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Screening tools for the assessment of prescribing in older patients. Should we STOPP & START?

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Abbreviations	Definitions
ACE(I)	Angiotensin Converting-Enzyme Inhibitors
AchEIs	AcetylCholinEsterase Inhibitors
ACOVE	Assessing Care Of Vulnerable Elders
ADE	Adverse Drug Event
ADL	Activity of Daily Living
ADR	Adverse drug reaction
AF	Atrial Fibrillation
AGS	American Geriatrics Society
AMO-tool	Appropriate Medication for Older people-tool
AOU	Assessment Of Underutilization index
ARB	Angiotensin Receptor Blocker
ATC	Anatomical, Therapeutic and Chemical classification system
b.i.d	*bis in die*, twice a day
BFC80+	BELFRAIL cohort
BMI	Body Mass Index
BNF	British National Formulary
CCB	Calcium Channel Blocker
CDSS	Clinical/Computerized Decision Support Systems
CGA	Comprehensive Geriatric Assessment
CHADS2	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischemic attack history (cardio-embolic risk)
CI	Confidence interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COREQ	Consolidated criteria for reporting qualitative research
(Cr)Cl	(Creatinine) Clearance
(e)GFR	(Estimated) Glomerular Filtration Rate
EUGMS	European Union Geriatric Medicine Society
FEV1	Forced Expiratory Volume at the end of the first second
FG	Focus Group
GDS-15	Geriatric Depression Scale
GEM	Geriatric Evaluation and Management
GI	Gastro-Intestinal
GP	General Practitioner
HEMORR2HAGES	Hepatic or renal failure, Ethanol abuse, Malignancy, Older age, Reduced platelet count or function, Rebleed risk, uncontrolled Hypertension, Anaemia, Genetic factors, Excessive fall risk, Stroke (bleeding risk)
HTA	Hypertension
IGCT	Impatient Geriatric Consultation Teams
IPET	Improved Prescribing in the Elderly Tool
ISAR	Identification of Seniors At Risk
IT	Information Technology
INR	International Normalized Ratio
MAI	Medication Appropriateness Index
MDRD	Modification of the Diet in Renal Disease
MMSE	Mini Mental State Examination

NOACs	New Oral Anticoagulants
NORGEP	Norwegian General Practice
NS	Non significant
NSAID	Non Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
p.r.n.	*pro re nata*, as needed
PIM	Potentially Inappropriate Medication
PIP	Potentially Inappropriate Prescribing
PPO	Potential Prescribing omission
PPV	Positive Predictive Value
QE	Quality of Evidence
RA	Rheumatoid Arthritis
RASP	Rationalisation of home medication by an Adjusted STOPP list in older Patients
RCT	Randomized Control Trial
SD	Standard Deviation
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
SPSS	Statistical Package for the Social Sciences
SR	Strength of Recommendation
SSRI	Selective serotonin re-uptake inhibitors
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions
t.i.d.	*ter in die*, three times a day
TCA	Tricyclic antidepressant
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist

French Abbreviations	**Definitions**
AFMPS	Agence Fédérale des Médicaments et des Produits de Santé
AINS	Anti-Inflammatoire Non Stéroïdien
AVK	Anti Vitamine K
BPCO	Broncho-Pneumopathie Chronique Obstructive
CI	Contre Indication
GLEMs	Groupes Locaux d'Evaluation Médicale (local continuous training)
IEC(A)	Inhibiteur de l'Enzyme de Conversion (de l'Angiotensine)
IPP	Inhibiteur de la Pompe à Proton
ISRS	Inhibiteur Sélectif de la Recapture de Sérotonine

FOREWORD

This research was undertaken as part of the clinical pharmacy activities of the Geriatric Medicine department at the Cliniques universitaires Saint-Luc (Brussels), starting a few years ago. Over the past few years, there has been growing interest in clinical pharmacy, and the implementation of clinical pharmacy services in Belgium has increased. Key factors in this recent development include important publications on the impact of clinical pharmacy services [1, 2], the success of local projects in both academic and non-teaching hospitals, the federal funding for pilot projects throughout the country [3, 4], and the essential confidence of local health care teams.

The clinical pharmacy activities in Saint-Luc offered research opportunities into the impact of pharmaceutical care, but also more generally into pharmacotherapy. One of my aims, as clinical pharmacist, was to find and incorporate practical tools that would improve the appropriateness of treatments in our geriatric ward. This led us to consider a recently published screening tool called STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) [5], which was the starting point for this project in 2009.

This project was able to develop in a favourable context for several reasons. Firstly, adverse drug events in elderly patients are a priority concern, not just for the pharmacist, but for the entire geriatric team, due to their frequency [2, 6, 7], the severity of their consequences for the patient and for the society (re-admissions, costs) [7-14], and the possibility of preventing them by reducing the burden of inappropriate medications [7, 15]. Hospital admission is an opportunity to screen for inappropriate prescribing. This research was initiated by Pr. B. Boland, geriatrician and coordinator of the geriatric liaison team at Saint-Luc, and had the full support of this team, all of whom were interested in the potential use of STOPP&START as a screening tool. Secondly, the Université catholique de Louvain (UCL) is a pioneer in the development of clinical pharmacy. The first Belgian PhD thesis on clinical pharmacy was conducted at UCL in 2006 on the implementation of clinical pharmacy in a department of geriatric medicine [1, 2]. This research was undertaken by Pr A. Spinewine, who is promotor of this project. In 2009, UCL created its first academic position in clinical pharmacy and set up the Clinical Pharmacy Research Group (CLIP) within the Louvain Drug Research Institute (LDRI). Several research projects are currently being undertaken at the Cliniques universitaires Saint-Luc, in collaboration with the CHU UCL Mont-Godinne-Dinant. Finally, the Belgian Federal Public Health is funding two pilot projects at Saint-Luc:

one of the aforementioned clinical pharmacy pilot projects [3, 4], and a pilot project on the implementation of a geriatric consultation team for inpatients [16]. This provided a favourable background for this research.

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INTRODUCTION

This thesis presents and discusses original data on the use of STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) in clinical practice as a way of screening for inappropriate prescribing and optimising the appropriateness of pharmacological treatment in elderly patients.

The Introduction is divided into three sections. First is a presentation of the particularities and challenges of prescribing for elderly patients, including an excerpt from a book chapter on drugs in older people. This excerpt also introduces the concept of inappropriate prescribing and the tools available for detecting inappropriate prescribing. This is followed by an article written for general practitioners describing the STOPP&START tool, from its development to useful lessons for general practice. Finally, a review summarises the current knowledge about STOPP&START and compares this tool with others aimed at screening for inappropriate prescribing.

INTRODUCTION I – Drugs and the elderly

I.1. General introduction

I.2. Clinical pharmacy in geriatrics

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Excerpt from the textbook "Pharmacie clinique et thérapeutique" (4e édition, 2012)

I.1. General introduction

This general introduction gives an overview on issues related to prescribing in older patients and interventions to optimize pharmacotherapy in the elderly, and summarizes the key messages of the next section, "Clinical pharmacy in geriatrics".

Older patients present a challenge for clinical pharmacy, often presenting with multiple co-morbidities, atypical symptoms, polypharmacy (approximately 40% of patients aged over 75 years take at least 5 medications a day [1]), and frailty features. The risk for adverse drug events in this population is particularly high. Adverse drug events are approximately twice as frequent in older patients when compared with younger adults, yet a substantial proportion of these are preventable [2].

WHY ARE OLDER PATIENTS MORE AT RISK OF ADVERSE DRUG EVENTS?

First, older patients often present with multicomorbidities, which require the prescribing of several drugs. Higher is the number of drugs taken, as increased is the risk for ADEs [2]. Second, pharmacodynamic and pharmacokinetic age-related changes modify the sensitivity to the drugs [2]. Third, the risk for adverse drug events (ADEs) is increased by frailty [3], a feature presented by several older patients defined by Clegg et al. as "*a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability*" [4]. Fourth, compliance issues, due for example to isolation, multiple prescribers or cognitive impairment, might precipitate ADEs [2]. Fifth, little evidence is available in older patients. This population is frequently excluded from clinical trials. Therefore use of drugs in older patients is more often based on an extrapolation of guidelines in younger patients than on evidence-based medicine.

Finally, ADEs are associated with the use of potentially inappropriate medications in older adults [2]. Inappropriate prescribing is a preventable cause of ADEs. Optimization of appropriateness of prescribing is a priority for clinical pharmacists in geriatrics.

INAPPROPRIATE PRESCRIBING

Inappropriate prescribing is a well-known problem in older patients, in ambulatory care, in nursing homes and in acute care, and is related to adverse clinical outcomes, higher costs and decreased quality of life [5]. Inappropriate prescribing can be divided into three categories: overprescribing (use of a drug without valid indication); misprescribing (use of a drug with a valid indication but with problems i.e. inappropriate duration, dose, choice of molecule, costs, interactions, or route of administration) or underprescribing (lack of an indicated drug). Several implicit (judgement-based) and explicit (criterion-based) screening tools are available for use to screen for inappropriate prescribing. Use of the explicit Beers list, for example, is frequently reported in the medical literature. Beers list, developed in the United States of America, deserves attention for being the first tool to be published and for drawing attention to some high-risk drugs. However, many of the drugs listed are not available in Europe, some of the drugs listed still have valid indications, and this tool does not address underprescribing. The STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) tool, which was developed in Ireland and published in 2008, presents some advantages over the Beers list in terms of relevance, comprehensiveness, and predictive validity. STOPP&START has potential to be used by European clinical pharmacists. The implicit MAI tool is very comprehensive and has potential educational value, but is more time consuming. Screening tools are further described in Introduction III.

OPTIMIZATION OF PHARMACOTHERAPY IN OLDER PATIENTS

Several approaches can be implemented to improve appropriateness of prescribing in older patients, on the individual or on the population scale.

Extension of knowledge

To help clinical decision-making in older patients, evidence in this population should be enhanced. Therefore, older patients, presenting frailty and multimorbidity, should be enrolled in clinical trials. The European Union Geriatric Medicine Society and the American Geriatrics Society advocate age-specific regulations in drug registrations [6].

Clinical practice guidelines are rarely including information related to older patients with multimorbidity [7]. The Italian project CRIteria to assess appropriate Medication use among Elderly complex patients (CRIME) develops guidance on common diseases in older patients, taking into account geriatric conditions, functional and cognitive status and life expectancy [8].

Educational interventions

Continuing education, including interactive teaching, mailed educational material combined with feed-backs, and face-to-face visits to physicians have mixed effects on appropriateness of prescribing [9]. Passive dissemination of guidelines is not effective but educational interventions including workshops, meetings and regular reports improved the drug treatment [5, 9]. Sensitization of healthcare professionals about prescribing in older patients by individualized, interactive, multidisciplinary and multi-faceted programs should be encouraged.

Multidisciplinary approaches

Multidisciplinary teams allow the management of the older patient complexity at several levels, including pharmacotherapy. Case conferences involving for example general practitioners, pharmacists, geriatricians, and nurses reduce inappropriate prescribing in nursing homes [9]. Multidisciplinary team work and geriatric evaluation and management units have a positive impact on the drug treatment [9].

Pharmacotherapy optimization is not only the role of the physician and the pharmacist anymore. Nurses are increasingly involved in medication reviews in addition to activities related to the administration of the drugs [6]. Among others, the nurses have an important role in detecting and documenting ADEs.

Interventions to improve adherence

As poor adherence increases the risk for ADEs, some interventions target that aspect specifically. Older age itself is a poor predictor of non adherence to the treatment. However, older patients might cumulate several risk factors such as higher

co-morbidities, cognitive impairment, ADEs, and logistic barriers [6]. Multifaceted interventions most frequently involve patient education, combined with behavioural interventions including packaging changes (pillboxes), provided cues for medication taking and involvement of the patient in self-monitoring of symptoms and/or managing medications [6]. Interventions can also include a medication review, to simplify the drug regimen. Pharmacists, in collaboration with nurses, physicians and other healthcare professionals can be actively involved in adherence improvement.

Medication review

Pharmacists- or multidisciplinary-conducted medication reviews have been described in nursing homes, ambulatory setting and in hospitals and showed improvements in appropriateness of prescribing [10].

Medication review will inevitably lead to decision-making regarding the drug regimen. The pharmacist can ensure the good conduct of the process both in case of initiation or discontinuation of drugs. Recommendations for the discontinuation of medicines in the elderly include: assessment of actual use of the drug by the patient, discontinuation of one drug at a time, tapering, monitoring of withdrawal effects, communication with the patient and shared-decision making about the discontinuation.

Pharmaceutical care in older patients.

Optimization of prescribing through pharmaceutical care is a process in which the pharmacist collaborates with the patient or other healthcare professionals to design, implement and monitor specific, individualized goals in relationship with the drug regimen [10]. Pharmaceutical care is a comprehensive process, that goes beyond medication review and that put the patient at the centre. Treatment goals should be individualised, taking into account the patient's medical and functional status, quality of life, and preferences [11]. Identification and management of drug related problems require a good knowledge of the patient issues with prescriptions, follow-up, administration and compliance.

The impact of pharmaceutical care on appropriateness of prescribing has been studied in different settings, i.e. hospital, ambulatory care and nursing home [9, 10] (e.g.

the Fleetwood Model of Pharmaceutical Care, that combines medication review, screening for high-risk medicines and ADEs, communication with the prescriber and management of drug-related problems in nursing home residents [12]). Pharmaceutical care has a favourable effect on appropriateness of prescribing but also, when conducted in acute care, on hospital visit after discharge [10, 13]. Frail older patients may particularly benefit from pharmaceutical care.

MULTISTEP APPROACH TO GERIATRIC DRUG TREATMENT

Pharmacotherapy management in older patient is a complex process. Topinková et al. suggest a four-step approach to geriatric drug management [6]. The pharmacist, in collaboration with the other healthcare professionals, can play an leading role at each step of the process.

The first step consists of information gathering about the current drug treatment, but also about the medical needs, the preferences and individual health goals of the patient, and adherence. This information gathering should be part of a multidisciplinary comprehensive geriatric assessment (CGA). The CGA will help having a global overview of the patient complexity, i.e. the presence of geriatric syndromes, functionality, cognitive status, social environment and co-morbidities. The data collected allows the detection of risk factors for ADEs and consequently the patients who could benefit the most from a medication review and a screening of their treatment to detect potentially inappropriate prescribing.

The second step relates to prescribing. Structured medication reviews, case conferences and individualized goal-driven medication selection are important components of this step. Pharmacists or other healthcare professionals will perform at this stage detection of potentially inappropriate prescribing.

Medication dispensing and administration, the next step, gives the pharmacist the opportunity to assess medication adherence.

The fourth and last step, encompass the follow-up and monitoring of the drug treatment effectiveness. Particular attention should be paid to transitions and seamless care. The pharmacist has an important role on continuity of care. Periodic reassessment of appropriateness of drug regimen should be encouraged.

KEY MESSAGES

- Older patients are at higher risk of ADEs.
- Drug treatment must be tailored to geriatric particularities and to the patient individual situation and health goals.
- Pharmaceutical care are useful in this population. The pharmacist contributes to the detection of inappropriate prescribing and optimization of pharmacotherapy.
- Screening tools, such as STOPP&START, help to the systematic detection of inappropriate prescribing.
- Other approaches to optimize pharmacotherapy include educational interventions, multidisciplinary teams, optimizing adherence and medication reviews.

I.2. Clinical pharmacy in geriatrics

This text is an excerpt from the French-language textbook on clinical pharmacy and pharmaceutical care entitled "Pharmacie clinique et thérapeutique" (Calop, J., Limat S. And C. Fernandez-Maloigne, fourth edition, 2012, Elsevier Masson). This excerpt is taken from the chapter on drug management in the elderly, written by us at the behest of the book's first author.

MÉDICAMENTS ET PERSONNES ÂGÉES

Généralités

Le vieillissement de la population est une réalité à l'échelle mondiale, et ce phénomène va se poursuivre dans les décennies à venir, avec comme caractéristique importante une progression démographique plus marquée pour les personnes de 85 ans et plus. D'ici 2025, presque 1 personne sur 5 sera âgée de 65 ans ou plus, et les personnes âgées de 85 ans et plus représenteront quant à elles 3% de la population. ***[...]*** Les personnes âgées dites « fragiles », ou « à profil gériatrique », doivent certainement retenir toute notre attention.

La fragilité peut être envisagée comme un ensemble de caractéristiques d'un patient âgé qui le prédispose à une évolution vers le déclin fonctionnel (perte de capacité), ou qui augmente chez lui le risque d'apparition de syndromes gériatriques. Ces syndromes sont les suivants: instabilité et chutes, confusion aiguë (delirium), incontinence, dénutrition, infections, immobilisation, effets iatrogènes. Les effets iatrogènes sont donc reconnus, à juste titre, comme un élément important dans le concept de fragilité.

D'un point de vue clinique et pharmaceutique, les personnes âgées ont souvent de multiples comorbidités qui nécessitent la prise de plusieurs médicaments. En moyenne, 40% des personnes âgées de plus de 75 ans prennent au moins 5 médicaments par jour, et les chiffres sont généralement plus élevés pour les personnes

institutionnalisées et hospitalisées. Dans une étude récente menée dans plusieurs hôpitaux en Europe, le nombre médian de médicaments pris était de 6 et 44% des patients prenaient plus de 5 médicaments par jour [1]. Une autre particularité de la population âgée concerne la présentation clinique des problèmes médicaux qui est souvent atypique. ***[...]***

Problèmes liés à l'utilisation des médicaments chez la personne âgée: généralités

Epidémiologie

La littérature internationale met clairement en évidence que l'utilisation dite "inappropriée" des médicaments chez les personnes âgées est courante. Les événements iatrogènes sont environ deux fois plus fréquents chez les personnes âgées par rapport aux adultes en général. Cette utilisation inappropriée peut avoir des conséquences délétères en termes cliniques, économiques, et de qualité de vie des patients. Quelques exemples chiffrés pour illustrer la problématique: une étude à très large échelle réalisée aux Etats-Unis, chez des personnes âgées non institutionnalisées, a rapporté que sur plus de 1500 événements iatrogènes détectés, plus d'1/4 d'entre eux auraient pu être évités ***[...]***. Une conséquence clinique importante de ces événements iatrogènes est l'hospitalisation. On estime qu'entre 5 et 25% des admissions à l'hôpital sont la conséquence d'un événement iatrogène, et qui aurait pu être évité dans presque un cas sur deux. En termes économiques, une étude américaine a évalué pour chaque dollar dépensé pour l'achat d'un médicament, le coût de la prise en charge des événements iatrogènes s'élève à 1.33 dollars.

Pourquoi la personne âgée est-elle plus à risque ?

Tout d'abord, les personnes âgées souffrent souvent de plusieurs comorbidités, qui nécessitent la prescription concomitante de plusieurs médicaments. ***[...]***. Or, il est bien démontré que plus le nombre de médicaments prescrits augmente, plus le risque d'événement iatrogène est grand.

Ensuite, ***[...]***, les modifications pharmacocinétiques et pharmacodynamiques augmentent le risque iatrogène si le prescripteur n'en tient pas compte (principalement

pour adapter les doses). D'autres facteurs moins directement liés à l'aspect médical peuvent jouer un rôle déterminant dans l'iatrogenèse. Il s'agit par exemple de problèmes de compliance, dont les causes peuvent être nombreuses.

Enfin, il est important de mentionner que l'on dispose de relativement peu de données de type « evidence-based medicine » spécifiques à la population âgée fragile. Ces personnes sont souvent exclues des études cliniques, et on ne peut donc se contenter que d'extrapolation de données d'études cliniques réalisées avec des personnes plus jeunes et/ou en meilleure santé. C'est une limitation importante, qui peut expliquer que l'approche thérapeutique est souvent plus « empirique », et donc en partie plus susceptible de mener à des effets iatrogènes.

Prescription et suivi de la prescription

Catégories de prescription inappropriée

Les erreurs de prescription, ou prescriptions dites « inappropriées », sont une des causes principales d'événements iatrogènes chez la personne âgée. On distingue en général trois catégories de prescriptions inappropriées. Le tableau 1 illustre quelques exemples fréquents pour chacune de ces catégories.

Premièrement, il peut s'agir d'une utilisation (ou prescription) sans indication valable (appelée "*overprescribing*" en anglais). Bien que la polymédication soit souvent justifiée par la présence de plusieurs comorbidités, un message-clé est de réévaluer régulièrement le traitement afin d'arrêter les médicaments non nécessaires. On est souvent frappé de voir qu'aussi bien le médecin que le patient ne se rappellent pas toujours l'indication d'un médicament prescrit depuis plusieurs années.

Deuxièmement, la prescription peut être justifiée, mais être inappropriée par rapport aux critères suivants:

- choix de médicament: certains médicaments sont considérés comme n'étant pas appropriés pour les personnes âgées, parce que les risques liés à leur utilisation l'emportent sur les bénéfices ; dans la plupart des cas, il existe une option thérapeutique plus acceptable ou plus appropriée ;
- dose ;

- modalités d'administration, qui peuvent être non correctes ou non pratiques pour le patient;
- interaction médicament-médicament ou médicament-maladie ;
- durée de traitement (ce qui peut de surcroit avoir des conséquences sur le coût pour le patient et la société) ;
- coût.

Le terme de "*misprescribing*" est alors utilisé. La cascade médicamenteuse en est un cas particulier. Elle débute lorsqu'un effet indésirable d'un médicament est interprété comme étant un nouveau problème médical, et qu'un nouveau médicament est introduit pour traiter ce problème, alors qu'il faudrait en priorité envisager une alternative au médicament ayant provoqué l'effet secondaire initial. ***[...]***.

Enfin - et il s'agit d'une catégorie souvent oubliée -, la non-prescription d'un médicament alors qu'il y a une indication pour prévenir ou traiter une maladie (appelée "*underprescribing*") est également très fréquente. Une des raisons à l'origine de cette sous-prescription est appelée « âgisme », c'est à dire que le médecin décide de ne pas donner le médicament « parce que le patient est trop âgé ». Prendre l'âge seul comme critère de décision thérapeutique n'est pas acceptable. Ce type de décision doit plutôt venir d'une réflexion globale sur le statut du patient, ses préférences, et les objectifs du traitement.

Outils pour évaluer la prescription chez la personne âgée

Afin d'optimiser la prescription chez la personne âgée et de minimiser les risques d'effets indésirables, il est important d'évaluer le rapport bénéfice-risque des médicaments prescrits, de réévaluer régulièrement la pharmacothérapie, de prioriser les pathologies selon le processus évolutif et de revoir les mesures pharmacologiques selon les résultats recherchés.

Différents outils existent afin de pouvoir évaluer au mieux la prescription de médicaments chez la personne âgée. Ces outils trouvent leur intérêt en routine clinique, en recherche, ou encore dans un cadre pédagogique.

Certains consistent en des listes explicites de médicaments ou situations à risque impliquant des médicaments. Par exemple, aux Etats-Unis et au Canada, des consensus

d'experts ont établi des listes de médicaments à éviter chez la personne âgée, parce que les risques liés à leur utilisation sont supérieurs aux bénéfices. La liste la plus connue est celle de Beers [14, 15]. Cette liste a le mérite d'attirer l'attention sur le rapport bénéfice: risque régulièrement défavorable chez la personne âgée. Elle présente toutefois de nombreux inconvénients. Tout d'abord, plusieurs médicaments figurant sur cette liste ne sont pas commercialisés dans d'autres pays, et inversement il est probable que certains médicaments commercialisés dans d'autres et non aux Etats-Unis pourraient y être ajoutés. Plusieurs équipes en Europe ont utilisé cette liste pour développer une liste plus adaptée à leur pays. C'est par exemple le cas de la France [16]. Ensuite, il y a des controverses sur certains médicaments inclus dans ces listes, comme par exemple l'amiodarone. Enfin, il ne faut pas tomber dans le travers de limiter la prescription inappropriée à la prescription de médicaments « à éviter en gériatrie ». En effet, les chiffres issus de la littérature montrent clairement que d'autres problèmes tels que la sur- ou sous-prescription ou que les problèmes d'interactions sont au moins aussi fréquents.

Un nouvel outil intéressant a été créé en 2008 par une équipe irlandaise [17]. Il s'agit des critères STOPP et START. Ces critères reprennent 65 situations cliniques où un médicament ne devrait pas être prescrit (STOPP) et 22 situations où un traitement devrait être introduit (START). Cette liste présente plusieurs avantages par rapport à la liste de Beers, en termes de pertinence, d'exhaustivité et de valeur prédictive pour les événements iatrogènes. Il a même été démontré que l'utilisation de cette liste en routine clinique permettait de diminuer les conséquences cliniques délétères en lien avec la prescription inappropriée. Une nouvelle version est en préparation. Il est à ce jour tout à fait envisageable pour des pharmaciens d'utiliser cette liste pour les aider à évaluer les prescriptions chez les personnes âgées.

D'autres outils sont moins explicites et proposent une liste de questions à se poser ainsi qu'une méthode pour y répondre. La plus connue est le MAI (« Medication Appropriateness Index ») [18]. Cet outil propose, pour chaque médicament pris par le patient, de répondre à 10 questions permettant d'évaluer la qualité de prescription de ce médicament. Une question concerne la surprescription (« y a-t-il une indication valable ? »), les neuf autres concernent le « misprescribing ». Son avantage principal est qu'il est très complet, avec donc pour inconvénient le temps nécessaire pour pouvoir l'appliquer. D'un point de vue pédagogique, l'utilisation de cet outil est un excellent

moyen de former les pharmaciens à la démarche d'analyse des prescriptions en gériatrie.

TABLEAU 1. Exemples prescriptions dites « inappropriées » chez la personne âgée

Catégorie 1. Prescription sans indication valable (« OVER-prescribing »)	
Médicament	**Problème**
Neuroleptiques	Utilisation pour des indications non valables chez des patients déments (par exemple troubles du sommeil, agitation légère, confusion, errance)
Diurétique de l'anse	Utilisation pour des oedèmes des membres inférieurs uniquement causés par une insuffisance veineuse.*
Catégorie 2. Médicament nécessaire mais prescription inappropriée en termes de: («MIS-prescribing »)	
Type de problème	**Exemples**
Dose trop élevée	Ranitidine 300mg/j chez un patient avec insuffisance rénale modérée (risque de confusion) Aspirine 160mg/j chez un patient ayant besoin d'une prévention cardiovasculaire, mais avec antécédent de pathologie ulcéreuse (→ 75-100mg/j tout aussi efficace, mais moins risqué).*
Interaction médicamenteuse	Inhibiteur de l'acétylcholinestérase (type donépézil) pour traiter une démence + anticholinergique pour traiter de l'incontinence urinaire → interaction pharmacodynamique, avec effet antagoniste des deux médicaments Antidépresseurs tricycliques en association à un traitement par opiacés (risque de constipation sévère).*
Interaction médicament-pathologie	Benzodiazépine chez une personne faisant des chutes à répétition, ou ayant des problèmes cognitifs* Prescription d'un médicament à fortes propriétés anti-cholinergiques chez un patient confus, ou avec hypotension orthostatique, hypertrophie prostatique, …*
Catégorie 2. Médicament nécessaire mais prescription inappropriée en termes de: («MIS-prescribing »)	
Mauvais choix de principe actif	prescription prolongée de prazepam pour des troubles du sommeil (longue demi-vie et métabolite actif, risque plus élevé de chute et autres effets secondaires)* Diurétique thiazidique chez un patient avec antécédents de goutte (risque de crise de goutte)*

Formulation non correcte / non pratique pour le patient	Analgésique en gouttes chez un patient vivant seul, avec des problèmes de vue, qui ne pourra que très difficilement compter les gouttes
Coût trop élevé	Spécialité originale alors qu'une alternative meilleur marché existe, et que le patient se plaint du coût de son traitement
Catégorie 3. Pas de prescription alors qu'il y a une indication (« UNDER-prescribing »)	
Pathologie	**Problème**
Ostéoporose	Pas de prise de calcium, vitamine D, bisphosphonate chez des patients avec antécédent de fracture et ostéoporose connue (→ risque de nouvelle fracture, et donc dépendance etc…)*
Insuffisance cardiaque	Non prescription d'un IECA (ou sartan) alors que l'on sait que cette classe de médicament améliore le pronostic (en termes de morbi-mortalité)*

Abréviations: IECA:inhibiteur de l'enzyme de conversion de l'angiotensine ; IPP: inhibiteur de la pompe à proton (type oméprazole), ISRS: inhibiteur sélectif de la recapture de sérotonine (type citalopram)

* Indicateur de prescription inappropriée retrouvé dans les critères STOPP&START.

Soins pharmaceutiques pour les personnes âgées

Eléments clés de la démarche

Les personnes âgées fragiles ayant un risque particulièrement élevé d'événements iatrogènes, elles constituent une population qui peut tirer un bénéfice particulier des soins pharmaceutiques. Toutes les étapes des soins pharmaceutiques s'appliquent à la personne âgée, avec quelques caractéristiques particulières qu'il nous semble utile de mentionner.

La détermination des objectifs du traitement est une étape importante, dont le contenu pourra être très différent de celui d'une personne plus jeune ou non fragile. Les objectifs de la prise en charge globale d'une personne âgée fragile ciblent en général plus le maintien de l'indépendance (activités de la vie journalière) et le maintien de la qualité de vie, que la réduction de la mortalité. Ces choix ont des implications importantes pour les décisions ultérieures en termes de pharmacothérapie. Il est donc capital que les objectifs soient clairement définis dès le départ, et si possible avec la participation du patient et/ou de ses proches. Si on prend l'ostéoporose fracturaire comme exemple, on pourrait dans un cas avoir un patient fragile mais qui reste mobile et pour lequel l'objectif prioritaire sera de diminuer le risque d'une nouvelle fracture. Chez ce patient, on envisagera la prescription d'un bisphophonate, de calcium et de

vitamine D. A l'inverse, dans un autre cas, chez un patient avec la même comorbidité mais qui se trouve dans un état grabataire, avec une mobilité nulle, l'objectif principal ne sera pas de limiter le risque d'une nouvelle fracture mais plutôt d'assurer le confort du patient, y compris en lien avec d'éventuelles douleurs associées à une fracture récente. La prescription d'un bisphosphonate ne sera donc clairement pas envisagée.

Au niveau de l'identification des problèmes reliés à la pharmacothérapie et de l'identification des solutions possibles, il est important de bien connaître les problèmes de prescription, de suivi, d'administration et de compliance ***[...]***. Le tableau 2 reprend certains éléments importants associés à la prescription de nouveaux médicaments ou l'arrêt de médicaments.

Enfin, les personnes âgées transitent fréquemment entre milieux de soins, par exemple en lien avec une hospitalisation. Il est donc particulièrement important d'optimiser la continuité des soins – et des traitements. Lors de l'arrivée dans un nouveau milieu, l'obtention d'une anamnèse médicamenteuse complète est indispensable mais souvent plus difficile (par exemple car le patient est confus ou parce qu'il ne s'occupe pas lui-même de ses médicaments au domicile). L'hétéro-anamnèse peut donc s'avérer souvent nécessaire. Outre la liste des médicaments pris par le patient, le pharmacien aura à ce moment un rôle important dans l'identification de problèmes liés à la prise et à la gestion des médicaments par le patient (et/ou les proches). Une anamnèse complète permettra également de préparer la sortie d'hospitalisation et d'éviter les discordances entre les prescriptions de sortie et les traitements habituels du patient. Une information individualisée est indispensable à la sortie du patient, et la communication avec les aidants du domicile est essentielle.

TABLEAU 2 – Recommandations pour une prescription appropriée chez le patient âgé

Avant l'introduction d'un nouveau médicament	**Lorsqu'un nouveau médicament est introduit**
Pour éviter une polymédication inutile et potentiellement dangereuse**,** toujours évaluer si les	<u>Débuter à faible dose</u>: Compte tenu des modifications pharmacocinétiques et pharmacodynamiques, de la possibilité

signes et symptômes présentés par le patient sont les conséquences de l'ajout d'un médicament ou d'une modification de dose afin d'éviter une cascade médicamenteuse. Plusieurs syndromes gériatrique (par exemple les chutes, la confusion, la constipation) ont souvent une cause iatrogène.	d'interactions médicamenteuses et du risque accru d'iatrogénicité, un médicament devrait être débuté à posologie réduite chez une personne âgée. De manière générale il faudrait débuter au quart ou à la moitié de la posologie initiale habituellement recommandée chez l'adulte. Cela permet souvent d'éviter les effets secondaires. Construire progressivement: Il est important de définir le plan de suivi de façon assez précise pour distinguer l'émergence d'un syndrome gériatrique d'un effet indésirable atypique et réversible d'un médicament. Pour cette raison et lorsque la condition de la personne âgée le permet, on préfère ajouter, stopper ou modifier un médicament à la fois et s'accorder une période d'observation adéquate avant de poursuivre l'ajustement de la thérapie.

Lorsque l'on arrête un médicament:

- déterminer l'utilisation réelle que le patient fait du médicament ;
- si possible, diminuer ou stopper un seul médicament à la fois, selon la priorité des problèmes ;
- s'il n'y a pas d'urgence, procéder au retrait graduel et progressif du médicament ;
- surveiller l'apparition de symptômes de sevrage ainsi que la réapparition du problème qui était traité par le médicament. De même, si le médicament arrêté était en interaction avec un autre médicament, il peut y avoir une modification de son métabolisme et un déséquilibre de la condition traitée par ce deuxième médicament.

Dans la mesure du possible tout changement de traitement devrait être discuté avec la personne âgée (et proches si nécessaire). De plus les motivations de ces changements ainsi que la liste des médicaments pris par le patient doivent figurer dans le dossier du patient. Ces efforts de communication font partie intégrante de toute stratégie visant à optimiser la prescription des médicaments, et la continuité des soins.

Modèles de pratique

Les autorités sanitaires de plusieurs pays ont mis en place des structures favorisant le développement des soins pharmaceutiques pour les personnes âgées. En parallèle, de nombreuses études expérimentales ont démontré l'impact des soins pharmaceutiques pour les personnes âgées. Plusieurs revues de la littérature sont disponibles à ce sujet et mentionnées dans la bibliographie de ce chapitre.

A titre d'exemple, aux Etats-Unis la législation impose qu'un pharmacien revoie le traitement de chaque résident en maison de repos au moins une fois par mois. Cela a permis, par exemple, de diminuer la prescription inappropriée de neuroleptiques. Le même type de développement des soins pharmaceutiques pour des résidents en maisons de repos a lieu dans de nombreux autres pays, comme l'Australie, l'Angleterre, les Pays-Bas. ***[...]***.

Ce qu'il faut retenir

Les personnes âgées fragiles présentent un risque particulièrement élevé d'événements iatrogènes secondaires à des problèmes de prescription, d'administration, de suivi ou de compliance. L'utilisation des médicaments doit absolument être adaptée en conséquence. Les soins pharmaceutiques en gériatrie sont particulièrement pertinents pour cette population à risque.

Le pharmacien contribue à la détection et à l'optimisation des prescriptions dites « inappropriées », qu'il s'agisse de surprescription, de sous prescription ou de prescription inadéquate par rapport à d'autres critères comme la dose ou les interactions. Des outils à utiliser en routine clinique, tels que les critères STOPP&START, peuvent l'aider dans sa démarche.

Les traitements doivent tenir compte d'objectifs thérapeutiques adaptés à la situation individuelle de chaque patient. Le patient (ou un proche), au cœur de la démarche, doit être consulté à plusieurs niveaux, que ce soit lors de l'anamnèse médicamenteuse qui permettra par exemple d'identifier dans le traitement habituel du patient la cause d'un symptôme ou un problème de compliance, lors d'une discussion pour planifier l'arrêt d'un traitement, ou encore à la sortie d'hospitalisation pour assurer la continuité des soins. *[...]*

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INTRODUCTION II – STOPP&START: a practical tool to screen for inappropriate prescribing in older patients

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STOPP&START : Dépister nos prescriptions inappropriées chez les patients âgés. La Revue de la Médecine Générale (RMG), 2013(305): p. 30-38.

This article was written for general practitioners and aims to describe the STOPP&START tool in a practical way.

SUMMARY IN ENGLISH

STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) is a tool aimed at improving prescribing in older patients over 65 years. It was published in 2008 by an Irish multidisciplinary team. The use of a tool to improve prescribing in older people is important because older people are more sensitive to adverse drug events and are often polymedicated. Evidence on the pharmaceutical management of multimorbid patients is also lacking for this population. The most frequent instances of inappropriate prescribing encountered upon hospital admission are presented. Cardiovascular prevention and the use of psychotropic drugs are the two domains where optimisation is prioritised.

General practitioners play a key role in managing the pharmacological treatment of older people and could incorporate this screening tool into their daily clinical practice. The STOPP&START lists of criteria allow the identification of potentially inappropriate prescribing by excess (STOPP) or by default (START) within minutes, once all of the relevant medical and pharmacological information has been collected. The tool can be used as a check list when reviewing or changing treatments.

This tool can be of valuable assistance in general practice for several reasons: 1) STOPP&START is easy to use and may help the general practitioner to adopt a systematic way of reviewing drug treatments; 2) The criteria contained within the tool are based on frequent clinical conditions in the elderly and are relevant to primary care, and 3) STOPP&START has potential as a tool for preventing hospital admission. However, the use of such a tool will never replace good clinical judgment, and a comprehensive view of the patient's status is required for a relevant medication review.

Finally, the article suggests the use of the tool in primary care as part of an annual medical consultation devoted to medication review, in a shared decision process with the patient.

MG & GERIATRIE

STOPP&START

Dépister nos prescriptions inappropriées chez les patients âgés

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ABSTRACT

STOPP&START is a simple and practical tool that is intended to improve the prescription in elderly patients over 65 years. These two lists of criteria allow to identify within a few minutes potentially inappropriate prescription, either by excess (STOPP) or by default (START). They can be a valuable aid in general practice.

Keywords:
geriatrics, inappropriate prescribing, STOPP/START

***Primum non nocere*, tel était l'adage qui introduisait nos cours de pharmacologie. Cet adage s'avère plus pertinent encore chez nos patients âgés, les plus fragiles de nos patients. L'outil STOPP&START vient à notre secours pour l'optimalisation de nos prescriptions chez ces patients âgés. Le présent article présente cet outil. Tout généraliste devrait désormais l'avoir à sa disposition dans sa mallette.**

PRÉTEST

	VRAI	FAUX
1. L'aspirine reste indiquée en prévention primaire, même chez la personne âgée.	○	○
2. Les anticoagulants sont toujours indiqués en cas de fibrillation auriculaire au-delà de 75 ans.	○	○
3. Les prescriptions inappropriées sont généralement responsables de 5 à 10 % des admissions en service d'urgence.	○	○

Réponses ici.

STOPP&START est un outil simple et pratique constitué de deux listes (STOPP, START) mises à disposition de tout clinicien soucieux de l'adéquation de la prescription chez les patients âgés de 65 ans et plus[1,2]. Depuis sa publication en 2008, de nombreux gériatres, des pharmaciens et, bien entendu, des médecins généralistes, s'en servent[3]. Mais que peut vraiment nous apporter STOPP&START au quotidien?

Pourquoi l'outil STOPP&START

Nos prescriptions médicamenteuses visent à être adéquates. Elles deviennent cependant inappropriées lorsque la balance entre leurs bénéfices et leurs risques n'est pas favorable au patient. Des médicaments qui seraient inappropriés car présents en excès, inutiles ou

RÉSUMÉ

STOPP&START est un outil simple et pratique destiné à améliorer la prescription chez les patients âgés de plus de 65 ans. Il s'agit de deux listes de critères qui permettent en quelques minutes d'identifier les prescriptions potentiellement inappropriées par excès (STOPP) ou par défaut (START) peuvent constituer une aide appréciable en médecine générale.

Mots clefs: Gériatrie, prescription inappropriée, STOPP&START

dangereux (overuse) peuvent être détectés par l'outil STOPP (Screening Tool of Older Person's Prescriptions). A l'inverse, des médicaments utiles à un patient mais qui font défaut (underuse), vont quant à eux être détectés grâce l'outil START (Screening Tool to Alert Doctors to Right Treatment)[1,2]. Les listes STOPP&START sont disponibles aux *Tableaux 1 et 2*, dans une version adaptée à la pratique quotidienne.

Pourquoi la prescription chez les patients âgés requiert-elle une attention particulière et peut-elle bénéficier de l'aide d'un outil? Plusieurs raisons l'expliquent. Tout d'abord, les patients âgés présentent une sensibilité accrue aux effets indésirables médicamenteux. Ainsi, la survenue de chutes et de fractures peut être précipitée chez des patients âgés par la prise de médicaments inappropriés (benzodiazépines, opiacés, neuroleptiques, vasodilatateurs, antihistaminiques selon STOPP) ou l'absence de médicaments indiqués (calcium et vitamine D en présence d'ostéoporose d'après START). De plus, les patients âgés présentent souvent de nombreuses comorbidités, et font l'objet d'une polymédication. Ils reçoivent alors des médicaments qui leur sont souvent prescrits par de multiples prescripteurs. Cette complexité est bien souvent difficile à gérer. Par ailleurs, on dispose d'assez peu de données quant à la sécurité et l'efficacité des médicaments dans la population gériatrique : un manque de preuves cliniques persiste donc dans ce domaine.

Pour ces raisons, on a tout intérêt à rationnaliser l'usage des médicaments chez ces patients, afin de toujours garder la balance bénéfice-risque en faveur du traitement administré. La population vieillissant, le médecin généraliste rencontre de plus en plus de patients âgés, chez qui il doit exercer un rôle central dans la prise en charge souvent complexe du traitement médicamenteux. La remise en question régulière des médicaments à prendre fait partie intégrante des missions du généraliste.

STOPP&START, une démarche originale

La double liste STOPP&START est le fruit d'une initiative de cliniciens irlandais. Au début des années 2000, une équipe multidisciplinaire s'est rassemblée pour développer de façon validée cet outil (en consensus, selon la méthode DELPHI) qui a été publié pour la première fois en 2008 et dont l'adaptation en français est parue en 2009[2]. L'équipe irlandaise comprenait des médecins généralistes et gériatres, des pharmacologues, des psychiatres et autres. Ils ont mis en place une liste de 65 critères avec des médicaments à éviter dans des conditions médicales précises (STOPP, *tableau 1*) et une liste de 22 critères comprenant des médicaments qui devraient au contraire être prescrits (START, *tableau 2*) dans des cir-

→→→

constances spécifiques. Chaque critère STOPP fait donc le lien entre une situation médicale précise (par exemple un antécédent médical ou un risque de chute) et une prescription potentiellement inappropriée (par overuse ou underuse).

Cet outil STOPP&START s'utilise au quotidien pour passer en revue les traitements médicamenteux de son patient. L'utilisation de l'outil comme une check-list (tel que proposée dans les tableaux 1 et 2) va permettre de se mettre en alerte vis-à-vis de certaines prescriptions et d'intégrer à sa pratique la démarche de révision systématique des traitements. L'application des listes chez un patient ne prend que quelques minutes, à condition d'avoir sous la main un dossier complet (et à jour) reprenant ses antécédents, problèmes actifs et médicaments en cours.

Les auteurs de STOPP&START préparent une mise à jour de l'outil pour 2014 et un projet d'informatisation. L'informatisation des critères STOPP&START n'est pas encore disponible en Belgique mais pourrait être envisagée à l'avenir. Elle est pressentie comme particulièrement utile pour l'application de ces critères. Par ailleurs, une équipe de la KULeuven évalue actuellement une adaptation belge de STOPP appelée RASP. Notons que STOPP&START n'est pas le seul outil disponible pour cibler les médicaments potentiellement inappropriés. En 2012, une révision des critères de Beers a été publiée, qui inclut un niveau de preuve et possède la force de la recommandation pour chaque critère proposé. Une version de poche est téléchargeable sur le *site de la Société américaine de gériatrie* [4], et est également disponible sur le *la page "outils" du site de la SSMG*. Y figure également un lien vers *la version complète de ces critères et des recommandations* qui en découlent.

Des médicaments à cibler

Tant STOPP que START ont déjà été utilisés dans plusieurs études pour décrire les prescriptions inappropriées, notamment en Belgique où ils ont été utilisés pour observer les traitements médicamenteux à domicile. Ainsi, les prescriptions du domicile les plus souvent inappropriées chez les patients âgés fragiles (≥ 75ans) admis en 2008 aux Cliniques universitaires Saint-Luc sont présentées dans le *tableau 3* [5]. Les antécédents de chutes, la polymédication, et certaines pathologies comme le diabète, la fibrillation auriculaire, l'ostéoporose et les antécédents de maladie ischémique sont associées à un nombre accru de prescriptions inappropriées. Les patients présentant ces caractéristiques devraient faire l'objet d'une attention particulière. Il est à noter que les résultats de cette étude sont comparables à ceux provenant d'autres pays d'Europe[3 6]. Les duplications de traitements sont également un critère STOPP très fréquemment rencontré (par exemple la prescription de benzodiazépines différentes ou de deux antidépresseurs).

Dans cette même étude [5], une admission aiguë à l'hôpital sur quatre pouvait être potentiellement reliée à une prescription inappropriée. Dans un grand nombre de cas, des patients étaient admis pour chute avec fracture alors qu'ils avaient des antécédents de chute et recevaient des médicaments qui affectent les chuteurs épinglés par STOPP tels que les benzodiazépines ou neuroleptiques (46/302 admissions) ou ne recevaient pas de calcium, vitamine D ou bisphosphonates (19/302) pourtant recommandés par START vu l'existence d'une ostéoporose. De la même façon, quelques (5/302) hospitalisations pour accident coronaire aigu ont été observées chez des patients qui auraient dû selon START bénéficier d'une prévention cardiovasculaire secondaire par aspirine voire par statine. →→→

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Tableau 1.
Liste des critères STOPP, organisée par molécule ou famille et fréquence observée(%) chez 302 patients âgés fragiles admis aux Cliniques Saint-Luc

Médicaments STOPP	***considérés comme inappropriés dans les situations suivantes (>65ans)***	***Fréquence observée, %****
Digoxine	→ > 125µg/j & insuffisance rénale (Cl créatinine < 50 ml/min)	<1%
Diurétique de l'anse	→ 1ère ligne contre HTA → Insuffisance veineuse	<1%
Thiazide	→ Goutte (crise dans les antécédents)	<1%
B-bloquant	→ Diabète avec hypoglycémies → Non cardio-sélectif & BPCO → Association au Verapamil.	**6 %**
Diltiazem/ Verapamil	→ Insuffisance cardiaque sévère (NYHA classe III ou IV)	<1%
Antagoniste du calcium	→ Constipation chronique sévère	1%
Vasodilatateur	→ Chute & hypotension orthostatique démontrée (- 20 mmHg de systolique en position debout)	<1%
Aspirine	→ Dose élevée (≥ 150 mg/j). → En prévention cardiovasculaire 1aire → Associée à un anticoagulant sans protection digestive (anti-H2/IPP) → Ulcus gastro-duodénal sans protection digestive (anti-H2/IPP) → Haut risque hémorragique → Contre les vertiges périphériques	**12%**
Dipyridamole	→ En prévention cardiovasculaire 2daire en monothérapie → Haut risque hémorragique	<1%
Clopidogrel	→ Haut risque hémorragique	<1%
AVK	→ Haut risque hémorragique → Durée excessive (>6 mois si TVP; >12 mois si embolie pulmonaire)	<1%
Tricyclique	→ Démence → Constipation → Glaucome → Bloc cardiaque → Association avec opiacés ou anticalciques → Prostatisme	**5%**
Benzodiazépine	→ Chute → Molécule à longue durée d'action > 1 mois	**24%**
Neuroleptique	→ Chute → Contre l'insomnie > 1 mois → Parkinson → Phénothiazine & épilepsie	**4%**
Antiparkinsonien anticholinergique	→ Contre un syndrome extra-pyramidal induit par un neuroleptique	<1%
ISRS	→ Hyponatrémie persistante (>2 mois ; < 130 mEq/L)	<1%
Anti-Histaminique de 1ère génération	→ Durée excessive (> 1 semaine) → Chute	2%
Loperamide, Codéine	→ Diarrhée d'origine inconnue → Gastroentérite infectieuse sévère	<1%
Metoclopramide	→ Syndrome extra-pyramidal	<1%
IPP	→ Durée excessive (> 8 sem) à dose thérapeutique pour ulcère peptique	<1%
Antispasmodique anticholinergique	→ Constipation chronique	<1%
Théophylline	→ Monothérapie dans la BPCO	<1%
Ipratropium	→ Glaucome	<1%
Corticoide systémique	→ BPCO modérée à sévère, au lieu de corticoïdes inhalés. → Durée excessive (> 3 mois) en monothérapie contre l'arthrose ou la polyarthrite rhumatoïde	**3%**

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Tableau 1. (suite)

Médicaments STOPP	***considérés comme inappropriés dans les situations suivantes (>65ans)***	***Fréquence observée, %****
AINS	→ Arthrose faible à modérée & durée excessive (> 3 mois) → HTA (≥ 160 mmHg). → Insuffisance cardiaque → Insuffisance rénale (Cl créatinine < 50 ml/min) → Association à un anticoagulant → Ulcus peptique dans les antécédents, sans protection digestive → Goutte en traitement chronique, hors Cl allopurinol	**3 %**
Colchicine	→ Goutte en traitement chronique, hors Cl allopurinol	<1%
Opiacé	→ Chute → Douleurs modérées → Constipation chronique (> 2 sem) sans laxatif → Démence sans indication palliative	**8%**
Anti-diabétique oral	→ Longue durée (glibenclamide, chlorpropamide)	<1%
Oestrogènes	→ Cancer du sein. → Antécédent de TVP-embolie pulmonaire → Sans progestatif chez femme non-hystérectomisée	<1%
α-bloquant	→ Sonde urinaire au long cours (>2mois) → Homme incontinent	<1%
Anti-muscarinique	→ Démence → Glaucome → Prostatisme → Constipation chronique	1%
Ipratropium	→ Glaucome	<1%
Corticoïde systémique	→ BPCO modérée à sévère, au lieu de corticoïdes inhalés. → Durée excessive (> 3 mois) en monothérapie contre l'arthrose ou la polyarthrite rhumatoïde	**3%**
Duplications		

Autrement dit, l'utilisation de STOPP&START à usage préventif prend tout son sens puisqu'elle pourrait diminuer le nombre d'admissions pour cause médicamenteuse. STOPP a déjà montré qu'il permettait d'identifier des médicaments impliqués dans des effets indésirables[3]. À l'heure actuelle, des équipes de recherche étudient la valeur prédictive de l'outil STOPP&START.

STOPP&START, pour ou contre?

Parmi les forces que présente l'outil STOPP&START, on compte sa simplicité d'utilisation. Les critères sont en effet courts et explicites, permettent ainsi au praticien d'effectuer une revue systématique du traitement médicamenteux. Les critères reprennent des médicaments et pathologies fréquemment rencontrés. L'outil est donc représentatif de la pratique de la médecine générale de tous les jours. De plus, même s'il n'a pas encore fait l'objet de nombreuses études, il est pressenti comme étant d'une

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Tableau 2.
Liste des critères START, organisée par situations médicales fréquence et observée(%) chez 302 patients âgés fragiles admis aux Cliniques Saint-Luc

Médicaments START	***considérés comme inappropriés dans les situations suivantes (>65ans)***	***Fréquence observée, %****
Fibrillation Auriculaire	→ Anticoagulant (AVK) → Aspirine (si AVK contre-indiqué)	**11 %** 1%
Prévention cardiovasculaire 2ère	→ Aspirine (ou clopidogrel) → Statine**	**14%** **8%**
Hypertension arterielle (≥ 160 mmHg à plusieurs reprises)	→ Anti-hypertenseur	**7%**
Diabète type 2 & autre facteur de risque cardiovasculaire	→ Antiagrégant plaquettaire (risque cardiovasculaire) → Statine (risque cardiovasculaire) → IEC (néphropathie) → Metformine (sauf si Cl créatinine < 50 ml/min)	**11 %** **13%** **5%** **8%**
Insuffisance Cardiaque	→ IEC	2%
Infarctus du myocarde	→ IEC	2%
Angor stable	→ β -bloquant	2%
BPCO légère à modérée	→ β2 mimétique ou anticholinergique inhalé	**7%**
BPCO modérée (si VEMS < 50%)	→ Corticoïde inhalé	1%
Insuffisance respiratoire (p02 <60mmHg)	→ O_2	<1%
Parkinson idiopathique invalidant	→ L-dopa	<1%
Affects dépressifs > 3 mois	→ Antidépresseur	**5%**
Reflux gastro-oesophagien sévère	→ IPP	**24%**
Diverticulose colique avec constipation	→ fibres	**4%**
Polyarthrite rhumatoïde modérée à sévère > 12 mois	→ Anti-rhumatismaux biologiques	<1%
Corticoïde par voie orale en entretien	→ Bisphosphonate	<1%
Ostéoporose connue	→ Calcium et vitamine D	2%

Prescriptions inappropriées les plus fréquemment observées* -
*Dalleur O, et al. Drugs Aging. 2012; 29: 829-37 ; **Si indépendance fonctionnelle et si espérance de vie > 5ans.

Abréviations : AINS : anti-inflammatoire non-stéroïdien ; AVK : anti-vitamine K ; BPCO : broncho-pneumopathie chronique obstructive ; CI : contre-indication ; Cl : clairance ; IEC : antagoniste de l'enzyme de conversion de l'angiotensine ; HTA : hypertension ; IPP : inhibiteur de la pompe à protons; ISRS : inhibiteur sélectif de la recapture de la sérotonine; TVP : thrombose veineuse profonde.

D'après Lang PO, et al. Can J Public Health. 2009; 100: 426-31.

Tableau 3.
Médicaments les plus fréquemment considérés comme potentiellement inappropriés selon STOPP&START chez les patients âgés fragiles admis aux Cliniques Saint-Luc (n=302).

Médicaments de la liste STOPP (% de patients concernés)	Médicaments de la liste START (% de patients concernés)
Benzodiazépines (24%)	Aspirine, en prévention secondaire (21%)
Aspirine, en prévention primaire et surdosage (12%)	Statines (19%)
Opiacés (8%)	Calcium et vitamine D (17%)
Bétabloquants (6%)	Anticoagulants (11%)
Antidépresseurs tricycliques (5%)	Bisphosphonates (10%)

grande utilité, notamment pour son usage en prévention afin de diminuer la charge en médicaments inappropriés chez les personnes âgées. L'application des critères STOPP&START permet directement au généraliste d'optimiser le traitement de ses patients.

Cependant, l'outil STOPP&START présente également des limites. Un certain temps d'adaptation est nécessaire pour apprivoiser l'outil au vu de la longueur de la liste de critères, et pour intégrer la démarche de révision régulière du traitement à sa pratique. Une première étape pourrait consister à évaluer les rapports risque-bénéfice des critères STOPP&START les plus souvent observés (mis en évidence dans les tableaux 1 et 2). À force de les utiliser, la question de savoir si le médicament est approprié vient comme un réflexe au moment de prescrire. En fait, ces outils ont un fort potentiel éducationnel. Comme mentionné précédemment, il est indispensable d'avoir sous la main une liste claire et exhaustive des médicaments pris par le patient, y compris les médicaments non soumis à prescription, et une vision complète de la situation médicale du patient, mises face à face. Une fois ces informations disponibles, il ne faut que quelques minutes pour repérer les médicaments inappropriés. Le système du dossier médical informatisé peut par ailleurs faciliter et accélérer l'application de l'outil STOPP&START.

Il ne faut pas perdre de vue que tous les médicaments et toutes les situations de médicaments inappropriés ne vont pas avoir les mêmes conséquences d'un patient à l'autre. Une analyse a montré qu'en prenant en compte les comorbidités et le statut fonctionnel cognitif et social du patient, l'importance clinique de l'arrêt ou de l'initiation d'un médicament peut prendre des formes variables. Dans certains cas, les recommandations peuvent être majeures pour un patient et mineures pour un autre. Ceci souligne l'importance, une fois certaines prescriptions épinglées par STOPP&START, de considérer le patient dans sa globalité afin d'en juger le caractère approprié ou non. Comme dit précédemment, le médecin généraliste, en tant que personne-clé, devra rassembler les informations et pourra discuter avec les autres prescripteurs de la situation du patient et de ses médicaments. Le jugement clinique et la connaissance individuelle du patient permettront de nuancer le caractère approprié des prescriptions. Certains cas ont été soulevés lors de rencontres avec des utilisateurs des outils. Par exemple une benzodiazépine ou un neuroleptique inapproprié selon STOPP chez un "chuteur" n'aura pas la même portée selon qu'on parle de chutes répétées ou d'une chute accidentelle, isolée. Les médicaments à visée neurologique (antidépresseurs, neuroleptiques, antidouleurs) sont parmi les plus difficiles à évaluer. Pourtant, il est clair que rationnaliser l'usage des psychotropes est prioritaire pour la qualité et la sécurité du traitement du patient âgé. STOPP permettra d'attirer l'attention sur ce point. Un autre cas est celui des patients diabétiques qui font des hypoglycémies fréquentes et qui reçoivent un bétabloquant. STOPP considère dans ce cas le bétabloquant comme inapproprié. Cependant, bon nombre des patients diabétiques présentent également des pathologies ischémiques. Chez ces patients, arrêter le bétabloquant serait délétère tandis que l'ajustement du traitement hypoglycémiant serait la première mesure à adopter.

La discussion et la décision autour des médicaments doit bien sûr impliquer les patients, même lorsqu'il s'agit d'un patient âgé. Tout le monde sait qu'il est difficile d'arrêter une benzodiazépine à laquelle le patient est habitué depuis plus de trente ans. Informer et appliquer une décision concertée avec le patient est primordial. STOPP&START peut ouvrir la porte à la discussion avec le patient. Pourquoi, concrètement, ne pas organiser une révision des traitements médicamenteux et consacrer, une fois par an, une consultation médicale à cet effet?

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En conclusion

Pour adopter STOPP&START dans sa pratique au bénéfice de nos patients âgés, il est important d'avoir organisé une liste complète de ses principaux problèmes de santé et de ses médicaments correspondants. Ces données étant disponibles, l'application de l'outil est aisée, rapide et efficace pour réduire la charge en prescriptions inappropriées. Appliquer les critères STOPP&START en médecine générale devrait faire naturellement partie de notre prise en charge de la population fragile et particulièrement sensible que sont nos patients âgés. En particulier, il faut être vigilant chez les patients qui ont des antécédents de chutes, celles-ci étant régulièrement associées à la prise inappropriée de médicaments psychotropes. Egalement, il faut être particulièrement attentif aux médicaments qui sont utilisés en prévention cardiovasculaire. En effet, c'est dans ces deux domaines, neurologique et cardiovasculaire, que se concentre la grande majorité des prescriptions inappropriées.

Cette démarche d'optimisation thérapeutique ne peut cependant se faire correctement que si elle considère le patient dans sa globalité. De plus, il importe de travailler en concertation avec les collègues également impliqués dans le traitement et d'informer le patient. Une consultation (voire deux par an en maison de repos) pourrait/devrait être consacrée à cette révision des traitements médicamenteux.

En pratique, nous retiendrons

I **L'outil STOPP&START est**
- **Un outil simple et rapide, basé sur des preuves ou des expériences cliniques**
- **Un outil à considérer dans la prise en charge globale du patient**

II **L'outil STOPP&START permet**
- **Une optimisation des traitements médicamenteux chroniques au bénéfice des patients âgés**
- **Une démarche systématique pour revoir les traitements des patients âgés**

III **Une consultation (voire deux par an en maison de repos) pourrait/devrait être consacrée à une révision des traitements médicamenteux.**

La Rédaction

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INTRODUCTION III – In quest of appropriate prescribing for older patients: the use of explicit tools

INTRODUCTION

Caring for older patients is a major concern in our ageing society. Individuals older than 65 years of age are the most active consumers of health care, and this group continues to increase more rapidly than most other sections of the population [1]. The prescription of medicines is an important component in the care of older people. However, evidence has shown that the use of medicines in this population is often inappropriate for many different reasons, including complexities of prescribing, patient factors, and health system factors [2]. The appropriateness of prescriptions is a key issue in older patients since they are particularly sensitive to adverse drug events (ADEs) and because these events increase the utilisation of health care services and related costs [3-5]. ADEs have been documented as affecting 5-35% of older patients in the community and leading to hospital admissions in 6-16% of these cases [6]. The cost to society of these drug-related hospitalisations could be reduced, since a substantial percentage of ADEs (32-88%) are potentially preventable [5, 7].

This review aims to provide an overview of the use of explicit tools for improving the appropriateness of prescribing in older people and to summarise current knowledge about the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) [8].

APPROPRIATE AND INAPPROPRIATE PRESCRIBING IN THE ELDERLY

Good prescribing takes into account the benefits and the risks of prescribing a specific medication, as well as other factors such as cost and patient preference [9]. An evaluation of appropriateness in prescribing for older patients should include an assessment of the context of multicomorbidities, functional and cognitive status, and life expectancy [10]. There are three main categories of inappropriate prescribing: 1) overprescribing (when more drugs are prescribed than are clinically needed); 2) misprescribing (incorrect prescribing of a justified drug i.e. with regard to drug choice, dosage, duration of therapy, duplication, drug-disease interaction, drug-drug interaction of drug-food interaction [11]), and 3) underprescribing (when the drug regimen lacks an indicated drug) [10, 12]. Although polypharmacy has always traditionally been the main concern, underuse is now under more scrutiny as being widespread and related to significant geriatric adverse events [13]. In 2007, a Belgian study on geriatric inpatients

found that almost 60% of prescriptions had an inappropriate rating, that approximately 30% of patients were taking at least one drug that ought to have been avoided, and that underprescribing of indicated medicines was taking place in half of patients [14].

There are several tools available to clinical pharmacists and other health care professionals for assessing the appropriateness of medicines in older patients, using either implicit (judgement-based) or explicit (criterion-based) criteria [10-12]. Implicit tools may question several aspects of prescribing, including choice of molecule, evaluation of dosage, indication, route of administration, duration, adverse reactions, drug-drug interaction, drug-disease interaction, duplication costs, adherence, and patient preference. The Medication Appropriateness Index (MAI) [15] seems to be the most comprehensive and validated implicit tool available to date, but its application is particularly time-consuming. In addition, the MAI does not address underprescribing, but this can be evaluated using another tool, namely the Assessment of Underutilization index (AOU) [16].

A COMPARISON OF COMMONLY USED EXPLICIT TOOLS

A variety of explicit tools are available. Most address overprescribing and misprescribing (either with or without reference to comorbidity conditions). Some also tackle underprescribing. Their advantages include: their rapid application, because they require little judgement and their lower cost of application. Explicit tools also ensure a more equal care [11].

Explicit tools have usually been developed using literature reviews, expert opinions, and consensus techniques [10-12]. The validity of the methods used to develop sets of explicit criteria for use in older people has been questioned [12, 17]. Frequent weaknesses include: a lack of transparency concerning the literature used, the poor reliability of the Delphi method, findings of the Delphi rounds not being appropriately presented, inter-rater reliability not having been assessed, and conflicts of interest of the expert panel not having been disclosed [17].

There must be conclusive evidence that the use of explicit tools in clinical practice is worthwhile if this approach is to be endorsed. The relationship between what the tools identify as inappropriate prescribing and the actual incidence of adverse health

outcomes needs to be established. However, evidence for the predictive validity of explicit tools is currently inconclusive.

The Beers criteria

The Beers criteria are the best known and best studied of the explicit tools and have been adopted by the American Geriatrics Society (AGS). Several updates have been published since their initial publication in 1991 [18-21]. The most recent update classifies inappropriate medications as: 1) drugs to avoid, 2) drugs to avoid, depending on diagnosis/condition, or 3) drugs to use with caution.

Several extensive studies have looked at the Beers criteria in a variety of settings: primary care (prevalence 12.5-42%) [22, 23], hospitals (14-44%) [23], and long-term care (18-35%) [23]. Several studies reported a link between the use of Beers drugs and adverse outcomes. One study reported that 4% of emergency visits for adverse drug reactions were caused by drugs on the Beers list [24]. Amongst hospitalised older patients, other studies reported that drugs listed on the Beers list were responsible for a small percentage of ADEs (6-9%) [25, 26]. Beers-listed drugs increase the use of health care resources [27, 28] and nursing home admissions [29]. According to one adapted Beers list, inappropriate medications were related to falls in the community-dwelling elderly [30]. A recent study showed that 16.5% of ADE occurring within 45 days after hospital discharge implicated medications on the 2012 update of the Beers list [31]. By contrast, other studies found no significant relationship between the use of drugs from the Beers list and either mortality [4, 26, 32-35], ADEs [26, 34, 36] and self-reported ADEs [37], health-related quality of life [38], admissions [33], or length of stay [26, 34]. So far, no randomised controlled trial has unequivocally been able to show that the application of the Beers list decreases ADEs, morbidity, mortality, hospitalisation, or costs [10].

STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment)

The STOPP&START tool was developed by an academic team from Ireland [8]. The criteria were designed for patients over 65 years of age. The tool was validated through a Delphi consensus process in which 18 experts in geriatric pharmacotherapy participated. The STOPP&START criteria have shown good inter-rater reliability

between physicians and between pharmacists [39, 40] and have been adopted by the European Union Geriatric Medicine Society (EUGMS).

The tool links clinical situations to evidence-based drugs usage and covers drugs widely used in Europe (in contrast to the Beers list). The criteria are organised according to physiological systems, plus two prevalent geriatric syndromes (fall and pain). The 65 STOPP criteria address overprescribing while the 22 START criteria concentrate on underprescribing. The combined coverage of aspects of both over- and underuse makes this tool particularly interesting.

This tool seems to be increasingly used for both clinical research and clinical practice in Belgium, although few publications on the subject are available so far. The use of this tool has also been reported in several recent studies in other countries [10, 41]. Hill-Taylor et al. published a systematic review of the application of the STOPP&START tool in 2013 [42]. Based on recent data, this tool seem to be more sensitive than other explicit tools, such as the Beers criteria, at detecting inappropriate prescribing. The application of STOPP&START in daily practice seems to be feasible, in contrast to the MAI. Current knowledge about STOPP&START is summarised in the next section.

Other explicit tools

To the best of our knowledge, the other tools, which are briefly described in Table 1, have not been evaluated for predictive validity. Most of the tools are derived from the Beers criteria [11].

Chang (2010) compared the statements of seven explicit tools (Beers, Mc Leod, Rancourt, Laroche, STOPP, Winit-Watjana, and Norwegian General Practice (NORGEP) Criteria) and found few similarities [23]. Only long-acting benzodiazepines and tricyclic antidepressants were inappropriate according to all seven tools. Other medication classes that were often present (although not in all tools) were: non-steroidal anti-inflammatory drugs, anticholinergics, first generation anti-histamines, and long-acting oral hypoglycaemic agents. Some cardiovascular drugs, such as digoxin and dipyridamole, were also frequently targeted, as were some antipsychotics (e.g. chlorpropamide). The length of the tools vary greatly (see Table 1). These differences in which drugs are considered inappropriate illustrate the fact that appropriateness of

therapy is a complex concept, involving little scientific evidence in older persons and influenced by medications availability and the force of local habits and guidelines. Drugs considered as inappropriate in one country, might be acceptable in another. For example, amiodarone is listed in the Beers criteria because of the risk of prolongation of QT interval. In contrast, European tools do not mention amiodarone. Moreover, amiodarone is recommended as a strategy of heart rhythm control in French guidelines for older patients having atrial fibrillation [43]. There is no international consensus on which drugs should be targeted to optimise appropriateness.

TABLE 1. Brief description of a selection of explicit tools for screening for potentially inappropriate prescribing.

Criteria	Description	No. items:
Beers [21] 2012	American criteria, last updated in 2012.	99
McLeod [44] 1997	These Canadian criteria identify drugs to be avoided as well as drug-disease and drug-drug interactions and offer alternatives [44]. In long-term care residents, a computerised application of these criteria detected a prevalence of 15% of inappropriate prescribing [45].	38
Improved Prescribing in the Elderly Tool (IPET) [46] 2000	The Canadian Improved Prescribing in the Elderly Tool (2000) covers the 14 most frequently encountered inappropriate prescribing events according to McLeod [46].	14
Zhan's Criteria [47] 2001	Zhan's Criteria (USA) are derived from Beers and categorise inappropriate medications as: 1) drugs to avoid, 2) drugs rarely appropriate to prescribe, and 3) drugs that have some indications but are often misused [47].	33
Rancourt criteria [48] 2004	This tool comprise statements on medications, duration, dosage, and drug-drug interactions (Canada) [48]. 55% of long-term care residents in Canada have experienced inappropriate prescribing according to this tool [48].	111
French Consensus Panel List [49] 2007	Also called the Laroche criteria [49], this list was based on other tools, including Beers, IPET, and Mc Leod [44], but adapted to French drug availability and guidelines. The list comprises drugs and drug classes to avoid, along with alternatives. This list is unusual in targeting patients aged over 75 while most of the other tools are aimed at patients aged over 65. No published study has so far used these criteria to measure treatment appropriateness [10].	36

Criteria	Description	No. items:
Assessing Care of Vulnerable Elders (ACOVE) indicators [50] 2007	This set of quality-of-care indicators was developed in the USA and has been updated several times [50]. 68 of these indicators address prescribing (including underprescribing).	68
Australian Prescribing Indicator Tool [51, 52] 2008	These indicators were derived from Australian clinical guidelines, prescribing databases, and the most common reasons that older Australians seek or receive health care [51, 52]. The tool comprises indicators for both over- and underprescribing.	41
Thailand criteria [53] 2008	These Asian criteria by Winit-Watjana include statements on high-risk medications, including drug-drug interactions [53].	77
STOPP&START [8] 2008	This Irish tool addresses over- and underprescribing.	87
Norwegian General Practice (NORGEP) Criteria [54] 2009	These criteria target inappropriate medications, inappropriate doses, and drug-drug interactions [54]. This tool has not yet been assessed outside of Norway [10].	36
PRISCUS List [55] 2010	The German PRISCUS list (Latin for "old and venerable" [55]) is made up of potentially inappropriate drugs, accompanied by alternatives and recommendations for clinical practice in case the drug is clinically necessary (e.g. monitoring recommendations) [55]. In a study using administrative data, the incidence of injuries strongly increased with the prescription of drugs of the PRISCUS list [56].	83

CURRENT KNOWLEDGE ABOUT STOPP&START

Prevalence

The STOPP&START tool has been used to describe inappropriate prescribing in many different parts of the world: Europe [57-66], Asia [67-70], the United States of America [71, 72], Mexico [73], and Australia [74]. Studies have been conducted in several types of settings: primary care [58, 69, 72, 74, 75], hospitals (often assessing medications used at home) [57, 62, 63, 66, 67, 71, 76-80], long-term care [60, 68, 70, 81-83], day-care geriatric hospitals [84], and community pharmacies [85]. All of the studies but one [79] were observational.

The proportion of older patients having at least one instance of inappropriate prescribing varies greatly between settings and countries (see Table 2). An international multi-centric study [57] showed an average prevalence of 51% for STOPP-listed inappropriate medications (35 to 77% by country) and of 59% (51-73%) for START-listed prescribing omissions in older patients acutely admitted to a geriatric unit.

TABLE 2. The prevalence of STOPP and START events in older patients (% of patient having at least one instance of inappropriate prescribing in their drug treatment).

Setting	Prevalence of STOPP events	Prevalence of START events
Treatment at home of community - dwelling patients or inpatients	15-60% [58, 65, 69, 71, 75, 76, 80, 86]	0-68% [62, 69, 71, 75, 77]
Hospital treatment of inpatients	23-36% [65, 67]	42% [67]
Long-term care patients	24-70% [68, 70, 81-83]	34-42% [70, 81]

In every study [57, 64, 74-76, 78, 83] but one [68], STOPP showed higher sensitivity when compared with the Beers list. STOPP also showed higher sensitivity than PRISCUS in one German study [64]. STOPP&START was recently compared with the Australian Prescribing Indicator Tool [60, 74]. The latter tool detected more patients with potentially inappropriate medications and potential omissions. This high sensitivity of the Australian Prescribing Indicator Tool is probably due in part to the methods used to design the tool. Indeed, criteria for this tool were deliberately chosen to include the most frequently prescribed drugs [51].

Several risks factors to have inappropriate prescribing were reported with inconsistency between studies. STOPP events were related to polypharmacy, age, institutionalisation, and increased comorbidity (as measured by the Charlson comorbidity Index [87]), while START events were variably related to age, female gender, and increased comorbidity [41, 42].

Outcomes

The potential link between ADEs and drugs on the STOPP list has been assessed twice by the tool's creators [76, 78]. Hamilton (2011) found that 52% of ADEs on admission to hospital were related to drugs on the STOPP list. By comparison, in the same study, only 20% of the ADEs were related to drugs on the Beers list. After multiple adjusting (for age, sex, comorbidity, dementia, baseline activities of daily living function, and number of medications), STOPP-listed drugs significantly increased the risk of serious avoidable ADEs (odds ratio OR 1.85; 95% CI 1.51, 2.26; p <0.001). This was not the case for Beers-listed medications [78].

An initial experimental study yielded evidence that the application of the STOPP & START screening tool to the treatment of older patients can significantly improve the quality of prescribing [79]. In this randomised controlled trial, the application of STOPP&START decreased the MAI score (absolute risk reduction of 36%) and the AOU index (absolute risk reduction of 21%). This improvement was sustainable at 6 months. However, the study could not show any significant decrease in falls, all-cause mortality, or primary care visits. Again, this study was conducted by the team of the authors of the tool, which may potentially affect the external validity of the results.

A randomised controlled trial is currently underway to assess the effect of the prospective application of STOPP on ADE incidence, re-admissions, and costs (http://clinicaltrials.gov/ct2/show/NCT01467050). A Belgian team is also currently carrying out another randomised controlled trial involving a modified STOPP list called the RASP list (RASP = Rationalisation of home medication by an Adjusted STOPP list in older Patients) (http://clinicaltrials.gov/show/NCT01513265). This project aims to assess the effect of the use of the RASP list by a hospital clinical pharmacist on treatment modifications at discharge, and, as secondary outcomes, on mortality, quality of life, falls, and re-admissions. The results of these two studies will provide valuable evidence on the validity of the STOPP&START tool.

Costs associated with potentially inappropriate prescribing, according to STOPP, were evaluated in Northern Ireland and in the Republic of Ireland [58, 77, 86]. These analyses, however, are country-dependant and, more importantly, included no analysis of the cost-effectiveness of the application of the tool on either clinical or quality of life outcomes.

Other considerations

The studies published have mentioned practical information regarding the use of the tool. It takes an average of 3 to 6 minutes to apply the criteria once the required documentation has been gathered [42, 66, 75, 79]. Multiple sources of medical history documentation were used to the apply the tool, including letters from general practitioners, patient lists, hospital admission records, and patient interviews. However, there is no mention of the time required to collect this information [42], despite the fact that comprehensive and detailed information is crucial for a reliable evaluation of potentially inappropriate prescribing [85].

Interestingly, STOPP&START was used as quality indicator to quantify the appropriateness of prescribing in interventional studies that did not involve the use of the tool as part of the intervention. The tool was used before and after an intervention which consisted of an interdisciplinary collaboration between geriatricians, psychiatrists, and the health care team for patients with mental comorbidities who were hospitalised for any acute somatic condition [88]. Similar use of STOPP&START was made to assess the effect of home-based primary care teams in the USA [72] and of interventions by clinical pharmacists in Sweden [89].

It has recently been suggested that STOPP&START be used in combination with an implicit tool. The Appropriate Medication for Older people-tool (AMO-tool), an implicit tool for general practitioners comprising eight open-ended questions, was tested in a pilot study (not controlled) in nursing homes in combination with the explicit STOPP&START tool, with a follow-up of 6 months [90]. Outcomes included the opinions of GPs on the feasibility of using the tool. The appropriateness of treatment following the use of the tool was not assessed. GPs stated that STOPP&START was easy to use in a nursing home and that when used in combination with the implicit tool, it added to the effectiveness of the latter. Further studies on the use of STOPP&START in combination with implicit tools would be interesting.

A remarkable recent development has been the implementation of STOPP&START in Clinical Decision Support Systems (CDSS). A Spanish project encouraging collaborative work among health professionals for multimorbidity patient care incorporated STOPP&START into the CDSS of a shared platform [91]. The shared platform also included a social network. Another ambitious international project, known

as SENATOR, is currently ongoing. The objective of this project is to develop software to optimise drug therapy in older people. The software will include an assessment of appropriateness according to STOPP&START (http://www.ucc.ie/en/charge-ucc/senator/).

Advantages of STOPP&START over other tools

The STOPP&START tool presents some advantages over other tools. Unlike most other tools, STOPP&START addresses both over- and under-prescription, which makes the medication review more comprehensive. Therefore, the use of both STOPP and START lists in combination should be recommended in practice. The tool was developed in Europe and refers mainly to drug classes (as opposed to molecules, as sometimes used in other tools), which makes applicability to Belgium easier. The tool is organised by physiological system but also includes some criteria under relevant geriatric syndromes such as falls. The tool was developed according to a validated method and good inter-rater reliability was reported. Initial studies have shown that the tool is sufficiently sensitive to detect potentially inappropriate prescribing in older people in several different settings. The specificity of the tool in terms of detecting inappropriate prescribing related to adverse outcomes has not been established. However, initial studies on the predictive validity of the tool have yielded promising results.

Some disadvantages of STOPP&START should also be mentioned. The length of the tool (87 criteria) hampers his application in clinical practice. Neither the severity of the risk in case of prescribing, nor the strength of the evidence is mentioned, which would extend the internal validity of the tool and help prioritization of implementation of criteria. Proper application of the criteria require detailed information about the patient's drugs list and co-morbidities. If the application of the tool is reported to be rapid, the collection of these data might be long [66]. As for any other explicit tool, regular updates are mandatory [92]. Finally, a complementary implicit review of the drug treatment is required for careful clinical decision-making [92], especially as some STOPP criteria are controversial when applied to certain patients [65].

OTHER APPROACHES TO OPTIMISING DRUG TREATMENT IN THE ELDERLY

Besides the use of screening tools, several other approaches have been investigated as potential means of improving the prescription of medicines in older people [12, 22, 93]. These include educational approaches, multidisciplinary team interventions, the involvement of geriatric evaluation and management (GEM) teams, pharmacist interventions, and computerised decision support systems (CDSS). Positive effects on the quality of prescribing – and in some cases on clinical adverse outcomes – have been shown for multidisciplinary interventions, including GEM teams, and interventions provided by clinical pharmacists within the context of a multidisciplinary team.

CONCLUSIONS

Inappropriate prescribing in older people is a widespread and major public health problem. Although several tools are available to screen for potentially inappropriate medications and omissions, their predictive validity on strong outcomes remains unknown. Only Beers and STOPP have been used in outcome studies. The use of explicit tools in clinical practice has yet to be proven to be a worthwhile approach.

A large amount of research is currently being done on the STOPP&START tool all over the world, which is showing a high prevalence of inappropriate prescribing and room for improvement in the older population. This tool presents several advantages over the other available tools. Comparison with the Beers list is particularly interesting because the latter has until now been the most widely used. Evidence in favour of the use of STOPP&START is emerging, but further randomised controlled studies on outcomes such as adverse drug events, hospital admissions, mortality, quality of life, and costs are required. Combination of the use of STOPP&START and an implicit evaluation of the medication regimen is most likely to have a favourable impact on appropriateness of prescribing and should be the approach adopted in clinical practice.

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AIM AND OBJECTIVES

1. OBJECTIVES

The aim of this research was to extend the knowledge on a screening tool for the assessment of appropriateness of drug treatment in elderly patients, namely the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START).

To that end, three major questions for research were raised :

How much?

The first step was to quantify the pharmacological information that the systematic application of STOPP&START criteria would bring on (in)appropriate prescribing in older patients.

The objectives were :

- to measure the level of appropriateness of home pharmacological treatment.
- to describe inappropriateness (overuse, misuse and underuse) in terms of prevalence, medications involved and underlying factors.

How valid?

The second question related to various validity domains of this screening tool.

To address this question, approaches were :

- to compare the detection of appropriateness using STOPP&START and other screening tools (concurrent validity).
- to observe to which extent inappropriate prescribing according to STOPP&START was related to adverse outcomes (predictive validity).
- to evaluate the clinical relevance of the STOPP&START criteria with experts and users (content validity).
- to identify factors influencing the use of the tool by general practitioners (face/content validity).

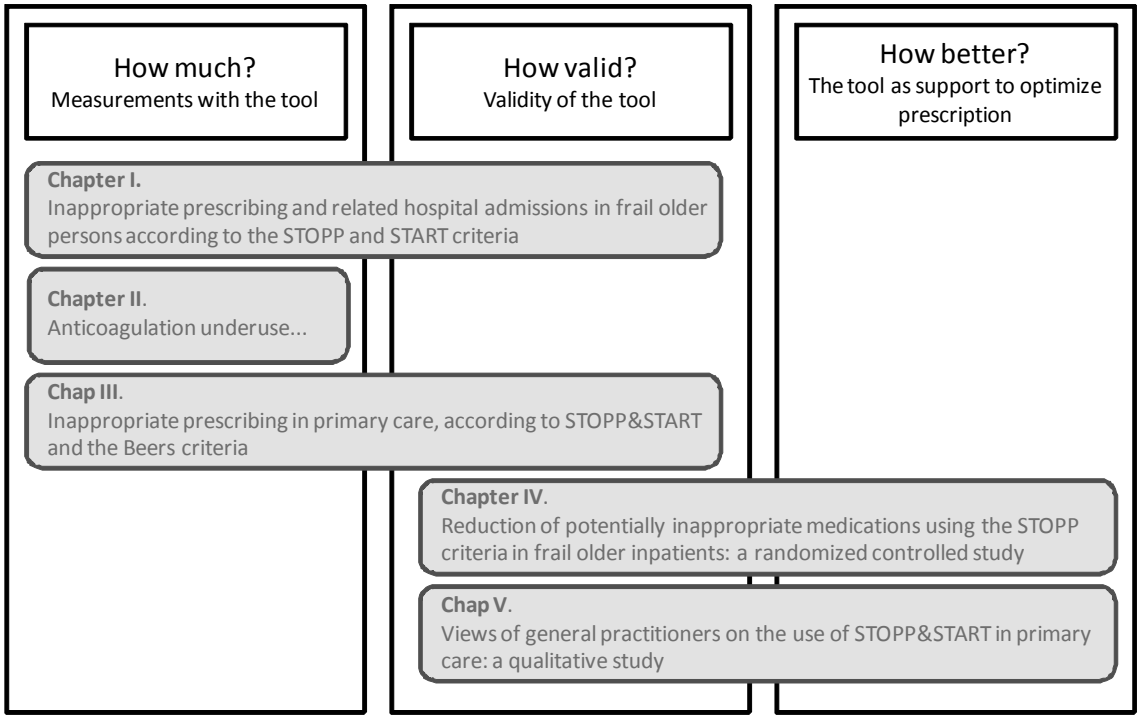
How better?

Finally, the tool had to be tested as a support to optimize drug prescription in the elderly.

The goals were :

- to quantify the improvement of appropriateness of home medications after systematic use of the tool during a hospital stay.
- to observe whether the improvement is sustainable one year after hospital discharge.
- to discuss the potential benefits and barriers of using the tool in the general practice.

2. PROJECT OVERVIEW



RESULTS

CHAPTER I – Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria

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Chapter I at a glance

What is already known about this subject

- Inappropriate prescribing is frequent in older people at home.
- Inappropriate prescribing increases the risk for adverse drug events and other adverse health outcomes such as hospital admissions.
- STOPP&START tool allows to screen the treatment and detect inappropriate prescribing by overuse, misuse and underuse.

- This chapter investigates the prevalence and the nature of inappropriate prescribing at home in frail older patients admitted to hospital and the potential link between inappropriate prescribing and the reason of hospital admission.

What this chapter adds

- Inappropriate prescribing in frail older patients admitted to hospital mainly involves overuse of **benzodiazepines**, **aspirin** and **opiates**, and underuse of **calcium and vitamin D**, **aspirin** and **statins**.
- **One admission out of four** could be related to inappropriate prescribing according to STOPP&START.
- **Fall-**induced osteoporotic fracture was the most frequent cause of hospital admission related to inappropriate prescribing and should be a priority target for further improvement of prescribing.

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ORIGINAL RESEARCH ARTICLE

Inappropriate Prescribing and Related Hospital Admissions in Frail Older Persons According to the STOPP and START Criteria

Olivia Dalleur · Anne Spinewine · Séverine Henrard · Claire Losseau · Niko Speybroeck · Benoit Boland

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Abstract

Background Over the last few years, the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria have been increasingly used to evaluate the prevalence of inappropriate prescribing. However, very few studies have evaluated the link between these criteria and clinical outcomes.

Objectives The objectives of this study were to evaluate the prevalence of inappropriate prescribing according to STOPP and START in a population of frail elderly persons admitted acutely to hospital; to evaluate whether these inappropriate prescribing events contributed to hospital admissions; and to identify determinants of hospital admissions potentially related to inappropriate prescribing.

Methods This was a cross-sectional study including all frail older patients admitted to a 975-bed teaching hospital over a 12-month period. A pharmacist and a geriatrician independently detected events of prescribing of potentially inappropriate medication (PIM) and potential prescribing omission (PPO), using the STOPP and START criteria, respectively, in all patients included in the study. They determined whether the inappropriate prescribing event was the main cause or a contributory cause of hospital admission. Demographic, clinical and geriatric clinical syndromes (i.e. cognitive impairment, falls) were evaluated as potential determinants of hospital admissions related to inappropriate prescribing, using multivariate methods (i.e. logistic regression and a classification tree).

Results 302 frail older persons (median age 84 years) were included in the study. PIMs (prevalence 48 %) mainly involved overuse and/or misuse of benzodiazepines, aspirin and opiates. PPOs (prevalence 63 %) were mainly related to underuse of calcium and vitamin D supplementation, aspirin and statins. Overall, inappropriate prescribing according to STOPP (54 PIMs) and/or START (38 PPOs) led or contributed to hospital admission in 82 persons (27 %). The multivariate analyses indicated a relation between PIM-related admissions and a history of previous falls ($p < 0.001$), while the PPO-related admissions were associated with a history of osteoporotic fracture ($p < 0.001$) and atrial fibrillation ($p = 0.004$).

Conclusions Using the STOPP and START criteria, it was found that inappropriate prescribing events (both PIMs and PPOs) were frequent and were associated with a substantial number of acute hospital admissions in frail older persons. Fall-induced osteoporotic fracture was the most important cause of hospital admission related to

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inappropriate prescribing and should be a priority for pharmacological optimization approaches.

1 Introduction

Inappropriate prescribing is a major concern in frail older patients, as these patients are particularly sensitive to adverse drug events (ADEs) and related outcomes such as hospital admission [1]. Several tools are available to evaluate prescribing in older patients, including implicit (e.g. the Medication Appropriateness Index [MAI]) [2] and explicit (e.g. the Beers list) [3–5] criteria [6].

The Screening Tool of Older Person's Prescriptions (STOPP) and the Screening Tool to Alert doctors to Right Treatment (START) are explicit tools to assess medication appropriateness in patients aged 65 years and above. These tools were validated through a Delphi consensus process with 18 experts in geriatric pharmacotherapy [7].

The STOPP criteria include 65 situations of potential clinical risk where a medication (or a medication class, $n = 27$) should be stopped, while the START criteria include 22 situations where a medication (or a medication class, $n = 20$) should be started.

The STOPP criteria—and to a lesser extent the START criteria—have been used to evaluate the prevalence of inappropriate prescribing in different settings and various countries [8–11]. Furthermore, in a recent randomized controlled trial, Gallagher et al. [12] reported that the use of STOPP/START criteria to screen hospitalized older patients' medications, coupled with feedback provided to the attending hospital team, led to significant and sustained improvements in the appropriateness of prescribing. These tools have several advantages over other existing ones: they link clinical situations with evidence-based use of medications; the medications listed are available and used in Europe; the criteria encompass events of overuse, underuse and misuse of medications; and they are relatively easy to apply. According to the creators of the tools, application of the criteria takes only a few minutes to detect inappropriate prescribing events in a patient, providing that comprehensive data on the patient's medications and co-morbidities are available.

However, only a few studies have evaluated the link between these events and clinical outcomes [13, 14]. Hamilton et al. [14] compared the Beers and STOPP criteria as risk factors for preventable serious ADEs. They concluded that the STOPP criteria are more sensitive to inappropriate prescribing resulting in ADEs than the Beers criteria. Furthermore, there is a lack of data on factors that place patients at risk of adverse consequences related to inappropriate prescribing. Identification of such factors could help clinicians to identify patients at risk. Geriatric syndromes and frailty should be taken into account.

The objectives of this study were (a) to determine the prevalence of potentially inappropriate prescribing according to the STOPP and START criteria in a population of frail elderly people acutely admitted to hospital; (b) to evaluate to what extent these inappropriate prescribing events contributed to hospital admissions; and (c) to identify determinants of hospital admissions potentially related to inappropriate prescribing. Among the determinants, geriatric syndromes were analysed.

2 Methods

2.1 Study Population

This study was cross-sectional and included all frail older patients consecutively admitted to a 975-bed teaching hospital in Brussels (Belgium) over a 12-month period (December 2007–November 2008) and assessed by the interdisciplinary geriatric liaison team upon admission to the ward [15, 16]. The following inclusion criteria to receive a comprehensive geriatric assessment by the geriatric liaison team were used for the present study: age 75 years or older; admission for acute illness (as opposed to elective admission); a positive frailty profile (as defined by the presence of two or more of the six Identification of Seniors At Risk (ISAR) items: need for help in activities of daily living; an increase in this need related to the current illness; memory problems; significantly altered vision; hospitalization in the previous 6 months; and daily use of $\geq$3 medications at home) [17]. The geriatric liaison team (a nurse, dietitian, occupational therapist, physiotherapist, speech therapist, psychologist and geriatrician) aims to improve the care of older patients hospitalized in non-geriatric units by the means of recommendations following comprehensive geriatric assessment. Such geriatric liaison teams are widespread in Belgium, since they benefit from federal funding.

The study protocol was approved by the local clinical research ethics committee.

2.2 Data Collection

Demographic, clinical and medication data were collected upon hospital admission by the multidisciplinary geriatric liaison team, using the electronic patient record. The medication data included prescriptions as well as over-the-counter medicines that the patient was taking daily just before admission to hospital.

Because the medication data were routinely collected by the geriatric liaison team, the researchers could record

whether the patient was taking each of the 27 and 20 drugs (or drug classes) listed in the STOPP and START criteria, respectively (see Online Resource 1). The presence or absence of each comorbidity listed in the STOPP criteria ($n = 31$) and the START criteria ($n = 18$) was also registered (see Online Resource 1).

Information regarding the patient's frailty scores (ISAR and Katz [18]) and the presence or absence of six geriatric syndromes 2 weeks before hospital admission were obtained during interviews with the patient (or relatives in cases of cognitive impairment). These geriatric syndromes are those routinely evaluated by the geriatric liaison team: multiple falls (≥2 falls in the last 6 months), polypharmacy (≥5 daily medications), cognitive disorder (known dementia and/or an impaired Mini Mental State Examination [MMSE] score of <24/30) [19], malnutrition (a body mass index of <21 kg/m^2 and/or a mid-arm circumference <23 cm), living alone, and functional dependency in activities of daily living (a Katz score of ≥9/24).

2.3 Analysis

We evaluated the prevalence of inappropriate prescribing of medications used at home, as well as determinants of this inappropriate prescribing. To detect events of potentially inappropriate prescribing according to the 65 STOPP and 22 START criteria, a clinical pharmacist (O.D.) with experience in evaluation of prescribing for older patients and a geriatrician (B.B.) independently analysed all of the patient's medications and co-morbidities. The presence of contraindications to specific medications was taken into account, on the basis of information available in the electronic patient record. Discrepancies in the identification of potentially inappropriate prescribing events were discussed until a consensus was reached between both researchers. In addition, both researchers evaluated whether the inappropriate prescribing event was the main cause or contributed to the main reason for admission. Positive predictive values (PPVs) were calculated for inappropriate prescribing potentially linked to hospital admission (PPV = the number of patients having an admission potentially related to the use of an inappropriately prescribed drug divided by the number of patients having this drug inappropriately prescribed).

Comorbidities (renal failure [i.e. a glomerular filtration rate of <50 mL/min]; atrial fibrillation; presence or history of cardiovascular disease, hypertension, heart failure, angina, diabetes, chronic obstructive pulmonary disease [COPD], chronic type 1 respiratory failure, Parkinson's disease, depression, gastroesophageal acid reflux disease, diverticular disease, rheumatoid disease or osteoporosis), demographic characteristics (age, gender, place of residence, number of medications before admission, ISAR score) and the six previously mentioned geriatric syndromes were evaluated as potential determinants of inappropriate prescribing as well as related hospital admissions.

2.4 Statistical Analysis

Continuous variables were analysed using medians (with 25th–75th percentiles [P_{25}–P_{75}]) because they were not normally distributed. For categorical variables, numbers and percentages are presented. A univariate analysis (see Online Resource 1) and a multivariate logistic regression analysis were used to identify determinants of potentially inappropriate prescribing and related hospital admissions.

Variables with a p value of <0.20 in the univariate analysis were submitted for multivariate regression analysis. A stepwise elimination procedure using Akaike's information criterion was used to identify independent multivariate predictors. A p value of <0.05 was considered statistically significant. A classification tree analysis was conducted to analyse determinants of hospital admissions related to potentially inappropriate prescribing [20, 21]. The one-standard-error rule was used to select the best tree [22]. Statistical analyses were performed using R software version 2.12.0 (Free Software Foundation, Inc., Boston, MA, USA) and CART version 6.6 (Salford Systems, San Diego, CA, USA).

3 Results

The inclusion criteria were met by 302 frail older patients (median [P_{25}–P_{75}] age 84 [81–88] years; proportion of females 62.6 % ($n = 189$); median [P_{25}–P_{75}] ISAR score 3 [3–4]). Upon hospital admission, the median [P_{25}–P_{75}] number of geriatric syndromes per patient was 2 [2–3] (out of 6). The three most frequent geriatric syndromes were polypharmacy [≥5 daily medications] (74.5 %), multiple falls in the last 6 months (58.3 %) and dependency in activities of daily living (43.7 %). The three most prevalent co-morbidities were hypertension (55.0 %), ischaemic disease (40.7 %) and renal failure (37.4 %) (Table 1). Overall, the 302 patients used 2,028 medications daily (median [P_{25}–P_{75}] 6 [4–9]). The medications and/or medication classes listed in the STOPP and START criteria that were most frequently used at home were for cardiovascular and neurological conditions (Table 1). Patients were mainly admitted to the hospital because of falls (34.0 %, $n = 104$) or cardio-respiratory problems (37.4 %, $n = 113$). Other reasons for admission were gastro-intestinal symptoms ($n = 38$), infectious diseases ($n = 31$) or miscellaneous ($n = 16$).

Table 1 Characteristics of the study population ($n = 302$)

Variable	Value
Sociodemographic variables	
Age (years; median [P_{25}–P_{75}])	84 [81–88]
Sex (n [%])	
Female	189 [62.6]
Male	113 [37.4]
Place of residence (n [%])	
Home	252 [83.4]
Nursing home	50 [16.6]
No. of medications per patient (median [P_{25}–P_{75}])	6 [4–9]
ISAR score (median [P_{25}–P_{75}])	3 [3–4]
Geriatric syndromes (n [%])	
Polypharmacy (≥5 medications/day)	225 [74.5]
≥2 falls in the last 6 months	176 [58.3]
Dependency in activities of daily living (Katz score ≥9/24)	132 [43.7]
Living alone	131 [43.4]
Malnutrition[a]	90 [29.8]
Cognitive disorder	75 [24.8]
Most frequent comorbidities (n [%])	
Hypertension	166 [55.0]
Ischaemic disease (heart/cerebral)	123 [40.7]
Renal failure (glomerular filtration rate <50 mL/min)	113 [37.4]
Osteoporosis with fracture	78 [25.8]
Persistent atrial fibrillation	77 [25.5]
Depression	76 [25.2]
Diabetes	69 [22.8]
Medication classes most frequently used at home (prevalence >20 %; n [%])	
Antithrombotic agents (including aspirin and vitamin K antagonist)	181 [59.9]
Psycholeptics (benzodiazepines and antipsychotics)	156 [51.7]
Agents acting on the renin-angiotensin system	142 [47.0]
β-blockers	115 [38.1]
Diuretics	102 [33.8]
Psychoanaleptics (antidepressants)	82 [27.2]
Analgesics	80 [26.5]
Lipid-modifying agents (statins)	66 [21.9]
Calcium channel blockers	65 [21.5]

ISAR Identification of Seniors at Risk

[a] Malnutrition was defined as a body mass index of <21 kg/m^2 or a mid-arm circumference of <23 cm

3.1 Inappropriate Prescribing According to STOPP

According to the STOPP criteria, 210 events of prescribing of potentially inappropriate medication (PIM) were detected. Three drug classes accounted for 61 % of these PIMs, namely benzodiazepines (33 %, $n = 72$), aspirin (17 %, $n = 35$) and opiates (11 %, $n = 24$). Specifically, fall-risk-increasing drugs (referred to in the STOPP criteria as "drugs that adversely affect fallers"), accounted for half of all PIMs (53 %, $n = 112$): benzodiazepines ($n = 70$), opiates ($n = 24$), neuroleptics ($n = 13$) and first-generation antihistamines ($n = 5$). PIMs were found in 144 of the 302 frail older persons, giving a prevalence of 47.7 %, with the following distribution: 1 PIM (29 %), 2 PIMs (16 %) and ≥ 3 PIMs (3 %). The five most frequent PIMs according to STOPP (benzodiazepines, aspirin, opiates, β-blockers and tricyclic antidepressants), their prevalence and their corresponding STOPP items are listed in Table 2. A multivariate logistic regression analysis identified two geriatric syndromes as strong determinants of PIM, namely a history of recent multiple falls (odds ratio (OR) [95 % confidence interval (CI)] 2.7 [1.6, 4.7]; $p < 0.001$) and polypharmacy (≥5 daily medications) (OR [95 % CI] 1.9 [1.1, 3.5]; $p = 0.026$). No significant association was observed with any other geriatric syndrome, demographic characteristic or co-morbidity in the multivariate analysis.

3.2 Inappropriate Prescribing According to START

362 events of potential prescribing omission (PPO) were detected according to the START criteria. Three medical conditions accounted for 52 % of all PPO events, namely diabetes (31 %), ischaemic disease (19 %) and osteoporotic fracture (14 %). The prevalence of PPOs was 62.9 % (190/302), with the following distribution: 1 (29 %), 2 (19 %), and ≥3 (15 %). Table 3 lists the prevalence of the five most frequent co-morbidities linked with PPOs, namely type 2 diabetes, osteoporosis, ischaemic disease/secondary cardiovascular prevention, persistent atrial fibrillation and COPD. The most frequent corresponding omitted medications were aspirin; statins; metformin; calcium, vitamin D and bisphosphonates; warfarin; and bronchodilators. In a multivariate analysis, PPOs were significantly associated with five co-morbidities, namely diabetes (OR [95 % CI] 13.1 [5.0, 34.2]; $p < 0.001$), atrial fibrillation (OR [95 % CI] 7.9 [3.5, 17.9]; $p < 0.001$), osteoporotic fracture (OR [95 % CI] 4.3 [2.0, 9.2]; $p < 0.001$), COPD (OR [95 % CI] 3.8 [1.3, 10.6]; $p = 0.012$) and ischaemic disease (OR [95 % CI] 2.1 [1.1, 4.2]; $p = 0.037$). No significant association was found with any other comorbidity, demographic data or geriatric syndrome.

3.3 Hospital Admissions Related to Inappropriate Prescribing

Overall, inappropriate prescribing (PIMs and/or PPOs) according to the STOPP and/or START criteria led or contributed to hospital admissions in 82 of the 302 patients

Table 2 Prevalence of the most frequent prescribing of inappropriate medications according to the STOPP criteria ($n = 302$)

Inappropriate medication	Related medical condition	(n [%])[a]
Benzodiazepines		72 [24]
	Fall in the last 3 months	61 [20]
	Long acting and long term (>1 month)	14 [5]
Aspirin		35 [12]
	Dosage >150 mg/day	25 [8]
	Primary cardiovascular prevention	7 [2]
Opiates		24 [8]
	Fall in the last 3 months	14 [5]
	Powerful opiate for mild to moderate pain	2 [1]
β-blockers		19 [6]
	Diabetes and hypoglycaemic episodes	13 [4]
	Non-selective β-blockers and COPD	4 [1]
Tricyclic antidepressants		15 [5]
	Dementia	6 [2]
	Glaucoma	2 [1]

COPD chronic obstructive pulmonary disease, *STOPP* Screening Tool of Older Person's Prescriptions

[a] As patients could have several inappropriate prescribing events, the numbers may not add up to the stated totals

Table 3 Prevalence of the most frequent potential prescribing omissions according to the START criteria ($n = 302$)

Medical condition	Omitted medication	(n [%])
Type 2 diabetes		112 [37][a]
	Aspirin	33 [11]
	Statin	39 [13]
	Metformin	25 [8]
Osteoporosis		80 [26]
	Calcium and vitamin D (used in cases of osteoporotic fracture)	51 [17]
	Bisphosphonates (used in cases receiving maintenance corticosteroids)	29 [10]
Ischaemic disease/need for secondary cardiovascular prevention		64 [21]
	Aspirin	41 [14]
	Statin	23 [8]
Persistent atrial fibrillation		37 [12]
	Vitamin K antagonists	34 [11]
	Aspirin (used in cases of contraindications to vitamin K antagonists)	3 [1]
COPD or asthma		22 [7]
	Inhaled β_2-agonist/anticholinergic agent (used in mild to moderate cases)	20 [6]
	Inhaled corticosteroid (used in moderate to severe cases)	2 [1]

COPD chronic obstructive pulmonary disease, *START* Screening Tool to Alert doctors to Right Treatment

[a] Only the most frequent prescribing omissions are listed for this condition

(27.1 %). Table 4 summarizes the medical problems leading to these admissions and the medications involved.

Fifty-four of the 302 admissions (17.9 %) were related to PIMs, of which 46 involved a fall associated with a major fracture. The latter 46 patients were receiving 66 inappropriately prescribed drugs (35 benzodiazepines, 13 opiates, 12 neuroleptics and 2 antihistamines) at home. The proportion of PIM-related admissions for a fall with a fracture in patients inappropriately receiving fall-risk-increasing drugs was 67.6 % (PPV = 46/68 [0.68]). A multivariate logistic regression analysis indicated that a history of recent falls was a strong independent determinant of admissions related to PIMs (OR [95 % CI] 5.2 [2.2, 12.3]; $p < 0.001$). No other geriatric syndrome nor any comorbidity was a significant determinant of PIM-related admissions. The classification tree (Fig. 1a) confirmed the role of a history of multiple falls as a determinant of PIM-related admissions, the prevalence of which was 26.1 % ($n = 46$) in the 176 patients with a history of multiple falls as compared with 6.3 % ($n = 8$) in the 126 other patients.

Table 4 Description of acute hospital admissions related to inappropriate prescribing ($n = 82$)

Main reason for admission	Medications prescribed/omitted inappropriately	n	PPV[b]
PIM-related admission		54[a]	
Fall with fracture	Fall-risk-increasing drugs[c]	46	0.68
Bleeding	Aspirin/NSAID	3	0.07
Heart failure	NSAID	2	0.25
PPO-related admission		38[a]	
Fall with fracture	Calcium, vitamin D and bisphosphonates	19	0.25
Ischaemic heart disease	Platelet aggregation inhibitors	5	0.07
	Statins	5	0.09
Stroke	Antithrombotic agents	2	0.06
Heart failure	ACE inhibitors	3	0.25
COPD exacerbation	Regular inhaled β_2 agonist or anticholinergic agent	2	0.10

ACE angiotensin-converting enzyme, *COPD* chronic obstructive pulmonary disease, *NSAID* nonsteroidal anti-inflammatory drug, *PIM* prescribing of potentially inappropriate medication, *PPO* potential prescribing omission, *PPV* positive predictive value

[a] Only the most frequent inappropriate prescribing events are listed

[b] PPV = the number of patients who had an admission potentially related to inappropriate prescribing of a drug divided by the number of patients who had that drug prescribed inappropriately

[c] Fall-risk-increasing drugs: benzodiazepines ($n = 35$), opiates ($n = 10$), neuroleptics ($n = 12$) and antihistamines ($n = 2$)

In the group of fallers, the next splitter was a history of myocardial infarction. The prevalence of PIM-related admission was higher in the group of fallers who had no history of myocardial infarction. Prescribing of ≥3 daily medications used at home was a further determinant of PIM-related hospital admission in the last group of patients.

PPOs were related to 38 of the 302 admissions (12.6 %). The large majority of PPOs were for drugs used to treat musculoskeletal ($n = 19$) or cardiovascular ($n = 16$) conditions. Amongst patients not receiving musculoskeletal drugs (such as calcium, vitamin D and bisphosphonates), the proportion of patients with a PPO-related admission for a fall with a fracture was 25 % (PPV = 0.25). In the multivariate logistic regression analysis, osteoporotic fracture (OR [95 % CI] 5.0 [2.2, 11.4]; $p < 0.001$) and atrial fibrillation (OR [95 % CI] 3.4 [1.5, 8.0]; $p = 0.004$) were significantly associated with PPO-related admissions. The classification tree (Fig. 1b) confirmed that PPO-related admissions were more frequent when a history of osteoporotic fracture was present than when it was absent (26.9 % [21/78] vs. 7.6 % [17/224]; $\chi^2_{1df} = 19.66$; $p < 0.001$). In the 224 patients without osteoporotic fracture, severe functional dependency (a Katz score of ≥21/24) was the next determinant of PPO-related admission.

4 Discussion

The present study showed that inappropriate prescribing of medications used at home was frequent, as 48 % of frail older patients received an inappropriately prescribed medication (PIM) according to STOPP and 63 % had a prescribing omission (PPO) according to START. Importantly, these events of inappropriate prescribing contributed or led to 27 % of hospital admissions. A history of previous falls and of osteoporotic fractures were the main determinants of PIM- and PPO-related admissions, respectively. To our knowledge, this is the first study investigating hospital admissions possibly related to events of inappropriate prescribing according to both STOPP and START in a population of older patients with frailty features. Our data are enriched by the evaluation of possible determinants, including geriatric syndromes.

Our prevalence results are consistent with those of previous studies of inappropriate prescribing according to STOPP and START. A recent international multicentre study of patients in acute geriatric units found prevalence rates of 51 % for PIMs and 59 % for PPOs on admission [23]. Other studies with older inpatients reported prevalence rates of 35–77 % for PIMs [13, 24] and 58–66 % for PPOs [24, 25]. In contrast, the prevalence of PIMs and PPOs was lower in studies of community-dwelling older people [8, 9].

Several risk factors for PIMs have been previously identified in the literature, namely polypharmacy [9, 23, 24], a history of recent falls [24], cognitive impairment [24], hospitalization in the preceding year [24], female gender [9] and advanced age [9, 23]. The first two, which are geriatric syndromes, were confirmed by our multivariate analysis.

The multivariate analysis showed that PPOs were associated with five co-morbidities (diabetes, atrial

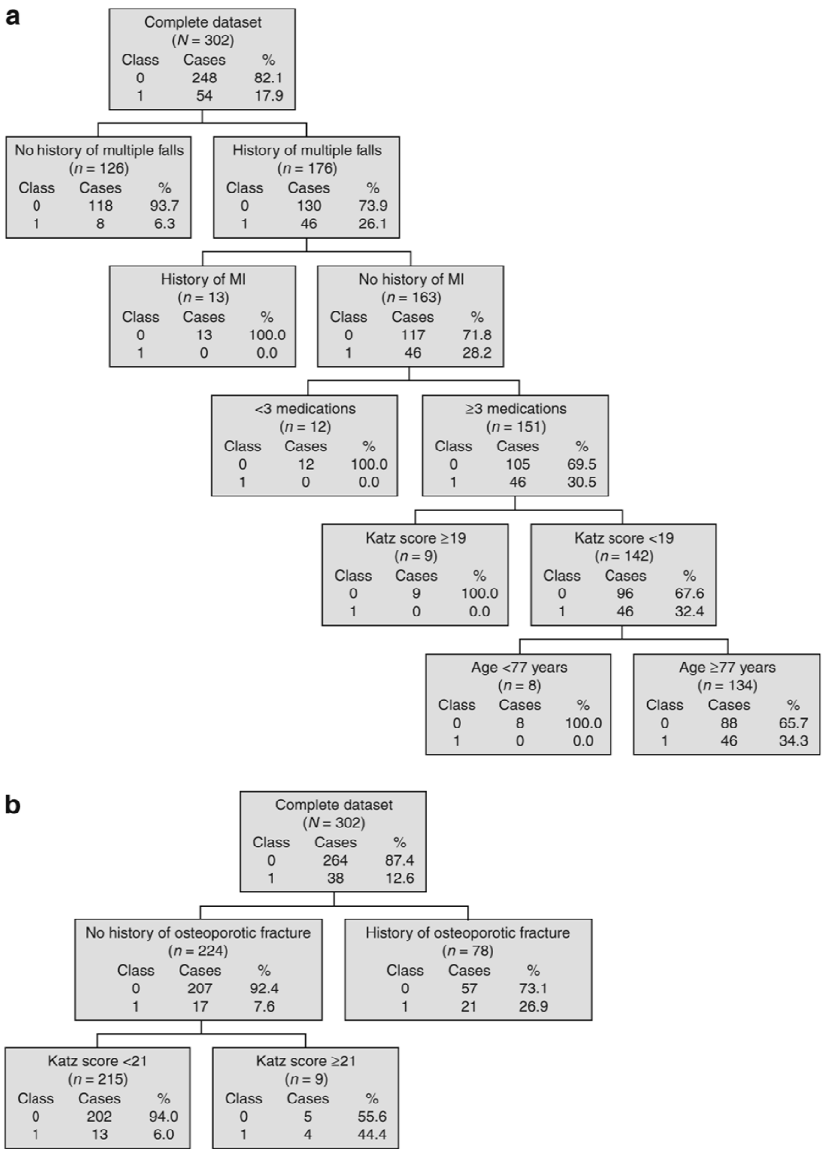

Fig. 1 Classification trees showing the main determinants of hospital admissions following (**a**) prescribing of potentially inappropriate medications (PIMs; according to the STOPP criteria) and (**b**) potential prescribing omissions (PPOs; according to the START criteria). Class 1 represents the number of patients who had a hospital admission related to inappropriate prescribing, and class 0 represents the others. *START* Screening Tool to Alert doctors to Right Treatment, *STOPP* Screening Tool of Older Person's Prescriptions

fibrillation, osteoporotic fracture, COPD and ischaemic disease). This finding is consistent with published data on the number of co-morbidities [23, 24]. Living in an institutional setting was a predictor of both PIMs and PPOs in a study by Lang et al. [24] but was not significant in our study, probably because of the limited number of institutionalized patients. Polypharmacy was related to PIM events but not to PPO events, as was previously reported by Steinman et al. [26].

Acute hospital admission was related to PIMs and PPOs in 18 % and 13 % of patients, respectively. A similar study of acutely ill older patients, using the STOPP criteria, found that PIMs contributed to 12 % of all admissions [13]. Furthermore, the same research group found that PIMs were significantly associated with preventable ADEs causing or contributing to hospital admission [14]. These results suggest good predictive validity of the STOPP criteria.

In contrast, to our knowledge, no study has addressed the link between hospital admissions and PPOs according to the START criteria. The present work shows that a significant percentage of patients are possibly admitted to

hospital because of prescribing omissions. Further studies are needed to confirm these results.

The use of classification trees in this study allowed us to segment the population into subgroups, using cut-off values that may be used in future risk-assessment exercises. Particular attention should be given to a subgroup of patients with a history of falls and/or osteoporosis, which should be studied further. The Katz threshold might be the object of validation in similar future studies.

Inappropriate use of medication in patients who experience falls is of particular concern. Similarly to previous studies, a substantial number of patients with previous falls were receiving fall-risk-increasing drugs ($n = 50$), and/or were not receiving medications that decrease the risk of fractures ($n = 71$) [8, 13, 14, 23–25]. These criteria were also those with the highest PPVs for hospital admission. Importantly, we found that recent falls were a significant determinant of medication-related admission. Falls are a major concern in older people, as they increase morbidity (including hospital admission) and mortality [27, 28]. Withdrawal of fall-risk-increasing drugs has been proven to be effective and cost-effective in older persons for fall prevention [29–31]. Such withdrawals, particularly of benzodiazepines, remain a challenge in daily practice.

Other clinical situations deserve special attention. First, cardiovascular prevention and inappropriate use of aspirin accounted for a significant proportion of inappropriate prescribing events, mainly misuse (a daily dose of >150 mg) and underuse. Moreover, six and two admissions were related to underuse or overuse of aspirin, respectively [32, 33]. Second, as has been highlighted in many other studies, underuse of vitamin K antagonists in patients with chronic atrial fibrillation was frequent [34–37]. Our analysis identified atrial fibrillation as an independent determinant of PPO-related hospital admissions. Third, diabetes was a significant determinant of PPOs (mainly of aspirin, metformin and ACE inhibitors) but did not predict PPO-related hospital admissions. There is evidence that such medications can decrease morbidity or mortality in adults but not in older persons. Therefore, clinicians often face difficulties to find the right balance between recommendations and therapies that are acceptable for older patients [38–40]. If we had applied the criteria to the 69 diabetic patients in our study, their mean number of daily drugs would have risen from 8.0 to 9.6. Therefore, the START criteria related to diabetes might need some revision.

This study had limitations. First, it was observational and monocentric. Second, the evaluation of the link between inappropriate prescribing events and hospitalization was based on clinical judgment. Similarly to previous studies, two types of professionals (i.e. a geriatrician and a clinical pharmacist) were involved. No inter-rater reliability (i.e. kappa coefficient) was calculated to measure the researchers' agreement, and no evaluation of preventability was performed.

The findings of this study underline the importance of regularly evaluating pharmacological treatment of frail older patients, knowing that inappropriate prescribing can be related to hospital admissions. Clinicians' attention should be drawn particularly to the treatment of patients with a history of falls, osteoporosis or cardiovascular disease such as atrial fibrillation. Use of the STOPP and START criteria should be encouraged, as these tools are useful and efficient in screening patients' medications and detecting inappropriate prescribing [12].

5 Conclusion

The use of the STOPP and START criteria revealed a high prevalence of inappropriate prescribing of medications used at home by a frail older population. Moreover, inappropriate prescribing in this population contributed to one in four acute hospital admissions. Optimizing prescribing of medications in patients with previous falls and osteoporotic fractures should be a priority for clinicians as well as evaluative researchers.

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ELECTRONIC SUPPLEMENTARY MATERIAL

(available at http://link.springer.com)

Medications Listed in the STOPP and START Criteria

STOPP Criteria (n = 20)

- Alpha-blockers
- Long-acting oral antidiabetic agents
- First-generation antihistamines
- Nonsteroidal anti-inflammatory drugs
- Benzodiazepines
- Calcium channel blockers
- Codeine phosphate
- Colchicine
- Digoxin
- Diphenoxylate
- Estrogens
- Loop diuretics
- Loperamide
- Metoclopramide
- Neuroleptics
- Opiates
- Prochlorperazine
- Theophylline
- Thiazide diuretics
- Vasodilators

START Criteria (*n* = 13)

- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Antihypertensive therapy
- Bisphosphonates
- Calcium
- Disease-modifying antirheumatic drugs
- Fibre supplements
- Inhaled β_2 agonists
- Levodopa
- Metformin
- Continuous oxygen
- Statins
- Vitamin D

Both STOPP and START Criteria (n = 7)

- Anticholinergic agents
- Antidepressants
- Aspirin/antiplatelet agents
- β-Blockers
- Corticosteroids
- Proton pump inhibitors
- Warfarin/vitamin K antagonists

Comorbidities Listed in the STOPP and START Criteria

STOPP Criteria (*n* = 23)

- Bleeding disorder
- Breast cancer
- Cardiac conductive abnormalities
- Deep venous thrombosis
- Dementia
- Dependent ankle oedema
- Diarrhoea
- Dizziness
- Epilepsy
- Glaucoma
- Gout
- Hyponatraemia
- Impaired renal function (glomerular filtration rate <50 mL/min according to the Modification of the Diet in Renal Disease [MDRD] study calculation)
- Incontinence
- Infective gastroenteritis
- Osteoarthritis
- Pain
- Peptic ulcer disease
- Postural hypotension
- Prostatism
- Pulmonary embolus
- Recent fall
- Urinary retention

START Criteria (*n* = 10)

- Asthma
- Atrial fibrillation
- Stable angina
- Chronic respiratory failure
- Depression
- Disease
- Gastro-esophageal acid reflux disease
- Peptic stricture requiring dilation
- Diabetic nephropathy
- Osteoporosis [fragility fracture or acquired dorsal kyphosis]

Both STOPP and START Criteria (*n* = 8)

- Constipation
- Chronic obstructive pulmonary disease
- Heart failure
- Hypertension
- Ischemic disease/secondary cardiovascular prevention
- Parkinson’s disease
- Rheumatoid disease
- Type 2 diabetes

Results of the Univariate Analysis

As shown in Table S1, the univariate analysis highlighted four characteristics as determinants of PIMs (according to the STOPP criteria); five determinants of PPOs (according to the START criteria); four significant predictors of admissions related to PIMs; and three significant determinants of admissions related to PPOs.

TABLE S1. Significant determinants of inappropriate prescribing and related hospital admissions

Determinant	OR [95 % CI]	*p* value
Determinants of PIMs		
Polypharmacy	2.1 [1.3, 3.2]	0.002
History of recent falls	2.6 [1.6, 4.2]	<0.001
Depression	1.9 [1.1, 3.2]	0.021
Osteoporosis	1.9 [1.1, 3.1]	0.021
Determinants of PPOs		
Age	0.93 [0.9, 0.97]	0.002
Atrial fibrillation	4.9 [2.4, 9.8]	<0.001
History of cardiovascular disease	1.9 [1.2, 3.1]	0.011
Diabetes	7.3 [3.2, 16.6]	0.001
COPD	4.4 [1.8, 10.8]	0.001
Osteoporosis	2.6 [1.5, 4.8]	0.001
Determinants of admissions related to PIMs		
History of previous falls	5.2 [2.4, 11.5]	<0.001
Older age	1.1 [1.0, 1.2]	0.009
Living in a nursing home	2.7 [1.3, 5.2]	0.005
Higher ISAR score	1.35 [1.0, 1.8]	0.044
Determinants of admissions related to PPOs		
History of atrial fibrillation	2.6 [1.4, 5.6]	0.005
COPD	2.4 [1.1, 5.4]	0.032
Osteoporosis	4.5 [2.2, 9.1]	<0.001

Abbreviations : CI confidence interval ; COPD chronic obstructive pulmonary disease ; ISAR Identification of Seniors At Risk ; OR odds ratio ; PIM prescribing of potentially inappropriate medication ; PPO potential prescribing omission

CHAPTER II – Anticoagulation underuse is inappropriate and associated with aspirin use in frail older patients with atrial fibrillation

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* The first two authors (Maes F., Dalleur O.) have contributed equally to the work (design, data collection, analysis and writing of the manuscript).

Chapter II at a glance

What is already known about this subject

- Inappropriate prescribing by underuse of indicated treatment is an underestimated problem, less described than over/misuse, and can be detected using the START criteria.
- START includes a recommendation on the use of anticoagulants in atrial fibrillation. This instance of potentially inappropriate underprescribing was frequently observed in Chapter I and in previous studies using STOPP&START, as well as in other studies about anticoagulation in older people with atrial fibrillation.
- Underuse of anticoagulant in atrial fibrillation exposes most frail older patients to a high risk of stroke; however, overuse - a much less frequent condition - seriously increases the risk for bleedings and hospital admissions. Therefore, decision to anticoagulate a frail older patient should take into account the balance between the risks of stroke and severe bleedings.

- This chapter further describes a frequent case of underuse detected by START and related to important clinical outcomes: the inappropriateness of antithrombotic management of atrial fibrillation in frail older people. This is a joint project with the cardiology department of the Cliniques universitaires Saint-Luc (Brussels) aiming at highlighting determinants of anticoagulants underuse and providing consequently educational and practical targets for improvement in the management of frail older patients in atrial fibrillation.

What this chapter adds

- **Half** of the frail older people with atrial fibrillation lack anticoagulation despite indication.
- Anticoagulation underuse is **not lower** in patients with a lower bleeding risk or a higher stroke risk.
- Anticoagulation underuse is markedly increased in patients taking **aspirin**.
- Anticoagulation could be considered as **favourable** in all patients, as the individual risk of stroke is always higher than the risk of severe bleeding.

ABSTRACT

Background. Anticoagulation for the prevention of cardio-embolism is most frequently indicated but largely underused in frail older patients with atrial fibrillation (AF).

Objectives. This study aimed at identifying new characteristics associated with anticoagulation underuse and inappropriateness.

Design. Cross-sectional study

Patients. Consecutive geriatric patients aged ≥ 75 years, AF and clear anticoagulation indication ($CHADS_2 \geq 2$) upon hospital admission.

Main Measures. Risks of stroke and bleeding were predicted using $CHADS_2$ and $HEMORR_2HAGES$ scores, respectively; the latter was weighted to predict the risk of severe bleeding (fatal or intracranial). The main endpoints were underuse of anticoagulation and inappropriateness of antithrombotic therapy.

Key Results. Anticoagulation underuse was observed in 384 (50%) of 773 geriatric patients with AF (median age 85 years, female 57%, cognitive disorder 33%, nursing home 20%). Anticoagulation underuse was markedly increased in patients with aspirin (Odds Ratio [95% CI]: 5.3 [3.8; 7.5]). Other independent predictors of anticoagulation underuse were ethanol abuse (OR: 4.0 [1.4; 13.3] and age ≥ 90 years (OR: 2.0 [1.2; 3.4]). Anticoagulation underuse was not lower in patients with a lower bleeding risk or a higher stroke risk, in particular those with a previous stroke. As the risk of stroke in every frail older patient of our sample was higher than the risk of severe bleeding, the antithrombotic therapy was appropriate in all patients on anticoagulation and inappropriate in all patients not receiving anticoagulation.

Conclusions. In frail older patients with AF, prescribers should consider anticoagulation and not aspirin. Anticoagulation is favourable in all frail older patients, as the individual risk of stroke is always higher than the risk of severe bleeding.

INTRODUCTION

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia in the elderly and its prevalence increases with age [1]. Two-thirds of AF cases concern patients aged 75 years and over [2], in whom AF prevalence exceeds 10%. Consequently, AF management is everyday practice for physicians in charge of older patients. As this arrhythmia largely increases the risk for cardio-embolism and specifically stroke [3], oral anticoagulant therapy, is recommended in patients at high risk of stroke (≥ 4% par year), while antiplatelet agents offer a possible alternative in patients at low risk an infrequent situation in older patients [4, 5].

Even if there is strong evidence that antithrombotic treatment is beneficial in older patients [6-8], data shows that approximately half of the older patients with AF do not receive an appropriate cardio-embolic prophylaxis [9, 10]. Patient-related reasons cited to refrain the prescription of anticoagulant therapy in the elderly include straight contra-indications, advanced age, comorbidities, history or increased risk of bleeding, falls and low compliance [11-16]. Some of these reasons are supported by evidence (e.g. previous major bleed) while others are not (e.g. risk of falls, advanced age) [17]. There is obviously a need for revisiting the appropriateness of prescribing (or withholding) of anticoagulant therapy in the light of the individual assessment of the overall risks and benefits. Prescribing anticoagulation can be considered as appropriate if the risk of stroke is higher than the risk of severe bleeding. The perception of these two opposite risks varies among physicians [15, 18].

Tools are currently available to help physicians assess these two risks (clotting or bleeding) in the older patients with AF, i.e. the $CHADS_2$ score [19] to predict the annual stroke risk and the $HEMORR_2HAGES$ score [20] to predict the risk of major bleeding. The aim of this study was to identify new characteristics related to the underuse of anticoagulant therapy in frail older patients and to assess this underuse of anticoagulants in terms of appropriateness.

MATERIAL & METHODS

Study design and patient population

We conducted a cross-sectional study including consecutive older patients with AF admitted between January 2008 and December 2010 in our academic hospital. Inclusion criteria were 1) age ≥ 75 years; 2) evidence of current or recent AF; 3) indication for anticoagulation defined by a $CHADS_2$ [19] score ≥ 2; and 4) comprehensive geriatric assessment upon hospital admission by the acute geriatric unit or by the inpatient geriatric consultation team (the latter provides geriatric counselling in non-geriatric wards for older patients with frailty defined by an Identification of Seniors At Risk (ISAR) [21] score ≥2). We excluded the few patients with another indication for anticoagulants (e.g. metallic valve, history of deep venous thrombosis/pulmonary embolism in the last 6 months) or with anticoagulants contra-indication (surgery in the last 3 weeks, peptic ulcer in the last 3 months).

Data collection

Socio-demographic data included age, gender and residency (private home *vs.* nursing home). Geriatric profile was assessed through functional dependency for basic activities of daily living using the Katz scale [22], frailty profile (ISAR) and the presence of cognitive disorder (clinical diagnosis or Mini Mental State Examination < 24/30) [23], malnutrition (a body mass index of <21 kg/m² and/or a mid-arm circumference <23 cm and/or albumin < 3g/dl), history of recent fall (in the past 3 months), and excess risk of falls (history of recent fall, dementia, Parkinson's disease, or evidence according to the team's physiotherapist). The use of antiplatelet therapy and/or anticoagulation therapy (Vitamin K antagonists VKAs or low molecular weight heparin at a dosage offering effective anticoagulation) at home the day before admission was recorded. Medical data specifically included the presence or absence of the items of the $CHADS_2$ and the $HEMORR_2HAGES$ scores.

Risks of cardio-embolism and bleeding

The AF-related risks of stroke and of bleeding were assessed using, respectively, the $CHADS_2$ score and the $HEMORR_2HAGES$ score. The $CHADS_2$ score (range 2-6/6 in this study) gives 1 point for the presence of each cardio-embolism risk factor, namely **C**ongestive heart failure (within last year), **H**ypertension (antihypertensive regimen or ≥ 160/90 mmHg on several occasions), **A**ge ≥75 years, **D**iabetes mellitus (anti-diabetic drugs or fasting blood glucose ≥ 126 mg/dl on several occasions), and 2 points for **S**troke or transient ischemic attack (TIA) history. We chose to use the $CHADS_2$ score for several reasons. In contrast to the CHA_2DS_2-VASc score [18], which is another recently developed score to predict stroke risk in patients with atrial fibrillation, the $CHADS_2$ score 1) was developed in a population of older patients (mean age 81 years [19] *vs*. 66 years in CHA_2DS_2-VASc [18]) ; 2) correlates with the stroke risk in a linear, precise (narrow confidence intervals) and valid (C statistics) manner; 3) allows easy calculation of the predicted absolute stroke risk (which in fact is twice the score, i.e 4% for score 2, 6% for score 3, ~8% for score 4), 4) correlates with the prescription habits in geriatric patients [20]; 5) is easy to remember and to use in the daily practice; and 6) was available at the time of anticoagulation decision in this study. The CHA_2DS_2-VASc score [18] performs well at identifying AF patients at very low risk of cardio-embolism [21], which is a very infrequent situation in frail older patients [8]. Moreover, according to this latter score, all the patients aged over 75 years should be on anticoagulation, which is controversial in older patients with lower annual stroke risk (<4%) and significant bleeding risk.

The $HEMORR_2HAGES$ score (range 1-12 in this study) is computed by adding 1 point for each of the following bleeding risk factor: **H**epatic (cirrhosis with Child-Pugh score ≥ 3) or renal failure (estimated Glomerular Filtration Rate eGFR [27] < 30 ml/min), **E**thanol abuse, **M**alignancy, **O**lder age, **R**educed platelet count (<150.000/µl) or function (use of platelet aggregation inhibitors), uncontrolled **H**ypertension, **A**naemia (haemoglobin < 10 g/dl), **G**enetic factors, **E**xcessive fall risk, **S**troke, and by adding 2 points for **R**ebleed risk, i.e. history of a major bleeding event (haemoglobin decline of ≥ 2 g/dl, blood transfusion of ≥ 2 units, or bleeding in a major organ) and recent (last three years) [28]. The $HEMORR_2HAGES$ score seemed to us more appropriate than the more recent HAS-BLED score [22] for the following reasons: 1) it was developed in a

population of older patients (80.2 years vs. 66.8 in HAS-BLED [22]; 2) it includes items relevant to the geriatric population (e.g.: age > 75 years, malignancy, anaemia, reduced platelet function due to antiplatelets, and excessive fall risk), 3) it precisely predicts (narrow confidence intervals) the risk of major bleeding events when treated by anticoagulation; and 4) it correlates with the actual prescription of anticoagulants in geriatric patients [20]. These features are not present in the HAS-BLED score. Although $HEMORR_2HAGES$ acronym is longer than HAS-BLED, the items are not more difficult to remember, as some HAS-BLED items stand for several conditions. Furthermore, the HAS-BLED item "labile INR" is not available at the time of decision-making on starting anticoagulation [22]. $HEMORR_2HAGES$ is the most suitable score to assess bleeding risk in older patients according to a recent French expert consensus on the management of atrial fibrillation in older people [8].

For the sake of assessment of antithrombotic treatment appropriateness, we aimed to weigh the risk of suffering a severe ischemic *vs*. a haemorrhagic cerebral event with similar clinical consequences in terms of mortality, morbidity and functional consequences. Two methods were used. Firstly, we compared the individual stroke risk of each patient with an approximated risk of severe cerebral bleeding events. As about 30% of all major bleeding events under anticoagulants are severe (intracranial haemorrhages or fatal events) in severe prospective cohorts [24, 25, 38], we multiplied by 0.30 the bleeding risk calculated with the $HEMORR_2HAGES$ score. Secondly, the individual annual stroke risk was compared to the major cerebral bleeding risk reported by Poli et al. in a population of very old patients under anticoagulants presenting similarities with our patients (75-79 years old: rate of major cerebral bleeding event = 0.7 *100 patient/year; 80-84 years: 2.2 *100 patient/year; ≥ 85 years : 1.8 *100 patient/year) [41].

Study endpoints

The main endpoint was the underuse of anticoagulation before admission, in older patients with clear clinical indication of anticoagulation according to the $CHADS_2$ score. As secondary endpoint, the management of AF was considered appropriate in patients on anticoagulants if their stroke risk was higher than their risk of severe bleeding events and in patients not receiving anticoagulants if their stroke risk was lower than their risk of severe bleeding events.

Statistical Analysis

All continuous variables not normally distributed were summarized using the median and the inter-quartile range [P25-P75] and were compared between groups using Wilcoxon rank sum test or Kruskal-Wallis test. Categorical variables were expressed using percentages and were compared using Chi-squared test or the Fischer's exact test. Multivariate logistic regression was used to assess the independent predictors of anticoagulation underuse. In order to avoid co-linearity, the correlation coefficients between covariates were calculated. In case of co-linearity (r-value > 0.90), only one of the two covariates was considered in the multivariate model. Variables with a P-value ≤ 0.20 in univariate analysis were submitted to the multivariate model. A stepwise procedure using Akaike's information criterion was used to select independent multivariate predictors of anticoagulation underuse. Model goodness of fit was examined using Hosmer-Lemeshow test (null hypothesis: the model is a good fit for the data). All statistical analyses were performed using R version 2.15.1 and a p-value < 0.05 was considered as statistically significant.

RESULTS

Patient's characteristics

773 frail older patients (median age 85.0 years; female gender 57%) met the inclusion criteria. Geriatric syndromes were frequent (e.g. malnutrition 47%, recent fall 42%, cognitive disorder 33%). Half of the patients were dependant (median Katz score: 9) and one fifth were nursing home residents.

Half of the patients included were hospitalised in the geriatric ward (53.7%, n = 415/773). These patients presented a frailer profile than the included patients hospitalised in non-geriatric wards. Indeed, these patients were older (median age 86.0 *vs.* 84.0, p<0.001), more frequently suffered from malnutrition (56% *vs.* 36%, p<0.001), from more cognitive disorders (42% *vs.* 23%, p<0.001), and were more dependant according to their Katz score (median Katz score 10 *vs.* 8, p<0.001). However, as the outcome of this study is on the anticoagulation strategy before hospital admission, data

of the patients admitted in geriatric and non geriatric-ward were pooled for further analysis.

The annual risk of stroke was high (mean ± SD: 6.9 ± 3.3%) as predicted by the $CHADS_2$ score and its items (congestive heart failure 49%, hypertension 83%, age ≥ 75 years 100%, diabetes 21%, and stroke/TIA 32%). The mean annual risk of anticoagulant-associated bleeding was high also (9.7 ± 2.2%), based on the $HEMORR_2HAGES$ score and its prevalent items (e.g. risk of fall 63%, reduced platelet function/count 56%). When restricting the bleeding risk to severe events, the mean predicted annual rate was 2.9 ± 0.7%, thus lower than the stroke risk.

Underuse of anticoagulation

Half of the patients (50.3%, n=389) was on VKA (n=330) or low molecular weight heparin (n=59), while the other half received no anticoagulant (49.7%, n=384) at home before the hospital admission. Table 1 compares patients on anticoagulation to those with no anticoagulation in terms of socio-demographic data, geriatric syndromes as well as risk factors and predicted annual rates of stroke and bleeding.

Patients with no anticoagulation significantly had older age (86 *vs*. 85 years), higher use of antiplatelet therapy (61 *vs*. 27%), and globally higher annual bleeding risk according to HEMORR2HAGES (10.4 [8.4;12.3] *vs*. 10.4 [8.4;10.4], p<0.001). However, the bleeding risks were not different if corrected for antiplatelet agents use (i.e. withdrawing one point to all the patients on antiplatelets therapy; 8.4 [8.4;10.4] *vs*. 8.4 [8.4;10.4], p=0.41).

TABLE 1. Characteristics of older patients in atrial fibrillation on anticoagulation or not

	On anticoagulation n = 389	No anticoagulation n = 384	p-value
Socio-demographic			
Age, median [P_{25}-P_{75}]	85 [81-88]	86 [82-89]	0.004
Female gender, %	54.8	58.6	0.28
Living in nursing home, %	17.2	23.2	0.04
Geriatric features, %			
Malnutrition	45.0	48.6	0.32
Recent fall	42.7	42.2	0.89
Cognitive disorder	31.9	34.6	0.42
Dependency in ADL (Katz score ≥10/24)	45.9	49.3	0.33
$CHADS_2$, stroke risk			
Score, median [P_{25}-P_{75}]10	3 [2-4]	3 [2-4]	0.17
Risk, %/year, median [P_{25}-P_{75}]	5.9 [4.0-8.5]	5.9 [4.0-8.5]	
Items, %			
Congestive heart failure	50.4	47.1	0.37
Hypertension	82.2	83.1	0.77
Age ≥ 75 years	100	100	
Diabetes mellitus	21.6	21.0	0.80
Stroke or TIA	34.0	30.7	0.34
$HEMORR_2HAGES$, bleeding risk			
Score, % median [P_{25}-P_{75}]	4 [3-4]	4 [3-5]	<0.001
Risk, %/year, median [P_{25}-P_{75}]	10.4 [8.4-10.4]	10.4 [8.4-12.3]	
Items, %			
Hepatic / renal failure	14.6	13.8	0.74
eGFR<30ml/min	13.4	11.5	0.42
Ethanol abuse	1.3	3.6	0.03
Malignancy	9.0	10.7	0.43
Reduced platelets	45.0	68.0	<0.001
Antiplatelet therapy	26.5	60.7	<0.001
Thrombopenia	18.3	7.0	<0.001
Rebleeding	6.9	4.9	0.24
Anaemia (Hb<10 g/dl)	16.5	16.9	0.86
Excessive fall risk	60.4	65.4	0.15
Stroke	30.8	28.4	0.45

Abbreviations: ADL activites in daily living; eGFR estimated Glomerular filtration rate (using the MDRD-4 formula), Hb haemoglobin; TIA transient ischemic attack

Univariate analysis confirmed that anticoagulation underuse was not associated with geriatric syndromes (malnutrition, falls, cognitive disorder, functional dependency) nor with the $CHADS_2$ score. Predictor factors associated (p-value $\leq$ 0.2) with anticoagulation underuse were antiplatelet therapy, ethanol abuse, age older than 90 years, fall risk, and nursing home residency (Table 2). The $HEMORR_2HAGES$ score, which includes three of the above mentioned risk factors, was associated with anticoagulation underuse in the univariate analysis. The multivariate analysis (Table 2) identified three variables as independent predictors of anticoagulation underuse, namely antiplatelet therapy (OR 5.3), ethanol abuse (OR 4.0) - a feature present in only 2.5% of the patients - and age older than 90 years (OR 2.0).

TABLE 2. Determinants of anticoagulation underuse in 773 frail older patients

	Univariate analysis			**Multivariate analysis**		
	OR	[95% CI]	P-value	OR	[95% CI]	P-value
Antiplatelets use	4.28	[3.17-5.83]	<0.001	5.27	[3.75-7.48]	<0.001
Ethanol abuse	2.91	[1.10-9.07]	0.043	4.00	[1.39-13.31]	0.014
Age						
≥ 90 years	1.67	[1.03-2.71]	0.039	2.00	[1.18-3.43]	0.011
≥ 85 and <90 years	1.07	[0.70-4.66]	0.745	1.11	[0.69-1.79]	0.673
≥ 80 and < 85 years	0.99	[0.64-1.54]	0.976	0.86	[0.53-1.40]	0.549
≥ 75 and < 80 years	1.00			1.00		
Excess fall risk	1.24	[0.92-1.66]	0.154	1.36	[0.95-1.93]	0.090
Living in nursing home	1.45	[1.02-2.08]	0.038	1.37	[0.93-2.03]	0.115

Hosmer-Lemeshow goodness-of-fit p-value = 0.76, indicating that the model is a good fit for the data.

Anticoagulation underuse and antiplatelet therapy

As antiplatelet therapy was the strongest determinant of anticoagulation underuse, we raised the hypothesis that patients on antiplatelet agents but no anticoagulation (n=233) had been at higher bleeding risk ($HEMORR_2HAGES$ score) and/or lower stroke risk ($CHADS_2$ score) than those on anticoagulation (n=389). Table 3 shows that this was not the case. These two groups showed difference neither in $CHADS_2$ score nor in $HEMORR_2HAGES$ score when corrected for antiplatelet agents use (i.e. withdrawing one point to all the patients on antiplatelets therapy).

TABLE 3. Comparisons between patients on anticoagulant and patients on antiplatelet agents.

Significant variables	Anticoagulant* (n=389)	Antiplatelet† (n=233)	p-value
Antiplatelet therapy	26.5	100	< 0.001
Vascular disease	48.9	62.2	0.003
Ethanol abuse	1.3	3.9	0.036
Risk prediction			
$CHADS_2$ score			
Median score [P_{25}-P_{75}]	3 [2-4]	3 [2-4]	NS
Risk, %/year, median [P_{25}-P_{75}]	5.9 [4.0-8.5]	5.9 [4.0-8.5]	
$HEMORR_2HAGES$ score			
Median score [P_{25}-P_{75}]	4 [3-4]	4 [4-5]	< 0.001
Risk, %/year, median [P_{25}-P_{75}]	10.4 [8.4-10.4]	10.4 [10.4-12.3]	
Corrected $HEMORR_2HAGES$‡			
Median score [P_{25}-P_{75}]	3 [3-4]	3 [3-4]	NS
Risk, %/year, median [P_{25}-P_{75}]	8.4 [8.4-10.4]	8.4 [8.4-10.4]	

Abbreviations : NS = non significant

* Anticoagulant: with or without antiplatelet therapy

†Antiplatelet: without anticoagulation

‡Corrected HEMORR2HAGES: no point given for antiplatelet therapy

Anticoagulation underuse after stroke

We further studied the 229 patients with AF and a history of stroke, in whom anticoagulation underuse was expected to be lower. Surprisingly, anticoagulation underuse was present in 109 (48%) of these patients with a previous stroke, and not lower than in those free of stroke (51%) (p = 0.45). The geriatric profile of these 229 frail older stroke patients was similar to this of the overall study group. In multivariate analysis, the single independent factor associated with anticoagulation underuse in these stroke patients was antiplatelet agent use (OR [95%CI]: 5.0 [2.9;8.8] (p<0.001). Neither $CHADS_2$ nor $HEMORR_2HAGES$ score was determinant of anticoagulation underuse in patients with AF and history of stroke.

Appropriateness of antithrombotic treatment

In all the 389 patients on anticoagulation, regardless of concomitant use of antiplatelet therapy, the individual $CHADS_2$-related risk of ischemic stroke was higher

than the approximated risk of severe cerebral bleeding, and than the risk reported by Poli et al. [32], to the benefit of the anticoagulation use. In the 384 patients not receiving anticoagulation, again, the absolute difference in severe cerebral events, using the same calculation, was in favour of anticoagulation use in every patient. Using these criteria, in these frail older patients with a $CHADS_2$ score ≥ 2, the antithrombotic treatment would be appropriate in all patients on anticoagulation, and inappropriate in all patients not receiving anticoagulants.

DISCUSSION

The main finding of this study in frail older patients with AF was that the strongest predictor of anticoagulation underuse was the use of antiplatelet therapy, a reversible characteristic allowing improvement in stroke prevention. Aspirin (acetylsalicylic acid) is known to be of limited efficacy in stroke prevention [33], especially as age increases [34]. Warfarin is more effective that aspirin, also in older patients [35]. Moreover, warfarin is safer than aspirin in octogenarians, as shown in the WASPO trial which found significantly more adverse events with aspirin (33%) than with warfarin (6%), including serious bleeding [36]. Surprisingly, the large anticoagulation underuse (69%) in our patients on antiplatelet therapy was not explained by a lower risk of cardio-embolism or a higher risk of bleeding. We found no clinical rationale underlying the withholding of anticoagulation. We suspect that aspirin was prescribed in some patients for AF-related stroke prevention, while in the others - the majority probably - for cardiovascular ischemic disease. It has been proposed not to add aspirin for associated stable vascular disease [23] in a patient with AF receiving anticoagulation, as there is no evidence that adding aspirin to warfarin reduces stroke or other vascular events in these patients [24, 25], while aspirin increases the bleeding risk. In such patients, in line with recent guidelines, we suggest that aspirin should be withdrawn and anticoagulation prescribed in monotherapy if the coronary ischemic event occurred more than one year ago [8, 26]. Further research on the sample of older patients of our hospital receiving aspirin and anticoagulants is planned to assess overuse of this dual therapy with regards to the occurrence of the coronary event.

The observation that stroke history was not related to higher use of anticoagulation is another important finding of our study. Nearly half (48%) of these

high risk patients in secondary stroke prevention presented with anticoagulation underuse, despite no significant difference in their geriatric profile, stroke risk or bleeding risk.

Medical-decision making in terms of anticoagulation in older patients is complex. We used the $CHADS_2$ and the $HEMORR_2HAGES$ scores to mathematically compare the absolute predicted risks. Nevertheless, neither the $CHADS_2$ score nor the corrected $HEMORR_2HAGES$ score was found to be independent determinant of VKA underuse in these older inpatients. Our observations differ from those reported in long-term care residents where warfarin use increased with higher stroke risk and with lower bleeding risk [27]. However, our results confirm the observation of Marcucci and colleagues, that cardio-embolic and bleeding risks are not the determinant of the therapeutic choice in older patients with AF [28]. We had initially made the hypothesis that underuse was explained probably both because of underestimation of thromboembolic risk and overestimation of bleeding risk. However, our results did not show less underuse in patients neither with higher $CHADS_2$, nor in those with lower $HEMORR_2HAGES$ scores. Further studies should assess physician-related reasons for this lack of relationship between prescribing patterns and the stroke and bleeding risks, i.e. lack of knowledge about the risks, giving more weight to the low compliance in elderly patients, previous experience, or responsibility feeling [33]. Indeed, the most obvious reason of under-prescribing is probably that general practitioners would feel personally responsible for a haemorrhagic complication of the anticoagulant treatment, as opposed to a "natural" thromboembolic event in the absence of anticoagulation [34].

We believe that risk prediction tools, such as the $CHADS_2$ and the $HEMORR_2HAGES$ scores, should be more generally used in primary care practice to help physicians balance the risk-benefit ratio for anticoagulation in individual frail older patients. This assessment, in our opinion, is rather easy and quick. The balance of these risks showed in our study to be in favour of anticoagulation. As already observed by Friberg et al. [44], the cerebral risk of ischemic stroke without anticoagulant treatment exceeds the cerebral risk of intracranial bleeding with anticoagulant treatment at almost every combination of stroke and bleeding risks.

Our study confirms the general tendency among physicians to underuse anticoagulants in the elderly with AF. This large underuse rate (~50%) is concordant with previous literature data [9, 10, 15, 45-49]. Besides antiplatelet therapy, discussed above,

two other characteristics were found to be independent predictor of anticoagulation underuse in our multivariate analysis: ethanol abuse and patient's very old age (≥ 90 years). The former was infrequent and strong, while the latter was frequent and weak. Although age is an independent risk factor for bleeding with all anticoagulation modalities [34, 50], age should not be regarded as a contraindication to anticoagulation treatment. In a large study on very old patients (median age 84 years) on VKA therapy carefully monitored by anticoagulation clinics, the rate of major bleeding was low (1.9%/year) [31]. Moreover, the risk for stroke increases with older age in patients with AF [1, 51]. Therefore, non prescription of anticoagulation on the sole reason of older age can be considered as ageism [42]. We did not find any association between anticoagulation underuse and geriatric syndromes [10], neither with gender, haemorrhage history or malignancy [9, 52].

Our study presents several strengths. Firstly, it focuses on a highly relevant topic in the daily medical practice, as the elderly population continues to expand and anticoagulation drugs are frequent long-term medications. Secondly, it is quite original, as few previous studies analyzed in a large and representative frail older population with AF both medical and geriatric characteristics as potential predictors of anticoagulation underuse. Thirdly, and importantly, our analysis of the prescribing appropriateness in terms of cardio-embolic and hemorrhagic risk balance may bring a fresh insight into this complex decision-making problem.

The study shows some limitations. It was retrospective and based on risk assessments conducted during a hospital stay. Nevertheless, we had access to a large and valuable amount of information brought by the comprehensive geriatric assessment. We could not explore all the potential factors affecting the anticoagulation decision, particularly the general practitioner-related reasons or the patient's preferences. Finally, it was not possible to evaluate patient's compliance in our cross-sectional study, which is a crucial point with that type of medication in geriatric patients. Complementary further qualitative work would help understand reasons underlying anticoagulant underuse.

This study was conducted before the marketing of new oral anticoagulants (NOACs) (e.g. apixaban, dabigatran or rivaroxaban) in our country (2012), nowadays used in AF. We believe that these NOACs will be of little help in decreasing the anticoagulation underuse in the frail older population with atrial fibrillation. Due to

short half-life, adherence to treatment remains a challenge with these drugs. The lack of reliable monitoring tests, of reversal agent and cost are other barriers to the prescribing of NOACs which were not encountered with VKAs [23]. Three characteristics associated with anticoagulation underuse in our study, namely renal impairment, antiplatelet use, and ethanol abuse, will not disappear with the use of NOACs. 1) NOACs require dosage adjustment according to age and renal function. Half of our patients presented with eGFR lower than 50 ml/min. Therefore, distrust to anticoagulate older patients with frequent renal impairment, is more likely to continue. 2) Cautious concomitant use with aspirin is recommended for these NOACs. In our study, many patients not on anticoagulation were receiving antiplatelets. 3) Although chronic ethanol abuse is not mentioned as a contra-indication for NOACs, hepatic disease and dysfunction, its feared consequence, is. Furthermore, the use of newly marketed drugs should always be considered with caution in older patients, who are often excluded from clinical trials. Clinical trials on NOACs included subjects aged above 75 years, but only a small number of frail older patients aged above 80 years [24-26]. We believe that the decision to prescribe anticoagulation is a global concept and that the type of molecule (VKA *vs.* NOACs) is not influencing significantly the decision-making in this specific population. In a future study, we plan to compare the prevalence of underuse a few years after the marketing of NOACs with the present results in order to test this hypothesis.

In summary, our study showed that underuse of anticoagulation concerns half of the frail older patients with AF and yet anticoagulation indication. Underuse of anticoagulation could not be clinically explained in this population, and was mainly related to use of aspirin. Anticoagulation is a favorable option in all older patients with AF and a HEMORR$_2$HAGES score not higher by two points or more than the CHADS$_2$ score.

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CHAPTER III – Inappropriate prescribing in primary care, according to STOPP&START and the Beers criteria

III.1. 2012 Updated Beers criteria: Greater applicability to Europe?

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III.2. Inappropriate prescribing in subjects aged 80 and older: the BELFRAIL population

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Chapter III at a glance

What is already known about this subject

- Very old patients represent a sensitive population regarding the adverse geriatric outcomes and therefore a priority for security improvements of drug treatments.
- STOPP&START were designed to detect inappropriate prescribing in patients aged over 65 but little is known on the prevalence of inappropriate prescribing in very old patients.
- Beers criteria, which are American, have been widely used in research to detect inappropriate prescribing. However, they present poor transferability to Europe.
- Beers criteria have been updated in 2012.

- This chapter presents the prevalence of inappropriate prescribing according to STOPP&START and Beers in community-dwelling patients aged over 80 years.

What this chapter adds

- The **applicability** to Europe of the updated **Beers** criteria has **improved** in comparison to the previous version.
- STOPP and the Beers tools share some similar criteria, but significant **differences** exists and STOPP detects more potentially inappropriate medications than Beers.
- The clinical **relevance** of the STOPP&START screening **varies** among patients and with the extent of clinical data available.
- Some potentially inappropriate prescribing detected by STOPP&START are actually appropriate when considering the patient in a **holistic** way.

III.1. 2012 Updated Beers criteria: Greater applicability to Europe?

2012 UPDATED BEERS CRITERIA: GREATER APPLICABILITY TO EUROPE?

To the Editor: We read with interest the article on the 2012 Beers Criteria updated by the American Geriatrics Society and recently published in the *Journal of the American Geriatrics Society*.[1] The authors are to be commended for this important work. As clinicians and researchers, we particularly appreciate the evidence-based approach and the addition of several medications recently marketed for diseases that are prevalent in older people. Nevertheless, we would have appreciated additional information on the underlying reasons for the removal of some medications from this new list, such as fluoxetine, long-term use of stimulant laxatives, and high-sodium content drugs with heart failure.

The relevance of this updated list for European countries is particularly important to address for two main reasons. First, the inappropriate use of medicines in older adults in Europe has been under increased scrutiny over the last 10 years, and the Beers criteria—although frequently used—have weaknesses when applied to European countries.[2,3] Second, other explicit tools have been developed in Europe, and their comparison with the Beers criteria is of interest.[3,4]

An important criticism of the Beers criteria is their restricted applicability to Europe. Fialova and colleagues reported that, overall, half of the medications listed in the previous Beers criteria were not approved in most European countries. Therefore, one could wonder whether the applicability to Europe has increased with the 2012 Beers criteria.[2] Analyzing the Belgian situation, we came to a positive answer. We systematically compared the Belgian national formulary with the inappropriate medications and medication classes of the Beers list and checked whether each criterion was applicable to Belgium. The results are presented in Table 1. The proportion of individual criteria applicable in Belgium rose from 71.2% to 84.8%. Although the Belgian situation cannot be extrapolated to all Europe, it is likely that a similar observation could be made for several other countries, because Belgium has an average profile of medication availability.[2]

The Screening Tool of Older Person's Prescriptions (STOPP) criteria are being increasingly used in Europe and are to some extent considered to be the "European Beers criteria."[4] Several studies have shown a greater prevalence of inappropriate prescribing using these criteria than the Beers criteria, and a link with clinical outcomes has been shown in a few STOPP studies.[5,6] We therefore compared the 2012 Beers criteria with the STOPP criteria to identify similarities and differences. The comparison can be summarized as follows; 25 of the 99 Beers criteria are common or very similar to the STOPP criteria, meaning that three-quarters of the Beers criteria do not overlap with STOPP criteria. Similarly 36 of the 65 STOPP criteria (55%) are not part of the Beers criteria. The two lists thus share a minority of criteria. Among them, both lists suggest avoiding benzodiazepines in individuals with history of falls or fractures, calcium channel blockers in individuals with chronic constipation, and long-duration sulfonylureas. Among the differences between the two lists, we would like to point out a few things. The new Beers criteria highlight the danger of anticholinergics in a more explicit way than the STOPP criteria, and they include delirium and dementia in the medical situations of concern, which are prevalent syndromes in frail older adults, but the STOPP list includes several criteria regarding the use of warfarin—a medication frequently associated with adverse drug events in older adults—as well as specific criteria on opiates.[7]

Summarizing the European-based studies that used the STOPP criteria, we observe that the four most prevalent criteria were benzodiazepines in individuals prone to falls, duplicate drug class prescription, aspirin in primary cardiovascular prevention, and proton pump inhibitors at full therapeutic dosage for longer than 8 weeks.[8] Beers 2012 would identify such an overuse of benzodiazepines and aspirin, but neither the drug duplications nor the excessive duration of proton pump inhibitors. The latter is important from an economic and a safety perspective (greater risk of fractures and pneumonia).[9,10]

In conclusion, we believe that the 2012 Beers criteria have greater relevance for European countries. Because the majority of criteria for inappropriate prescribing do not overlap in Beers and STOPP, both lists will continue to coexist. Furthermore, the addition to Beers of criteria

Table 1. Applicability of the 2003 and 2012 Beers Criteria to Belgium

	n/N (%)	
Level of Analysis	2003	2012
Medications or medication classes[a]	38/48 (79.2)	49/53 (92.5)
Molecules listed[b]	60/100 (60.0)	100/177 (56.5)
Individual criteria[c]	47/66 (71.2)	84/99 (84.8)

Example to illustrate method of calculation.
[a]First-generation antihistamines counted as one medication class.
[b]All molecules listed under first-generation antihistamines were counted (n = 12).
[c]Each recommendation related to a medication or medication class was counted unless one recommendation duplicated another (first-generation antihistamines should always be avoided because of anticholinergic properties, thus the criteria first-generation antihistamines in chronic constipation was not counted).

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regarding the underuse of medications in older persons would be most appreciated in the future.[3] We are eager to see how the new 2012 Beers criteria will perform when applied in observational and experimental research and how well they will predict adverse clinical or economical outcomes.

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III.2. Inappropriate prescribing in subjects aged 80 and older: the BELFRAIL population

ABSTRACT

Background. The pharmacological treatment of very old patients is an important component of their care. Medication review with screening tools may help detect inappropriate prescribing. Little is known about the prevalence of potentially inappropriate prescribing in the very old living in the community, and about the clinical relevance of screening tools in that population.

Methods. Post-hoc analysis of baseline data of the BELFRAIL cohort, which included 567 Belgian patients aged 80 and older in primary care. The main objective was to compare the prevalence of potentially inappropriate prescribing (PIP) according to (1) STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment), and (2) the 2012 Beers list. Secondary objective included the assessment of the clinical importance of the recommendations to modify the patients' treatment according to STOPP&START and Beers, on a subsample of PIPs.

Results. The screening of drug treatment of the patients (median age 84 years, 63% female) detected 638 START-PIPs in 59 % of the patients and 331 STOPP-PIPs in 41% of the patients. The drugs which were most frequently underused according to START were: antiplatelets in secondary cardiovascular prevention, calcium and vitamin D in osteoporosis, and angiotensin-converting-enzyme inhibitor in heart failure, while STOPP-detected overuse involved most frequently: aspirin in primary cardiovascular prevention, duplication of treatment, and long-acting benzodiazepines. The application of the Beers criteria pointed out 249 Beers-PIP as drugs to avoid or to avoid in the presence of certain conditions in 32% of the patients. Frequent Beers-PIP (that did not overlap with STOPP-PIP) included: Z-drugs, benzodiazepines in the presence of cognitive decline, and tricyclic antidepressants. Assessment of the clinical importance of the PIPs revealed that the most frequent ones are of moderate or major importance. Importantly, the relevance of the criteria varied from major to deleterious when considering the global medical, functional and social background of the patient.

Discussion. Potentially inappropriate prescribing is highly prevalent in the very old. Some STOPP&START and Beers criteria should be modified to improve their clinical relevance. Criteria of major importance should be prioritized for implementation in

clinical practice. Screening tools should be used within a global assessment of the patient, to improve the relevance of the screening of the drug treatment.

INTRODUCTION

In our aging population, the proportion of patients aged 80 and older is increasing. This very old population represents a challenge for healthcare, because the patients often present with multiple comorbidities, polypharmacy, frailty features and increased sensitivity to adverse drug events. The pharmacological treatment of these patients is an important part of their management in primary care. Unfortunately, potentially inappropriate prescribing (PIP) is highly prevalent in older adults and has been associated with adverse drug events, hospitalization and death [1-4]. Inappropriate prescribing can be described as overuse, misuse or underuse. Overuse refers to the use of drugs presenting higher risk than benefit for the patient, misuse is the inadequate prescribing of a needed drug (with regards to the dose, the way of administration,...) and underuse is defined by the absence of a required drug [2]. A recent review reported that the median rate of inappropriate prescribing in primary care was around 20 % in patients aged over 65 years old [5]. But little is known about the prevalence of inappropriate prescribing in the very old, who yet represent a particularly sensitive population.

Several approaches exist to detect and reduce the burden of inappropriate prescribing in elderly [6]. The use of tools is one of these approaches. Some tools are implicit (i.e. judgement based), while others are explicit (criterion-based) [2]. The explicit tool that has been the most studied is the Beers list, which was first published in 1991 [7] and regularly updated since. The last update was published in 2012 [8]. The transferability in Europe of the Beers list has been frequently questioned but is seems that the last update includes more drugs marketed in Belgium than the previous versions [9]. In recent years, another explicit tool published by an Irish team, the STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) [10], was increasingly used in European studies [1]. The tool aims at detecting PIP in patients aged over 65 years old, which was the population target of most of the published studies using this tool. While Beers and STOPP address over- and misuse of inappropriate medications, the START tool allows for the detection of potentially inappropriate drug omissions.

Some overlap of content between the STOPP and the 2012 Beers criteria has been described [9, 11]. Comparisons between the applicability and sensitivity of STOPP and the 2002 version of the Beers criteria showed that STOPP was more sensitive [1].

However, to the best of our knowledge, no comparison with the updated 2012 Beers list has been performed.

The clinical importance of the criteria might vary. The clinical relevance of modifications of treatment after the detection of PIP takes on an added importance in octogenarians, because they are particularly sensitive, and more prone to frailty.

The primary objective of this study was to determine the prevalence of potentially inappropriate prescribing (PIP) in a population-based cohort of patients aged 80 and older (the BELFRAIL population) according to START (START-PIP) and STOPP (STOPP-PIP).

Secondary objectives included a comparison with the PIPs detected by the Beers' list (Beers-PIP), and an assessment of the clinical importance of a subsample of PIPs by a panel of experts in the context of each patient. The latter objective aims at differentiating *potentially* inappropriate prescribing from *actually* inappropriate prescribing.

METHODS

Study design, setting and participants

We performed a post-hoc analysis of the baseline data of the BELFRAIL cohort (BF_{C80+}). The BELFRAIL study is a prospective, observational, population-based cohort study of Belgian subjects aged 80 years and older [12]. The subjects were recruited by their general practitioners (GPs) between November 2, 2008 and September 15, 2009 in 3 regions of Belgium, as described elsewhere [12]. This cohort excluded patients with severe dementia (mini mental state examination [13] MMSE <15/30), palliative care and medical emergency.

The protocol of this study was approved by the Biomedical Ethics Committee of the Medical School of the Université catholique de Louvain (UCL) of Brussels, Belgium (B40320084685). All participants gave informed consent.

Data collection

Medical data

For all the 567 patients included, the GPs recorded background variables, medical history and performed a detailed anamnesis and clinical examination [12]. The GPs listed important elements of the medical history and current medical problems. Additionally, a structured questionnaire assessed the presence or absence of a list of 22 chronic conditions. These 22 conditions and selected comorbidities of the problems list (i.e. active diseases, all the conditions listed in STOPP&START and Beers, and other elements collected for the purpose of another research analysis on the BELFRAIL cohort) were encoded in a SPSS table. Two researchers coded independently the selected comorbidities of the problems list (OD and PB). In case of discrepancies, the problems list of the patients was examined and discussed with a third researcher (BV) until a consensus was reached on which problem to encode for that patient.

Drugs and inappropriate prescribing

GPs were asked to list the drugs the patient was taking. Drugs were coded in an Excel file and classified according to the Anatomical, Therapeutic and Chemical (ATC) classification system (at level 5, which relates to the chemical substance) (MA) [14]. Using the coded data on comorbidities and drugs, the chronic treatments of the patients were screened with the STOPP&START tool [10] and the 2012 Beers list [8]. Two researchers (OD and AD) independently applied the criteria, taking strictly into account the drugs and pathologies mentioned in the tool. Discrepancies were discussed until consensus.

The STOPP&START tool includes 65 criteria on over-prescribing within the STOPP list and 22 criteria on under-prescribing within the START list. Beers list addresses inappropriate prescribing in 3 categories: drugs to avoid, drugs to avoid regarding certain conditions/diseases, and drugs to use with caution. For the analysis of the secondary outcomes, the drugs to use with caution were not considered, with the exception of the criteria "*Aspirin in primary prevention over 80*", because this criterion is common to the STOPP list.

For the application of the criteria, some adjustments of the criteria was performed by the research team, i.e.: asthma and chronic obstructive pulmonary disease were grouped, angiotensin-converting-enzyme inhibitor and angiotensin receptor blockers (ARBs) were approximated, life expectancy was considered lower than 5 years in the presence of active cancer, dementia (when listed as such by the GP) or age > 85 years. STOPP criteria "*Duplications of treatment*" were considered when drugs had the same level 4 ATC code [15], which represents the chemical or pharmacological subgroup, or in the presence of several beta-blockers, opiates or nonsteroidal anti-inflammatory drugs. The following associations were not considered as duplications even if they had the same level 4 ATC code: aspirin and dipyridamole, aspirin and clopidogrel, immediate release pro re nata (*p.r.n.)* and controlled-release nitrates, long- and short-acting insulins, short- *p.r.n.* and long-action inhaled bronchodilators, long-acting and rapid-release *p.r.n.* opiates, benzodiazepines and z-drugs, cinnarizine and betahistine, trazodone and venlafaxine, trazodone and mirtazapine.

Data available at baseline did not allow to assess some of the criteria. All criteria related to the risk of fall could rarely be assessed because the GPs were not asked if the patient was prone to fall. Therefore, only few GPs recorded history of falls in the problems list. Criteria related to delirium and dementia could not be assessed as these were exclusion criteria of the cohort. Hypoglycaemic episodes were not reported, so STOPP criteria "*beta-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes*" was not assessed. Beers criteria "*Insulin, sliding scale*" was rarely assessed because few GPs specified the way insulin was prescribed (fixed doses versus sliding scale).

Clinical importance

On a subsample of 30 patients, an expert panel (a general practitioner, a geriatrician and a clinical pharmacist) were asked to independently rate the actual clinical importance for the patient of the recommendation to add the drugs suggested by START to the treatment, and to discontinue the drugs detected by STOPP or Beers. The Adapted Medication Appropriateness Index was available for each molecule pointed out by STOPP and/or by Beers [16] as supplementary informative data.

Recommendations were classified following a previously defined method using a 6-point rating scale (minor, moderate, major, extreme, deleterious, not applicable) [17]. Members rated the recommendations independently. Consensus on the clinical importance was reached when 2 experts agreed.

Importantly, the expert panel had access to the full record of the patients to be able to assess the importance of the recommendation in the rich context of the patient. Medical (comprehensive list of comorbidities, clinical examination), functional (MMSE [13], geriatric depression scale score GDS-15 [18], Tinetti fall risk score [19], activities of daily living ADL score [20]), and social (familial status, place of residence) data were provided within the full record. The full record of the patients allowed the experts to assess if the potentially inappropriate prescribing events were actually inappropriate.

Statistic analysis

Normally distributed continuous variables are expressed as mean ± standard deviation. Continuous variables which were not normally distributed were summarized using the median and the inter-quartile range [Q25;Q75]. For categorical variables, numbers and percentages are presented. Comparisons between different categories of subjects were performed using Student's t test or the Mann-Whitney U test (for nonparametric data). Statistical analyses were performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline data

The 567 patients included at baseline in the cohort are presented in table 1. Patients had a median age of 84 years, 63% were female and they lived mainly at home (90%). The most frequent comorbidities they presented were: hypertension (70%), osteoarthritis (57%) and ischemic disease (i.e. atherosclerotic coronary, cerebral or peripheral vascular disease ; 37%).

TABLE 1: Characteristics of the patients of the BELFRAIL cohort (N=567)

Characteristics of the patients	
Age (years), median [Q25;Q75]	84.0 [81.7;86.6]
Gender, women: men, n (%)	356: 211 (62.8: 37.2)
Resident in a nursing home, n (%)	57 (10.1)
Number of drugs/day, median [Q25;Q75]	5 [4;7]
Geriatric features	
Polymedication (≥ 5 drugs/day), n (%)	337 (61)
Activities of daily living, median [Q25;Q75]	25 [21;27]
Living alone at home, n (%)	212 (37.4)
Urinary incontinence, n (%)	126 (22.2)
Recurrent falls, n (%)	3 (0.5)
Cognitive impairement, n (%)	89 (15.7)
BMI < 21 kg/m², n (%)	49 (8.6)
GDS-15, median [Q25;Q75]	2 [1;4]
MMSE, median [Q25;Q75]	28 [25;29]
Tinetti score, median [Q25;Q75]	27 [24;28]
Most frequent comorbidities	
Hypertension, n (%)	396 (69.8)
Osteoarthritis, n (%)	324 (57.1)
Ischemic disease, n (%)	210 (37.0)
Chronic heart failure, n (%)	166 (29.3)
Chronic renal disease (GFR < 50 ml/min), n (%)	143 (25.2)
Osteoporosis, n (%)	125 (22.0)
Diabetes, n (%)	107 (18.9)
Depression, n (%)	74 (13.1)
COPD, n (%)	65 (11.5)
Atrial fibrillation, n (%)	58 (10.2)
Most frequent comorbidities	

Anaemia, n (%)	50 (8.8)
Cerebro-vascular accident, n (%)	46 (8.1)
Asthma, n (%)	27 (4.8)
Parkinson disease, n (%)	16 (2.8)
Most frequent drugs prescribed, n patients (%)	
Antithrombotic agents (B01)	312 (55.0)
Beta-blocking agents (C07)	238 (42.0)
Agents acting on the renin-angiotensin system (C09)	237 (41.8)
Psycholeptics (N05)	220 (38.8)
Diuretics (C03)	189 (33.3)
Lipid Modifying Agents (C10)	180 (31.7)
Drugs for acid related disorders (A02)	138 (24.3)
Calcium Channel Blockers (C08)	135 (23.8)
Psychoanaleptics (N06)	131 (23.1)
Cardiac Therapy (C01)	115 (20.3)

Abbreviations: BMI body mass index ; COPD Chronic obstructive pulmonary disease ; GDS geriatric depression scale ; GFR Glomerular filtration rate ; MMSE mini mental state examination

Inappropriate prescribing

Using the START tool, 638 potentially inappropriate omissions were detected (1.13±1.34 START-PIP per patient (range 0-8), in 59 % of the patients. The use of the STOPP criteria allowed to detect 331 potentially inappropriate medications, (0.58±0.92 STOPP-PIP per patient; range 0-10). Forty-one percent of the patients had at least one STOPP-PIP in their treatment.

The application of the Beers criteria pointed out 249 Beers-PIP as drugs to avoid or to avoid in the presence of certain conditions (0.44±0.79 per patient; range 0-6). Thirty-two percent of the patients had at least one Beers-PIP in their treatment. Beside the drugs to avoid, the Beers list detected also 318 drugs to be used with caution including 96 cases of use of aspirin in primary prevention.

Some patients had several PIPs for the same drug (e.g.: overuse of a nonsteroidal anti-inflammatory drug (NSAID) because of hypertension (STOPP criteria E2) *and* heart failure (STOPP criteria E3); underuse of angiotensin converting enzyme inhibitor because of heart failure (START criteria A6) *and* previous myocardial infarction (START criteria A7), which explains large ranges of PIPs per patients. 108 patients out of the 567 (19%) had no PIP at all when considering START, STOPP and Beers. There

was no difference in the prevalence of PIP between patients recruited in different regions.

The most frequent PIPs are presented in tables 2 and 3. Potential underuse situations according to START included omission of: aspirin or clopidogrel with a documented history of ischemic disease (prevalence = 15%), calcium and vitamin D supplement in patients with known osteoporosis (14%), angiotensin converting enzyme inhibitor with chronic heart failure (13%) (table 2).

TABLE 2: Most frequent potentially inappropriate underprescribing events according to START.

START-PIP	Prevalence % (n)
Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm	15,0 (85)
Calcium and vitamin D supplement in patients in the presence of known osteoporosis	13,9 (79)
ACE inhibitor in the presence of chronic heart failure	12,7 (72)
Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is greater than 5 years	9,5 (54)
Antiplatelet therapy in diabetes mellitus with coexisting major cardiovascular risk factors (hypertension, hypercholesterolemia, smoking history)	9,5 (54)
Statin in the presence of in diabetes mellitus if coexisting major cardiovascular risk factors present	8,8 (50)
Beta-blocker in the presence of chronic stable angina	6.0 (34)
Regular inhaled beta2-agonist or anticholinergic agent for mild-to-moderate asthma or COPD	5,29 (30)
ACE inhibitor following acute myocardial infarction	5,1 (29)
Metformin with type 2 diabetes ± metabolic syndrome (if GFR>50ml/min)	4,4 (25)

Abbreviations: ACE Angiotensin converting enzyme ; COPD Chronic obstructive pulmonary disease ; GFR Glomerular filtration rate ; PIP potentially inappropriate prescribing

Aspirin in primary prevention, long-acting benzodiazepines and long term use of NSAIDs are the most frequent PIPs which are common to STOPP and Beers' list with a

prevalence of 17%, 5% and 2% respectively. Nineteen of the 26 theoretical overlapping criteria were observed in this study [11]. Besides shared criteria, other frequent STOPP-PIPs are: any duplicate drug class prescription (prevalence = 6%), aspirin at dose > 150 mg/day (4%), NSAIDs and hypertension (4%). Other frequent Beers-PIP include: Z-drugs (6%), benzodiazepines and dementia or cognitive impairement (6%), tertiary tricyclic antidepressants (3%) (table 3).

Among the 567 patients, 163 (29%) are considered as having a potentially inappropriate treatment by both STOPP and Beers, 86 (15%) had only been pointed out by Beers and 69 (12%) by STOPP only. The other patients (44%) had neither Beers-PIP, nor STOPP-PIP. Patients having Beers-PIP and those having STOPP-PIP did not differ except for the presence of cognitive impairment (higher in patients having Beers-PIP) (Appendix 1).

Besides the detection of PIP with STOPP&START and Beers, we observed 162 patients, among the 183 patients who were taking benzodiazepines, who had no mention of insomnia or anxiety as active pathology in their record. Benzodiazepines were used in 34 patients at high fall risk (i.e. Tinetti score < 19 [19]).

TABLE 3: Most frequent potentially inappropriate over-/misprescribing events according to STOPP and/or Beers criteria.

Therapeutic Class/Medication (± disease)	Prevalence % (n)	Criteria
Aspirin for primary cardiovascular prevention [1]	16,9 (96)	STOPP and Beers
Nonbenzodiazepine ("Z") hypnotics (i.e., eszoplicone, zaleplon, zolpidem)	6,2 (35)	Beers
Any duplicate drug class prescription	6,2 (35)	STOPP
Benzodiazepines in the presence of dementia and cognitive impairment	5,8 (33)	Beers
Long-acting benzodiazepines	4,9 (28)	STOPP and Beers
Aspirin at dose > 150 mg/day	4,4 (25)	STOPP
NSAIDs with moderate to severe hypertension	3,7 (21)	STOPP
Tertiary TCAs, alone or in combination	2,6 (15)	Beers
Antiarrhythmic drugs (class Ia, Ic, and III drugs in Beers 2012) for atrial fibrillation	2,6 (15)	Beers
Long-term non–COX-selective NSAIDs	2,4 (13)	STOPP and Beers
Alpha-Blockers in the presence of urinary incontinence[2]	2,1 (12)	STOPP and Beers
GI antispasmodics (e.g., dicyclomine, hyoscyamine)	1,9 (11)	Beers
NSAIDs in the presence of heart failure	1,4 (8)	STOPP and Beers
PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks	1,4 (8)	STOPP
Dipyridamole (immediate-release) as monotherapy	1,2 (7)	STOPP and Beers
Nondihydropyridine calcium channel blockers in the presence of heart failure	1,2 (7)	STOPP and Beers
Digoxin >0.125 mg/d [3]	1,1 (6)	STOPP and Beers
Loop diuretic for ankle edema (i.e., no clinical signs of heart failure) or as first-line monotherapy for hypertension	0,9 (5)	STOPP
Long-term corticosteroids as monotherapy for RA or osteoarthistis	0,9 (5)	STOPP
Thiazide diuretic in the presence of gout	0,9 (5)	STOPP
Estrogen[4]	0,7 (4)	STOPP and Beers
Glyburide/glibenclamide [5]	0,7 (4)	STOPP and Beers
Bladder antimuscarinic drugs in the presence of dementia and cognitive impairment	0,7 (4)	STOPP and Beers
Anticholinergics in the presence of lower urinary tract symptoms	0,7 (4)	STOPP and Beers

Abbreviations: GI gastro-interstinal ; NSAIDs Nonsteroidal anti-inflammatory drugs ; PPI Proton pump inhibitor ; RA Rheumatoid arthritis ; TCA tricyclic antidepressant.

1. To be used with caution in adults >80 years old for primary prevention of cardiac events in Beers 2012; to be avoided in those with no history of coronary, cerebral, or peripheral vascular symptoms or occlusive events in STOPP.
2. Stress or mixed urinary incontinence, avoid in women in Beers 2012; avoid in men with frequent incontinence in STOPP.
3. Digoxin at a long-term dose > 125 µg/day with renal function < 50ml/min in STOPP (n=0).
4. Estrogen with or without progestins in Beers 2012; estrogen without progestin in patients with intact uterus in STOPP.
5. Sulfonylureas, long-duration to be avoided in Beers 2012 ; n=21 when accounting sustained release formulations.

Clinical importance of the recommendations to modify the treatment in the presence of PIP

In the subsample of 30 patients, the experts examined 72 PIP instances (i.e.: 18 STOPP-PIPs, 31 START-PIPs, 23 Beers-PIPs). The experts agreed on the clinical importance of 35 out of the 72 PIPs. Twelve PIPs were rated of "major" importance, while 22 PIPs were considered of moderate importance. Examples are provided in table 4. The Beers list includes the level of evidence and the strength of each recommendation. Strong recommendations were also rated as of major importance by the experts (e.g. "*Anticholinergics in dementia and cognitive impairment* ", "*Diltiazem in heart failure*"). One PIP was rated "minor" by the experts (Beers-PIP "*Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation*").

The 37 other PIPs were rated differently between the experts or could not be rated for different reasons. Several reasons were sometimes encountered for the same PIP. Firstly, the rating varied due to differences in the implicit judgement of the appropriateness of drug treatment. The experts interpreted differently the background of the patient (e.g. how severe is a disease in the context of the patient), or the criteria (e.g. when to consider a duplication of treatment), which led to differences in the clinical importance assessment (n=12, 17%). Secondly, the detailed full record of the patient brought nuance to the data encoded and used for analysis (i.e. level of severity of a disease, particular indication of a drug, date of a medical history, uncertainty of a diagnostic) (n=28, 39%). As a consequence, the presence of some of the PIPs was not obvious anymore. The experts considered 14 (19%) of the PIP instances as actually appropriate when considering the detailed data. START criteria were the most frequently affected by this issue. Thirdly, the content validity of several STOPP criteria

was questioned by the experts (n=11). Examples of these three issues are provided in table 5.

TABLE 4. Examples of potentially inappropriate prescribing criteria of major or moderate importance

Examples
Major clinical importance (n=12) *Modification of the treatment according to this criteria may prevent serious morbidity, including readmission, serious organ dysfunction, serious adverse drug event*
Criterion: **START**-PIP "Angiotensin converting enzyme (ACE) inhibitor with chronic heart failure" *Context*: The GP reports chronic heart failure, with marked limitation of physical activity and dyspnoea, and a recent episode of congestive heart failure.
Criterion: **STOPP**-PIP "Calcium channel blockers with NYHA class III or IV heart failure"/**Beers**- PIP "Diltiazem in heart failure". *Context*: The medical history and the clinical examination confirm that the patient has NYHA class III heart failure
Criterion: **Beers**- PIP "Anticholinergics in dementia and cognitive impairment". *Context*: The patient has cognitive impairment (MMSE = 22/30[1]) and takes several drugs with anticholinergic properties (amisulpride, trihexyfenidyl)
Moderate clinical importance (n=22) *Modification of the treatment according to this criteria brings care to a more acceptable and appropriate level of practice or that may prevent an adverse drug event of moderate importance*
Criterion: **START**-PIP "Statin therapy in diabetes mellitus if coexisting major cardiovascular risk factors present". *Context*: The patient is 87 years, and still has good cognitive and functional status. She has diabetes, hypertension and hypercholesterolemia.
Criterion: **STOPP**-PIP "Long-term long-acting benzodiazepines". *Context*: The patient takes 8mg prazepam every day. She has low fall risk (Tinetti score 26/28[2]) but she has cognitive impairment (MMSE=18/30).
Criterion: **STOPP**-PIP/**Beers**-PIP "Aspirin in primary cardiovascular prevention". *Context*: The patient has no history of coronary, cerebral or peripheral vascular symptoms or occlusive event.
Criterion: **Beers**- PIP "Tertiary tricyclic antidepressants". *Context*: The patient is on clomipramine for "depressive tendencies" according to the GP. The GDS-15 score is low (3/15[3]). Non pharmacologic or safer alternatives are available.

Abbreviation: GDS-15 geriatric depression scale ; MMSE mini mental state examination ; PIP potentially inappropriate prescribing

1. MMSE<25 was considered as "cognitive impairement".
2. Tinetti score >24 was considered as "low fall risk".
3. GDS-15 score >4 was considered as "possible depression".

TABLE 5. Issues in the assessment of the clinical relevance of potentially inappropriate prescribing criteria

Examples	Improvement recommendation
Issue 1. Differences in the implicit judgement (n = 12) *The inter-rater variability in the understanding of the patient background or of the criteria applicability leads to differences in the importance attached to the PIP.*	
Criterion: **START**-PIP "Regular inhaled beta-2-agonist or anticholinergic agent for mild-to-moderate asthma or COPD". *Context*: The GP listed COPD in the medical history of his patient, but the clinical examination revealed no symptoms and the patient had no treatment for this comorbidity. *Experts' rating*: One of the expert considered the patient as having no COPD, giving therefore little relevance to this PIP, while the other took that comorbidity into account and accredited importance to the PIP.	Detailed patient's record Definition of asthma or COPD in terms of predicted FEV1
Criterion: **STOPP**-PIP "Any duplicate drug class prescription". *Context*: The patient received lorazepam at night and alprazolam during the day. *Experts' rating*: One of the expert considered this as a duplication, while another not because one drug is used during the day as anxiolytic and the other is used at night as hypnotic.	Definition of duplications in terms of ATC level
Issue 2. Influence of the knowledge of the patient's background (n=28) *A comprehensive knowledge of the patient's medical (including: level of severity of a disease, particular indication of a drug, date of a medical history, uncertainty of a diagnostic), functional and social background increase the relevance of the PIPs detected in comparison to the screening for PIPs on the sole basis of the comorbidities listed in the tools.*	
Criterion: **START**-PIP " Statin therapy in diabetes mellitus if coexisting major cardiovascular risk factors present". *Context*: The patient had previous cutaneous reaction on statins. *Experts' rating*: Non-prescribing of a statin was appropriate in this patient. This criterion is deleterious to this patient.	Detailed patient's record Mention of contra-indications in the criteria

Examples	Improvement recommendation
Criterion: **STOPP**-PIP " Neuroleptics as long-term hypnotics (i.e. > 1 month). *Context*: The database did not mention the indication of risperidone. The full record showed that this patient was suffering from dementia (low MMSE) with behavioural problems and that the frequency of use of the risperidone was unclear. *Experts' rating*: Experts could not rate this PIP. They considered a sporadic *p.r.n.* use of the neuroleptic as appropriate.	Detailed patient's record Precise indication and dosage of each drug
Issue 3. Content validity of the criteria (n=11) *The validity of the criteria is challenged by the application in real cases and situations of multimorbidity and polypharmacy.*	
Criterion: **STOPP**-PIP/**Beers**-PIP "Aspirin in primary cardiovascular prevention". *Context*: Three diabetic patients having no history of ischemic disease but presenting cardio-vascular risk factors (hypertension, hypercholesterolemia, smoking history). *Experts' rating*: Due to the presence of cardiovascular risk factors and diabetes, this aspirin was appropriate according to the experts. Moreover, the absence of this aspirin would have been a START-PIP.	Addition of an exclusion criterion for diabetic patients with cardio-vascular risk factors
Criterion: **START**-PIP "Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm" and "Antiplatelet therapy in diabetes mellitus with coexisting major cardiovascular risk factors". *Context*: The patient is already treated by oral anticoagulants. *Experts' rating*: Deleterious for the patients' health.	Addition of an exclusion criterion for patients with stable cardiovascular disease already treated by anticoagulants
Criterion: **START**-PIP "Proton pump inhibitor with severe gastroesophageal acid reflux disease". *Context*: The patient is already on ranitidine. *Experts' rating*: Non-prescription is appropriate.	Modification for "proton pump inhibitor or H_2-receptor antagonists"
Criterion: **START**-PIP "Warfarin in the presence of chronic atrial fibrillation". *Context*: The patient is at low stroke risk (i.e. $CHADS_2$= 1). *Experts' rating*: Non-prescription is appropriate.	Modification for "chronic atrial fibrillation and increased stroke risk ($CHADS_2 \geq 2$)"

Examples	Improvement recommendation
Criterion: **Beers**- PIP " Avoid antidepressants in dementia & cognitive impairment". *Context*: The patient is taking paroxetine for severe depression. *Experts' rating*: Discontinuation of the drug is inappropriate.	Addition of an exclusion criteria for patient with severe depression treated by SSRIs Definition of cognitive impairment Suggestion of non-pharmacological alternatives
Criterion: **Beers**-PIP "Drugs to use with caution": *e.g.* "Vasodilators"	Monitoring tips *e.g.* Check for history of syncope before prescribing

Abbreviations: ATC Anatomical Therapeutic Chemical Classification System ; COPD Chronic obstructive pulmonary disease ; $CHADS_2$ [21] Congestive heart failure - Hypertension - Age ≥75 years - Diabetes mellitus - Prior Stroke or TIA or Thromboembolism ; FEV1 Forced expiratory volume at the end of the first second ; MMSE mini mental state examination ; SSRI Selective serotonin re-uptake inhibitors.

DISCUSSION

This study assessed inappropriate prescribing in a large representative sample of very old patients. The prevalence of potentially inappropriate prescribing was high in this population. Potentially inappropriate omissions, detected by the START tool were more prevalent (60% of the patients) than overuse of treatment as detected by STOPP (41%) or Beers list (drugs "to avoid": 32%). Our study focussed on the use of STOPP&START in very old patients, which had not been purposively performed before. Previous studies using STOPP&START, in primary and secondary care, included mainly patients aged over 65 years old [1], for whom the tool has been designed. A recent systematic review on the use of STOPP&START reported that the mean age of studies participants ranged from 74.9 to 86.9 years old [1]. Patients aged over 65 years might present heterogenic profiles, ranging from robust to frail. The consequences of inappropriate prescribing in this large target of population might therefore assume variable importance. The prevalence detected in our patients aged 80 and older did not differ from the prevalence reported in the literature with populations including younger patients, i.e. prevalence of START-PIP ranged from 23 to 68% [22-24], STOPP-PIP 18-60% [23, 25-29] and Beers-PIP 12.5-42% [30, 31]. It should be noted that prevalence of PIPs varies greatly from studies.

Beers criteria revealed more PIPs than the STOPP tool if taking into account both drugs to avoid and drugs to use with caution. However, the sensitivity of STOPP was higher than Beers when accounting only for the "drugs to avoid" category to which we added, as explained in the methods section, the criterion relative to aspirin in primary prevention. When looking at the drugs detected (mainly cardiovascular and psychotropic drugs), or the patients flagged by STOPP and Beers, no tool seems to outperform the other as they bring similar findings. The combined detection of over- and underuse gives a practical advantage for STOPP&START. Further comparison of their respective content (clinical importance) and predictive validity (association with clinical events) would be the best test to decide between the tools. When comparing STOPP with the previous version of Beers, STOPP detected more PIPs potentially related to adverse drugs events and hospital admissions [25, 32], but no data is yet available for the 2012 version of Beers. A tool combining STOPP and Beers criteria would logically more largely detect inappropriate prescribing. However, we don't believe the development of such potential new combined tool to be an effective option for clinical practice. First, the list of criteria would be very long, therefore not convenient for clinical practice implementation. Secondly, the most frequently encountered criteria are similar with the two tools, so combination would only improve the detection of rare instances of PIP. Instead, the most relevant criteria of the tools (Beers, STOPP and START) should be assessed and compared, in terms of prevalence, clinical importance, predictive validity and related costs, to establish a new short list. In line with this view on explicit tools, the clinical importance of some PIPs were examined in this study.

The clinical importance assessment of the PIPs revealed important findings about the validity of STOPP&START, Beers and more globally the use of explicit tools. Firstly, the experts did not rate similarly the clinical importance of the criteria in 17% of cases. This illustrates the subjectivity of the assessment of the patient’s context and the variable importance acknowledged to inappropriate prescribing according to the evaluator. The STOPP&START list of criteria does not mention the level of severity in case of inappropriate prescribing (in contrast to the Beers list). Our study is the first to highlight differences in the perceived clinical importance of these criteria. The general practitioner, who has the most comprehensive knowledge of the patient is likely in the best position to assess the clinical importance of a PIP in his/her patient.

Secondly, the detected PIPs were not always relevant when considering the full record of the patient. It seems obvious that a comprehensive analysis of the patient's record will bring more accurate assessment of appropriateness of the drug regimen. Explicit tools require variable clinical information for their application according to the criteria content [33]. Ryan and al. previously showed that STOPP-PIP detection was overestimated and START-PIPs were underestimated when STOPP&START was used in isolation of clinical information [34]. However, we did not expect to have a 19% of the potentially inappropriate prescribing mis-detected when applying the criteria on our databases. The pathologies had been encoded with a rigorous method by general practitioners and pharmacists, with a double check. This coding approximated what a general practitioner would encode in his electronic medical record. Furthermore, the screening for potentially inappropriate prescribing was performed independently by two clinical pharmacists having experience in using STOPP&START. Our results therefore question the application of explicit screening tools on administrative databases. This approach, which was regularly performed in previous studies [26, 35], is valuable to have a global insight of potentially inappropriate prescribing patterns and the most frequently encountered drugs. But the prevalence and frequencies should be interpreted with caution. The calculations of costs related to potentially inappropriate prescribing should also be read with particular prudence when based on administrative databases analysis.

More importantly, some of the criteria appeared of questionable relevance. STOPP&START criteria were chosen by experts in geriatric pharmacology, according to the Delphi method [10] which prevails when developing such tools and selecting the most theoretically relevant criteria [33, 36]. Authors of STOPP&START were guided by the principle that any tool should be sensitive to inappropriate prescribing related to serious adverse drug events [37]. However, this study challenges the relevance of some criteria in real-life setting. In some patients, the recommendation to modify the drug regimen was considered as deleterious, which is not acceptable.

Only a few previous studies looked at the clinical importance of PIPs detected by explicit tools in patients [38, 39]. To the best of our knowledge, this study is the first to evaluate the clinical importance of STOPP&START criteria. Steinman and colleagues compared Beers-PIP (2003 version) with drugs considered as problematic by a team of clinicians. Sixty-one percent of Beers-PIP were not considered as inappropriate by the clinicians [39]. In another study conducted with elderly surviving an intensive care unit

hospitalisation, only 36% of Beers-PIP were considered as actually inappropriate [38]. In both studies, the percentage varied according to the drug type, with higher concordance between potential and actual inappropriate medications for anticholinergics. Our analysis on a small sample of STOPP&START-PIP showed the same trends: a substantial proportion of PIPs were actually appropriate and some criteria appeared less controversial than others.

Based on this analysis, we suggest some important modifications to the tools to improve their validity and applicability (summarized in table 6). Future versions of STOPP&START and Beers should (1) state the precise range of application of the criteria (i.e. age, life expectancy, disease severity level), (2) avoid contradictions and overlap between criteria, (3) mention the time to benefit [40, 41] and contra-indications for drugs listed in START. Other improvements include: clear definitions, monitoring tips and suggestion of pharmacological and non-pharmacological alternatives. Beers-listed drugs "*to use with caution*" are difficult to manage in practice and fail to provide clear recommendations to prescriber. Again, monitoring tips should be provided for these drugs. The main suggestion for the future use of screening tools is that these tools can only be used with full access to the patient's history. The tools are best used by a clinician who knows the patient. The application of screening tools on administrative data should not be recommended.

TABLE 6. Recommendations to improve the validity and applicability of STOPP&START and Beers criteria

General comments	Recommendations to improve the validity of the criteria	Recommendations to improve the applicability of the criteria
Provision of detailed patient context • level of severity of diseases • certainty of diagnostics • date of a medical history • detailed information on cardiovascular and neurologic diseases • allergies Provision of detailed drug information • indication • precision of drugs taken "as needed" • previously tried and failed therapeutic options	• mention of contra-indications • no contradictions between criteria • no overlap between criteria • precise range of application of the criteria • mention of time to benefit	• clear definitions • monitoring tips • suggestions of alternatives (pharmacological and non-pharmacological)

This study present some limitations. Our results might have been influenced by the fact that the data used to detect PIPs were not prospectively collected for the purpose of this analysis. Therefore, some criteria could not be assessed, as explained in the methods section, and the quantity of PIPs might have been underestimated. PIPs related to the history of falls were seldom detected in our study but they were frequently reported in previous studies [42]. Even if we did not count them as PIPs, we believe benzodiazepines to be overused in the BELFRAIL cohort. Indeed, 29% of the cohort were taking benzodiazepines without any stated indication. Furthermore, 19% of the patients on benzodiazepines were at high fall risk. We might also have underestimated PIPs in the over-the-counter drugs because the drugs lists were provided by the general practitioners. We had no information about the duration of each drug treatment. The detection of PIPs would have been more accurate if directly performed on the full

patients record instead of pre-encoded data. The analysis on the clinical relevance of the criteria was only performed on a small subsample of PIPs. The experts rated the PIPs independently, while a discussion between experts could have explained or diminished divergences. Direct discussion with the general practitioner would have helped having a better understanding of the drug regimen and the reasons to maintain some PIPs. Further studies should in larger extent assess the actual inappropriateness of drugs listed on STOPP&START and Beers lists. This assessment of the clinical importance of the criteria was designed to have an insight at the relevance of the criteria on a small subsample, but did not intend to comprehensively evaluate the content of the full criteria lists. However, the assessment on this subsample allowed to discuss the most frequent PIPs and enabled us to identify several important points for discussion on the validity of the tools.

Perspectives for future research are provided by this baseline analysis of the BELFRAIL cohort. In future studies, we recommend to detect PIPs on the basis of the full record of the patient, to ensure the relevance and the applicability of the criterion within the individual and global context of the patient. The sensitivity of the tool in detecting clinically relevant PIP related to adverse outcomes should also be evaluated. This study was a cross-sectional analysis of data at baseline of the BELFRAIL cohort. Follow-up data should be analysed in further work. Longitudinal analysis should compare the incidence of geriatric adverse events (death, hospital admissions, adverse drug events) and costs of care in patients having or not PIPs at baseline. Potential confounders (e.g. age, sex, educational level, place of residency, comorbidity, cognitive and functional status, malnutrition, smoking) should be taken into account in the analysis. Clinical consequences of these PIPs should be compared (1) between patients aged over 65 years and very old patients, who are more prone to frailty, and (2) between STOPP&START and the Beers list.

Our observations highlight the importance to gather sufficient information to appropriately use explicit tools. The importance of the required clinical information varies from tool [33], but the application of explicit tools has little sense anyway without knowing the global context of the patient, and leads to the misdetection of inappropriate prescribing. The medication review should be part of a comprehensive process to optimize pharmacotherapy. Explicit criteria help to revise the treatment but will never replace good clinical judgement [33]. Both the general practitioner and the pharmacist

play a key-role in the management of chronic drug treatment and are therefore potentially in the best position to collaborate and to apply the explicit criteria. A good understanding of the patients' medical, functional and social context is crucial to assess the actual appropriateness of drug treatment.

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APPENDIX 1. COMPARISON OF PATIENTS HAVING STOPP AND BEERS-PIP

Patients characteristics	Patients having STOPP-PIP (n=232)	Patients having Beers-PIP (n=249)
Age (years), median [Q25;Q75]	84.3 [81.8;86.8]	84.3 [81.9;86.9]
Institutionalized, n (%)	46 (19.8)	49 (19.7)
Number of drugs/day median [Q25;Q75]	5 [4 ;8]	6 [4 ;8]
Geriatric features		
Polymedication (≥ 5 drugs/day), n (%)	145 (62.5)	157 (63.0)
Cognitive decline, n (%)*	36 (15.6)	58 (23.3)
Incontinence, n (%)	56 (24.1)	61 (24.5)
Most frequent comorbidities		
Hypertension, n (%)	155 (66.8)	183 (73.5)
Osteoarthritis, n (%)	144 (62.1)	154 (61.8)
Ischemic disease, n (%)	69 (29.7)	77 (30.9)
Chronic heart failure, n (%)	74 (31.9)	85 (34.1)
Chronic renal disease (GFR < 50 ml/min), n (%)	70 (30.2)	66 (26.5)
Osteoporosis, n (%)	51 (21.9)	59 (23.7)
Diabetes, n (%)	44 (19.0)	65 (26.1)
Depression, n (%)	41 (17.7)	41 (16.5)
COPD, n (%)	30 (12.9)	29 (11.6)
Atrial fibrillation, n (%)	22 (9.5)	28 (11.2)
Anaemia, n (%)	26 (11.2)	28 (11.2)
Asthma, n (%)	11 (4.7)	12 (4.8)
Parkinson disease, n (%)	5 (2.1)	8 (3.2)

Abbreviations: COPD Chronic obstructive pulmonary disease ; GFR Glomerular filtration rate ; PIP potentially inappropriate prescribing

* significative difference p=0.032

CHAPTER IV – Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: a randomized controlled study

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Chapter IV at a glance

What is already known about this subject

- Hospital admissions may provide an opportunity to discontinue Potentially Inappropriate Medications (PIMs) in older patients.
- Inpatient geriatric consultation teams perform comprehensive geriatric assessment of geriatric inpatients and provide recommendations for the care of these patients.
- Inpatient geriatric consultation teams do not routinely use an explicit tool to review the medication.

- This chapter presents a randomized controlled study to test the effect of the systematic use of STOPP on overuse and misuse of inappropriate medications used at home in frail older persons.

What this chapter adds

- Recommendations by the inpatient geriatric consultation team successfully **double the discontinuation rate** of inappropriate medications at hospital discharge.
- Most modifications in the drug treatment **persist** one year after discharge.
- Although most of the STOPP recommendations are of **major or moderate clinical importance**, 8% could have deleterious effects.

ABSTRACT

Background. Hospital admissions may provide an opportunity to discontinue Potentially Inappropriate Medications (PIMs) in older patients. Little is known about the effect of using the Screening Tool of Older People's potentially inappropriate Prescriptions (STOPP) in that purpose.

Methods. Randomized controlled study in 146 frail older inpatients. The intervention consisted in recommendations to discontinue PIMs provided to ward physicians by the inpatient geriatric consultation team, using the STOPP list, in addition to usual geriatric advice. The main outcome was the discontinuation rate of PIMs at discharge.

Results. Intervention (n=74) and control (n=72) groups were similar in patient's characteristics (median age: 85 years, median number of daily drugs: 7) and PIMs distribution (68 *vs.* 57 PIMs in 53% and 51% of patients, respectively). At discharge, the reduction in PIMs was twice as high in the intervention as in the control group (39.7% *vs*. 19.3%, p=0.013). The proportion of patients still having ≥1 PIM at discharge did not differ between groups. In the 50 patients followed at one year, the majority of PIMs that had been stopped during hospitalisation had not been restarted after discharge (17/28). The clinical relevance of PIMs identified at baseline in those patients was considered major (29%), moderate (37%), minor (5%), deleterious (8%) or not-assessed (11%). Discontinuation rate was not associated with the clinical importance.

Conclusion. Specific STOPP recommendations provided to hospital physicians doubled the reduction of PIMs at discharge in frail older inpatients. To further improve the appropriateness of prescribing in older patients, clinicians should focus on the STOPP criteria of major clinical importance and general practitioners should be actively involved.

INTRODUCTION

Inappropriate prescribing is well-described in older patients [1-5]. It increases the risk of adverse drug events and thereby morbidity, mortality and costs of care [2, 6]. Hospitalisation is a vulnerable period when considering the prescribing process [7]. Nevertheless, hospital admission can be a good opportunity for thorough medication review.

Upon admission in a geriatric unit, patients usually benefit from a comprehensive geriatric assessment (CGA) [8], which consists of a "*multidisciplinary process to achieve a coordinated and integrated plan for treatment, taking into account the patient's medical, psychosocial and functional capability*" [9]. In non-geriatric wards, frail older patients receive a CGA from an inpatient geriatric consultation team (IGCT) [9]. The IGCT offers also recommendations to improve the management of the patients [10]. A recent meta-analysis showed that IGCTs have favourable effects on mortality up to eight months after discharge [11]. However, little is known about the efficacy of geriatric counselling on the discontinuation of Potentially Inappropriate Medications (PIMs) prescribed at home.

Validated tools to detect inappropriate prescribing could be useful to help the IGCT assessing the patient's medications. The Screening Tool of Older People's potentially inappropriate Prescriptions (STOPP) is a European tool addressing over- and misprescribing in older patients [12, 13]. This tool is increasingly used in observational studies to describe the prevalence of inappropriate prescribing [5, 14-18]. To the best of our knowledge, only one randomized controlled trial has evaluated the effect of applying the STOPP criteria. Significant improvements in prescribing appropriateness were documented in the hospital setting [19].

The objective of the present study was to evaluate the impact of using the STOPP criteria by an IGCT on the discontinuation of PIMs upon hospital discharge.

METHODS

Design

We conducted a randomized controlled study in consecutive frail older medical patients admitted from February to June 2011 to a 975-bed teaching hospital (Cliniques universitaires Saint-Luc) in Brussels, Belgium. The protocol was approved by the local Ethics Committee (Commission d'Éthique Biomédicale Hospitalo-Facultaire, Faculté de Médecine, Université catholique de Louvain).

Inclusion and exclusion criteria

Inclusion criteria were: (1) 75 years of age or older, (2) frailty defined by an Identification of Seniors At Risk (ISAR [20]) score ≥ 2/6, (3) admission in a medical ward, and (4) availability of a CGA performed by the IGCT. Surgical admissions were not included because revision of chronic medications by surgeons was not considered as part of usual care. We excluded from analysis patients with incomplete medication data in the discharge letter.

IGCT

The IGCT performs CGA upon request of non-geriatric wards in patients in whom screening for frailty comes out positive (ISAR [20] score ≥ 2/6). This multidisciplinary team consists in our hospital of nurses, geriatricians, a dietician, an occupational therapist, a physiotherapist, a speech therapist, and a psychologist. As usually, no clinical pharmacist is involved in the IGCT of our hospital. The initial evaluation of the patient is made by a nurse, who refers to other team members depending on patient's features and needs. A geriatrician supervises the CGA for each patient. Recommendations are communicated orally to the ward colleagues and are available in the electronic medical record. The IGCT report is also sent to the general practitioner (GP) at discharge.

Randomization

Eligible patients were allocated by the IGCT nurse to the control or intervention group by simple randomization using drawing of lots [21]. After randomization, the nurse assigned the patient to the geriatrician allocated to the intended group. In order to avoid contamination bias, of the four geriatricians involved in the IGCT during the study period, two were allocated to the intervention group because they were already using the STOPP criteria in their current practice, while the other two, who had never worked with the STOPP criteria, were allocated to the control group. The geriatricians of both groups presented similar age and clinical experience.

The attending physician (responsible for prescriptions during hospital stay and at discharge), the evaluator (OD), and the patients were blinded to group assignment. The evaluator received from the IGCT nurse a listing of the included patients, without mention of the allocation group, in order to look for the primary outcome.

In the control group, the IGCT provided usual care. Patient's medications were routinely reviewed by the geriatrician using an implicit approach (i.e. no explicit tool was used). In the intervention group, in addition to the usual IGCT care, the geriatricians acted in two steps: (1) a systematic screening of the list of medications taken by the patient on admission, looking for PIMs using 64 STOPP criteria (the criterion "Duplicate drug classes" was not considered), followed by (2) oral and written recommendations to discontinue PIMs provided to the ward physician during hospitalisation.

Outcome measures

The primary outcome was the proportion of PIMs discontinued (or corrected in case of dosage-related PIM) from admission to discharge (according to the discharge medical letter). Secondary outcomes were: the characteristics associated with PIMs discontinuation at discharge, the proportion of PIMs discontinued one year after discharge and the clinical significance of the STOPP-related recommendations.

Characteristics associated with discontinuation of at least one PIM at discharge were evaluated in the patients with PIMs on admission. Thus, we compared patients

with still all PIMs at discharge ('No Amelioration' group) to patients with at least one PIM discontinued at discharge ('Amelioration' group).

One year after hospital discharge, a follow-up questionnaire was sent to GPs of all patients who presented with PIMs on admission. In order to maximize response rate, a single question was asked: "*Could you please indicate if the patient is currently receiving the following drug(s)"* followed by the list of PIMs identified on admission. Anonymity was guaranteed. A stamped return envelope was provided and a reminder was sent two months later [22].

The clinical relevance of STOPP-related recommendations in patients followed at one year was evaluated by three experts (a geriatrician [BB], a general practitioner [JMD] and a clinical pharmacist [AS]), using a 6-point rating scale (minor, moderate, major, extreme, deleterious, non-applicable) employed in a previous study [23]. The panel had access to the full medical record and their implicit judgment was based on rich contextual information. Members first rated each recommendation independently and then met to discuss discrepancies.

Sample size

We calculated the study size defining a 50% discontinuation rate of PIMs at discharge in the intervention group as clinically relevant, assuming a 20% discontinuation rate in the control group, using usual levels for type I and II errors (α = 0,05 and β = 0,8), and assuming that the average number of PIMs in this population was 0.7 per patient, based on our previous study [16]. On this basis, 112 patients (56 per arm) were required. We aimed at 150 patients (75 per arm).

Statistical methods

Control and intervention group were compared using the student t-test for normally distributed variables, the Mann-Whitney Wilcoxon test for not normally distributed continuous variables, and the CHI-square test or Fisher's exact tests for categorical comparisons. A classification tree analysis was conducted to analyse determinants of PIMs persistence at discharge [24]. The one standard error rule was used to select the best tree. Statistical analyses were performed using SPSS version 20 for

Windows (SPSS, Chicago, IL), R software version 2.12.0 (Free Software Foundation, Inc., Boston, Massachusetts, USA) and CART version 6.6 (Salford Systems, San Diego, CA, USA).

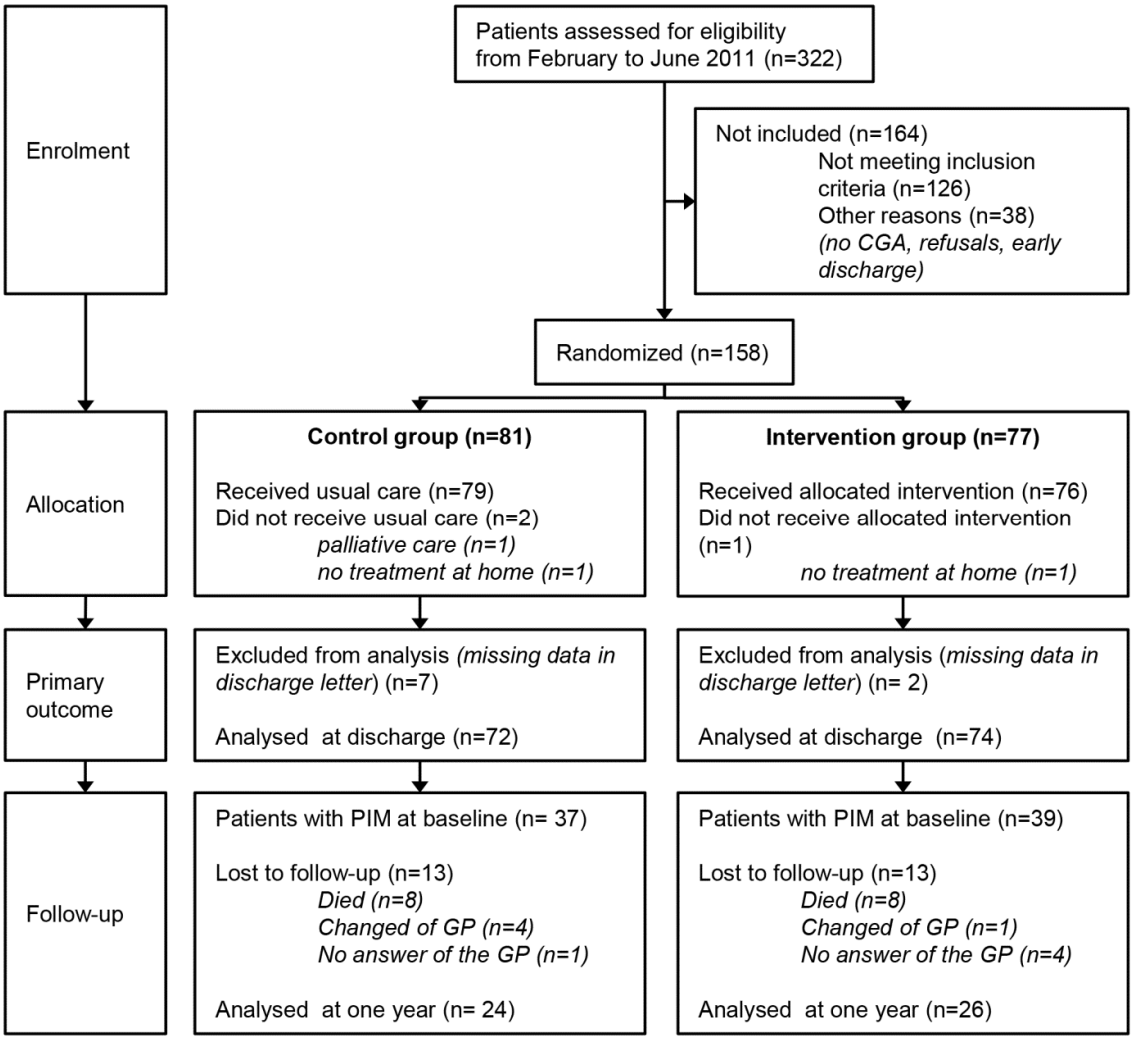
RESULTS

Patient's characteristics

Figure 1 presents the patient flow from enrolment to follow-up. A total of 158 eligible patients were randomized. Twelve patients had to be excluded afterwards, resulting in 146 frail older patients for analysis (median age [P_{25};P_{75}] 85 years [81;88], 63% women, median ISAR score [P_{25};P_{75}] 3 [3;4]). The intervention (n=74) and the control (n=72) groups did not differ in terms of patient's socio-demographics, geriatric features (functional dependency (50%), recent falls (45%), malnutrition (29%)), and numbers of medications (median 7) and inappropriate medications (median 1) (Table 1).

Half of the patients had PIMs according to STOPP at home (Table 1). Overall, 125 PIMs were detected. Six classes of medications accounted for 80% of them, belonging to the central nervous and the cardio-vascular systems, namely benzodiazepines (n=41; 33%), antiplatelet agents (n=19; 15%), opiates (n=13; 10%), beta-blockers (n=10; 8%), tricyclic antidepressants (n=9; 7%) and neuroleptics (n=8; 6%) (Table 2).

FIGURE 1. Patient flow.



Abbreviations: CGA comprehensive geriatric assessment ; GP general practitioner ; PIMs potentially inappropriate medications

TABLE 1. Patient's characteristics upon admission.

	Control (N=72)	Intervention (N=74)	p-value
Socio-demographic data			
Female gender, n (%)	49 (68.1)	43 (58.1)	0.213
Age, median [P_{25};P_{75}]	86 [81;89]	84 [81;87]	0.122
Living at home, n (%)	65 (90.3)	66 (89.2)	0.829
Living at home and alone, n (%)	28 (39.4)	30 (40.5)	0.892
Geriatric features			
ISAR, median [P_{25};P_{75}]	3 [3;4]	3 [3;4]	0.457
Cognitive decline, n (%)	14 (19.4)	12 (16.4)	0.637
Malnutrition, n (%)	20 (28.2)	22 (29.7)	0.836
Recent fall, n (%)	28 (39.4)	37 (50.0)	0.201
Katz, median [P_{25};P_{75}]	8 [7;12]	8 [7;11]	0.566
eGFR			
< 50 ml/min, n (%)	33 (45.8)	31 (41.9)	0.631
Drugs used at home			
Median [P_{25};P_{75}]	7 [5;9]	7 [5;9]	0.987
Total, n	528	533	
Polymedication (≥5 drugs/day), n (%)	59 (81.9)	61 (82.4)	0.939
Inappropriate Medications (PIMs)			
Patients having ≥ 1PIM, n (%)	37 (51.4)	39 (52.7)	0.874
Total, n	57	68	

Abbreviations: eGFR estimated Glomerular Filtration Rate; ISAR Identification of Seniors At Risk score; PIMs potentially inappropriate medications; SD standard deviation.

TABLE 2. Potentially inappropriate medications (PIMs) according to STOPP on admission and at discharge.

	Control group PIMs number		Intervention group PIMs number	
Main classes of medications	Admission	Discharge	Admission	Discharge
Total	**57**	**46**	**68**	**41**
Benzodiazepines, n	15	14	26	17
Anti-platelet, n	10	8	9	7
Opiates, n	5	3	8	5
Beta-blockers, n	4	4	6	5
TCA, n	4	3	5	2
Neuroleptics, n	4	4	4	3
Others, n	15	10	10	2

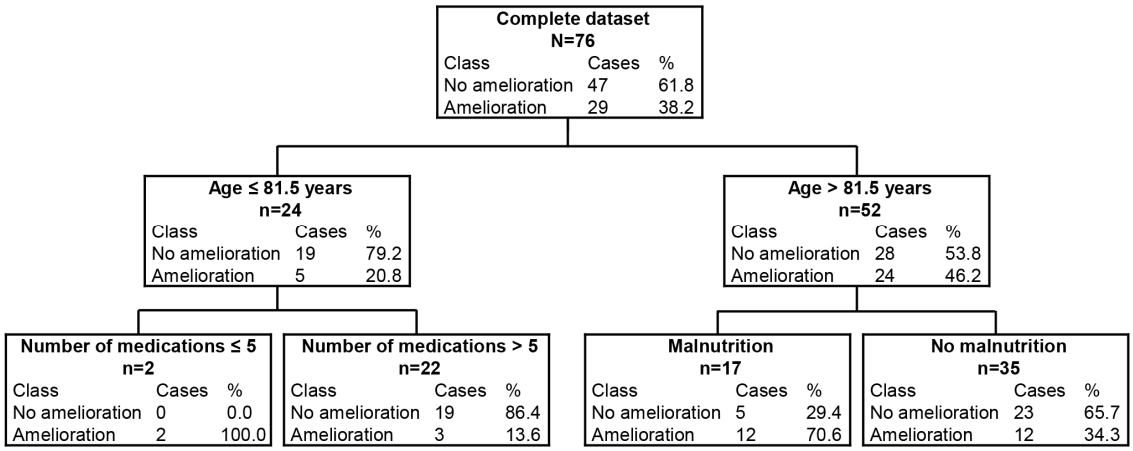
Abbreviations: PIMs potentially inappropriate medications ; TCA Tricyclic antidepressants

Discontinuation of PIMs at discharge

The discontinuation at discharge of PIMs present on admission was twice as high in the intervention group as in the control group (39.7% *vs.* 19.3%; OR [95% CI] = 2.75 [1.22; 6.24], p=0.013). This 20.4% absolute difference in PIMs discontinuation rate related to five PIMs needed to be screened and advised to be stopped in order to yield one discontinuation on hospital discharge. Although this study was not powered to detect differences in PIMs discontinuation according to drug classes, PIMs discontinuation rate of benzodiazepines tended to be higher in the intervention than in the control group (34.6% *vs.* 6.7%, p=0.063) (Table 2).

At the patient level, the reduction in PIMs prevalence (i.e. patients having ≥ 1 PIM) was not different in the intervention as compared to the control groups (23.1 % *vs.* 16.1 %, OR [95% CI]= 1.5 [0.49;4.89], p=0.454).

FIGURE 2. Independent predictors of PIM discontinuation (classification tree).



Abbreviations: ISAR Identification of Seniors At Risk score ; PIM potentially inappropriate medication
'No Amelioration' group: patients with still all PIMs at discharge
'Amelioration' group: patients with at least one PIM stopped at discharge

The first predictor of PIMs discontinuation at discharge using classification trees was the age (Figure 2.). PIM discontinuation was achieved more frequently in older than younger patients (46.2 *vs.* 20.8%). In the older ones (> 81.5 years in this model), malnutrition was the second predictor of PIM discontinuation. In the younger patients, polymedication (> 5 medications daily) increased the persistence of PIMs in discharge treatment.

One-year follow-up and clinical importance of PIMs

The GPs of the patients with PIM at baseline were contacted by postal mail after one year, and 93% responded. One-year follow-up data was obtained for 50 patients (Figure 1, bottom). The intervention (n=26) and control (n=24) groups were comparable for patient's age, geriatric profile and PIMs (n=48 *vs.* 36) on admission.

The clinical importance of these 84 admission-PIMs was considered by the panel of experts as follows: major: 29% (e.g.: "*Benzodiazepine or Neuroleptics in fallers*"), moderate: 37% (e.g.: "*Long-term opiates in those with recurrent falls*", "*Long-term neuroleptics (> 1 month) in those with parkinsonism*"), minor: 5% (e.g. *"theophylline as monotherapy in chronic obstructive pulmonary disease")*. Seven recommendations were considered as deleterious (8%; "*β-blockers in those with diabetes mellitus and frequent hypoglycemic episodes*" in patients with ischemic disease (n=4), "*Vasodilator drugs with persistent postural hypotension*" leading to stop an angiotensin converting enzyme inhibitor in patients with cardiac failure (n=2), "*Long-term opiates in those with recurrent falls*" in a patient with severe pain requiring morphine (n=1)). Other recommendations (n=17) were not rated by the panel because of low prevalence of the criteria (not discussed) or due to insufficient information in patients' medical records.

The one year follow-up showed that in both groups, the majority of PIMs that had been stopped during hospitalisation had not been restarted after hospital discharge (38% (8/21) PIMs restarted in intervention and 43% (3/7) in control group; p=0.999). The clinical importance of PIMs was not predictive of discontinuation at one year. The higher the clinical importance, the lower the discontinuation rate: 25.0% of major PIMs were discontinued compared to 32.3% of moderate and 75.0% of minor. However, deleterious recommendations were mostly rejected (71.4%).

DISCUSSION

This study illustrates the positive effect of a systematic screening using the STOPP criteria can play in improving the appropriateness of medications in frail older inpatients, but also its limitations. Half of frail older inpatients presented PIMs according to STOPP on admission. Identification and counselling by the IGCT

successfully doubled the reduction of PIMs prescriptions at discharge. However, many PIMs persisted at discharge and the proportion of patients with PIMs at discharge did not differ between groups. Most treatment modifications made during hospitalisation were maintained after discharge, reinforcing our opinion that hospital admission can be a good opportunity for medication review in older patients, but also highlighting the role of GPs to further optimize prescribing.

This is one of the first studies to document the impact of IGCT on PIMs. Previous evaluative research on IGCTs mainly focused on outcomes such as mortality, readmissions or functional status but not specifically on medications [11]. Hogan and colleagues showed a decrease in the total number of oral medications but appropriateness was not evaluated [25]. The limited effectiveness of the IGCT found in the present study is likely due to the advisory role of this structure. The geriatrician suggested modifications in the prescription but did not modify the prescription him/herself. Compliance to the recommendations by the ward teams therefore remains a key determinant of effectiveness, similarly to what was reported in other studies [8, 26].

The STOPP criteria are increasingly used to describe inappropriate use of medications in older patients, both in primary and secondary care [14]. The prevalence of patients having at least one PIM in our study (52%) is similar to observations made in other cohorts with community-dwelling patients admitted to acute care (prevalence 35-59%) [15-18, 27]. These studies were observational in nature. Importantly, our study was experimental. To the best of our knowledge, there has been only one randomized controlled trial evaluating the effect of implementing the STOPP criteria in clinical practice, a study conducted in the hospital setting by the authors of this tool, therefore potentially affecting generalizability of the results [14]. The authors reported significant improvements in appropriateness of treatment at discharge according to the Medication Appropriateness Index (MAI) [19, 28]. Our study shows some similarities with this study: similar population; criteria applied by a physician, followed by oral and written counselling to the attending medical team. However, the authors did not assess the clinical relevance of recommendations, as we did.

Our analysis provides new data on the validity and operationalisability of the STOPP criteria. In contrast to the criteria that were considered as highly relevant by the panel of experts (i.e.: "Benzodiazepines in fallers", "Selective serotonin re-uptake inhibitors with a history of clinically significant hyponatremia"), several other criteria

were rated as deleterious when applied to individual cases. We would suggest either considering removal of these criteria from the list or editing them by adding explicit reasons for not applying the criteria, in order to improve the validity of the STOPP list. This also confirms that explicit tools for assessment of inappropriate prescribing should enhance but not replace good clinical judgment [1]. Finally, proper application of several criteria required detailed information which was not always available in electronic medical records (e.g. pain assessment, psychiatric history). This weakness was also highlighted when applying the STOPP criteria in a community pharmacy setting [29].

This study has limitations. First, this was a monocentric study. Generalisation of results to other IGCTs may not be straightforward. In our setting, the IGCT has an advisory-role only. The effect might have been higher if the team had had direct control over prescriptions, which is the case in a few other IGCTs in Belgium [8]. A clustering of outcomes is possible and might alter the results since several geriatricians were involved and were each taking care of multiple patients. Second, we did not evaluate the appropriateness of prescribing using other tools such as the MAI, because our main objective was to focus on the use and effect of the STOPP criteria specifically. However, the measure of the effect of the intervention on the MAI score would have strengthened our results. We also did not evaluate the effect on clinical outcomes such as adverse drugs events or length of stay, but we nevertheless provided interesting data on clinical relevance. Prevalence of PIMs were underestimated because "*duplications*" were not taken into account. "Duplications" were reported has highly prevalent in previous studies [17]. Finally, optimisation of under-prescribing using the Screening Tool to Alert doctors to the Right Treatment (START) was not evaluated [12, 30]. Larger studies are needed to confirm the findings.

In conclusion, this study brings new insights on the systematic use of STOPP criteria in the hospital setting through an IGCT. Discontinuation of PIMs at discharge is higher if the IGCT actively recommends discontinuing PIM according to STOPP. In order to further improve appropriateness of prescribing, it seems essential to adapt the use of STOPP to the individual situation of the patient, to focus on the most important criteria and to actively collaborate with general practitioners. Additional data are also needed on the feasibility to discontinue PIMs and on the predictive validity of explicit tools, namely the effect on relevant clinical, economic and humanistic outcomes.

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CHAPTER V – Views of general practitioners on the use of STOPP & START in primary care: a qualitative study

O. Dalleur, J-M. Feron, A. Spinewine

Chapter V at a glance

What is already known about this subject

- STOPP&START tool is designed to screen for inappropriate prescribing in the chronic drug treatment of older people
- General practitioners play a key-role in the management of chronic treatment thanks to their global overview of the patient's situation.
- STOPP&START might be of interest for general practitioners but their perspectives about using such a tool has not yet been explored.

- This chapter explores the perception of STOPP&START by general practitioners, using a qualitative approach.

What this chapter adds

- General practitioners agree that this tool helps implementing **systematic revision** of the treatment, and that its use may improve quality of care.
- Some **barriers** to the implementation of STOPP&START in general practice include insufficient time for medication review and patient disagreement to modify some treatments.
- General practitioners have **diverging views** on the usefulness, the comprehensiveness and the relevance of the STOPP&START criteria.
- To maximize the effectiveness of the use of the tool, STOPP&START should be **computerized**, taught in **educational** sessions and used in **multidisciplinarity**.

ABSTRACT

Background and objective: STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert Doctors to Right Treatment) criteria aim at detecting potentially inappropriate prescribing in older people. The objective was to explore general practitioners' (GPs) perceptions regarding the use of the STOPP&START tool in their practice.

Design: We conducted three focus groups which were conveniently sampled. Vignettes with clinical cases were provided for discussion as well as a full version of the STOPP&START tool. Knowledge, strengths and weaknesses of the tool and its implementation were discussed. Two researchers independently performed content analysis, classifying quotes and creating new categories for emerging themes. Additionally, a survey of GPs was performed in order to identify tools they used for decision support in older patients (including STOPP&START) and barriers to appropriate prescribing.

Results: Discussions highlighted incentives (e.g. systematic procedure for medication review) and barriers (e.g. time-consuming application) influencing the use of STOPP&START in primary care. Usefulness, comprehensiveness and relevance of the tool were also questioned. Another important category emerging from the content analysis was the projected use of the tool. The GPs imagined key elements for the implementation in daily practice: computerized clinical decision support system, education, and multidisciplinary collaborations, especially at care transitions and in nursing homes.

Conclusion: Even if the GPs did not use the tool regularly, they expressed view on how STOPP&START should be implemented and used.

INTRODUCTION

Inappropriate prescribing in older patients is known to be prevalent and difficult to tackle. In primary care, approximately one in five prescriptions to the older persons is inappropriate [1]. Several tools exist to help the prescriber review medications and detect potentially inappropriate prescribing. One of them, the STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert Doctors to Right Treatment) tool [2], is more and more under scrutiny in Europe [3]. STOPP&START is a double list of explicit criteria published in 2008. STOPP addresses over- and mis-prescribing of potentially inappropriate medications (use of a drug without valid indication or incorrectly prescribed), while START allows to detect situations of potential under-prescribing (lack of an indicated drug).

General practitioners (GPs) p lay a key-role in the management of chronic treatment of older patients because of their longstanding relationship with the patient and their global overview of the patient's situation [4]. Therefore, they might be considered as the main potential users of tools such as STOPP&START. On the one hand, there is a demand from the GPs to learn about the tool. Belgian scientific associations of GPs have organised several educational sessions on STOPP&START since their publication. On the other hand, the use of the tool in general practice seems to be low [5]. Moreover, potentially inappropriate medications detected by explicit criteria are not always inappropriate [6, 7] and some STOPP criteria may be controversial when applied to the patient [8]. Therefore, exploring the views of GPs on the use of the tool is essential. The prevalence of inappropriate prescribing using STOPP&START was widely reported [3, 9], but to the best of our knowledge, no qualitative approach has been performed so far to look at implementation challenges regarding the use of this tool in the everyday practice.

The objective of this study was to explore the views of GPs on the use of STOPP&START in daily practice.

METHODS

Study design

Qualitative research encompasses a variety of methods (interviews, observation, and analysis of documents) for identifying what really matters to individuals, describing processes, detecting barriers, and explaining why improvement does or does not occur [10].

Three approaches were used in this study: a brainstorming session, focus groups (FGs) and a survey.

The brainstorming session was performed to gain insight about positive and negative perceptions on the tool. The results were used to construct the discussion guide for the FGs.

The FGs extensively explored the views of GPs on the use of STOPP&START in their daily practice. FGs are useful at exploring participants knowledge and experiences [11], which was the objective of this study. This method was selected because – in contrast to individual interviews – we expected to benefit from the group dynamics [11, 12]. FGs provide a setting in which participants can discuss their attitudes and ideas and generate new questions [13]. Other advantages of FG are: economical way to collect data, encouragement of spontaneity in the views expressed, 'safe' environment for participant because they are not obliged to answer to every question and they can feel empowered by the group membership and its cohesiveness [12].

Finally, a survey was conducted to collect quantitative data from a larger sample of GPs which could be used to triangulate the answers of the FGs [14].

Authors used the COREQ checklist when reporting this qualitative study [15]. The protocol was approved by the local Ethics Committee (Commission d'Éthique Biomédicale Hospitalo-Facultaire, Faculté de Médecine, Université catholique de Louvain). All participants of the FGs provided written informed consent. The consent to participate to the survey and the brainstorming was implied by completion and return of the answers.

Sampling strategy

Brainstorming

The brainstorming session was organised during a symposium on the STOPP&START tool at the Université catholique de Louvain (March 2013). The participants included pharmacists and physicians (geriatricians and GPs) .

Focus groups

Three FGs were organised. In each FG, most of the participants knew each other before the meeting. The participants of the two first FGs were recruited by convenience sampling [10] amongst the participants of a one-week continuous educational program organised abroad by the Belgian Scientific Society of General Practice (April 2013). The principal investigator (OD) had been invited as a speaker for a session on drug interactions. All 220 GPs attending the program were invited to participate on a voluntary basis and recruited by advertisements during the educational sessions. A third FG was organised in May 2013 with last-year medical school students from the Université catholique de Louvain and planning to become GPs. This sample was purposively chosen to collect the views of younger GPs as the participants of the first two FGs appeared to have long practice experience. Students were recruited by email and by advertisement during courses.

Survey

The 220 GPs attending the continuous educational week aforementioned were invited to participate in the survey.

Instruments and data collection

Brainstorming

Each participant of the symposium was asked to write down on sticky notes at least one strength and one weakness of the STOPP&START tool itself or related to its use. The sticky notes were gathered and discussed with the auditorium.

Focus groups

Two GPs with previous experience in qualitative research moderated the first two FGs. The third FG was moderated by the principal investigator (OD, clinical pharmacist). The moderators encouraged the participants to talk and interact. An observer (OD during the first two FG, another pharmacist during the third FG) took field notes during each FG on attitudes, non-verbal expression and interactions between participants.

A guide for discussion with open-ended questions was constructed on the basis of the results of the brainstorming and on previous experience by the research team (appendix1). The guide was pretested with two GPs not involved in the study. Key questions were on the advantages and pitfalls when using the tool. A full version of the STOPP&START tool and three vignettes were given to the participants. The vignettes, adapted from real cases, were used to illustrate the detection of inappropriate prescription with STOPP&START (appendix 2). Each vignette presented the medical history, social background, list of drugs and recommendations according to STOPP&START for a particular patient. Vignettes were chosen to (a) illustrate STOPP&START recommendations from different systems (cardio-vascular, nervous, endocrine, drugs related to falls,...) (b) include the most frequent inappropriate prescribing events according to a previous Belgian study (benzodiazepines and falls, inadequate cardiovascular prevention) [16], (c) present recommendations according to STOPP&START that are usually well accepted (stopping duplicate treatment, starting secondary cardiovascular prevention after stroke) as well as recommendations that are more difficult to implement (benzodiazepine withdrawal) or controversial (stopping beta-blocker in a patient with hypoglycaemia but recent myocardial infarction).

FG lasted on average one hour, were set in a quiet room, sitting at a round table, and refreshments were provided.

Survey

A two-pages questionnaire with multiple choice questions was distributed to the GPs to collect data on their experience of prescribing in elderly, tools they used for decision support in older patients (including STOPP&START) and barriers to appropriate prescribing (appendix 3). One open-ended question asked to provide ideas to improve prescribing in older patients. The questionnaire was adapted from a questionnaire used in an Irish study with the agreement of the authors [17].

Data processing and analysis

Discussions of the FGs were audio-taped and transcribed *verbatim* [12]. Data was analysed independently by two coders for content, with an inductive approach for coding (i.e. the key themes and concepts were identified in the transcripts and categorised, in a process of moving from the data towards generalisation and hypotheses) [13, 14, 18]. The first coder (OD, pharmacist) was previously involved in research on the STOPP&START tool, while the second (JMF, a GP with previous experience in qualitative research) was not. The coders used a systematic and rigorous "cutting and pasting" method with a word processor. No software package was used, as those are mainly useful for larger data set and are no less time consuming [18]. The results were then sent by e-mail to participants of the FGs who were asked to provide feedback.

The closed questions answers to the survey were quantitatively analysed. The answers to the open ended question were grouped by themes for the development of a coding frame [13]. For triangulation, the themes emerged from the analysis of the FGs were compared to the questionnaire and the answers to the open-ended question.

RESULTS

Forty-three persons (pharmacists, hospital pharmacists, GPs and geriatricians) attended the STOPP&START symposium and were invited to the brainstorming session. The FGs gathered 27 GPs. Size of the groups varied from eight to ten participants. The survey questionnaire was completed by 129 GPs, generating a 59% response rate (129/220). Their characteristics are presented in table 1.

TABLE 1. Profile of the survey participants (n=129).

Characteristics	**Median (minimum ; maximum) or % of answers**
Years in medical practice	33 years (3 ; 50)
Percentage of patients over 65 years of age cared for by the GP	40% (5 ; 80)
Working in nursing homes	
Often	51,6%
Sometimes	34,9%
Rarely	9,5%
Never	4%
On a scale from 1 (limited experience) to 10 (extremely experienced), professional experience caring for persons over 65 years	7 (3 ; 10)
I have confidence in my ability to prescribe appropriate medications for the elderly	
Strongly Agree	1,6%
Agree	49,2%
Neutral	39,8%
Disagree	8,6%
Strongly Disagree	0,8%

Abbreviations: GP general practitioner

Table 2 and 3 summarises the main themes that emerged from the analysis. Four participants of the FGs gave feed-back on the findings. All agreed with the results.

Awareness and use of STOPP&START

Most of the participants of the FGs had already heard about the STOPP&START tool. Some of them had even organised training sessions on STOPP&START. Two-thirds of survey respondents knew the existence of STOPP&START. Interestingly, only one quarter of respondents were aware of the Beers criteria [19-21], which are other explicit criteria published before STOPP&START and more frequently quoted in the literature (appendix 4).

Only one participant of the FGs reported using of the STOPP&START tool on a regular basis. The answers to the survey corroborated these findings. Among the respondents who knew the tool, 18% used the tool often (1 to several times a week), 36% sometimes (1 to several times a month), 35% rarely (1 to several times a year), and 1% never (appendix 4).

Discussions highlighted incentives and barriers underlying the use of the STOPP&START and some controversy about characteristics of the tool or its use (table 2). The projected use of the tool emerged from the content analysis as another important category (table 3).

TABLE 2. Categories underlying the use of STOPP&START in general practice.

Agreement between general practitioners	Incentives to use the tool	• The tool is easy to understand and logical • The tool allows a systematic revision of the treatment • The tool improves quality of care • The tool enhances the skills of the general practitioner
	Barriers to use the tool	• The tool is difficult to implement • The application of the tool is time-consuming • The patient might disagree with treatment modifications
Diverging views between general practitioners		• Usefulness of the tool • Comprehensiveness • Relevance of the criteria

Incentives to use the tool

The participants of the FGs and the brainstorming session reported appreciating the fact that the tool was easy to understand and logical. They said that the tool took into account the multiple aspects of the complex task of the GPs when managing the drug regimen. The tool was considered as a decision support and a way to improve security, as it drew attention on main inappropriate prescribing events. It allows a systematic revision of the patient's therapy. Participants reported that STOPP would help GPs to withdraw useless drugs, which was perceived to be particularly welcome in polymedicated patients, and that START would help them remembering to prescribe required medications. This medication review was considered as essential by the participants but currently insufficiently achieved.

> *The advantage is that you can maybe put your finger on things you had overlooked. (FG 3, Participant 9)*

> *…the fact of ... having in mind that there is this list available in the office and that there could be some point in using it, you'll maybe be a lot more careful. (FG 3, Participant 4)*

Several participants pointed up the educational role of the tool and the improvement of the use of the GPs' skills. One of the participants mentioned the tool allowed GPs to enter a dynamic of quality management in patient care.

> *I think that by using a tool systematically, you get more familiar with the ins and outs of it and you will get prescriptions that are better thought out and more automatic, more systematic too for our elderly people, both in terms of starting a treatment, of thinking of really everything that is preventive, or of stopping a treatment. (FG 1, Participant 6)*

> *... it can make the most effective use of the doctor's effort in terms of skill, you think of everything, well, you can think of more things, or even of everything, (FG 1, Participant 9)*

Barriers to use the tool

Although considered as interesting for both patients and GPs, the tool was perceived as difficult to implement in daily practice. The time required for applying the

tool was one of the most frequently reported barrier, especially as detection of inappropriate medications was not automated. Most of the survey responders confirmed that lack of time was a barrier to appropriate prescribing in older patient (24% strongly agreed, 44% agreed) (table 4).

> *P3: You really have to make the effort to say to yourself, "OK, now it's been six months, or a year has gone by, maybe it's time to…", in other words, it's not something automatic, you really have to…*
> *P: You have to want it!*
> *P3: You have to want it! Have to force yourself, you know.(FG 2)*

Time required to negotiate treatment modifications with the patient was also considered as a limit. The applicability of the recommendations to the patient and the compliance of the patient to the recommendations was also frequently mentioned. This problem is not inherent of STOPP&START but appeared to be a significant barrier to the application of the recommendations. GPs often feared that patients would disagree to change their treatment, as they were attached to their medications.

> *If…if you start implementing that, you need to allow twenty minutes, in fact even more, half an hour just to check the list to see what will be added or removed and also another quarter of an hour for talking with the patient. (FG 3, Participant 2)*

> *But these are the kinds of medication they have an obsessive psychological attachment to. (FG 2, Participant 1)*

However, in the survey, GPs had mixed views on the impact of the patient request as barrier to optimising prescribing. Approximately one third considered the patients' requests as a barrier, on third did not and the last third was neutral (table 4).

The layout of the tool was also suboptimal according to GPs and should be improved to become more interactive.

Controversies

Some characteristics of the tool were perceived positively by some GPs and negatively by others, bringing some controversies.

The first controversy was on the **usefulness** of STOPP&START. The tool was globally regarded as useful by the participants, but when looking at particular cases with the vignettes, some of the recommendations of the tool were considered as useless, because only telling the GPs to be cautious or giving information the GPs would already be aware of. The usefulness of the tool was finally thought to be more related to its property to enforce a systematic review of the treatment than to the exact content of its recommendations.

> *But I think we are all pretty well aware of all the points that are required by START&STOPP. I mean to say, it doesn't teach us anything! Well, not much, anyway. What it will do is remind us…that we have to stop and think about things. (FG 2, Participant 5)*

The second controversy was about the **comprehensiveness** of the tool. While some participants thought the tool was too long and indigestible, others mentioned it was too short and incomplete. In the vignettes, GPs found inappropriate medicines which were not tackled by the STOPP tool (e.g. betahistine, statines). They regretted that the tool insufficiently addressed acute therapy and drug-drug interactions. Some participants said that the tool included items relevant to daily practice, as it mentioned common pathologies and frequently used drugs. Others did not consider the tool as practical and said that modifications were required before using it in daily practice (in the presentation, the structure and the content).

The organisation by system was also a subject of controversy. Some GPs thought it was a good way of presenting the recommendations while others would have preferred an classification by drugs. This element was also mentioned in the brainstorming.

> *M: Do you think STOPP should be organised by medication and not by system, because when you implement it, your starting point is a medication and not a pathology?*
> *P1: Yeah, I would agree with that.*
> *P8: Me, I think. In any case you would need both.*
> *P2: Me, I think it's important that it stays by system.*
> *P8: Me, I operate completely differently. (FG 1)*

Validity of the criteria

A decisive factor influencing the views on the tool and its potential use is the **relevance** of the criteria. Discussions with the vignettes highlighted the attention the GPs bring to the validity of the criteria. Several participants asked whether the tool was evidence-based, up-to-date, or associated with a decreased risk of adverse events. The lack of information on the actual risks caused by inappropriate prescribing of a particular drug and on the level of evidence was an important concern raised by a few participants.

> *Where are the clinical endpoints? (brainstorming)*

The tool was doubted during the discussions on the vignettes as it did not fully meet the needs of the GPs in terms of flexibility to particular indications and patients. GPs might apply a same criteria differently according to the patient context. Similarly, some criteria might not be applicable anymore when life expectancy diminishes. The brainstorming had also brought out these pitfalls.

> *Everyone is different, so sometimes there are cases where I wouldn't follow the START&STOPP list because I reckon that for my patient I don't see the advantage of stopping or of following it, but, on the other hand, consulting it to help me remember all the rules a little – that OK, but it's not going to become some kind of precise rule for everyone. (FG 2, Participant 1)*

> *And then you can't, you can't subject medicine to norms; we don't have an ISO 9000 or I don't know what on a patient, because every case is individual and it's always case by case that we do things. (FG 2, Participant 4)*

Projected use of the tool

The GPs imagined key elements for the implementation of STOPP&START in daily practice. Projected implementation and use of the tool was described in the following terms: required adaptations for practice, best moment of use, teamwork, voluntary use, and particularities related to the setting.

TABLE 3. Projected use of the STOPP&START tool.

Adaptations for practice	• Improvement of availability of the tool • IT development • Individualization to the GP, to Belgian practice • Education of GPs to use the tool
Best moment of use	• Pre-established schedule for treatment review *vs*. at each treatment modification • In selected patients • In early career of the GP
Team work	• Use in collaboration with other GPs or healthcare professionals
Voluntary use	• No external control on the use of the tool • Therapeutic freedom protected
Particularities related to the setting	• Implementation in nursing homes • Hospital discharge: use by hospitals and GPs

Abbreviations: IT information technology ; GP general practitioner

Adaptations for practice

To improve implementation of the tool, most GPs reported that several adaptations were needed, including: better availability, adaptation to the practice of the GPs and individualization to their actual needs, flexibility and updates to address new molecules and evolution of knowledge. Whether these adaptations should be made by the GP individually or/and in an official revised set of criteria was not established.

> *I think it's a tool that has the merit of existing, that can be improved and that should be adapted to everyone and it's by using it and adapting it that it's going to develop. (FG1, Participant 9)*

Computerization of the tool, as a clinical decision support system linked to the electronic medical record of the patient was cited by the majority of the interviewees as a *sine qua non* to the implementation of the tool. This would also meet the need of having a system that can be easily adapted. For example, an alert system appearing at the end of consultation or at the time of prescribing was suggested. GPs expressed several conditions for efficiency and reliability of the computerized tool i.e.: 1) ability to take into account patients' medical conditions and age (exhaustive coding of medical

conditions would then be a prerequisite), 2) up-to-date list, 3) availability in the medical office as well as in nursing homes, 4) screening for inappropriate medications according to STOPP&START but also for drug-drug interactions, 5) accreditation of the system by professional organizations. Participants insisted that the computer system should not be restrictive.

> *But we always have our skills, well, we always have our ability as a doctor to be critical and to say to ourselves, "Is the computer actually right or not?", but at least you have the warning, whereas you mightn't have thought of it if you didn't have the programme. (FG 3, Participant 7)*

The survey confirmed the importance of Information Technology (IT) support. When asking the GPs initiatives to improve appropriateness of prescribing in older patients, 24 of the 129 respondents spontaneously answered "use of a software" or "computerized prescription order entry". IT was the most frequent category of answers (table 5).

Participants reported that increasing knowledge of the tool and training were needed in order to boost use of the tool. Some GPs reported that the tool could be particularly useful early in their careers. Participants from the FGs considered using STOPP&START after specific training. A similar suggestion was made by fourteen respondents of the survey (table 5). Half of the GPs (strongly) agreed that lack of education on prescribing in elderly was a potential barrier to appropriate prescribing (table 4).

Best moment of use

GPs discussed the best moment and frequency for using the tool. Different opinions emerged: on a pre-established regular basis (e.g. reviewing the whole treatment once a year, use of timetables), upon treatment modification, automatically at the end of the consultation, in polymedicated patients, in new patients, after transitions across settings (at hospital discharge, when entering a nursing home).

Team work

General practitioners thought that effectiveness could be increased by working with other healthcare profesionnals such as physician colleagues, geriatricians, (clinical) pharmacists, nurses from nursing homes, and medical trainees. However, not all participants agreed to discuss the treatment of their patients with other professionals. Collaboration with other professionals was spontaneously cited as a way to improve appropriateness of prescribing by 10 respondents of the survey (table 5).

> *maybe using it individually for each patient like that is not feasible in practice, because you would indeed need an hour to do it. On the other hand, using the tool with the help of the head nurse, with the idea that "Well, we'll have a look at the treatment and see if…" To me, it would be more plausible to do that than case by case, at every consultation, or at every visit by the doctor. (FG2, Participant 1)*

Involving the patients was also mentioned in the FGs. The application of the tool must be followed by time allocated to discussing treatment modifications with the patient.

Voluntary use

STOPP&START pleased the GPs as long as it remained a tool and did not diminish their therapeutic freedom.

> *For my part, I want to come back to the fact that it's a TOOL. That means that it's always the doctor who is behind it and who assesses, depending on this or that element of the file, whether he will adapt or take or start or stop. It's the doctor, after all, who decides. The tool just tells you: hey, look. But OK, afterwards, you weigh things up according to the clinical case. (FG 2, Participant 1)*

All the participants strongly disagreed with the idea of a mandatory use of the tool and with some form of external control (e.g. governement, healthcare organisation) on the application of the tool.

If a higher authority like the federal ministry, er….comes along and imposes, er, this kind of thing. That might result in improved care, but we're not robots either, you know. (FG 3, Participant 2)

I think that if it's compulsory you're going to have a lot of friction. (FG 2, Participant 7)

Interestingly, a few GPs mentioned the need to have financial incentives for reviewing the drug treatment or using the tool.

Particularities related to the setting

In addition to the implementation of the tool during a consultation at the practice, GPs highlighted the importance to use the tool in nursing homes and at discharge of hospital.

Nursing homes

According to the GPs, the nursing home represented a particular complex setting and therefore a priority to improve appropriateness of prescribing and to implement the tool. The GPs reported that this setting is characterized by: higher prevalence of polymedication and inappropriate prescribing, own organization (prescriptions ready to be signed, many (sometimes unknown) patients to quickly examine), difficult role for the coordinator to ensure availability of STOPP&START to all GPs working with the nursing home, uncommon access to computerized records and order entry systems.

Hospital

The hospital discharge was considered as a critical juncture. GPs said that patients were discharged with an elevated number of drugs and they often had to tell the patient not to take the full list of drugs prescribed upon hospital discharge. Some GPs mentioned that the tool should also be applied during hospital stay by the geriatrician or the other specialists, to avoid that GPs alone carry the responsibility to use STOPP&START and review medications.

TABLE 4. Barriers to appropriate prescribing in older patients according to the 129 survey participants (% of answers).

Potential barriers	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Large number of medications a patient is taking	**49,2**	42,9	6,3	1,6	0
Potential drug interactions	26,4	**56,8**	13,6	3,2	
Unwillingness to discontinue a medication prescribed by another physician	7,9	**44,9**	22	18,9	6,3
Lack of time in the office schedule	23,8	**43,7**	21,4	7,9	3,2
Cost to patient	7,9	**40,9**	29,9	17,3	3,9
Lack of formal education on prescribing for the elderly	13,5	**35,7**	31,7	15,9	3,2
Lack of acceptable therapeutic alternatives	0,8	34,7	**41,9**	21	1,6
Patient request	7,1	32,3	**33,1**	23,6	3,9
Difficulty communicating with other physicians who participate in a patient's care	9,4	27,6	**29,1**	27,6	6,3
Lack of access to a pharmacist	1,6	10,3	26,2	**45,2**	16,7

TABLE 5. Survey answers to the open-ended question " *In your opinion, what initiative would possibly lead to the greatest improvement in the use of medication by older people*?".

Themes	Number of quotations
IT tool (including or not STOPP&START recommendations, detection of the interactions)	25
Trainings (workshops, GLEMs,…)	14
Improvement of the access to the references	10
Increase of intra and inter-disciplinary collaborations	10
Polymedication targeted	8
Regular medication review (with or without STOPP&START)	5
Others (inform the patient on the risks, availability of an updated list of the drugs the patient is on, ...)	19

Abbreviations: IT information technology ; GLEMs Groupes locaux d'Evaluation Médicale (local continuous trainings).

DISCUSSION

Incentives and barriers underlay the use of STOPP&START by GPs, but it was also influenced by some controversy about the usefulness and the relevance of the tool. Even if the GPs did not use the tool regularly in their clinical practice, they had a projected view on how it should be implemented and used. As previously shown, there was a demand for a GP-friendly tool [4], but participants did not established this tool to be STOPP&START.

General practitioners mainly appreciated the **systematic revision** of their patients' treatment offered by the use of a tool such as STOPP&START. Medication review was reported in the discussions to be important and desired but insufficiently performed. Medication review should be encouraged because effective in optimizing prescription in elderly [22, 23], including when performed by GPs [24, 25]. Routine medication review is mandatory in several countries. Our results showed that GPs fully agreed with the need to have systematic regular medication review. However the participants strongly disagreed with a mandatory implementation of STOPP&START.

In the hospital setting, the application of STOPP&START in a randomized controlled trial has already shown significant improvement in the appropriateness of treatment [26], but similar data in primary care are not available yet.

Several important **weaknesses** of the tool were identified. The tool was considered as time-consuming and difficult to implement. Yet the application of the tool takes less than 5 minutes for experienced users [3], so the time issue was probably overestimated. Lack of time and organizational constraints have previously been reported as barriers to adherence to guidelines [27]. The GPs workload might diminish the time available for both drug treatment revision and discussion with the patient. GPs did not agree on whether the tool and criteria were useful, comprehensive and relevant. It is important to remember that STOPP&START is a screening tool detecting "potentially" inappropriate prescribing and that its use should be individualized to the patient context. A study showed that 36% of potentially inappropriate medications according to the Beers criteria were actually inappropriate [7]. The percentage of actual inappropriate prescribing and their clinical relevance among the STOPP&START flagged drugs is not known. Another weakness was the lack of level of evidence of the recommendations. This might be a disadvantage of STOPP&START in favour of the use of the last updated Beers criteria that include the level of evidence for each recommendation [19]. Our study confirmed that the GPs expect data on the risks and benefit of treatment options [28].

The vast majority of participants heavily insisted on the need for **IT support** for improving prescribing globally and more specifically for expanding the use of STOPP&START. Although IT support is definitively a promising opportunity [23], having effective, reliable and valid systems currently remains a major challenge for various reasons. The effectiveness of Computerized Decision Support Systems (CDSSs) varied among studies and settings [23]. In primary care, the use of a CDSS did not increase the discontinuation rate of pre-existing inappropriate prescribing in older patient, but decreased the new prescribing of potentially inappropriate medications [29]. In the hospital setting, CDSS have shown to be effective in diminishing inappropriate prescribing in older patients at discharge [30, 31]. With regard to reliability, operating such a system requires that medical and medication data are coded in a standardized and sufficiently detailed manner. Such coding is not widely implemented in any setting of care in Belgium, although this is likely to evolve in the future. Finally, low relevance

and overriding of alerts are frequent barriers [32]. A European project (SENATOR) is now in preparation to develop and assess a " *software engine capable of individually screening the clinical status and (non-) pharmacological therapy of older people with multimorbidity in order to define optimal drug therapy, highlight adverse drug reaction risk, indicate best value drug brand for selection and provide advice on appropriate non-pharmacological therapy*" (http://www.ucc.ie/en/charge-ucc/senator/). This software will apply STOPP&START.

Training on appropriateness of prescribing in older patients and on using the tool were frequently mentioned as well. Our sample of participants was particularly sensitive to education because recruited at education sessions. Even if not sufficient to ensure appropriate prescribing, education is an essential preliminary step [23, 33, 34].

Multidisciplinary use of the tool was another opportunity according to the GPs. This theme, although not expected by the researchers, is in line with several projects on multidisciplinary management of the geriatric patient to optimize pharmacotherapy [23, 35]. Teamwork with hospital specialists at discharge was also required. Multidisciplinary management of drug regimen might also be an option to overcome the barriers related to the GPs workload and limited time.

Similarly to previous studies, **patients' conservatism** was cited as a barrier to optimising prescribing, and use of STOPP&START would not eliminate this difficulty [4, 36]. Interestingly a recent review highlighted that patients could be both barriers or enablers to de-prescribe drugs [37]. This reinforce the perceived idea that patients are partners in optimizing the treatment [38]. Appropriate information about the treatment should be provided to the older patients in order to improve adherence and, as a consequence, health outcomes [38, 39]. Further studies should assess the patient point of view on the medication review and the use of tools.

The present study had several **limitations**. The number of FGs was small but information collected during the discussion was close to data saturation. Both independent coders observed that each FG brought very little new concepts. We believe that one or two further FGs would have confirmed the data saturation. All the FGs were not run by the same pair of moderator and observer. Although moderator skill may influence the quality of the data collected [12], we do not believe this to be a major limit of our study as the data collected were similar across the FGs. The discussion guide was

not refined between FGs. Importantly, as for any qualitative approach, the results can not be generalised, in the present case to all GPs and to all general practice settings [12]. Our sample of participants was selected amongst general practitioners having interest in continuous education and therefore potentially more eager than others to learn about new tools to improve their medical practice. Most of them had previously heard about STOPP&START, during a previous continuous education training, which is not representative of the general population [5]. However, we observed similar views in GPs with short and long experience. Our sampling also allowed us to gather GPs from different regions and settings (independent or working in a team, working or not with a nursing home; Table 1.).

Despite these limitations, the present study addressed for the first time the perception of an important group of potential users of STOPP & START, namely GPs. Several precautions were taken to ensure the quality and the validity of the study [40]. The COREQ checklist was used to design and report the study [15]. Two independent researchers analysed and coded the FG discussions [10], and took into account field notes taken by co-researchers [12]. The results were triangulated with the data of the brainstorming and the survey. Finally, participants were offered to give feed-back on the results, to ensure accuracy of the data-coding [40].

CONCLUSION

A tool such as STOPP&START has a projected place in general practice but with some adaptations, the most important being the development of a computerized version. Controversy about usefulness, comprehensiveness and relevance hinders large implementation of STOPP&START. Trainings on the appropriate use of medicines in elderly are desired by the GPs. A multidisciplinary collaborative use of the tool was suggested. Further studies could focus on the impact of the use of the tool as part of a multidisciplinary management of nursing homes residents.

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APPENDIX 1: GUIDE OF DISCUSSION FOR FOCUS GROUPS: IN GENERAL MEDICINE, WHAT COULD BE THE PLACE GRANTED TO SCREENING TOOLS FOR INAPPROPRIATE PRESCRIBING IN THE ELDERLY?

The questions are presented in a frame.

Notes under the frame are comments for the moderator. Some "additional" questions are to be asked if their theme was not raised yet.

1. Introduction

We are going to discuss together the place which could be granted in general medicine for tools to detect the so-called inappropriate drugs in the elderly. What do we understand by “inappropriate”? "Inappropriate" means, for example, that either these are drugs which the patients should not receive because the risk exceeds the benefit at their age, or because they are underused. If you do not know these tools, it is not a problem for the discussion. You are going to discuss together based on a series of questions which I am going to ask. The idea is not to answer me, but to discuss it between you. My experience tells me that some people speak more that others... If I interrupt you, please do not take it badly. The discussion is recorded and an observer takes notes. The anonymity is guaranteed for the analysis.

2. Opening topics

I suggest a round table to get acquainted. Could you please introduce yourself? Please mention your name and where you come from.

Name, place, city, medical house, nursing home...

Do you have the feeling that you often meet old patients who take inappropriate medicines?

This is a brief and closed question, to see if they feel concerned, and to initiate the discussion.

3. Transition topics: Knowledge of tools

You have under eyes the STOPP&START tool which allows to detect inappropriate prescribing in older people. Did you know that tools as this on exist? Which one do you know?

4. Key topics

4.1. Vignettes

This tool was already used in several studies. Here are three patients observed during studies in Belgium and the inappropriate medicines (to stop or to introduce) that STOPP&START tool allowed to detect. What do you think about it?

Read the vignettes together.

4.2. Strengths

I would like to mention strengths and weaknesses connected to the tool and its use. If you do not know STOPP&START, you can express your opinion with regard to the use of such tools "in general". Let us begin with the strengths only. According to you, what are the strengths of this tool?

This question was put during a workshop on STOPP&START, organized in the UCL (4/3/13). The majority of the participants were pharmacists.

Here are some themes evoked during the workshop and which could come out of the discussion in the focus group.

A. *Tools are easy to use*
B. *Tools are easy to understand*
C. *Tools are easy to implement*
D. *Tools are close to the practice*
E. *Tools make a clear link with adverse drug events*

Additional question: *If these elements are not raised during the focus group, ask the question: Do you think that … (A-E)*

4.3. Advantages connected to the use.

What are the advantages when we use the tool?

Make a link with what was evoked during the discussion of the vignettes.

4.4. Weaknesses

On the opposite, according to you, what are the weaknesses of this tool?

Again, this question was put during the workshop.

A. *Tools are difficult to implement*
B. *The recommendations are not accepted/acceptable enough*
C. *Tools do not make the link with outcomes*
D. *An information about the severity would be needed, all the criteria do not have the same consequences*

Additional question: *If these elements are not raised during the focus group, ask the question: Do you think that … (A - D)*

4.5. Disadvantages

What are the disadvantages when we use the tool?

Additional question: *If the* ***length*** *of the criteria list was not evoked in the strengths and the weaknesses, ask the following question: What do you think of the length of the criteria list?*

Additional question: *If the* ***relevance*** *of the criteria was not explored in the strengths and the weaknesses, ask the following question: What do you think of the relevance of the criteria?*

Additional question: *If the* ***utility*** *of the criteria was not evoked in the strengths and the weaknesses, ask the following question: Do you think that this tool, or others, are useful in general medicine?*

5. Conclusion and perspectives.

5.1. Place

As is, what could be the place of this screening tool for inappropriate prescribing in general practice?

Additional question: *If* ***IT*** *was not previously evoked, ask the following question: Let's imagine that the tool is included into your prescription software, as for the drug-drug interactions, for example. Could you tell me what you would think of it?*

Additional question: *What* ***other ideas*** *do you propose to improve the access to the tool and to its use?*

5.2. Compulsory use of STOPP&START

This tool is more and more "in vogue" and interests a lot of people, of whom potentially decision-makers. Let's imagine that we arrive at a situation where its application would become compulsory, for example once every six months for the patients in nursing home. What would you think of this situation?

6. Conclusion

Do you want to add anything? If you wish to add personal comments on this subject, we can have one-to-one meetings.

Synthesis and thanks

APPENDIX 2: VIGNETTES FOR FOCUS GROUPS

Patient A.

Ms. A is 80 years old. She is a widow and lives in a nursing home (MMSE = 22), where she regularly has the visit of two of her children and her grandchildren.

Medical history: valvular disease, stroke, depression, degenerative osteoarthritis, essential tremor, epilepsy and oesophageal reflux.

Usual medicine:

- Alprazolam 0.5 mg *t.i.d.*
- Nexiam 20 mg *p.r.n*.
- Steovit D3 not systematically taken
- Inderal 160 mg daily
- Zaldiar 325/37.5 *p.r.n.*
- Depakine Chrono 500 *b.i.d.*
- Seroxat 20 mg daily
- Betahistine 16 mg *t.i.d.*
- Lorazepam 1 mg daily

STOPP:

⇨ Duplicate drug classes: lorazepam + alprazolam (2 intermediate benzodiazepines)

Any duplicate drug class prescription, e.g. two concurrent opiates, NSAIDs, SSRIs, loop diuretics, ACE inhibitors (*optimization of monotherapy within a single drug class should be observed prior to considering a new class of drug*)

START:

⇨ Aspirin and statin in secondary cardiovascular prevention of the stroke

Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm

Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is greater than 5 years

Patient B.

Ms. B is 88 years old. She lives alone in her house, with the help of a nurse twice a week. Ms. B had several falls these last twelve months. She is afraid of falling and has impaired balance.

Medical history: hypertension, hypercholesterolemia, angina pectoris, transient ischemic attack several years ago, osteoporosis (multiple fractures), operated cataract.

Usual medicine:

- Cardiaoaspirine 100 mg daily
- Bisoprolol 2.5 mg daily
- Hyperlipen 100 mg daily
- Movicol *p.r.n.*
- Loramet 1mg daily

STOPP:

⇨ Lormetazepam and falls

Drugs that adversely affect fallers: Benzodiazepines (*sedative, may cause reduced sensorium, impair balance*)

START:

⇨ Treatment of the known osteoporosis

Calcium and vitamin D supplement in patients with known osteoporosis (previous fragility fracture, acquired dorsal kyphosis)

Patient C.

Ms. C is 89 years old. She lives alone in her house since the death of her companion. She takes regularly the bus to visit a friend.

Medical history: recent infarct, hypertension and insulino-requiring diabetes (Hb1Ac = 6.9 %).

Usual medicine:

- Asaflow 80 mg daily
- Zocor 40 mg daily
- Emconcor 10 mg daily
- Lysomucil 600 mg daily since a few days
- Aprovel 300 mg daily
- L- thyroxine 50 µg daily

STOPP

⇨ Bisoprolol and diabetes “too much "controlled thus probably associated with hypoglycaemias (Hb1Ac lower than 7 %).

β-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes i.e. ≥1 episode per month (*risk of masking hypoglycaemic symptoms*)

APPENDIX 3: SURVEY QUESTIONNAIRE: MEDICATION AND OLDER PATIENTS IN GENERAL PRACTICE

Adapted from "Parsons, C., et al., Assessment of factors that influence physician decision making regarding medication use in patients with dementia at the end of life. Int J Geriatr Psychiatry, 2013".

Within the framework of a research project on medicine in geriatrics, this survey will allow to illustrate your habits and the difficulties which you meet, as general practitioner, when prescribing to the elderly. Your consent to participate in this study will be implied by completion and return of this questionnaire; we do not require you to complete a consent form. We can assure you that all information gathered will be treated in the strictest confidence and will be used solely for research purposes. As the questionnaire is anonymous, it will not be possible for anyone to link you to the information given.

1. How many years have you been in medical practice? _____

2. Approximately what percentage of your patients are over 65 years of age? _____%

3. Do you work in a nursing home?
   Often$_{\text{(once or several times a week)}}$ ☐$_1$ Sometimes$_{\text{(once or several times a month)}}$ ☐$_2$
   Rarely$_{\text{(once or several times a year)}}$ ☐$_3$ Never ☐$_4$

4. On a scale from 1 (limited experience) to 10 (extremely experienced), please rate (by circling the appropriate number) how much professional experience you have caring for persons over 65 years (i.e. in your work as a GP).

1	2	3	4	5	6	7	8	9	10
Limited experience									Extremely experienced

5. **Please indicate the extent to which you agree or disagree with the following statement.**
   I have confidence in my ability to prescribe appropriate medications for the elderly.
   Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

6. **In the past three months, which of the following sources of information have you used regarding medication prescribing in the elderly?**

Physician colleagues:
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Local Pharmacists:
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Summary of Product Characteristics (Compendium / AFMPS):
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Information gained at Conferences/meetings:
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Software on handheld device:
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Online search:
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Textbook:
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Advertisements in professional journal:
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Information from Pharmaceutical representatives:
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

Educational Journal articles (print or online):
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$

7. **Please indicate how often you use the following resources to guide medication prescribing in your elderly patients.**

Beers Criteria for Potentially Inappropriate Medication Use in Older Patients
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$ I do not know these criteria ☐$_5$

STOPP and START criteria (Screening Tool of Older Patients Prescriptions and Screening Tool to Alert the doctor to the Right Treatment):
Often used ☐$_1$ Sometimes used ☐$_2$ Rarely used ☐$_3$ Never used ☐$_4$ I do not know these criteria ☐$_5$

8. **Please indicate the degree to which you agree that the following are BARRIERS to appropriate prescribing for your elderly patients.**

Lack of time in the office schedule:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Lack of acceptable therapeutic alternatives:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Potential drug interactions:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Cost to patient:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Patient request:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Lack of formal education on prescribing for the elderly:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Lack of access to a pharmacist:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Large number of medications a patient is taking:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Unwillingness to discontinue a medication prescribed by another Physician:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Difficulty communicating with other physicians who participate in a patient's care:
Strongly Agree ☐$_1$ Agree ☐$_2$ Neutral ☐$_3$ Disagree ☐$_4$ Strongly Disagree ☐$_5$

Others_____
_____
_____

9. **In your opinion, what initiative would make possible the greatest improvement in the use of medication by elderly people?**

_____
_____
_____

APPENDIX 4: SOURCES OF INFORMATION USED REGARDING MEDICATION PRESCRIBING IN THE ELDERLY IN THE PAST THREE MONTHS (% OF SURVEY ANSWERS)

Sources of information	Often used (1 to several times a week)	Sometimes used (1 to several times a month)	Rarely used (1 to several times a year)	Never used	Tool unknown
STOPP (Screening Tool of Older Patients Prescriptions) and START (Screening Tool to Alert the doctor to the Right Treatment) criteria	11,9	23,8	23	7,1	34,1
Beers Criteria for Potentially Inappropriate Medication Use in Older Patients	0,8	4,1	4,9	13,1	77
Summary of Product Characteristics	**50,8**	31,7	12,7	4,8	
Information gained at conferences/meetings	32	**50**	14,1	3,9	
Textbook	30,7	**43,3**	14,2	11,8	
Physician colleagues	16,7	**42,9**	28,6	11,9	
Educational journal articles (print or online)	13,4	**41,7**	33,1	11,8	
Information from pharmaceutical representatives	7,9	**37,8**	36,2	18,1	
Online search	24	**36,4**	19,4	20,2	
Local pharmacists	3,9	33,9	**39,4**	22,8	
Advertisements in professional journal	3,9	23,3	**38**	34,9	
Software on handheld device	18,9	13,4	15	**52,8**	

GENERAL DISCUSSION

Attention to medications is an everyday issue for clinicians who care for older patients. This research work began from my wish to use a tool as a hospital clinical pharmacist to easily screen the drug regimen of patients on the geriatric ward for inappropriate medications. From my clinical practice observations, several research questions emerged and we were given the opportunity to consider the use of the STOPP&START tool [1, 2]. Now it is time to come back to clinical practice with the key messages learned from the present research work.

There were several reasons why this work was important to be conducted. First, healthcare is facing a constantly ageing population. We know that these older patients are consuming large amounts of drugs and that inappropriate prescribing has become an important issue in this specific population. Second, pharmacists, general practitioners (GPs), and geriatricians should be equipped with reliable methods and efficient tools to assess the pharmacological treatments of older patients. Implicit (e.g. medication appropriateness index MAI [3]) and explicit (e.g. the Beers list [4-6]) tools are available but so far, they failed at being widely implemented [7]. The routine use of these tools would theoretically improve the appropriateness of drug treatments, but the difference between potential and actual inappropriateness was so far hardly assessed. Third, the relationship between potentially inappropriate medications according to explicit tools and the incidence of adverse drug reactions or adverse geriatric events is still controversial [7, 8]. Finally, at the beginning of our project, the interest for the STOPP&START tool was growing, for several reasons: recent publication, European origin, attractive structure, availability of a French adaptation. The tool was drawing the attention of clinical pharmacists, geriatricians and GPs. The implementation of the tool was not yet achieved but there was a demand to extend the knowledge about it. STOPP&START had a potential for being implemented at hospital (not only in the geriatric ward), in general practice, in community pharmacies, in addition to being used by clinical pharmacists.

The following pages summarize the principal findings of this work, discuss the validity of our results and the added value of this thesis on the body of current evidence. Finally, key messages for practice and perspectives for further work will be discussed.

1. PRINCIPAL FINDINGS OF THIS WORK

The use of the STOPP&START tool and the inappropriateness of prescribing in patients aged 75 years and more have been widely illustrated in this work, in a variety of studies and approaches. The research was divided in three relevant questions *("how much?", "how valid?", "how better?"*) to have a structured progress of the investigations and a comprehensive vision of the impact of STOPP&START in clinical practice. Important findings can be identified, answering our three research questions.

1.1 How much?

The first approach aimed at quantifying inappropriate prescribing when using STOPP&START in order to learn "*How much*" prescribing in elderly is inappropriate. Our observational studies looked at this aspect (**chapter I and III**). The level of inappropriateness of prescribing was assessed looking at the medications taken at home by older patients. Approximately forty to fifty percent of the patients had overuse or misuse of inappropriate medications according to STOPP, and sixty percent of the patients had underuse of drugs in their treatment according to START.

The drugs most frequently involved in overuse situations were benzodiazepines (8-34% of the potentially inappropriate prescribing events detected in our work according to STOPP). Rationale use of benzodiazepines is a national challenge. Ten percent of the population takes benzodiazepines on a regular basis and this rate rises up to 50% in nursing homes [9, 10]. Our data confirm the need to be more cautious when prescribing benzodiazepines and other psychotropic drugs in frail older patients prone to fall. Discontinuation of benzodiazepines, often in long-term users, is considered as difficult by the prescribers because of the patient resistance and the adverse drug withdrawal effects [11] but evidence shows it is feasible [12].

Inappropriate prescribing of cardiovascular drugs was another highly prevalent phenomenon in terms of both overuse and underuse. Inappropriate use of aspirin in primary cardiovascular prevention was frequently detected (17-37% of the STOPP events detected in our work). In other patients, however, underuse of recommended cardiovascular prevention medications (antiplatelet agents or statins) was present (38% of the START events). Our work confirms that the underuse of anticoagulants in older

patients with chronic atrial fibrillation is a major problem in terms of prevalence (half of these patients, 3-9% of all START events). We had the opportunity to further study this particular START criterion in **chapter II.** The potentially inappropriate omission of anticoagulation was seen in the context of the individual stroke and bleeding risks. Interestingly, the prescribing pattern of anticoagulants was neither related to the risk of stroke nor to the risk of severe bleeding. Our work shows that there is true potential for improvement in the prescribing of cardiovascular drugs and specifically for high clinical benefit in many older patients in atrial fibrillation.

Falls and polypharmacy were predictors of potentially inappropriate medications according to STOPP, while diabetes, atrial fibrillation and osteoporosis predicted potentially inappropriate omissions according to START. These main predictors of inappropriate prescribing are logically factors involved in the frequent inappropriate prescribing situations. Lack of osteoporosis prevention was indeed frequently encountered (14-22% of START events detected). One option to tackle polypharmacy would be to discontinue duplicated treatments (11% of STOPP events).

The higher prevalence of underuse than over/misuse is a remarkable result. Literature report several factors that might influence the prescriber's and the pharmacist's behaviour [13-16] and lead to underuse of appropriate medications. Firstly, factors increasing underprescribing can be patients-related. These include: polypharmacy (although not statistically related to START events in chapter I and III), poor compliance, limited life-expectancy, patient's refusal, economic problems, and multimorbidity. (However, the latter appeared as protective towards START in a sub-analysis of the BELFRAIL cohort.) Secondly, underprescribing can be triggered by environmental and organisational elements. Third, prescribers-related factors are described: fear for adverse events (as supposed in chapter II), low perceived benefit, lack of knowledge and scientific evidence (although START is presented as an evidence-based tool), disagreement with the recommendations (because of its content as observed in chapter III or because of lack of agreement with guidelines "in general" as observed in some general practitioners interviewed in chapter V), unclear responsibility (general practitioner thinking that prescribing of a certain drug is the responsibility of the specialist *vs*. the specialist believing that the management of chronic drugs is the responsibility of the general practitioner), fear of poor compliance, and, importantly, ageism. These aspects deserve to be further explored in future studies.

1.2 How valid?

The second approach aimed at evaluating some aspects of the validity of the STOPP&START tool. Validity refers to the degree to which the conclusions derived from the results of any assessment can legitimately be trusted [17]. So "*validity is a property of the inference, not the instrument*" [17]. This approach of validity answered a frequently reported question in the literature about the use of explicit tools for screening of inappropriate prescribing. Furthermore, the focus groups (**chapter V**) taught us also that the validity was a concern for prescribers.

Concurrent validity is the correlation of scores with those from other assessments [18]. We focused in this work on the STOPP&START tool, but other explicit tool are available, the most well-known and studied being the Beers list of criteria [4-6]. During this research, an update of the Beers list was published [19], so we took the opportunity to look at the concurrent validity of the STOPP tool and this new updated Beers list. The latter appeared to have an increased applicability in our country (**chapter III**). STOPP and Beers share similar criteria and show some overlap [20]. We wanted to know whether the patients flagged by both lists were similar and also if the detected medications were the same. Overlap was actually observed for overuse of aspirin, benzodiazepines and NSAIDS. We cannot determine at this stage if one of these two tools is to be preferred to the other one for daily clinical practice. The comparison of predictive validity of these screening tools in a prospective analysis would be the ultimate comparative approach to adopt in further work.

Another aspect of validity that we addressed was content validity (i.e. the relationship between a tool's content and the construct it intends to measure [18]) (**chapters III,IV,V)**. We aimed at answering the following question: *"Are the potentially inappropriate prescribing events actually inappropriate?"* We evaluated the clinical relevance (minor, moderate, major, or deleterious) of the STOPP&START criteria in the clinical context of the individual patients. The criteria aroused mixed feelings about their clinical relevance. The most frequent recommendations to discontinue drugs triggered by STOPP or to initiate START-listed drugs were considered as of moderate or major clinical importance. However, application of some criteria appeared as deleterious when considering the patient's global background. This issue could hamper the use of the STOPP&START tool and the confidence of the

potential users. As a consequence, clarifying or removing deleterious criteria should be considered in the future upcoming version of the STOPP&START list.

The validity of the strict application of the criteria without accounting for the patient background was particularly challenged by the analysis of the BELFRAIL cohort (**chapter III**). Indeed, we compared two methods for screening inappropriate medications: on the one hand, an application of the criteria on the basis of a pre-encoded database (including the pathologies mentioned in the tool), and on the other hand a screening taking into account the medical record of the patient with a holistic point of view. There was a noteworthy difference. Some potentially inappropriate prescribing detected with the database were actually appropriate when considering the patient comprehensive record. We suggest recommendations to improve the content validity of the criteria and to refine the applicability of the tool (e.g. precision of the range of application of the criteria in terms of age, life expectancy, disease severity level, contra-indications). The validity of the application of explicit screening tools on administrative database was doubted, as well as the detection of inappropriate medication in a computerized medical record that would lack the necessary sophistication to trigger relevant alerts. As an important proportion of studies using explicit criteria rely on large administrative databases, our results question their validity. This exercise highlighted the importance to take each patient globally into account when applying the STOPP&START tool in the future.

The qualitative study (**chapter V**) gave us a deeper understanding of the factors influencing the use of such tools in practice. GPs discussed the relevance of the STOPP&START regarding vignettes but also the applicability and operationalisability of the tool in their daily practice. Incentives (such as the allowance for a systematic approach for medication review) and disincentives to the use of STOPP&START (time-consuming application) were mentioned. Even though the tool was overall perceived as useful, views on comprehensiveness and relevance were mixed. These aspects are important to keep in mind and to be addressed in order to improve the implementation of a systematic medication review and optimisation strategies in daily clinical practice.

Predictive validity of a tool is a critical aspect. Good predictive validity (correlation of scores with outcomes [18]) of the STOPP&START tool was mentioned in the focus groups as a potential incentive to the implementation of the tool. The predictive validity of the STOPP&START tool on hospital admissions was raised in

chapter I. We assessed whether a potential link could be established between the reason for admission at hospital and the presence of potentially inappropriate prescribing events in the treatment at home. We determined that 27% of the patients admitted at the Cliniques universitaires Saint-Luc had an inappropriate prescribing event potentially related to the reason of admission. This result seems to us a good argument to try to improve the situation and to encourage the use of this tool in primary care. We could not assess the occurrence of adverse drug events in older patients in this work. This question should be the object of a future research project.

1.3 How better?

Finally, the third question "*how better?*" was the logical last step of our investigations. We tested the application of STOPP&START as potential improver of the appropriateness of prescribing in an intervention study. We designed a randomised controlled study in which we compared the systematic use of the STOPP criteria with usual care by the geriatric consultation team (**chapter IV**). We evaluated the impact on the appropriateness of treatment at discharge but also one year after hospital discharge. We observed that the systematic use of the STOPP criteria was successful in decreasing the inappropriate prescribing by 50% at discharge and that this effect persisted at one year. However, there was no difference in the number of patients being spared of potentially inappropriate medication exposure. This double observation reinforces our opinion that 1) that dissemination of knowledge on pharmacotherapy in older persons is essential and useful in non-geriatric ward, 2) that hospital admission is a good opportunity to review medications but that collaborating with GPs and empowering them remains essential in the pharmacological management of geriatric patients. GPs had the opportunity to give their views on the improvement potential of the tool on appropriateness of treatment in a qualitative study (**chapter V**).

2. ADDED VALUE

2.1 Comparison

Many previous studies described inappropriate prescribing (both overuse and underuse) in elderly at home, in nursing homes or in hospital. As mentioned before, several European research teams are using STOPP&START to detect inappropriate prescribing. From this perspective, our work was not quite original. Our data on the prevalence of inappropriate prescribing is consistent with other studies, using STOPP [21], START [22] or both [23]. However, our approach, combining quantitative data with (semi-) qualitative reflexions to answer to our three complementary research questions "*how much?, how valid? and how better?*", as well as our findings bring new relevant information to the previous body of knowledge, particularly on the validity of assessments of the tool. Furthermore, our work brings clear messages for Belgian clinicians on the main opportunities for improvement.

2.2 Strengths

Frail and very old persons

First, this work included a large sample of patients. Altogether, we thoroughly examined the pharmacological treatment of over 1000 patients, aged on average over 80 and frequently presenting frailty features. We are confident that the results of this work are quite representative of prescribing patterns in Belgian frail or very old patients. Precisely, we looked at two different types of older patients: frail admitted patients and primary care patients aged over 80 years, which were both appropriately selected samples. Frail older admitted patients were those in which we tested our intervention. These patients are also those encountered by many Belgian clinical pharmacists as older patients are the most popular target for the implementation of clinical pharmacy in Belgium [24]. Patients aged over 80 years are good target for the application of the tool in primary care because this population is growing and highly susceptible to adverse drug reactions and adverse geriatric events.

STOPP&START screen for inappropriate prescribing in patients aged over 65 years old. This population is broad, heterogeneous and continuously increasing. We

focused on those who would benefit the most from improvements in quality of prescribing.

Real-life setting

Even if the studies were initiated by a hospital team, we assessed the drug treatments used at the place of living (home or nursing home), which is the natural setting of the old persons. So we avoided the bias of analysing a temporary situation by addressing the hospital prescriptions. We looked at the most relevant situation for the patient: his/her place of daily living.

Comprehensive geriatric assessment

Another of our strengths was the availability of a comprehensive geriatric assessment of the patients included in the intervention study. We deeply believe that the application of the STOPP&START tool makes sense only if the user has a comprehensive knowledge of the patients' medical and therapeutic situation. The analysis conducted on the BELFRAIL cohort is the best evidence of this statement (see **chapter III**).

We deliberately embedded our implementation of the use of STOPP within the geriatric assessment of our inpatient geriatric liaison team for the following reasons: a systematic structured review of medication should be part of the global patient's assessment, the other components of the comprehensive geriatric assessment (medical, social and functional) enlighten the drug treatment review, the process of the comprehensive geriatric assessment is a good opportunity to implement the use of the tool.

Clinical importance

STOPP&START screens for "potentially" inappropriate prescribing. As in few previous studies, we challenged and explored this "potentially" status [25, 26]. A study by Steinmam compared the degree to which potentially inappropriate drugs according to Beers (2003 version [6]) criteria were also considered as inappropriate by a team of clinicians (pharmacist and physician). They observed that 61% of the potentially

inappropriate medications according to Beers were not considered as problematic by the expert team [25].

Similarly, we examined prescriptions flagged by STOPP&START to determine if they were actually inappropriate. A panel of experts discussed the clinical importance that the application of the STOPP&START criteria would have. These issues were also debated during focus groups. Important comments were: some criteria (especially those involving psychotropics) are considered as highly relevant; proper application of the tool requires detailed information on the patient; other criteria should be removed or better defined because their application could be deleterious. These comments should be taken into account for the application of the tool and for future researches. Again, the importance of a global assessment of the patient is highlighted. We think that a shorter list of criteria, focusing on the few criteria of major clinical importance could be suggested to clinicians, to ease the implementation of the tool and to optimize the pharmacological treatment in the elderly.

General practitioners' point of view

In many ways, the GP appears as the foremost potential user of STOPP&START. Primary care is probably the best setting for the use of the tool. Indeed, the GP knows the patient the best, thanks to a long relationship and global vision of the patient medical, social and functional status. His/her role as a coordinator of care is essential. It is known that GP would like to have decision support when dealing with multicomorbid older patients and several guidelines [27, 28]. Therefore, we estimated that the point of view of the GPs on the use of tools such as STOPP&START in daily practice was essential to explore within this thesis. This qualitative approach was innovative and brings new light on the previously published quantitative data on STOPP&START or other explicit tools. New explicit tools or adaptation of pre-existing tools are developed and published frequently but qualitative analysis on their use is seldom. For the first time, our study gave the floor to GPs on their vision of the use of STOPP&START.

2.3 Limitations and validity of our work

Some limitations of this research work need to be addressed, although we believe they do not discredit our results.

The findings of the focus groups, as for any qualitative work, are barely generalizable to another context. However, the answers to the survey, which was based on a large sample, corroborated our results. Our study confirmed other qualitative findings on prescribing in elderly and in primary care [27, 29-31]. The internal validity of the qualitative approach is lent by the triangulation of methods (focus groups and semi-qualitative analysis of a survey), the inclusion of GPs with different experiences in the focus groups, the inductive approach and the coding by two researchers [32]. The use of vignettes helped the participants express their point of view on the use of such a tool. The option to combine quantitative and qualitative work was a good approach to provide innovative insights to the pre-established quantitative knowledge on prevalence of inappropriate prescribing and to generate new hypotheses and research questions for investigation [33].

One could also wonder about the generalizability of the interventional study. The tool was integrated to the geriatric assessment of frail older inpatients compared to usual care. This intervention was monocentric, small-sampled and embedded in the work of the inpatient geriatric consultation team of an academic Belgian hospital. Geriatric consultation teams do not work nor perform equally across hospitals [34]. A multi-centric design could have helped improve the generalizability of the results. However, our results are in line with the single other published controlled trial on STOPP&START [35]. The intervention was purposively designed to test the implementation in a simple, practical and defined way, to insure its generalizability.

The screening and intervention was performed by the geriatrician of the internal geriatric consultation team. Involvement of a clinical pharmacist, embedding the use of STOPP&START to pharmaceutical care, would also have been interesting to assess. Previous studies showed a positive impact of clinical pharmacists liaising with geriatric evaluation and management teams [36]. The effect of the intervention might have been greater if involving pharmaceutical care.

Another limit in the intervention study was that we only focused on the STOPP tool. This was decided to simplify the intervention and separate the study of overuse from underuse. We showed that underuse, addressed by START, is yet an important problem. Further studies should evaluate the implementation of START as well. Some important outcomes potentially related to the improvement of prescribing, and highly relevant to justify the use of the tool, were not measured at this stage because this was out of the scope of the present research work, but should be the object of another research project: clinical outcomes, falls incidence, quality of life, adverse drug events and cost-effectiveness of the intervention using STOPP&START.

Finally, we tested the implementation of the tool in the hospital setting, but another intervention study in primary care would have been complementary. However, conscious that hospital admission is only a transitory stage in the life of the patient, we added a follow-up at home, which extended the scope of our intervention with a relevant secondary outcome.

Over-the-counter medications could have been underestimated in all our studies. Contact with the community pharmacies to ask for consumption of over-the-counter drugs could prevent that bias.

2.4 Next steps: research perspectives

Each of the conducted studies of this work provides some answers, but also generates new hypotheses and new questions. The table 1 proposes topics for future research agenda based on each chapter of this thesis.

TABLE 1. Research agenda

Chapter	Topics	Research agenda
I. Inappropriate prescribing at home in older inpatients	*How better?*	• prospective cohort study with assessment of adverse drug events leading to hospital admission, in order to have a better understanding of the predictive validity of the tool and each of its criteria. • establishment of the relationship between the use of inappropriate prescribing and adverse drug events using a validated causality scale. • evaluation of the influence of comorbidities burden (e.g. according to the Charlson Comorbidity Index [37] or the Cumulative Illness Rating Scale [38]) and frailty (e.g. according to the Frailty index) on the risk of hospital admission related to inappropriate prescribing. • measure of the impact of fall-related fractures on length of stay, institutionalisation, morbidity and mortality • qualitative approach to understand reasons underlying the higher prevalence of underuse
II. Underuse of anticoagulation	*How much?*	• in the older patients with atrial fibrillation receiving both anticoagulants and antiplatelet therapies, evaluation of the rationale of dual therapy, regarding the history of last ischemic event* • assessment of potential evolution of underuse pattern since the marketing of new oral anticoagulants*
	How better?	• establishment of a practical formula to balance the stroke and bleeding risks and benefits in older patients • qualitative approach to understand reasons underlying underuse
III. Inappropriate prescribing in primary care	*How much?*	• assessment of the relationship with functional status and comorbidity burden on the prevalence of inappropriate prescribing*
	How valid?	• longitudinal analysis of the BELFRAIL cohort to assess the impact of inappropriate prescribing on death, morbidity, hospital admissions, costs.* • comparison of the tools regarding hard outcomes in case of inappropriate prescribing • analysis of the clinical importance of the criteria on a larger sample of patients, to distinguish potential from actual inappropriate prescribing. • refinement of the criteria and re-evaluation; validation of a short list of STOPP&START criteria based on frequency, relevance, predictive validity and cost-effectiveness.

Chapter	Topics	Research agenda
	How better?	• evaluation of the potency of STOPP and Beers to diminish the anticholinergic burden*
IV. Intervention with STOPP	*How valid?*	• evaluation of the intervention on the readmissions, institutionalisations, death. • comparison of the clinical importance assessment of this study and the BELFRAIL study
	How better?	• intervention using START in addition to STOPP • involvement of a clinical pharmacist performing the screening with STOPP&START as part of pharmaceutical care • multicentre intervention on the screening with STOPP&START with evaluation of outcomes such as length of stay, and adverse drug events.
V. View of general practitioners	*How valid?*	• exploration of barriers related to the general practitioner workload in the implementation of STOPP&START • assessment of feasibility of the screening of medications with STOPP&START by other healthcare professionals • qualitative approach to assess the patient's point of view on systematic medication review • qualitative approach to compare the STOPP&START criteria with the patient individuals health goals.
	How better?	• intervention with medication review in nursing homes, using STOPP&START as a tool.* • intervention involving a clinical pharmacist to improve communication at hospital discharge regarding the STOPP&START recommendations

* A study involving our research team (CLIP, LDRI, UCL) is already planned on this topic

3. PERSPECTIVES

3.1 Perspectives on STOPP&START and its use

STOPP detects potentially inappropriate medications. But what's next? Unfortunately, the tool does not explain how to discontinue inappropriate drugs. Much of the effort has been made on the prescribing process. However, discontinuation of the drugs is another challenge, also important to consider in order to improve appropriateness of the drug regimen [11, 39]. Factors influencing the general practitioners

deprescribing include: the preventive objective of the drug (considered as particularly difficult to discontinue in very old patients), beliefs concerning the patient (e.g. patient conservatism), guidelines for treatment (seen as an obligation to prescribe something) and organisation of healthcare [27]. Even if stopping drugs is sometimes difficult and time-consuming, evidence shows that drug discontinuation is needed, beneficial and feasible in older patients [39]. To help the clinician, tools addressing discontinuation of drugs with a systematic approach were developed [39-41] and tested. For example, a tool suggesting the discontinuation of multiple medications was successful in community dwelling adults in decreasing polypharmacy, without significant adverse events related to the discontinuation [41]. A qualitative study in mostly older patients showed that the latter were accepting trials of cessation of medications if their physician considered the drug as no more necessary [42]. Withdrawal plan, alternatives, monitoring tips would be appreciated in a future version of the STOPP list.

Regarding the initiation of drugs recommended according to the START list, again, some important information for the management of the recommendation is lacking. The START tool targets patients aged over 65, but obviously the importance of a recommendation to initiate a new drug differs if it concerns a frail patient or a "successfully aging" one. Time to benefit information could help improve the applicability of the START list [43]. Initial dosage and adaptations information could be useful.

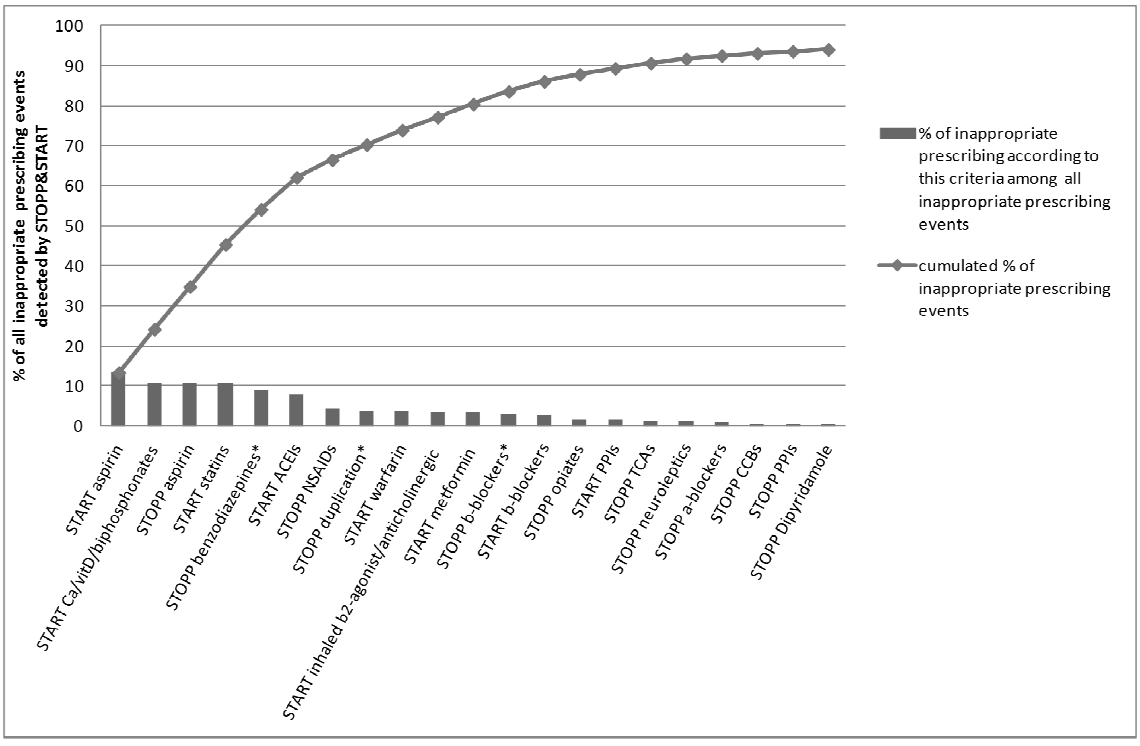
As every other explicit tool, STOPP&START it is fixed and requires regular updates.

STOPP&START is helping healthcare professionals detect potentially inappropriate prescribing in older patients. The combination of the detection of overuse/misuse with STOPP and underuse with START allows a systematic and complementary analysis of the appropriateness of the drug regimen. STOPP and START should be used together in clinical practice. Our work illustrated that STOPP&START is efficient at detecting inappropriate prescribing, offering targets for improvement of prescribing, but importantly that the elements detected are only "potentially" inappropriate. This confirms that explicit tools should enhance but not replace good and global clinical judgment [44, 45]. Actually, at the conclusion of this work, we would recommend to always combine the explicit application of STOPP&START with an implicit judgement, which appears definitively essential to go

beyond the screening for potentially inappropriate medication towards the detection of actual prescribing problems. Combined tools might be worth being further studied.

Some STOPP&START criteria are hardly encountered in clinical practice. Across studies from this work and the literature, some criteria clearly appear as more prevalent. Targeting the few most prevalent drugs has the potential of eliminating the majority of the inappropriate prescribing events in the population of older patients. Figure 2 illustrates that phenomena on the basis of the weighted average of the potentially inappropriate prescribing events detected in the studies of this work, which were conducted in very old and/or frail patients. The most frequent criteria detected in this Belgian population present similarities to those detected in a multicentre international study [46].

FIGURE 1: Pareto graph presenting the most frequent potentially inappropriate prescribing events according to STOPP&START (cumulated percentage of the most frequent drugs detected by STOPP&START).



Abbreviations: ACEIs angiotensin-converting enzyme inhibitors; Ca Calcium; CCBs calcium channel blockers; NSAIDS non steroidal anti-inflammatory drugs; PPIs proton pump inhibitor; TCAs tricyclic antidepressants.

* Percentages are calculated and weighted on the basis of the results of chapter I and III. Additional correction were performed for benzodiazepines (underestimated in chapter III), duplications (not measured in chapter I) and b-blockers (not measured in chapter III).

BOX 1: STOPP&START criteria frequently rated as of major clinical importance based on the results of the present work (chapters III and IV).

STOPP

- Use of diltiazem or verapamil with NYHA class III or IV heart failure
- Use of aspirin and warfarin in combination
- Long-term (i.e. > 1 month), long-acting benzodiazepines
- Selective serotonin re-uptake inhibitors (SSRIs) with a history of clinically significant hyponatremia
- Neuroleptic drugs in fallers
- Duplicate drug classes

START

- Warfarin in the presence of chronic atrial fibrillation
- Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease
- Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease
- Angiotensin converting enzyme (ACE) inhibitor with chronic heart failure
- ACE inhibitor following acute myocardial infarction
- Calcium and vitaminD supplement in patients with known osteoporosis

As just a few criteria cover the majority of events, one could be tempted to apply a short version of STOPP&START, restricted to those most frequently encountered. However, the selection of criteria in such a short list should take account of other considerations including: 1) their predictive validity regarding adverse events, 2) their clinical relevance, and 3) pharmaco-economic aspects. The predictive validity of each individual STOPP&START criterion is not yet described. From our work and other studies published [21, 35], it can be argued that the criteria relative to drugs increasing the risk for fall (benzodiazepines, neuroleptics) or preventing fracture, are likely to have a good predictive validity for adverse events (falls and hospital admissions). The clinical relevance of the modification of treatment in case of detection of inappropriate prescribing varied from patients due to their individual context. However, some criteria, mostly from the cardiovascular and neurologic system, were often rated as of major importance during this work (chapter III and IV; see Box 1). These criteria should be considered in the short list. Selection of criteria on the basis of pharmaco-economic

aspects require a comprehensive analysis taking into account direct expenditures and indirect costs related to inappropriate prescribing (adverse drug events management, hospital admissions, utilisation of health care services,...).

Table 1 suggests a short STOPP&START list, taking into account the criteria's prevalence, predictive validity (according to chapter I and Gallagher et al. [21]) and relevance (according to the experts in chapters III and IV). Pharmaco-economic aspects are not included in this short list.

TABLE 1: Proposition of drugs to include in a short version of STOPP&START.

		Top 10 of most frequent inappropriate prescribing[a]	Good predictive validity[b]	Major relevance[c]
	START			
1	ACEIs	*		*
2	aspirin	*		
3	statins	*		*
4	warfarin	*	*	*
5	Ca/vitD/ biphosphonates	*	*	*
6	inhaled b2-agonist/ anticholinergic	*		
	STOPP			
7	benzodiazepines	*	*	*
8	aspirin	*		*
9	CCBs			*
10	duplication	*		*
11	NSAIDs	*		
12	neuroleptics		*	
13	SSRIs			*

Abbreviations: ACEIs angiotensin-converting enzyme inhibitors; Ca Calcium; CCBs calcium channel blockers; NSAIDS non steroidal anti-inflammatory drugs; PPIs proton pump inhibitor; SSRI selective serotonin reuptake inhibitor; TCAs tricyclic antidepressants.

a. most frequent criteria detected in chapters I and III; b. according to chapter I and Gallagher et al. [21]; c. according to the experts in chapters III and IV.

3.2 Impact of this work…

for healthcare policy makers

Regular medication review in older people is a healthcare priority in the context of the aging population and the costs related to drugs. The use of the STOPP&START tool has an important potential for improving appropriateness of treatments in older patients. Healthcare policy makers should encourage the implementation of screening tools for potentially inappropriate prescribing in primary care. Incentives should be provided to help the implementation of the tool: the specific reimbursement of one medical consultation a year devoted to medication review, implementation of the criteria in accredited computerized clinical decision support system (CDSSs), creation of a framework for collaborative medication review with GPs and pharmacists, fees for community pharmacists performing medication reviews for the local nursing home.

Education on appropriate prescribing in older people should also be promoted. Little curricular time is currently devoted to geriatric pharmacology and pharmacotherapy [47]. STOPP&START has an educational role that should be exploited.

Our results show that there is room for improvement in the appropriateness of drug treatment in older patients admitted to the hospital. The involvement within the internal geriatric consultation team of a clinical pharmacist, who has 1) specific knowledge on geriatric pharmacotherapy, 2) skills in multidisciplinary team work and education, and 3) global quality and safety focus, would be an option to improve the quality of drug therapy in older inpatients, both within the hospital and their (nursing) home, and should be advocated.

for general practitioners

At the conclusion of this work, we have clear practical messages for GPs, summarized in box 2.

A **consultation** could be annually dedicated to medication review in the general practice. This consultation could be the opportunity to apply the STOPP&START tool and to rethink the drug treatment of the patient. Some time within this consultation

should be devoted to discussion with the patient about treatment modifications and the reasons that underlie these changes.

BOX 2: Key learning from this thesis for general practitioners

- Potentially inappropriate prescribing at home is **highly prevalent**
- As **key-players** in the care of older patients, GPs have a potential to improve the situation.
- Inappropriate **underuse** is even more prevalent than overuse, although older patients are thought to be already taking too many medications.
- STOPP&START is an easy, rapid, educative tool to help the prescriber detect potentially inappropriate events. It could be **implemented in clinical practice on a regular basis** to review the drug regimen of the patients.
- Five actions would prevent > 60% of the encountered potentially inappropriate prescribing events according to both STOPP and START:
    1. To avoid long term use of **benzodiazepines**
    2. To discontinue **duplication** of drug treatments
    3. To prescribe a rational **cardiovascular prevention** (aspirin and statins) (to be used in secondary prevention, but avoided in primary prevention unless diabetes with cardiovascular risk factors)
    4. To consider **osteoporosis** prevention with calcium-vitamin D supplementation
    5. To initiate anticoagulation in **atrial fibrillation**
- When applying the STOPP&START tool, the patient situation should be taken **globally** into account in order to detect relevant inappropriate prescribing events. The treatment review should be part of the global assessment of the patient.
- The role of STOPP&START is restricted to his "tool" aspects. STOPP&START does not replace good **clinical judgement**.
- **Education** in geriatric pharmacotherapy should be encouraged in continuous education programs to complement the use of the STOPP&START tool in practice.

When asking GPs about their views on the use of STOPP&START in the qualitative study, nursing homes appeared as a key setting for the implementation of the

tool. We believe indeed that the organisation of medication reviews in nursing homes, in multidisciplinary case discussions including a pharmacist, would be relevant and effective in optimizing pharmacotherapy in these older persons and should be the object of further studies. A Belgian project of multidisciplinary case conferences in nursing homes just began in 2013. STOPP&START is tipped to be used to detect inappropriate medications to target for improvement.

for clinical pharmacists

Medication review and screening for inappropriate prescribing is part of the pharmaceutical care activity [48]. The involvement of pharmacists in medication review is successful at diminishing inappropriate medications, in hospital [36], but also in the ambulatory setting [49] and in nursing homes [50]. It is then logical that pharmacists are involved in the implementation of tools such as STOPP&START to review the treatment of their patients.

The adoption of a screening tool as a help for the medication review in pharmaceutical care should be encouraged. The five actions mentioned before could be the object of specific clinical pharmacy interventions for improvement. Our findings confirm that the clinical pharmacist needs to access to this comprehensive information about the patient in order to address appropriateness of treatment [51, 52].

Clinical pharmacists could prioritize their intervention to the patients which appeared in our work as being more at risk of inappropriate prescribing, namely patients presenting with history of falls, osteoporosis, atrial fibrillation, diabetes, ischemic disease, chronic obstructive pulmonary disease , and of course polypharmacy. Another option could be to target older patients globally more at risk of adverse drug events. The GerontoNet Adverse Drug Reaction Risk Score detects these patients and could be used by clinical pharmacists [53].

But the pharmacists should not use the tool in isolation. The pharmacist plays an important role of education on pharmacotherapy for the other members of the healthcare team. In that, the pharmacist can actively participate in the diffusion of STOPP&START. Once the revision of treatments with STOPP&START by the other healthcare professionals is implemented, the pharmacist saves time for an implicit

revision of the treatment and the management of complex pharmacotherapeutic problems that are not addressed by the tool.

A collaboration framework with specialists [27, 28] is expected by the GPs. The importance of a good collaboration between the hospital and the GP was pointed out in the results of our randomized controlled study and in our qualitative study. Although our collaboration with GPs in the randomized controlled study could have been more proactive (e.g. through phone contact before discharge) we aim at increasing it in the future, e.g. through the involvement of the hospital pharmacist.

for clinical pharmacy researchers

Important elements for clinical pharmacy research were taught by this work on STOPP&START. Assessment of appropriateness of treatment on the basis of the full record of the patient (including detailed medical data, social and functional status) should be preferred to retrospective analysis of databases for the sake of results validity. The results of previous studies on inappropriateness of prescribing conducted on administrative data should be challenged.

This work opens areas for future researches where the pharmacists could have a leading role. One could evaluate the impact of a clinical pharmacist, joining the internal geriatric consultation team and performing, not only the screening for inappropriate prescribing but this screening integrated in a pharmaceutical care approach. Previous studies showed the beneficial effect of clinical pharmacists in geriatrics [36, 54]. However, involvement of a pharmacist in a mobile geriatric team has not been evaluated yet in terms of quality of drug treatment and cost-effectiveness of the activity. Collaboration between hospital and primary care and the role of the pharmacist as coordinator of the pharmacotherapeutic plan for the patient at hospital discharge should be explored. Would specific information relative to STOPP&START, given by the pharmacist at discharge, improve the long-term appropriateness of prescribing and prevent adverse outcomes?

Finally, collaborative approaches in primary care are promising and should be studied. An underpowered study on pharmaceutical care in primary care suggests a trend for decrease of medication-related hospital admissions [55]. The intervention should include key elements for successful medication review collaboration between

GPs and pharmacists (e.g. sharing of medical record, case conference between GP and pharmacist, action plan, follow-up and patient interview by the pharmacist) [56]. In nursing homes, evidence suggests that pharmaceutical care diminishes the use of inappropriate psychoactive medications [50] and that clinical pharmacist interventions have high uptake when discussed with both the medical and nursing staff [57, 58].

3.3 Are computerized clinical decision support systems the future of STOPP&START?

The integration of STOPP&START in a computerized clinical decision support system (CDSS) was repeatedly suggested by GPs during this work as a way to widely implement this tool. We would like to examine and discuss that option. Several CDSS interventions have the potential to decrease inappropriate prescribing in elderly [59, 60]. But the effect on appropriateness varies from design and setting [59-61] and the impact on clinical outcomes are mixed [59, 62, 63]. Although prescribers report being satisfied with CDSS, the overriding of alerts persists [60, 64] and questions the effectiveness of the intervention. Inaccurate and insignificant alerts are barriers [60, 65]. To diminish the risk of alert fatigue, we suggest to implement the most relevant STOPP&START criteria in a potential CDSS.

Our work showed that the systematic use of STOPP decreases inappropriate prescribing but that the relevance of the tool varies according to the patient context. Therefore, to insure relevance of computer-generated alerts based on STOPP&START, the medical history of the patient must be encoded in a standardized and highly detailed manner. The coding of sufficient nuance in the computerized medical record seems barely feasible. However, a promising Belgian project called "Soins aux Aînés Fragiles: Adaptation à la Réalité Individuelle par une Évaluation Structurée" (SAFARIES) embed medication review in a computerized tool to perform a comprehensive geriatric assessment (www.safaries.be).

The educational role of a computer-based reminder regarding the use of sedative-hypnotics was reported by physicians in a hospital [66]. However, there is a risk of too heavy reliance on such systems for professionals who use them. Informatics technology improves the security at several levels of care, but healthcare professionals have to remain critical in order to avoid new types of errors [67].

A European project (SENATOR) is now in preparation to develop and assess a "software engine capable of individually screening the clinical status and (non-) pharmacological therapy of older people with multimorbidity in order to define optimal drug therapy, highlight ADR risk, indicate best value drug brand for selection and provide advice on appropriate non-pharmacological therapy" (http://www.ucc.ie/en/charge-ucc/senator/). This large scale study and other future studies will certainly bring valuable data on the potential role of Information Technology in improvement of prescribing.

3.4 Patients' involvement

Balanced prescribing should include communication with the patient [68]. More and more, the patients are considered as partners in decision-making [69]. For time reasons patient involvement was not assessed in this work. We applied STOPP&START without taking into account the patient's preference. Actually, guidelines rarely incorporate the patient preference [70]. Yet, the involvement of patient in drug decision-making was recommended before and mentioned in our focus groups. Do older patients want to be involved in decision-making? Older patients have mixed feelings about it, but information sharing would be appreciated [71]. The views of the patients on medication reviews and more specifically on STOPP&START criteria could be the object of future research. Patients having inappropriate prescribing according to STOPP&START could be involved in prioritizing treatment modifications to be made. Recently, goal-oriented care has been suggested as an approach to ensure patient-centeredness [72]. Instead of focusing on traditional outcomes (survival, biomarkers, disease-specific symptoms), this new paradigm promotes the patient's own health goals (i.e. symptoms, functional status, social and role function). The concordance between the patient's personal health objectives and the recommendations by STOPP&START should be assessed.

4. CONCLUSION: SHOULD WE STOPP&START?

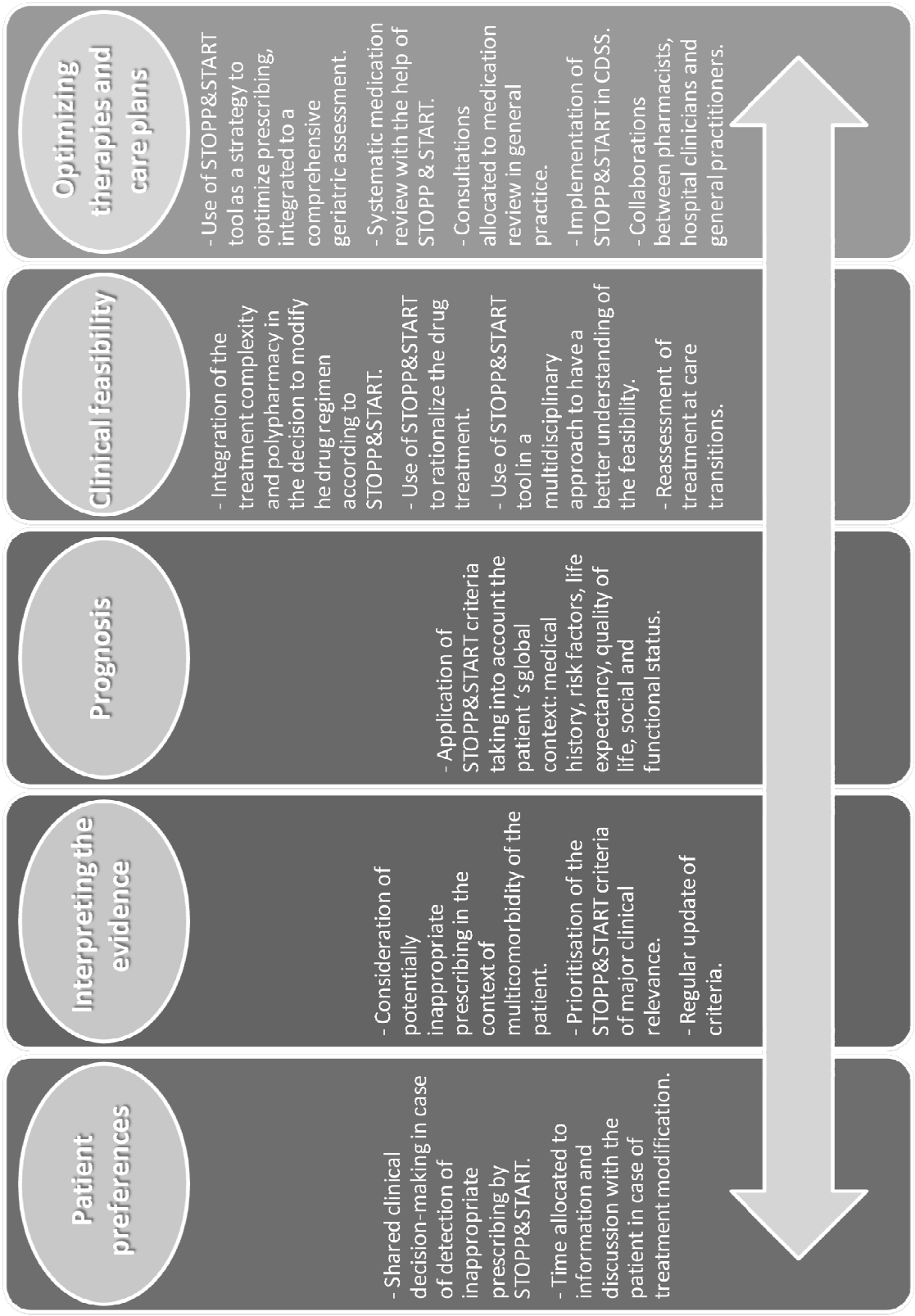
The progressive implementation of an explicit screening and "think-promoting" tool such as STOPP&START is promising. It is clearly rooted in an approach to improve the global management of older patients. However, the single application of the tool would not be recommended as the validity of its assessments is still questionable. We would rather envisage the implementation of the tool as part of a multidimensional effort to improve appropriateness of prescribing, including a collaborative multidisciplinary approach, some educational aspects, and the use of the tool within the global assessment of the patient. A recent Italian study focused on physicians with a multifactorial intervention to reduce inappropriate prescribing [73]. They combined three elements: dissemination of a list of potentially inappropriate medications along with a list of alternatives, annual reviews of potentially inappropriate medications prevalence, and educational sessions. This tridimensional approach was successful at decreasing the incidence rates of inappropriate prescribing.

In 2012, the American Geriatrics Society (AGS) published an approach guided by five principles for a patient-centered care of older adults with multiple conditions [74, 75]. Our findings and recommendations for the future use of STOPP&START are in line with these principles (see Figure 2). One of the five principles is to elicit and incorporate the **patient's preferences** into medical decision making. The objectives of the drug regimen should be in line with the patient's individual health goals [72]. This should be encouraged when applying STOPP&START, as mentioned before. Another step is to **interpret the evidence**, recognizing its limitations and applying it to the older patients with multimorbidity. Our works showed how much the patient global context might influence the application of yet evidence based recommendations. Most of the common clinical practice guidelines do not address the applicability to older patients presenting multicomorbidities [76, 77]. Future trials should use multimorbidity as an inclusion factor instead of as an exclusion factor. This approach also suggests to frame the clinical management decisions into the context and **prognosis** of the patient, which is again in line with the conclusions of our work. A fourth principle according to the AGS is to consider treatment complexity and **feasibility**. Indeed, we encountered cases of polymedication in which adding a new drug would have been deleterious (e.g.: the addition of aspirin to a patient under anticoagulation therapy). The use of STOPP&START in a multidisciplinary approach would allow to have a better

understanding of the feasibility of treatment modifications. The last principle is the **optimizing of therapies** and care plans. This step is directly related to the detection of inappropriate prescribing, and the application of algorithmic tools, or indices, such as STOPP&START. They mentioned that partnering with pharmacists and other clinicians could help reach that objective of optimization.

We believe, as others, that no perfect tool will ever be published [78]. The question is not to have a fully relevant and comprehensive list of criteria. What matters most is to implement a philosophy of medication review and reassessment of long-term used drugs. Attention of the prescriber should be drawn on the efficacy and security of the pharmacological treatments, the costs and the patients' preferences. STOPP&START is a good candidate to help implementing that philosophy in practice. When asking "What's the biggest advantage of the STOPP&START tool?", some of the physicians participating in the focus groups interestingly answered "It does exist".

FIGURE 2: Recommendations on the use of STOPP&START tool and concordance with guiding principles for the care of older adults with multimorbidity according to the American Geriatrics Society [74, 75].



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APPENDICES

APPENDIX 1: STOPP (SCREENING TOOL OF OLDER PERSON'S PRESCRIPTIONS) AND START (SCREENING TOOL TO ALERT DOCTORS TO RIGHT TREATMENT)

Gallagher, P., et al., STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther, 2008. 46(2): p. 72-83.

TABLE 1. STOPP: Screening Tool of Older People's potentially inappropriate Prescription

STOPP: Screening Tool of Older People's potentially inappropriate Prescription.
The following drug prescriptions are potentially inappropriate in persons aged ≥ 65 years of age.

A. Cardiovascular system

1. **Digoxin at a long-term dose > 125 µg/day with impaired renal function*** (increased risk of toxicity) [Cusack et al. 1979, Gooselink et al. 1997, Haas and Young 1999].
2. **Loop diuretic for dependent ankle edema only i.e. no clinical signs of heart failure** (no evidence of efficacy,compression hosiery usually more appropriate) [Alguire and Mathes 1997, Kolbachetal.2004].
3. **Loop diuretic as first-line monotherapy for hypertension** (safer, more effective alternatives available) [Williams et al. 2004].
4. **Thiazide diuretic with a history of gout** (may exacerbate gout) [Gurwtiz et al. 1997].
5. **Non-cardioselective beta-blocker with Chronic Obstructive Pulmonary Disease** (COPD) (risk of in-creased bronchospasm) [van der Woude et al. 2005, Salpeter et al. 2005].
6. **Beta-blocker in combination with verapamil** (risk of symptomatic heart block) [BNF 2006].
7. **Use of diltiazem or verapamil with NYHA class III or IV heart failure** (may worsen heart failure) [BNF 2006].
8. **Calcium channel blockers with chronic constipation** (may exacerbate constipation) [Dougall and McLay 1996].
9. U**se of aspirin and warfarin in combination without histamine H2-receptor antagonist** (except cimetidine because of interaction with warfarin) **or proton pump inhibitor** (high risk of gastrointestinal bleeding) [Garcia Rodriguez et al. 2001, Holbrook et al. 2005].
10. **Dipyridamole as monotherapy for cardiovascular secondary prevention** (no evidence for efficacy) [De Schryver et al. 2006].
11. **Aspirin with a past history of peptic ulcer disease without histamine H2-receptor antagonist or proton pump inhibitor** (risk of bleeding) [Garcia Rodriguez et al. 2001].
12. **Aspirin at dose > 150 mg/day** (increased bleeding risk, no evidence for increased efficacy)[Fisher and Knappertz 2006].
13. **Aspirin with no history of coronary, cerebral or peripheral vascular symptoms or occlusive**

STOPP: Screening Tool of Older People's potentially inappropriate Prescription.
The following drug prescriptions are potentially inappropriate in persons aged ≥ 65 years of age.

event (not indicated).

14. **Aspirin to treat dizziness not clearly attributable to cerebrovascular disease** (not indicated).
15. **Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration** (no proven added benefit) [Pinede et al. 2001].
16. **Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration** (no proven benefit) [Pinede et al. 2001].
17. **Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder** (high risk of bleeding) [BNF 2006].

B. Central nervous system and psychotropic drugs

1. **Tricyclic antidepressants (TCAs) with dementia** (risk of worsening cognitive impairment) [Smith 1998, Sommer et al. 2003].
2. **TCAs with glaucoma** (likely to exacerbate glaucoma) [Smith 1998, Sommer et al. 2003].
3. **TCAs with cardiac conductive abnormalities** (pro-arrhythmic effects) [Smith 1998, Sommer et al. 2003].
4. **TCAs with constipation** (likely to worsen constipation) [Smith 1998, Sommer et al. 2003].
5. **TCAs with an opiate or calcium channel blocker** (risk of severe constipation) [Smith 1998, Sommer et al. 2003].
6. **TCA's with prostatism or prior history of urinary retention** (risk of urinary retention) [Smith 1998, Sommer et al. 2003].
7. **Long-term (i.e. > 1 month), long-acting benzodiazepines**, e.g. chlordiazepoxide, fluazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites, e.g. diazepam (risk of pro-longed sedation, confusion, impaired balance, falls) [Gray et al. 2006, Hanlon et al. 1998, Tamblyn et al. 2005].
8. **Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics** (risk of confusion, hypotension, extra-pyramidal side effects, falls) [Alexopoulos et al. 2004, Maixner et al. 1999].
9. **Long-term neuroleptics (> 1 month) in those with parkinsonism** (likely to worsen extrapyramidal symp-toms) [Smith 1998, van de Vijver et al. 2002].
10. **Phenothiazines in patients with epilepsy** (may lower seizure threshold) [Alexopoulos et al. 2004, BNF 2006].
11. **Anticholinergics to treat extrapyramidal side effects of neuroleptic medications** (risk of anticholinergic toxicity) [Mintzer and Burns 2000, Tune 2001].
12. **Selective serotonin re-uptake inhibitors (SSRIs) with a history of clinically significant hyponatremia** (non-iatrogenic hyponatremia <130mmol/l within the previous 2 months) [Jacob and Spinler 2006].
13. **Prolonged use (> 1 week) of first-generation antihistamines**, i.e. diphenhydramine, chlorpheniramine, cyclizine, promethazine (risk of sedation and anti-cholinergic side effects) [Sutter et al. 2003].

C. Gastrointestinal system

1. **Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhea of unknown**

STOPP: Screening Tool of Older People's potentially inappropriate Prescription.
The following drug prescriptions are potentially inappropriate in persons aged ≥ 65 years of age.

cause (risk of delayed diagnosis, may exacerbate constipation with overflow diarrhea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognized gastroenteritis) [Lustmanet al. 1987, Thielman and Guerrant 2004].

2. **Diphenoxylate, loperamide or codeine phosphate for treatment of severe infective gastroenteritis**, i.e. bloody diarrhea, high fever or severe systemic toxicity (risk of exacerbation or protraction of infection) [Thielman and Guerrant 2004].
3. **Prochlorperazine or metoclopramide with parkinsonism** (risk of exacerbating parkinsonism) [Smith 1998].
4. **PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks** (dose reduction or earlier discontinuation indicated) [BNF 2006, NICE guideline 2000/022].
5. **Anticholinergic antispasmodic drugs with chronic constipation** (risk of exacerbation of constipation) [Bosshard et al. 2004].

D. Respiratory system

1. **Theophylline as monotherapy for COPD** (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index) [Ramsdell 1995].
2. **Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-to-severe COPD** (unnecessary exposure to long-term side effects of systemic steroids) [Buistetal.2006, McEvoy and Niewoehner 1997].
3. **Nebulized ipratropium with glaucoma** (may exacerbate glaucoma) [BNF 2006].

E. Musculoskeletal system

1. **Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H2 -receptor antagonist, PPI or misoprostol** (risk of peptic ulcer relapse) [Hooper et al. 2004].
2. **NSAID with moderate-to-severe hypertension** (risk of exacerbation of hypertension) [Whelton2006].
3. **NSAID with heart failure** (risk of exacerbation of heart failure) [Slørdal and Spigest 2006].
4. **Long-term use of NSAID (> 3 months) for symptom relief of mild osteoarthritis** (simple analgesics pref-erable and usually as effective for pain relief) [Altman et al. 2000].
5. **Warfarin and NSAID together** (risk of gastrointestinal bleeding) [Battistella et al. 2005].
6. **NSAID with chronic renal failure*** (risk of deterioration in renal function) [Cheng and Harris 2005].
7. **Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthrtitis or osterarthritis** (risk of major systemic corticosteroid side-effects) [Altman et al. 2000, Kwoh et al. 2002, Lee and Weinblatt 2001].
8. **Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to allopurinol** (allopurinol first-choice prophylactic drug in gout) [Schlesinger 2004, Terkeltaub 2004].

F. Urogenital system

STOPP: Screening Tool of Older People's potentially inappropriate Prescription.
The following drug prescriptions are potentially inappropriate in persons aged ≥ 65 years of age.

1. **Bladder antimuscarinic drugs with dementia** (risk of increased confusion, agitation) [Kay et al. 2005, Staskin 2005].
2. **Antimuscarinic drugs with chronic glaucoma** (risk of acute exacerbation of glaucoma) [Staskin2005].
3. **Antimuscarinic drugs with chronic constipation** (risk of exacerbation of constipation) [Staskin 2005].
4. **Antimuscarinic drugs with chronic prostatism** (risk of urinary retention) [Staskin 2005].
5. **Alpha-blockers in males with frequent incontinence**, i.e. one or more episodes of incontinence daily (risk of urinary frequency and worsening of incontinence) [Sarkar and Ritch 2000].
6. **Alpha-blockers with long-term urinary catheter in situ**, i.e. more than 2 months (drug not indicated).

G. Endocrine system

1. **Glibenclamide or chlorpropamide with type 2 diabetes mellitus** (risk of prolonged hypoglycemia) [Cheillah and Burge 2004].
2. **Beta-blockers in those with diabetes mellitus and frequent hypoglycemic episodes** i.e. ≥ 1 episode per month (risk of masking hypoglycemic symptoms) [Cheillah and Burge 2004].
3. **Estrogens with a history of breast cancer or venous thromboembolism** (increased risk of recurrence) [Beral et al. 2002, Collaborative Group on Hormonal Factors in Breast Cancer 1997, Grady and Sawaya 1998].
4. **Estrogens without progestogen in patients with intact uterus** (risk of endometrial cancer) [Lethabyetal. 2000].

H. Drugs that adversely affect fallers

1. **Benzodiazepines** (sedative, may cause reduced sensorium, impair balance) [Tinetti 2003].
2. **Neuroleptic drugs** (may cause gait dyspraxia, parkinsonism) [Tinetti 2003].
3. **First-generation antihistamines** (sedative, may impair sensorium) [Sutter et al. 2003].
4. **Vasodilator drugs with persistent postural hypotension**, i.e. recurrent >20mmHg drop in systolic blood pressure (risk of syncope, falls) [Leipzig et al. 1999].
5. **Long-term opiates in those with recurrent falls** (risk of drowsiness, postural hypotension, vertigo) [American Geriatrics Society Panel on Persistent Pain in Older Persons 2002, Leipzig et al. 1999].

I. Analgesic drugs

1. **Use of long-term powerful opiates**, e.g. morphine or fentanyl as first-line therapy for mild-to-moderate pain (World Health Organization analgesic ladder not observed) [American Geriatrics Society Panel on Persistent Pain in Older Persons 2002].
2. **Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives** (risk of severe constipation) [Walsh 1999].

STOPP: Screening Tool of Older People's potentially inappropriate Prescription.
The following drug prescriptions are potentially inappropriate in persons aged ≥ 65 years of age.

3. **Long-term opiates in those with dementia unless indicated for palliative care or management of moderate/severe chronic pain syndrome** (risk of exacerbation of cognitive impairment) [American Geriatrics Society Panel on Persistent Pain in Older Persons 2002].

J. Duplicate drug classes

Any duplicate drug class prescription, e.g. two concurrent opiates, NSAIDs, SSRIs, loop diuretics, ACE inhibitors (optimization of monotherapy within a single drug class should be observed prior to considering a new class of drug).

* Serum creatinine > 150 µmol/l, or estimated GFR < 50 ml/min [BNF 2006].

TABLE 2. START: Screening Tool to Alert doctors to Right, i.e. appropriate, indicated Treatments.

START: Screening Tool to Alert doctors to Right, i.e. appropriate, indicated Treatments.
These medications should be considered for people ≥ 65 years of age with the following conditions, where no contraindication to prescription exists

A. Cardiovascular system

1. **Warfarin in the presence of chronic atrial fibrillation** [Hart et al. 1999, Ross et al. 2005, Mant et al. 2007].
2. **Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin** [Hart et al. 1999, Ross et al. 2005].
3. **Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm** [Smith et al. 2006].
4. **Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg** [Williams et al. 2004, Papademetriou et al. 2004, Skoog et al. 2004, Trenkwalder et al. 2005].
5. **Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is greater than 5 years** [Brown and Moussa 2003, Amarenco et al. 2004, Smith et al. 2006].
6. **Angiotensin converting enzyme (ACE) inhibitor with chronic heart failure** [Hunt et al. 2005].
7. **ACE inhibitor following acute myocardial infarction** [ACE Inhibitor Myocardial Infarction Collaborative Group 1998, Antman et al. 2004].
8. **Beta-blocker with chronic stable angina** [Gibbons et al. 2003].

B. Respiratory system

1. **Regular inhaled beta2-agonist or anticholinergic agent for mild-to-moderate asthma or COPD** [Buist et al. 2006].

START: Screening Tool to Alert doctors to Right, i.e. appropriate, indicated Treatments.
These medications should be considered for people ≥ 65 years of age with the following conditions, where no contraindication to prescription exists

2. **Regular inhaled corticosteroid for moderate/severe asthma or COPD, where predicted FEV1 < 50%** [Buist et al. 2006].
3. **Home continuous oxygen with documented chronic type 1 respiratory failure** (pO_2 < 8.0 kPa, pCO_2 < 6.5 kPa) or type 2 respiratory failure (pO_2 < 8.0 kPa, pCO_2 > 6.5 kPa) [Cranston et al. 2005, Buist et al. 2006].

C. Central nervous system

1. **L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability** [Kurlan 1998, Danisi 2002].
2. **Antidepressant drug in the presence of moderate/severe depressive symptoms lasting at least three months** [Lebowitz et al. 1997, Wilson et al. 2006].

D. Gastrointestinal system

1. **Proton pump inhibitor with severe gastroesophageal acid reflux disease or peptic stricture requiring dilation** [Hungin and Raghunath 2004].
2. **Fiber supplement for chronic, symptomatic diverticular disease with constipation** [Aldoorietal.1994].

E. Musculoskeletal system

1. **Disease-modifying antirheumatic drug (DMARD) with active moderate/severe rheumatoid disease lasting > 12 weeks** [Kwoh et al. 2002].
2. **Bisphosphonates in patients taking maintenance corticosteroid therapy** [Buckley et al. 2001].
3. **Calcium and vitamin D supplement in patients with known osteoporosis** (previous fragility fracture, acquired dorsal kyphosis) [Gass and Dawson Hughes 2006].

F. Endocrine system

1. **Metformin with type 2 diabetes ± metabolic syndrome** (in the absence of renal impairment*) [Mooradian 1996, Johansen 1999].
2. **ACE inhibitor or angiotensin receptor blocker in diabetes with nephropathy**, i.e. overt urinalysis proteinuria or microalbuminuria (>30mg/24hours) ± serum biochemical renal impairment*[Sigaletal. 2005].
3. **Antiplatelet therapy in diabetes mellitus with coexisting major cardiovascular risk factors** (hypertension, hypercholesterolemia, smoking history) [Sigal et al. 2005].
4. **Statin therapy in diabetes mellitus if coexisting major cardiovascular risk factors present** [Sigal et al. 2005].

* Serum creatinine > 150 µmol/l, or estimated GFR < 50 ml/min [BNF 2006].

APPENDIX 2: 2012 AGS BEERS CRITERIA FOR POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER ADULTS

American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 2012. 60(4): p. 616-631

TABLE 1. 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System/Therapeutic Category/Drug(s)	**Recommendation, Rationale,** ***Quality of Evidence (QE) & Strength of Recommendation (SR)***
Anticholinergics (exclude TCAs)	
First-generation antihistamines (as single agent or as part of combination products) **- Brompheniramine** **- Carbinoxamine** **- Chlorpheniramine** **- Clemastine** **- Cyproheptadine** **- Dexbrompheniramine** **- Dexchlorpheniramine** **- Diphenhydramine (oral)** **- Doxylamine** **- Hydroxyzine** **- Promethazine** **- Triprolidine**	**Avoid.** Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; increased risk of confusion, dry mouth, constipation, and other anticholinergic effects/toxicity. Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate. *QE = High (Hydroxyzine and Promethazine), Moderate (All others); SR = Strong*
Antiparkinson agents **- Benztropine (oral)** **- Trihexyphenidyl**	**Avoid.** Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease. *QE = Moderate; SR = Strong*
Antispasmodics **- Belladonna alkaloids** **- Clidinium-chlordiazepoxide** **- Dicyclomine** **-Hyoscyamine** **- Propantheline** **- Scopolamine**	**Avoid except in short-term palliative care to decrease oral secretions.** Highly anticholinergic, uncertain effectiveness. *QE = Moderate; SR = Strong*
Antithrombotics	
Dipyridamole, oral short-acting* ***(does not apply to the extended-release combination with aspirin)***	**Avoid.** May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing. *QE = Moderate; SR = Strong*
Ticlopidine*	**Avoid.** Safer, effective alternatives available. *QE = Moderate; SR = Strong*
Anti-infective	

Organ System/Therapeutic Category/Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
Nitrofurantoin	**Avoid for long-term suppression; avoid in patients with CrCl <60 mL/min.** Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with CrCl <60 mL/min due to inadequate drug concentration in the urine. *QE = Moderate; SR = Strong*
Cardiovascular	
Alpha1 blockers **- Doxazosin** **- Prazosin** **- Terazosin**	**Avoid use as an antihypertensive.** High risk of orthostatic hypotension; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile. *QE = Moderate; SR = Strong*
Alpha agonists **- Clonidine** **- Guanabenz*** **- Guanfacine*** **- Methyldopa*** **- Reserpine (>0.1 mg/day)***	**Avoid clonidine as a first-line antihypertensive. Avoid others as listed.** High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension. *QE = Low; SR = Strong*
Antiarrhythmic drugs (Class Ia, Ic, III) **- Amiodarone** **- Dofetilide** **- Dronedarone** **- Flecainide** **- Ibutilide** **- Procainamide** **- Propafenone** **- Quinidine** **- Sotalol**	**Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation.** Data suggest that rate control yields better balance of benefits and harms than rhythm control for most older adults. Amiodarone is associated with multiple toxicities, including thyroid disease, pulmonary disorders, and QT interval prolongation. *QE = High; SR = Strong*
Disopyramide*	**Avoid.** Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred. *QE = Low; SR = Strong*
Dronedarone	**Avoid in patients with permanent atrial fibrillation or heart failure.** Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or heart failure. In general, rate control is preferred over rhythm control for atrial fibrillation. *QE = Moderate; SR = Strong*
Digoxin >0.125 mg/day	**Avoid.** In heart failure, higher dosages associated with no additional benefit and may increase risk of toxicity; decreased renal clearance may increase risk of toxicity. *QE = Moderate; SR = Strong*
Nifedipine, immediate release*	**Avoid.** Potential for hypotension; risk of precipitating myocardial ischemia. *QE = High; SR = Strong*
Spironolactone >25 mg/day	**Avoid in patients with heart failure or with a CrCl <30 mL/min.** In heart failure, the risk of hyperkalemia is higher in older adults if taking >25 mg/day.

Organ System/Therapeutic Category/Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
	QE = Moderate; SR = Strong
Central Nervous System	
Tertiary TCAs, alone or in combination: **- Amitriptyline** **- Chlordiazepoxide-** **- mitriptyline** **- Clomipramine** **- Doxepin >6 mg/day** **- Imipramine** **- Perphenazine-amitriptyline** **- Trimipramine**	**Avoid.** Highly anticholinergic, sedating, and cause orthostatic hypotension; the safety profile of low-dose doxepin (≤6 mg/day) is comparable to that of placebo. *QE = High; SR = Strong*
Antipsychotics, first- (conventional) and second- (atypical) generation *(see table 3)*	**Avoid use for behavioral problems of dementia unless non-pharmacologic options have failed and patient is threat to self or others.** Increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia. *QE = Moderate; SR = Strong*
Thioridazine **Mesoridazine**	**Avoid.** Highly anticholinergic and greater risk of QT-interval prolongation. *QE = Moderate; SR = Strong*
Barbiturates **- Amobarbital*** **- Butabarbital*** **- Butalbital** **- Mephobarbital*** **- Pentobarbital*** **- Phenobarbital** **- Secobarbital***	**Avoid.** High rate of physical dependence; tolerance to sleep benefits; greater risk of overdose at low dosages. *QE = High; SR = Strong*
Benzodiazepines ***Short- and intermediate-acting:*** **- Alprazolam** **- Estazolam** **- Lorazepam** **- Oxazepam** **- Temazepam** **- Triazolam** ***Long-acting:*** **- Chlorazepate** **- Chlordiazepoxide** **- Chlordiazepoxide-amitriptyline** **- Clidinium-chlordiazepoxide** **- Clonazepam** **- Diazepam** **- Flurazepam** **- Quazepam**	**Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium.** Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents. In general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults. May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anesthesia, end-of-life care. *QE = High; SR = Strong*
-Chloral hydrate*	**Avoid.** Tolerance occurs within 10 days and risk outweighs the benefits in light of overdose with doses only 3 times the recommended dose.

Organ System/Therapeutic Category/Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
	QE = Low; SR = Strong
Meprobamate	**Avoid.** High rate of physical dependence; very sedating. *QE = Moderate; SR = Strong*
Nonbenzodiazepine hypnotics **- Eszopiclone** **- Zolpidem** **- Zaleplon**	**Avoid chronic use (>90 days)** Benzodiazepine-receptor agonists that have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); minimal improvement in sleep latency and duration. *QE = Moderate; SR = Strong*
Ergot mesylates* **Isoxsuprine***	**Avoid.** Lack of efficacy. *QE = High; SR = Strong*
Endocrine	
Androgens **- Methyltestosterone*** **- Testosterone**	**Avoid unless indicated for moderate to severe hypogonadism.** Potential for cardiac problems and contraindicated in men with prostate cancer. *QE = Moderate; SR = Weak*
Desiccated thyroid	**Avoid.** Concerns about cardiac effects; safer alternatives available. *QE = Low; SR = Strong*
Estrogens with or without progestins	**Avoid oral and topical patch. Topical vaginal cream: Acceptable to use low-dose intravaginal estrogen for the management of dyspareunia, lower urinary tract infections, and other vaginal symptoms.** Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women. Evidence that vaginal estrogens for treatment of vaginal dryness is safe and effective in women with breast cancer, especially at dosages of estradiol <25 mcg twice weekly. *QE = High (Oral and Patch), Moderate (Topical); SR = Strong (Oral and Patch), Weak (Topical)*
Growth hormone	**Avoid, except as hormone replacement following pituitary gland removal.** Effect on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose. *QE = High; SR = Strong*
Insulin, sliding scale	**Avoid.** Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. *QE = Moderate; SR = Strong*
Megestrol	**Avoid.** Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults. *QE = Moderate; SR = Strong*
Sulfonylureas, long-duration **- Chlorpropamide** **- Glyburide**	**Avoid.** Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH Glyburide: higher risk of severe prolonged hypoglycemia in older

Organ System/Therapeutic Category/Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
	adults. *QE = High; SR = Strong*
Gastrointestinal	
Metoclopramide	**Avoid, unless for gastroparesis.** Can cause extrapyramidal effects including tardive dyskinesia; risk may be further increased in frail older adults. *QE = Moderate; SR = Strong*
Mineral oil, given orally	**Avoid.** Potential for aspiration and adverse effects; safer alternatives available. *QE = Moderate; SR = Strong*
Trimethobenzamide	**Avoid.** One of the least effective antiemetic drugs; can cause extrapyramidal adverse effects. *QE = Moderate; SR = Strong*
Pain Medications	
Meperidine	**Avoid**. Not an effective oral analgesic in dosages commonly used; may cause neurotoxicity; safer alternatives available. *QE = High; SR = Strong*
Non-COX-selective NSAIDs, oral **- Aspirin >325 mg/day** **- Diclofenac** **- Diflunisal** **- Etodolac** **- Fenoprofen** **- Ibuprofen** **- Ketoprofen** **- Meclofenamate** **- Mefenamic acid** **- Meloxicam** **- Nabumetone** **- Naproxen** **- Oxaprozin** **- Piroxicam** **- Sulindac** **- Tolmetin**	**Avoid** chronic use unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol). Increases risk of GI bleeding/peptic ulcer disease in high-risk groups, including those ≥75 years old or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents. Use of proton pump inhibitor or misoprostol reduces but does not eliminate risk. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months, and in about 2%–4% of patients treated for 1 year. These trends continue with longer duration of use. *QE = Moderate; SR = Strong*
Indomethacin **Ketorolac, includes parenteral**	**Avoid**. Increases risk of GI bleeding/peptic ulcer disease in high-risk groups (See Non-COX selective NSAIDs) Of all the NSAIDs, indomethacin has most adverse effects. *QE = Moderate (Indomethacin), High (Ketorolac); SR = Strong*
Pentazocine*	**Avoid**. Opioid analgesic that causes CNS adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs; is also a mixed agonist and antagonist; safer alternatives available. QE = Low; SR = Strong
Skeletal muscle relaxants **- Carisoprodol**	**Avoid**. Most muscle relaxants poorly tolerated by older adults, because of

Organ System/Therapeutic Category/Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
- Chlorzoxazone **- Cyclobenzaprine** **- Metaxalone** **- Methocarbamol** **- Orphenadrine**	anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults is questionable. *QE = Moderate; SR = Strong*

*Infrequently used drugs.

Abbreviations: ACEI, angiotensin converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CNS, central nervous system; COX, cyclooxygenase; CrCl, creatinine clearance; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SR, Strength of Recommendation; TCAs, tricyclic antidepressants; QE, Quality of Evidence

TABLE 2. 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Due to Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome

Disease or Syndrome	Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
Cardiovascular		
Heart failure	NSAIDs and COX-2 inhibitors Nondihydropyridine CCBs (avoid only for systolic heart failure) - Diltiazem - Verapamil Pioglitazone, rosiglitazone Cilostazol Dronedarone	**Avoid.** Potential to promote fluid retention and/or exacerbate heart failure. *QE = Moderate (NSAIDs, CCBs, Dronedarone), High (Thiazolidinediones (glitazones)), Low (Cilostazol); SR = Strong*
Syncope	Acetylcholinesterase inhibitors (AChEIs) Peripheral alpha blockers - Doxazosin - Prazosin - Terazosin Tertiary TCAs Chlorpromazine, thioridazine, and olanzapine	**Avoid.** Increases risk of orthostatic hypotension or bradycardia. *QE = High (Alpha blockers), Moderate (AChEIs, TCAs and antipsychotics); SR = Strong (AChEIs and TCAs), Weak (Alpha blockers and antipsychotics)*
Central Nervous System		
Chronic seizures or epilepsy	Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene	**Avoid.** Lowers seizure threshold; may be acceptable in patients with well-controlled seizures in whom alternative agents have not been effective. *QE = Moderate; SR = Strong*

Disease or Syndrome	Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
	Tramadol	
Delirium	All TCAs Anticholinergics *(see table 4)* Benzodiazepines Chlorpromazine Corticosteroids H2-receptor antagonist Meperidine Sedative hypnotics Thioridazine	**Avoid.** Avoid in older adults with or at high risk of delirium because of inducing or worsening delirium in older adults; if discontinuing drugs used chronically, taper to avoid withdrawal symptoms. *QE = Moderate; SR = Strong*
Dementia & cognitive impairment	Anticholinergics *(see table 4)* Benzodiazepines H2-receptor antagonists Zolpidem Antipsychotics, chronic and as-needed use	**Avoid.** Avoid due to adverse CNS effects. Avoid antipsychotics for behavioral problems of dementia unless non-pharmacologic options have failed and patient is a threat to themselves or others. Antipsychotics are associated with an increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia. *QE = High; SR = Strong*
History of falls or fractures	Anticonvulsants Antipsychotics Benzodiazepines Nonbenzodiazepine hypnotics - Eszopiclone - Zaleplon - Zolpidem TCAs/SSRIs	**Avoid unless safer alternatives are not available; avoid anticonvulsants except for seizure.** Ability to produce ataxia, impaired psychomotor function, syncope, and additional falls; shorter-acting benzodiazepines are not safer than long-acting ones. *QE = High; SR = Strong*
Insomnia	Oral decongestants - Pseudoephedrine - Phenylephrine Stimulants - Amphetamine - Methylphenidate - Pemoline Theobromines - Theophylline - Caffeine	**Avoid.** CNS stimulant effects. *QE = Moderate; SR = Strong*
Parkinson's disease	All antipsychotics (*see table 3, except for quetiapine and clozapine*) Antiemetics - Metoclopramide - Prochlorperazine - Promethazine	**Avoid.** Dopamine receptor antagonists with potential to worsen parkinsonian symptoms. Quetiapine and clozapine appear to be less likely to precipitate worsening of Parkinson disease. *QE = Moderate; SR = Strong*
Gastrointestinal		
Chronic constipation	Oral antimuscarinics for urinary incontinence	**Avoid unless no other alternatives.** Can worsen constipation; agents for

Disease or Syndrome	Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
	- Darifenacin, - Fesoterodine - Oxybutynin (oral) - Solifenacin - Tolterodine - Trospium Nondihydropyridine CCB - Diltiazem - Verapamil First-generation antihistamines as single agent or part of combination products - Brompheniramine (various) - Carbinoxamine - Chlorpheniramine - Clemastine (various) - Cyproheptadine - Dexbrompheniramine - Dexchlorpheniramine (various) - Diphenhydramine - Doxylamine - Hydroxyzine - Promethazine - Triprolidine Anticholinergics/antispasmodics *(see table 4)* - Antipsychotics - Belladonna alkaloids - Clidinium-chlordiazepoxide - Dicyclomine - Hyoscyamine - Propantheline - Scopolamine - Tertiary TCAs (amitriptyline, clomip-ramine, doxepin, imipramine, and trimipramine)	urinary incontinence: antimuscarinics overall differ in incidence of constipation; response variable; consider alternative agent if constipation develops. *QE = High (For Urinary Incontinence), Moderate/Low (All Others); SR = Strong*
History of gastric or duodenal ulcers	Aspirin (>325 mg/day) Non–COX-2 selective NSAIDs	**Avoid unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol).** May exacerbate existing ulcers or cause new/additional ulcers. *QE = Moderate; SR = Strong*
Kidney/Urinary Tract		
Chronic kidney disease stages IV and V	NSAIDs Triamterene (alone or in combination)	**Avoid.** May increase risk of kidney injury. May increase risk of acute kidney injury. *QE = Moderate (NSAIDs), Low (Triamterene); SR = Strong (NSAIDs), Weak (Triamterene)*

Disease or Syndrome	Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen)	**Avoid in women.** Aggravation of incontinence. *QE = High; SR = Strong*
Lower urinary tract symptoms, benign prostatic hyperplasia	Inhaled anticholinergic agents Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see Table 9 for complete list).	**Avoid in men.** May decrease urinary flow and cause urinary retention. *QE = Moderate; SR = Strong (Inhaled agents), Weak (All others)*
Stress or mixed urinary in-continence	Alpha-blockers - Doxazosin - Prazosin - Terazosina	**Avoid in women.** Aggravation of incontinence. *QE = Moderate; SR = Strong*

Abbreviations: CCBs, calcium channel blockers; AChEIs, acetylcholinesterase inhibitors; CNS, central nervous system; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs; SR, Strength of Recommendation; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; QE, Quality of Evidence

TABLE 3. 2012 AGS Beers Criteria for Potentially Inappropriate Medications to Be Used with Caution in Older Adults

Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
Aspirin for primary prevention of cardiac events	**Use with caution in adults ≥80 years old.** Lack of evidence of benefit versus risk in individuals ≥80 years old. *QE = Low; SR = Weak*
Dabigatran	**Use with caution in adults ≥75 years old or if CrCl <30 mL/min.** Increased risk of bleeding compared with warfarin in adults ≥75 years old; lack of evidence for efficacy and safety in patients with CrCl <30 mL/min *QE = Moderate; SR = Weak*
Prasugrel	**Use with caution in adults ≥75 years old.** Greater risk of bleeding in older adults; risk may be offset by benefit in highest-risk older patients (eg, those with prior myocardial infarction or diabetes). *QE = Moderate; SR = Weak*
Antipsychotics **Carbamazepine** **Carboplatin** **Cisplatin** **Mirtazapine** **SNRIs** **SSRIs** **TCAs** **Vincristine**	**Use with caution.** May exacerbate or cause SIADH or hyponatremia; need to monitor sodium level closely when starting or changing dosages in older adults due to increased risk. *QE = Moderate; SR = Strong*
Vasodilators	**Use with caution.**

	May exacerbate episodes of syncope in individuals with history of syncope. *QE = Moderate; SR = Weak*

Abbreviations: CrCl, creatinine clearance; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors; SR, Strength of Recommendation; TCAs, tricyclic antidepressants; QE, Quality of Evidence

TABLE 4. First- and second generation Antipsychotics

First-Generation (Conventional) Agents	**Second-Generation (Atypical) Agents**
Chlorpromazine	Aripiprazole
Fluphenazine	Asenapine
Haloperidol	Clozapine
Loxapine	Iloperidone
Molindone	Lurasidone
Perphenazine	Olanzapine
Pimozide	Paliperidone
Promazine	Quetiapine
Thioridazine	Risperidone
Thiothixene	Ziprasidone
Trifluoperazine	
Triflupromazine	

TABLE 5. Drugs with strong anticholinergic properties

Antihistamines	
Brompheniramine	Dimenhydrinate
Carbinoxamine	Diphenhydramine
Chlorpheniramine	Hydroxyzine
Clemastine	Loratadine
Cyproheptadine	Meclizine
Antiparkinson agents	
Benztropine	Trihexyphenidyl
Skeletal Muscle Relaxants	
Carisoprodol	Orphenadrine
Cyclobenzaprine	Tizanidine
Antidepressants	
Amitriptyline	Imipramine
Amoxapine	Nortriptyline
Clomipramine	Paroxetine
Desipramine	Protriptyline
Doxepin	Trimipramine
Antipsychotics	
Chlorpromazine	Pimozide
Clozapine	Prochlorperazine
Fluphenazine	Promethazine
Loxapine	Thioridazine
Olanzapine	Thiothixene
Perphenazine	Trifluoperazin
Antimuscarinics	
(urinary incontinence)	
Darifenacin	Solifenacin
Fesoterodine	Tolterodine
Flavoxate	Trospium
Oxybutynin	
Antispasmodics	
Atropine products	Hyoscyamine products
Belladonna alkaloids	Propantheline
Dicyclomine	Scopolamine
Homatropine	

CURRICULUM VITAE

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AWARDS

- Young Researcher Award oral presentation European Union Geriatric Medicine Society EUGMS 2012 (*Aspirin Misuse At Home According To START And STOPP In Frail Older Persons*).
- Award Best Oral Presentation 2011 European Society of Clinical Pharmacy ESCP (*Prescribing Omissions according to START and related hospital admissions in frail older patients*).
- Prix SBGG Juniors 2011 Sociéte Belge de Gérontologie et de Gériatrie (*Overuse and underuse of aspirin according to STOPP and START in frail older persons*).

COMMUNICATIONS IN RELATIONSHIP WITH THIS THESIS

Scientific publications

Dalleur O, Boland B, Spinewine A. *2012 updated Beers Criteria: greater applicability to Europe?* J Am Geriatr Soc. 2012 Nov;60(11):2188-9.

Dalleur O, Spinewine A, Henrard S, Losseau C, Speybroeck N, Boland B. *Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria.* Drugs Aging. 2012 Oct;29(10):829-37.

Book chapter

Anne Spinewine, Olivia Dalleur. "*Médicaments et personnées âgées*", in Calop J, Limat S, Fernandez-Maloigne C., *Pharmacie clinique et thérapeutique* (4 Éd.) 2012.

Oral presentations at national and international meetings

O. Dalleur , B. Boland, D. Wouters , A. Spinewine *2012 Beers updated criteria: increased applicability to Europe?* 41th ESCP Symposium on Clinical Pharmacy (29-31/10/12), Barcelona, Spain

O. Dalleur , F. Maes , S. Henrard , D. Wouters , C. Scavée , A. Spinewine , B. Boland . *Risk factors for underuse of anticoagulation in frail elderly patients with atrial fibrillation* 41th ESCP Symposium on Clinical Pharmacy (29-31/10/12), Barcelona, Spain

O. Dalleur, C. Losseau, S. Henrard, D. Wouters, N. Speybroeck, A. Spinewine, B. Boland. *Reduction Of Inappropriate Medications In Frail Older Inpatients Through Recommendations By The Internal Liaison Team*. Pharmcare 2012 (15/09/2012), Brussels, Belgium

O. Dalleur, B. Boland, A. Spinewine. *Aspirin Misuse At Home According To START And STOPP In Frail Older Persons*. 8th Congress of the EUGMS (26-28/09/12), Brussels, Belgium

O. Dalleur, A. Spinewine, S. Henrard, N. Speybroeck, B. Boland. *Overuse and underuse of aspirin according to STOPP and START in frail older persons*. SBGG Journées d'Automne 2011 (21/10/2011), Liège, Belgium

O. Dalleur, A. Spinewine , S. Henrard , N. Speybroeck, B. Boland. *Prescribing Omissions according to START and related hospital admissions in frail older patients.* 40th ESCP Symposium on Clinical Pharmacy (21/10/2011), Dublin, Ireland

O. Dalleur, C. Deliens , C. Losseau, A. Spinewine, B. Boland. *Inappropriate Prescriptions according to STOPP and related hospital admission in geriatric patients.* ESCP International Symposium in Geriatrics (6/05/2011), Utrecht, the Netherlands

O. Dalleur, C. Deliens , A. Spinewine, B. Boland. *Inappropriate Prescribing according to STOPP and related hospital admission in frail older people.* 34e WinterMeeting BVGG (25/02/2011), Ostende, Belgium

Poster presentations at national and international meetings

O. Dalleur, B. Boland, A. Spinewine, J.M. Degryse. *STOPP criteria in frail older patients: one year follow-up and clinical importance.* SBGG Journées d'Automne 2013 (25/10/2013), Liège, Belgium

O. Dalleur, B. Boland , A. Spinewine , J. Degryse. *STOPP criteria: Evaluation of their clinical importance.* 9th Congress of the EUGMS (26-28/09/12), Venice, Italy

O. Dalleur , S. Henrard , A. Spinewine , B. Boland. *Hospital Admissions Related To Inappropriate Prescribing According To STOPP And START Criteria In Frail Older Persons.* 8th Congress of the EUGMS (26-28/09/12), Brussels, Belgium

O. Dalleur, C. Losseau, S. Henrard, N. Speybroeck, A. Spinewine, B. Boland. *Result of recommendations to discontinue inappropriate medications according to STOPP by the geriatric liaison team in hospitalized older patients.* 35e WinterMeeting BVGG (2/03/2012), Ostende, Belgium

O. Dalleur on behalf of the Working Group Clinical Pharmacology Pharmacotherapy and pharmaceutical Care of the Belgian Society of Gerontology and Geriatrics. *Use of STOPP & START in Belgium to screen elderly patient's treatments: data of the Working Group Clinical Pharmacology, Pharmacotherapy and Pharmaceutical Care.* 35e WinterMeeting BVGG (2/03/2012), Ostende, Belgium

O. Dalleur, A. Spinewine, S. Henrard, N. Speybroeck, B. Boland. *Hospital admission in geriatric patients related to prescribing omissions according to START.* SBGG Journées d'Automne Liège 2011 (21/10/2011), Liège, Belgium

SUMMARY

SUMMARY

The prescription of medicines is a fundamental component of the care of older people, but evidence suggests that the use of medicines in this population is often inappropriate. The STOPP (Screening Tool of Older Person's Prescriptions) & START (Screening Tool to Alert doctors to Right Treatment) tool aims to assess and improve the appropriateness of prescriptions for older people. This thesis explores the use of STOPP&START, using three different but complementary approaches: measurements taken using the tool ("how much" inappropriate prescriptions are detected?), the validity of the tool ("how valid" is the tool?), and use of the tool as a means of optimising prescribing ("how better"? Is prescription appropriateness improved through use of the tool?). This work illustrates the strengths and limitations of the use of STOPP&START and offers perspectives for future improvement of appropriateness of treatment in older patients.

"How much?"

We applied STOPP&START to two different cohorts of older patients: 302 frail older patients who were being admitted to hospital and 567 patients aged 80 and older in primary care. Inappropriate prescribing appeared to be highly frequent in both populations. Over half of patients were being prescribed at least one inappropriate medication, according to STOPP and had at least one inappropriate prescribing omission, according to START. There are three major areas where improvement efforts should be targeted: drugs associated with falls causing fractures (psychotropic drugs increasing the risk of falls or lack of calcium and vitamin D for bone protection), drugs used for the prevention of cardiovascular disease (which are often overused in primary prevention and underprescribed in secondary prevention), and anticoagulant drugs prescribed for atrial fibrillation.

"How valid?"

The validity of the tool was assessed using several approaches. First, we compared this tool with another frequently used tool: the Beers list. STOPP criteria were compared with the most recent update of the Beers criteria. Both lists address the

overuse of inappropriate medications. Second, experts and general practitioners discussed the clinical relevance of the treatment modifications recommended by STOPP&START. There was agreement on the importance of addressing the three areas listed above. Interestingly, when comorbidities and functional status were taken into account, some of the instances of potentially inappropriate prescribing detected by STOPP or START appeared to become appropriate. This finding highlights the importance of considering the patient as a whole when performing a medication review. The third approach involved asking general practitioners to share their views on the use of the tool in their daily practice, either as part of a focus group or by completing a survey questionnaire. General practitioners are the key potential users of the tool, due to their broader knowledge of the patient's situation. The general practitioners surveyed considered the tool to be useful and to increase their awareness of the issues associated with prescribing for older people. However, they also considered the tool to be too time-consuming and insisted on the potential usefulness of integrating STOPP&START into a clinical decision support system. Finally, we assessed the number of times that inappropriate prescribing according to STOPP&START was potentially related to hospital admissions in frail older inpatients. The ability of a tool to prevent adverse outcomes is a critical aspect of its validity. We found that inappropriate prescribing according to STOPP&START was potentially related to hospital admissions in 27% of frail older inpatients. This observation would suggest that the future application of STOPP&START as a preventive measure should be encouraged.

"How better?"

Finally, we performed a prospective controlled study to determine the tool's potential for improving the appropriateness of prescribing. The systematic use of STOPP, followed by counselling by the inpatient geriatric consultation team successfully decreased inappropriate prescribing at hospital discharge, and this effect remained one year after discharge. However, further improvements are necessary. Hospital admission is a good opportunity to review medications, but collaborating with and empowering general practitioners remains essential in the management of geriatric patients.

Should we STOPP&START?

The usefulness of STOPP&START for screening chronic drug regimens of older patients looks promising. However, the single application of the tool cannot be recommended, as the validity of the assessments remains unclear. STOPP&START appears to have potential as a tool to help with implementing medication review in clinical practice, as part of a multidimensional effort to improve the appropriateness of prescribing that should include a global assessment of the patient and a collaborative, multidisciplinary approach.

RÉSUMÉ

Bien que la prescription médicamenteuse soit une composante fondamentale du soin des personnes âgées, divers témoignages suggèrent que l'utilisation de médicaments dans cette population est souvent inappropriée. L'outil STOPP&START (Screening Tool of Older Person's Prescriptions & Screening Tool to Alert doctors to Right Treatment) vise à évaluer et à améliorer l'adéquation des médicaments prescrits aux personnes âgées. Cette thèse explore l'utilisation de STOPP&START en utilisant trois approches différentes et complémentaires: 1) la réalisation de mesures au moyen de l'outil en question ("combien?" de prescriptions inappropriées sont détectées), 2) un questionnement sur la validité de l'outil ("validité?" du contenu de l'outil et des mesures effectuées grâce à celui-ci), 3) ainsi que l'utilisation de l'outil comme support à l'optimisation de la prescription ("amélioration?" de la prescription grâce à l'utilisation de l'outil). Ce travail illustre aussi bien les forces que les limitations de l'outil STOPP&START et offre des perspectives pratiques quant à l'amélioration de l'adéquation des traitements des patients âgés.

1. "Combien?"

Nous avons appliqué STOPP&START aux traitements de deux groupes différents de patients âgés: 302 patients âgés et fragiles en hôpital, et 567 patients de plus de 80 ans recrutés en médecine générale. Dans ces deux populations, des prescriptions inappropriées ont fréquemment été détectées. Plus d'un patient sur deux avait au moins un médicament inapproprié selon STOPP et plus d'un patient sur deux au moins une omission inappropriée selon START. Trois domaines devraient être prioritairement visés pour améliorer la prescription: les médicaments impliqués dans des chutes avec fracture (diminution des médicaments psychotropes augmentant le risque de chute, et prescription de protection osseuse), la prévention cardiovasculaire (souvent utilisée en excès en prévention primaire et sous-utilisée en prévention secondaire) et le traitement par anticoagulants dans la fibrillation auriculaire.

2 ° "Validité?"

La validité de l’outil a été évaluée de plusieurs manières. Nous avons d'abord confronté cet outil à un autre fréquemment utilisé: les critères de Beers. Les listes de STOPP et Beers, détectent les médicaments inappropriés par excès. Une comparaison de la sensibilité de ces deux liste a été effectuée. Aucun outil ne s’est avéré surpasser l'autre. Deuxièmement, des experts et des médecins généralistes ont discuté la pertinence clinique de modifier le traitement selon STOPP&START. Il y avait accord sur l'importance majeure d’aborder les trois domaines mentionnés ci-dessus. Notons que certaines prescriptions potentiellement inappropriées selon STOPP&START apparaissaient appropriées en prenant en compte les comorbidités et le statut fonctionnel du patient. Cette observation met en évidence l'importance de considérer et de connaître le patient de manière globale lors du passage en revue de son traitement médicamenteux. Troisièmement, nous avons demandé aux médecins généralistes de partager leurs avis sur l'utilisation de l'outil STOPP&START dans leur pratique journalière – étant donné leur connaissance globale de la situation du patient, les médecins généralistes sont potentiellement les utilisateurs privilégiés de l’outil. Ceci a été réalisé dans des groupes de discussion ou en répondant à un questionnaire d'enquête. Selon les médecins généralistes, l'outil est utile et les rend davantage conscients de la particularité des prescriptions pour les personnes âgées. Ils considèrent cependant que l'outil prend trop de temps à l’utilisation, et ont insisté sur l'intérêt éventuel d'intégrer STOPP&START à un système de prescription médicale informatisée. Finalement, un aspect important de la validité d'un outil est sa capacité à prévenir des événements défavorables. Une prescription inappropriée selon STOPP&START était potentiellement liée à l'admission à l'hôpital de 27 % des patients âgés et fragiles. Cette observation encourage à la future application de STOPP&START en tant que mesure préventive.

3 ° "Amélioration?"

Finalement, nous avons réalisé une étude pour déterminer le potentiel de l'outil à améliorer l’adéquation des prescriptions. L'utilisation systématique de STOPP, combinée à un suivi par l'équipe de liaison gériatrique, a diminué avec succès les prescriptions inappropriées à la sortie de l’hôpital. L'effet perdurait un an après la sortie.

L'admission hospitalière constitue donc une bonne opportunité pour revoir la prescription des médicaments habituels du patient âgé. Des améliorations supplémentaires demeurent cependant nécessaires pour obtenir des traitements médicamenteux optimaux à la sortie de l'hôpital. La collaboration avec les médecins généralistes et leur autorité restent essentielles dans la gestion des médicaments chez les patients gériatriques.

Devrions-nous utiliser STOPP&START ?

L'utilisation de STOPP&START pour passer en revue les traitements médicamenteux chroniques des patients âgés est prometteuse. Cependant, son application comme outil unique ne serait pas recommandée, car la validité du contenu de l'outil et des mesures effectuées avec celui-ci n'est pas encore établie. L'utilisation de STOPP&START s'intègre parfaitement dans une approche multidimensionnelle, incluant une évaluation globale du patient et une collaboration multidisciplinaire, pour améliorer l’adéquation des prescriptions aux personnes âgées.