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POTENTIALLY INAPPROPRIATE PRESCRIPTION OF DRUGS IN HOSPITALIZED OLDER PATIENTS

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ACKNOWLEDGMENTS

ABBREVIATIONS

CKD Chronic Kidney Disease

CNS Central Nervous System

COPD Chronic Obstructive Pulmonary Disease

CVD Cerebrovascular Disease

DALY Disability-Adjusted Life Years

DRG Diagnose Related Group

DRP Drug Related Problems

ED Emergency Department

EHR Electronic Health Record

HRQOL Health Related Quality of Life

MBDS Minimum Basic Data Set

MD Medical Doctor

MEPS Medical Expenditure Panel Survey

NSAIDs Non Steroid Anti Inflammatory Drugs

PAD Peripheral Arterial Disease

PIM Potentially Inappropriate Medication

PIP Potentially Inappropriate Prescriptions

PPO Potential Prescribing Omissions

RCT Randomized Controlled Trials

SSRIs Selective Serotonin Reuptake Inhibitors

STOPP Screening Tool of Older Persons' Prescriptions

START Screening Tool to Alert doctors to the Right Treatment

WHO World Health Organization

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INTRODUCTION

1. Ageing

1.1 Older people definition

People everywhere are living longer, according to the "World Health Statistics 2014" published by the World Health Organization (WHO).

So far, there is not a worldwide specific age threshold for the definition of ¨older people¨. Despite this, the majority of scientists and sociologists accept the retirement age as an appropriate dividing line between adults and the elderly [1]. According to Gorman, chronological time plays a key role in the developed world but in many developing countries old age is seen to begin at the point when active contribution is no longer possible [2].

The World Health Organization defines an older person as ¨a person who has reached a certain age that varies among countries but is often associated with the age of normal retirement¨ [3].

This definition has changed and it is constantly changing with the transforming demographic profile of the world's population towards old age. Two definitions are accepted recently regarding ¨the geriatric patient¨ compiled by the German Association of Geriatrics: 1) multiple pathologies typical for the elderly* and age 70 years or more; 2) age ≥ 80 years and increased vulnerability assocated with age (eg. because of the occurrence of complications and sequelae, the risk of chronicity and the increased risk of loss of autonomy with deterioration of self-help status) [4,5].

* when at least 2 of the following 14 characteristic complexes exist simultaneously in a patient: Immobility, tendency to fall and dizziness, cognitive deficits, incontinence, pressure ulcers, missing and deficient nutrition, disturbances in fluid and electrolyte balance, depression or anxiety disorders, chronic pain, sensibility disturbances, reduced capacity, strong visual or hearing impairment, medication problems, high risk for complications.

1.2 Demographic trends

According to a report by the United Nations, the global share of older people (aged 60 years or over) increased from 9.2% in 1990 to 11.7% in 2013 and will continue to

grow, reaching 21.1% by 2050. These figures are much higher in the developed countries; the proportion of older people rose to 23% in 2013 and is expected to reach 32 per cent in 2050. Information available for 45 European countries in 2012 showed that the male retirement age was more than 65 years only in Iceland, Norway and Italy, it was exactly 65 years in 25 countries, and between 60 and 64 years in 17 countries. For women, the retirement age was most commonly, between 60 years and 64 years [6].

Globally, from 1990 to 2012, life expectancy at age 60 increased from 16.6 years to 18.5 years for men and from 19.7 years to 21.5 years for women. The increase in life expectancy was higher in high-income countries. Better management of risk factors for cardiovascular diseases and declining rates of smoking are the major contributors to increased life expectancy in developed countries [7]. The efforts on the management of noncommunicable diseases have resulted in higher life expectancy, mainly due to decreased mortality from heart diseases.

The reduced mortality in children under 5 years of age, improved maternal health, the decline of new HIV infections (33% between 2001 and 2012), the decrease of the incidence of malaria, tuberculosis and tropical diseases, and the larger access to essential medicines in developing countries are other factors leading to higher life expectancy, as reported by The United Nations Millennium Development Goals [8].

It is estimated that globally by 2050, there will be the same number of old as young in the world, with 2 billion people aged 60 or over and another 2 billion under age 15, each group accounting for 21% of the world's population [9].

Extracting data from the last WHO statistics, we built a graphic that compares the percentage of the population aged over 60 years and the one aged under 15 years old among various countries of the world (Figure 1). It can be clearly seen that in the majority of the represented countries, the proportion of the population aged over 60 years old outweighs the proportion of the population aged under 15 years old. The difference between the older and younger population is higher for Japan, respectively 32% and 13%. In the USA, the % of both groups is approximately the same (19% and 20%), whereas Albania, Ireland and India have more people aged under 15 years than people aged over 60 years old. Particularly in India, 29% of the population is aged less than 15 years and just 8% is aged more than 60 years old.

Figure 1. Comparison of the proportion of the population aged over 60 years and under 15 years old in various countries
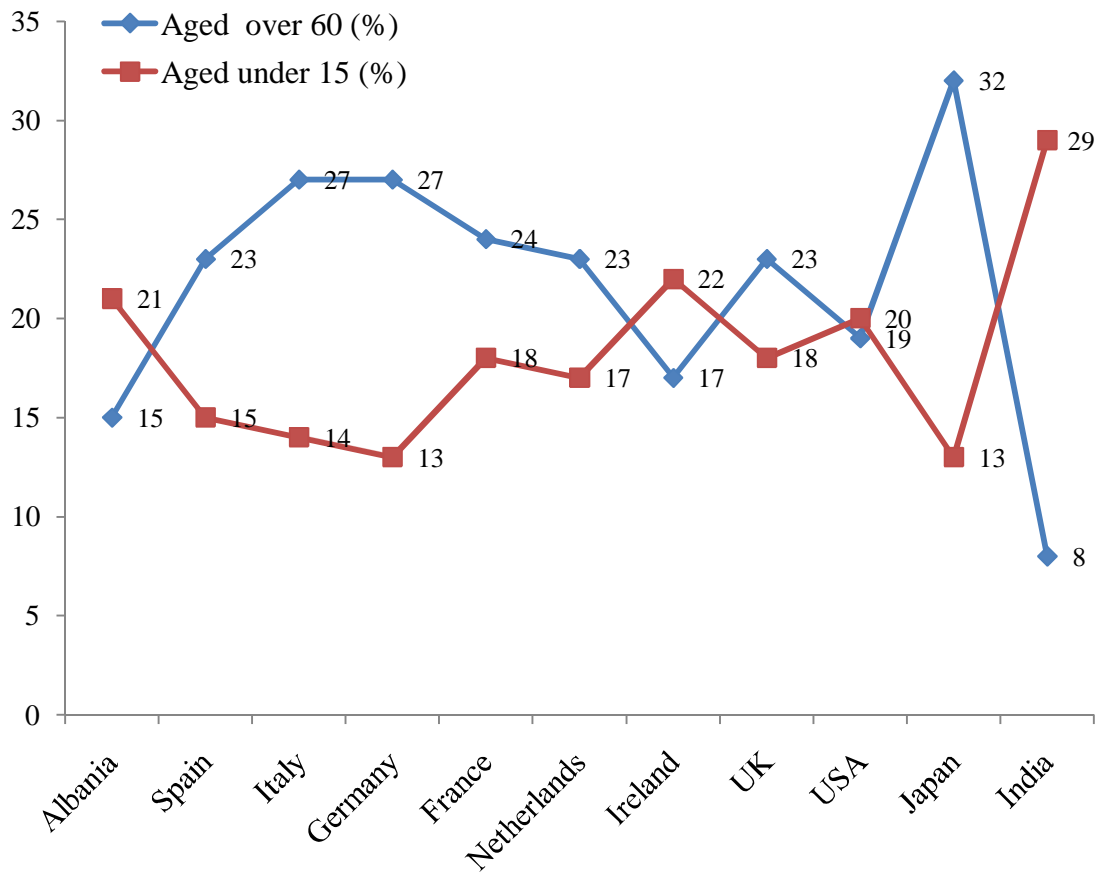
In Spain, according to the World Health Statistics published by WHO, life expectancy at birth in 2012 was 82 years old, with a notable difference among men and women (79 years for men versus 85 years for women). For Albania, this figure is 74 years old with a slighter difference among men and women (73 years for men versus 75 years for women) [10]. Spain has the second-highest life expectancy in the world among women, surpassed only by Japan (87 years) [11]. Table 1 shows the top ten countries regarding life expectancy at birth for men and women in 2012.

Table 1. Life expectancy at birth for men and women in top ten countries (2012)

Men			Women		
Rank	Country	Life expectancy at birth	Rank	Country	Life expectancy at birth
1	Iceland	81,2	1	Japan	87,0
2	Switzerland	80,7	2	Spain	85,1
3	Australia	80,5	3	Switzerland	85,1
4	Israel	80,2	4	Singapore	85,1
5	Singapore	80,2	5	Italy	85,0
6	New Zealand	80,2	6	France	84,9
7	Italy	80,2	7	Australia	84,6
8	Japan	80,0	8	Korea	84,6
9	Sweden	80,0	9	Luxembourg	84,1
10	Luxembourg	79,7	10	Portugal	84,0

Another main characteristic of population ageing is the continuous ageing of the older population itself. Increasing numbers of centenarians and the oldest old (often defined as people aged more than 85 years old) account for higher levels of disability that require long term care (nursing homes, residential care, long-stay hospitals, community care and assisted living). Other implications deriving from the oldest old population growth are: the higher health care costs needed to manage disability, the necessity for higher retirement incomes to cover longer time periods, changes in intergenerational relation patterns.

The economic impact of this demographic trend is enormous, especially due to the decline in the proportion of the workforce and the increasing demand for resources to sustain children and older people [9-12].

1.3 Health problems in the older population

Population aging has become a global issue as older people are more likely to develop multiple diseases, visit different hospitals and receive many screening tests and prescriptions simultaneously. Therefore, this poses a challenge toward the realization of a better aged society, emphasizing the importance of adequate health care [13].

Older people are more prone to chronic diseases and other conditions such as dementia, Alzheimer, Parkinson, arthritis, osteoporosis, cancer, coronary diseases etc., thus increasing the need for treatment with drugs. Chronic diseases do not resolve spontaneously and despite the treatment received, they are generally not cured completely [14].

The metabolic syndrome is a highly prevalent condition in the older people population (45% in individuals aged 60–69). This syndrome is present when patients have at least 3 of 5 chronic conditions: obesity, hypertriglyceridemia, low-serum high-density lipoprotein (HDL), hypertension, and glucose intolerance. It is proved its association with increased risk of cardiovascular disease and all cause mortality [15, 16].

Cognitive changes also go along with normal ageing; in particular some memory, language, executive function abilities and processing speed [17].

Approximately 9% of people aged 65 years or older suffer from dementia, a syndrome which is characterized by cognitive or memory impairments. It typically involves loss of memory, inability to recognize or identify objects and to execute adequate motor activities, difficulties in the comprehension and use of words. Alzheimer's disease is the most common cause of dementia and may account for about 70% of cases. The WHO recognized dementia as one of the major causes of disability and dependency among older people with multiple physical, psychological, social and economical impacts on society [18, 19].

A recent study conducted in Spain concluded that the number of chronic comorbidities was associated to poorer quality of life and disability, with depression, anxiety and stroke having the greatest impact [20].

Despite the persistent increase in the average life expectancy of European citizens (about 0.25 years annually), no change has been observed recently in the number of healthy life years. Chronic diseases still remain the principal cause of unhealthy life years in older people. For EU member states, the disease burden of non-communicable diseases (including major chronic conditions) expressed in disability-adjusted life years (DALY) was 82% in 2010. The main conditions contributing to this figure were: cardiovascular and circulatory diseases (about 24% of DALY), cancer (15%), musculoskeletal disorders (12%), mental disorders (10%), neurological disorders such as Alzheimer, dementia, Parkinson and multiple sclerosis (4%), chronic respiratory diseases (4%) and diabetes (2%). It is predicted that the burden of disease will continue to grow in the coming years because of the high prevalence of

risk behaviours (alcohol and tobacco use, less physical activity, unhealthy diet) and the ageing of the European population [21, 22].

During the last decades, huge progress and innovations have been made in the medical field leading to advances in the diagnosis and treatment of most pathological conditions. These include the elucidation of the pathogenic mechanisms of various care and pharmaceutical innovations. However, the full comprehension of the aging process still remains a challenge [23].

Ageing is clearly associated with pharmacokinetic and pharmacodynamics changes in older patients, which can alter drug metabolism and increase their vulnerability when exposed to different treatments. The reluctance in recruiting older people to participate in clinical trials leads to lack of information regarding the real benefit/risk ratio of pharmacotherapy in this particular group [24]. This constitutes a limitation to the current knowledge on drug safety in older people populations. For this reason, the prescription of new drugs should always be the result of a careful consideration, taking into account patient´s comorbidity, its cognitive and functional limitations, polypharmacy and potential adverse events. The old but still valuable ethical principle of non-maleficence ¨Primum non nocere!¨ (First do no harm!), compels the prescriber to consider if the risk of harm outweighs the prospect of benefit [24, 25].

1.4 Pharmacokinetic and pharmacodynamic changes

The physiological and morphological transformations which are common in the elderly are linked with considerable changes in the pharmacokinetics and pharmacodynamics of drugs in this particular group [26, 27]. The progressive decline in the functional reserve of various organs can influence drug disposition, leading to important clinical implications in older patients. Along with advanced age, an increase in body fat and a decrease in lean mass and total body water are observed [28, 29]. That is why the distribution volume of hydrophilic drugs is decreased in older people, whereas that of lipophilic drugs is augmented.

Moreover, the time-related loss of functional units (e.g. alveoli, nephrons, neurons), the failure to maintain homeostasis under stress conditions and the disruption of some regulatory processes are among the identified characteristics among older people [27].

Pharmacokinetics includes the actions of the human body on the administered drugs, namely the absorption, distribution and elimination (metabolism and excretion). A schematic representation is given in Figure 2.

Figure 2. Pharmacokinetics
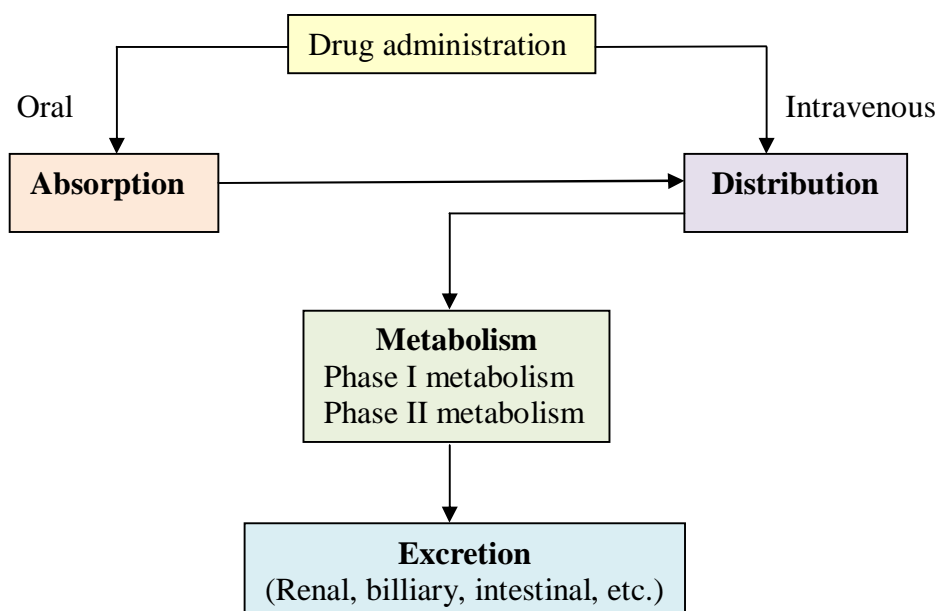
The most significant pharmacokinetic changes in older adults are those related to hepatic metabolism. Old age is associated with a reduction in hepatic blood flow of about 40% and in liver size. Therefore, it is clearly understood why the hepatic clearance of drugs may be subject to change among elderly, as it depends either on hepatic blood flow (in this case, it is called flow-limited) or intrinsic clearance determined by enzyme activity and liver mass (called capacity-limited) [30, 31].

Table 2 shows the effect of advancing age on the hepatic metabolism of selected drugs.

The metabolism of drugs such as morphine, propranolol, verapamil and amitryptiline is decreased by about 40%, consistent with the reduction in blood flow in older people. Also, phase I metabolism seems to be affected more than phase II metabolism by older age. Drugs metabolized by phase I reactions such as ibuprofen, imipramin and theophylline have reduced hepatic clearance in older people, unlike most drugs undergoing phase II reactions (e.g. paracetamol, temazepam and isoniazid) whose hepatic metabolism does not change.

Table 2. The effect of ageing on the hepatic metabolism of selected drugs

Hepatic metabolism	Drug	Effect
Flow-limited	Morphine	↓
	Pethidine	↓
	Lignocaine	↓
	Verapamil	↓
	Propranolol	↓
	Amitryptiline	↓
Capacity-limited	Warfarin	–
	Phenytoin	–
	Valproic acid	–
	Diazepam	–
	Theophylline	↓

Reduced (↓) Unchanged (–)

Prodrugs that require activation by hepatic metabolism may be less effective among elderly patients due to the slower first-pass activation. ACE (angiotensin-converting-enzyme) inhibitors that are activated in the liver (e.g. enalapril) may be affected in older people suffering from heart failure and hepatic congestion. As they are mainly excreted by glomerular filtration and tubular secretion, their plasmatic concentration increases in patients with renal damage, particularly with a creatinine clearance lower than 30 ml/min. A lower maintenance dose of digoxin is usually needed in older patients because of the reduction of its systemic clearance by the kidney. The dose is generally calculated by the creatinine clearance and body weight. Renal impairment among older people has also a significant effect in the clearance of other drugs such as lithium, NSAIDs, digoxin, diuretics, and water soluble antibiotics. The subsequent accumulation of drugs with a narrow therapeutic index (lithium, digoxin, and aminoglycosides) may lead to serious adverse effects [27, 31].

The marked heterogeneity in drug metabolism is another factor which should be taken in consideration when prescribing for older people [32].

Pharmacodynamic changes are also an inevitable part of the ageing process. It is difficult to summarize or generalize pharmacodynamic alterations with advancing age since they differ from drug to drug. Some examples of the age-related changes in the pharmacodynamic effect of commonly used drugs are illustrated in Table 3 [27].

The responsiveness of β-adrenoreceptors decreases with ageing; consequently, the effect of drugs such as propranolol (β-adrenoreceptor antagonist) and salbutamol (β2-adrenoreceptors agonist) is reduced. This is explained by the decreased synthesis of cAMP after receptor stimulation. Clinical implications include lowered antihypertensive effect of β-blockers, despite their widespread use in this population. On the other hand, α-adrenoreceptors function is preserved in the geriatric population. Older people experience more side effects from major tranquilizers, particularly extrapyramidal symptoms, delirium, arrhythmias and postural hypotension. Minor tranquilizers like benzodiazepines induce sedation at smaller doses among elderly people because of the higher sensitivity of the Central Nervous System (CNS). The cellular mechanism responsible for this is still unknown [33-35].

Table 3. Examples of pharmacodynamic changes in older people

Drug	Pharmacodynamic effect	Age-related change
Diazepam	Sedative	Increase
Morphine	Analgesic	Increase
Diltiazem	Antihypertensive	Increase
Verapamil	Antihypertensive	Increase
Furosemide	Diuretic	Decrease
Enalapril	ACE inhibitor	No significant change
Warfarin	Anticoagulant	Increase

1.5 Health and Social Needs

Population ageing puts forward huge healthcare challenges as the demand for human, economic and infrastructure resources rises. The higher level of disability, frailty,

cognitive and physical decline, dependence and comorbidities in the older population requires a better understanding of these conditions, appropriate organization and efficient management of the healthcare system in order to adequately meet these particular needs.

Further research on the ageing process and its clinical implications, as well as on the factors associated with active ageing is needed.

As people live longer, a much higher number of caregivers and healthcare providers in various health institutions (nursing homes, residential care, hospitals) will become necessary. Society and governments should ensure proper access to primary care, long-term care, pharmaceuticals, public services, and to other facilities for this vulnerable part of the population. Rethinking the role of older people in society and promoting their active participation and involvement in the social, economic and cultural life is an important step towards the realization of a better aged society.

Keeping people healthy for as long as possible and treating pathological conditions as better and sooner as possible should be the goal of all healthcare systems. To achieve this, good health policies and good will are often not enough [13, 36].

2. Polypharmacy

2.1 Definition

More than 24 different definitions have been formulated until now to describe the term 'polypharmacy', with the majority of them focusing on the number of medications prescribed to a patient. The threshold number of drugs prescribed stipulated as polypharmacy differs from more than 5 drugs to 10 drugs or more [37, 38], however most researchers agree that polypharmacy occurs when a medical treatment comprises at least one unnecessary medication [39].

Recently, it has been proposed to define polypharmacy "as patients going to more than one pharmacy for their prescriptions" [40]. Besides, recent reviews have outlined that rather polypharmacy per se, it is the inappropriate prescription of drugs which should be tackled to optimize pharmacotherapy in older people [25, 41-43].

2.2 Health and economic impact

Since polypharmacy in older people is more the rule than the exception, it is essential to evaluate its impact on health, society and economy [33].

The balance between the beneficial effect of drugs and an acceptable level of drug related problems (DRPs) is almost always difficult to be assessed in older people due to the necessity to treat multiple diseases and improve the quality of life on one hand and the scanty clinical evidence of adverse drug effects in this population on the other hand [44, 45].

Moreover, as previously mentioned, the care of the same patient by different specialists in different settings carries an augmented risk for failure of adequate communication between healthcare professionals.

Polypharmacy is often made worse by acute admission to hospital, as studied by Betteridge in New Zealand [46].

Although pharmacological treatment is important for the control of chronic diseases, non-pharmacological treatments such as changes in lifestyle, especially diet therapy should be considered first for treating older adults with chronic conditions, as they may provide a valuable alternative to medications. The adoption of non-pharmacological treatments among the elderly population has proved to be associated with significant beneficial and almost no harmful effects. Nevertheless, therapies such as psychotherapy, physiotherapy, occupational therapy, speech and language therapy, nutritional therapy are still underused. Therefore it is essential to enhance non-pharmacological strategies that are effective and accessible to the elderly [47].

Apart from the negative outcomes on patients' health, polypharmacy or the use of extra unnecessary drugs may also waste limited medical resources in terms of drugs costs, healthcare services utilization, nursing staff time to administer medications, and add costs to treat adverse drug events associated with polypharmacy [48].

However, in patients with multiple comorbidities even the underuse of medications should be avoided to ensure the adequate pharmaceutical care for their complex health condition.

Mixed results are reported in literature as regards to the relation between polypharmacy and adverse outcomes in older people. The majority of studies are observational and there is still need for solid evidence from randomized controlled trials (RCT) [49].

Table 4 gives a detailed overview of the studies that analyzed the outcomes of polypharmacy exposure in older people in various settings.

As it can be seen from this table, 29 studies reported that polypharmacy was a risk factor or predictor for inappropriate prescribing in almost all healthcare settings. Fewer studies (5) identified underprescribing or potentially inappropriate omissions (PPO) as a negative outcome of polypharmacy. Furthermore, other negative outcomes of polypharmacy exposure included: drug related problems (DRPs), adverse drug reactions (ADR), adverse drug events (ADE), hospital admissions and readmissions, falls, and mortality.

Table 4. Studies on polypharmacy among older people and its outcomes

Study (year)	Setting / Country	Ref
Outcome: *Inappropriate prescribing*		
McMahon CG et al. Age Ageing (2014)	Hospital / Ireland	50
Frankenthal D et al. Int J Clin Pharm (2013)	Hospital / Israel	51
Prithviraj GK et al. J Geriatr Oncol (2012)	Hospital / USA	52
Gallagher P et al. Eur J Clin Pharmacol (2011)	Hospital / Europe (Switzerland, Spain, Belgium, Italy, Czech Republic, Ireland)	53
Varallo FR et al. J Pharm Pharm Sci (2011)	Hospital / Brazil	54
Holguín-Hernández E et al. Rev Salud Publica (Bogota) (2010)	Hospital /Colombia	55
Gallagher PF et al. Age Ageing (2008)	Hospital / Ireland	56
Hanlon JT et al. Ann Pharmacother (2004)	Hospital / USA	57
Onder G et al. Eur J Clin Pharmacol (2003)	Hospital / Italy	58
Terán-Álvarez L et al. Semergen (2014)	Primary care / Spain	59
Rasu RS et al. Clinicoecon Outcomes Res (2014)	Primary care / Bangladesh	60
Cassoni TC et al. Cad Saude Publica (2014)	Primary care / Brazil	61
Galvin R et al. Eur J Clin Pharmacol (2014)	Population based / Ireland	62
Bradley MC et al. BMC Geriatr (2014)	Primary care / UK	63
Baldoni Ade O et al. Int J Clin Pharm (2014)	Primary care / Brazil	64
Zimmermann T et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz (2013)	Primary care / Germany	65
Holmes HM et al. Pharmacoepidemiol Drug Saf (2013)	Primary care / USA	66
Bell JS et al. Eur J Clin Pharmacol (2013)	Primary care / Finland	67
Oliveira MG et al. Int J Clin Pharm (2012)	Primary care / Brazil	68
Buck MD et al. Am J Geriatr Pharmacother (2009)	Primary care / USA	69

Stafford AC et al. J Clin Pharm Ther (2011)	Residential care / Australia	70
Steinman MA et al. J Am Geriatr Soc (2006)	Residential care / USA	71
Gray SL et al. Ann Pharmacother (2003)	Residential care / USA	72
Sloane PD et al. J Am Geriatr Soc (2002)	Residential care / USA	73
Hosia-Randell HM et al. Drugs Aging (2008)	Nursing home / Finland	74
Mamun K. et al. Ann Acad Med Singapore (2004)	Nursing home / Singapore	75
Lao CK et al. Int J Clin Pharm (2013)	Nursing home / Macao	76
Hamano J et al. J Prim Care Community Health (2014)	Home care / Japan	77
Vieira de Lima TJ, et al. BMC Geriatr (2013)	Home care / Brazil	78
Outcome: Underprescribing or PPO		
Blanco-Reina E et al. Eur J Clin Pharmacol (2014)	Population based / Spain	79
Galvin R et al. Eur J Clin Pharmacol (2014)	Population based / Ireland	62
Hamano J et al. J Prim Care Community Health (2014)	Home care / Japan	77
Parodi López N et al. Aten Primaria (2014)	Primary care / Spain	80
Kuijpers, MA et al. Br J Clin Pharmacol (2008)	Out-patient clinic, day-hospital, or geriatric ward / Netherlands	81
Outcome: DRPs*		
Urbina O et al. Ther Clin Risk Manag (2014)	Hospital / Spain	82
Tigabu BM et al. J Res Pharm Pract (2014)	Hospital / Ethiopia	83
Nickel CH et al. Scand J Trauma Resusc Emerg Med (2013)	Hospital / Switzerland	84
Zaman Huri H et al. BMC Endocr Disord (2013)	Hospital / Malaysia	85
Andreazza RS et al. Gac Sanit (2011)	Hospital / Brazil	86
Kheir N et al. Int J Clin Pharm (2014)	Primary care / Qatar	87
Outcome: ADR		
Ahmed B et al. PLoS One (2014)	Hospital / Pakistan	38
De Paepe P et al. Acta Clin Belg (2013)	Hospital / Belgium	88

Kojima T et al. Geriatr Gerontol Int (2012)	Hospital / Japan	89
Varallo FR et al. J Pharm Pharm Sci (2011)	Hospital / Brazil	54
Hanlon JT et al. J Gerontol A Biol Sci Med Sci (2006)	Primary care / Brazil	90
Veehof LJ et al. Eur J Clin Pharmacol (1999)	General practice / Netherlands	91
Outcome: ADE		
Varallo FR et al. Clinics (Sao Paulo) (2014)	Hospital / Brazil	92
Härkänen M et al. J Clin Nurs (2014)	Hospital / Finland	93
Roulet L et al. J Emerg Med (2014)	Hospital / France	94
Chen YC et al. Eur J Intern Med (2014)	Hospital / Taiwan	95
Calderón-Larrañaga A et al. Br J Gen Pract (2012)	Primary care / Spain	96
Reason B et al. Fam Pract (2012)	Primary care / Canada	97
Field TS et al. Arch Intern Med (2001)	Nursing home / USA	98
Gray SL et al. Ann Pharmacother (1999)	Following hospital discharge / USA	99
Outcome: Hospitalization / hospital admissions and readmissions		
Pedrós C et al. Eur J Clin Pharmacol (2014)	Hospital / Spain	100
Sganga F et al. Geriatr Gerontol Int (2015)	Hospital / Italy	101
Jensen GL et al. Am J Clin Nutr (2001)	Hospital / USA	102
Ruiz B et al. Eur J Clin Pharmacol (2008)	Hospital / Spain	103
Onder G et al. J Am Geriatr Soc (2002)	Hospital / Italy	104
Sehgal V et al. J Family Med Prim Care (2013)	Hospital / USA	105
Aljishi M e al. N Z Med J (2014)	Primary care / New Zealand	106
Outcome: Falls		
Bennett A et al. Drugs Aging (2014)	Hospital / Australia	107
Wu TY et al. Ann Acad Med Singapore (2013)	Hospital / Taiwan	108
Corsinovi L et al. Arch Gerontol Geriatr (2009)	Hospital / Italy	109
Richardson K et al. Age Ageing (2015)	Population based / Ireland	110
Huang ES et al. J Gen Intern Med (2010)	Population based / USA	111
Ziere G et al. Br J Clin Pharmacol (2006)	Population based /	112

	Netherlands	
Murphy MP et al. Rehabil Nurs (2014)	Residential care / USA	113
Kojima T et al. Geriatr Gerontol Int (2012)	Out-patients / Japan	89
Kojima T et al. Geriatr Gerontol Int (2011)	Out-patients / Japan	114
Outcome: Mortality		
Gómez C et al. Gerontology (2014)	Population based / Spain	115
Jyrkkä J et al. Drugs Aging (2009)	Population based / Finland	116
Espino DV et al. J Gerontol A Biol Sci Med Sci (2006)	Population based / USA	117
Onder G et al. J Am Med Dir Assoc (2013)	Nursing home / Italy	118
Shah SM et al. Age Ageing (2013)	Nursing home / UK	119
Alarcón T et al. Age Ageing (1999)	Hospital / Spain	120

*According to the PCNE Classification, DRPs (Drug Related Problems) are defined as "events or circumstances involving drug therapy actually or potentially interfering with desired health outcomes" [121].

2.3 Factors associated with polypharmacy - including ageing

Several studies have shown that polypharmacy was more frequent with an increasing number of visits to different healthcare institutions. By switching prescriber there is a higher risk for medication overlap [122-124].

Specific diseases were found to be associated with polypharmacy.

A population-based study conducted in Finland among older people reported that diabetes mellitus, depression, pain, heart disease, and obstructive pulmonary disease were significantly associated with the use of more than 6 drugs [125].

In a study conducted in 57 nursing homes in 8 European countries, excessive polypharmacy was also associated with depression and pain, with chronic diseases, dyspnea and gastrointestinal symptoms [126].

Among community-dwelling older people in Spain, the factors positively associated with polypharmacy were comorbidity, limitations in activities of daily living (ADL), and being prescribed a drug acting on the cardiovascular or nervous system, as reported by Blanco-Reina et al [79]

A great number of studies in various setting revealed that advancing age is an important independent factor for polypharmacy; within the elderly population, polypharmacy occurs more with increasing age [127].

However, there are studies that have not established a clear association between advancing age and polypharmacy among elderly. Lu J et al found a low prevalence of polypharmacy among chinese nonagenarians and centenerians, despite the presence of chronic diseases in the study population. In this case, the factors associated with polypharmacy (taking 5 drugs or more) were illiteracy, hypertension and cancer [128].

3. Potentially Inappropriate Prescriptions (PIP)

3.1 Concept

Potentially inappropriate prescriptions (PIP) are frequently found in health care settings. They can generate negative outcomes (adverse effects and readmissions,

higher cost) and are largely avoidable [129–134]. Older people are particularly susceptible because they often suffer from more than one chronic disease. Complex co-morbidity entailing the prescription of multiple drugs may result in complex therapeutic regimens. Age-related changes in physiology that alter the pharmacokinetics and pharmacodynamics of drugs imply a decreased functional reserve in patients. Moreover, the higher the number of prescribed drugs, the more difficult it is for older people to achieve adherence to the treatment [135].

There is general agreement about the definition of PIP: (A) one for which the risk of an adverse event exceeds the clinical benefit, especially when there is evidence in favour of a safer or more effective alternative for the same conditions, (B) which is not cost-effective, or (C) which holds not enough scientific evidence to use.

PIP avoidance is one of the strategies which aim to reduce drug-related adverse health effects [136].

Still, it is unclear which the best method to measure PIP is. The two types of methods proposed to improve prescribing are implicit methods and explicit methods. The former are based on expert assessment of the clinical history; they may be subjective, time consuming and not always reproducible [137]. Explicit methods, in turn, focus on not recommending the use of drugs in view of a potentially unacceptable risk/benefit profile, either generally or in certain pathologies.

Targeting the risk factors associated with PIP might improve the allocation of specific medical or pharmaceutical care to prevent potential adverse health outcomes.

The continuing education and training of prescribers should be adequate to ensure appropriate prescribing, or at least, minimize as much as possible inappropriate prescriptions leading to negative outcomes for the older patient. It should include proper and updated knowledge on the pathophysiology of clinical problems, on the pharmacology of the drugs that treat these problems - their pharmaceutical, pharmacokinetic and pharmacodynamic characteristics and how those are translated into a therapeutic response along the chain of biochemical and physiological events -, on geriatric pharmacotherapy, on adverse drug reactions and drug-drug interactions as well as on drug therapy monitoring [138].

3.2 Alternatives to measure PIP

As a support to prescribers, different screening tools are available for measuring and evaluating drugs' appropriate prescribing. The majority of them focus on the inappropriate prescription of drugs among older people as this part of the population represent a target group with a high risk for PIP. Nevertheless, recently have been developed also tools to identify PIP and improve prescribing in middle-aged people and pediatrics, respectively PROMPT (PRescribing Optimally in Middle-aged People's Treatments) and POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions) [11, 12].

A recent review by Kaufmann et al summarizes 46 tools to assess inappropriate prescribing and the relation between them. The link between 21 of these tools is represented schematically in Figure 3. An even wider range of tools aiming to assess prescription appropriateness can be encountered in the scientific literature, each of them having its own advantages and limitations.

The best possible tool to measure inappropriateness of prescribing should: deal with all aspects of prescribing; demonstrate significant causal association between the level of inappropriate prescribing and negative outcomes; derive from evidence-based methodology; and be easily implemented in everyday clinical practice, possibly in all health settings.

Unfortunately, until now, no tool has achieved to cover all aspects of inappropriate prescribing [141].

Figure 3. Schematic representation of the various tools developed for assessing the adequacy of prescriptions and the relation between these tools. The tools most often used as the basis for the development of others are shown in boxes [141].
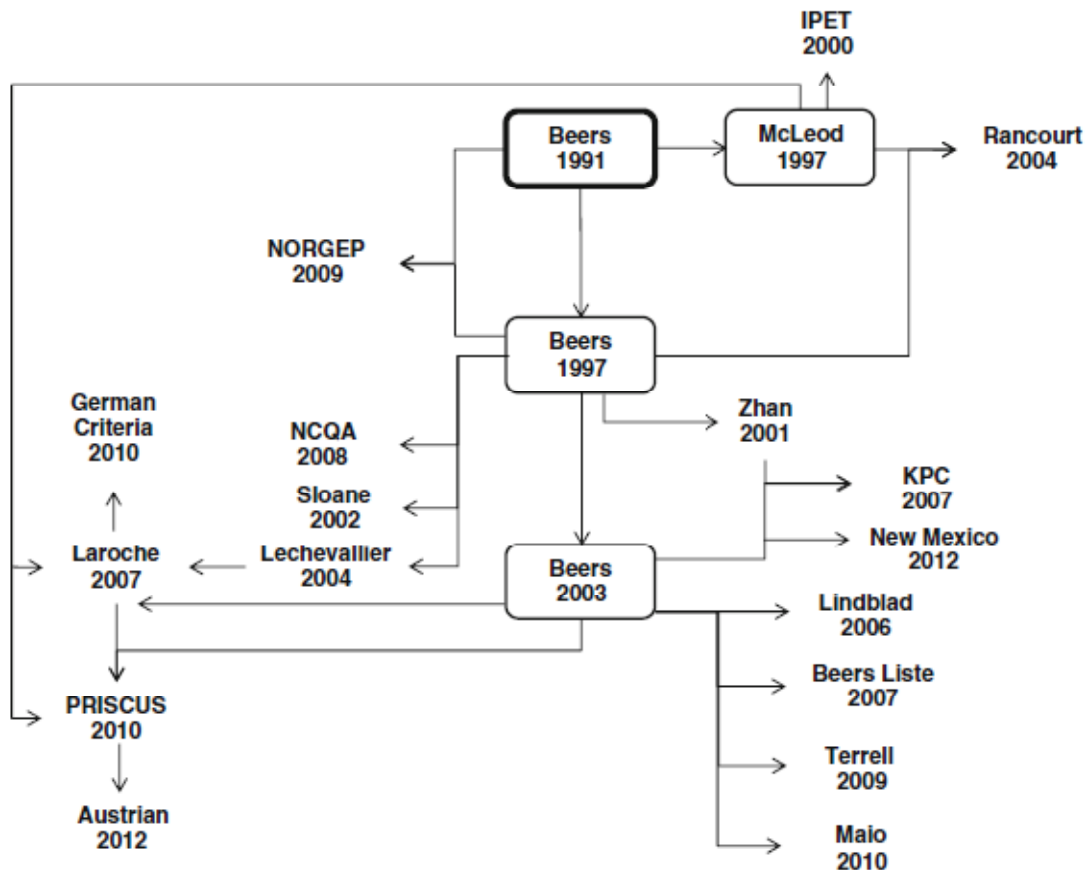
(In alphabetical order: Austrian: Austrian Criteria [142]; Beers: Beers Criteria, different versions [143-146]; Beers Liste [147]; German Criteria: Unangemessene Arzneistoffe für geriatrische Patienten [148]; IPET: Improving Prescribing in the Elderly Tool [149]; KPC: Kaiser Permanente Colorado Criteria [150]; Laroche: Laroche Criteria [151];Lechevallier: Lechevallier Criteria [152]; Lindblad: Lindblad's List of Clinically Important Drug-Disease Interactions [153]; Maio: Maio Criteria [154]; McLeod: McLeod Criteria [155]; NCQA: NCQA Criteria – High Risk Medications (DAE-A) and potentially harmful Drug-Disease Interactions (DDE) in the Elderly [156]; New Mexico: New Mexico Criteria [157]; NORGEP: Norwegian General Practice Criteria [158]; PRISCUS: The PRISCUS List [159]; Rancourt: Rancourt Criteria [160]; Sloane: Sloane List of Inappropriate Prescribed Medicines [73]; Terrell: Terrell Computerized Decision Support System to reduce potentially inappropriate prescribing [161]; Zhan: Zhan Criteria [162])

There are two different kinds of approaches to measure the appropriateness of prescribing – implicit and explicit.

Implicit criteria are also called judgement-based because they involve the assessment of prescriptions by trained clinicians consulting their clinical data. Implicit criteria application is individualized for each patient and encompasses various elements of prescribing to be addressed by means of a clinical judgement approach.

Explicit criteria are known as criterion-based and can be used as checklists to detect potentially inappropriate prescriptions by reviewing patients' medications and related pathologies. They are usually applied by extracting pertinent clinical data from electronic medical records or computerized databases.

Implicit criteria put the focus on the drugs used and the diseases, whereas explicit criteria focus more on the patient.

Explicit criteria (among them, STOPP-START, Beers etc.) are applied by checking a list of drugs considered potentially inappropriate for particular conditions or situations (drugs-to-avoid).

These tools are not intended to act as substitutes of the prescriber´s clinical judgment and decision-making but to help them by highlighting the most common potentially inappropriate prescription patterns which should be carefully considered. Their intention is to serve as guidance to good geriatric care and alert for a potential hazard. Therefore, they should be viewed as supporting tools for the proper prescription of drugs, with evidence-based proposals tailored for the older people population [135-137, 141].

3.3 Advantages and Disadvantages of the tools used to measure PIP

Some of the implicit tools used to identify PIP in older people are: the Medication Appropriateness Index (MAI); Screening Medications in the Older Drug User (SMOG); Assess, Review, Minimize, Optimize, Reassess (ARMOR) tool; the Tool to Improve Medications in the Elderly via Review (TIMER); Assessing Care of Vulnerable Elders-3 (ACOVE-3); the Good Palliative-Geriatric Practice Algorithm (GPGPA); and the Assessment of Underutilization (AOU) [163].

One of the most widely used implicit criteria is the MAI (Medication Appropriateness Index), developed more than 20 years ago. The MAI consists of just 10 questions which assess ten elements of prescribing which should be answered by evaluators (generally, clinical pharmacists) by three rating choices; "A" being appropriate, "B" being marginally appropriate and "C" being inappropriate.

1. Is there an indication for the drug?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Are the directions correct?
5. Are the directions practical?
6. Are there clinically significant drug-drug interactions?
7. Are there clinically significant drug-disease/condition interactions?
8. Is there unnecessary duplication with other drugs?
9. Is the duration of therapy acceptable?
10. Is this drug the least expensive alternative compared with others of equal usefulness?

Of course, these questions are accompanied by numerous and updated appendices as references and instructions to help evaluators to accurately answer them [164, 165].

Limitations of implicit criteria include: evaluators with different clinical experience may give different results (eg. different MAI scores); moreover, it is difficult to apply implicit criteria when there is limited data or lack of clinical information. The application of implicit criteria is quite time consuming and subjective.

In turn, explicit criteria can be applied in the routine clinical practice and can be easily adapted to computerized systems; their application is quite inexpensive and time efficient compared to implicit criteria [4, 5].

However, explicit criteria do not take into account patient preferences, life expectancy or prescribers' knowledge of the patient. This way, there is a possibility to miss certain types of inappropriateness that need the full assessment of the patient to come up. They should be frequently updated in order to be relevant and useful in clinical practice taking into account new evidence regarding drugs and clinical conditions; otherwise they would become only rigid guidelines.

Explicit criteria are developed from published reviews, expert opinions, and consensus techniques. They do not take into account all quality indicators of health care or the peculiarities of the individual patient.

Some of the explicit tools used to identify PIP in older people include: the Austrian criteria; the Beers criteria; the Beers Liste (German adaptation of the Beers criteria 2003); MAIO criteria (Italian adaptation of the Beers criteria 2003); Lechevallier criteria (French adaptation of the Beers criteria 1997); Laroche criteria (designed for

use in the French health care system); Rancourt criteria; McLeod criteria (or the Canadian criteria); Improving Prescribing in the Elderly Tool (IPET) (shorter version of the McLeod criteria); the Norwegian General Practice criteria (NORGEP); the PRISCUS list (designed for use in the German health care system); Unangemessene Arzneistoffe für geriatrische Patienten (German adaptation of Laroche criteria); Kaiser Permanente Colorado criteria (KPC); New Mexico criteria; Sloane List of Inappropriate Prescribed Medicines; Zhan criteria; Screening Tool of Older Persons' Prescriptions (STOPP); Screening Tool to Alert doctors to the Right Treatment (START).

The most cited and utilized explicit criteria, Beers criteria, were first developed by Beers et al. in 1991 for nursing home residents. They have been subsequently revised in 1997, in 2003 and recently in 2012 with the support of The American Geriatrics Society (AGS) to update their content and broaden their applicability to all geriatric care settings [143-146].

Nevertheless, the main target of the Beers criteria remains the practicing clinician and they are primarily intended to be used in ambulatory and institutional settings of care for patients aged 65 years old and more in the USA. Numerous articles have been published (more than 200) analyzing their application in different countries and health care settings.

An evidence-based approach has been used to develop the last version of the Beers criteria. The 2012 AGS version of the Beers criteria comprises 53 medications or medication groups organized into three categories:

1) Potentially Inappropriate Medications (PIMs) and classes to avoid in older adults
2) PIMs and classes to avoid in older adults with certain diseases and syndromes that the drugs listed can aggravate
3) Medications to be used with caution in older adults

The complete indicators included in the 2012 update of the Beers criteria are given in Annex 1.

Some of the limitations of the Beers criteria: drugs not available in Europe are included; some kinds of PIMs are overlooked (for example, prescribing omissions, drug/drug interactions, therapeutic duplication); the needs of patients receiving palliative care are not addressed; drugs are not organized by physiological systems or chemical groups [146].

STOPP-START criteria were first developed in Ireland in 2008 by a multidisciplinary team of geriatricians, pharmacologists, pharmacists and primary care doctors and they were validated by a consensus panel through the Delphi process.

They consisted of 65 STOPP indicators including drug–drug and drug–disease interactions, drugs that adversely affect older patients at risk of falls, and duplicate drug class prescriptions as well as 22 START indicators for prescribing omissions.

STOPP is the acronym that stands for 'Screening Tool of Older Persons' Prescriptions' (suggesting when to "stop" a specific prescription), whereas START stands for 'Screening Tool to Alert doctors to the Right Treatment' (suggesting when there is clinical evidence of benefit to "start" a specific prescription) [136].

This set of criteria is organised on the basis of physiological systems, as shown in Figure 4.

Figure 4. Physiologic organization of STOPP-START criteria

STOPP Criteria (65)

- Cardiovascular system
- CNS and psychotropic drugs
- Gastrointestinal system
- Respiratory system
- Musculoskeletal system
- Urogenital system
- Endocrine system
- Drugs that adversely affect those prone to falls
- Analgesics
- Repetition of drugs in the same group
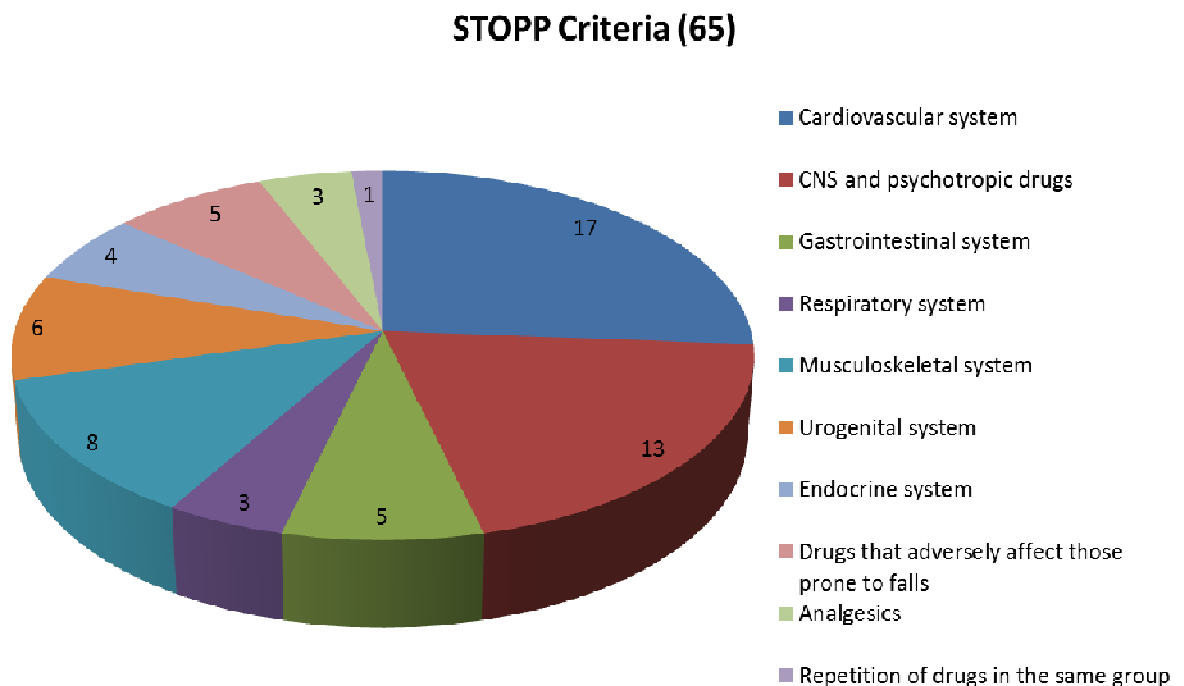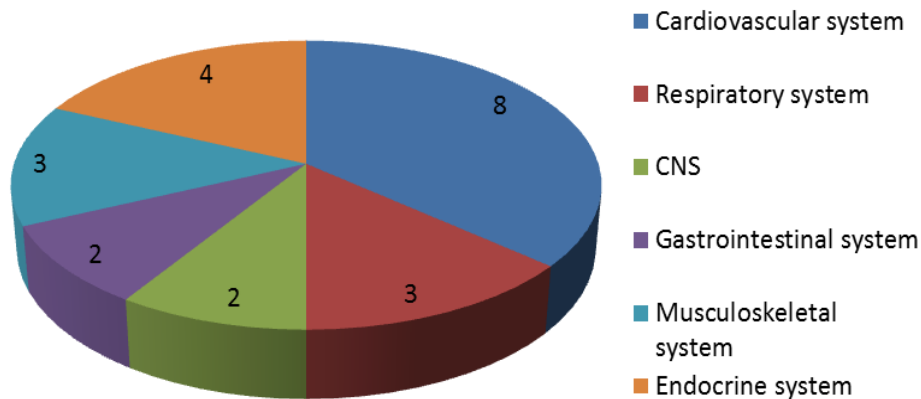
START Criteria (22)

The complete indicators included in the STOPP-START criteria (2008 version) are given in Annex 2.

Beers criteria were initially created in the USA and were developed to be used in the USA, whereas STOPP-START have a broader application in Europe. This is reflected also in the drugs included in each set of criteria; some of the Beers criteria PIMs that are absent nowadays from European drug formularies such as reserpine, guanabenz, trimethobenzamide, estazolam etc. have been omitted in the STOPP-START criteria.

The STOPP/START criteria are reported to be more sensitive and identified more medications associated with adverse drug events than the more-frequently-cited Beers criteria (2003 version) in almost all studies [168].

STOPP criteria PIMs were found to be significantly associated with preventable adverse drug events (ADEs), unlike Beers 2003 criteria PIMs [169].

STOPP-START criteria can be implemented in less than 5 minutes (90 + / -35 seconds in a multicentric study conducted in six European countries) [53], facilitating their application. STOPP criteria identify potentially inappropriate prescriptions, whereas START the omitted prescriptions of indicated drugs in the clinical situation of the patient; thus, their combined use can help in assessing both excessive and insufficient drug treatment. To enable their use as a helping tool in the everyday clinical practice, these criteria should be adapted (tailored) to the local characteristics of drug availability and prescriptions.

STOPP/START criteria have been applied for both research and practical clinical reasons in various countries and settings in almost all continents (Europe, North and South America, Asia, Australia) and more than 84 published articles about them can be accessed in the PubMed database. This is an indicator of their widespread use and potential applicability worldwide [170]. They have been translated into various European languages: French [171], Spanish [172], Czech [173] and Dutch [174].

STOPP-START criteria have been very recently (October 2014) updated and expanded. For example, in version 2 of these criteria, several categories have been added such as: antiplatelet/anticoagulant drugs, drugs affecting, or affected by, renal function and drugs that increase anticholinergic burden [170].

Studies show that STOPP-START have good inter- rater reliability between pharmacists working in different sectors (hospital and community pharmacy) and between physicians in different European countries [175, 176].

The effectiveness of a new software to optimise prescribing among hospitalized older people based on STOPP-START criteria is being evaluated by the SENATOR project (Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older peRsons), an international multicentre RCT (randomized controlled trial) funded by the European Commission Seventh Framework Programme (2012-2017) [177].

To ensure validity of these instruments measuring prescribing inappropriateness, causal association with negative outcomes (such as mortality, adverse drug events) should be proved [21]. Numerous studies performed have demonstrated mixed and sometimes controversial results. Some of them are summarized in Table 5.

Given the heterogeneity of the studies performed until now that differ in the study setting, study sample, type of criteria used for PIP identification and type of intervention it is difficult to draw robust conclusions.

Table 5. Studies assessing misprescribing and adverse patient outcomes

Study (year)	Study sample / Country	Criteria used	Outcome	Ref
Laroche ML et al. Br J Clin Pharmacol (2007)	2018 patients admitted to the acute geriatric unit of a teaching hospital / France	Beers 1997	No significant increased risk of ADR (OR 1.0, 95% CI 0.8–1.3)	131
Fick DM et al. J Managed Care Pharm (2001)	2336 managed care patients / USA	Beers 1997	Higher cost and use of health care (p=0.0001)	178
Perri M III et al. Ann Pharmacother (2005)	1117 residents in 15 Georgia nursing homes / USA	Beers 1997	Higher risk of death/admission/ emergency visit (OR 2.34, 95% CI 1.61–3.40)	179
Chang CM et al. Pharmacotherapy (2005)	882 patients in outpatient clinics / Taiwan	Beers 1997	Higher rate of ADR (RR 15 · 3, 95% CI 4.0–5.88)	180
Raivio MM et al. Drugs Aging (2006)	425 patients admitted to seven nursing homes and two hospitals / Finland	Beers 1997	No significant difference in mortality (HR 1.02, 95% CI 0.7–1.37) and admissions (0R 1.40, 95% CI 0.93–2.11)	181
Fu AZ et al. J Am Geriatr Soc (2004)	2305 community-dwellers (MEPS) / USA	Beers 1997	Poor self-rated health (p=0.006)	182
Lau DT et al. Arch Intern Med (2005)	3372 nursing home residents (MEPS) / USA	Beers 1997	Higher risk of death (OR 1.21, 95% CI 1.00–1.46) and admission (OR 1.28, 1.10–1.50)	183
Zuckerman IH et al. Med Care (2006)	487383 community-dwellers / USA	Beers 2003	Increased risk of nursing home admission over the next 2 years (RR 1.31; 99% CI 1.26–1.36)	184
Onder G et al. Eur J Clin Pharmacol (2005)	5152 patients in 81 hospitals, Italy	Beers 2003	No significant difference in mortality (OR 1.05, 95% CI 0.75–1.48), length of stay (OR 1.09, 95% CI 0.95–1.25), and	185

			ADR (OR 1.20, 95% CI 0.89–1.61)	
Page RL et al. Am J Geriatr Pharmacother (2006)	389 admitted to two adult internal medicine services / USA	Beers 2003	No significant difference in ADE (OR 1.51, 95% CI 0.98–2.35), length of stay (1.03, 0.64–1.63), discharge to higher levels of care (1.39, 0.82–2.34), and in-hospital mortality (1.49, 0.77–2.92)	186
Lin HY et al. Drugs Aging (2008)	5741 ambulatory patients / Taiwan	Beers 2003	Significant association with hospitalization in the multivariate logistic regression analysis	187
Albert SM et al. Drugs Aging (2010)	7459 retirees from prescription and hospitalization claims database / USA	Beers 2003	Increased risk of hospitalization (OR 2.3, 95% CI 2.1–2.6)	188
Ruggiero C et al. Drugs Aging (2010)	1716 nursing home residents / Italy	Beers 2003	Increased risk of hospitalization (HR 1.73; 95% CI 1.14–2.60)	189
Dedhiya SD et al. Am J Geriatr Pharmacother (2010)	7594 nursing home residents / USA	Beers 2003	Higher risk of hospitalization (OR 1.27; 95% CI 1.10-C1.46) and mortality (OR 1.46; 95% CI 1.31-C1.62)	132
Reich O et al. PLoS One (2014)	16 490 managed care patients on PIM and 33 178 not on PIM / Switzerland	Beers 2012	aHR 1.13 (95% CI 1.07-1.19) for 1 PIM, 1.27 (95% CI 1.19-1.35) for 2 PIM, 1.35 (95% CI 1.22-1.50) for 3 PIM, and 1.63 (95% CI 1.40-1.90) for more than 3 PIM compared to no PIM use.	190
Price SD et al. Ann Pharmacother (2014)	251 305 elderly from pharmaceutical claims / Western Australia	Beers 2012	Association with an elevated risk of unplanned hospitalization (aOR = 1.18; 95% CI 1.15-1.21)	191
Pasina L et al. J Clin Pharm Ther (2014)	1380 inpatients in 66 internal medicine and geriatric wards / Italy	Beers 2003 & Beers 2012	No higher risk of adverse clinical events, re-hospitalization and all-cause mortality at 3-month follow-up in both univariate and multivariate analysis.	192

Schmader KE et al. Ann Pharmacother (1997)	208 community-dwellers / USA	MAI	Higher hospital admission (p=0.07) and unscheduled visit (p=0.05); better blood pressure control (p=0.02)	193
Hamilton H et al. Arch Intern Med (2011)	600 patients admitted to a teaching hospital / Ireland	STOPP 2008	Increased risk for ADE (OR 1.847; 95% CI 1.506-2.264; P < .001)	169
Gallagher P et al. Age Ageing (2008)	715 acute patients admitted to a teaching hospital / Ireland	STOPP 2008	Increased hospital admissions (Mann–Whitney Z = −15.33; p<0.001)	56
Gosch M et al. Gerontology (2014)	457 hip fracture patients admitted to hospital / Austria	STOPP-START 2008	Predictor of long-term mortality (OR 1.28 1.07-1.52)	194
Tosato M et al. Age Ageing (2014)	871 in-hospital patients / Italy	STOPP-START 2008	ADR (OR 2.36; 95% CI 1.10-5.06) and decline in physical function (OR 2.00; 95% CI: 1.10-3.64)	195
Cahir C et al. Br J Clin Pharmacol (2014)	931 community dwelling patients in 15 general practices / Ireland	STOPP 2008	Increased ADE (aOR 2.21; 95% CI 1.02, 4.83, P < 0.05), a significantly lower mean HRQOL utility (adj coef. -0.09, SE 0.02, P < 0.001) and increased risk in the expected rate of A&E visits (aIRR 1.85; 95% CI 1.32, 2.58, P < 0.001)	196

ADR □ adverse drug reactions; ADE □ adverse drug events; MEPS □ Medical Expenditure Panel Survey; HRQOL □ health related quality of life

A&E visits □ Accident & Emergency visits

3.4 Economic impact of PIP

Prescribing, as one of the main therapeutic interventions, is a complex process, especially when the patient is older, frail and suffers from multiple comorbidities. This activity should be clinically effective, cost-effective, and safe [197].

Various studies have analyzed the impact of inappropriate prescribing on cost outcomes and have clearly demonstrated that PIP are associated with significant cost consequences.

In a cross-sectional study carried out in Northern Ireland, when applying a subset of the STOPP criteria to 166108 primary care prescriptions from 2009 to 2010, the gross cost of PIP was estimated over 6 million euro [133]. Another large population-based study among 338 801 Irish older patients applying 30 indicators from the STOPP criteria to the pharmacy claims database estimated a total PIP expenditure of 45 631 319 euro which accounts for 9% of the overall expenditure on pharmaceuticals in this population [198].

A study conducted in the USA found that PIM use among community-dwelling older people was a significant predictor for higher healthcare expenditures with an added cost of $7.2 billion associated with it [199].

Therefore, interventions to taper PIP are crucial, not only to prevent negative health consequences associated with them, but also to minimize the waste of monetary resources. In a randomized clinical trial among residents from a chronic care geriatric facility of Israel, a medication intervention with STOPP/START criteria reduced the average drug costs by US$ 29 per participant per month [200].

3.5 Epidemiology (Frequency and Characteristics of PIP)

The frequency of PIP is most often measured as the proportion of studied patients who have at least one PIP. Prevalence varies in a wide range according to different groups, from 15 to 89 %, although figures are generally around 25–35 % [146, 201]. Such substantial differences could be partly explained by the different tools used for assessment. Table 6 clearly shows this difference by comparing the results of recent studies that have applied the same criteria as in our study, both Beers (2012 version)

and STOPP (2008 version). The highest frequency of PIP has been identified by Grace et al in an emergency department of a tertiary hospital in Ireland (Beers: 89.1%, STOPP 84.8%). Certainly, there exist differences in the methodology of these studies. Another possible reason for the variations in the prevalence of PIP may be the distinct prescribing habits of each country.

Table 6. Studies that measure potentially inappropriate prescriptions according both Beers criteria (2012) and STOPP criteria (2008)

Study (year)	Setting / Country	Frecuency of PIP		Ref.
		Beers 2012	STOPP 2008	
Oliveira MG et al. J Eval Clin Pract (2015)	Primary care / Brazil	51.8%	33.8%	202
Grace AR et al. J Am Med Dir Assoc (2014)	ED of tertiary hospital / Ireland	89.1%	84.8%	203
Cahir C et al. Ann Pharmacother (2014)	Primary care / Ireland	28%	42%	204
Blanco-Reina E et al. J Am Geriatr Soc (2014)	Primary care / Spain	44%	35.4%	205
Tosato M et al. Age Ageing (2014)	Hospital / Italy	58.4%	50.4%	195
McMahon CG et al. Age Ageing (2014)	ED / Ireland	44.0%	53.1%	50

In Spain it is estimated that between 25 and 79 % of patients over 65 years old have at least one PIP, a proportion slightly higher than those of neighbouring countries [206, 207]. The environment in which measurements are performed also accounts for some variability. The vast majority of studies to determine these frequencies are either carried out in community, nursing homes or on hospital admissions [132, 136, 208]. Table 7 summarizes the prevalence of PIP found from various studies conducted in Spain.

Table 7. Studies that measure the prevalence of potentially inappropriate prescriptions in Spain using STOPP-START criteria

Study (year)	No. of patients	Prevalence		Observations	Ref
		STOPP	START		
Hospital					
Galán Retanal C et al. Farm Hosp (2014)	179	55.5% 57.5%		Only a subset of 26 STOPP criteria was applied	209
Yeste-Gómez I et al. Rev Calid Asist (2014)	131	35,9 %	31,3 %	STOPP: duplicated medication, BZD in patients who fall and bladder antimuscarinics in dementia START: statins in diabetics with one or more CVRF, antiplatelet agents in diabetics with one or more CVRF and oral bisphosphonates if CCT	210
Galván-Banqueri M et al. Aten Primaria (2013)	244	56%		STOPP: duplicated drug, prolonged use of neuroleptics as hypnotics and prolonged use of BZD with long half-life START: ACE inhibitors in CI, statins in diabetics with one or more CVRF and antiplatelet therapy in diabetic patients with one or more CVRF	211
Iniesta C et al. Aten Farm (2012)	382	25.4%		STOPP: prolonged use of potent opiates as first-line analgesic for mild-moderate pain, prolonged use of BZD with long half-life and NSAIDs with hypertension	212
Gómez-Lobón A et al. Farm Hosp (2012)	171	15%	30%	It was applied only to cardiovascular drugs	213
Delgado Silveira E et al. Rev Esp Geriatr Gerontol (2012)	182	48.9%	57.1%	STOPP: Loop diuretics as first-line monotherapy in hypertension, calcium antagonists in chronic constipation and NSAIDs with hypertension START: statins in diabetics with one or more CVRF, ACE inhibitors in CI and statins with arteriosclerotic disease	214
Sevilla-Sánchez D et al.Rev Esp Geriatr Gerontol (2012)	134	53.4%	46.5%	STOPP: BZD, neuroleptics in patients who fall and cardiovascular drugs START: drugs acting on the endocrine, cardiovascular and musculoskeletal system	215
Regueiro M et al. Rev Peru Med Exp Salud Publica (2011)	97	26%		STOPP: ASA> 150 mg, glibenclamide in type 2 diabetes and duplicated drug	216
Community					
Parodi Lóper N et al. Aten Primaria (2014)	247	32.8%	29.6%	STOPP: prolonged use of BZD START: statins in patients with	80

				diabetes and one or more CVRF	
Blanco-Reina E et al. J Am Geriatr Soc (2014)	407	35.4%		STOPP: ASA with no indication	205
Filomena Paci J et al. Aten Primaria (2014)	467	51.4%	53.6%	STOPP: Prolonged use or prescription without indication of antiplatelet agents. Prolonged use of BZD. Duplicated drug. START: Antiplatelet agents	217
Castillo-Páramo A et al. Semergen (2013)	272	37.5%	45.9%	STOPP: PPI with no indication, duplicate medications, NSAIDs for more than three months, ASA with no indication START: calcium+vitamin D, antiplatelet and statins in patients with diabetes and associated risk factors	218
Hernández Perela J et al. Rev Esp Geriatr Gerontol (2013)	363	36.1%	20.1%	STOPP: NSAIDs with CKD START: metformin in type 2 diabethes ± metabolic syndrome in diabetic and antiplatelet one or more CVRF	219
Candela Marroquín E et al. Rev Esp Salud Publica (2012)	471	34.3%	24.2%	STOPP: duplication of drugs, prolonged use of BZD with long half-life and use of ASA without requiring secondary prevention START: antiplatelet agents and statins in diabetics with one or more CVRF, calcium and vitamin D in osteoporosis and metformin in type 2 diabetes ± metabolic syndrome	220
Mera F et al. Rev Esp Geriatr Gerontol (2011)	78	37%		STOPP: prolonged use of BZD with long half-life, loop diuretics as first-line monotherapy in hypertension and SSRIs with hyponatremia	221
Conejos MD et al. Eur Geriatr Med (2010)	50	36%	28%	STOPP: ASA with no history of ischemic cardiopathy, CVD or peripheral arterial disease, vasodilators in a persistent postural hypotension and BZD in patients who fall START: metformin in type 2 DM ± metabolic syndrome, calcium and vitamin D in osteoporosis and ASA or clopidogrel in arteriosclerotic disease	222
Nursing homes					
García-Gollarte F et al. J Am Med Dir Assoc (2014)	94	79%	74%	STOPP: PPI use without indication and use of BZD and neuroleptics in patients who fall START: calcium and vitamin D in osteoporosis, statins in arteriosclerotic disease and aspirin or clopidogrel in arteriosclerotic disease	223
Ubeda A et al.	81	48%	44%	STOPP: prolonged use of neuroleptics as hypnotics,	224

Pharmacy Practice (2012)				prolonged use of BZD with long half-life and ASA> 150 mg START: calcium and vitamin D in osteoporosis, statins in diabetics with one or more CVRF and acenocoumarol in permanent AF	
Sotoca JM et al. FAP. 2011	121	65.3%	29.7%	STOPP: duplication of drugs, ASA with no history of ischemic cardiopathy, CVD or peripheral arterial disease and prolonged use of BZD with long half-life. START: calcium and vitamin D in osteoporosis, acenocoumarol in permanent AF and antiplatelet agents in diabetics with one or more CVRF	225

AF □ Atrial Fibrillation, ASA □ Acetylsalicylic Acid, BZD Benzodiazepines, CCT □ Corticosteroid Therapy, CI □ Cardiac Insufficiency, CKD □ Chronic Kidney Disease, CVD = cerebrovascular disease, CVRF □ Cardiovascular Risk Factors, SSRIs □ Selective Serotonin Reuptake Inhibitors

3.6 Factors associated with PIP

Different approaches have been undertaken to identify and reduce PIP [161, 226, 227], and the outcomes of these approaches have shown that PIP can be minimized and even prevented. Widespread agreement exists regarding the notion that it is necessary to identify those patients with a higher risk of PIP [201, 228, 229] as well as those drugs with a higher risk of being involved in PIP [230-232].

Along with advanced age, the main reported factors that increase the risk of receiving PIP and the negative outcomes associated with these medications are polypharmacy (a higher risk is associated with a greater number of drugs prescribed) and female sex [201, 232, 233]. In a few studies, the number of prescribers, [66, 130] multiple diseases [234], black skin color [68], and institutionalization [230] were also associated with a higher risk of PIP. Most such studies were performed in the primary care setting or at hospital admission. Very few [235, 236] have analyzed the factors associated with PIP at hospital discharge, which is an especially critical period with respect to the transition between levels of care. Hospital discharge represents a potentially effective target for the reduction of PIP.

3.7 Interventions to reduce PIP

Large evidence exists on the type and effect of various specific interventions to improve suboptimal medicines use, although fewer data are available regarding the cost-effectiveness of such interventions [237].

The effectiveness of such interventions may be influenced by a variety of factors such as the extent of the intervention, the success of its implementation, the characteristics of the participants and other specific aspects of the intervention models.

The most widely used types of interventions to improve prescribing and reduce PIP among older people are:

- Educational interventions

- Review of prescriptions

- Computerized decision-making support systems

Generally, the outcome of these strategies consists on adding beneficial drugs to the patients' treatment as well as removing medications with no valid indication.

- Educational interventions

A vast educational intervention program among Australian general practitioners, pharmacists, and veterans found that the interventions with clear and very specific message (for example, diminish NSAIDs use in high risk patients, decrease the use of high dose proton pump inhibitors) were more successful than those with generic messages (such as, reduce PIM use in older people, avoid interactions between antidepressants) [238]. Another 3 year educational physician-focused intervention in Italy resulted in a reduction of PIM incidence with a positive impact on physician's awareness and prescribing behaviour [227].

- Review of prescription

The review of prescriptions is conducted by health professionals by consulting the full medical records of the patient with the collaboration of the patient and their caregiver [239]. As reported by several studies, review of prescriptions (performed especially by clinical pharmacists alone or in multidisciplinary teams) promoted beneficial changes in terms of improvement of appropriateness of prescribing in hospitalized and primary care older patients [240-243].

Moreover, in a RCT conducted in Sweden among 400 patients 80 years or older, by adding a pharmacist to the intervention group reduction in drug-related readmissions (by 80%), in emergency department visits (by 47%) and in all hospital visits (by 16%)

was reported. The savings as a result of this intervention were $230 per patient [244]. However, time to perform the review for the prescribed medications and patients' preferences are often an obstacle that limit the applicability and feasibility of this kind of intervention in the clinical practice [245].

- Computerized decision-making support systems

Computerized decision-making support systems have led to prevention or discontinuation of PIP in some studies [246, 247] Nonetheless, the application of information technology interventions implies also a potential hazard, if not accompanied with the collaboration and clinical decision of pharmacists and physicians [248].

The marked heterogeneity in the design, setting and outcome measures of these studies does not allow to make generalization of the level of amelioration regarding prescribing or patients' health [249].

Better knowledge on the health and economic impact of specific interventions on prescribing optimization would help to indicate the key areas which should be prioritized and enable informed decision-making.

4. Hospital discharge

4.1 PIP and hospital discharge

Coleman defined care transition as "a set of actions designed to ensure the coordination and continuity of health care as patients transfer between different sites or levels of care" [250]. Hospital discharge, as a period associated with discontinuities in providers and in location of care, as well as with inadequate communication between hospital and community doctors, is commonly prone to medical errors. It represents a step of critical importance in care transition, especially in older patients, and it is often reported to be associated with adverse drug events and medication errors [251-253]. In a very recent study conducted in Israel among 300 hospitalized older patients, hospitalization resulted to an increase in the prevalence of PIP from 39.3% on admission to 46% at discharge [254].

A study performed in a Canadian teaching hospital found that about one in five patients had an adverse event after hospital discharge (laboratory abnormalities,

symptom or MD visit, emergency department visits, hospital readmissions or death) and almost three quarters of the adverse events were related to medication [252]. In a similar study, almost all ADEs were due to newly prescribed medications or modifications in previously prescribed medications [253].

Table 8 shows the studies that have measured the frequency of PIP on hospital admission and at hospital discharge.

Table 8. Studies that compare PIP frequency on hospital admission and discharge

Study (year) [reference]	Setting / Country	Frecuency of PIP		Criteria used
		On admission	At discharge	
Frankenthal D et al. Int J Clin Pharm (2015) [254]	Acute geriatric division / Israel	39.3%	46.0%	STOPP
Galán Retamal C et al. Farm Hosp (2014) [209]	Internal medicine department / Spain	71%	48%	Various
Poudel A et al. Ann Pharmacother (2014) [255]	Acute care hospital / Australia	54.4%	49.5%	Beers
Onatade R et al. Drugs Aging (2013) [256]	Acute care hospital / UK	26.7%	22.6%	STOPP
Bakken MS et al. Scand J Prim Health Care (2012) [235]	Intermediate-care nursing home unit and hospital wards / Norway	24%	35%	NORGEP
Mansur N et al. Ann Pharmacother (2009) [257]	Hospital / Israel	43.5%	44.4%	Beers
Laroche ML et al. Drugs Aging (2006) [258]	Acute geriatric unit / France	66%	43.6%	Beers

The augmented risk for health problems in older people at the particular moment of hospital discharge is also explained by the recent change in health state as well as the frequent and sometimes drastic changes in medications prescriptions, which is rarely reflected by community care providers due to incomplete communication [253, 259, 260].

The most frequently identified types of PIP at hospital discharge according to STOPP criteria in different studies can be seen in Table 9.

Table 9. Most frequently identified potentially inappropriate prescriptions (PIP) at hospital discharge according to STOPP criteria in other studies

Study (year)	Country	Participants and setting	Most frequent PIP	Ref.
Galán Retamal C et al. Farm Hosp (2014)	Spain	179 polypharmacy patients ≥ 65 years old / Internal medicine department	Long-term (> 1 month), long-acting benzodiazepines	209
Manias E et al. Australas J Ageing (2014)	Australia	200 patients ≥ 65 years old / Public teaching hospital	Aspirin with no history of coronary, cerebral or peripheral arterial disease or occlusive arterial events	261
Onatade R et al. Drugs Aging (2013)	UK	195 patients ≥ 65 years old / Acute care hospital	Drugs adversely affecting patients at risk of falls	256
Liu CL et al. Arch Gerontol Geriatr (2012)	Taiwan	520 patients ≥ 65 years old / Veterans General Hospital	Drugs adversely affecting patients at risk of falls	262
Delgado Silveira E et al. Rev Esp Geriatr Gerontol (2012)	Spain	189 older patients / Geriatric Department of university hospital	Loop diuretic as first-line monotherapy for hypertension	214
Pyszka LL et al. Consult Pharm (2010)	USA	111 patients > 70 years old / Veterans Affairs hospital	Medications without an appropriate diagnosis	263

Better organized primary care, especially coordination of care, would minimize avoidable hospitalization rates, especially for patients with multiple chronic conditions [264].

The fragmentation of healthcare makes it necessary to follow patients more closely after discharge.

OBJECTIVES

1. To measure the frequency of PIP in older people ($\geq$ 65 years old) at hospital discharge identified by two different tools (Beers and STOPP criteria)

2. To analyze the association of PIP with different predictive factors (age, gender, Charlson Comorbidity Index, number of drugs prescribed at discharge, pharmacological group of each drug prescribed, the Hospital Specialty, length of hospital stay etc.)

3. To identify the drugs most commonly involved in PIP according to both criteria.

4. To identify the patients´ characteristics that may influence the occurrence of PIP

5. To study the association between PIP in older patients at hospital discharge and health outcomes measured in the short to medium term, particularly mortality, number of hospital readmissions, primary care consultations, home visits and emergency treatment recorded from the date of hospital discharge to the last contact with the health system.

MATERIAL AND METHOD

1. Study design

Cross sectional study

2. Reference population

The reference population consisted of older people (65 years and more) discharged from the University Specialty Hospital San Cecilio, Granada, during the period from July 1, 2011 to June 30, 2012. The hospital belongs to the Andalusian Health Service, serving the Granada Midwest Hospital area population of 346,682 inhabitants (about 50,962 older than 64 years).

3. Inclusion criteria

• Presenting a discharge between July 2011 and June 2012, both inclusive, from the services of surgery, traumatology, internal medicine and other medical specialties (including cardiology, gastro-intestinal, respiratory, endocrinology and nephrology).

• 65 years old or more

• Charlson Comorbidity Index ≥ 2 (obtained through personal history and diagnoses reflected in the hospital discharge report)

4. Exclusion criteria

• Discharge due to transfer to another hospital

• Discharge due to death

• Discharge from the services of dermatology, ophthalmology and otorhinolaryngology.

5. Study population

The documentation service provided a list of patients 65 years old or more discharged during the study period for whom the reason of discharge was different from death or transfer to another hospital (N = 8154). A 15 % random sample of this group (N = 1,004) was drawn using the resampling option of Stata software (Stata Corp LP, College Station, TX, USA), in order to warrant 3 % accuracy after dropout patients who did not meet inclusion criteria. In total, 361 (40.0 %) patients were excluded

because the Charlson Comorbidity Index was lower than 2 and another 19 patients (1.9 %) because they were discharged from any one of the hospital services listed in the exclusion criteria. The final sample therefore included a total of 624 patients that fulfilled the inclusion criteria. This number allowed us to estimate a proportion of 20 % with an accuracy of 3 %, and arrive at significant differences for a 6 percentage point difference with a minimum power of 80 %.

6. Information Sources

– The Hospital database, provided through the Documentation Service for the period of study, gave each patient´s history number, age, gender, Unified Medical Record Number, service of discharge, dates of admission and discharge, principal diagnosis and Diagnosis Related Group (DRG) code was directly obtained from the hospital Minimum Basic Data Set (MBDS).

– Clinical history: Discharge report.

Subsequently, detailed information including the primary diagnosis, the comorbidities, and the prescribed treatment at discharge was collected from patients´ discharge reports (Spanish: informe de alta).

The minimum set of data that should be included in the clinical discharge reports of the National Health System in Andalucia are stated in the Royal Decree 1093/2010. Obligatory administrative and clinical data for each patient discharged from an Andalusian hospital are part of his electronic discharge report [265].

Patients data include:

- Name, First surname, second surname, date of birth, sex,

- ID, Passport number, European CIP, NASS, CIP of C. Autonoma, SNS code, No. of clinical history

- Domicile (Street type, number and name; floor, postal code, province, telephone)

- Reason of discharge (transfer to other service, to other hospital, to social health centre, to home, voluntary discharge, for exitus, other reason)

- Reason for hospitalization

- Type of hospitalization

- Antecedents (family hereditary diseases, previous illness, neonatal, obstetric and surgical history, allergies, toxic habits, preventive actions such as vaccinations, previous medication, functional situation, social and professional background)

- Current history

- Physical examination

- Summary of additional tests (laboratory, image, other tests)

- Evolution and comments

A study evaluating the quality of hospital discharge reports in 11 hospitals of Andalusia categorized 97.4% of these reports as adequate in terms of legislation requirements and expert recommendations. Among the inadequacies observed are the use of abbreviations, underreporting of relevant diseases, the absence of treatment plan description or follow-up recommendations and problems associated with the reconciliation of treatment [266].

When the required information regarding clinical and therapeutic data was unavailable or insufficient to apply the criteria, we consulted the electronic clinical history to review the complete medical history of the patient.

7. Collection of information

The initial assessment including the review of patients' hospital discharge information was conducted between October 2012 and February 2013. We also collected information after discharge between December 2012 and March 2013 by consulting the database of the Clinical History Diraya* for these patients.

* Diraya (knowledge in Arabic language) is the software used since 2000 by the public health system in the region of Andalusia in Spain. The essence of this computing system is the electronic health file called health history (Spanish: historia de salud) which lists the administrative and health data of the patient. It gives detailed information about the patient including previous hospitalisations, health problems, treatments and performed tests, the family and medical history, allergies and more. Diraya is a unified Electronic Health Record (EHR) that enables the integration of all the information systems and healthcare management in the Primary Healthcare

Centers as well as mental health and emergency services, and outpatient specialized care in Andalusia [267, 268].

8. Study variables

The independent study variables were: age; gender; Charlson Comorbidity Index (from 2 to 37, calculated using the calculator type.xls of Hall) [269]; number of drugs prescribed at discharge; pharmacological group of each drug prescribed (according to the Anatomical Therapeutic Chemical Pharmacological Subgroup Code, consisting of one letter, two numbers and two more letters); hospital service (we grouped the cases into three categories: surgery, internal medicine and other medical services); length of hospital stay and DRG code.

The dependent variables were: the number of PIP according to the two criteria used and the number of patients with at least one PIP in their treatment plan, according to the two criteria used (Beers 2012 update and STOPP 2008).

Using Excel 2007 (Microsoft Corporation, Redmond, WA, USA) we recorded the prescription of each drug included under either of the two criteria as well as the presence or absence of related pathologies. Subsequently, and independently for each of the indexes, an "ad hoc" algorithm was constructed by applying the conditions in Table 9 in order to catalog as appropriate or inappropriate each of these drugs. In this study we have used an adapted version of the 2008 version of the STOPP criteria and the 2012 version of the Beers criteria for PIP identification. For each drug included in the respective PIP criteria (Beers and STOPP) a value of 0 or 1 was assigned, being 1 when any of the grounds of inadequacy was satisfied and 0 when the drug was not prescribed or when it was not considered inappropriate. We finally noted the number of inadequacies.

We excluded from the Beers and STOPP criteria drugs not available in Spain. START criteria were not applied because patient follow-up was required. PIP associated with a history of falls and fractures were also omitted as only information at discharge was consulted, without follow-up data (a detailed list of the adapted criteria is given in Table 10).

In order to obtain the necessary information after discharge for the assessment of health outcomes associated with PIP, an independent researcher was provided with a list which contained for each patient the Unified Medical Record Number, the patient´s date of birth and sex, the date of admission that determined the inclusion in the study and the Charlson index. The individualized consultation of each clinical history (via Diraya) allowed collecting information about the following variables from the date of hospital discharge to the date of history revision: PIP at discharge according to Beers criteria; PIP at discharge according to STOPP criteria; total number of drugs; main diagnosis at discharge; comorbidities. Mortality, number of hospital readmissions, primary care consultations, home visits and emergency treatment for each patient from the date of hospital discharge to the last contact with the health system were recorded.

Table 10. Adaptation of Beers criteria and STOPP criteria

Beers Criteria			STOPP Criteria			
Drug Group (Specific drugs)	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	**Drug Group (Specific drugs)**	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	Inappropriate Prescription in association with
NSAIDs	Gastroduodenal Ulcer		NSAIDs	Gastroduodenal Ulcer without H2 antihistamines or PPI or misoprostol		
	Heart Failure			Moderate to severe hypertension		
	Renal Failure			Digestive bleeding		
COX-2 Inhibitors	Heart Failure		COX-2 Inhibitors			
Aspirin			Aspirin	Gastroduodenal Ulcer without H2 antihistamines or PPI or misoprostol		
					Antecedents of ischemic cardiopathy, cerebrovascular disease, peripheral arterial disease or arterial occlusion	
				Hemorrhagic disease		
						Warfarin without H2 antihistamines or PPI
Aspirin > 150 mg/d			Aspirin > 150 mg/d	Always		
Aspirin > 325 mg/d	Gastroduodenal Ulcer		Aspirin > 325 mg/d			
Indometacin Ketorolac Pentazocine	Always		Indometacin Ketorolac Pentazocine			
Meperidine	Delirium		Meperidine			
Tramadol	Epilepsy		Tramadol			

Beers Criteria			STOPP Criteria			
Drug Group (Specific drugs)	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	**Drug Group (Specific drugs)**	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	Inappropriate Prescription in association with
Diphenhydramine		Acute treatment of severe allergic reaction	Diphenhydramine			
H1 Antihistamines Brompheniramine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Diphenhydramine Doxylamine Hidroxyzine Prometazine Triprolidine	Delirium / Dementia / Chronic constipation / Prostatism		H1 Antihistamines Brompheniramine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Diphenhydramine Doxylamine Hidroxyzine Prometazine Triprolidine			
Prometazine	Parkinson disease		Prometazine	Parkinson disease		
H2 Antihistamines Cimetidine Famotidine Ranitidine	Delirium / Dementia		H2 Antihistamines Cimetidine Famotidine Ranitidine			
Antispasmodics Belladonna alkaloids Chlordiazepoxide Scopolamine		Palliative treatment	Antispasmodics Belladonna alkaloids Chlordiazepoxide Scopolamine			

Beers Criteria			STOPP Criteria			
Drug Group (Specific drugs)	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	**Drug Group (Specific drugs)**	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	Inappropriate Prescription in association with
Bladder relaxants Antimuscarinics Fexofenadine Oxybutynin Solifenacin Tolterodine Trospium	Dementia		Bladder relaxants Antimuscarinics Fexofenadine Oxybutynin Solifenacin Tolterodine Trospium	Dementia		
				Chronic constipation		
	Chronic constipation			Prostatism		
				Glaucoma		
				Extrapyramidalism		
Dipyridamole Ticlopidine Clopidogrel			Dipyridamole Ticlopidine Clopidogrel	Hemorrhagic disease		
Dipyridamol rapid release not associated	Always		Dipiridamol rapid release not associated			
Cilostazol	Heart Failure		Cilostazol			
Warfarin			Warfarin	Hemorrhagic disease		
Nitrofurantoin	Renal Failure		Nitrofurantoin			
Alpha blockers Doxazosin Prazosin Terazosin	Syncope		Alpha blockers Doxazosin Prazosin Terazosin	Urinary incontinence		
	Hypertension					
	Urinary incontinence					
Alpha agonists Clonidine Methyldopa	Always		Alpha agonists Clonidine Methyldopa			
Beta blockers			Beta blockers			Verapamil
Non cardioselective beta blockers (Carteolol, Carvedilol, Nadolol, Oxprenolol, Propranolol, Sotalol, Timolol, Labetalol, Levobunolol)			Non cardioselective beta blockers (Carteolol, Carvedilol, Nadolol, Oxprenolol, Propranolol, Sotalol, Timolol, Labetalol, Levobunolol)	Chronic Obstructive Pulmonary Disease (COPD)		

Beers Criteria			STOPP Criteria			
Drug Group (Specific drugs)	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	**Drug Group (Specific drugs)**	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	Inappropriate Prescription in association with
Antiarrhythmics Ia, Ic, III Amiodarone Dronedarone Flecainide Procainamide Propafenone Sotalol	Atrial fibrillation		Antiarrhythmics Ia, Ic, III Amiodarone Dronedarone Flecainide Procainamide Propafenone Sotalol			
Dronedarone	Heart Failure		Dronedarone			
Calcium antagonists Diltiazem Verapamil	Heart Failure		Calcium antagonists Diltiazem Verapamil	Heart Failure		
	Chronic constipation			Chronic constipation		
Digoxin > 0,125 mg/d	Always		Digoxin > 0,125 mg/d	Renal Failure		
Spironolactone > 25mg/d	Heart Failure		Spironolactone > 25mg/d			
	Renal Failure					
Triamterene	Renal Failure		Triamterene			
Loop diuretics Torasemide Furosemide			Loop diuretics Torasemide Furosemide	Hypertension without other antihypertensive drug		
Thiazides Hydrochlorothiazide Chlorthalidone Indapamide			Thiazides Hydrochlorothiazide Chlorthalidone Indapamide	Gout		

Beers Criteria			STOPP Criteria			
Drug Group (Specific drugs)	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	**Drug Group (Specific drugs)**	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	Inappropriate Prescription in association with
Tricyclic Antidepressants Amitriptyline Chlordiazepoxide Clomipramine Doxepin Imipramine Perphenazine Trimipramine	Dementia		Tricyclic Antidepressants Amitriptyline Chlordiazepoxide Clomipramine Doxepin Imipramine Perphenazine Trimipramine	Dementia		
	Chronic constipation			Chronic constipation		
	Prostatism			Prostatism		
	Syncope			Arrhythmia		
	Delirium			Urinary retention		
				Glaucoma		
						Opioids or calcium antagonists
Bupropion	Epilepsy		Bupropion			
SSRI Fluoxetine Citalopram Duloxetine Escitalopram Paroxetine Fluvoxamine Sertraline			SSRI Fluoxetine Citalopram Duloxetine Escitalopram Paroxetine Fluvoxamine Sertraline	Hyponatremia		
Phenothiazines Chlorpromazine Clozapine Maprotiline Olanzapine	Epilepsy		Phenothiazines Chlorpromazine Clozapine Maprotiline Olanzapine	Epilepsy		
	Parkinson disease					
	Dementia					
Chlorpromazine	Delirium		Chlorpromazine			
	Syncope					
Olanzapine	Syncope		Olanzapine			
All antipsychotics	Dementia					

Beers Criteria			STOPP Criteria			
Drug Group (Specific drugs)	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	**Drug Group (Specific drugs)**	Inappropriate Prescription in presence of	Inappropriate Prescription except in case of	Inappropriate Prescription in association with
Benzodiazepines Alprazolam Lorazepam Oxazepam Triazolam Clorazepate Chlordiazepoxide Clonazepam Diazepam Flurazepam Quazepam	Dementia Insomnia Agitation Delirium		Benzodiazepines Alprazolam Lorazepam Oxazepam Triazolam Clorazepate Chlordiazepoxide Clonazepam Diazepam Flurazepam Quazepam			
Zolpidem	Dementia		Zolpidem			
Chlorpropamide Glibenclamide	Always		Chlorpropamide Glibenclamide	Always		
Metoclopramide	Parkinson disease		Metoclopramide	Parkinson disease		
Loperamide Codeine Diphenoxylate			Loperamide Codeine Diphenoxylate	Diarrhea without cause Severe infectious acute gastroenteritis		
Acetylcholinesterase Inhibitors Pyridostigmine Neostigmine Galantamine Donepezil Chlorpromazine	Syncope		Acetylcholinesterase Inhibitors Pyridostigmine Neostigmine Galantamine Donepezil Chlorpromazine			
Oral corticosteroids	Delirium		Oral corticosteroids	COPD instead of inhaled corticosteroids		
Inhaled ipratropium			Inhaled ipratropium	Glaucoma		
Any regular prescription of two drugs of the same class			Always			

Drugs in Beers criteria not considered in our study

Disopyramide

Nifedipine immediate release

Phenobarbital

Testosterone

Estrogens

Growth hormone

Insulin, sliding scale

Megestrol

Pioglitazone, Rosiglitazone

Oral Pseudoephedrine

Oral Phenylephrine

Amphetamine

Methylphenidate

Theophylline

Caffeine

Drugs in STOPP criteria not considered in our study

Estrogens

Theophylline

9. Data analysis

The statistical package Stata, version 10.0 (Stata Corp LP) was used for data analysis.

• Descriptive analysis of the study population characteristics: frequency distribution for the qualitative variables, and measures of central tendency and dispersion for the quantitative variables.

• Estimated prevalence of PIP for each criteria and its 95 % confidence interval (CI), globally and stratified for different categories of the study variables.

• Degree of agreement between the two criteria (Beers and STOPP) using the Kappa statistic.

• We estimated the strength of the association between each variable and the presence of at least one PIP by calculating the odds ratio (OR) and 95% confidence interval (CI). Adjustment for confounding variables was performed using a multiple logistics regression model that included all variables with a statistically significant effect, along with the patients' sex and age. Both saturated and selected models were estimated by a stepwise forward algorithm with an entry level of $p < 0.25$.

RESULTS

1. Description of the study population

A population of 624 patients, with somewhat more men than women, was included in our study.

Figure 5. Flowchart showing the inclusion of patients in the study

Reference population: **8154** patients

15% random sample: **1004** patients

Final sample included in the study: **624** patients
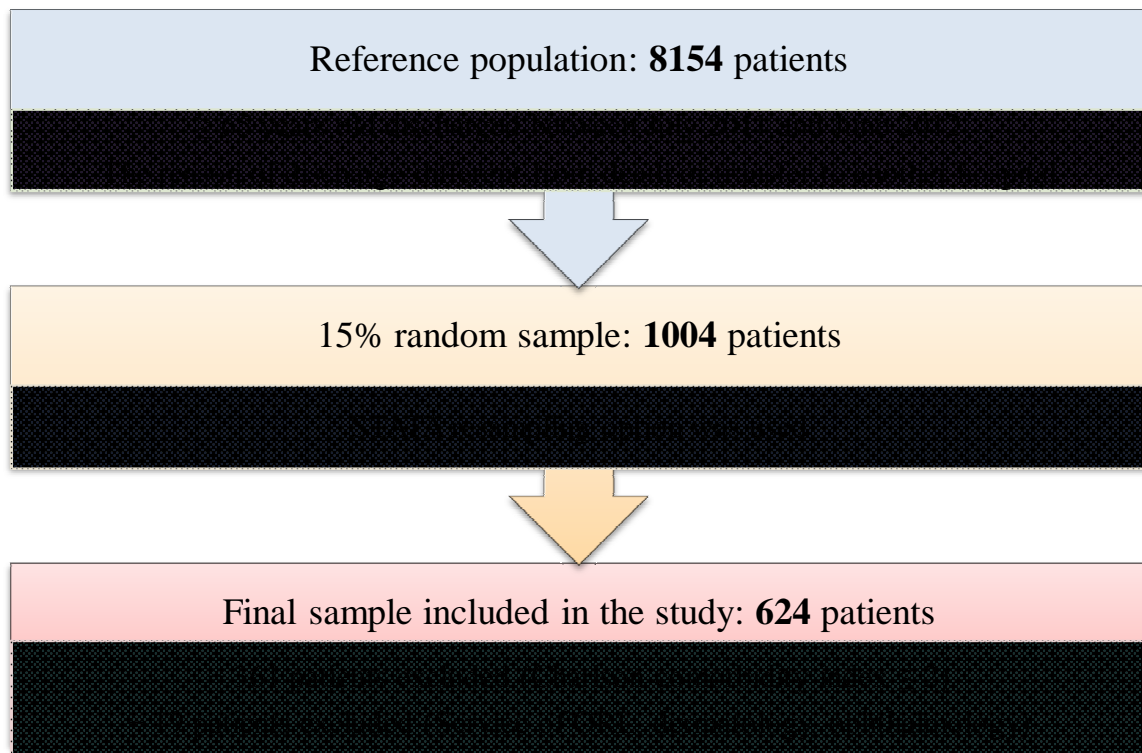
The median age was 78 years old (range 65–95). The population was distributed evenly in three groups of services: Surgery, Internal Medicine and Other Medical Services, and 32.5 % of the sample suffered from high comorbidity (Charlson Comorbidity Index $\geq$ 4). The number of drugs prescribed presented a median value of eight (range 1–21). Around 30% of all patients took 6 or less drugs and more than 20% of them took more than 11 drugs. The median length of stay in hospital was 7 days, ranging from 1 to 105 days.

Table 11 offers a detailed description of the population.

Table 11. Description of the population

Variable	Category	N	%

Gender	Men	343	54.97%
	Women	281	45.03%
Age (years)	65 - 74	216	34.62%
	75 – 84	296	47.44%
	≥ 85	112	17.95%
	Mean (SD)	77.71 (6.87)	
	Mediana (Range)	78.00 (65, 95)	
Service	Surgery	191	30.61%
	Internal Medicine	177	28.37%
	Other Medical Services	256	41.03%
Charlson Comorbidity Index	2	253	40.54%
	3	168	26.92%
	4	100	16.03%
	>= 5	103	16.51%
	Mean (SD)	3.21 (1.43)	
	Mediana (Range)	3 (2, 10)	
Drugs number	6 or less	185	29.65%
	7, 8	140	22.44%
	9, 10, 11	165	26.44%
	More than 11	134	21.47%
	Mean (SD)	8.57 (3.62)	
	Mediana (Range)	8 (1, 21)	
Length of stay	7 days or less	318	50.96
	More than 7 days	306	49.04
	Mean (SD)	9.55 (8.84)	
	Mediana (Range)	7 (1, 105)	

A very high proportion of patients (63.3%) suffered from moderate to severe hypertension. Frequent pathologies identified in our study population were also: antecedents of ischemic cardiopathy, cerebrovascular disease (CVD), peripheral arterial disease (PAD) or arterial occlusion, renal failure, cardiac failure, chronic

obstructive pulmonary disease (COPD) and arrhythmia. The complete distribution of pathologies in the study population is given in Table 12.

Table 12. Distribution of pathologies in the study population

Pathology	N	%
Moderate to severe hypertension	395	63,30
Antecedents of ischemic cardiopathy, CVD, PAD or arterial occlusion	209	33,49
COPD	165	26,44
Cardiac failure	172	27,56
Arrhythmia	159	25,48
Permanent atrial fibrillation	105	16,83
Renal failure	191	30,61
Gastro duodenal Ulcer	22	3,53
Prostatism	67	10,74
Dementia	42	6,73
Parkinson Disease	8	1,28
Gout	33	5,29

A total of 5350 medications were prescribed to the patients included in our study.

The median number of medications per patient was 8 (range 1-21)

The most commonly prescribed groups of drugs according to the Anatomical Therapeutic Chemical (ATC) classification system were in this order: C (Cardiovascular system), A (Alimentary tract and metabolism), R (Respiratory system) and N (Nervous system).

Omeprazole was the most frequently prescribed drug (72.6% of patients), followed by furosemide (44.7% of patients) and aspirin (36.7% of patients).

Table 13 offers a detailed summary of the frequency of drugs (or drugs groups) prescribed in the studied sample.

Table 13. Global frequency of drugs (or drugs groups) prescribed

Drugs (or drugs group)	Global frecuency of use in the studied sample	
	N	%
Proton Pump Inhibitors	453	72,60%
Aspirin	206	33,01%
Benzodiazepines	165	26,44%
Beta-blockers	184	29,49%
Non-cardioselective beta-blockers	72	11,54%
Loop diuretics	279	44,71%
Thiazides	80	12,82%
Selective Serotonin Reuptake Inhibitors	42	6,73%
NSAIDs	111	17,79%
Dipyridamole	66	10,58%
Warfarin	81	12,98%
Oral corticosteroids	134	21,47%
Inhaled corticosteroids	157	25,16%
Ipratropium	68	10,90%
Calcium channel antagonists	52	8,33%
Verapamil	4	0,64%
Digoxin	19	3,04%
Spironolactone	17	2,72%
Aspirin > 150 mg	21	3,37%
Aspirin > 325 mg	2	0,32%
Zolpidem	19	3,04%
Metoclopramide	9	1,44%
Loperamide	9	1,44%
H2 Antihistamines	16	2,56%
Alpha-blockers	73	11,70%
Antimuscarinics	1	0,16%
Opioids	30	4,81%
Tramadol	21	3,37%
Antipsychotics	1	0,16%
Other Antipsychotics	38	6,09%
Tricyclic antidepressants	5	0,80%
Clorpromazine	2	0,32%
Olanzapine	2	0,32%
Quetiapine	7	1,12%
H1 Antihistamines	9	1,44%
Cholinesterase inhibitors	8	1,28%
Procainamide	13	2,08%
Dronedarone	1	0,16%

Antispasmodics	1	0,16%
COX-2 Inhibitors	3	0,48%
Cilostazol	1	0,16%

2. Results according to specific objectives

1. To measure the frequency of PIP in older people (≥ 65 years old) at hospital discharge identified by two different tools (Beers and STOPP criteria)

The overall frequency of PIP was 22.9 % according to the Beers criteria (95 % CI 19.6–26.2 %) and 38.5 % (95 % CI 34.6–42.3 %) according to the STOPP criteria; in 13.6 % of the patients the prescriptions were simultaneously inappropriate for Beers and STOPP criteria.

Only 13 out of 143 patients with PIP showed more than one prescribed drug that met Beers criteria for inappropriateness; under STOPP criteria there were 64 patients (from 240) with more than one PIP (Table 14).

Table 14. Number of PIP / patient according to Beers and STOPP criteria

	Number of PIP / patient	N	%
PIP according to Beers	0	481	77,08
	1	130	20,83
	2 or more	13	2,08
PIP according to STOPP	0	384	61,54
	1	176	28,21
	2 or more	64	10,25

We estimated that the degree of agreement between the two criteria is 65.9 %, with Kappa 21.9 (SD 3.7) underlining a poor agreement between them (Table 15).

Table 15. Agreement between Beers and STOPP criteria

		PIP according to STOPP criteria		Total
		Yes	No	
PIP according to Beers criteria	Yes	85 (13.62 %)	58 (9.29 %)	143 (22.92 %)
	No	155 (24.84 %)	326 (52.24 %)	481 (77.08 %)
Total		240 (38.46 %)	384 (61.54 %)	624

Observed agreement = 65.87 %

Expected agreement = 56.25 %

Kappa = 0.2198; SE = 0.0374

2. To analyze the association of PIP with different predictive factors (age, gender, Charlson Comorbidity Index, number of drugs prescribed at discharge, pharmacological group of each drug prescribed, the Hospital Specialty, length of hospital stay etc.)

No differences were found in the proportion of inappropriateness by age (Figure 6), gender or length of hospital stay (Table 16).

Figure 6. Frequency of PIP identified by Beers, STOPP and both criteria among three age groups of older people (N □ 624)
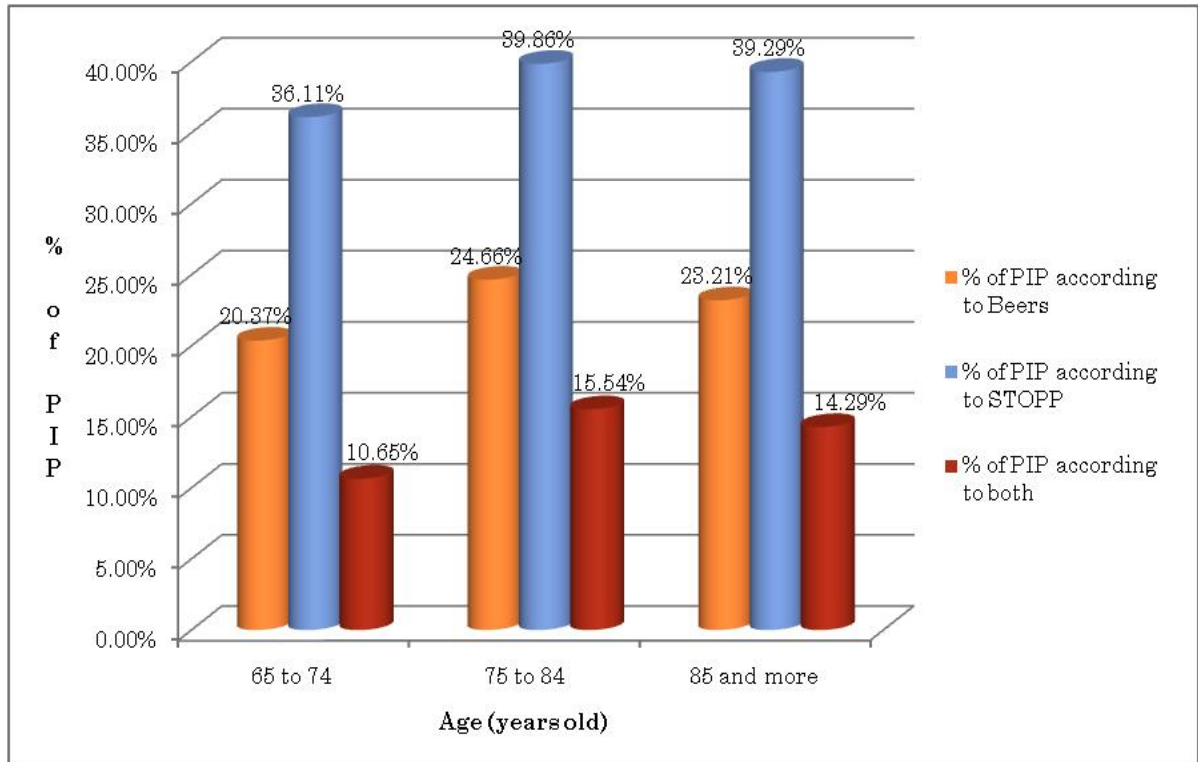
Differences were, however, found in view of discharge service (Table 16), the frequency being significantly higher among patients from Internal Medicine (33.33% vs. 19.92% in other medical services and 17.28% in Surgery according to STOPP; 50.28% vs. 35.55% in other medical services and 31.41% in Surgery according to Beers criteria). There was a significantly higher frequency of PIP when the Charlson Index was 4 or 5 compared to an index of 3 or less, but only under Beers criteria ($p < 0.005$). PIP frequency was seen to rise significantly with the number of drugs prescribed according to both criteria ($p < 0.01$).

Table 16. PIP frequency according to the criteria used, global and stratified for the study variables

	PIP according to Beers			PIP according to STOPP			PIP according to both		
Total	N	%	CI 95%		N	%	CI 95%		N	%	CI 95%
	143	22.92%	19.61% - 26.22%		240	38.46%	34.63%	42.29%	85	13.62%	10.92%	16.32%
Gender											
Men	77	22.45%	18.02% - 26.88%		129	37.61%	32.47%	42.75%	40	11.66%	8.25%	15.07%
Women	66	23.49%	18.51% -28.46%		111	39.50%	33.76%	45.24%	45	16.01%	11.71%	20.32%
		NS				NS				NS		
Age (years)											
65-74	44	20.37%	14.98%	25.76%	78	36.11%	29.68%	42.54%	23	10.65%	6.52%	14.78%
75-84	73	24.66%	19.73%	29.59%	118	39.86%	34.27%	45.46%	46	15.54%	11.40%	19.68%
>=85	26	23.21%	15.34%	31.08%	44	39.29%	30.18%	48.39%	16	14.29%	7.76%	20.81%
		NS				NS				NS		
Service in charge											
Surgery	33	17.28%	11.89%	22.66%	60	31.41%	24.80%	38.03%	19	9.95%	5.68%	14.21%
Internal Medicine	59	33.33%	26.36%	40.31%	89	50.28%	42.88%	57.68%	41	23.16%	16.92%	29.41%
Other Medical Services	51	19.92%	15.01%	24.83%	91	35.55%	29.66%	41.43%	25	9.77%	6.12%	13.42%
		p<0.01				P<0.01				P<0.01		
Charlson Comorbidity Index											
2	47	18.58%	13.77%	23.39%	89	35.18%	29.27%	41.09%	25	9.88%	6.19%	13.57%
3	32	19.05%	13.08%	25.01%	68	40.48%	33.02%	47.94%	19	11.31%	6.50%	16.12%
4	29	29.00%	20.04%	37.96%	42	42.00%	32.26%	51.74%	19	19.00%	11.26%	26.74%
5	35	33.98%	24.77%	43.19%	41	39.81%	30.29%	49.32%	22	21.36%	13.39%	29.33%
		p < 0.005				NS				p<0.01		
Number of drugs											
6 or less	24	12.97%	8.11%	17.84%	45	24.32%	18.11%	30.54%	13	7.03%	3.33%	10.73%
7, 8	26	18.57%	12.09%	25.05%	50	35.71%	27.73%	43.70%	17	12.14%	6.70%	17.58%
9, 10, 11	49	29.70%	22.69%	36.70%	69	41.82%	34.25%	49.38%	29	17.58%	11.74%	23.41%
More than 11	44	32.84%	24.84%	40.83%	76	56.72%	48.28%	65.15%	26	19.40%	12.67%	26.14%
		P<0.01				P<0.01				P<0.005		
Length of stay											
7 days or less	66	20.75%	16.28%	25.23%	114	35.85%	30.56%	41.14%	35	11.01%	7.55%	14.46%
More than 7 days	77	25.16%	20.28%	30.04%	126	41.18%	35.64%	46.71%	50	16.34%	12.18%	20.50%
		NS				NS				P=0.052		

NS – Not significant

The crude and adjusted association between study variables and PIP defined for Beers and STOPP criteria is shown in Table 17.

Table 17. Crude and adjusted association between study variables and PIP defined for Beers and STOPP criteria

Variable	Beers Criteria						STOPP Criteria					
	cOR	CI 95%		aOR[4]	CI 95%		cOR	CI 95%		aOR[4]	CI 95%	
Gender[1]	1,00	0,69	1,46	1,04	0,70	1,54	1,05	0,76	1,44	1,07	0,76	1,55
Age (years)	1,02	0,99	1,05	1,03	1,00	1,06	1,01	0,99	1,04	1,02	0,99	1,04
Internal Medicine Service[2]	2,39	1,47	3,90	2,74	1,44	5,21	2,21	1,44	3,38	2,31	1,34	4,00
Other Medical Services[2]	1,19	0,73	1,93	1,60	0,86	2,99	1,20	0,81	1,79	1,43	0,85	2,38
Charlson comorbidity Index	1,16	1,03	1,32	1,00	0,84	1,20	1,05	0,94	1,18	0,98	0,85	1,13
Number of drugs	1,14	1,08	1,20	1,14	1,08	1,20	1,15	1,09	1,20	1,15	1,10	1,21
Length of hospital stay	1,01	0,99	1,03	1,01	0,98	1,03	1,01	0,99	1,03	1,00	0,99	1,03
Revision of clinical history[3]	1,46	0,96	2,22	1,76	1,13	2,74	1,31	0,90	1,91	1,52	1,02	2,26
Moderate to severe hypertension[3]	2,19	1,43	3,35	1,76	1,13	2,76	2,69	1,88	3,86	2,24	1,54	3,28
Antecedents of ischemic cardiopathy, CVD, PAD or arterial occlusion[3]	0,57	0,37	0,87	0,44	0,28	0,70	0,51	0,36	0,73	0,39	0,26	0,57
COPD[3]	1,32	0,88	1,99	1,08	0,69	1,68	2,01	1,40	2,89	1,79	1,21	2,63
Cardiac failure[3]	2,80	1,89	4,15	2,40	1,54	3,73	1,54	1,08	2,19	1,19	0,80	1,77
Arrhythmia[3]	2,57	1,72	3,83	2,29	1,50	3,48	1,46	1,02	2,11	1,25	0,85	1,83
Permanent	2,91	1,86	4,54	2,51	1,58	4,00	1,19	0,78	1,82	0,98	0,62	1,53

atrial fibrillation[3]												
Renal failure[3]	2,74	1,86	4,04	2,36	1,52	3,65	1,27	0,90	1,80	1.03	0,70	1,54
Gastro duodenal Ulcer[3]	0,33	0,08	1,42	0,41	0,09	1,84	0,74	0,30	1,84	1,00	0,39	2,58
Prostatism[3]	2,21	1,30	3,78	2,71	1,48	4,97	0,70	0,41	1,21	0,68	0,38	1,22
Dementia[3]	7,23	3,73	14,03	8,21	4,05	16,62	1,50	0,80	2,80	1,50	0,77	2,89
Parkinson Disease[3]	2,04	0,48	8,64	1,44	0,31	6,75	1,61	0,40	6,50	1,05	0,24	4,66
Gout[3]	2,64	1,29	5,41	2,08	0,97	4,44	2,59	1,27	5,32	2,22	1,04	4,72

[1]Reference: men; [2]Reference: surgical services; [3]Reference: patients without this condition

[4]Adjusted by sex, age, Charlson comorbidity index, number of drugs, and revision of clinical history

Abbreviations: CVD = cerebrovascular disease, PAD = peripheral arterial disease, COPD = chronic obstructive pulmonary disease

3. To identify the drugs most commonly involved in PIP according to both criteria.

Figure 7 and 8 indicate the drugs most commonly resulting in inappropriate prescribing. We found, for Beers criteria that they were (in this order): alpha blockers, NSAIDs, and calcium channel antagonists. For STOPP criteria, they were aspirin and NSAIDs. When stratified by sex, the most noteworthy difference is the predominance of calcium antagonists and digoxin in women and alpha blockers in men for Beers criteria, whereas for STOPP criteria they were NSAIDs in men and calcium channel antagonists and loop diuretics in women. Only five drugs were responsible for 81.1 and 76.7 % of PIP for Beers and STOPP criteria, respectively.

Figure 7. Drugs involved in Potentially Inappropriate Prescriptions according to Beers criteria (N = 156) a. globally: b. stratified by sex
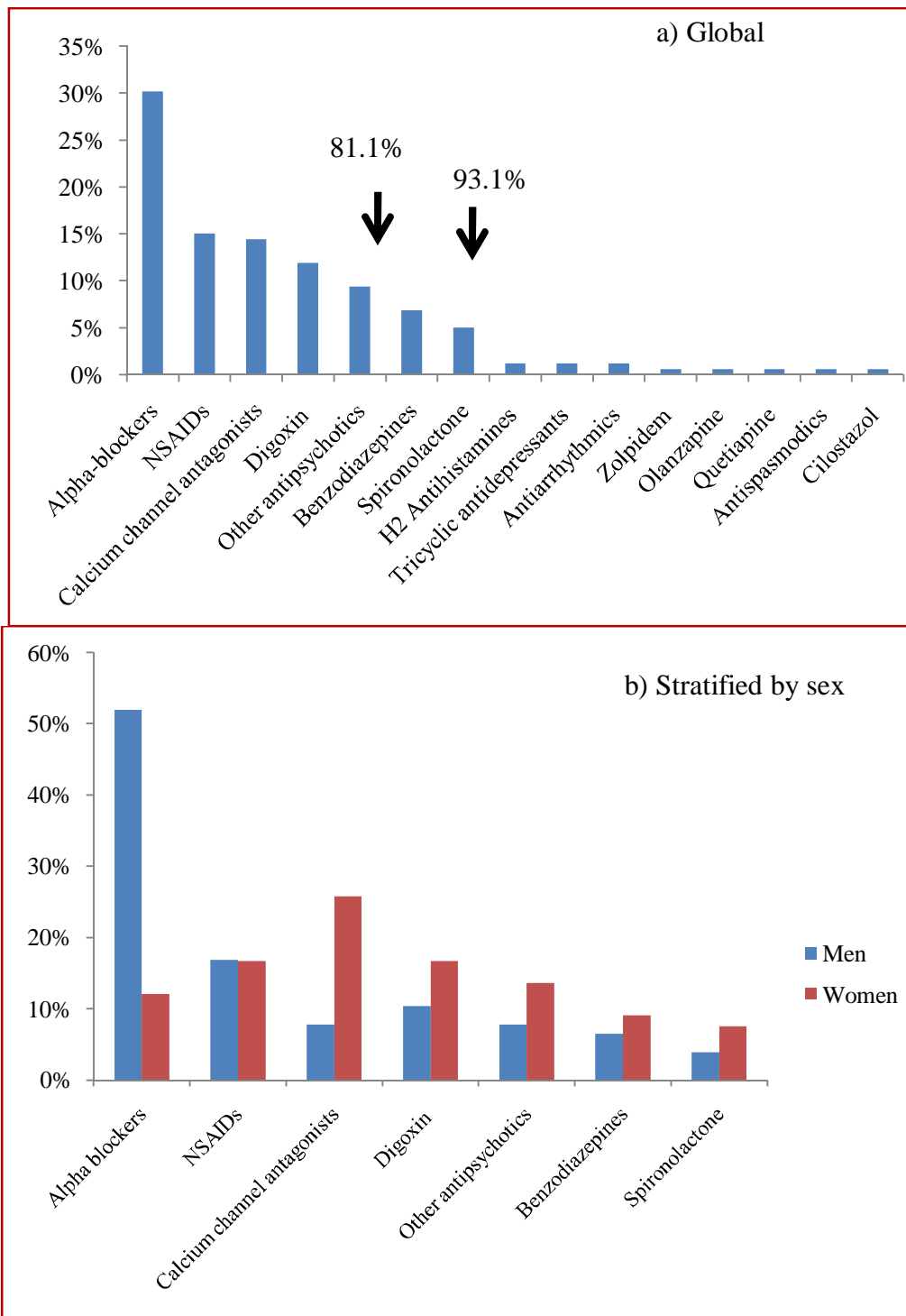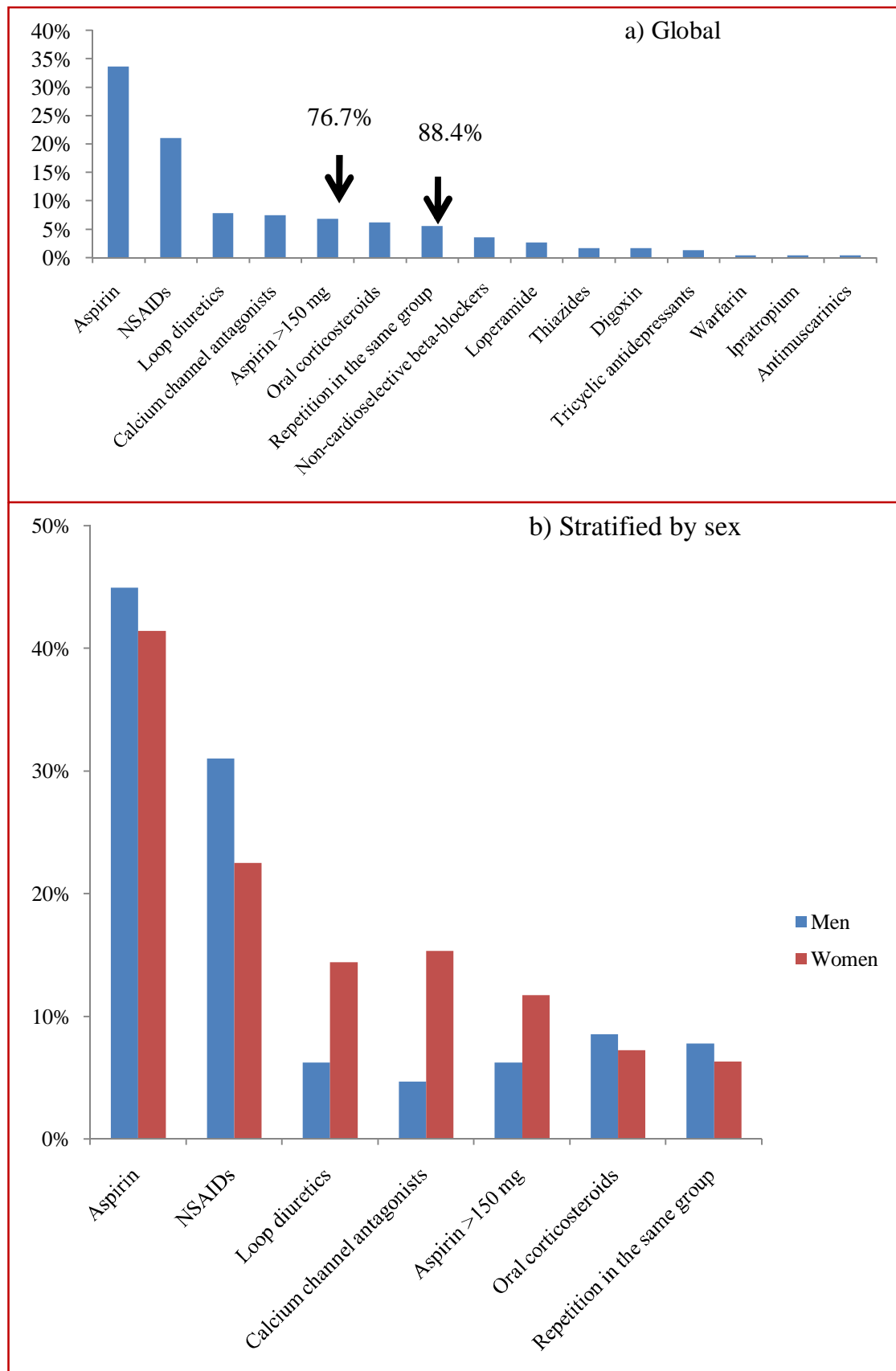
Figure 8. Drugs involved in Potentially Inappropriate Prescriptions according to STOPP criteria (N = 241) a. globally; b. stratified by sex

The most frequent drugs that contributed to PIP using the Beers criteria were alpha-blockers (such as doxazosin, prazosin, and terazosin), which were considered to be potentially inappropriate in 65.7% of the prescriptions or 48 patients (when prescribed in the presence of syncope, hypertension, or urinary incontinence). While digoxin at a dose of >0.125 mg was inappropriate in all 19 prescriptions according to the Beers criteria, calcium antagonists were considered to be inappropriate in only 23 patients (44.2% of the prescriptions, which were those associated with heart failure or chronic constipation).

When the STOPP criteria were used for PIP identification, the most common causes of inappropriateness were nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, which were inappropriate in 65 (59.1%) and 104 (50.5%) of the prescriptions, respectively. NSAIDs are classified as inappropriate when prescribed in the presence of gastroduodenal ulceration without the concomitant use of antiulcer drugs, in the presence of digestive bleeding, or in patients with moderate to severe hypertension. The prescription of aspirin is potentially inappropriate in the presence of hemorrhagic disease or gastroduodenal ulceration, as for NSAIDs, as well as when associated with warfarin without the concomitant use of antiulcer drugs. Aspirin at a dose of >150 mg accounted for another 21 prescriptions, all of which were identified as inappropriate by the STOPP criteria. The latter constituted 3.3% of all prescriptions.

Table 18 shows the most important drugs or drugs groups classified as PIP and their global frequency of use in the studied sample.

Table 18. Most frequent drugs or drug groups involved in potentially inappropriate prescriptions

Drugs or drugs groups	Global frequency of use in the studied sample (N = 624)		PIP according to Beers criteria		PIP according to STOPP criteria	
	N	%	N	%	N	%
Alpha blockers	73	11,70	48	65,75	0	
NSAIDs	111	17,79	24	21,82	65	59,09
Aspirin	206	33,01	-		104	50,49
Calcium channel antagonists	52	8,33	23	44,23	23	44,23
Digoxin	19	3,04	19	100	5	26,32
Loop diuretics	279	44,71	-		24	8,60
Benzodiazepines	165	26,44	11	6,67	-	
Aspirin 150 mg	21	3,37	-		21	100

4. To identify the patients´ characteristics that may influence the occurrence of PIP

The patients' sex and length of hospital stay did not seem to be associated with PIP, unlike the type of hospital service, which was found to have a statistically significant influence ($p < 0.01$) according to both criteria (Table 16). The risk of PIP was higher among patients discharged from the internal medicine service (Beers: aOR, 2.7; 95% CI, 1.4–5.2; STOPP: aOR, 2.3; 95% CI, 1.3–4.0) than among patients discharged from surgical services (Table 17). The higher risk of PIP among patients discharged from the internal medicine service was not maintained when adjusting for confounding variables. Increasing age was a significant risk factor for PIP only when adjusting for other pathological conditions and the number of drugs using the Beers criteria. The Charlson comorbidity index was a risk factor for PIP according to the Beers criteria (aOR, 1.1; 95% CI, 1.0–1.3), but not when PIP were defined by the STOPP criteria.

The number of prescribed drugs was another evident risk factor for PIP, as shown in Table 19 and more clearly in Figure 9. Each additional drug increased the risk of PIP by 14% (Beers criteria) or 15% (STOPP criteria).

Table 19. Association of the number of drugs prescribed with the number of PIP detected according to Beers and STOPP criteria

Number of drugs prescribed	Beers criteria		STOPP criteria	
	Patients without PIP	Patients with PIP	Patients without PIP	Patients with PIP
3 or less	46	4	42	8
4 to 6	115	20	98	37
7 to 9	157	40	128	69
10 to 12	103	47	74	76
More than 12	60	32	42	50
Total	481 (77.1%)	143 (22.9%)	384 (61.5%)	240 (38.5%)

Figure 9. Association of the number of drugs prescribed with the number of PIP detected according to Beers and STOPP criteria
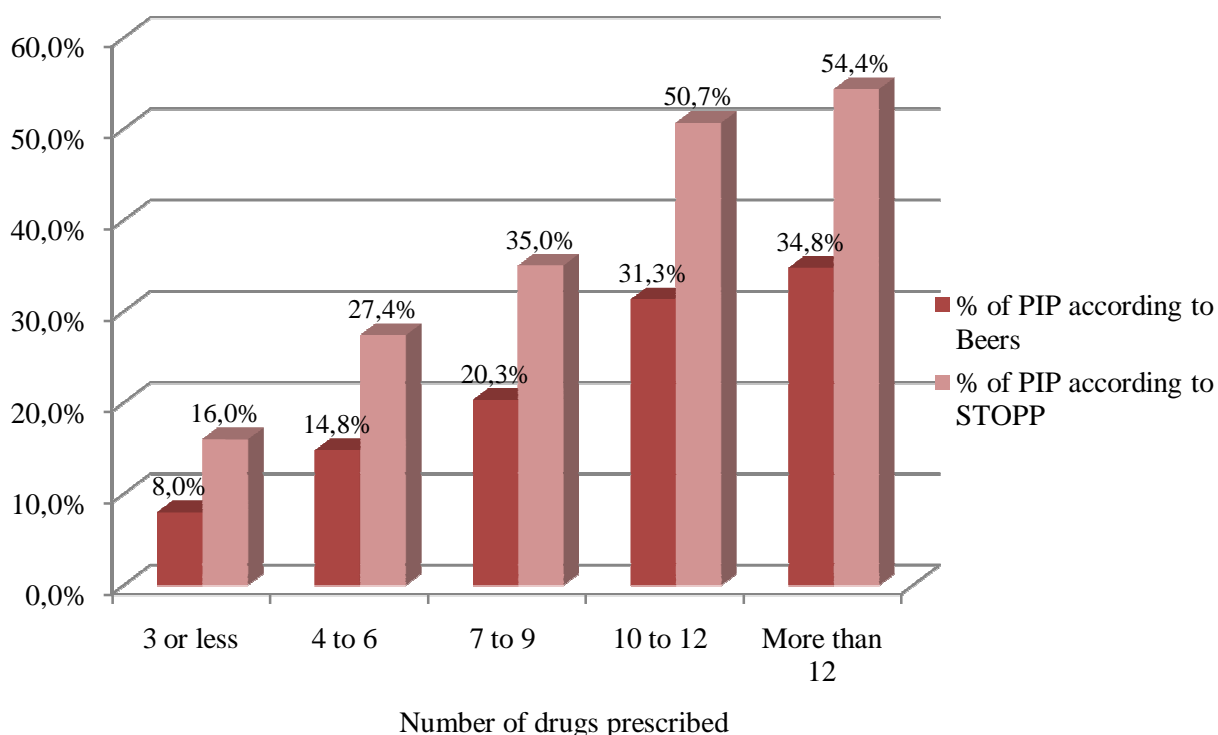
Specific pathological conditions that influenced the occurrence of PIP as identified by the Beers criteria were hypertension, cardiac failure, arrhythmia, permanent atrial fibrillation, renal failure, prostatism, and particularly dementia (aOR, 8.2; 95% CI, 4.0–16.6). Conversely, preexisting ischemic cardiopathy, cerebrovascular disease, and peripheral arterial disease acted as protective factors (aOR, 0.4; 95% CI, 0.2–0.7). Analysis of the remaining analyzed pathological conditions revealed no significant association.

When the STOPP criteria were used for PIP identification, only hypertension, chronic obstructive pulmonary disease, and gout increased the risk of PIP, while the protective factors were identical to those identified using the Beers criteria (aOR, 0.3; 95% CI, 0.2–0.5).

Considering only the PIP associated with the five drugs or drugs groups most frequently used (Beers criteria: alpha-blockers, NSAIDs, calcium channel antagonists, digoxin, and benzodiazepines; STOPP criteria: aspirin, NSAIDs, loop diuretics, calcium channel antagonists and aspirin dose of >150 mg), the frequency of PIP was reduced from 22.9% to 19.7% and from 38.4% to 30.4%, respectively. The associated factors were almost identical between the two criteria (data not shown), the only difference being a lower effect of dementia in the STOPP criteria than in the Beers criteria (OR, 3.1; 95% CI, 1.5–6.3).

5. To study the association between PIP in older patients at hospital discharge and health outcomes measured in the short to medium term, particularly mortality, number of hospital readmissions, primary care consultations, home visits and emergency treatment recorded from the date of hospital discharge to the last contact with the health system.

Table 20 summarizes the events detected during follow-up after hospital discharge highlighting, according to STOPP criteria, the frequency of hospital readmissions within 30 days after discharge, which was higher for patients without PIP (p = 0.053) and a significant increase in the average number of domiciliary visits (43.7 versus 29.7) in patients with PIP, almost significantly.

Table 20. Detected events during stratified follow-up based on the existence or non-existence of PIP according to STOPP criteria

STOPP	With PIP (N = 215)				Without PIP (N = 340)			
	N	%	Mean	SD	N	%	Mean	SD
Exitus	49	22,79	-	-	63	18,52	-	-
Hospitalization in the first month (**)	16	7,44	-	-	43	12,64	-	-
Number of hospitalizations			0,46	0,75			0,48	0,8
0	75	34,88	-	-	114	33,52	-	-
1	56	26,05	-	-	76	22,35	-	-
2	13	6,05	-	-	30	8,82	-	-
≥3	6	2,8	-	-	8	2,35	-	-
Number of emergency hospital visits	133	46,51	1,4	2,00	205	60,29	1,4	1,9
Number of primary care consultations			6,49	5,11			6,07	5,78
0	10	4,65			13	3,82		
1-3	65	30,23			123	36,17		
4-6	49	22,79			87	25,58		
7-9	36	16,74			47	13,82		
≥10	55	25,58			70	20,58		
Number of domiciliary visits (**)			0,43	1,07			0,29	0,96
0	167	77,67			281	82,64		
1	23	10,69			37	10,88		
2	17	7,90			16	4,70		
≥3	8	3,72			6	1,76		

** Statistically significant differences (p≤0.05)

For PIP identified by Beers criteria (Table 21), no difference regarding health outcomes was observed between the two groups of patients generated.

Table 21. Detected events during stratified follow-up based on the existence or non-existence of according to Beers criteria

Beers	With PIP (N = 126)				Without PIP (N = 429)			
	N	%	Mean	SD	N	%	Mean	SD
Exitus	27	21,42	-	-	85	19,81	-	-
Hospitalization in the first month	13	10,31	-	-	46	10,72	-	-
Number of hospitalizations			0,5	0,9			0,4	0,74
0	44	34,92	-	-	145	33,79	-	-
1	27	21,43	-	-	105	24,48	-	-
2	13	10,32	-	-	30	6,99	-	-
≥3	4	3,17	-	-	10	2,33	-	-
Number of emergency hospital visits	78	61,90	1,4	1,9	260	60,60	1,3	1,9
Number of primary care consultations			6,06	5,12			6,29	5,65
0	5	3,96			18	4,19		
1-3	44	34,92			144	33,56		
4-6	32	25,39			104	24,24		
7-9	18	14,28			65	15,15		
≥10	27	21,42			98	22,84		
Number of domiciliary visits			0,38	0,83			0,34	1,05
0	98	77,77			350	81,58		
1	13	10,31			47	10,95		
2	13	10,31			20	4,66		
≥3	2	1.59			12	2.79		

The effect of the collected variables on mortality is given in table 22. No association was found with sex; on the contrary, it was associated with age (4% increase of the annual risk) and with the Charlson comorbidity index with an increased mortality risk of 42% for each point increase.

Patients discharged from the Internal Medicine service showed higher mortality rates than those discharged from Surgery. Besides, the comorbidities associated with increased mortality were arrhythmia and dementia. Neither STOPP, nor Beers criteria had a significant influence on mortality, nor did the intersection between the two types of criteria.

The possible effect of the most frequent groups of drugs classified as potentially inappropriate by either of the two criteria was assessed. For Beers criteria, no significant association was found; however spironolactone and digoxin stood out for the magnitude of the association which was maintained even when adjusted. For STOPP criteria, a significant and independent increase in mortality was observed when aspirin was inappropriately prescribed. This association was not found when all prescriptions of aspirin were analyzed.

Table 22. Effect of PIP on mortality after discharge

	cOR	CI		aOR	CI	
Sex (ref. men)	1.10	0.73	1.67	1.04	0.66	1.62
Age (per year increase)	**1.04**	**1.01**	**1.07**	**1.04**	**1.00**	**1.07**
Internal Medicine	**2.09**	**1.21**	**3.63**	1.65	0.89	3.07
Surgery	1.35	0.80	2.29	1.20	0.69	2.11
Charlson comorbidity index	**1.42**	**1.24**	**1.63**	**1.42**	**1.23**	**1.64**
Number of drugs	0.99	0.94	1.05	0.96	0.90	1.02
Arrhythmia	**1.83**	**1.18**	**2.86**	**1.63**	**1.01**	**2.64**
Permanent atrial fibrillation	**2.03**	**1.23**	**3.34**	**1.76**	**1.03**	**2.99**
Dementia	**2.54**	**1.20**	**5.36**	1.92	0.87	4.26
Beers	1.10	0.68	1.80	1.05	0.68	1.64
Spironolactone_b	3.02	0.67	13.70	2.41	0.48	12.12
Digoxine according Beers	2.25	0.74	6.86	2.31	0.72	7.37
STOPP	1.30	0.85	1.98	1.19	0.76	1.87
Aspirin_s	**1.72**	**1.04**	**2.85**	**1.74**	**1.02**	**2.97**
Beta blockers_s	2.41	0.57	10.24	2.84	0.63	12.80
Digoxine according Stopp	8.04	0.72	89.43	4.98	0.41	59.85
Loop diuretics	2.39	0.92	6.23	1.69	0.62	4.63
PIP Both criteria	1.34	0.88	2.03	1.28	0.82	2.00

Adjusted for age, sex, service of discharge, Charlson index and number of drugs

DISCUSSION

1. Discussion of the study methodology

1.1 Study design

A cross sectional, retrospective study was designed including the period from 1 July 2011 to 30 June 2012. This type of design is the best to determine prevalence and is also used to identify associations with different variables. However, cross sectional studies do not provide an explanation whether this association is a cause or effect; neither do they establish the sequence of events [270].

1.2 Representativity of the study population

1.3 Quality of the collected information

2. Discussion of the study results

2.1 Frequency of PIP

In our study we observed a very high frequency of PIP at the time of discharge. Yet there was also a wide variation depending on the indicator used—22.9 % for Beers criteria and 38.4 % for STOPP criteria. Altogether, 13.6 % of the prescriptions were identified as potentially inappropriate simultaneously for both criteria.

Comparisons with other studies must take into account the differences in the study setting and the health care system, which may be particularly affected by the authorized drugs and the funding model. Furthermore, the population included and their level of health care should be considered. Our study focuses on older people ≥65 years old; and we chose hospital discharge in view of the fact that the transition of care between hospital and domicile is associated with an increased risk of adverse events for patients.

The values obtained in patients´ admission in a multicenter European study were higher than in this study. The overall PIM prevalence rate was 51.3% using STOPP

criteria, varying from 34.7% in Prague to 77.3% in Geneva, and 30.4% using Beers criteria, varying from 22.7% in Prague to 43.3% in Geneva, but as well as in our results a higher prevalence of PIP according to STOPP than according to Beers criteria was recorded [53].

Appraising 1,329 older patients in general practice, Ryan et al. [271] identified a somewhat lower prevalence of PIP, though very similar with both criteria, of 18.3 and 21.4 %. Almost the same results were reproduced in Germany; 21.7% (119,482) and 18.2% (98,465) of patients 65 years or older received at least one PIM prescription in 2003 and 2004, respectively (p < 0.001) [272]

A study conducted in India [273] determined prevalences of PIP of 24.6 and 13.3 %, respectively for Beers and STOPP criteria—the only example we found that attributes higher sensitivity to the Beers criteria. Our results, like those of other studies [53, 56, 271], point to higher PIP with STOPP than with Beers criteria.

No indicators led to significant differences related to gender or age, similarly to the findings of Ryan et al. [274] and unlike Nyborg et al. [130] and Goltz et al. [272]. The PIP percentage does not change with the length of hospital stay. PIP frequency increases with the number of drugs prescribed (P<0.01), as was reported by Gallagher et al. [53]. This is not surprising, as many of the items included under both criteria are based on the incompatibility between specific drugs and drugs with specific diseases.

Differences concerning the type of specialty are also observed, with a higher frequency of PIP in Internal Medicine; similarly, Blasco Patiño [207] found 36.6 % PIP on admission in a Department of Internal Medicine, which may be explained by the complex co-morbidity of these patients.

Perhaps the most interesting finding of our study is that, under either Beers or STOPP criteria, intervening on just five specific drugs (or drug groups) could mean as much as an 80 % reduction of PIP. The percentage rises to about 90 % if we focus on the seven most common drugs. Acting on the two drugs most often repeated in both criteria (alpha blockers, NSAIDs), the frequency of PIP could be reduced by 30 % according to Beers and 25 % with STOPP criteria.

These results suggest that simplifying the criteria by reducing the number of covered items would make it possible to apply them more readily, without reducing their usefulness.

There is very poor agreement between the two types of criteria studied here. The Kappa Index of 23.0 % obtained highlights the differences between the drugs

analyzed by each of these indices and the evaluation criteria used. Even when the inappropriateness refers to the same drug, it does not always coincide in terms of prescribed use. In fact, only calcium channel antagonists are listed as inappropriate in the same circumstances (23 cases) under both criteria. In contrast, NSAIDs are inappropriate in 65 cases according to STOPP and just 24 cases according to Beers criteria.

According to STOPP criteria, digoxin is assessed as inappropriate in only five cases, while Beers criteria list it as inappropriate in 19 cases; tricyclic antidepressants are inappropriate in four and two cases, respectively, for STOPP and Beers criteria. There were no cases of inappropriateness found for any of the other drugs included under both criteria.

2.2 Factors associated with PIP

A reduced frequency of PIP is a targeted intervention strategy for improved pharmacotherapy in older patients [42]. Identifying both the risk and protective factors associated with PIP would greatly help in their detection and careful consideration [201].

In various studies involving hospitalized older patients, polypharmacy was associated with or predicted the use of PIP using both criteria (Beers and STOPP) [53], only the STOPP criteria, [236, 275] or only the Beers 2012 updated criteria [276]. In the present study, a higher number of prescribed drugs was also found to be an important risk factor regardless of the criteria used for PIP identification. Even though the estimated HR is overestimated due to the high frequency of the studied event, the magnitude of the effect, an increase of 14% or 15% for each added drug respectively according to Beers and STOPP criteria, strongly suggests that this variable acts as a risk factor.

Being discharged from the internal medicine service was associated with a significantly higher risk of PIP than being discharged from surgical services. This may have been owing to the higher age of patients admitted to the internal medicine service; such patients generally have more comorbidities and prescribed drugs. However, this effect was maintained when the analysis was adjusted for these variables, including adjustment for the need to review the clinical history, which indirectly assesses the quality of the discharge report.

Unlike other studies, [130, 201, 233] we found no association between the frequency of PIP and increasing age or sex, with the exception of increasing age with the Beers criteria after adjustment for other pathological conditions and the number of drugs. The pathological conditions mostly associated with PIP in both criteria were moderate to severe hypertension (risk factors) and preexisting ischemic cardiopathy, cerebrovascular disease, and peripheral arterial disease (protective factors). Hypertension as an important risk factor is most clearly understood by analyzing both criteria because specific drug groups are considered to be inappropriate when prescribed in patients with hypertension (Beers: alpha blockers; STOPP: NSAIDs and loop diuretics). Preexisting ischemic cardiopathy, cerebrovascular disease, or peripheral arterial disease act as a protective factor for PIP according to both criteria. This can be easily explained for STOPP criteria by the fact that aspirin is not considered to be inappropriate in the presence of these conditions, however we have no any comparable explanation for Beers criteria.

When factors associated with PIP are analyzed separately for Beers and STOPP, other pathological conditions seem to have a greater influence, particularly dementia for Beers and chronic obstructive pulmonary disease for STOPP. Dementia ceased to be a risk factor with application of the STOPP criteria. This is explained by the fact that benzodiazepines are considered to be potentially inappropriate when prescribed in the presence of dementia only according to the Beers criteria. Chronic obstructive pulmonary disease acts as a risk factor only for the STOPP criteria because of the inappropriate prescription of non cardioselective beta-blockers. These drugs are always inappropriate according to the Beers criteria; however, when the STOPP criteria are used, they are considered to be inappropriate only in the presence of chronic obstructive pulmonary disease.

The pathological conditions that acted as risk factors for PIP only with the Beers criteria are explained by the specific drug–disease interactions described in this set of criteria, such as NSAIDs and spironolactone prescribed in the presence of renal failure and cardiac failure or antiarrhythmic drugs prescribed in the presence of permanent atrial fibrillation.

The differences identified in the present study reflect the different contents of the two criteria, suggesting the need for consensus on the optimal tool for PIP identification, as already noted by Vishwas et al. [273]. In the present study, the most prevalent drugs associated with PIP were alpha-blockers in the Beers criteria and NSAIDs and

aspirin in the STOPP criteria. Different studies exhibit wide variations in the drugs most frequently involved in PIP depending on the study setting and the tool used for PIP detection [232, 233, 262, 273].

Even after narrowing the PIP definition to only the five drug groups associated with more frequent PIP, the associated factors remained the same. However, the effect of dementia was reduced in the Beers criteria, which accounts for the omitted PIP (the potentially inappropriate prescription of H2 antihistamines, tricyclic antidepressants, and zolpidem).

The validation of prescribed treatment at discharge by clinical pharmacists would improve the quality of such treatment; unfortunately, human resources, at least in Spain, are often insufficient to perform it. Identifying the factors associated with increased risk of PIP would enable to select the groups of patients who would benefit more from medication reconciliation by pharmacists, therefore improving the efficiency of the intervention. It could also allow to generate an alert for a closer monitoring of these patients in primary care.

2.3 Polypharmacy and PIP

A strong association between polypharmacy and negative clinical consequences has been reported in different healthcare settings, including hospital discharge [277]. A study conducted in 38 internal medicine wards in Italy found that 67% of patients were prescribed five or more drugs at hospital discharge [278], similarly to our findings.

Our study, like previous studies in this level of healthcare [72, 279], observed a clear increase in the number of PIP with higher number of drugs prescribed. Explicit criteria such as Beers and STOPP may be used as helping tools to identify PIP and to potentially avoid negative consequences associated with PIP. Using two different explicit criteria for PIP detection, we identified 30% and 38.5% of patients (according to Beers and STOPP criteria, respectively) with at least one PIP. These figures are lower than the prevalence of unnecessary drugs (44%) found by Hajjar et al. by applying an implicit set of criteria (MAI) for PIP detection [279]. Consistently with most studies [168], STOPP criteria were more sensitive than Beers criteria in detecting PIP.

2.4 PIP and health outcomes

Our results show little relationship between potentially inappropriate prescriptions and health needs expressed in the short to medium term, although an almost significant increase is found in the number of domiciliary visits by the physician in the PIP group and a higher percentage of hospital readmissions in the first 30 days in the group without PIP.

Data is difficult to compare with previous studies, since potentially inappropriate prescriptions are generally measured in primary care. An increase of acute hospital admissions in the frail elderly is described secondary to potentially inappropriate prescriptions using STOPP criteria by Dalleur et al [129], but the sense of this association is not completely clear. A recent study among older patients in primary care showed that patients with PIP (identified by STOPP) had about two-fold increased risk in the expected rate of hospital accident and emergency visits [196].

In the study by Reich O. et al [190] cumulative levels of PIM use (defined by Beers criteria and Priscus list) acted significantly as a factor related to greater hospitalization rates. Also, Lau DT et al. found an association between inappropriate prescriptions in elderly nursing home residents and subsequent hospitalization and death, when the Beers criteria were used to identify PIP [183], while in another study among patients after hospital discharge, Beers criteria medications did not play an important role in adverse drug events [280]. Our study, similarly to that from Pasina L. et al [192] in hospitalized elderly patients found no association between PIP and death or return visits to the emergency department with neither of the two criteria.

The drugs most frequently classified as inappropriate according to Beers were the alpha blockers, NSAIDs, and calcium channel antagonists; none of them was independently associated with increased rate of hospitalization or increased use of services.

When STOPP criteria were used for PIP detection, aspirin and NSAIDs were responsible for over 50% of the cases classified as patients with PIP; in this case, there was a significant association between aspirin and patient mortality, which remained significant when adjusting for confounding variables.

If we accept, as noted repeatedly in the literature that the prescription of potentially inappropriate drugs is associated with increased healthcare costs and adverse events

[183, 189, 190, 194, 204, 281], and that this effect is preventable [227, 282, 283], it is essential to identify tools that truly detect inappropriate prescribing and act on it, improving the safety of drug treatments, particularly among older patients with multiple pathologies.

2.5 Strength and weaknesses

The main strength of our study is the detection of PIP, with two different tools, in a moment of transition of care associated with a high risk for the patient, when a pharmacists´ intervention may be implemented. The essential weakness is the limitation of the study population to a single hospital. The results need to be reproduced in hospitals and populations with other characteristics.

One limitation of the study is that data was collected from the clinical history, so patients' adherence is unknown. There may be probably an underreport of pathological conditions in the medical history, especially for those difficult to be identified during hospitalization, but included in Beers and STOPP criteria (such as pain, life expectancy, home oxygen therapy etc.).

We might have underestimated the prevalence of polypharmacy due to the application of an adapted version of Beers and STOPP criteria, where some groups of drugs were omitted, for example PIP associated with falls or fractures. The reason for this was the inavailability of follow-up data regarding falls or fractures.

Limitations of the study

Regarding the contacts with the health system, only the data of the last contact has been collected, so we can only assess medium-term effects. It is logical to consider that the impact of PIP is higher in the first weeks after discharge.

Moreover, we lack information on the maintenance of potentially inappropriate prescriptions; in fact, the primary care physician might have changed some of the medications, which would lead to a reduced frequency of potentially inappropriate prescriptions, thus mitigating their potential effects. Additionally, the collected variables are not sufficient to correct the confusion. PIP are not considered as the only cause of health care utilization; factors such as polypharmacy or comorbidity factors might increase the demand on resources and healthcare costs [106, 281].

Finally, we must mention the absence of information on health care contacts outside the Andalusian Health Service. We lack information on 69 patients (11.1%), except in 22 cases listed as passive without the primary care record showing the date of exitus. This group has a significantly higher percentage of deaths compared to that obtained from followed-up patients (34.38% vs. 20.18%).

The limitations discussed above may explain the lack of association but we would also have to ask if inappropriate prescribing has been assessed correctly. We used two different indices, but elaborated with the same philosophy.

Successful approaches and interventions applied in other countries could serve as examples for safer prescribing.
There does not exist a separate geriatric service in the San Cecilio Hospital, neither does in Granada or Andalusia.

2.6 The challenge of PIP reduction and some recommendations

The selection of the best therapeutic option is far from easy in older patients with multiple comorbidities as a highly individualized assessment is required. Scarce data is available to guide the appropriate use of drugs in older people and a lack of age-specific protocols and guidelines is observed. Our study suggests that there is need for a nationwide strategy to reduce the high prevalence of PIP in older people, taking into account the factors associated with them.

As already suggested by Morandi et al [284], there is need for better coordination at this transition point, with attention to the rationale for each medication initiation and the discussion of the possibility to deprescribe. Possible solutions for reducing potential inappropriate drugs may include electronic medical records surveillance, routine clinical evaluation (performed by the geriatrician and clinical pharmacist) as well as medication reconciliation, and improved communication between discharging and accepting healthcare providers.

During hospital stay, the prescription of new medications should be considered in the context of the age-related physiological changes among older adults as well as the existing therapeutic regimens already established by previous prescribers.

Consideration of initial dose adjustment, along with frequent medication reconciliation and analysis of the medication list, are key to providing optimal pharmaceutical care for elderly patients.

Further research should shed light on the specific changes in the pharmacokinetics and pharmacodynamics processes in older patients, helping in the compilation of treatment protocols tailored to the particular needs of these patients.

At hospital discharge, a review of the complete medications prescribed to the older patient should be performed, either by the geriatrician or the clinical pharmacist. Through implementation of explicit and implicit criteria, discussion between health professionals and cautious analysis, a decision to minimize polypharmacy or deprescribe by reducing unnecessary medications is often required. It is undoubtedly a difficult task to be performed, yet finding solutions to this problem has become a critical priority among older people.

Although all medical conditions should be properly treated, simplifying drug regimens by removing medications that have limited clinical benefit, redundant or not indicated has to be considered.

Such a decision should be supported by a multidisciplinary team approach after a thorough analysis of the benefit / risk ratio of each drug prescribed.

Healthcare professionals involved in elderly care should be trained to become acquainted with available information tools and to consult electronic medical records.

The strengths and weaknesses of each type of criteria should be taken into consideration both when choosing a method for assessment and when interpreting the results. A selected group of drugs prone to be prescribed inappropriately should be carefully evaluated and monitored.

Educational interventions among health personnel to avoid inappropriate prescribing should be endorsed.

Detailed guidelines should be compiled in order to endorse evidence-based decisions about prescribing, individualisation of prescriptions among older people, continuous monitoring of therapeutic outcomes, and collaboration between medical professionals.

3. Future perspectives / Application to the Albanian context

- Development of an adapted Albanian version of STOPP-START criteria and their application

Harmonization of recommendations and guidelines regarding prescribing in the older population has become indispensable in view of the rapid changes in global medical research and the necessity to offer the best possible treatment.

Using the same method in different European countries to identify potentially inappropriate prescriptions in the geriatric population promotes consistency and comparability of the results, but it also arises the need for their adaptation to the local context. STOPP criteria identify potentially inappropriate prescriptions, whereas START the omitted prescriptions of indicated drugs in the clinical situation of the patient; thus, their combined use can help in assessing both excessive and insufficient drug treatment. To enable their use as a helping tool in the everyday clinical practice, these criteria should be adapted (tailored) to the local characteristics of drug availability and prescriptions. Adapted versions of them are compiled in the majority of the European countries, such as the Netherlands [174], Spain [172] and France [171] and we have adapted an Albanian version for being an effective and valuable instrument in clinical practice in Albania and other Albanian-speaking countries.

The original STOPP-START criteria [285, 286] along with their adapted versions in other countries were taken into consideration [171-174]. Two authors from Albania (K.H. and E.B.) and one from Kosovo (D.Sh.) performed independently a first translation in a blind manner to determine which should be the final version. Their translations were compared and discrepancies were resolved by discussion. When necessary, a fourth person was also consulted (D.Xh.) to reach a consensus. Afterwards, a check regarding drugs available in Albania and Kosovo was conducted, to exclude possible unnecessary criteria. The required information was obtained from the National Center for the Control of Drugs of Albania and the Kosovo Agency for Medicinal Products.

The final document in Albanian included all 65 STOPP and 22 START criteria and it is fully presented in Annex 3.

There have been no previous attempts to adapt or implement any helping tool for identifying inappropriate prescription in the geriatric population in Albania, unlike

other countries [171-174]. The challenge to mitigate potentially inappropriate prescriptions can be addressed only if there is a dissemination of the methods and tools to identify them among the medical community. This first attempt to adapt the criteria will be followed by their application in clinical practice, for research and preventive reasons, and their subsequent validation in Albania.

We believe that further research about prescription appropriateness in older people in our country would allow understanding the extent of the problem and contribute in the potential preventability of medication error.

Future studies are warranted to evaluate the appropriateness of prescribing in older adults across different hospital facilities in Spain and especially in Albania, as well as the association with adverse drug events, hospitalization and mortality.

As an essential part of multidisciplinary teams, the role of clinical pharmacists in drug therapy optimization, on monitoring and reducing inappropriate prescribing should be furthermore defined and promoted.

CONCLUSIONS

1. The frequency of PIP at discharge is very high, as it affects about one in five patients with reference to the more restrictive criteria of Beers, or four out of 10 with STOPP criteria. Moreover, it increases with the number of prescribed drugs. This high prevalence of PIP at discharge should be a concern in Spanish hospitals.

2. It is possible to identify a few drugs responsible for most cases of PIP, which means that more efficient surveillance and control procedures could reduce it. By intervening in five drug groups, about 80 % of PIP might be avoided according to either of the two criteria. The limited number of drugs involved in the majority of PIP suggests that simplifying STOPP and Beers criteria by reducing the number of covered items could facilitate their use without affecting usefulness.

3. Pharmacists must be involved in PIP detection at hospital discharge; establishing an appropriate target population group and choosing a few drugs to review could be the most efficient approach.

4. Risk factors for PIP according to both criteria used (Beers and STOPP) were discharge from the internal medicine service, a higher number of prescribed drugs, and the presence of moderate to severe hypertension. Conversely, preexisting ischemic cardiopathy, cerebrovascular disease, peripheral arterial disease, and arterial occlusion acted as protective factors. For the Beers criteria, additional pathological conditions were found to increase the risk of PIP, namely cardiac failure, arrhythmia, permanent atrial fibrillation, renal failure, and particularly dementia.

5. Overall, the results of this study revealed differences between the risk factors for PIP depending on the type of criteria used to define PIP. However, both sets of criteria highlight the importance of polypharmacy and hypertension management on prevention of PIP.

6. Our results do not confirm the existence of a relationship between potentially inappropriate prescriptions identified by Beers or STOPP criteria and the use of health services in the medium term, although a significantly higher number of visits was recorded.

7. No association was found between the prescription of potentially inappropriate drugs and post-hospital mortality with any of the two sets of criteria used for

their detection. However, the inappropriate prescription of aspirin according to the STOPP criteria behaved as an independent risk factor for mortality.

8. We lacked information that would allow us to limit follow-up periods after discharge; furthermore, we had no information on the treatment changes performed by general practitioners. Future research needs to be done to determine the short-term effects of PIP at discharge on the use of health care resources or on mortality, as well as the influence of medications review and monitoring of prescriptions by general practitioners (family doctors), ideally in collaboration with clinical pharmacists.

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ANNEXES

1. Beers 2012 criteria

Table 1. 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults [146]

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics (excludes 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	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; greater risk of confusion, dry mouth, constipation, and other anticholinergic effects and toxicity. Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate	Avoid	Hydroxyzine and promethazine: high; All others: moderate	Strong
Antiparkinson agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more-effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong

Antispasmodics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine	Highly anticholinergic, uncertain effectiveness	Avoid except in short-term palliative care to decrease oral secretions	Moderate	Strong
Antithrombotics				
Dipyridamole, oral short acting* (does not apply to extendedrelease combination with aspirin)	May cause orthostatic hypotension; more-effective alternatives available; intravenous form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Ticlopidine*	Safer effective alternatives available	Avoid	Moderate	Strong
Anti-infective				
Nitrofurantoin	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	Avoid for long-term suppression; avoid in patients with CrCl < 60 mL/min	Moderate	Strong
Cardiovascular				
Alpha1 blockers Doxazosin Prazosin Terazosin	High risk of orthostatic hypotension; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile	Avoid use as an antihypertensive	Moderate	Strong
Alpha agonists, central Clonidine	High risk of adverse CNS effects; may cause bradycardia and	Avoid clonidine as a first-line	Low	Strong

Guanabenz* Guanfacine* Methyldopa* Reserpine (> 0.1 mg/d)*	orthostatic hypotension; not recommended as routine treatment for hypertension	antihypertensive. Avoid others as listed		
Antiarrhythmic drugs (Class Ia, Ic, III) Amiodarone Dofetilide Dronedarone Flecainide Ibutilide Procainamide Propafenone Quinidine Sotalol	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	Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation	High	Strong
Disopyramide*	Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	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	Avoid in patients with permanent atrial fibrillation or heart failure	Moderate	Strong
Digoxin > 0.125 mg/d	In heart failure, higher dosages associated with no additional	Avoid	Moderate	Strong

	benefit and may increase risk of toxicity; slow renal clearance may lead to risk of toxic effects			
Nifedipine, immediate release*	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Spironolactone > 25 mg/d	In heart failure, the risk of hyperkalemia is higher in older adults especially if taking > 25 mg/d or taking concomitant NSAID, angiotensin converting-enzyme inhibitor, angiotensin receptor blocker, or potassium supplement	Avoid in patients with heart failure or with a CrCl < 30 mL/min	Moderate	Strong
Central nervous system				
Tertiary TCAs, alone or in combination: Amitriptyline Chlordiazepoxide-amitriptyline Clomipramine Doxepin > 6 mg/d Imipramine Perphenazine-amitriptyline Trimipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/d) is comparable with that of placebo	Avoid	High	Strong
Antipsychotics, first (conventional) and second (atypical) generation (see Table X for full list)	Increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia	Avoid use for behavioral problems of dementia unless nonpharmacological options have failed and patient is threat to	Moderate	Strong

		self or others		
Thioridazine Mesoridazine	Highly anticholinergic and risk of QT-interval prolongation	Avoid	Moderate	Strong
Barbiturates Amobarbital* Butabarbital* Butalbital Mephobarbital* Pentobarbital* Phenobarbital Secobarbital*	High rate of physical dependence; tolerance to sleep benefits; risk of overdose at low dosages	Avoid	High	Strong
Benzodiazepines *Short and intermediate acting:* Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam *Long acting:* Clorazepate Chlordiazepoxide Chlordiazepoxide-amitriptyline Clidinium-chlordiazepoxide Clonazepam Diazepam Flurazepam Quazepam	Older adults have increased sensitivity to benzodiazepines and slower 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.	Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium	High	Strong
Chloral hydrate*	Tolerance occurs within 10 days,	Avoid	Low	Strong

	and risks outweigh benefits in light of overdose with doses only 3 times the recommended dose			
Meprobamate	High rate of physical dependence; very sedating	Avoid	Moderate	Strong
Nonbenzodiazepine hypnotics Eszopiclone Zolpidem Zaleplon	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 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	Avoid chronic use (> 90 days)	Moderate	Strong
Ergot mesylates* Isoxsuprine*	Lack of efficacy	Avoid	High	Strong
Endocrine				
Androgens Methyltestosterone* Testosterone	Potential for cardiac problems and contraindicated in men with prostate cancer	Avoid unless indicated for moderate to severe hypogonadism	Moderate	E dobët
Desiccated thyroid	Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong
Estrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and	Avoid oral and topical patch. Topical vaginal	Oral and patch: high Topical: moderate	Oral and patch: strong Topical: weak

	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 µg twice weekly	cream: acceptable to use low-dose intravaginal estrogen for the management of dyspareunia, lower urinary tract infections, and other vaginal symptoms		
Growth hormone	Effect on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose	Avoid, except as hormone replacement after pituitary gland removal	High	Strong
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long duration Chlorpropamide Glyburide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes syndrome of inappropriate antidiuretic hormone secretion. Glyburide: greater risk of severe prolonged hypoglycemia in older adults	Avoid	High	Strong
Gastrointestinal				

Metoclopramide	Can cause extrapyramidal effects including tardive dyskinesia; risk may be even greater in frail older adults	Avoid, unless for gastroparesis	Moderate	Strong
Mineral oil, oral	Potential for aspiration and adverse effects; safer alternatives available	Avoid	Moderate	Strong
Trimethobenzamide	One of the least effective antiemetic drugs; can cause extrapyramidal adverse effects	Avoid	Moderate	Strong
Pain				
Meperidine	Not an effective oral analgesic in dosages commonly used; may cause neurotoxicity; safer alternatives available	Avoid	High	Strong
Non–COX-selective NSAIDs, oral Aspirin > 325 mg/d Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam	Increases risk of GI bleeding and peptic ulcer disease in high-risk groups, including those aged > 75 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 approximately 2–4% of patients treated for 1 year. These trends continue with longer duration of	Avoid chronic use unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)	Moderate	Strong

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Sulindac Tolmetin	use			
Indomethacin Ketorolac, includes parenteral	Increases risk of GI bleeding and peptic ulcer disease in high-risk groups. (See above Non-COX selective NSAIDs.) Of all the NSAIDs, indomethacin has most adverse effects	Avoid	Indomethacin: moderate Ketorolac: high	Strong
Pentazocine*	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	Avoid	Low	Strong
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Most muscle relaxants are poorly tolerated by older adults because of anticholinergic adverse effects, sedation, risk of fracture; effectiveness at dosages tolerated by older adults is questionable	Avoid	Moderate	Strong

The primary target audience is the practicing clinician. The intentions of the criteria are to improve the selection of prescription drugs by clinicians and patients; evaluate patterns of drug use within populations; educate clinicians and patients on proper drug usage; and evaluate health-outcome, quality of care, cost, and utilization data.

* Infrequently used drugs.

CNS = central nervous system; COX = cyclooxygenase; CrCl = creatinine clearance; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; TCA = tricyclic antidepressant.

Table 2. 2012 American Geriatrics Society 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	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Cardiovascular					
Heart failure	NSAIDs and COX-2 inhibitors Nondihydropyridine CCBs (avoid only for systolic heart failure) Diltiazem Verapamil Pioglitazone, rosiglitazone Cilostazol Dronedarone	Potential to promote fluid retention and exacerbate heart failure	Avoid	NSAIDs: moderate CCBs: moderate Thiazolidinediones (glitazones): high Cilostazol: low Dronedarone: moderate	Strong
Syncope	AChEIs Peripheral alpha blockers Doxazosin Prazosin Terazosin Tertiary TCAs Chlorpromazine, thioridazine, and olanzapine	Increases risk of orthostatic hypotension or bradycardia	Avoid	Alpha blockers: high TCAs, AChEIs, and antipsychotics: moderate	AChEIs and TCAs: strong Alpha blockers and antipsychotics: weak
Central nervous system					

Chronic seizures or epilepsy	Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene Tramadol	Lowers seizure threshold; may be acceptable in patients with well-controlled seizures in whom alternative agents have not been effective	Avoid	Moderate	Strong
Delirium	All TCAs Anticholinergics (see Table Y for full list) Benzodiazepines Chlorpromazine Corticosteroids H2-receptor antagonist Meperidine Sedative hypnotics Thioridazine	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	Avoid	Moderate	Strong
Dementia and cognitive impairment	Anticholinergics (see Table Y for full list) Benzodiazepines H2-receptor antagonists Zolpidem Antipsychotics, chronic and as-needed use	Avoid because of adverse CNS effects. Avoid antipsychotics for behavioral problems of dementia unless nonpharmacological options have failed, and patient is a threat to themselves or others. Antipsychotics are	Avoid	High	Strong

		associated with an increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia			
History of falls or fractures	Anticonvulsants Antipsychotics Benzodiazepines Nonbenzodiazepine hypnotics Eszopiclone Zaleplon Zolpidem TCAs and selective serotonin reuptake inhibitors	Ability to produce ataxia, impaired psychomotor function, syncope, and additional falls; shorter-acting benzodiazepines are not safer than long-acting ones	Avoid unless safer alternatives are not available; avoid anticonvulsants except for seizure disorders	High	Strong
Insomnia	Oral decongestants Pseudoephedrine Phenylephrine Stimulants Amphetamine Methylphenidate Pemoline Theobromines Theophylline Caffeine	CNS stimulant effects	Avoid	Moderate	Strong
Parkinson's disease	All antipsychotics (see Table X for full list, except for quetiapine	Dopamine receptor antagonists with potential to worsen parkinsonian	Avoid	Moderate	Strong

	and clozapine) Antiemetics Metoclopramide Prochlorperazine Promethazine	symptoms. Quetiapine and clozapine appear to be less likely to precipitate worsening of Parkinson's disease			
Gastrointestinal					
Chronic constipation	Oral antimuscarinics for urinary incontinence 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	Can worsen constipation; agents for urinary incontinence: antimuscarinics overall differ in incidence of constipation; response variable; consider alternative agent if constipation develops	Avoid unless no other alternatives	For urinary incontinence: high All others: Moderate to low For urinary incontinence: high All others: Moderate to low	Weak

	Dexbrompheniramine Dexchlorpheniramine (various) Diphenhydramine Doxylamine Hydroxyzine Promethazine Triprolidine Anticholinergics and antispasmodics (see Table Y for full list of drugs with strong anticholinergic properties) Antipsychotics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine Tertiary TCAs (amitriptyline, clomipramine, doxepin, imipramine, and trimipramine)				
History of gastric	Aspirin (>325 mg/d)	May exacerbate existing	Avoid unless other	Moderate	Strong

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or duodenal ulcers	Non–COX-2 selective NSAIDs	ulcers or cause new or additional ulcers	alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)		
Kidney and urinary tract					
Chronic kidney disease Stages IV and V	NSAIDs Triamterene (alone or in combination)	May increase risk of kidney injury	Avoid	NSAIDs: moderate Triamterene: low	NSAIDs: strong Triamterene: weak
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen)	Aggravation of incontinence	Avoid in women	High	Strong
Lower urinary tract symptoms, benign prostatic hyperplasia	Inhaled anticholinergic agents Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see Table Y for complete list)	May decrease urinary flow and cause urinary retention	Avoid in men	Moderate	Inhaled agents: strong All others: weak
Stress or mixed urinary incontinence	Alpha blockers Doxazosin Prazosin Terazosin	Aggravation of incontinence	Avoid in women	Moderate	Strong

CCB = calcium channel blocker; AChEI = acetylcholinesterase inhibitor; CNS = central nervous system; COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug; TCA = tricyclic antidepressant.

Table 3. 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medications to Be Used with Caution in Older Adults

Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Aspirin for primary prevention of cardiac events	Lack of evidence of benefit versus risk in individuals aged ≥ 80	Use with caution in adults aged ≥ 80	Low	Weak
Dabigatran	Greater risk of bleeding than with warfarin in adults aged ≥ 75; lack of evidence for efficacy and safety in individuals with CrCl < 30 mL/min	Use with caution in adults aged ≥ 75 or if CrCl < 30 mL/min	Moderate	Weak
Prasugrel	Greater risk of bleeding in older adults; risk may be offset by benefit in highest-risk older adults (e.g., with prior myocardial infarction or diabetes mellitus)	Use with caution in adults aged ≥ 75	Moderate	Weak
Antipsychotics Carbamazepine Carboplatin Cisplatin Mirtazapine Serotonin–norepinephrine reuptake inhibitor Selective serotonin reuptake inhibitor Tricyclic antidepressants Vincristine	May exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatremia; need to monitor sodium level closely when starting or changing dosages in older adults due to increased risk	Use with caution	Moderate	Strong
Vasodilators	May exacerbate episodes of syncope in individuals with history of syncope	Use with caution	Moderate	Weak

CrCl = creatinine clearance

Table X. First- and Second-Generation Antipsychotics

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

Table Y. Drugs with Strong Anticholinergic Properties

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

| Tolterodine | Scopolamine | |
| Trospium | | |

2. STOPP-START criteria (2008)

STOPP – Screening Tool of Older People´s potentially inappropriate Prescriptions

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[a] (increased risk of toxicity)

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)

3. Loop diuretic as first-line monotherapy for hypertension (safer, more effective alternatives available)

4. Thiazide diuretic with a history of gout (may exacerbate gout)

5. Non-cardioselective β-blocker with Chronic Obstructive Pulmonary Disease (COPD) (risk of increased bronchospasm)

6. β-blocker in combination with verapamil (risk of symptomatic heart block)

7. Use of diltiazem or verapamil with NYHA class III or IV heart failure (may worsen heart failure)

8. Calcium channel blockers with chronic constipation (may exacerbate constipation)

9. Use of aspirin and warfarin in combination without histamine H_2-receptor antagonist (except cimetidine because of interaction with warfarin) or proton pump inhibitor (high risk of gastrointestinal bleeding)

10. Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence for efficacy)

11. Aspirin with a past history of peptic ulcer disease without histamine H_2-receptor antagonist or proton pump inhibitor (risk of bleeding)

12. Aspirin at dose > 150 mg/day (increased bleeding risk, no evidence for increased efficacy)

13. Aspirin with no history of coronary, cerebral or peripheral vascular symptoms or occlusive event (not indicated)

14. Aspirin to treat dizziness not clearly attributed to cerebrovascular disease (not indicated)

15. Warfarin for first uncomplicated venous thrombosis for longer than 6 months duration (no proven added benefit)

16. Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration (no proven benefit)

17. Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder (high risk of bleeding)

a. Serum creatinine > 150 µmol/l, or estimated GFR < 50 ml/min

B. Central nervous system and psychotropic drugs

1. Tricyclic antidepressants (TCAs) with dementia (risk of worsening cognitive impairment)

2. TCAs with glaucoma (likely to exacerbate glaucoma)

3. TCAs with cardiac conductive abnormalities (pro-arrhythmic effects)

4. TCAs with constipation (likely to worsen constipation)

5. TCAs with an opiate or calcium channel blocker (risk of severe constipation)

6. TCAs with prostatism or prior history of urinary retention (risk of urinary retention)

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 prolonged sedation, confusion, impaired balance, falls)

8. Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics (risk of confusion, hypotension, extra-pyramidal side effects, falls)

9. Long-term neuroleptics (> 1 month) in those with parkinsonism (likely to worsen extra-pyramidal symtoms)

10. Phenotiazines in patients with epilepsy (may lower seizure threshold)

11. Anticholinergics to treat extrapyramidal side effects of neuroleptic medications (risk of anticholinergic toxicity)

12. Selective serotonin re-uptake inhibitors (SSRIs) with a history of clinically significant hyponatremia (non-iatrogenic hyponatremia < 130mmol/l within the previous 2 months)

13. Prolonged use (> 1 eek) of first-generation antihistamines, i.e. diphenhydramine, chlorpheniramine, cyclizine, promethazine (risk of sedation and anti-cholinergic side effects)

C. Gastrointestinal system

1. Diphenoxilate, loperamide or codeine phosphate for treatment of diarrhea of unknown 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)

2. Diphenoxilate, loperamide or codeine phosphate for treatment of severe infective gastroenteritis, e.e. bloody diarrhea, high fever or severe systemic toxicity (risk of exacerbation or protraction of infection)

3. Prochlorperazine (Stemetil) or metoclopramide with parkinsonism (risk of exacerbation of constipation)

4. PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated)

5. Anticholinergic antispasmodic drugs with chronic constipation (risk of exacerbation of constipation)

D. Respiratory system

1. Theophylline as monotherapy for COPD (safer, more effective alternative, risk of adverse effects due to narrow therapeutic index)

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)

3. Nebulized ipratropium with glaucoma (may exacerbate glaucoma)

E. Musculoskeletal system

1. Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H_2-receptor antagonist, PPI or misoprostol (risk of peptic ulcer relapse)

2. NSAID with moderate-to-severe hypertension (risk of exacerbation of hypertension)

3. NSAID with heart failure (risk of exacerbation of heart failure)

4. Long-term use of NSAID (> 3 months) for symptom relief of mild osteoarthritis (simple analgesic preferable and usually as effective for pain relief)

5. Warfarin and NSAID together (risk of gastrointestinal bleeding)

6. NSAID with chronic renal failure[b] (risk of deterioration in renal function)

7. Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthritis or osteoarthritis (risk of major systemic corticosteroid side-effects)

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)

b. Serum creatinine > 150 µmol/l, or estimated GFR 20 - 50 ml/min

F. Urogenital system

1. Bladder antimuscarinic drugs with dementia (risk of increased confusion, agitation)

2. Antimuscarinic drugs with chronic glaucoma (risk of acute exacerbation of glaucoma)

3. Antimuscarinic drugs with chronic constipation (risk of exacerbation of constipation)

4. Antimuscarinic drugs with chronic prostatism (risk of urinary retention)

5. α-blockers in males with frequent incontinence, i.e. one or more episodes of incontinence daily (risk of urinary frequency and worsening of incontinence)

6. α-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)

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

3. Estrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence)

4. Estrogens without progestogen in patients with intact uterus (risk of endometrial cancer)

H. Drugs that adversely affect failure

1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance)

2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism)

3. First-generation antihistamines (sedative, may impair sensorium)

4. Vasodilator drugs with persistent postural hypotension, i.e. recurrent > 20 mmHg drop in systolic blood pressure (risk of syncope, falls)

5. Long-term opiates in those with recurrent falls (risk of drowsiness, postural hypotension, vertigo)

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)

2. Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives (risk of severe constipation)

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)

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).

START (Screening Tool to Alert doctors to Right, i.e. appropriate, indicated Treatments)

These medications should be considered for people $\geq$ 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

2. Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin

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

4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg

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

6. Angiotensin converting enzyme (ACE) inhibitor with chronic heart failure

7. ACE inhibitor following acute myocardial infarction

8. β-blocker with chronic stable angina

B. Respiratory system

1. Regular inhaled β2-agonist or anticholinergic agent for mild-to-moderate asthma or COPD

2. Regular inhaled corticosteroid for moderate/severe asthma or COPD, where predicted $FEV_1 < 50\%$

3. Home continuous oxygen with documented chronic type 1 respiratory failure (pO2 < 8.0 kPa, pCO2 < 6.5 kPa) or type 2 respiratory failure (pO2 < 8.0 kPa, pCO2 < 6.5 kPa)

C. Central nervous system

1. L-DOPA in idiopathic Parkinson´s disease with definite functional impairment and resultant disability

2. Antidepressant drug in the presence of moderate/severe depressive symptoms lasting at least three months

D. Gastrointestinal system

1. Proton pump inhibitor with severe gastroesophageal acid reflux disease or peptic stricture requiring dilation

2. Fiber supplement for chronic, symptomatic diverticular disease with constipation

E. Musculoskeletal system

1. Disease-modifying antirheumatic drug (DMARD) with active moderate/severe rheumatoid disease lasting > 12 weeks

2. Biphosphonates in patients taking maintenance corticosteroid therapy

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

F. Endocrine system

1. Metformin with type 2 diabetes ± metabolic syndrome (in the absence of renal impairment[c])

2. ACE inhibitor or angiotensin receptor blocker in diabetes with nephropathy, i.e. overt urinalysis proteinuria or microalbuminuria (> 30 mg/24 hours) ± serum biochemical renal impairment[c])

3. Antiplatelet therapy in diabetes mellitus with coexisting major cardiovascular risk factors (hypertension, hypercholesterolemia, smoking history)

4. Statin therapy in diabetes mellitus if coexisting major cardiovascular risk factors present

c. Serum creatinine > 150 µmol/l, or estimated GFR < 50 ml/min

3. Albanian version of STOPP-START criteria (2008)

Mjeti i Shqyrtimit të Përshkrimeve potencialisht të papërshtatshme në të Moshuarit (STOPP)

Përshkrimet e mëposhtme janë potencialisht të papërshtatshme në personat me moshë mbi 65 vjeç:

Sistemi kardiovaskular

1. Digoksina me dozë afatgjatë >125µg/ditë në prani të dëmtimit të funksionit renal[a] (rrezik i rritur për toksicitet)

2. Diuretikët e ansës të përdorur vetëm për edemë të kaviljes dmth. pa shenja klinike të insufiçencës kardiake (nuk ka prova të efektshmërisë, kompresioni me çorape është zakonisht më i përshtatshëm)

3. Diuretikët e ansës si monoterapi e linjës së parë për hipertensionin (të disponueshme alternativa më të sigurta, më të efektshme)

4. Diuretikët tiazidik me një histori gute (mund ta përkeqësojë gutën)

5. Betabllokuesit jo-kardioselektiv në Sëmundjen Pulmonare Obstruktive Kronike (SPOK) (rrezik për bronkospazmë)

6. Betabllokuesit e kombinuar me verapamil (rrezik për bllokim simptomatik të zemrës)

7. Përdorimi i diltiazemit ose verapamilit në pacientët me insufiçencë kardiake të klasës IIII ose IV sipas NYHA (mund të përkeqësojë insufiçencën kardiake)

8. Bllokuesit e kanaleve të kalciumit në prani të konstipacionit kronik (mund të përkeqësojë konstipacionin)

9. Përdorimi i njëkohshëm i aspirinës dhe warfarinës pa antagonist të receptorëve H2 të histaminës (me përjashtim të cimetidinës për shkak të ndërveprimit me warfarinën) ose inhibitor të pompës protonike (rrezik i rritur për hemorragji gastro-intestinale)

10. Dipiridamoli si monoterapi për parandalimin e sëmundjeve sekondare kardiovaskulare (nuk ka prova për efektshmërinë)

11. Aspirina në pacientë me një histori të kaluar të ulçerës peptike pa përdorimin e antagonistëve të receptorëve H2 të histaminës ose inhibitorëve të pompës protonike (rrezik për hemorragji)

12. Aspirina në doza >150 mg/ditë (rrezik i rritur për hemorragji, nuk ka prova të rritjes së efektshmërisë)

13. Aspirina pa histori të simptomave koronare, cerebrale ose të sëmundjeve arteriale periferike ose eventeve arteriale okluzive (nuk indikohet)

14. Aspirina për trajtimin e marramendjeve që nuk i atribuohen në mënyrë të qartë sëmundjeve cerebrovaskulare (nuk indikohet)

15. Warfarina për trajtimin e një episodi të parë të trombozë venoze të thellë të pakomplikuar për një kohëzgjatje më të madhe se 6 muaj (nuk është provuar asnjë përfitim shtesë)

16. Warfarina në emboli pulmonare të pakomplikuar të parë për një kohëzgjatje më të madhe se 12 muaj (nuk është provuar asnjë përfitim shtesë)

17. Aspirina, klopidogreli, dipiridamoli ose warfarina në prani të një çrregullimi hemorragjik (rrezik të lartë për hemorragji)

Sistemi nervor qëndror dhe barnat psikotrope

18. Antidepresivët triciklikë në prani të demencës (rrezik për përkeqësim të dëmtimit kognitiv)

19. Antidepresivët triciklikë në prani të glaukomës (gjasa të përkeqësojnë glaukomën)

20. Antidepresivët triciklikë në prani të çrregullimeve kardiake të përçimit (efekte pro-arritmike)

21. Antidepresivët triciklikë në prani të konstipacionit (gjasa të përkeqësojnë konstipacionin)

22. Antidepresivët triciklikë njëkohësisht me opiatet ose antagonistët e kanaleve të kalciumit

23. Antidepresivët triciklikë në prostatizëm ose histori të mëparshme të retencionit urinar (rrezik për retencion urinar)

24. Benzodiazepina me veprim të gjatë me përdorim afatgjatë (dmth. >1 muaj) p.sh. klordiazepoksid, fluazepam, nitrazepam, klorazepat dhe benzodiazepina me metabolitë me veprim të gjatë p.sh. diazepam (rrezik për sedacion të zgjatur, konfuzion, dëmtim të ekuilibrit, rënie)

25. Neuroleptikë me përdorim afatgjatë (dmth. >1 muaj) të përdorur si hipnotikë me përdorim afatgjatë (rrezik për konfuzion, hipotension, efekte anësore ekstrapiramidale, rënie)

26. Neuroleptikë me përdorim afatgjatë (dmth. >1 muaj) në prani të parkinsonizmit (gjasa për të përkeqësuar simptomat ekstrapiramidale)

27. Fenotiazinat në pacientët me epilepsi (mund të ulin pragun e konvulsioneve)

28. Antikolinergjikët për trajtimin e efekteve anësore ekstrapiramidale të barnave neuroleptike (rrezik për toksicitet antikolinergjik)

29. Inhibitorët selektivë të rikapjes së serotoninës (SSRI) në prani të një historie të hiponatremisë domethënëse klinikisht (hiponatremi jo-jatrogjene <130 mmol/l brenda 2 muajve të fundit)

30. Përdorimi i zgjatur (>1 javë) i antihistaminikëve të gjeneratës së parë dmth. difenhidraminë, klorfeniraminë, ciklizinë, prometazinë (rrezik për sedacion dhe efekte anësore antikolinergjike)

Sistemi gastrointestinal

31. Difenoksilati, loperamidi ose fosfati i kodeinës për trajtimin e diarresë me shkak të panjohur (rrezik për vonesë të diagnozës, mund të përkeqësojë konstipacionin, mund të precipitojë kolonin megatoksik në sëmundjen e zorrës së irritueshme, mund të vonojë shërimin në gastroenteritin e padiagnostikuar)

32. Difenoksilati, loperamidi ose fosfati i kodeinës për trajtimin e gastroenteritit të rëndë infektiv dmth. diarre me gjak, temperaturë të lartë ose toksicitet të rëndë sistemik (rrezik për përkeqësim ose zgjatje të infeksionit)

33. Proklorperazina (Stemetil) ose metoklopramidi në Parkinsonizëm (rrezik për përkeqësim të Parkinsonizmit)

34. Inhibitorët e pompës protonike në ulçerën peptike në dozë të plotë terapeutike për >8javë (indikohet ndërprerja më herët ose pakësimi i dozës për trajtimin mbajtës/profilaktik të ulçerës peptike, ezofagitit ose refluksit gastroezofageal)

35. Barnat antispazmatike antikolinergjike në prani të konstipacionit kronik (rrezik për përkeqësim të konstipacionit)

Sistemi respirator

36. Teofilina si monoterapi në Sëmundjen Pulmonare Obstruktive Kronike (SPOK) (ka alternativa më të sigurta, më të efektshme; rrezik për efekte anësore për shkak të indeksit të ngushtë terapeutik)

37. Kortikosteroidët sistemikë në vend të kortikosteroidëve inhalatorë për terapi mbajtëse në SPOK të moderuar-të rëndë (ekspozim i panevojshëm ndaj efekteve anësore afatgjata të steroideve sistemike)

38. Ipratropiumi i nebulizuar në prani të glaukomës (mund të përkeqësojë glaukomën)

Sistemi muskuloskeletik

39. Barnat Anti Inflamatore Jo Steroide (AIJS) në histori të ulçerës peptike ose hemorragjisë gastrointestinale, me përjashtim të rasteve kur përdoren njëkohësisht antagonistë të receptorëve H2 të histaminës, inhibitorë të pompës protonike ose misoprostol (rrezik për rikthim të ulçerës peptike)

40. AIJS në prani të hipertensionit të moderuar-të rëndë (i moderuar: 160/100 mmHg – 179/109 mmHg; i rëndë: >180/110 mmHg) (rrezik për përkeqësim të hipertensionit)

41. AIJS në prani të infarktit kardiak (rrezik për përkeqësim të infarktit)

42. Përdorimi afatgjatë i AIJS (>3 muaj) për lehtësimin e dhimbjes së lehtë të artikulacioneve në osteoartrit (analgjezikët e thjeshtë janë të preferuar dhe zakonisht njëlloj të efektshëm për lehtësimin e dhimbjes)

43. Warfarina dhe AIJS së bashku (rrezik për hemorragji gastrointestinale)

44. AIJS në insufiçencën renale kronike[b] (rrezik për përkeqësim të funksionit renal)

45. Kortikosteroidet me përdorim afatgjatë (>3 muaj) si monoterapi në artritin reumatoid ose osteoartrit (rrezik për efekte anësore madhore të kortikosteroideve sistemike)

46. AIJS me përdorim afatgjatë ose kolkicina në trajtimin kronik të gutës kur nuk ka asnjë kundërindikacion ndaj allopurinolit (allopurinoli është bari profilaktik i zgjedhjes së parë në gutë)

Sistemi urogenital

47. Barnat antimuskarinike vezikale në prani të demencës (rrezik për konfuzion, axhitim të shtuar)

48. Barnat antimuskarinike vezikale në prani të glaukomës kronike (rrezik për përkeqësim akut të glaukomës)

49. Barnat antimuskarinike vezikale në prani të konstipacionit kronik (rrezik për përkeqësim të konstipacionit)

50. Barnat antimuskarinike vezikale në prani të prostatizmit kronik (rrezik për retencion urinar)

51. Alfabllokuesit në meshkuj me inkontinencë të shpeshtë dmth. një ose më shumë episode të inkontinencës në ditë (rrezik për frekuencë urinare dhe përkeqësim të inkontinencës)

52. Alfabllokuesit në prani të kateterit in situ urinar afatgjatë dmth. më shumë se 2 muaj (bari nuk indikohet)

Sistemi endokrin

53. Glibenklamidi ose klorpropamidi në diabetin mellitus të tipit 2 (rrezik për hipoglicemi të zgjatur)

54. Betabllokuesit në pacientët me diabet mellitus dhe episode të shpeshta hipoglicemie dmth. >1 episod në muaj (rrezik për maskimin e simptomave të hipoglicemisë)

55. Estrogjenët në një histori të kancerit të gjirit ose tromboembolizmit venoz (rrezik i rritur për rekurrencë)

56. Estrogjenët pa progestagjen në pacientët me uterus të paprekur (rrezik për kancer të endometrit)

Barnat që ndikojnë negativisht në personat e prirur ndaj rënieve (>1 rënie në 3 muajt e fundit)

57. Benzodiazepinat (sedativë, mund të shkaktojnë pakësim të perceptimit, të dëmtojnë ekuilibrin)

58. Barnat neuroleptike (mund të shkaktojnë dëmtim të ecjes, Parkinsonizëm)

59. Antihistaminikë të gjeneratës së parë (sedativë, mund të dëmtojnë perceptimin)

60. Barnat vazodilatatore që shkaktojnë hipotension në pacientët me hipotension persistent postural dmth. rënie e përsëritur >20 mmHg në presionin sistolik (rrezik për sinkop, rënie)

61. Opiate për përdorim afatgjatë në pacientët me rënie të përsëritura (rrezik për përgjumje, hipotension postural, vertigo)

Barnat analgjezike

62. Përdorimi i opiateve të fuqishme për përdorim afatgjatë p.sh. morfinë ose fentanil si terapi e linjës së parë në dhimbjen e lehtë-të moderuar (nuk respektohet shkalla analgjezike e OBSh)

63. Përdorimi i opiateve për më shumë se dy javë në pacientët me konstipacion kronik pa përdorur njëkohësisht laksativë (rrezik për konstipacion të rëndë)

64. Opiatet për përdorim afatgjatë në pacientët me demencë me përjashtim të rasteve kur janë të indikuar për kujdes paliativ ose menaxhim të sindromës së dhimbjes kronike të moderuar/të rëndë (rrezik për përkeqësim të dëmtimit kognitiv)

Dyfishimi i barnave të grupeve të njëjta

65. Çdo përshkrim i rregullt i dyfishtë i barnave të të njëjtit grup p.sh. njëkohësisht dy opiate, AIJS, SSRI, diuretikë të ansës, ACE inhibitorë (optimizimi i monoterapisë me një bar të vetëm duhet të merret në konsideratë para një grupi të ri barnash). Kjo përjashton përshkrimin e dyfishtë të barnave që mund të kërkohen kur lind situata (PRN) p.sh. agonistë beta 2 inhalatorë (me veprim të shkurtër e të gjatë) në astmë ose SPOK, dhe opiate për menaxhimin e dhimbjes depërtuese

a. GFR <50 ml/minutë

b. GFR 20–50 ml/minutë

Mjeti i Shqyrtimit për të Lajmëruar mjekët për Trajtimin e Duhur (të përshtatshëm) të indikuar (START)

Këto barna duhet të merren në konsideratë për personat mbi 65 vjeç në kushtet e mëposhtme, kur nuk ekziston asnjë kundërindikacion ndaj përshkrimit:

Sistemi kardiovaskular

1. Warfarina në prani të fibrilacionit atrial kronik

2. Aspirina në prani të fibrilacionit atrial kronik, ku warfarina është e kundërindikuar, por jo aspirina

3. Aspirina ose klopidogreli në pacientët me një histori të dokumentuar të sëmundjes vaskulare periferike, koronare aterosklerotike, cerebrale në pacientët me ritëm sinusal

4. Terapia antihipertensive kur presioni sistolik i gjakut është vazhdimisht >160 mmHg

5. Terapia me statina në pacientët me një histori të dokumentuar të sëmundjes vaskulare periferike, koronare ose cerebrale, ku gjendja funksionale e pacientit mbetet e pavarur për aktivitete të jetës së përditshme dhe pritshmëria e jetës është >5 vite

6. Inhibitorët e Enzimës Shndërruese të Angiotensinës (ACE) në insufiçencën kardiake

7. ACE inhibitor pas infarktit akut të miokardit

8. Betabllokues në anginën e qëndrueshme kronike

Sistemi respirator

9. Beta 2 agonist inhalator ose agjent antikolinergjik rregullisht për astmën e lehtë deri të moderuar ose SPOK

10. Kortikosteroid inhalator rregullisht për astmën e moderuar-të rëndë ose SPOK, ku parashikohet FEV1<50%

11. Oksigjen i vazhdueshëm në insufiçencën respiratore kronike të tipit 1 të dokumentuar (pO2<8.0 kPa, pCO2<6.5 kPa) ose insufiçencën respiratore të tipit 2 (pO2<8.0 kPa, pCO2>6.5 kPa)

Sistemi nervor qëndror

12. L-DOPA në sëmundjen e Parkinsonit idiopatik në prani të dëmtimit funsksional të caktuar dhe paaftësisë rezultante

13. Antidepresiv në prani të simptomave të moderuara-të rënda depresive që zgjasin të paktën 3 muaj

Sistemi gastrointestinal

14. Inhibitor i pompës protonike në sëmundjen e refluksit acid gastro-ezofageal të rëndë ose ngushtimin peptik që kërkon dilatacion

15. Shtesa (suplemente) fibrash për sëmundjen divertikulare simptomatike kronike me konstipacion

Sistemi muskuloskeletik

16. Barna antireumatike sëmundje-modifikuese në sëmundjen reumatoide aktive të moderuar-të rëndë që zgjat >12 javë

17. Bifosfonate në pacientët që marrin terapi mbajtëse orale me kortikosteroidë

18. Shtesa të kalciumit dhe vitaminës D në pacientët me osteoporozë të njohur (prova radiologjike ose thyerje të mëparshme nga brishtësia ose kifozë dorsale të fituar)

Sistemi endokrin

19. Metformina në diabetin e tipit 2, sindromën metabolike (në mungesë të insufiçencës renale[c])

20. ACE inhibitor ose bllokues të receptorit të angiotensinës në diabetin me nefropati dmth. proteinuri ose mikroalbuminuri të qartë (>30 mg/24 orë)

21. Terapi antiagregante në diabetin mellitus nëse është i pranishëm një ose më shumë faktorë risku madhorë kardiovaskular (hipertension, hiperkolesterolemi, histori duhanpirjeje)

22. Terapi me statina në diabetin mellitus nëse është i pranishëm një ose më shumë faktorë risku madhorë kardiovaskular bashkë-ekzistues

c. GFR<50 ml/minutë.

4. List of publications