE increased by 84.7% with each STOPP criteria PIM (odds ratio, 1.847; 95% confidence interval, 1.506-2.264; $P<.001$) (eTable; http://www.archinternmed.com). In contrast, prescription of a Beers criteria PIM did not significantly increase the likelihood of an ADE (odds ratio, 1.276; 95% confidence interval, 0.945-1.722; $P=.11$).

COMMENT

The principal findings of this study include the following:

1. Adverse drug events in acutely ill older patients presenting to a hospital involved STOPP criteria PIMs 2.54 times more frequently than Beers criteria PIMs.

2. Avoidable or potentially avoidable ADEs identified in these patients involved STOPP criteria PIMs in 67.7% of instances, compared with Beers criteria PIMs in 28.5% of instances.

3. Adverse drug events that were definitely or possibly avoidable and simultaneously causal or contributory to urgent hospitalization were listed in STOPP criteria almost 2.8 times more frequently than in Beers criteria—a significant difference.

4. After adjusting for age, sex, ADL functional status, comorbidity, cognitive impairment, and number of medications, the likelihood of patients experiencing an ADE was almost 85% higher if they were prescribed STOPP criteria PIMs than if they were not prescribed STOPP criteria PIMs—a significant difference. In contrast, being medicated with Beers criteria PIMs did not significantly increase patients' odds of experiencing an ADE.

The present study results indicate that STOPP criteria are more sensitive to PIMs that result in ADEs than Beers criteria and are therefore more clinically relevant. To be clinically relevant, PIMs included in a prioritized list to assist the prescriber or medication reviewer in minimizing drug-related adversity should contain a high proportion of drugs that actually cause or predict clinically significant ADEs. The data from the studies by Onder et al[1] (2005) and Laroche et al[7] (2007) indicate that Beers criteria were insufficient in this regard and are therefore of questionable relevance to the prevention of ADEs in

older people. Particular strengths of the present study include its prospective design and the fact that all relevant clinical and laboratory data were collected contemporaneously, enabling the full deployment of Beers criteria both independent of and considering diagnosis (unlike most studies to date). This study also examined ADE avoidability using the widely cited Hallas criteria to determine the proportion of ADEs that could reasonably have been predicted and prevented, as distinct from those ADEs resulting from unpredictable idiosyncratic medication reactions, or ADEs arising from medications that are clinically appropriate (eg, bleeding with anticoagulants). The scrutiny of all possible or suspected ADEs by a panel of experts in geriatric pharmacotherapy is likely to have maximized the detection of potential ADEs, unlike most published studies to date, which are retrospective and either do not define ADEs at all or in some instances rely on patients' self-reports of ADEs.[12] Using a more rigorous approach, we show that the PIMs listed in STOPP criteria are significantly more likely to be associated with carefully identified ADEs than were PIMs listed in Beers criteria. Thus, STOPP criteria as a process measure of prescribing appropriateness can be clearly linked to an important health outcome, ie, ADEs. In contrast, Beers criteria PIMs in the present study were not significantly associated with a significantly higher risk of ADEs. We believe that this finding strengthens the argument for the use of STOPP criteria in everyday clinical practice as a means of reducing the risk of ADEs in older patients.

Previously published data from our group show that the prevalence of STOPP criteria PIMs in older people is appreciable in various clinical settings, ie, 21.4% in primary care,[20] 34.5% in secondary (hospital) care,[2] and 73.1% in nursing home care.[21] Given the current data showing that PIMs are clinically significant in relation to ADEs, application of the STOPP criteria to drug prescribing and dispensing in older people could be highly valuable as a routine screening tool. This is particularly relevant currently, given the recent indication that ADEs constitute the fifth leading cause of death in the United States[22] and other data showing that ADEs are a major cause of hospitalization in older people[2,23] as well as excess cost to the US taxpayer to a level of over $200 billion annually.[24] While there is a lack of research data from prospective studies to show that routine application of STOPP criteria results in significantly fewer major ADEs, recent data from a single-center randomized controlled trial carried out by our research group[25] show that older hospitalized patients randomized to receive single time point–structured application of STOPP criteria to their medication lists had significantly improved medication appropriateness on hospital discharge compared with patients receiving routine pharmaceutical care. Importantly, the improvement in medication appropriateness was maintained at 6 months' follow-up after discharge.

The STOPP criteria are not designed to capture all instances of potentially inappropriate prescribing in older people. Such a list would be too unwieldy to be of practical value in regular clinical practice. Rather, STOPP criteria represent the more common *avoidable* instances of inappropriate prescribing in older people in day-to-day clinical practice. For this reason, instances of obvious ADEs such as bleeding associated with coumarin use and hypoglycemia associated with insulin use are not included in STOPP criteria. STOPP criteria are designed to be used in tandem with START (Screening Tool to Alert doctors to Right Treatment) criteria.[14] START criteria have been validated[14] in the same fashion as STOPP criteria and represent the more common instances of inappropriate *omission* of potentially beneficial medication for no valid clinical reasons. As with STOPP criteria, the prevalence of potentially inappropriate omission of beneficial drugs is substantial in older person populations in primary care (22.7%)[20] and hospital care (57.8%).[25]

The clinical benefit of using STOPP criteria as a tool to prevent ADEs in older people remains unknown. However, given the data showing that routine application of STOPP criteria significantly improves medication appropriateness compared with standard pharmaceutical care,[24] there are reasonable grounds to propose that STOPP as an intervention tool might also attenuate ADE incidence in older people. However, another randomized controlled trial is needed to address this research question. A further important question is whether routine application of STOPP and START criteria leads to significant reductions in medication costs and health care utilization costs.

There were some limitations to the present study. Nonprescription OTC medications were not included in the data collection, and there is a possibility that some ADEs were related to OTC drugs not included in the analysis of PIMs. However, it is unlikely that OTC drugs had a significant influence on ADEs in the present study. Recent unpublished data (2011) from our research group on OTC drugs taken by older people with acute unselected illness who are seen at the same hospital as described in the present study show that the only OTC drug taken with any regularity is acetaminophen on an as-occasion-requires basis for pain relief. Also, the strength of the temporal relationship between the introduction of PIMs and the onset of ADE symptoms was not determinable in the present data set. Similarly, the duration of treatment with PIMs identified in this study was not recorded. Often, however, the onset of ADEs relating to PIMs in older people is subtle and insidious, eg, toxic effects of digoxin in patients with chronic kidney disease of gradual progression and falls relating to the use of neuroleptics. Instead, the study was firmly focused on the presence or absence of PIMs, regardless of duration of treatment.

Criteria for PIMs are not meant to replace clinical judgment; rather, they are designed to enhance clinical evaluation of pharmacotherapy in older patients. Criteria for PIMs in older people should be of benefit for prevention of avoidable ADEs associated with prescription of such PIMs. The present data indicate that STOPP criteria meet this necessary requirement, whereas Beers criteria do not.

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INVITED COMMENTARY

Medication Safety

Are We There Yet?

Despite over 2 decades of research into medication safety, preventable adverse drug events (ADEs) continue to be a problem of epidemic proportions in the outpatient setting. A recent systematic review estimates that 18 ADEs and almost 7 preventable ADEs occur per 100 outpatients annually.[1] Reasons for the relative lack of progress include the ever-increasing use and types of medications at our disposal, an incomplete understanding of the causes and predictors of ADEs, and the lack of tools and techniques proven effective in improving medication safety, particularly in the outpatient setting. But by far the biggest problem is the lack of implementation of those tools already shown to be effective. For example, in Massachusetts in 2007,

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only 35% of surveyed practices used an electronic health record, and between 2005 and 2007 there had been no significant increase in the availability or use of 9 of 10