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Potentially Inappropriate Prescribing and Frailty in Hospitalised Older Adults

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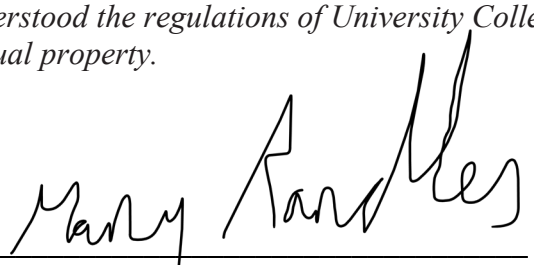
Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

Signed: 

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ADE	Adverse Drug Event
ADL	Activity of Daily Living
ADR	Adverse Drug Reaction
AKI	Acute Kidney Injury
ARB	Angiotensin Receptor Blocker
ATC	Anatomical and Therapeutic Classification
AUC	Area Under Curve
BPSD	Behavioural and Psychological Symptoms of Dementia
Ca	Calcium
CCB	Calcium Channel Blocker
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CK	Creatinine Kinase
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
COX-2	Cyclooxygenase-2
CYP450	Cytochrome P450
DDI	Drug-Drug Interaction
DMARD	Disease-Modifying Antirheumatic Drug
DOAC	Direct Oral Anticoagulant
eGFR	Estimated Glomerular Filtration Rate
FI	Frailty Index
FRID	Falls Risk Increasing Drug
H2 antagonist	Histamine-2 Receptor Antagonist
HB	Haemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HIV	Human Immunodeficiency Virus
HX	History
IBM SPSS	International Business Machines Corporation Statistical Package for the Social Sciences
ICD-10	International Classification of Disease-10
ICU	Intensive Care Unit
IQR	Interquartile Range
K	Potassium
KDIGO	Kidney Disease Improving Clinical Outcomes
LFT	Liver Function Test
L-DOPA	Levodopa
LUTS	Lower Urinary Tract Symptoms
kPa	Kilopascal
MAI	Medication Appropriateness Index
MAO	Monoaminoxidase Inhibitor
MAX	Maximum
Mg	Magnesium
MIN	Minimum
NA	Sodium

NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OPERAM	OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people
P-gp	P-glycoprotein 1
PPI	Proton Pump Inhibitor
PIM	Potentially Inappropriate Medication
PPO	Potential Prescribing Omission
PIP	Potentially Inappropriate Prescribing
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSSA	Prescription Sequence Symmetry Analysis
NICE	National Institute of Clinical Excellence
SD	Standard Deviation
SNRI	Selective Noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
START	Screening Tool to Alert doctors to Right Treatments
STOPP	Screening Tool of Older Persons' potentially inappropriate Prescriptions
TB	Tuberculosis
TCA	Tri-Cyclic Antidepressant
TILDA	The Irish Longitudinal Study of Aging
VIG	Valoración Integral Geriátrica

List of Statistical Symbols

CI	Confidence Interval
df	Degrees of Freedom
HR	Hazard Ratio
N	Population Size
M	Mean
Md	Median
n	Sample Size
OR	Odds Ratio
p	Statistical Probability
r	Correlation Coefficient
SE	Standard Error
t	Test statistic for t-test or Test statistic for Wilcoxon's matched-pairs signed-rank test
U	Test statistic for Mann-Whitney test

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Overview

Continued advances in medical therapeutics have undoubtedly contributed the global increase in longevity and health gains over the last century. However, this increase in life expectancy has led to a concomitant rise in older adults experiencing frailty and co-morbidity. More older people are now chronically treated for conditions that may have previously been l acutely life limiting (cardiovascular disease, diabetes, chronic kidney disease, some cancers) often with complex evidence-based therapies. Previously, prescribing tools have been developed and validated to identify and reduce Potentially Inappropriate Prescribing (PIP) in the general older adult population and in the frailest cohort of older patients. Different levels of frailty may require a tailored approach to prescribing. In robust older people the focus of therapy may be preventative. As characteristics of frailty emerge; vigilance is required to ensure that delirium, falls and functional decline are not provoked by inappropriate medication use. Finally, as older people become increasingly frail, the use of multiple medications may result in more harm than benefit. Nonetheless, there remains a lack of evidence regarding the prevalence of inappropriate prescribing in frail older adults presenting acutely to hospital in Ireland.

This doctoral thesis was initiated in 2020 to explore the relationship between frailty and potentially appropriate prescribing with the goal of identifying the forms of inappropriate prescribing experienced by frail older people presenting acutely to hospital. The manuscript comprises of 9 chapters. The first chapter is an introduction, divided into 3 sections: (i) what is frailty and why is it important? (ii) potentially inappropriate prescribing, (iii) potentially inappropriate prescribing and frailty. The 4 main studies are included in chapters 2-5. Chapter 2 examines the association between frailty and PIP as defined by STOPP/START Version 2 criteria in a population of acutely hospitalised older adults. Chapter 3, evaluates the prevalence of falls risk increasing drug (FRID) use in older people who have experienced a fall in the previous 12 months. Chapter 4, explores

the prevalence of potential drug-drug interactions and frailty in a cohort of acutely hospitalised older adults. Chapter 5, describes the development of an explicit list of prescribing cascades based on the published literature and expert opinion its application to investigate the prevalence of potential cascades at admission and discharge from hospital in multimorbid older people hospitalized with acute illness. In chapter 6 I discuss the findings of studies included in this thesis and potential implications for future research and clinical practice. References and appendices are detailed in chapters 7 and 8 respectively.

CHAPTER 1

Introduction

1.1 What is Frailty and why is it important?

One of the most striking demographic characteristics of the 20th century has been the marked increase in longevity and improved health of older adults. Arising from the combination of increased longevity and reduced birth rate in most countries, the population of adults aged over 65 years is projected to almost double to 1.6 billion globally between 2025 and 2050. At present, the greatest proportion of older adults resides in Europe and developed countries, accounting for over one third of the global population of people aged over 65 years and more than half of the world population aged 85 years and over. Less developed countries in Latin America and Asia are expected to see a rapid rise in their older populations by 2050 due to improved healthcare (1).

While the global increase in longevity is considered a positive thing, it has also led to a concomitant rise in older adults experiencing frailty. Although there is a lack of consensus on the operational definition of frailty, it can theoretically be understood as an age-related state of decreased physiological system reserve characterized by a weakened response to stressors and an increased risk of poor clinical outcome arising from life-threatening illness (2). Data from the Irish Longitudinal Study of Aging (TILDA) indicate the prevalence of frailty as being 15% among those aged over 65 years rising to 46% in those aged over 85 years(3). It is estimated that 80,600 people aged ≥70 years living with frailty in Ireland and may require informal and formal community support at present, with significant implications for future healthcare resource planning (3) .

Given the growing global prevalence of frailty and its association with adverse outcomes such as falls, functional decline, hospitalisation, need for long-term nursing home care and higher mortality, there has been increasing interest in the elements that may affect the rate of progression of frailty along with interventions that may reduce frailty (4-6). Frailty has been identified as a multifactorial syndrome and characterized as a dynamic clinical state which may be improved with appropriate interventions, such as structured

physical exercise sessions, nutritional supplementation, cognitive training and combined multidisciplinary treatment, all of which demonstrate significant positive impacts on frailty up to 12 months following intervention (7, 8).

Less emphasis has been placed on the impact of potentially inappropriate prescribing as a modifiable factor in the progression to frailty, though medication review or assessment of polypharmacy has been included as a component of multifactorial interventions in randomised controlled trials to impede progression of pre-frailty and overt frailty (9, 10). When analysed as a syndrome with indicators such as falls, incontinence and hospitalisations, frailty seems to overlap with some of the recognised consequences of potentially inappropriate prescribing. In this introductory chapter, I will (i) explore the concept of frailty as a syndrome and (ii) endeavour to examine how frailer older adults may be at higher risk from potentially inappropriate prescribing (PIP) and its associations including polypharmacy, adverse drug events, drug-drug interactions, drug-disease interactions, prescribing cascades, and potentially inappropriate prescribing omissions. A conceptualisation of the overlap between the elements of PIP and frailty are illustrated in **Figure 1.1**

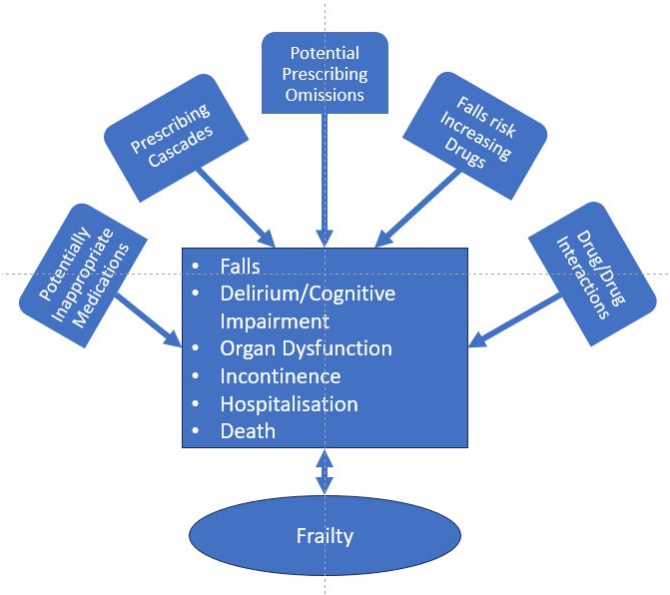


Figure 1.1. Conceptualisation of the interaction between forms of PIP and Frailty.

With the knowledge that polypharmacy and PIP are associated with adverse outcomes for multi-morbid older adults (11-13) , this chapter aims to explore the relationship between frailty and PIP and advocates for the incorporation of screening for PIP as part of a comprehensive frailty assessment and intervention in routine clinical care.

1.1.1 How is frailty measured?

While multidisciplinary Comprehensive Geriatric Assessment remains the gold standard of diagnosing and managing frailty, this holistic method of assessment is time consuming and resource intensive, taking from 45 minutes to 2 hours to fully assess an older person in a multidimensional manner and create a care plan (14, 15). The British Geriatrics Society (BGS) guidelines on the management of frailty acknowledge that frailty may not be detected unless screened for in a structured way in any one individual (14). This is particularly true for older people presenting with acute illness to hospital. Frequently, older people with multiple long-term conditions have concomitant frailty which may be overlooked if the focus is on disease-based care when dealing with long-term conditions such as diabetes mellitus or heart failure (14). Consequently, it is recommended that all interactions with health care professionals for older people should include frailty screening. Opportunistic assessment of frailty with the goal of actively addressing contributory and potentially reversible causes is encouraged for all older people interacting with healthcare services (14). Less time-consuming methods of accurately screening for and assessing frailty have been sought to identify those most at risk of frailty-related adverse outcomes in the community, in healthcare settings and peri-operatively (16-19). Detection of frailty may also trigger goals of care discussions and help avoid potentially detrimental procedures and interventions being performed (20-23)

Despite its growing prevalence, there is no universally accepted method to confirm a diagnosis of frailty (2). The terms *frail*, *pre-frail* and *robust* have emerged as descriptive categories with varying risk of adverse outcomes (4). The pre-frail category originally

emerged from the operationalisation of the Fried Frailty Phenotype to describe the intermediate group of older adults who displayed some of the characteristics of frailty but were not frail. This group were twice as likely to develop frailty over 3 years compared to robust older people (4). Pre-frailty is considered as a prodromal stage before the emergence of frailty and a potentially reversible condition (24, 25).

Although associated with multimorbidity, frailty is not in itself a surrogate for disease burden i.e. a person may have multimorbidity and not be frail (26). Over the last 20 years, various methods of accurately screening for and assessing frailty have been devised to identify those most at risk of adverse outcomes in the community, in healthcare settings and in hospital peri-operative situations (27-29). The choice of frailty instruments may also be determined by the time available, location of assessment, space and equipment required to carry out the assessment.

A selection of commonly used frailty instruments is shown in **Table 1.1**, with specific focus on their relationship with the assessment of medication use. Three of the selected tools incorporate medications in their assessment of frailty. This is not an exhaustive list; instruments were selected to demonstrate the numerous methods of quantifying frailty from identifying a phenotype to self-reported items.

Table 1.1 A selection of frailty assessment tools and a summary of their threshold scores for defining frailty and prefrailty, highlighting tools that incorporate medication assessment.

Frailty Instrument	Components	Classification	Pre-Frailty	**Medications Assessed**
(Physical/Fried) Frailty Phenotype[4]	Five items: Weight loss, low physical activity, exhaustion, slowness, weakness	Frailty: ≥3 present, pre-frailty:1-2 items, robust 0 items	Yes	**No**
Cumulative deficit Frailty Index [30, 31]	Minimum of 30 accumulated health deficits. Dichotomous Yes/No. Index scores 0(none present)-1(all present)	Frailty: >0.25	No	**If included in construction of index**
Clinical Frailty Scale(27)	Nine graded pictures on visual or written chart. 1=Very Fit-9 Terminally Ill	Frailty: ≥5	Yes	**No**
FRAIL scale[32]	Self-Rated Scale, Five Items: (Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight) (i.e., 1 point for each component; 0=best to 5=worst) and represent frail (3–5), pre-frail (1–2), and robust (0) health status	Frailty: ≥3, pre-frailty: 1-2, Robust: 0	Yes	**No**
Edmonton Frailty Scale[33]	Nine Questions: cognition, general health, self-described health, functional independence, social support, medication use, nutrition, mood, continence, functional performance.	Frailty: ≥ 7, prefrailty: 5-6, Robust ≤4	Yes	**Yes**
PRISMA-7[34]	Seven self-reported items: Age.85 years, male, social support, activities of daily living.	Frailty score≥3	No	**No**
FI-CGA[35]	Ten items: cognition, mood, communication, mobility, bowel function, balance, pADL/iADL, nutrition, social resources. Each domain scored 0 (no problem) to 2 (major problem).	Mild frailty=0-7, Mod=7-13, Severe >13	No	**No**
GroningenFrailty Indicator [36]	Fifteen self-reported Items across four domains: physical, cognitive, social, psychological.	Frailty score≥4	No	**No**
Frail-VIG(37)	Twenty-Five questions frailty index assessing 22 domains: Developed from CGA and designed for clinical use. No Deficit=0, Deficit=1	Frailty: >0.25	No	**Yes**

FI - frailty index; pADL - personal activities of daily living; iADL - instrumental activities of daily living; CGA - comprehensive geriatric assessment; CHSA-92 – Canadian Study of Healthy Aging in 1992.

In 2016, Buta et al. identified 67 frailty tools cited in the literature [17], of which nine had more than 200 citations. The most cited were the Physical Frailty Phenotype and the

Cumulative Deficit Frailty Index. A further systematic review in 2018 found that of the 51 instruments presented, 23 had the capacity to identify pre-frailty (38). Most frailty assessment instruments can be broadly divided into frailty phenotype or frailty index/cumulative deficit categories. Both categories have been internationally validated for use in identifying older people at high risk for adverse outcomes relating to frailty compared to other non-frail people of similar age.

The **Frailty Phenotype** was developed by Fried et al. in 2001 based on secondary analysis of the Canadian Cardiovascular Health Study involving 5210 men and women aged over 65 years and older(4). Participants were followed up at annual intervals for up to 7 years. It includes five variables: (i) unintentional weight loss, (ii) self-reported exhaustion, (iii) low energy expenditure, (iv) slow gait speed and (v) reduced hand grip strength. People categorised as frail (≥3 variables present) had higher rates of falls, impaired physical function and death compared to people categorised as robust (0 variables) or pre-frail (1-2 variables).

Validated in the community, long-term care and hospital in-patient settings (39-41), the Frailty Phenotype is the most cited frailty measurement in the literature. However, it has some limitations (42), including the substantial time required to translate the 5 variables into clinical practice, the narrow focus on physical characteristics, requirement for measurement equipment and the variable effect of acute illness on the frailty parameters. These limitations are potential obstacles to its routine clinical application (43).

The Frailty Index and the Clinical Frailty Scale

Mitnitski and Rockwood utilised a cumulative deficit model to create the frailty assessment tool (30). Using a holistic and multidimensional construct of frailty, they proposed that frailty is caused by the lifelong accumulation of deficits such as falls,

cognitive impairment, co-morbidities and abnormal laboratory variables (30). The original 92 deficit Frailty Index was from the cross-sectional and longitudinal components of the Canadian Study of Heath and Aging (CSHA). The index score for an individual was calculated by dividing the total number of deficits present by 92, and index of 0.25 of predicts frailty. The 70-deficit Frailty Index was later established using the CSHA data(44). The greater the number deficits present results in greater levels of frailty (30). A published standard procedure for the development of a frailty index using a minimum of 30 deficits allowed the cumulative deficit model to be applied to different sets of data resulting in the development of further indices such as the Electronic Frailty Index based on primary care electronic health record data (45).The use of a graded frailty index also discriminates moderate frailty from severe frailty based on increasing index number and a dose dependant relationship with death and institutionalisation and it has been validated across multiple clinical settings (31, 35, 39). The Frail-VIG Index has been shown to be a reliable, feasible, and valid instrument to quantify the level of frailty in both hospitalized and community-dwelling older people (46). Frail-VIG index (Appendix 1) is based on the comprehensive geriatric assessment with the aim of developing a pragmatic, easy-to-apply clinical assessment tool. Frail-VIG index utilises 25 deficits from eight different dimensions, has an AUC of 0.9 (0.88-0.92) with predictive validity of mortality, taking on average 5-10 minutes to administer (37). The re-test and inter-rater reliability of the Frail-VIG index has been demonstrated to be excellent in previous studies (46, 47).

Following from the Frailty Index, Rockwood et al. later developed a 7-point Clinical Frailty Scale (CFS). The outcomes of institutionalisation and mortality were highly correlated with a CFS 7-point range ($r = 0.80$) and with the original Frailty Index. Each category increment of the CFS significantly increased the medium-term risks of death by

21.2%, (95% confidence interval [CI] 12.5%–30.6%) and institutionalization by 23.9% (95% CI 8.8%–41.2%) in multivariable models that adjusted for age, sex and education based on CSHA data (27).

Figure 1. 2. 9 Point Clinical Frailty Scale Original Version 1 (CFS), Rockwood, K. et al. (2005), reprinted with permission (Appendix 2)

The CFS (Figure 1.2) is highly dependent on the clinical judgement of the user. Nevertheless, it is quick and easy to use and has been validated in primary care, hospital and long-term care settings (48, 49)The second version of the CFS (**Figure 1.3**) includes 9 grades in which the category of 'vulnerable' (CFS=4) was replaced with 'living with very mild frailty'(50). The creators of the CFS have expressed caution regarding the use of this usually when a person is clinically stable, and not in the setting of an acute illness or deterioration judgment-dependant instrument by those inexperienced in frailty evaluation (50).

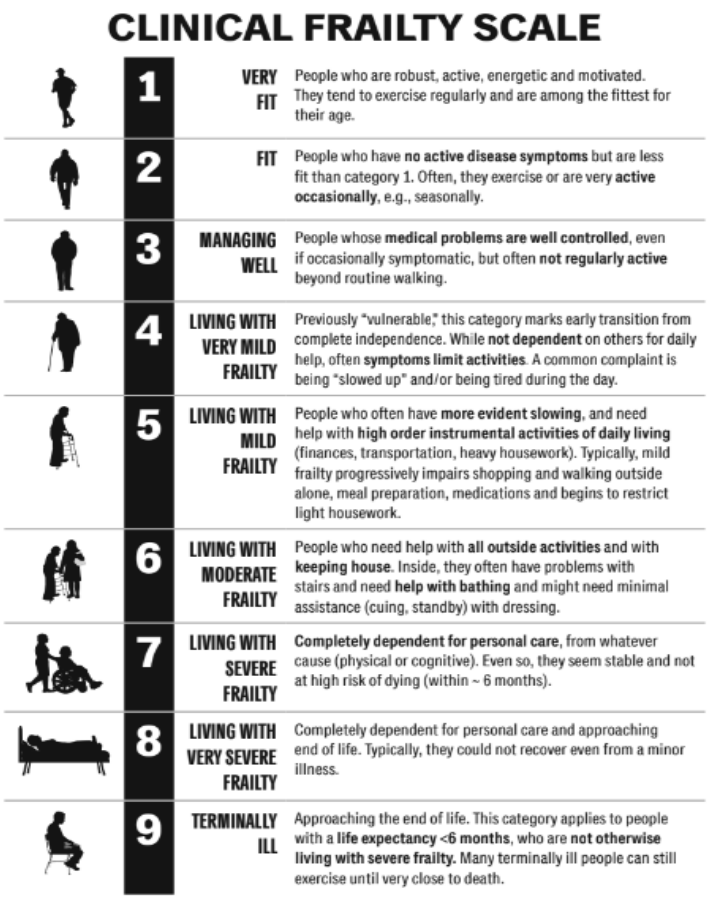


Figure 1. 3. 9 Point Clinical Frailty Scale Original Version 2 (CFS), Rockwood, K. et al. (2020), re-printed with permission (Appendix 2)

1.1.2 How Prevalent is Frailty?

Meta-analysis of prevalence studies has shown a pooled prevalence of frailty of 18% across all settings, with the highest rates of frailty in the hospital in-patient and long-term care settings (54.1%-54.2% and 62.1%-68.8%)(41, 51-53). Based on systematic review and meta-analysis involving over 61,500 participants, Collard et al. showed that up to 10.7% of community-dwelling older persons are frail and 41.6% are pre-frail. Nevertheless, the reported prevalence differed substantially within the included studies, ranging from 4.0% to 59.1% depending on how frailty was measured.(54). A large multi-national meta-analysis confirms this variance producing a pooled estimate of 12% (11%–13%) for physical frailty and 24% (22%–26%) for the deficit accumulation model (40) . In nursing home residents, the prevalence of frailty ranged from 36.4% (23.8%-51.1%,

95% CI) using the Fried phenotype to 71.8% (62.8%-79.5%, 95% CI) using the CFS (55). Systematic comparison has also shown a widely variable prevalence of pre-frailty of 19% to 54% with an average prevalence of 41.6% in community dwelling adults aged over 65 years. Both increasing age and female sex are associated with increased frailty(54). One study has shown that over a 3 year follow up period, 4.6% of robust older adults and 18.5% of pre-frail older adults go on to develop frailty (56).

1.1.3 Can frailty affect pharmacokinetics and pharmacodynamics?

Given that the physiological changes observed with the frailty syndromes overlap with the changes which result in altered drug pharmacokinetics and pharmacodynamics in older adults, it would seem plausible to propose that frailty predisposes to altered pharmacokinetics and pharmacodynamics. Several physiological systems show altered function in the context of frailty including the central nervous system, the sympathetic nervous system, hepatic clearance, endocrine system responses from the pituitary gland and the adrenal gland, and innate immune system responses. With loss of physiological reserve in other systems including the cardiovascular, respiratory and renal systems, a frail individual who already has compromised regulation within and across these systems may have more difficulty than others in tolerating stress effects from potentially inappropriate medications. A further integral component in the frailty phenotype is sarcopenia, the commonly observed age-related loss of skeletal muscle mass (57). Frailty-associated decline in renal function may affect the pharmacokinetics of some drugs and chronic kidney disease may worsen sarcopenia (58, 59). Older people often have a greater body fat: lean body mass ratio with an overall reduction in total body water and serum albumin concentration. This leads to a relative increase of the volume of distribution such that the half-life of lipophilic drugs such as benzodiazepines is often prolonged. Similarly, there is often an increased plasma concentration of water soluble drugs like lithium and

an increased proportion of free unbound highly protein bound drugs like ibuprofen and phenytoin (60).

Certain medications may also play a role in worsening measured variables of frailty i.e. delirium, falls, anorexia, functional impairment, cognitive impairment and gait/balance problems are commonly associated with adverse drug effects but may also be attributable to frailty (61). Hilmer and Kirkpatrick have highlighted the theoretical impact of frailty on physiological systems and pharmacokinetics but also emphasize that there is a concerning lack of research in this area, with the majority of studies on frailty and pharmacokinetics focusing on individual drugs rather than on polypharmacy (62). Their review of the studies of pharmacokinetic effects of frailty was limited by small study populations, failure to select distributions of frailty scores, lack of a clear definition of frailty and exclusion of participants with potential drug interactions.

1.2 Potentially inappropriate prescribing (PIP)

PIP occurs where there is a lack of indication for a medication, where there is avoidable adverse drug–disease or drug–drug interaction exposure, where risks of medications outweigh their benefits or where time-to-benefit from treatment exceeds individual life expectancy. PIP also encompasses omission of potentially beneficial medications that are clinically indicated for treatment or prevention of a disease, mis-prescribing and prescribing cascades [30-32]. Traditionally, the term PIP refers to the prescription of potentially inappropriate medications (PIM), potential prescribing omissions (PPO) or both.

PIP is associated with reduced health-related quality of life, excess adverse drug events, increased hospitalisation, re-hospitalisation and increased mortality [33]. To minimize exposure of frail older adults to PIP, structured medication review with appropriate deprescribing is a logical approach. Several tools have been developed to help identify

PIP. A recent systematic review which included 42 prescribing assessment tools found that only thirteen had been externally validated, with hospitalisation being the most commonly measured patient-related outcome [34]. Deprescribing tools are classified as either explicit, implicit or a combination of both. Explicit criteria tools such as Beers criteria, LaRoche criteria, EU-7 criteria and STOPP/START criteria typically contain lists drugs or drug classes that are known to expose older adults to potential harms that outweigh their benefits either in themselves or through adverse drug-disease interactions [35-38]. With STOPP/START criteria, there is also a list of 'potential prescribing omissions' (START criteria) i.e., drugs that probably should be prescribed in older people but are not for various inappropriate reasons, including perceived high-level frailty. Implicit PIP assessment tools such as the Medication Appropriateness Index (MAI) require knowledge of individual treatment goals and comorbidities in the context of each prescribed drug [39]. While MAI is patient-centred, it is highly time-consuming to apply to older adults with polypharmacy and requires comprehensive knowledge of the prescribed drugs.

Given the number and range of methods for measuring PIP, it is unsurprising that PIP prevalence, like frailty prevalence, varies greatly depending on which assessment tool is used and the patient population studied. A wide range of PIP prevalence (22%-79%) has been reported in several studies with the wide variance attributed to the different patient populations being assessed and the PIP assessment tool used [40, 41].

STOPP/START criteria

Designed and validated as an explicit, physiological systems-based screening tool for potentially inappropriate drug therapy in older people, STOPP/START criteria were developed using the Delphi validation method. STOPP/START criteria identify instances of potentially inappropriate prescribing as well as instances of prescribing omissions

commonly prescribed for older people in Europe. Inter-rater reliability for STOPP/START version 1 had a coefficient of 0.75 for STOPP and 0.68 for START. STOPP/START version 2 criteria were expanded and updated in 2015 to include 80 STOPP Criteria and 34 START criteria (63). STOPP/START version 3 criteria were published in 2023 and include 133 STOPP criteria and 57 START criteria (64) STOPPFrail, an explicit list of 27 PIMs was subsequently developed and validated to guide deprescribing for severely frail older people and those with limited life expectancy (65).

Beers Criteria

Beers et al. published the first explicit criteria designed for determining inappropriate prescribing in nursing home residents 1991(66). Subsequently adopted and endorsed by the American Geriatrics Society, Beers Criteria have been expanded include 30 individual criteria of medications or medication classes to be avoided in older adults and 16 criteria specific to more than 40 medications or medication classes that should be used with caution or avoided in certain diseases or conditions (67). Though widely utilised in North America, there has been difficulty adapting the criteria in Europe due to variances in available medications and prescribing patterns between the continents. The most recent (seventh) iteration of Beers Criteria was published in 2023 by the American Geriatrics Society expert review panel (68).

LaRoche PIM List

In 2007, La Roche et al. published an explicit criterion for identifying potentially inappropriate medication use in adults over 75 years of age in France. The list used Beers criteria as a starting point, amending it for use in France clinical practice. The Delphi method was used to identify drugs with an unfavourable benefit to risk ratio and drugs with questionable efficacy. In addition, safer therapeutic alternatives were also indicated

for each criterion. Of note the list was designed to be applicable to people over 75 years as the expert consensus felt that people younger than 75 were physiologically similar to middle-aged adults (69).

EU-7 Criteria

The EU-7 criteria were developed by the Delphi process with experts from 7 EU countries. The criteria were established to identify potentially inappropriate medications across EU drug markets. The emphasis of this list is on the chemical/pharmaceutical properties of the drug rather than clinical contexts. It was created to assess medication appropriateness at a primarily epidemiological level in older adults with dementia without detailed clinical history or context (70).

Medication Appropriateness Index

First published in 1992 by Hanlon et al., the Medication Appropriateness Index (MAI) is an implicit method of assessing the individual appropriates of each medication taken by a patient using ten criteria: indication, effectiveness, dose, correct direction, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and cost. A summative score gives each drug a rating of appropriate, marginally appropriate or inappropriate according to each of the ten criteria to give an overall score between 0 and 18 with 18 indicating completely inappropriate prescription (71).

NO-TEARS

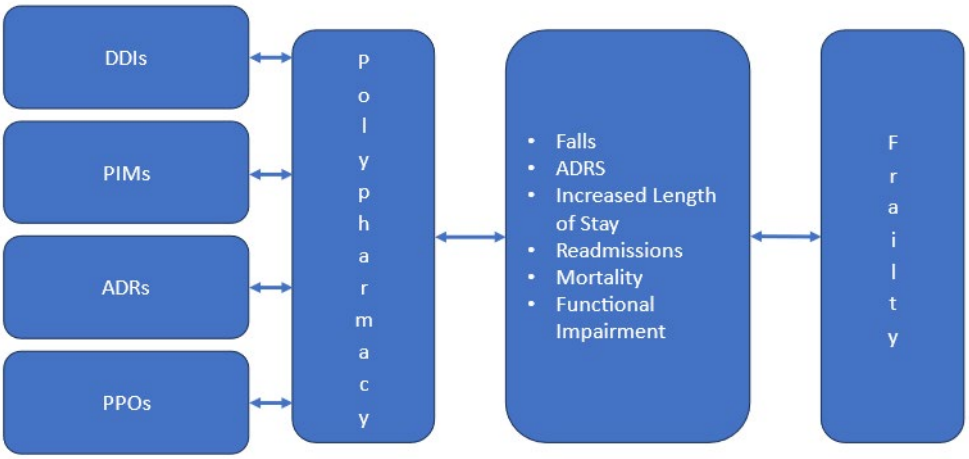
The NO-TEARS tool is a list of questions to guide medication appropriateness reviews in a patient centred manner. Developed as a 10-minute interview, it assesses patient goals of treatment, compliance and medication use in the primary care setting. It comprises 7 prompts; **n**eed and indication, **o**pen questions, **t**ests and monitoring, **e**vidence and guidelines, **a**dverse events, **r**isk reduction or prevention, **s**implification and switches (72).

This tool presents a practical, patient-centred method of optimising medications. However, evidence of reduction of adverse outcomes by using this tool as an intervention is yet to be demonstrated.

1.2.1 Polypharmacy

Polypharmacy is often defined as the use of 5 or more medications simultaneously or on daily basis while hyper-polypharmacy is defined as the use of 10 or more daily medications (73, 74). Polypharmacy has been considered by many to be a geriatric syndrome in itself given its ubiquity amongst older people (75). Polypharmacy is associated with adverse outcomes including falls, adverse drug reactions, increased hospital length of stay, early re-admission to hospital and mortality (13, 76-79). The risk of harm from adverse drug reactions, drug-drug interactions and drug-disease interactions increases as the number of simultaneously consumed medications increases (80). The risk of adverse effects and clinically significant harm increases with increasing numbers of medications (77, 80, 81). **Figure 1.4** illustrates the interaction of polypharmacy and frailty. Older people are at considerably higher risk of experiencing polypharmacy due to a much higher burden of multimorbidity than younger people. Polypharmacy, as the principal risk factor for ADRs, may also be engendered and exacerbated by older people attending multiple specialists for multiple concurrent diseases or conditions, leading to more and more evidence-based drug therapies. In one study, researchers found that taking more than 5 daily medications was associated with an odds ratio for ADEs of 1.88 (95%CI, 1.58–2.25) compared to patients taking 0-4 daily medications (102).

Figure 1.4. The overlapping associations between polypharmacy and frailty (77-79).



Legend: DDIs- drug-drug interactions, PIMs-potentially inappropriate medications, ADRS-adverse drug reactions, PPOs-potential prescribing omissions

Defining polypharmacy by counting medications may over-simplify the complex prescribing decisions required to manage multimorbid states (13). Davies et al. advocate for the greater use of the descriptors 'appropriate' and 'inappropriate' polypharmacy to increase the clinical relevance of studies assessing the association between polypharmacy and adverse outcomes rather than a simple numeric cut-off of ≥5 daily medications (13). Appropriate polypharmacy is defined as:

> "…. prescribing for individuals with complex or multiple conditions where medicine use has been optimised and prescribing aligns with best evidence" (82).

This concept recognises that there are cases where prescribing of multiple evidence-based medications in a carefully considered way can continue to be of benefit to patients provided that the prescribing reflects the patients' clinical needs and what matters most to them in terms of symptom control and disease prevention.

1.2.2 Prescribing Cascades

A prescribing cascade occurs when an adverse drug event (ADE) or adverse drug reaction (ADR) is misinterpreted as a new symptom or medical condition, with the subsequent

prescription of another, potentially inappropriate drug (83, 84) (**Figure 1.5)**. The prescribing cascade, an important source of potentially inappropriate prescribing, was first introduced by Rochon and Gurwitz almost 3 decades ago. Since then, prescribing cascades have been gaining greater recognition as a cause of potentially problematic polypharmacy. Prescribing cascades are another form of both inappropriate prescribing and a risk factor for drug-drug interactions presenting an important public health problem. Prescribing cascades have been associated with adverse health outcome and reduced quality of life (85, 86).

Compared to robust older adults, frailer individuals are exposed to greater levels of polypharmacy and have greater exposure to high-risk medication regimes leading to an increased risk of prescribing cascades (80, 87) . With polypharmacy comes increased risk of drug-drug and drug-disease interactions (88, 89). ADEs and ADRs in older adults can be misinterpreted as worsening frailty or geriatric syndromes due to their non-specific symptoms and clinical manifestations. Historically, potential adverse events in older adults have been under-reported in drug trials and it is generally accepted that older adults are underrepresented in clinical trials.(90-93).

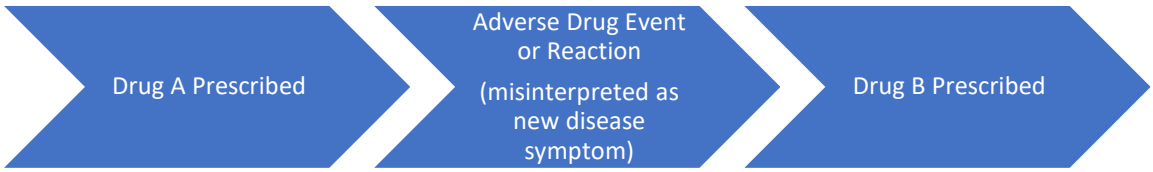


Figure 1.5. Diagram of the concept of the prescribing cascade

A recently published systematic review of 101 studies describing prescribing cascades in community-based adults found that the most commonly described prescribing cascades were:

(i) calcium channel blockers → loop diuretics to treat peripheral oedema

(ii) amiodarone → thyroxine to treat hypothyroidism

(iii) inhaled corticosteroids → topical antifungal to treat oropharyngeal candidiasis

(iv) antipsychotics → levodopa to treat Parkinsonism

(v) acetylcholinesterase inhibitors → drugs for urinary frequency (94).

This study specifically looks at cascades in all adults aged over 18, excluding studies conducted solely in nursing homes, residential care, inpatient settings or emergency departments and case reports. It demonstrates a tendency for the most widely known cascades to be the most frequently assessed and measured, such that less well-known cascades may be overlooked or undetected.

The true prevalence of prescribing cascades is yet to be elucidated, though individual cascades have been evaluated using population and cohort studies and shown to exist in clinically relevant frequency particularly in older adults (95-97). Prescription sequence symmetry analysis (PSSA) studies have gained substantial traction in recent years in the pharmacovigilance literature as a method for rapidly detecting and evaluating potential prescribing cascade signals (98). These PSSA-derived prescribing signals serve as a prompt for clinical review. In addition, clinical process mapping has been described as a method to screen for cascades when older people present with a new symptom (99, 100). At present, the prevalence of prescribing cascades is likely to be underestimated.

Another dilemma facing prescribers is how to intervene when a potential prescribing cascade is detected where a comprehensive explicit prescribing cascade list is lacking. Practical approaches to cascade detection include implicit algorithms that can be applied during routine medication review. ThinkCascades is a concise nine-item, international consensus-based list of clinically important prescribing cascades which was developed to raise awareness among clinicians of more common prescribing cascades that may represent inappropriate prescribing (101). While this tool serves to alert prescribers to

more common prescribing cascades, it is probably too short to be of practical value in routine clinical practice as, if used solely to screen for prescribing cascades, many potentially problematic cascades could be overlooked. In practice, a preventive approach to prescribing cascades is required by applying a systematic approach to prescribing in older adults, maintaining a high level of suspicion that any new symptom may be a result of a medication side-effect.

1.2.3 Cost of Potentially Inappropriate Prescribing

The adverse consequences of potentially inappropriate prescribing in older people are not only limited to clinical humanistic cost; there is also a significant associated economic cost. The sources of this economic cost are three-fold: firstly, the direct cost of the prescribed drugs themselves accounting for up to an estimated €318 per patient per year (102); secondly, the associated dispensing cost of PIP; and thirdly, the potential cost to healthcare systems from the consequences of adverse drug events and associated increased health service utilisation. In Ireland, the cost of PIP has been conservatively estimated in one study published in 2010 at €45,631,319 (9% of total pharmaceutical expenditure of people aged over 70 at the time of study)(102). In a more recent international study, total avoidable healthcare PIP-related expenditure was reported to range from €18.66 per patient per year in Northern Ireland to €1449.05 in France (103). Furthermore, a recent cohort study by Guldstein Robinson et al. demonstrated than on 3 month follow-up, older adults taking STOPP criteria PIMs had more frequent healthcare utilisation and greater overall healthcare costs than age-matched adults who were not prescribed STOPP criteria PIMs €1958 (€1428–€2616) vs €881 (€817–€1167), p=0.002) (104).

1.2.4 Adverse Drug Reactions & Adverse Drug Events

An adverse drug reaction was originally defined by the World Health Organisation in 1972 as: “A response to a drug that is noxious and unintended and occurs at doses

normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function"(105). Edwards and Aronson further defined an ADR as: "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or the alteration of the dosage regimen, or withdrawal of the product"(106). They expanded on this definition by clarifying that while an adverse drug effect and adverse drug reaction are often used interchangeably, an adverse drug effect is seen from the point of view of the drug whereas the adverse drug reaction is seen from the point of view of the patient (106). In 2010, this definition was expanded to include reactions occurring as a result of error, misuse or abuse and to suspected reactions to medicines that are unlicensed or used off label in addition to the authorised use of a medicinal product in normal doses (107).

When discussing adverse drug effects, some experts emphasize the need to differentiate between ADRs and ADEs. The difference depends essentially on the adverse effect. While an ADE can be defined as an adverse outcome that occurs while a patient is taking a drug, it is not necessarily directly attributable to the drug (106), such as the increased incidence of falls and fractures when older people are taking benzodiazepines.

As previously discussed, frail older adults are at substantially higher risk of ADRs due to diminished capacity to maintain homeostasis when under stress. Aging itself is associated with a decrease in the functional capacity of multiple organ systems leading to changes in absorption, distribution, metabolism and excretion of some drugs (60). Older age is associated with delayed gastric emptying, decreased splanchnic blood flow, and reduced surface area for absorption, coupled with increased gastric pH. Metabolism of drugs may be altered by aging also due to reductions in hepatic volume, renal and hepatic perfusion, and plasma protein binding. Older people who experience polypharmacy are more likely to take drugs that cause inhibition or activation of the cytochrome P450 (CYP) system

(108, 109). Normal physiological aging and common disorders such as cardiovascular disease, diabetes, heart failure and hypertension all contribute to reduced renal clearance and excretion of drugs (109). Multimorbidity, the co-occurrence of two or more chronic medical conditions has been shown to affect up to 95.1% of patients aged over 65 in the primary care setting in one systematic review of 39 studies (110).

Over the last 25 years, there has been a notable increase in treatment guidelines for many common conditions, particularly in the areas of cardiovascular disease and diabetes where treatment guidelines recommend multiple drugs for secondary prevention and ongoing management of these conditions. Worryingly, studies show that polypharmacy has increased in the last two decades, particularly after hospital admission (111, 112) which in turn increases the risk of drug-disease interactions and drug-drug interactions (113). Although older patients experience the greatest burden of multimorbidity and associated polypharmacy and are the largest group of patients receiving evidence-based pharmacotherapies, paradoxically they are often excluded from clinical drug trials *because of* their multimorbidity. An example of this discrepancy can be seen in several cancer drug trials. While people over 65 years represent over 60% of new cancer cases in Europe and the US annually, they account for only 22% of patients recruited into cancer trials. This proportion drops to 8%-13% in those over aged over 70 years (114). This degree of older patient exclusion from clinical trials is further illustrated in a review of 440 trials of drugs for type 2 diabetes (115). Despite being the most common long-term metabolic condition experienced by older adults, only 6 trials were specifically designed to study older adults; 289 trials excluded individuals based on an arbitrary age cut off and a further 76.8% of trials excluded people with co-morbidities.

1.2.5 Falls as an ADR in frail older people

Falls have been identified as a leading cause of injury-related morbidity and mortality in older adults and represent a major public health problem with over 1 in 4 older adults

over 65 experiencing falls annually (116). Of these falls, 1 in 5 leads to serious injury such as fractures or head trauma, with 95% of hip fractures attributed to falling (117). While falls in older adults are usually multifactorial, one of the more prominent and modifiable extrinsic risk factors is the use of falls-risk increasing drugs (FRIDs). Several drug classes including blood pressure-lowering cardiovascular drugs, psychotropics and anti-epileptic medications have been acknowledged by meta-analysis as increasing the risk of falling in older adults (118-120). Prevalence of FRID use in older people varies from 87% in primary care to 93% in older adults who have been admitted to hospital with hip fracture (121-123).

Medication review for FRIDs detection is strongly indicated by falls prevention guidelines such as the National Institute for Clinical Excellence (NICE) guidelines and the World Guidelines for Falls prevention and Management for Older Adults (124). However, there has been substantial variation between various sets of guidelines regarding what constitutes a FRID [125-127]. The STOPPFall (Screening Tool of Older Persons Prescriptions in older adults with high fall risk) list was created using a modified Delphi process with the aim of identifying by consensus and review of current literature, the medications most commonly associated with falls in older adults. Consensus was reached on 14 medication classes: benzodiazepines and benzodiazepine-related drugs, antipsychotics, opioids, antidepressants (all classes), antiepileptics, diuretics, alpha-blockers as antihypertensives and for benign prostatic hyperplasia, centrally-acting anti-hypertensives, sedative antihistamines, vasodilators used in cardiac disease and antimuscarinics for overactive bladder (128). This validated and structured screening tool has been recommended by the World Falls Guidelines to identify FRIDs and to guide appropriate deprescribing as part of a multidomain falls intervention (127).

Previous observational studies have shown that frailty is associated with an increased risk of falls and fractures in older people with the risk greatest in those over 75 years of age.

Furthermore, it has been noted that frailty is associated with a greater risk of further falls and fractures and shorter time to recurrent falls (129). This increased risk of recurrent falls has been shown to be consistently associated with frailty in meta-analyses despite the heterogenous methods of assessing frailty (114, 130).

In this thesis, one of my aims is to use the STOPPFall list of medications to assess the point-prevalence of falls-risk increasing drugs in older adults presenting to hospital after a fall or who having experienced a fall in the previous 12 months. I examine the relationship between FRIDs, falls and serious falls requiring hospital presentation. I also examine the relationship between FRIDs and frailty. This observational study should facilitate better understanding of the prevalence of FRIDs in the local population of older adults. We hope that establishing the prevalence of falls-risk increasing drugs in community dwelling adults with falls, will guide further multifactorial interventions, to prevent catastrophic or life changing falls in the future.

1.2.6 The risk of drug-drug interactions in multimorbid and frail older people

Medication management in older people experiencing multimorbidity (multiple medical conditions or illnesses) has been acknowledged as a complex challenge for healthcare professionals. As multimorbidity increases, so too does the number of medications a person is prescribed, potentially leading to polypharmacy and increasing the risk of clinically relevant drug-drug interactions. It has been demonstrated that the number of medications a patient is prescribed increases proportionately with the number of co-morbidities accumulated[(131)].

Drug-drug interactions (DDIs) are a growing subject of concern, as they are known to be related to adverse drug reactions and hospitalisations. DDIs can be classified into two main groups: pharmacokinetic and pharmacodynamic A strong relationship has been demonstrated between number of dispensed drugs and potential DDIs, especially for

potentially serious DDIs, which has implications for the importance of trying to minimise the number of drugs prescribed for older adults(113).

In a recent systematic review of the prevalence of DDIs in community dwelling older adults aged ≥ 65 years, the prevalence of DDIs ranged widely, 0.8% to 90.6%(132). Among older hospitalised adults in geriatric units, the variation was a little lower (80.5% to 90.5%) with a higher overall prevalence. There is significant heterogenicity between individual studies in relation to the definition of DDIs (133).

Many clinically relevant DDIs are regarded as predictable and avoidable and therefore may be considered as targets for education and interventions towards prevention. Hospital admission in multimorbid older people provides the opportunity for medication review of DDIs which are responsible for 4.8% of hospital admissions in older patients (134). Hospital admission also represents a time of increased risk for older adults, as the prescription of new drugs to treat acute medical problems and/or to prevent readmission may increase the risk of DDIs and ADRs.

1.3 Potentially inappropriate prescribing and frailty

There is growing interest in the relationship between PIP and frailty. As previously mentioned, physiological systems associated with susceptibility to impaired homeostasis in the context of frailty include the central nervous system, the sympathetic nervous system, the endocrine system (particularly pituitary and adrenal glands), and the immune system (135). With attenuated physiological reserve in other systems including the cardiovascular, respiratory and renal systems, an overtly frail individual with compromised reserve in one or more systems is more susceptible than non-frail or pre-frail persons to physiological stress of various kinds arising from adverse medications. Medications may also play a role in exacerbation of measured variables that characterize frailty. Delirium, falls, anorexia, functional impairment, cognitive impairment, renal

impairment and impaired balance are well-recognized commonly occurring ADEs that may be attributed incorrectly to irreversible aspects of age-related frailty.

Several studies have examined the relationship between frailty and PIP in hospital, community and institutional settings. A literature search of PubMed and Google Scholar databases was undertaken. Search terms included: Frailty OR Measured Frailty, Frailty OR Measured Frailty AND Potentially Inappropriate Prescribing OR Potentially Inappropriate Medication Use OR Potential Prescribing Omissions OR Medication Underuse. We included articles involving adults aged ≥ 65 years in all settings, i.e., community, hospital, and residential care. Studies with no access to the full-text article or English version of the article and studies exclusively describing patients aged < 65 years were excluded. **Table 1.2** summarises a selection of these studies and briefly summarizes the variable methods of assessment.

Table 1.2. A selection of studies exploring the association between Potentially Inappropriate Prescribing and Frailty.

Study (Year)	Type of Study	Population Characteristics	Frailty Criteria	Medication Appropriateness Measurement.	Main Findings
Cullinan *et al. (2016)(136)*	Retrospective analysis of randomised controlled trial database	n=711 sex=not reported age=not reported acute hospital inpatients	Novel 34 item Frailty Index developed using variables available in database	STOPP/START	The mean FI score above in which patients experienced at least one instance of PIP was 0.16. Patients above this threshold were twice as likely to experience PIP (OR = 2.6, (1.47, 3.044; P < 0.0001) and to develop an ADR (OR = 2.1, P < 0.0001). Patients taking more than six medications were 3 times more likely to experience PIP.
Dalleur et al. (2012)(137)	Cross-sectional study	n=302 female=62.6 % (189) median age [P25-P75] = 84 [81-88] acute hospital inpatients	Identification of Seniors at Risk (ISAR)	STOPP/START	PIMs were found in 144 of the 302 frail older adults (prevalence 47.7 %), with the following distribution: 1 PIM (29 %), 2 PIMs (16 %) and ≥ 3 PIMs (3 %). The prevalence of PPOs was 62.9 % (190/302), with the following distribution: 1 PPO (29 %), 2 PPOs (19 %), and 3 PPOs (15 %).
Hanlon et al. (2004)(138)	Cross-sectional, secondary analysis of data from a randomized controlled trial	n=397 female=2.8% (11) age ≥75 years =184 (46.4%), 65-74 years = 213 (53.6%) acute hospital inpatients*	>2 of 10 frailty criteria.	MAI	365 (91.9%) patients had ≥1 medications with ≥1 MAI criteria rated as inappropriate.
Récoché et al. (2017)(139)	Cross sectional study	n=229 female= 156 (68.1%) Age (SD)= 82.14 (6.22) day hospital patients	Gerontopole Frailty Screening Tool Fried phenotype	Criteria based on Laroche list and STOPP/START	Among the 229 frail patients included, 163 (71.2%) had ≥1 instance of PIP.
Muhlack et al. (2020)(140)	Longitudinal cohort study	n=2865 female= 1480 (51.7%) age (SD)= 70.2 (5.9) community dwelling older adults	Fried Phenotype	2015 Beers criteria 2015 Beers dementia sub-list PRISCUS EU (7)-PIM list	At baseline, 32.1% (919) participants were classified as robust, 58.8% (1685) were prefrail and 9.1% (261) were frail. The baseline PIM prevalence varied between 9.2% (Beers dementia PIM) and 37.5% (EU(7) PIM).21% of participants became frail during follow up. All PIM criteria were significantly associated with incident frailty in the unadjusted and in the age and sex-adjusted analyses,

					however not significant after adjustment for number of medicines and propensity scores.
Gutiérrez-Valencia et al. (2018)(141)	Cross-sectional analysis from a concurrent cohort study	n=110 female= 79 (71.8%) age (SD) 86.3 (7.3) nursing home residents	Fried Phenotype, Imputed Fried Frailty Criteria, Rockwood Frailty Scale & FRAIL in nursing homes scales	STOPP/START	Prevalence of frailty was 71.8%, 42.7%, 36.4% according to the Rockwood CFS, FRAIL-NH and FRIED Index respectively. (Fried phenotype was only assessed in 40% of participants). Under-prescription was more prevalent in frail participants but only reached significance when Fried criteria were used.
Maclagan et al. (2017)(142)	Retrospective Cohort study	n=41,351 Female = 26,748 (64.7%) age range: 65-74 = 3,691 (8.9%) 75-84 = 15,130 (36.6%) ≥85 =22,530 (54.5%) newly admitted to nursing homes with a history of cognitive impairment or dementia.	72-item frailty index	Beers criteria 2015	44% of patients were frail at admission, 36.9% were pre-frail and 19.1% were non-frail. 44.3% of the cohort had at least one PIM. PIMs were most prevalent among frail residents across the age cohorts i.e. 48.1% versus 42.7% versus 38.7%(P≤0.001). After adjustment for potential confounders, frail residents were also significantly more likely to be newly prescribed PIMs.
Bolina et al. (2019)(143)	Cross-sectional study as part of longitudinal study	n=1607 Female = 1036, (64.5%) age range: 60-70 years = 611 (38.0%) 70-80 years = 707 (44.0%) 80 years or more= 289 (18.0 %) community dwelling older adults**	Fried Frailty Phenotype components	Beers criteria 2012	Prevalence of frailty was 13.6% and pre-frailty was 51.1%. PIM use was 51.1% for the frail group, 33.2% for the pre-frail group and 17.0% in the non-frail group.

MAI-Medications Appropriateness Index, FI-Frailty Index, PIP-Potentially Inappropriate Prescribing, PIM-Potentially Inappropriate Medication, PPO-Potential Prescribing Omission, STOPP-Screening Tool of Older Persons' potentially inappropriate Prescriptions, START-Screening Tool to Alert doctors to Right Treatments) *Patients were excluded if they were admitted from a nursing home, were already receiving care at an outpatient clinic for geriatric evaluation and management, had previously been hospitalized in an inpatient unit for geriatric evaluation and management, were currently enrolled in another clinical trial, had a severe disabling disease or terminal condition or severe dementia; **those with cognitive decline and inability to undergo physical assessment were excluded

1.3.1 Frailty and the associated risk of PIP

Frail older adults are exposed to higher levels of polypharmacy and hyper-polypharmacy, both established independent risk factors for PIP [41]. Frail older people are more likely to experience increased clinical complexity, extreme vulnerability to stressors and reduced physiological reserve. With increasing multimorbidity, a related increase in the number of physician consultations often follows, resulting in higher risk of drug–drug and drug-disease interactions (144). The association between frailty and polypharmacy has been established, though meta-analysis in this area has also been hampered by lack of homogeneity in the definition of frailty (145). Cullinan et al. applied a frailty index developed using standard procedure for creating a frailty index escribed by Searle et al. (31) as a means of investigating the association between frailty and PIP defined by STOPP/START criteria in older hospitalized patients with multimorbidity and polypharmacy. This retrospective study (136) showed a significant correlation between a novel frailty index score and instances of potentially inappropriate prescribing using STOPP/START Version 1 Criteria. However, on reviewing the literature, I did not find any prospective studies evaluating the association between Frail-VIG and STOPP/START criteria Gutiérrez-Valencia et al. have reported that frail institutionalised older people had a significantly higher average number of START criteria PPOs compared to non-frail institutionalised age-matched control subjects, independent of polypharmacy (1.9 versus 1.0, p=0.017)(141). Another study designed to estimate the prevalence of PIMs among older adults with cognitive impairment and dementia in the long-term nursing home setting found that after adjustment for potential confounders, frail residents were more likely to be prescribed benzodiazepines, antipsychotics and anticholinergics (142). Using a 72-item frailty index and the 2015 Beers criteria, MacLagan et al. found that PIMs were most prevalent among frail residents, 48.1% versus 42.7% versus 38.7% ($P \leq 0.001$) in frail, pre-frail and robust adults respectively (142). In

a sample of ambulatory older people , Récoché et al., found that when assessing for frailty using the Gerontopole Frailty Screening tool and Fried's Phenotype, 71.2% of study participants had at least one identified STOPP/START or Laroche list-defined PIM (139). Frailer older people experience a greater sedative medication load compared to non-frail age-matched counterparts, which increased in proportion to greater levels of frailty (146). This predisposes to impaired psychomotor function, falls and cognitive impairment in frail older people.

1.3.2 PIP as a cause of increased frailty

While there are relatively few studies investigating the association between PIP and the risk of frailty, one cross-sectional study of 1607 community-dwelling older people by Bolina et al. found that PIP (defined by Beers criteria) was associated with a higher incidence of frailty and pre-frailty. In the adjusted model, a more frequent use of PIM was associated with frailty (OR = 1.70; CI = 1.16–2.49) and prefrailty (OR = 1.63;CI = 1.26–2.12), even after adjustment for confounding factors (age, ,gender and number of morbidities) (Fried Phenotype) (143). Similarly in a sample of community dwelling older adults (mean age was 70.2 years), Muhlack et al. demonstrated that Beers' criteria PIMs were significantly associated with incident frailty (Fried's Phenotype) in both the unadjusted as well as age- and sex-adjusted analyses, though not significantly associated after adjustment for the number of daily drugs. Users of PIMs were more likely to be frail compared to their peers in the Propensity Scored-adjusted model (OR (95%CI), 1.51 (1.04–2.17)).

Pazan et al. (95), examining the effects of medication optimisation and pharmacological interventions for frailty, concluded that evidence for a direct causal relationship between medications and frailty was inconclusive and emphasized the need for further research using an internationally consistent and reproducible measure of frailty.

1.4 Conclusion

Pharmacotherapy in frail older people requires an understanding not only of age-related physiological, pharmacokinetic and pharmacodynamic changes but also frailty-related physiological changes which predispose to adverse medication-related outcomes. Many studies investigating PIP in older adults focus on age alone as a prompt for medication review. It is thought that by identifying those with increased likelihood of 1-year mortality (very frail/frailest) or pre-frail (amenable to intervention), medical professionals can devise and provide more holistic and patient-centred management plan for their older patients. From my review of the literature, it is evident that there is a significant overlap in the common clinical presentations of ADRs and frailty (falls, delirium, organ disfunction). Furthermore, best practice guidelines recommend medication review using evidence-based screening tools for older people who have been identified as frail (14).

Over the last 30 years, there have been multiple tools, scales and indices developed to assess frailty with the Rockwood Clinical Frailty Scale (CFS) amongst those with the greatest predictive capability for mortality (147).

I conclude that measured frailty should be an important factor when considering new medication choices and when reviewing existing medications as well as when considering deprescribing decisions in older adults with limited life expectancy.

Based on this review of the literature I hypothesise that not only should the presence of frailty prompt structured medication review but patients who are identified as pre-frail may particularly benefit from judicious prescribing to avoid PIP. Changes in frailty status or accumulation of new deficits may be attributable to medication use and should trigger further analysis of medications including long term medications that may no longer be appropriate. Overall, different frailty measurement tools may be appropriate for different settings and different groups of patients, and having a baseline assessment and identifying

changes in vulnerability may assist the clinician in preventing medication-related morbidity. There is a need for further research on the role of inappropriate prescribing in those at risk of developing frailty syndromes such as falls, incontinence and cognitive decline, weight loss and lethargy in order to inform safe deprescribing strategies. Yet, there appears to be insufficient evidence from prospective studies exploring the prevalence of drug-drug interactions and prescribing cascades in frail older adults. There is also absence of comprehensive explicit screening tools for assessing potential prescribing cascades in older adults which may explain why there is an apparent gap in the literature relating to the prevalence of prescribing cascades in older adults admitted acutely to hospital.

In the following chapters, I will aim to address some of these gaps in the literature by exploring the association between frailty and PIP as defined by STOPP/START version 2 in a population of acutely hospitalised older adults. I will also expand the definition of PIP to prescribing cascades and falls risk increasing drugs. I will evaluate the prevalence of DDIs in the acutely hospitalised older adults. I hope that expanding the prevalence of PIP will facilitate clinicians' understanding of its effect on frail, multimorbid older people. Finally in order to build greater understanding about the prevalence of prescribing cascades, I will develop an explicit, evidence-based list of potential prescribing cascaded and estimate their prevalence in acutely hospitalised older adults

CHAPTER 2

Measured Frailty as a Predictor of Potentially Inappropriate Prescribing in Hospitalised Older Adults: A Prospective Observational Study.

2.1 Introduction

Medication management in older people experiencing multimorbidity (multiple medical conditions) is challenging for prescribers. As multimorbidity increases, so too does the number of medications prescribed, leading to polypharmacy. It has been demonstrated that the number of medications a person is prescribed increases in proportion to the number of co-morbidities they have accumulated (131). The Irish Longitudinal Study of Aging (TILDA) found that in community dwelling older adults, the prevalence of polypharmacy i.e. the daily consumption of $\geq$ 5 long-term medications was approximately 20% (148). To some extent, polypharmacy is generated by evidence-based prescribing. When multiple, evidence-based guidelines are applied to an older patient with multiple co-morbidities, polypharmacy is the usual outcome, with increased risk of adverse drug-drug and drug-disease interactions as well as adverse drug reactions (ADRs). A recent systematic review and meta-analysis showed that polypharmacy is associated with frailty (145) and with increased risk of falls, functional impairment, increased length of hospital stay, excess mortality and potentially inappropriate prescribing (149-152). In one study of PIP prevalence across 6 large European medical centres, researchers found that up to 51.3% of acutely hospitalised older adults were prescribed at least one potentially inappropriate medication using STOPP version 1 criteria (153). With increasing age, polypharmacy and potentially inappropriate prescribing, the potential for adverse drug events (ADEs) increases, with adults aged over 65 years experiencing twice as many ADE-related hospital admissions as younger adults (154).

However, rather than using *age* as an indicator for deprescribing in older people who are a heterogenous group with varying levels of health and functional ability, I will consider whether *frailty* may be associated with a risk of potentially inappropriate prescribing.

As identifying frailty in older adults is important for all clinicians and improving prescribing practices is a desirable, I aimed to investigate whether there is a significant association between measured frailty and PIP in older people with multimorbidity and associated polypharmacy

Primary aim:

(i) To assess the relationship between measured frailty and the prevalence of potentially inappropriate prescribing in older adults admitted to hospital with acute unselected illness.

Secondary aims:

(i) To compare the predictive value of selected frailty measurement tools for the presence of PIP in multimorbid older adults.

(ii) To measure the prevalence of frailty in older adults admitted to hospital with acute unselected illness.

(iii) To compare the prevalence of PIP in frail older adults compared to robust older adults.

2.2 Methodology:

2.2.1 Study Design

A prospective observational study was carried out in an acute model 4 university teaching hospital (Cork University Hospital). The local Clinical Research Ethics Committee approved the study protocol.

2.2.2 Participants

Acutely admitted (non-elective) older adults aged ≥ 65 years were recruited from the emergency department, acute medical assessment unit, medical short stay unit, and acute medical and surgical wards between October 2020 and August 2021. Participants were

recruited on a consecutive basis. Daily electronic and paper-based admissions lists were screened for eligibility criteria (**Table 2.1**).

Table 2.1 Inclusion and exclusion criteria

Inclusion Criteria	**Exclusion criteria**
Age ≥65 Years	Age <65 Years
Acute admission within the previous 72 hours	Actively Dying/Palliative a
Expected Length of stay >24 hours	Direct Admission to ICU
	Consent declined or patient unable to provide consent and proxy unavailable/declined consent
	Isolation due to infection control

Eligible participants were hospitalized older adults (aged ≥ 65 years), admitted acutely within the previous 72 hours with a projected admission duration of greater than 24 hours. Potential participants were approached directly, the study aims were explained and a participant information form was provided to them. Explicit written consent was sought in all cases. Potential participants were excluded if they were unable or unwilling to provide informed consent. Where potential participants were unable to provide consent due to illness or lack of mental capacity, written consent was sought from their legal representative where possible. If legal representative/proxy was not available in person to sign consent, the participant was ineligible to be recruited into the study. Patients who were in isolation due to active COVID-19 virus infection or high-risk exposure to COVID-19 were excluded from the study on the basis of adhering to hospital infection control policy.

2.2.3 Variables

Collected sociodemographic variables included: age, sex, place of residence, primary carer, co-habitants and requirement for assistance with activities of daily living. Details of past medical history, current co-morbidities, current medication history, history of

adverse drug reactions, admitting speciality and laboratory values and vital signs were collected along with a brief summary of the main clinical reason for the acute presentation. Medications at discharge, diagnosis on discharge and length of stay were also recorded (Appendix 2).

Acute kidney injury was defined using KDIGO guideline: increase in serum creatinine ≥ 26.5 µmol/l within 48 hours; or an increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the preceding 7 days (155). Hypernatremia was defined using the laboratory set lower limit of <132 mmol/l. The World Health Organisation definition of anaemia (haemoglobin (Hb) levels <12.0 g/dL in women and <13.0 g/dL in men) was applied (156).

2.2.4 Data Collection

Data were collected from the paper-based health care record, and electronic laboratory results and pharmacy medication reconciliation was achieved by direct history during a short interview with patient or caregiver as required. Where medication lists were unavailable at time of recruitment, permission was sought from the patient to contact their community pharmacist for specific medication details.

Sample Size calculation:

Based on previous studies of prevalence of potentially inappropriate prescribing in hospital of 51.3% and a confidence interval of 95%, a sample size of 384 was calculated (157).

$$\text{Sample size } (n) = \frac{\left(z_{1-\alpha/2}\right)^2 (p)(q)}{(d)^2}$$

n= Desired sample size

$z_{1-\alpha/2}$= Critical value and a standard value for the corresponding level of confidence. (At 95% CI or 5% level of significance (type-I error) it is 1.96).

p = Expected prevalence based on previous studies

$$q = 1-p$$

d = margin of error precision

Frailty was measured using the FRAIL-VIG index, the CFS, and the Frailty Index. Frailty index scores were calculated using the FRAIL-VIG index (Appendix 1). The CFS was used to assign a frailty score between 1 (very fit) and 9 (terminally frail). A CFS Score of 5 was used as a definition of frail, as per the instructions for using the CFS. I used a cut off Frailty Index (FI) of 0.25, as frequently used in previous studies (31, 158, 159). Frail-VIG index calculation was performed as per previous validation studies of the Frail-VIG index in which the index calculation of the degree of frailty used the following categorisation; no frailty (Frail-VIG index score ≤ 0.2), mild frailty (Frail-VIG index score 0.21–0.35), moderate frailty (Frail-VIG index score 0.36–0.5), and advanced frailty (Frail-VIG index score > 0.5) (46). Pre-frail was classified using the range defined by Hoover et al., (2013) i.e. index scores between 0.1 and 0.2 (Table 2.2). STOPP/START Version 2 criteria were used to assess for instances of PIP (Appendix 2) (160). As a prospective observational study, the availability of clinical and prescription information allowed for the STOPP criteria to be applied in their entirety.

Table 2.2 Frailty cut-offs applied in this study.

Clinical Frailty Scale Score	**Frail-VIG Index**
Non-Frail CFS <5	Non-Frail ≤0.2
Frail CSF ≥5	Frail >0.2
Robust CFS 1-2	Robust FI <0.1
Pre-frail CFS 3-4	Pre-frail FI 0.1-0.2
Mild/Mod Frailty CFS 5-6	Mild/Mod. Frailty FI 0.21-0.49
Severe Frailty CFS≥7	Severe Frailty FI >0.5

2.2.5 Statistical Analysis

Participants were allocated a unique study identification number. This number was used for all data collection forms.

Data from the data collection sheets were abstracted to an Excel master file. Statistical analysis was carried out using IBM SPSS® Statistics software (Version 28.0.0.0) for both descriptive and analytical statistics. Normality of distribution of variables was assessed using Q-Q plots and the Shapiro-Wilk test where significance of > 0.05 indicated normal (Gaussian) distribution. Variables with a normal distribution were analysed using means and standard deviation; correlation and difference were assessed using Pearson's correlation coefficient and the student's t-test. Non-parametric variables were evaluated using Spearman's rank correlation test and the Mann-Whitney U test. Odds ratios were calculated using binary logistic regression models.

2.3 Results

2.3.1 Baseline Characteristics

In total, 388 participants were recruited, 4 participants subsequently withdrew consent to participate and were not included in the final analysis. The results for the 384 participants included in the analysis are presented in **Table 2.2.,** The mean age was 79.8 years (standard deviation [SD ± 7.5]), over half of the participants were male (54.5%). Eighteen participants died in hospital during the index admission; the median length of stay was 7 days (Min 1, Max 77, IQR 12). The majority of participants resided in their own home (87.5%) prior to hospitalization. One third of participants lived alone. 61.2% of participants described themselves as caring for themselves independently, although 62.8% required assistance with at least one activity of daily living (ADLS).

Table 2.2 Baseline characteristics of patient population studied.

		N	%
Sex	Female	174	45.3
	Male	210	54.7
Residence	Own Home	336	87.5
	Relative's Home	18	4.7
	Nursing Home	14	3.6
	Other	16	4.2
Carer	Self	235	61.2
	Spouse	31	8.1
	Relative	74	19.3
	Other	44	11.5
Lives with	Alone	126	32.8
	Spouse/Partner	156	40.6
	Spouse and child	8	2.1
	Son	21	5.5
	Daughter	39	10.2
	Sibling	5	1.3
	Nursing Home	14	3.6
	Relative	7	1.8
	Other	1	0.3
	Convent/Friary	7	1.8
Falls in last year	Yes	213	55.5
Self-Reported History of Adverse Drug Reactions	Yes	133	34.6
Requires Activities of Daily Living Support	Yes	241	62.8
Admissions in last 12 months	Yes	193	50.3
Anaemia	Yes	173	45.1
Hyponatremia	Yes	54	14.1
	No	329	85.7
	Missing	1	0.3
Chronic Kidney Disease	Yes	135	35.2
	No	248	64.6
	Missing	1	0.3
Acute kidney injury	Yes	44	11.5
Hypertension	Yes	122	31.8
Hypotension	Yes	37	9.6
Tachycardia on admission	Yes	58	15.1
Bradycardia on admission	Yes	40	10.4

Clinical and laboratory data are presented in **Table 2.2**. Just under half of participants were classified as having anaemia using the WHO definition. Approximately one-third of participants were identified as having chronic kidney disease. Although 0.8% of participants were documented as having an acute kidney injury as the primary reason for admission, 11.5% of participants met the KDIGO criteria for acute kidney injury i.e. an increase in serum creatinine by greater than or equal to 26.5 micromol/l within 48 hours.

Table 2.3 Breakdown of participants by admitting speciality

Admission Specialty	N=384	%
Emergency Medicine	3	0.8
Acute Medicine	29	7.6
Cardiology	52	13.5
Endocrinology	19	4.9
Gastroenterology	22	5.7
GEMS/Geriatric Medicine	109	28.4
Haematology	4	1
Infectious Disease	7	1.8
General Medicine	10	2.6
Neurology	4	1
Oncology	4	1
Nephrology	19	4.9
Respiratory Medicine	21	5.5
Rheumatology	21	5.5
Stroke	10	2.6
Total admissions under internal medicine specialties	331	86
Neurosurgery	9	2.3
General Surgery	11	2.9
Colorectal Surgery	2	0.5
Orthopaedics	20	5.2
Plastic surgery	1	0.3
Urology	3	0.8
Vascular Surgery	4	1
Total admissions under surgical specialties	50	13

Older adults admitted across all specialities except intensive care medicine were eligible for inclusion though most of the participants were admitted under internal medicine specialities (n = 331); geriatric medicine accounted for 28.4% of admissions. There were

fewer participants admitted under surgical specialties, accounting for just over 1 in 10 of those included in the study. The most common primary reasons for admission amongst those recruited was falls resulting in fracture injuries and decreased mobility (35.9%) followed by acute infection (12%). Cardiovascular and cerebrovascular presentations combined accounted for 21.3% of these acute admissions. The breakdown according to admitting speciality and primary reason for admission is demonstrated in **Table 2.3** and **Table 2.4.**

Table 2.4 Reason for admission in order of frequency.

Documented Primary Reason for Admission	N=384	%
Falls/Fracture/Decreased Mobility	138	35.9
Acute Infection	46	12
Acute decompensated heart failure	20	5.2
Chest Pain	20	5.2
Stroke/Seizure/Primary intracerebral haemorrhage	23	6.0
Abdominal Pain/Distension/Constipation	17	4.4
Cardiac Arrythmia	12	3.1
Nausea/Vomiting/GI Bleeding	12	3.1
Pain/Arthritis/Gout	12	3.1
Malignancy	11	2.9
Fatigue	9	2.3
Other	9	2.3
Acute Coronary Syndrome	7	1.8
Hepatobiliary Disease	6	1.6
Surgical emergency	6	1.6
Weight Loss	6	1.6
Anaemia/Haematological Disease	5	1.3
Delirium	5	1.3
Ulcer	5	1.3
Incontinence/Urinary Retention	4	1
Acute Kidney Injury/Decompensated CKD	3	0.8
Venous thromboembolism	3	0.8
Diabetic ketoacidosis	2	0.5
Acute dyspnoea (non-specific)	2	0.5
Medication Toxicity	1	0.3

The 10 most common co-morbidities included hypertension, hyperlipidaemia, atrial fibrillation/flutter, type 2 diabetes, ischemic heart disease, other disease of the circulatory system, gout, osteoarthritis, joint replacement and heart failure. The co-morbidities were

coded using ICD-10 coding to allow for standardisation of active and past medical conditions (**Table 2.5**). Just under 10% of participants had a documented cognitive impairment; 7.5% of older people admitted acutely to hospital had a documented history of depression.

Table 2.5 Prevalence of comorbid medical conditions according to International Classification of Disease (ICD-10).

ICD10		N	%
I10	Hypertension	209	54.4%
E78.5	Hyperlipidaemia	139	36.2%
I48.92	Atrial Fibrillation/Flutter	126	32.8%
E11.40	Type 2 Diabetes	96	25.0%
I25.91	Ischemic Heart Disease	93	24.2%
Z86.792	Past History of other disease of Circulatory System	79	20.5%
M10.9	Gout	73	19.0%
M19.91	Osteoarthritis	66	17.2%
Z96.657	Presence of Orthopaedic Joint Replacement	64	16.7%
I50.812	Heart Failure	58	15.1%
N18.9	Chronic Kidney Disease	58	15.1%
E03.9	Hypothyroidism	52	13.5%
Z87.898	Personal History of Other Unspecified Condition	46	12.1%
J44.9	Chronic Obstructive Pulmonary Disease	40	10.4%
I63.9	Cerebral Infarction	36	9.4%
G31.84	Mild Cognitive Impairment	35	9.1%
K57.9	Diverticular Disease	35	9.1%
M81.8	Osteoporosis	35	9.1%
J45.99	Asthma	32	8.3%
Z87.19	Past History of Disease of GI system	31	8.1%
Z87.448	Past History of Disease of the Urinary system	30	7.8%
F33.9	Depressive Disorder	29	7.5%
I35.2	Non-Rheumatic Aortic Valve Disorder	29	7.5%
Z86.19	Personal History of Infectious or Parasitic Disease	28	7.3%
Z91.81	History of Falls	28	7.3%

2.3.2 Characteristics of Frailty

The prevalence of measured frailty varied from 52.6% (Frail-VIG) to 64.1% (CFS). The majority of participants included were classified as frail with a CFS of ≥5 (64.1%), the mean (±SD) CFS being 4.48 (±1.49). The distribution of frailty characteristics is presented in **Table 2.6.** and **Figure 2.1.** A total of 138 participants had a CFS less than 5 (35.9%) i.e. non-frail, while only 5.2% of participants were defined as robust. Almost 1 in 10 older patients included in the study were categorised as severely frail i.e. CFS score ≥ 7; most of the participants were living with mild/moderate frailty i.e. CFS scores of 5 or 6. Using the Frail-VIG index, only 2.3% were classified as being severely frail.

Table 2.6 Distribution of frailty as classified by Clinical Frailty Scale.

Clinical Frailty Scale Score				
	N=384	%	Mean	SD
CFS 1	4	1	4.87	1.49
CFS 2	16	4.2		
CFS 3	55	14.3		
CFS 4	63	16.4		
CFS 5	114	29.7		
CFS 6	96	25		
CFS 7	25	6.5		
CFS 8	1	0.3		
CFS 9	10	2.6		
Frail CFS				
Non-Frail CFS <5				
Frail CSF ≥5	138	35.9		
	246	64.1		
CFS Category				
Robust CFS 1-2	20	5.2		
Pre-frail CFS 3-4	118	30.7		
Mild/Mod Frailty CFS 5-6	210	54.7		
Severe Frailty CFS≥7	36	9.4		

The mean (±SD) Frail-VIG index score was 0.23 (±0.12). The Frail-VIG index categorised 47.4% of participants as non-frail when measured dichotomously into frail or

non-frail. However, when a pre-frailty range was applied (FI 0.1-0.2), over one-third of participants fell into this category (**Table 2.3.5)**.

Table 2.7 Distribution of frailty as classified by Frail-VIG

Frail-VIG Index	Mean	SD
	0.233	0.125
	N	%
Non-Frail ≤0.2	182	47.4
Frail >0.2	202	52.6
Frail-VIG categories		
Robust FI <0.1	55	14.3
Pre-frail FI 0.1-0.2	127	33.1
Mild/Mod. Frailty FI 0.21-0.49	193	50.3
Severe Frailty FI >0.5	9	2.3

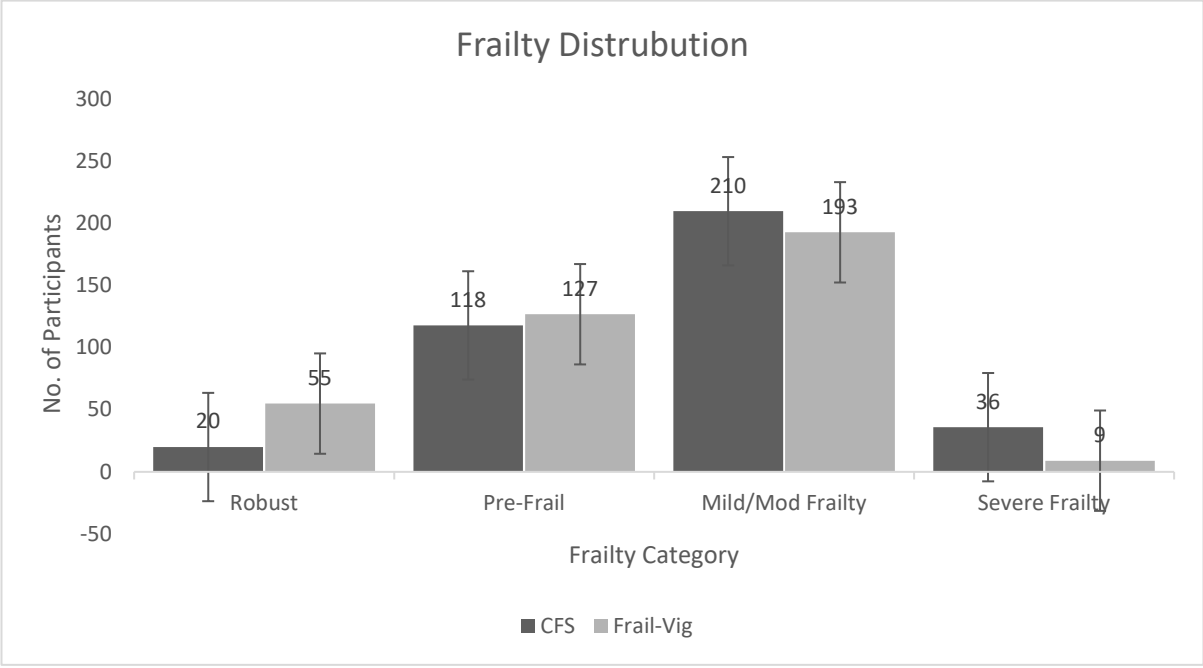


Figure 2.1 Comparative distribution of frailty using categorised CFS and Frail-VIG**.**

2.3.3 Characteristics of potentially inappropriate prescribing as defined by STOPP/START Version 2.

Polypharmacy was highly prevalent within the sample with a mean (±SD) number of medications prescribed regularly of 8.90 (± 3.92, Min 0, Max 21). Only 3 participants included in the study were not taking regular medications on admission, whilst over two thirds of patients were affected by polypharmacy (≥ 5 daily long-term medications; 88.0%) or hyper-polypharmacy (≥ 10 daily medications, 38.0%). Potentially inappropriate medications (PIMs) according to STOPP/START Version 2 were identified in 76% of patients with just under half of patients (49%) having 2 or more STOPP identified PIMs. Applying START criteria, 48.4% of participants were identified as having one or more potential prescribing omissions (PPOs). The most frequent STOPP criteria were (i) the prescription of any drug without documented evidence-based clinical indication (63.5%), (ii) inappropriate use of hypnotic z-drugs (9.6%), (iii) benzodiazepine use beyond 4 weeks (8.33%), (iv) drug prescription beyond recommended duration (7.81%), and (v) neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (3.67%). The frequency of individual STOPP criteria breaches can be seen in **Table 2.8.** Thirty-nine STOPP criteria and five START were not encountered in the present sample population. As can be seen in **Table 2.9.,** the most frequently encountered START criteria PPOs were (i) vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (11.72%), (ii) angiotensin converting enzyme inhibitors with systolic heart failure and/or documented coronary artery disease (8.33%), (iii) bone anti-resorptive or anabolic therapy in patients with documented osteoporosis (8.33%), (iv) fibre supplements for diverticulosis with a history of constipation (6%) and (v) bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy (4.69%) .

Table 2.8. Frequency of STOPP criteria-defined Potentially Inappropriate Medications (PIMs).

STOPP		N=384	% of patients (95% CIs)
A.1	Any drug prescribed without a documented evidence-based clinical indication	244	63.54 (58.9-68.5)
A.2	Any drug prescribed beyond the recommended duration	30	7.81 (5.2-10.7)
A.3	Any duplicate drug class prescription	4	1.04 (0.3-2.1)
B.1	Digoxin for heart failure with normal systolic ventricular function	1	0.26 (0.0-0.8)
B.2	Verapamil or diltiazem with NYHA Class III or IV heart failure	0	0.00
B.3	Beta-blocker in combination with verapamil or diltiazem	0	0.00
B.4	Beta blocker with bradycardia, type II heart block or complete heart block	1	0.26 (0.0-0.8)
B.5	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	2	0.52 (0.0-1.3)
B.6	Loop diuretic as first-line treatment for hypertension	5	1.30 (0.3-2.6)
B.7	Loop diuretic for dependent ankle oedema	8	2.08 (0.8-3.6)
B.8	Thiazide diuretic with current hypokalaemia, hyponatremia, hypercalcaemia, or hx gout	8	2.08 (0.8-3.6)
B.9	Loop diuretic for treatment of hypertension with concurrent urinary incontinence	2	0.52 (0.0-1.3)
B.10	Centrally-acting antihypertensives	0	0.00
B.11	ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia	0	0.00
B.12	Aldosterone antagonists with concurrent potassium conserving drugs	0	0.00
B.13	Phosphodiesterase type-5 inhibitors in severe heart failure or current nitrate therapy	0	0.00
C.1	Long-term aspirin at doses greater than 160mg per day	0	0.00
C.2	Aspirin with a past history of peptic ulcer disease without concomitant PPI	0	0.00
C.3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, or DOAC with concurrent significant bleeding risk	0	0.00
C.4	Aspirin plus clopidogrel as secondary stroke prevention.	0	0.00
C.5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation	2	0.52 (0.0-1.3)
C.6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease	1	0.26 (0.0-0.8)
C.7	Ticlopidine in any circumstances	0	0.00
C.8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors	0	0.00
C.9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors	0	0.00
C.10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	0	0.00
C.11	NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis	0	0.00
D.1	Tricyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	3	0.78 (0.0-1.8)
D.2	Initiation of Tricyclic Antidepressants (TCAs) as first-line antidepressant treatment	3	0.78 (0.0-1.8)
D.3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects with a history of prostatism or previous urinary retention	0	0.00
D.4	Selective serotonin re-uptake inhibitors with current or recent significant hyponatraemia	1	0.26 (0.0-0.8)
D.5	Benzodiazepines for ≥ 4 weeks	32	8.33 (5.5-11.2)

D.6	Antipsychotics (i.e., other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease	1	0.26 (0.0-0.8)
D.7	Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications	2	0.52 (0.0-1.3)
D.8	Anticholinergics/antimuscarinics in patients with delirium or dementia	2	0.52 (0.0-1.3)
D.9	Neuroleptic antipsychotic in patients BPSD unless symptoms are severe and other non-pharmacological treatments have failed	3	0.78 (0.0-1.8)
D.10	Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia	14	3.65 (1.8-5.5)
D.11	Acetylcholinesterase inhibitors with a known history of persistent bradycardia heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate	1	0.26 (0.0-0.8)
D.12	Phenothiazines as first-line treatment	0	0.00
D.13	Levodopa or dopamine agonists for benign essential tremor	0	0.00
D.14	First-generation antihistamines	4	1.04 (0.3-2.1)
E.1	Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m2	0	0.00
E.2	Direct thrombin inhibitors (e.g., dabigatran) if eGFR < 30 ml/min/1.73m2.	0	0.00
E.3	Factor Xa inhibitors (e.g., rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2	0	0.00
E.4	NSAID's if eGFR < 50 ml/min/1.73m2	0	0.00
E.5	Colchicine if eGFR < 10 ml/min/1.73m2	1	0.26 (0.0-0.8)
E.6	Metformin if eGFR < 30 ml/min/1.73m2	2	0.52 (0.0-1.3)
F.1	Prochlorperazine or metoclopramide with Parkinsonism	0	0.00
F.2	PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	4	1.04 (0.3-2.1)
F.3	Drugs likely to cause constipation	0	0.00
F.4	Oral elemental iron doses greater than 200 mg daily	0	0.00
G.1	Theophylline as monotherapy for COPD	0	0.00
G.2	Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	1	0.26 (0.0-0.8)
G.3	Anti-muscarinic bronchodilators with a history of narrow angle glaucoma or bladder outflow obstruction	0	0.00
G.4	Non-selective beta-blocker with a history of asthma requiring treatment	0	0.00
G.5	Benzodiazepines with acute or chronic respiratory failure i.e., pO2 < 8.0 kPa ± pCO2 > 6.5kPa	0	0.00
H.1	Non-steroidal anti-inflammatory drug other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	0	0.00
H.2	NSAID with severe hypertension or severe heart failure	2	0.52 (0.0-1.3)
H.3	Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried	0	0.00
H.4	Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis	2	0.52 (0.0-1.3)
H.5	Corticosteroids for osteoarthritis	1	0.26 (0.0-0.8)
H.6	Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor	0	0.00
H.7	COX-2 selective NSAIDs with concurrent cardiovascular disease	0	0.00
H.8	NSAID with concurrent corticosteroids without PPI prophylaxis	0	0.00
H.9	Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease	0	0.00

I.1	Antimuscarinic drugs with dementia, chronic cognitive impairment, narrow-angle glaucoma or chronic prostatism	7	1.82 (0.5-3.1)
I.2	Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope	2	0.52 (0.0-1.3)
J.1	Sulphonylureas with a long duration of action	0	0.00
J.2	Thiazolidinediones in patients with heart failure	1	0.26 (0.0-0.8)
J.3	Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes	1	0.26 (0.0-0.8)
J.4	Oestrogens with a history of breast cancer or venous thromboembolism	1	0.26 (0.0-0.8)
J.5	Oral oestrogens without progestogen in patients with intact uterus	0	0.00
J.6	Androgens in the absence of primary or secondary hypogonadism	0	0.00
K.1	Benzodiazepines	19	4.94 (2.9-7.3)
K.2	Neuroleptic drugs	2	0.52 (0.0-1.3)
K.3	Vasodilator drugs with persistent postural hypotension	5	1.30 (0.3-2.3)
K.4	Hypnotic Z-drugs	37	9.6 (6.8-12.8)
L.1	Use of oral or transdermal strong opioids as first line therapy for mild pain	3	0.78 (0.0-1.8)
L.2	Use of regular opioids without concomitant laxative	8	2.08 (0.8-3.6)
L.3	Long-acting opioids without short-acting opioids for break-through pain	7	1.82 (0.5-3.1)
N	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties	12	3.125 (1.6-4.9)

Table 2.9 Frequency of START criteria-defined Potential Prescribing Omissions (PPOs).

START		**N=384**	**% of patients (95% CIs)**
A.1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation	5	1.30 (0.3-2.6)
A.2	Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or DOACs are contraindicated	1	0.26 (0.0-0.8)
A.3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease	0	0.00
A.4	Antihypertensive therapy	2	0.52 (0.0-1.3)
A.5	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years	11	2.86 (1.4-4.7)
A.6	Angiotensin Converting Enzyme inhibitor with systolic heart failure and/or documented coronary artery disease	32	8.33 (5.5-11.5)
A.7	Beta-blocker with ischaemic heart disease	6	1.56 (0.5-2.9)
A.8	Appropriate beta-blocker with stable systolic heart failure	7	1.82 (0.5-3.4)
B.1	Regular inhaled β2 agonist or antimuscarinic bronchodilator for mild to moderate asthma or COPD.	16	4.17 (2.3-6.3)
B.2	Regular inhaled corticosteroid for moderate-severe asthma or COPD	0	0.00
B.3	Home continuous oxygen with documented chronic hypoxaemia	0	0.00
C.1	L-DOPA or a dopamine agonist in idiopathic Parkinson's disease	3	0.78 (0.0-1.8)
C.2	Non-TCA antidepressant drug in the presence of persistent major depressive symptoms	1	0.26 (0.0-0.8)
C.3	Acetylcholinesterase inhibitor for mild moderate Alzheimer's dementia or Lewy Body dementia.	7	1.82 (0.5-3.1)

C.4	Topical prostaglandin, Prostamide or beta-blocker for primary open-angle glaucoma	1	0.26 (0.0-0.8)
C.5	Selective serotonin reuptake inhibitor for persistent severe anxiety that interferes with independent functioning	4	1.04 (0.3-2.1)
C.6	Dopamine agonist for Restless Legs Syndrome	1	0.26 (0.0-0.8)
D.1	Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation	2	0.52 (0.0-1.3)
D.2	Fibre supplements for diverticulosis with a history of constipation	23	6.0 (3.6-8.6)
E.1	Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease	0	0.00
E.2	Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy	18	4.69 (2.6-7.0)
E.3	Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s)	18	4.69 (2.6-7.0)
E.4	Bone anti-resorptive or anabolic therapy in patients with documented osteoporosis	32	8.33 (5.5-11.2)
E.5	Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia	45	11.72 (8.6-15.1)
E.6	Xanthine-oxidase inhibitors with a history of recurrent episodes of gout	3	0.78 (0.0-1.8)
E.7	Folic acid supplement in patients taking methotrexate.	1	0.26 (0.0-0.8)
F	ACE inhibitor or Angiotensin Receptor Blocker in diabetes with evidence of renal disease	4	1.04 (0.3-2.1)
G.1	Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary	2	0.52 (0.0-1.3)
G.2	5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary	2	0.52 (0.0-1.3)
G.3	Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis	0	0.00
H.1	High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective	1	0.26 (0.0-0.8)
H.2	Laxatives in patients receiving opioids regularly	10	2.60 (1.0-4.2)

2.3.4 Frailty and Potentially Inappropriate Prescribing

Polypharmacy was highly prevalent within both the frail and non-frail groups with 92.7% and 97.0% of frail participants (CFS and Frail-VIG criteria respectively) prescribed greater or equal to 5 medications on admission to hospital. PIMs were also prescribed in 78.9% to 82.2% of frail participants and PPOs affecting 54.0% to 54.1% of those classified as frail. Due to the non-parametric distribution of PIMs, PPOs and PIP, The Mann-Whitney U test was used to test for significant difference between the frail and non-frail groups. The median, minimum and maximum number of STOPP/START identified incidences of potentially inappropriate prescribing are presented in **Table 2.10.** The median number of PIMs, PPOs and PIPs was significantly higher in frail patients than in non-frail patients, when

categorised using the CFS and Frail-VIG. A Mann-Whitney U test revealed a significant difference in the number of PIMs between frail (Md=2, n=194) and non-frail patients (Md = 1, n = 98), U = 21450, z = 4.39, p <0.001). There was also a statistically significant difference between frail and non-frail patients in relation to the number of PPOs (Md = 1, n = 133) vs (Md = 0, n = 53), U = 20147, z = 3.35, p<0.001 and the number of PIPs (Md = 2.5, n = 223) vs (Md = 1, n = 108), U = 22544, z = 5.42, p<0.001). When the Frail-VIG index was used to differentiate frailty from non-frailty, this statistically significant difference between frail and non-frail participants was once again manifest (**Table 2.10**).

Table 2.10 Potentially Inappropriate Prescribing (PIP) in frail versus non-frail patient groups at admission.

		Non-Frail					**Frail**					**Mann-Whitney U Test**		
		N	Median	IQR	Min.	Max	N	Median	IQR	Min.	Max	U-value	z-score	p-value
CFS	STOPP PIMs	98	1	2	0	6	194	2	2	0	6	21450	4.398	<0.001
	START PPOs	53	0	1	0	4	133	1	1	0	4	20147	3.348	<0.001
	Total PIP	108	1	1	0	7	223	2.5	3	0	8	22544	5.425	<0.001
Frail-VIG	STOPP PIMs	126	1	2	2	6	166	2	2	0	6	24199	5.492	<0.001
	START PPOs	77	0	1	1	4	109	1	1	0	4	21636	3.299	<0.001
	Total PIP	142	1	2	2	7	186	3	2	0	8	25326	6.499	<0.001

To assess for differences across different levels of frailty (robust, pre-frail, mild/moderate frailty and severe frailty), a Kruskal-Wallis test was performed using both the CFS and Frail-VIG index data. Statistically significance variance in potentially inappropriate prescribing was revealed across the different levels of frailty. For PIMs on admission, there was no significant difference in the median number of PIMs between patients who were robust and pre-frail compared to those who were mildly/moderately frail and those who were severely frail when categorised using the CFS. There was, however, a significant difference in PIMs between robust and mild/moderately frail older adults, robust and severely frail patients, pre-frail and mild/moderately frail and pre-frail and severely frail patients (**Table 2.11).** Statistically significant differences were also found for number of PPOs in pre-frail and mild/moderately frail people as well as for the total

number of PIPs in robust patients compared to patients at all levels of frailty, and between pre-frail and mild/moderately frail participants. Significant differences were also revealed between the various levels of frailty for prevalence of PIMs, PPOs and total PIP when frailty was measured using the Frail-VIG index.

Table 2.11 Kruskal-Wallis Test of difference in potentially inappropriate prescribing across categories of frailty as measured using Frail-VIG and CFS.

CFS	Median STOPP PIMs at Admission	Median START PPOs at Admission	Median Total PIP	Frail-VIG	Median STOPP PIMs at Admission	Median START PPOs at Admission	Median Total PIP
Robust, n=20	0.5	0	1	Robust, n=55	0.00	0	1
Pre-frail, n=118	1	0	2	Pre-frail, n=127	1.00	1	2
Mild/Moderate frailty, n=210	2	1	3	Mild/Moderate frailty, n=193	2	1.00	3
Severe frailty, n=36	2	1	2	4 Severe frailty, n=9	2	0.00	2
Pairwise Comparisons across CSF categories				Pairwise Comparisons across Frail-VIG			
Sample 1-Sample 2	Test Statistic	Sig.		Sample 1-Sample 2	Test Statistic	Sig.	
STOPP PIMs				STOPP PIMs			
1 Robust-2 Pre-Frail	3.3	0.069		**1 Robust-2 Pre-Frail**	**10.41**	**.001***	
1 Robust-3 Mild/Moderate	**9.982**	**0.002***		**1 Robust-3 Mild/Moderate**	**17.19**	**<.001***	
1 Robust-4 Severe	**8.737**	**0.003***		**1 Robust-4 Severe**	**6.952**	**0.01***	
2 Pre-Frail-3 Mild/Moderate	**12.461**	**<.001***		**2 Pre-Frail-3 Mild/Moderate**	**11.14**	**<.001***	
2 Pre-Frail-4 Severe	**4.57**	**0.033***		2 Pre-Frail-4 Severe	0.737	0.39	
3 Mild/Moderate-4 Severe	0.191	0.662		3 Mild/Moderate-4 Severe	0.248	0.62	
START PPOs				START PPOs			
1 Robust-2 Pre-Frail	0.115	0.735		1 Robust-2 Pre-Frail	2.112	0.15	
1 Robust-3 Mild/Moderate	2.581	0.108		**1 Robust-3 Mild/Moderate**	**13.56**	**<.001***	
1 Robust-4 Severe	1.634	0.201		**1 Robust-4 Severe**	**18.24**	**<.001***	
2 Pre-Frail-3 Mild/Moderate	**7.081**	**0.008***		2 Pre-Frail-3 Mild/Moderate	0.027	0.87	
2 Pre-Frail-4 Severe	2.152	0.142		2 Pre-Frail-4 Severe	0.728	0.39	
3 Mild/Moderate-4 Severe	0	0.991		**3 Mild/Moderate-4 Severe**	**10.06**	**.001***	
Total PIP				Total PIP			
1 Robust-2 Pre-Frail	**4.884**	**0.027***		**1 Robust-2 Pre-Frail**	**19.28**	**<.001***	
1 Robust-3 Mild/Moderate	**4.192**	**0.041***		**1 Robust-3 Mild/Moderate**	**3.898**	**0.05***	
1 Robust-4 Severe	**9.705**	**0.002***		**1 Robust-4 Severe**	**29.33**	**<.001***	
2 Pre-Frail-3 Mild/Moderate	3.121	0.077		2 Pre-Frail-3 Mild/Moderate	0.486	0.49	
2 Pre-Frail-4 Severe	**19.581**	**<.001***		**2 Pre-Frail-4 Severe**	**13.38**	**<.001***	
3 Mild/Moderate-4 Severe	1.171	0.279		3 Mild/Moderate-4 Severe	0.79	0.37	

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level is .050, statistically significant results are denoted with a*.

The relationship between frailty and potentially inappropriate prescribing was further investigated using Spearman's Rank Order Correlation test (*rho*). The number of mediations prescribed on admission was moderately correlated with CFS, Frail-VIG index, and total PIP at admission (*rho=.287*, p<0.001; *rho=.407*, p<0.001*; rho=.431,* p<0.001 respectively*)* and strongly correlated with the number of PIMs at admission (*rho=0.517*, p<0.001*).* A significant, moderate correlation was also found between the Frail-VIG index and both number of PIMs and total number of PIPs (*rho=0.353*, p=<0.001 and *rho=0.410*, p=<0.001*).* There was a small, yet significant association between CFS and inappropriate prescribing was demonstrated (**Table 2.12**). Measured frailty using CFS and Frail-VIG index were strongly correlated (*rho=.749,* p<0.001). The significant, positive correlation between degree of frailty measured by Frail-VIG index and number of PIMs was maintained when one controlled for number of medications, age and number of co-morbidities (r = 0.145, p = 0.001, r = 0.312, p = 0.001 and r = 0.358 p = 0.001). The number of PPOs and total number of PIPs also remained positively correlated with the Frail-VIG index after adjustment for potential confounders. In addition, frailty measured by CFS had a small but significant positive correlation with PIMs, PPOs and total PIP after adjustment for potential confounders.

Table 2.12 The relationship between frailty and potentially inappropriate prescribing using Spearman's Rank Order Correlation test.

		Los	Age	No. of Falls in Last Year	No. of Admissions	No. of Co-morbidities	**CFS Score**	**FVIG Index**	Charlson Co-Morbidity Index
Number of Medications	Correlation Coefficient	-0.04	0.01	-0.08	0.305**	0.460**	**0.287****	**0.407****	0.284**
	Sig. (2-tailed)	0.448	0.838	0.116	0	0	**0**	**0**	0
STOPP PIMs	Correlation Coefficient	-0.023	0.083	0.093	0.092	0.163**	**0.250****	**0.353****	0.057
	Sig. (2-tailed)	0.665	0.105	0.07	0.072	0.001	**0**	**0**	0.269
START PPOs	Correlation Coefficient	0.121*	0.223**	0.159**	0.051	0.233**	**0.173****	**0.227****	0.077
	Sig. (2-tailed)	0.021	0	0.002	0.323	0	**0.001**	**0**	0.132
Total PIP	Correlation Coefficient	0.024	0.180**	0.146**	0.120*	0.256**	**0.297****	**0.410****	0.081

2.3.5 Risk factors for receiving a potentially inappropriate prescription according to STOPP/START criteria.

Logistic regression was used to determine the influence of age, burden of co-morbidity, number of medications and frailty on the risk of receiving a potentially inappropriate medication according to STOPP criteria. The results are detailed in **Table 2.13** Further binomial logistic regression was used to investigate the effect of these variables on potential prescribing omissions according to START criteria (**Table 2.14).** Polypharmacy, pre-frailty and mild/moderate frailty (measured by Frail-VIG) were all significantly associated with an increased risk of receiving a STOPP-defined potentially inappropriate medication when controlling for age and co-morbidity. Patients who were prefrail were twice as likely to be prescribed a PIM compared to robust individuals when classified by the Frail-VIG index (Odds ratio 2.542, 95% CI 1.017 – 5.910, p = 0.046). Patients who were mildly/moderately frail were over three times more likely to be exposed to PIM versus robust patients (odds ratio 3.228, 95% CI 1.166-8.934, p = 0.024).

Table 2.13 Binary logistic regression model exploring risk factors for potentially inappropriate medications as defined by STOPP criteria.

	B	S.E.	Wald	df	p-value	Odds Ratio	95% C.I. for EXP(B) Lower	Upper
Age	0.008	0.020	0.163	1	0.686	1.008	0.970	1.047
Charlson Co-Morbidity Index	**-0.175**	**0.075**	**5.400**	**1**	**0.020**	**0.839**	**0.724**	**0.973**
CSF Robust			1.492	3	0.684			
CFS Pre-frail	-0.446	0.615	0.526	1	0.468	0.640	0.192	2.138
CFS Mild/Mod. Frailty	-0.803	0.704	1.301	1	0.254	0.448	0.113	1.781
CFS Severe Frailty	-0.760	0.852	0.797	1	0.372	0.467	0.088	2.482
FVIG Robust			7.013	3	0.071			
FVIG Pre-frail	**0.897**	**0.449**	**3.993**	**1**	**0.046**	**2.452**	**1.017**	**5.910**
FVIG Mild/Mod. Frailty	**1.172**	**0.519**	**5.089**	**1**	**0.024**	**3.228**	**1.166**	**8.934**
FVIG Severe Frailty	-0.032	1.093	0.001	1	0.977	0.968	0.114	8.246
Number of Medications on Admission	**0.297**	**0.050**	**35.869**	**1**	**0.000**	**1.346**	**1.221**	**1.483**
Constant	-1.685	1.525	1.220	1	0.269	0.185		

Hosmer and Lemeshow X^2 =10.019, df=8, p=.170 Model X^2=76.491, Cox & Snell R^2= .181, Nagelkerke R^2= .271 6. B= beta-value; SE = standard error; df = degrees of freedom; Exp (B) = Odds ratio
CFS: Clinical Frailty Scale; FVIG: Frailty-VIG index; CI: confidence interval.

Mild/moderate frailty as measured by Frail-VIG and age was significantly associated with a lower risk of START-defined potential prescribing omissions considering co-morbidities and number of medications on admission. Mild/moderate frailty was the only category of frailty that had a significant relationship with PPOs (Odds ratio 0.563, 95% CI 0.326 - 0.974, p = 0.04).

Table 2.14 Binary logistic regression model exploring risk factors for potential prescribing omissions as defined by START criteria.

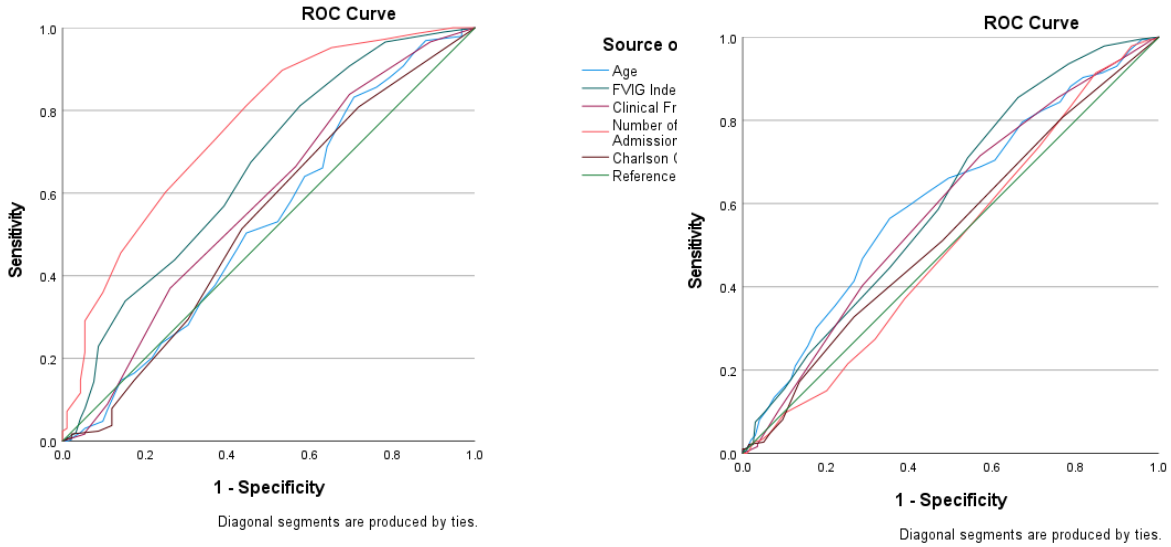
	B	S.E.	Wald	df	p-value	Odds ratio	95% C.I. for EXP(B) Lower	Upper
Age	**.039**	**.016**	**6.141**	**1**	**.013**	**1.040**	**1.008**	**1.072**
Charlson Co-Morbidity Index	.011	.062	.030	1	.863	1.011	.896	1.141
Number of Medications on Admission	-.029	.030	.967	1	.326	.971	.916	1.030
CFS Robust			.278	3	.964			
CFS Pre-frail	.147	.425	.120	1	.729	1.159	.503	2.667
CFS Mild/Moderate. frailty	.028	.491	.003	1	.955	1.028	.392	2.693
CFS Severe frailty	.091	.694	.017	1	.896	1.095	.281	4.265
FVIG Robust			5.932	3	.115			
FVIG Pre-frail	.254	.322	.624	1	.430	1.289	.686	2.423
FVIG Mild/Moderate frailty	**-.574**	**.279**	**4.215**	**1**	**.040**	**.563**	**.326**	**.974**
FVIG Severe frailty	-.340	.766	.197	1	.657	.711	.159	3.193
Constant	-2.846	1.411	4.070	1	.044	.058		

Hosmer and Lemeshow X^2 =9.709, df=8, p=.286 Model X^2=22.650, Cox & Snell R^2= .057, Nagelkerke R^2= .076
6. B =beta-value; SE = standard error; df = degrees of freedom; Exp (B) = Odds ratio
CFS: Clinical Frailty Scale; FVIG: Frailty-VIG index; CI: confidence interval.

A receiver operator curve is presented in **Figure 2.2.** demonstrating the discriminative value of age, Charlson comorbidity index (CCI), number of medications and frailty in predicting PIMs. The number of medications had the greatest discriminative value with an area under the curve (AUC) value of 0.759 (95% CI 0.701 - 0.817, p <0.001) followed by the Frail-VIG index with an AUC of 0.659. (95% CI 0.592 - 0.725, p <0.001), and CFS with an AUC of 0.577 (95% CI 0.507 - 0.648, p = 0.026). PPOs were more difficult to predict with age (AOC= 0.606, 95% CI 0.553 - 0.665, p <0.001),

Frail-VIG (AUC = 0.608, 95% CI 0.552 - 0.664, p = 0.001) and CFS (AUC = 0.584 95% CI 0.528 -0.641, p = 0.004) having small but statistically significant predictive power. In the case of PPOs, the number of medications was not associated with potential prescribing omissions (AOC = 0.501, 95% CI 0.443 - 0.559, p = 0.964)

Figure 2.2 Receiver operator curves demonstrating PIMs (left) and PPOs (right).



2.4 Discussion

The primary aim of this project was to assess the relationship between measured frailty and the prevalence of potentially inappropriate prescribing in older adults admitted with acute illness to hospital. This research question was addressed using a prospective cross-sectional design in 384 subjects.

The key findings of this study are:

1. Frailty was highly prevalent within the studied population with over half of participants included in this study classified as frail. The prevalence of frailty varied according to frailty assessment methods i.e. from 52.6% (Frail-VIG) to 64.1% (CFS).

2. PIMs were also prescribed in 78.9% to 82.2% of frail participants and PPOs affecting 54.0% to 54.1% of those classified as frail. The median number of PIMs, PPOs and PIPs was significantly higher in frail patients than in non-frail patients, when categorised using the CFS and Frail-VIG. There was a significant difference in the number of PIMs between frail and non-frail patients. There was also a statistically significant difference between frail and non-frail patients in relation to the number of PPOs and PIPs. This difference was also maintained when the Frail-VIG index was applied.

3. Increasing frailty measured by CFS and Frail-VIG was positively associated with increasing PIMs, PPOs and PIP. The Frail-VIG index had a stronger association.

Measured frailty was highly prevalent within this sample of 384 acutely hospitalised older adults as were both PIMs and PPOs. In this study, between 30.7% to 33.1% of participants could be classified as pre-frail. These findings are consistent with previous meta-analysis prevalence estimates of in-hospital pooled frailty prevalence and pre-frailty prevalence estimates of 47.4% (95% CI 43.7–51.1%), and 25.8% (95% CI 22.0–29.6%) respectively in patients aged ≥ 65 years (161). While over half of the patients admitted acutely to hospital in the present study were classified as frail, only 28.4% of patients were admitted under specialist geriatric medicine teams, emphasizing the need for easily applied screening tools for both frailty and PIP as part of routine assessment, given that increased frailty is associated with longer length of stay and increased in-hospital morbidity and mortality (162).

The exposure of older hospitalised adults to polypharmacy and hyper polypharmacy was also highly prevalent (88.8% taking ≥ 5 daily long-term medications and 38.0% taking ≥ 10 daily) in the overall sample. Additionally, potentially inappropriate

medicine (PIM) according to STOPP criteria was identified in 76% of patients with just under half of patients (49%) had 2 or more STOPP identified PIMs. 48.4% of participants were identified as having one or more START defined PPOs. Interestingly, 39 STOPP defined PIMs were not encountered in this population. There may be multiple potential explanations for this observation. Notably, STOPP C2 (Aspirin with a previous history of peptic ulcer disease without concomitant PPI) and STOPP H7 (COX-2 selective NSAIDs with concurrent cardiovascular disease) have both been removed from the recently published STOPP/START version 3 as they were found to be obsolete (163). These criteria were not encountered in this study.

Polypharmacy and PIM use was highly prevalent in the frail older adults observed in this study. The prevalence STOPP-defined PIMs is higher than previously reported prevalence between 35% and 51% although further studies using implicit methods of PIM classification in those classified as frail report PIM prevalence as high as 71% (139, 143, 164). Hyperpolypharmacy, itself a risk factor for functional decline (165) was present in almost half of the demonstrably frail participants (46.3% (CFS) & 49.0% (Frail-VIG)). Patients with higher prevalence of frailty tend to have higher prevalence of inappropriate prescribing (166).

There was a statistically significant difference between the median numbers of PIMs, PPOs and total PIPs in frail compared to non-frail older patients, with frailer older people exposed to more inappropriate medications overall, although patients in 'severe-frailty' category had a somewhat lower prevalence of inappropriate prescribing. This effect has previously been noted by Pazan et al, who commented that "clinicians often selectively discontinue/de-prescribe in those who are frailest, thereby creating a bias regarding applicability [of PIM criteria] to frail people at large" (167). We cannot say with certainty whether the severely frail participants in the present

study had undergone previous deprescribing or medication review. Frailty and polypharmacy were both significantly associated with inappropriate prescribing (as was pre-frailty). However, age-adjusted Charlson Co-morbidity index (CCI) was not significantly associated with PIMs or PPOs. In this patient sample, many of the most prevalent co-morbidities such as hypertension, COPD, osteoporosis and falls were not included in the CCI calculation.

2.4.1 Potential Limitations of this Research

A potential limitation we considered in this study was whether infection control guidelines during the Covid-19 pandemic led to a reduction in the number of severely frail participants admitted to hospital/recruited. The ethical approval granted to carry out this research stipulated that proxy consent for participants who were physically or mentally unable to provide consent must be completed in person. Depending on Covid-19 restrictions at the time of recruitment, patients who lacked capacity to consent to study participation due to delirium, severe dementia or severe illness, may not have had representatives present in the hospital at the time of recruitment and were thus excluded. However, when I compared the range of frailty in this study to that of Cullinane et al. (2019) who used frailty index (FI) scores among a similar population of 711 patients ranging from 0 to 0.51, with a mean FI of 0.15 (136), it is clear that there was a higher mean FI score in the present sample, indicating greater overall frailty. We also acknowledge that causal relationships cannot be inferred given the observational nature of this study. Furthermore, all data collection in this study was carried out by a single researcher leading to the possibility of researcher bias. I mitigated this potential bias by using standardised paper-based data collection sheets for each participant. Finally, it should be acknowledged that the most common STOPP criteria defined PIM encountered was “Any drug prescribed without a documented

evidence-based clinical indication" (STOPP A1; 63.53%). It is theoretically conceivable that although patients paper charts, referral letters and electronic health record (old clinic letters and discharges) were reviewed as a source of past medical history, drugs classified as inappropriate may have had an appropriate indication that was not available at the time of data collection.

2.4.2 Conclusion

As discussed in Chapter 1, The British Geriatrics Society (BGS) guidelines on the management of frailty acknowledge that frailty may not be detected unless screened for in a structured way in any one individual (14). From this study the Frail-VIG index had a greater association with PIM than the CFS. Based on this study's findings, I would have to advocate for the use of Frail-VIG for frailty screening to reduced PIMs in older people, particularly those who have concomitant polypharmacy.

In conclusion, given the association between frailty and PIP there is a strong case for frailty screening in all older adults presenting to acute hospitals and a heightened awareness for the risk of ADRs which may overlap with or mimic frailty syndromes. A potential target group for future intervention would be those participants who were classified as pre-frail as they may represent an opportunity for medication assessment prior to the development of frailty syndromes or adverse medication events such as falls, organ dysfunction, delirium and functional decline. While lower rates of PIP in severely frail patients is encouraging, there are very likely further opportunities for de-prescribing by applying a deprescribing tool such as STOPPFrail criteria (65) which could reduce potentially burdensome medication use this patient group.

CHAPTER 3

Falls Risk Increasing Drugs in Frail Older Adults Experiencing Falls: A Prospective Observational Study

3.1 Introduction

Falls have been identified as a leading cause of injury and mortality in older adults representing a major public health concern with over 1 in 4 older adults aged over 65 years falling per year (116). Of these, 20% will cause injury such as fractures or head injury, with 95% of hip fractures attributed to falling(117). While falls in older adults are recognised to be multifactorial, one of the more prominent and modifiable extrinsic risk factors for falls in older adults is the use of falls-risk increasing drugs (FRIDs). Cardiovascular drugs, psychotropics, Proton Pump Inhibitors (PPIs) and anti-epileptic drugs (AEDs) are acknowledged by meta-analysis as increasing the risk of falls in older adults (118-120). Studies have shown a prevalence of FRID use varying between 87% in primary care and 93% in older adults who have been admitted to hospital with hip fracture(121-123).

Medication review for FRIDs is strongly indicated by falls prevention guidelines such as the National Institute for Clinical Excellence (NICE) Guidelines (125)and the World Guidelines for Falls Prevention and Management for Older Adults, developed by the World Falls Task Force(124). However, there is heterogenicity between guidelines as to what constitutes a FRID [125-127].

The STOPPFall (Screening Tool of Older Persons Prescriptions in older adults with high fall risk) list was created using a modified Delphi process with the aim of identifying by consensus and review of current literature the medications that are most associated with falls in older adults(128). Consensus was reached on 14 medications; Benzodiazepines and Benzodiazepine related drugs, Antipsychotics, Opioids, Antidepressants, Antiepileptics, Diuretics, Alpha-Blockers as antihypertensives and for Benign Prostatic Hyperplasia, Centrally Acting Anti-Hypertensives, Sedative Antihistamines, Vasodilators used in Cardiac disease and Overactive Bladder

medicines (128). This validated and structured screening tool has been recommended by the World falls guidelines to identify FRIDs and to guide appropriate deprescribing as part of a multidomain falls intervention (127).

Previous observational studies have demonstrated that frailty is associated with an increased risk of falls and fractures in older people with the risk greatest in those over 75 years of age. Furthermore, it has been shown that frailty is associated with a greater risk of further falls and fractures and shorter time to recurrent fall events (129). This increased risk of recurrent falls has shown to be consistently associated with frailty in meta-analyses despite the heterogenous methods of assessing frailty (114, 130).

I aimed to use the STOPPFall consensus list of medications to assess the point-prevalence of falls-risk increasing drugs (FRIDs) in older adults presenting to hospital after a fall or who have experienced a fall in the previous 12 months. I examined the relationship between FRIDs, falls and serious falls requiring hospital presentation. I also examined the relationship between FRIDs and frailty. This observational study aimed to determine the prevalence of FRIDs in older adults presenting with falls to hospital.

Primary aim:

To determine the point-prevalence of falls-risk increasing drug use in older adults presenting to an acute hospital because of a fall.

Secondary aims:

- To compare the prevalence of falls risk increasing drugs (FRIDs) in older adults and number of falls experienced by older people in the preceding 12 months.
- To examine the level of frailty in older adults presenting to hospital post-fall.

3.2 Methods

3.2.1 Study Design

A prospective observational study was conducted in an acute model 4 tertiary referral hospital and a community rehabilitation unit in Cork city (Cork University Hospital and St. Finbarr's Hospital). The local Clinical Research Ethics Committee approved the study protocol.

3.2.2 Participants

Participants were recruited from the emergency department, the main trauma ward and a community rehabilitation unit attached to the hospital between. Participants were recruited on a consecutive basis between May 2021 and March 2022. Daily admissions lists were screened for eligibility criteria (Table 3.1). Eligible participants were hospitalized older adults (aged ≥ 65 years), admitted from any location with a history of a fall. Potential participants were approached directly, the study aims were explained and a participant information form was provided. On the same day, written informed consent was sought from the participants.

Table 3.1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
Age ≥65 Years	Age <65 Years
At least 1 fall within the last 12 months	Consent declined or patient unable to provide consent and proxy unavailable/declined consent

Potential participants were excluded if they were unable or unwilling to provide informed consent. Where potential participants were unable to provide consent due to illness or lack of mental capacity, written consent was sought from their legal

representative where possible. If legal representative/proxy was not available in person to sign consent, the participant was ineligible to be recruited into the study. Patients who were in isolation due to active Covid-19 virus infection or high-risk exposure to COVID-19 were excluded from the study on the basis of adhering to hospital infection control policy.

3.2.3 Sample Size Calculation

Based on a previously reported prevalence of 87% of older adults receiving one or more FRIDs, a confidence level 95% and a 5% level of significance, where n = desired sample size and P = expected prevalence based on previous research, a sample size of 175 was calculated.[123, 168]

3.2.4 Collected variables at recruitment

Two trained research physicians with experience in Geriatric Medicine (including the author) conducted patient and/or caregiver interviews and medical record reviews in order to collect the following information using a standardised data collection proforma: (i) sociodemographic data (sex, age, place of residence, activities of daily living (ADL) support, carer, diagnosis of cognitive impairment) , (ii) structured falls history (history of current admission, previous falls in last year, use of mobility aid, previous medication modifications due to falls, alcohol use, number of previous admissions due to falls), (iii) medications and co-morbidity status, (iv) laboratory and clinical investigations, (v) Clinical Frailty Scale (CFS) score, (vi) the point-prevalence of FRIDs was be established using the STOPPFall screening tool.

Age-adjusted Charlson Co-morbidity Index measurement was used to refine and standardise the number of co-morbidities experienced by participants. CFS score was

assessed based on the participants baseline function 2 weeks before admission or before the onset of the presenting acute illness.

Participants were allocated a unique study identification number. This number was used for all data collection forms. The study number was linked to patient identifiers on a paper file that was stored in a locked filing cabinet in a locked office in Cork University Hospital. All paper records were stored in the same locked office.

Data from the data collection sheets were abstracted to an Excel master file. Statistical analysis was carried out using SPSS® version 27 for both descriptive and analytical statistics. Variables with a normal distribution was analysed using means and standard deviations, correlation and difference were assessed using Pearson's product moment and student's t-tests. Non-parametric variables were investigated using Spearman's rank correlation, Mann-Whitney U test. Odds ratios were calculated using logistic regression models.

3.3 Results

3.3.1 Baseline Characteristics

In total, 179 patients were recruited to the study. The principal characteristics of participants are summarised in **Table 3.1**. The mean age (SD) of the participants was 81.34 (6.61) years. Approximately two-thirds of participants i.e. 117 were female (65.4%). Most of the older adults recruited lived in their own home (92.2%), though over 50% of participants received some assistance with activities of daily living. The mean (SD) CFS score was 4.63 (1.60) indicating pre-frailty to mild frailty. The mean Charlson Co-morbidity index score was 5.46 [SD 1.69] indicating a high level of co-morbidity within the sample population. Polypharmacy was highly prevalent with an

average of 8.67 [SD3.61] daily long-term medications taken by participants. All participants had suffered at least one fall within the preceding 12 months with a median of 2 falls experienced by participants in that time frame.

Table 3.1 Baseline patient characteristics.

Characteristic		N	%	
Sex	Female	117	65.4	
Residence	Own Home	165	92.2	
	Relative's Home	3	1.7	
	Nursing Home	5	2.8	
	Other	6	3.4	
Activities of Daily Living Support	Yes	107	59.8	
Cognitive Impairment	Yes	26	14.5	
Mobility Aid	Yes	114	63.7	
Anaemia	Yes	96	53.6	
Hyponatremia	Yes	25	14	
Hypokalaemia	Yes	19	10.6	
	Not Available	2	1.1	
Hyperkalaemia	Yes	5	2.8	
	Not Available	2	1.1	
Measured Orthostatic Hypotension	Not Available	150	83.8	
	Yes	9	5	
	No	20	11.2	
Hypotension	Yes	15	8.4	
	No	163	91.1	
	Not Available	1	0.6	
Bradycardia	Yes	12	6.7	
	No	166	92.7	
	Not Available	1	0.6	
Tachycardia	Yes	14	7.8	
	No	164	91.6	
Characteristic		**Mean**	**Standard Deviation**	
Age		81.34	6.61	
CCI		5.46	1.69	
No Medications on Admission		8.67	3.61	
		Median	**IQR**	**Max**
Number of Falls in Last 12 Months		2	3	50
Number Of Hospital Admissions in Last 12 Months		1	1	6
Number Of Admissions due to Falls		1	0	3
Total FRIDs		2	1	6
CFS		5	2	9

Abbreviations: CCI Charlson Co-Morbidity Index, FRIDs-Falls risk increasing drugs, CFS-Clinical Frailty Scale, IQR-Inter-Quartile Range.

3.3.2 STOPPFall Medications

Over half of the participants (51.4%) experienced polypharmacy (≥5 daily long-term medications) and over a third (37.4%) of participants were taking 10 or more daily medications. One hundred and forty-six patients (81.6%) were taking at least one STOPPFall defined FRID. As can been seen from **Table 3.2**, approximately 1 in 10 older adults experiencing a fall was using four or more FRIDs. The mean [SD] number of FRIDs consumed daily by older fallers was 1.72 [SD 1.34], the mean [SD] number of FRIDs in the frail subset (CFS≥5) was 1.88 [SD 1.37], with a mean of 1.51 [SD 1.27] in the non-frail group.

The most frequently prescribed STOPPFall defined FRIDs were anti-depressants with over 35% (64) of the patients experiencing falls prescribed anti-depressant medication. Over 30% of older fallers were prescribed diuretics, with 18% and 14.5% using opioids and anti-epileptics respectively. The frequency of individual drug class utilisation is demonstrated in **Table 3.3**.

Table 3.2 Prevalence of Polypharmacy and STOPPFall defined Falls Risk Increasing Drugs.

		N	%
Polypharmacy	≥5 drugs	92.00	51.4
	≥10 drugs	67.00	37.4
Falls Risk Increasing Drugs			
		N	%
	>=1	146.00	81.6
	>=2	90.00	50.3
	>=3	44.00	24.6
	>=4	19.00	10.6
		Mean	SD
Population Mean FRIDs		1.72	1.34
Frail CFS≥5		1.88	1.37
Non-Frail CFS <5		1.51	1.27

Table 3.3 Most frequently encountered Falls Risk Increasing Drugs as defined by STOPPFall Criteria in the population of 179 older patients presenting to hospital with falls.

Falls Risk Increasing Drug	N	%
Anti-depressants	64	35.75
Diuretics	55	30.73
Opioids	34	18.99
Anti-epileptics	26	14.53
Benzodiazepine related drugs (z-drug hypnotics)	25	13.97
Anticholinergics	18	10.06
Overactive bladder drugs	17	9.50
Alpha-blockers for BPH	16	8.94
Antipsychotics	12	6.70
Benzodiazepines	10	5.59
Vasodilators for cardiac disease	9	5.03
Alpha-blockers	6	3.35
Sedative antihistamines	2	1.12
Centrally-acting antihypertensives	1	0.56

3.3.3 Frailty

Over half of the participants were frail with a CFS of ≥ 5. The median CFS score was 5 (IQR 2, min 0, max 9), the distribution of CFS scores is demonstrated in **Table 3.4**. 10% of the participants were classified as robust with 34.1% of participants classified as pre-frail, 46.9% of participants classified as having mild/moderate frailty and 8.9% classified as having severe frailty.

Table 3.4 Frailty characteristics of population of 179 older adults classified by Clinical Frailty Scale.

Frailty Category	**N**	**%**		
CFS 1	7	3.9		
CFS 2	11	6.1		
CFS 3	25	14		
CFS 4	36	20.1		
CFS 5	40	22.3		
CFS 6	44	24.6		
CFS 7	14	7.8		
CFS 8	0	0		
CFS 9	2	1.1		
Frail CFS ≥5	100	55.9		
Non-Frail CFS <5	79	44.1		
Robust CFS 1-2	18	10.1		
Pre-frail CFS 3-4	61	34.1		
Mild/Mod Frailty CFS 5-6	84	46.9		
Severe Frailty CFS≥7	16	8.9		
CFS	Median	IQR	Min	Max
	5	2	1	9

3.3.4 Types of Falls

Self-reported/collateral history cause of falls are listed in **Table 3.5.** Falls classified as non-syncopal accounted for 49.72% of all falls.

Table 3.5 Types of falls at in older adults presenting to hospital post-fall.

Fall Type (N=179)	**N**	**%**
Non-syncopal	89	49.72
Pre-syncope	26	14.53
Syncope	22	12.29
Acute Illness	21	11.73
Un-specified	10	5.59
Unwitnessed	8	4.47
Alcohol related	2	1.12
Seizure	1	0.56

Clearly syncopal and pre-syncopal falls accounted for approximately 1 in 4 falls. Over 10% of the falls occurred in the context in an intercurrent illness. As non-syncopal falls represent a highly diverse category, I further divided these into subgroups based on the participants presenting history of falls. **Table 3.6** details the sub-groups of non-syncopal falls. The most prevalent self-reported causes of non-syncopal falls were trip, slip, unspecified and loss of balance/disequilibrium.

Table 3.6 Classification of non-syncopal fall subtypes.

Non-Syncopal Fall Subgroups (N=89)	**N**	**%**
Trip	30	33.71
Slip	13	14.61
Unspecified	10	11.24
Lost balance	10	11.24
Legs Gave way	9	10.11
Fell Backwards	6	6.74
Lost control of wheeled device	4	4.49
Pain	3	3.37
Freezing episode with Parkinson's Disease	1	1.12
Railing gave way	1	1.12
Reduced mobility	1	1.12
Missed railing	1	1.12

Just under half (79) of all participants sustained an injury post-fall (see details in **Table 3.7**). The most common type of injury associated with falls were fractures with almost 1 in 3 of participants overall sustaining a fracture. Fractures accounted for 70% of all fall-related injuries in this population.

Table 3.7 Fall related injuries at presentation to hospital.

Injury Type	N	%
No Injury	96	53.63
Fracture	59	32.96
Head injury	9	5.03
Pain (soft tissue)	4	2.23
Laceration	2	1.12
Intracranial Haemorrhage	2	1.12
Facial Trauma	1	0.56
Bleeding	1	0.56
Musculoskeletal Injury	1	0.56
Dislocation	2	1.12
Haematoma	1	0.56
Hemopneumothorax	1	0.56

3.3.5 Association between frailty and STOPPFall medications

The relationship between the prevalence of falls risk increasing drugs in older adults and number of falls was analysed using Spearman's rank correlation. (Extreme outliers were removed using transformation greater or equal to 10 falls).

There was no significant correlation between the number of falls in the previous 12 months and the number of daily FRIDs taken by the patients (Spearman's *rho*=0.069, sig. 0.357).

The relationship between frailty measured using the CFS and daily number of FRIDs was also investigated using Spearman's rank correlation statistic. There was a significant positive correlation between the two variables ($r=0.23$, $n=179$, $p<0.01$) with increasing frailty associated with increased FRID use.

The difference between frail and non-frail participants was further investigated in relation to FRID-positive and FRID-negative status. Independent-samples Mann-Whitney U-Test analysis was not statistically significant i.e. there was a trend towards more FRID exposure in frail patients (Median= 2, IQR= 2) compared to non-frail patients (Median=1, IQR= 1) that approached statistical significance, (U=3311,

p=0.056). **Figure 3.1** illustrates this comparison of FRID exposure in frail versus non-frail patient groups.

The relationship between number of daily medications at admission and number of daily FRIDs was also investigated using Spearman's rank correlation test. There was a strong positive correlation between these two variables (r=0.563, n=179, p=0.01).

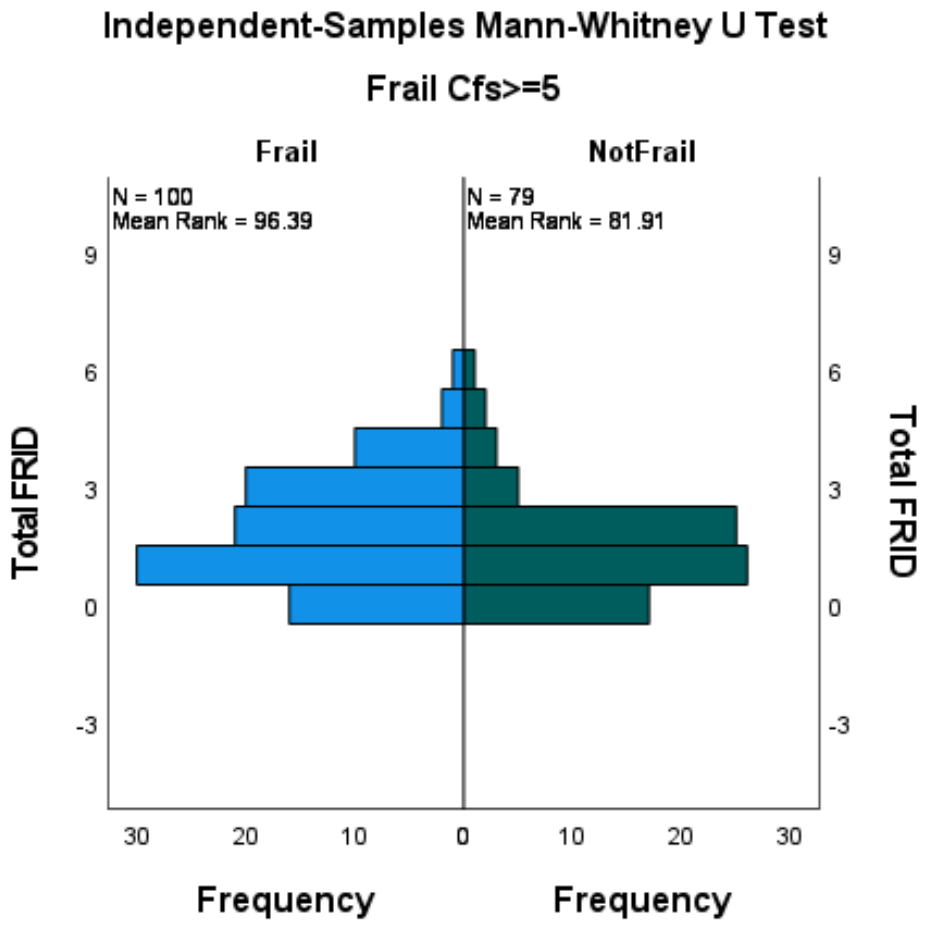


Figure 3.1 Independent-Samples Mann-Whitney U Test comparing total FRIDs in Frail vs Non-Frail Older patients presenting with falls.

Binary logistic regression analysis was performed to assess the impact of categorised frailty on the odds of participants taking a daily FRID. The strongest predictor of FRID use in the model was severe frailty (CFS>7) with an odds ratio of 12.000 (95% C.I.

1.294-111.323). For all levels of frailty compared to robust non-frail clinical status, unadjusted logistic regression analysis demonstrated significant positive odds ratios >1.0 (see **Table 3.8).** That is, all levels of clinical frailty were significantly associated with daily FRIDs exposure.

Table 3.8 Unadjusted odds ratio of FRIDs use at different levels of frailty.

	B-value	**S.E.**	**Wald**	**df**	**p-value**	**Odds Ratio**	**95% C.I.for Odds Ratio**	
							Lower limit	**Upper limit**
Robust			8.914	3	0.03			
Pre-Frail	1.531	0.596	6.595	1	0.01	4.622	1.437	14.868
Mild/Mod Frailty	1.303	0.553	5.545	1	0.019	3.680	1.244	10.885
Severe Frailty	2.485	1.137	4.78	1	0.029	12.000	1.294	111.323
Constant	0.223	0.474	0.221	1	0.638	1.250		

3.4 Discussion

In this study, I investigated the prevalence of FRIDs and types of falls in older adults presenting to hospital post-fall. This is the first prospective study that has used STOPPFall criteria to identify the prevalence of FRIDs in older people experiencing falls in the context of frailty. The most frequently prescribed FRID class was antidepressants with a prevalence of 35.75%. This prevalence is higher than that documented in a previous study carried out in an emergency department in the Republic of Ireland in 2009 in which the prevalence of antidepressant prescribing was 26% (169). Diuretics (30.73%), opioids (18.99%) and antiepileptics (14.53%) were the next most frequently prescribed FRIDs in the present study. My results are consistent with previous meta-analysis findings showing that antidepressants are one of the most common FRID classes taken by older people at the time of fall-related

injury, with a prevalence ranging from 15.0% to 40.0% (170). In the same study, the prevalence of opioid use ranged from 4.4% to 21.1% in older fallers (170). My prevalence estimate of antidepressant prescribing is higher than the prevalence of depression in reported in The Irish Longitudinal Study of Aging of 10-12%% (171, 172) and a general European older adult population reported in a recent systematic review and meta-analysis i.e. 21.1% (95%CI: 14.8–27.4%) (173). Antidepressant use and untreated depression itself have both been shown to independently increase falls risk (174). Therefore, careful structured medication review of antidepressant medication indication and dose are particularly important in older people who present with falls either in primary care or in hospital.

A previous study has shown that frail older adults were exposed to a greater number of FRIDs when compared to robust older adults overall (175). Overall, I did not detect a significant difference in FRIDs prevalence among non-frail patients who had at least one fall in the preceding 12 months compared to frail older people with falls., Severely frail patients as a subgroup had a 12-fold increased odds ratio of being prescribed one or more FRIDs compared to non-frail patients.

3.4.1 Potential limitations of this study:

One of the limitations of this study is that the median CFS was 5, indicating mild frailty. Arising from the restrictions on hospital visitors during the COVID-19 pandemic, there were multiple cases of very frail or cognitively impaired older adults who were not enrolled in the study due to unavailability of a proxy/legal representative to provide collateral history details and informed assent to enrolment. This may have skewed the overall level of frailty of the patient cohort towards lower levels of frailty. Furthermore, all the participants recruited to the study had experienced a fall. To further assess the impact of STOPPFall-defined FRIDs on the prevalence of falls in

older adults, I would have had to compare the prevalence of STOPP-Fall FRIDs in fallers with the prevalence of STOPPFall FRIDs in age- and comorbidity-matched non-fallers with similar levels of polypharmacy. The data collection in this study was carried out by 2 independent researchers, leading to a possibility of researcher bias. I mitigated this potential bias by using standardised paper-based data collection sheets for each participant. Finally, data on the number of falls participants experienced in the previous 12 months was calculated based on clinical case notes, electronic healthcare record and patient recollection. This could have led to a potential limitation due to recall bias and underreporting of near-miss incidents or those that did not lead to injury or hospitalisation.

3.4.2 Opportunities for further research

This study provides opportunities for future research into the use of the STOPPFall tool as a means to assist in medication rationalisation in high-risk older fallers. Results of cohort studies and controlled clinical trials have been variable in their level of success with regard to medication intervention in older people as a means of preventing falls (176, 177). Previous interventional trials examining the impact of deprescribing FRIDs have not shown a significant reduction in number of falls, prolongation of time to next fall or reduced number of FRIDs. Deprescribing may be challenging in multimorbid older people with polypharmacy and can be complicated by re-emergence of the conditions for which FRIDs were prescribed or new conditions that invite FRID prescription (177).

Given the high odds ratio of FRIDs prescriptions in severely frail older adults identified in the present study, there is the possibility that more severely frail older adults may benefit more from FRID deprescribing than less frail older people (178).

A prospective case-control interventional study would be required to address this question. Such a study was, however, beyond the scope of this thesis.

CHAPTER 4

Potentially clinically relevant drug-drug interactions and frailty in acutely hospitalised older people: a prospective observational study

4.1 Introduction

Drug-drug interactions, where two or more drugs interact with one another leading to toxicity or inhibition of the effects of a drug, leading to a diminished therapeutic, can have clinically important implications for both patients and prescribers. Drug-drug interactions can generally be divided into two main groups: pharmacokinetic and pharmacodynamic interactions. It has been demonstrated that the number of medications a patient is prescribed increases proportionately with the number of co-morbidities accumulated (131). Clinical guideline-based drug regimens often fail to take multi-morbidity into account and relatedly the risk of potentially harmful and avoidable drug-drug interactions (DDIs) has grown in recent years (179). Historically, frail older adults and people with complex co-morbidities have been excluded from clinical trials that lead to clinical guidelines (180). A cause-and-effect relationship has been demonstrated between number of dispensed drugs and potential DDIs, especially for clinically serious DDIs with potentially life-threatening consequences for older adults (181). This emphasizes the importance of trying to minimise the number of drugs prescribed in older multimorbid patients exposed to polypharmacy (113).

A recent systematic review reported a DDI prevalence range from 8.3% to 100%. Among older hospitalised people managed in specialist geriatric units, the wide variation was markedly lower i.e. 80.5% to 90.5% with a higher overall prevalence in older people. There is significant heterogenicity between individual studies in relation to the definition of DDIs (133). Many DDIs are regarded as predictable and avoidable; therefore, they may be considered as targets for education and deprescribing interventions. In prevalence studies that included all age groups, it has been shown that DDIs lead to clinically relevant ADRs in 4.6% of patients (182).

Acute hospital admission in multimorbid older people provides the opportunity for medication review of DDIs, a significant cause of hospital admissions accounting for up to 4.8% of hospital admissions in older patients (134, 183). Hospital admission also represents a time of increased risk for older adults, as the prescription of new drugs to treat acute medical problems and/or to prevent readmission may increase the risk of DDIs and adverse drug reactions (ADRs). Furthermore, increasing frailty is associated with a greater risk of ADRs and identification of frailty should prompt greater review of polypharmacy and trigger a search for potential DDIs (136).

In this study, I aimed to use a recently published Delphi consensus-validated list of 66 clinically relevant DDIs to prospectively assess the prevalence of DDIs in older adults presenting to an acute hospital (184). This list provides an explicit list of potential DDIs validated specifically for older people and was developed to address the need for consensus in identifying clinically significant DDIs in order to generate comparable results across studies. The extent to which the 66-item DDI list represents clinically relevant DDIs in a 'real-world' population of multimorbid older patients remains unknown.

Primary aim:

To assess the prevalence of potentially clinically relevant drug-drug interactions and frailty in older adults presenting acutely to a Level 4 University Teaching hospital in Ireland.

Secondary aims:

i. To compare the prevalence of DDIs at admission and discharge from hospital.
ii. To examine the prevalence of DDIs in both robust and frail older adults.
iii. To examine the incidence of DDIs during hospital stay and DDI-related ADRs.

4.2 Methodology

4.2.1 Study Design

A prospective observational study was conducted in an acute model 4, tertiary referral hospital between September 2021 and July 2022. The local Clinical Research Ethics Committee of the Cork Teaching Hospitals approved the study protocol.

4.2.2 Participant Recruitment

Acutely admitted (non-elective) older adults aged 65 years and older, were recruited from the emergency department, medical assessment unit, medical short stay unit and acute medical and surgical wards. Participants were recruited on a consecutive basis. Daily electronic and paper-based admissions lists were screened for eligibility criteria based on age and length of stay. Participants were included if they were aged over 65 years, admitted acutely within 72 hours and had an expected length of stay of over 24 hours. Participants were excluded if they were under 65 years of age, receiving end-of-life care, directly admitted to ICU or if they were unable or declined to provide informed consent and their next of kin/legal proxy declined consent or was unavailable.

Medical case notes of identified prospective participants were screened for suitability for inclusion. Potential participants were approached directly, the study aims were explained, and a participant information form was provided. On the same day, written informed consent was sought from the patients who agreed to participate in the study. Potential participants were excluded if they were unable or unwilling to provide informed consent. Where potential participants were unable to provide informed consent due to illness or lack of mental capacity, written consent was sought from their next-of-kin or legal representative. Patients who were in isolation due to active COVID-19 virus infection or high-risk exposure to COVID-19 were excluded from

the study on the basis of adhering to hospital infection control policy and contact restrictions during the COVID-19 pandemic.

4.2.3 Sample Size Calculation

Based on a previously published prevalence of 54% of older adults experiencing one or more DDIs from a retrospective sub-study of the OPERAM trial, a confidence level of 95% and a 5% level of significance, a sample size of 372 patients was calculated (168, 185).

4.2.4 Variables

Collected sociodemographic variables included sex, age, place of residence, primary carer, co-habitants and requirement for assistance with activities of daily living. Details of past medical history, current co-morbidities, admitting speciality, number of hospital admissions in the previous 12 months, clinical frailty score, current serum biochemistry data and vital signs were collected along with a brief summary of the principal clinical reason for the acute presentation. Medications at discharge, diagnosis at discharge and length of stay were also recorded.

Hyponatremia was defined using the laboratory set lower limit of 132mmol/l. The World Health Organisation definition of anaemia (haemoglobin (Hb) levels <12.0 g/dL in women and <13.0 g/dL in men) was applied (156).

Medication history details were collected including regular medications, recently prescribed or discontinued medications (in the 2 weeks preceding admission), self-reported history or documented history of adverse drug reactions. Medication changes in the first 5 days of admission and discharge medications were recorded.

4.2.5 Data Collection

Data were extracted manually from the medical case notes, GP referral letter and from discussion with the participant onto a standardised data collection form. A follow-up telephone call was made if information from the referral letter and chart was not sufficient and the participant agreed to same.

Participants were allocated a unique study identification number. This number was used for all data collection forms.

The prevalence of potentially clinically relevant drug-drug interactions (DDIs) was established at admission and discharge as well as the number of interactions per participant. The incidence of new clinically relevant DDIs were calculated. As the list of explicit DDIs specifically described potential harms from each potential DDI, this list was used to identify whether participants who had actual list-defined DDIs (so-called 'DDI positive' cases) experienced actual harm from their identified DDIs **(Figure 4.1)**.

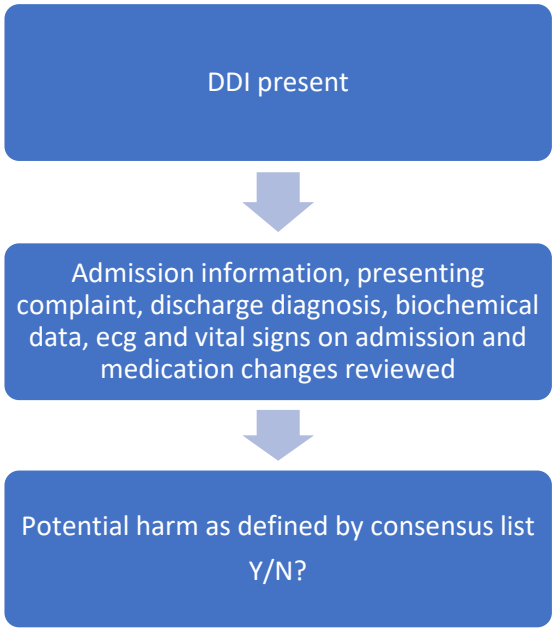


Figure 4.1 Process for adjudication of admissions due to potential harm from DDI.

The Clinical Frailty Scale (CFS) was used to assign a frailty score between 1 (very fit) and 9 (terminally frail). A CFS Score of 4 was used as a cutoff to identify patients who were frail based on the definitions in Version 2 of the CFS(186).

DDI's were also evaluated using Stockley's DDI checker deployed using the Medicines Complete application (187) .

4.2.6 Statistical Analysis

Extracted data were transferred to an Excel master file. Statistical analysis was carried out using IBM SPSS® Statistics (Version 28.0) for both descriptive and analytical statistics. Normality of distribution of variables was assessed using Q-Q plots and the Shapiro-Wilk test of normality where significance of >0.05 indicated normal distribution. Variables with a normal (Gaussian) distribution were analysed using means and standard deviations, and correlation and difference were assessed using Pearson's and the student's t-test respectively. Non-parametric variables were investigated using Spearman's rank correlation and the Mann-Whitney U test.

4.3 Results

4.3.1 Baseline Characteristics

In total 373 participants were recruited to the study. The baseline characteristics of the studies population are summarised in Table 4.1. The majority of participants were male (53.1%). The mean (SD) age of participants was 78.7 (7.65) years. Most of the older adults recruited lived in their own home (93%) and were self-caring (68.1%) although just over half of the participants also received some assistance for activities of daily living (51.2%); 1 in 5 participants were cared for by a spouse or relative.

The mean (SD) CFS score was 4.70 (1.77) indicating very mild to mild frailty. A high level of comorbidity was demonstrated within the population with a mean Charlson

Co-morbidity Index (SD) of 5.15 (1.77). Polypharmacy was highly prevalent within the studied population with an average (SD) of 8.08 (3.45) medications per participant at admission and 8.74 (3.34) daily long-term medications prescribed on discharge. Approximately 4 out of 5 participants (85.3%) were experiencing polypharmacy (≥ 5 daily medications); 114 participants (30.6%) were taking 10 or more daily medications indicating hyper-polypharmacy. Twenty-eight participants died prior to discharge and discharge prescriptions were not available for 6 patients.

Table 4.1 Baseline characteristics on admission to hospital.

Characteristic		N	%
Sex	Male	198	53.1
	Female	175	46.9
Residence	Own Home	347	93
	Relative's Home	15	4
	Nursing Home	9	2.4
	Other	2	0.5
Primary Carer	Self	254	68.1
	Spouse	19	5.1
	Relative	66	17.7
	Home Help	20	5.4
	Other	14	3.8
Falls in last Year	Yes	167	44.8
	No	206	55
Activities of Daily Living Support	Yes	191	51.2
	No	182	48.8
Polypharmacy	(≥5 Medications)	318	85.3
Hyperpolypharmacy	(≥10 Medications)	114	30.6
Hypernatremia	Yes	1	0.3
Hyponatremia	Yes	135	36.2
Hyperkalaemia	Yes	24	6.4
Hypokalaemia	Yes	33	8.8
eGFR <60ml/min	Yes	181	48.5
Bradycardia	Yes	26	7
Tachycardia	Yes	51	13.7
Hypertension	Yes	154	41.3
Hypotension	Yes	13	3.5
Characteristic	**Mean**	**Standard deviation**	
Age	78.77	7.65	
CCI	5.15	1.77	
CFS	4.7	1.76	
Number of medications on admission	8.08	3.45	
Number of medications on discharge	8.74	3.34	

Abbreviations: CCI- Charlson Co-Morbidity Index, CFS-Clinical Frailty Scale, eGFR-Estimated glomerular filtration rate

Most of the participants were admitted under the care of medical specialties with the majority of patients admitted under Geriatric Medicine, Respiratory Medicine and Cardiology (15.82%, 10.99% and 9.38% respectively). Just over 1 in 8participants (45,

12.06%) were admitted to a surgical specialty with orthopaedics accounting for the greatest proportion (5.90%) **Table 4.2.**

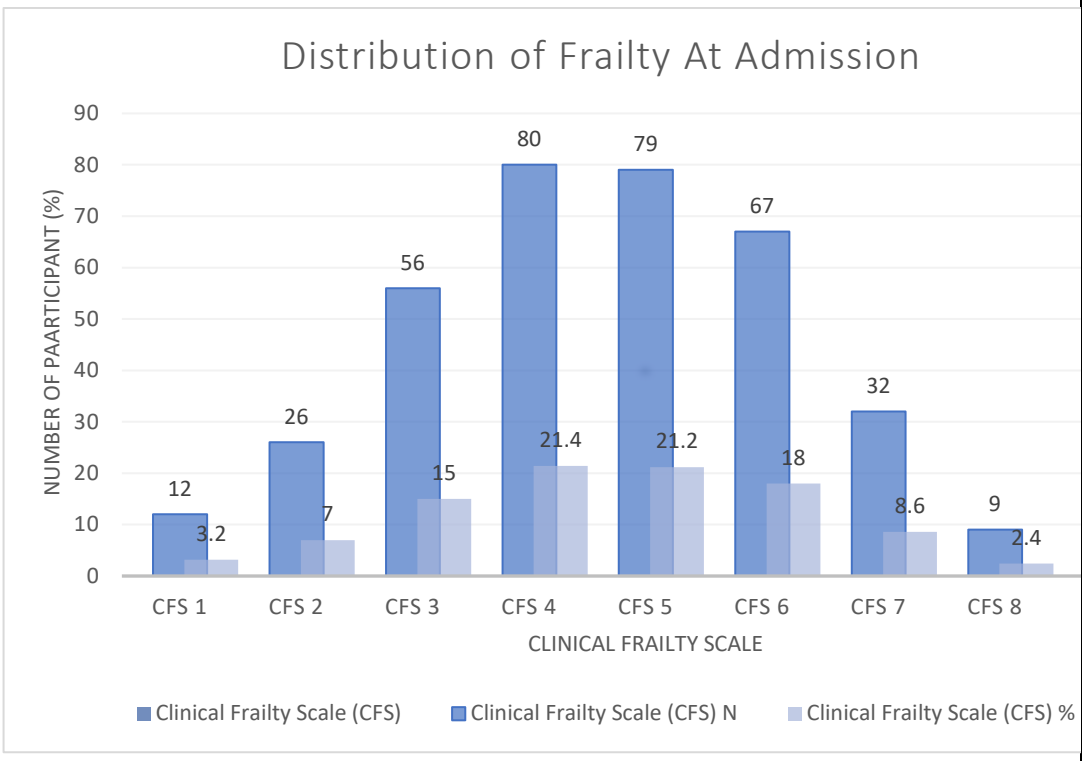
Table 4.2 Breakdown of Participants by Admitting Speciality.

Admission Speciality		
	N=373	**%**
Geriatric medicine	59	15.82
Respiratory medicine	41	10.99
Cardiology	35	9.38
Acute medicine assessment unit	28	7.24
Stroke	27	7.24
Gastroenterology	22	5.90
Orthopaedics	22	5.90
Nephrology	21	5.63
Endocrinology	20	5.36
General Internal Medicine	19	5.09
Oncology	16	4.29
Rheumatology	16	4.29
Infectious disease	13	3.49
Emergency medicine	7	1.88
General Surgery	6	1.61
Urology	6	1.61
Cardiothoracic	3	0.80
Neurosurgery	3	0.80
Vascular Surgery	3	0.80
Haematology	2	0.54
Neurology	2	0.54
Plastic Surgery	1	0.27
Trauma surgery	1	0.27

4.3.2 Frailty

Just under three quarters of the participants (74.8%, n=279) were overtly frail with a CFS of ≥ 4 (n = 279). The mean (SD) CFS score was 4.7 (1.7); the distribution of CFS scores is demonstrated in **Figure 4.2**. A total of 14.2% of older participants were considered severely frail, very severely frail or terminally ill i.e. CFS score ≥ 7.

Figure 4.2 Frailty characteristics of population of 373 older adults classified by Clinical Frailty Scale.



	N	%
Non-frail (CFS<4)	94	25.2
Frail (CFS≥4)	279	74.8
	Mean	SD
CFS score	4.7	1.8

4.3.3 Polypharmacy and Drug-Drug Interactions

Polypharmacy and hyper-polypharmacy were highly prevalent with 85.3% and 30.6% of participants taking five or more and 10 or more daily long-term medications respectively at admission. A total of 3009 individual drugs were prescribed at admission in the 373 patient participants. Using the Anatomical Therapeutic Chemical (ATC) classification system to the 4th level (Chemical, Pharmacological or Therapeutic subgroup), the most frequently prescribed daily medication subgroups were:

i.	C10AA07	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
ii.	A02BC05	Proton Pump Inhibitors
iii.	C07AB01	Beta-blocking agents, selective
iv.	B01AC06	Platelet aggregation inhibitors
v.	B01AF03	Direct Factor Xa Inhibitors

The 30 most frequently prescribed drug subgroups are listed in **Table 4.3.** More than half of the participants of the study was prescribed a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) or proton-pump inhibitor at admission (56% and 55.2% respectively).

Table 4.3 Prevalence of drugs at admission based to Anatomical Therapeutic Chemical (ATC) Classification to the 4th Level.

ATC CODE		N	%
C10AA07	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors	209	56.0
A02BC05	Proton Pump Inhibitors	206	55.2
C07AB01	Beta-blocking agents, selective	164	44.0
B01AC06	Platelet aggregation inhibitors	138	37.0
B01AF03	Direct Factor Xa Inhibitors	102	27.3
C03CA09	Sulphonamides, plain	96	25.7
C08CA51	Dihydropyridine derivatives	94	25.2
C09CA08	Angiotensin II receptor blockers	90	24.1
A11CC	Vitamin D and Analogues	77	20.6
C09AA05	ACE inhibitors, plain	71	19.0
N06AX22	Other antidepressants	63	16.9
A10BA02	Biguanides	50	13.4
N02BE01	Anilides	49	13.1
H03AA01	Thyroid Hormones	48	12.9
R03AK10	Adrenergics in combination with corticosteroids or other drugs	45	12.1
A06AD65	Osmotically acting laxatives	43	11.5
N06AB10	Selective serotonin reuptake inhibitors	43	11.5
A12AX	Calcium/VitaminD preparations	42	11.3
M04AA03	Preparations inhibiting uric acid production	42	11.3
H02AB09	Glucocorticoids	41	11.0
G04BD12	Drugs for urinary frequency and incontinence	40	10.7
G04CA04	Alpha-adrenoreceptor antagonists	39	10.5
N05CF05	Melatonin receptor agonists	37	9.9
A06AB15	Contact Laxatives	33	8.8
B03BB01	FolicAcid	33	8.8
R03BB07	Anticholinergics	31	8.3
B03AA02	Iron bivalent, oral preparation	30	8.0
R03AC02	Selective beta-2 adrenoreceptor agonists	25	6.7
R03AL08	Adrenergics in combination with anticholinergics	25	6.7
N02AA55	Natural Opium Alkaloids	23	6.2

The third most frequently prescribed class was beta-blockers (44%), followed by platelet aggregation inhibitors and direct factor Xa inhibitors (37% and 27%). The 25 most frequently prescribed individual drugs are presented in **Table 4.4.** Esomeprazole was the most prevalent daily prescribed medication at admission in the overall population.

Table 4.4 The 25 most frequently prescribed medications at admission.

ATC Code	**Drug Name**	**N**	**%**
A02BC05	Esomeprazole	142	38.1
C10AA05	Atorvastatin	119	31.9
B01AC06	Aspirin	116	31.1
C07AB07	Bisoprolol	116	31.1
A11CC	Vitamin D	77	20.6
B01AF02	Apixaban	63	16.9
C03CA02	Bumetanide	52	13.9
A10BA02	Metformin	50	13.4
C09AA05	Ramipril	49	13.1
C08CA13	Lercanidipine	48	12.9
C10AA07	Rosuvastatin	48	12.9
H03AA01	Thyroid Hormones	48	12.9
N02BE01	Paracetamol	48	12.9
A12AX	Calcium/Vitamin D combination	42	11.3
C03CA01	Furosemide	42	11.3
C07AB12	Nebivolol	42	11.3
C08CA01	Amlodipine	42	11.
A02BC03	Lansoprazole	34	9.1
C09CA03	Valsartan	34	9.1
B03BB01	Folic Acid	33	8.8
H02AB06	Prednisolone	33	8.8
M04AA01	Allopurinol	33	8.8
N06AX11	Mirtazapine	32	8.6
A06ab06	Senna Glycosides	31	8.3
B01AF01	Rivaroxaban	29	7.8

Over one third of older adults admitted acutely to hospital (145 patients, 38.87%) were exposed to at least one potential DDI based on the validated list of DDIs in older adults. At discharge, there was a slight reduction in potential DDI prevalence to 27.13%. The median number of DDIs at admission was 0 (min = 0, max = 4, IQR = 1; see **Table 4.5**).

Table 4.5 Prevalence of Polypharmacy and Potentially Clinically Relevant Drug-Drug Interactions.

Polypharmacy	≥5 drugs	318	85.3		
	≥10 drugs	114	30.6		
Potential drug-drug interactions at admission		**N**	**%**		
	≥1	145	38.9		
	≥2	41	11		
	≥3	12	3.2		
	≥4	2	0.5		
Potential drug-drug interactions at discharge (N=339)					
	≥1	92	27.13		
	≥2	27	7.9		
	≥3	3	0.8		
	≥4	1	0.3		
		Median	**IQR**	**Min**	**Max**
Population Admission DDI		0	1	0	4
Population Discharge DDI		0	1	0	4
CFS <4					
Admission DDI		0	1	0	4
Discharge DDI		0	0.25	0	2
CFS ≥4					
Admission DDI		0	1	0	4
Discharge DDI		0	1	0	4

While there was a statistically significant reduction in potential DDIs in the available discharge prescriptions ($z = -3.77$, $n = 339$, $p < .001$) with a small effect size of 0.147. The median number of potential drug-drug interactions in both groups was 0. The mean (SD) number of potential DDIs at presentation was 0.52 (±0.7) and the mean

(SD) number of potential DDIs at discharge was 0.36 (±0.67) there was statistically significant reduction in the mean number of potential DDIs at discharge (p=0.01).

The prevalence of each potentially clinically relevant DDIs as identified by the list is presented in **Table 4.6.** As previously discussed, there was a decrease in potential DDIs between admission and discharge. The overall mean reduction in DDI prevalence at discharge compared to admission prevalence was 0.98 (SD =2.66). A Wilcoxon signed-rank test indicated that DDIs were significantly higher at admission than at discharge (z = -3.04, p = 0.0.002]. The most frequently encountered DDI at admission was concomitant use of ≥ 3 centrally-acting drugs, affecting 46 patients (12.3%), details are shown in **Table 4.7**. The prevalence of this particular DDI decreased to 8.6% at discharge. DDIs involving drugs that affect potassium were the next most prevalent interactions at admission (DDI-65 and DDI-61). While the majority of DDIs reduced in prevalence from admission to discharge,), there were 3 potentially clinically relevant DDIs that *increased* in prevalence at discharge i.e. (i) digoxin + thiazide or loop diuretic, (ii) dabigatran + P-gp inhibitor and (iii) edoxaban + P-gp inhibitor. As described earlier, DDIs were assessed for potential harm using serum biochemistry data, presenting history and discharge diagnosis. The results of this analysis are demonstrated in **Table 4.8.**

Table 4.6 Potentially Clinically relevant Drug-Drug interactions in Older Adults at Admission and Discharge from an Acute Hospital.

		On Admission (n=373)		On Discharge (n=336)	
		N	%	N	%
	Total potentially relevant drug-drug interactions	134	35.9	91	27.1
DDI-1	digoxin + amiodarone	1	0.3	0	0.0
DDI-2	digoxin + verapamil or diltiazem	0	0	0	0.0
DDI-3	digoxin + propafenone	0	0	0	0.0
DDI-4	digoxin + quinidine	0	0	0	0.0
DDI-5	digoxin + some macrolides (i.e. erythromycin or clarithromycin or azithromycin or roxithromycin or telithromycin)	1	0.3	0	0.0
DDI-6	digoxin + thiazide or loop diuretic	5	1.3	7	2.1
DDI-7	vitamin K antagonist + a fibrate	0	0	0	0.0
DDI-8	vitamin K antagonist + cimetidine	0	0	0	0.0
DDI-9	vitamin K antagonist + metronidazole	0	0	0	0.0
DDI-10	vitamin K antagonist + amiodarone	1	0.3	0	0.0
DDI-11	oral anticoagulant (i.e. vitamin K antagonist or factor Xa inhibitor or direct thrombin inhibitor) + an oral NSAID	3	0.8	0	0.0
DDI-12	oral anticoagulant + an antiplatelet drug (including aspirin)	9	2.4	8	2.4
DDI-13	vitamin K antagonist + trimethoprim/sulfamethoxazole	0	0	0	0.0
DDI-14	vitamin K antagonist + a quinolone	0	0	0	0.0
DDI-15	vitamin K antagonist + a macrolide	0	0	0	0.0
DDI-16	dabigatran + a P-gp inhibitor (ketoconazole, itraconazole, verapamil, quinidine, amiodarone, dronedarone, ciclosporin, clarithromycin, erythromycin, ritonavir)	0	0	2	0.6
DDI-17	edoxaban + a P-gp inhibitor (same list as for DDI-16)	1	0.3	2	0.6
DDI-18	rivaroxaban + a P-gp inhibitor or a CYP3A4- inhibitor ‡ (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin clarithromycin, erythromycin, ritonavir)	2	0.5	1	0.3
DDI-19	apixaban + a P-gp inhibitor or a CYP3A4- inhibitor ‡	6	1.6	5	1.5
DDI-20	antiplatelet drug (including aspirin) + oral NSAID	7	1.9	3	0.9
DDI-21	concomitant use of ≥ 2 potassium-sparing drugs (i.e. amiloride, triamterene, eplerenone, spironolactone, ACE inhibitors, ARBs, NSAIDs, trimethoprim/sulfamethoxazole)	19	5.1	9	2.7
DDI-22	ACE inhibitor or ARB or a potassium sparing diuretic + a potassium supplement	0	0	2	0.6
DDI-23	ACE inhibitor or ARB + an oral NSAID	8	2.1	2	0.6
DDI-24	diuretic + oral NSAID	8	2.1	0	0.0
DDI-25	statin + gemfibrozil	0	0	0	0.0
DDI-26	atorvastatin or simvastatin or lovastatin + verapamil or diltiazem	1	0.3	1	0.3
DDI-27	simvastatin + amlodipine	4	1.1	0	0.0
DDI-28	atorvastatin or simvastatin or lovastatin + amiodarone	4	1.1	4	1.2
DDI-29	atorvastatin or simvastatin or lovastatin + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin)	3	0.8	1	0.3
DDI-30	calcium channel blocker + a CYP3A4 inhibitor ‡	0	0	0	0.0

DDI-31	isopyramide + some macrolides (i.e. erythromycin, clarithromycin telithromycin)	0	0	0	0.0
DDI-32	beta-blocker + verapamil or diltiazem	0	0	1	0.3
DDI-33	procainamide + amiodarone	0	0	0	0.0
DDI-34	procainamide + trimethoprim	0	0	0	0.0
DDI-35	furosemide + etacrynic acid	0	0	0	0.0
DDI-36	concomitant use of ≥ 3 centrally-acting drugs (i.e. opiates or antipsychotics or benzodiazepines/z-drugs or barbiturates or antiepileptics or antidepressants)	46	12.3	29	8.6
DDI-37	alprazolam or diazepam or midazolam or triazolam or zolpidem or zopiclone + a CYP3A4 inhibitor ‡	0	0	0	0.0
DDI-38	SSRI + another serotonergic drug (including tramadol)	4	1.1	4	1.2
DDI-39	oral NSAID + SSRI or SNRIs	4	1.1	2	0.6
DDI-40	fluoxetine + tricyclic antidepressant	0	0	0	0.0
DDI-41	lithium + NSAID	0	0	0	0.0
DDI-42	lithium + diuretic	0	0	0	0.0
DDI-43	lithium + ACE inhibitor or an ARB	0	0	0	0.0
DDI-44	MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + sympathomimetic	0	0	0	0.0
DDI-45	MAO-A inhibitor (i.e. moclobemide) or non-selective MAO inhibitor (i.e. phenelzine or linezolid) + levodopa	0	0	0	0.0
DDI-46	MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + some opioids (i.e. meperidine or fentanyl)	0	0	0	0.0
DDI-47	MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + an antidepressant (particularly a SSRI)	2	0.5	0	0.0
DDI-48	carbamazepine + verapamil or diltiazem	0	0	0	0.0
DDI-49	carbamazepine + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin)	0	0	0	0.0
DDI-50	acetylcholinesterase inhibitor + a drug that reduces heart rate (i.e. antiarrhythmic drugs or beta-blockers or verapamil or diltiazem)	2	0.5	2	0.6
DDI-51	theophylline + cimetidine	0	0	0	0.0
DDI-52	theophylline + a quinolone	0	0	0	0.0
DDI-53	theophylline + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin)	0	0	0	0.0
DDI-54	theophylline + fluvoxamine	0	0	0	0.0
DDI-55	thiopurines (e.g. azathioprine) + allopurinol	0	0	0	0.0
DDI-56	oral or parenteral corticosteroid + an oral NSAID	0	0	0	0.0
DDI-57	concomitant prescription of ≥ 2 anticholinergic drugs	7	1.9	5	1.5
DDI-58	ciclosporin + rifampicin	0	0	0	0.0
DDI-59	ergot alkaloid (e.g. ergotamine) + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin)	0	0	0	0.0
DDI-60	methotrexate + trimethoprim	0	0	0	0.0
DDI-61	phosphodiesterase type 5-inhibitor + nitrate	0	0	0	0.0
DDI-62	tamoxifen + vitamin K antagonist	0	0	0	0.0
DDI-63	tamoxifen + citalopram or escitalopram	1	0.3	0	0.0
DDI-64	tamoxifen + paroxetine or fluoxetine or bupropion	0	0	0	0.0
DDI-65	concomitant prescription of ≥ 2 drugs that reduce potassium (e.g. b2-agonists, thiazides, loop diuretics, corticosteroids)	21	5.6	17	5.1
DDI-66	SSRI + loop or thiazide diuretic	16	4.3	14	4.2

Table 4.7 Most frequently encountered potentially clinically relevant drug-drug interactions at admission in a sample of acutely admitted older adults.

DDI Number	Description of Drug-drug interaction	N	%
DDI-36	Concomitant use of ≥ 3 centrally-acting drugs (i.e. opiates or antipsychotics or benzodiazepines/z-drugs or barbiturates or antiepileptics or antidepressants)	46	12.3
DDI-65	Concomitant prescription of ≥ 2 drugs that reduce potassium (e.g. b2-agonists, thiazides, loop diuretics, corticosteroids)	21	5.6
DDI-21	Concomitant use of ≥ 2 potassium-sparing drugs (i.e. amiloride, triamterene, eplerenone, spironolactone, ACE inhibitors, ARBs, NSAIDs, trimethoprim/sulfamethoxazole)	19	5.1
DDI-66	SSRI + loop or thiazide diuretic	16	4.3
DDI-12	Oral anticoagulant + an antiplatelet drug (including aspirin)	9	2.4
DDI-23	ACE inhibitor or ARB + an oral NSAID	8	2.1
DDI-24	Diuretic + oral NSAID	8	2.1
DDI-20	Antiplatelet drug (including aspirin) + oral NSAID	7	1.9
DDI-57	Concomitant prescription of ≥ 2 anticholinergic drugs	7	1.9
DDI-19	Apixaban + a P-gp inhibitor or a CYP3A4- inhibitor ‡	6	1.6
DDI-6	Digoxin + thiazide or loop diuretic	5	1.3
DDI-27	Simvastatin + amlodipine	4	1.1
DDI-28	Atorvastatin or simvastatin or lovastatin + amiodarone	4	1.1
DDI-38	SSRI + another serotonergic drug (including tramadol)	4	1.1
DDI-39	Oral NSAID + SSRI or SNRIs	4	1.1
DDI-11	Oral anticoagulant (i.e. vitamin K antagonist or factor Xa inhibitor or direct thrombin inhibitor) + an oral NSAID	3	0.8
DDI-29	Atorvastatin or simvastatin or lovastatin + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin)	3	0.8
DDI-18	Rivaroxaban + a P-gp inhibitor or a CYP3A4- inhibitor ‡ (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin,, clarithromycin, erythromycin, ritonavir)	2	0.5
DDI-47	MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + an antidepressant (particularly a SSRI)	2	0.5
DDI-50	Acetylcholinesterase inhibitor + a drug that reduces heart rate (i.e. antiarrhythmic drugs or beta-blockers or verapamil or diltiazem)	2	0.5

Abbreviations: ACE; angiotensin converting enzyme inhibitor, ARB-angiotensin receptor blocker, NSAID-non-steroidal anti-inflammatory drug, SSRI-selective serotonin reuptake inhibitor, P-gp- P-glycoprotein 1, CYP3A4- Cytochrome P450 3A4.

There were 36 possible admissions due to a potential harm from a DDI identified using the DDI list. The most frequent reason for admission due to potential harm was participants experiencing a fall, fracture or impaired cognition while using ≥ 3 centrally acting drugs **Table 4.9**. Fourteen admissions could possibly be attributed to this particular DDI out of 46 cases where the DDI was present. While 3 admissions could have resulted from the concomitant use of an SSRI and a thiazide or loop diuretic and 3 further admissions due to deterioration of renal function, hyperkalaemia and congestive heart failure in the context of diuretic and oral NSAID use, potential

interactions that could lead to hyperkalaemia, while prevalent, did not appear to lead to admissions due to the potential harm from this interaction. There were 36 DDIs that were not present at either admission or discharge.

Table 4.8 A comparison of total number of potential DDIs and number of possible admissions due to potential harm.

DDI Number	Potential harm	Number of Potential DDIs	Possible admission due to potential harm	DDI Number	Potential harm	Number of Potential DDIs	Possible admission due to potential harm
DDI1	Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia	1	0	DDI35	Ototoxicity with risk of tinnitus, reversible or irreversible hearing impairment, deafness	0	0
DDI2	Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia	0	0	DDI36	Increased risk of falls and fracture, impaired cognition	46	14
DDI3	Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia	0	0	DDI37	Excessive sedation and prolonged hypnotic effects	0	0
DDI4	Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia	0	0	DDI38	Serotonin syndrome, with tramadol: seizures and diminished therapeutic response to tramadol	4	0
DDI5	Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia	1	1	DDI39	Bleeding, gastrointestinal bleeding	4	2
DDI6	Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia	5	1	DDI40	Serotonergic syndrome Tricyclic antidepressant toxicity, including cardiac arrhythmias	0	0
DDI7	Bleeding	0	0	DDI41	Lithium toxicity, potentially life-threatening	0	0
DDI8	Bleeding	0	0	DDI42	Lithium toxicity, potentially life-threatening	0	0
DDI9	Bleeding	0	0	DDI43	Lithium toxicity, potentially life-threatening	0	0
DDI10	Bleeding	1	0	DDI44	Hypertensive crisis	0	0

DDI11	Bleeding, gastrointestinal bleeding and toxicity (i.e. inflammation, ulceration and perforation)	3	0	DDI45	Hypertensive crisis	0	0
DDI12	Bleeding	9	1	DDI46	Serotonin syndrome		
DDI13	Bleeding	0	0		Respiratory depression, cyanosis, hypotension and coma	0	0
DDI14	Bleeding	0	0	DDI47	Serotonin syndrome	2	0
DDI15	Bleeding	0	0	DDI48	Carbamazepine toxicity	0	0
DDI16	Bleeding	0	0		Decreased therapeutic effect of verapamil and diltiazem		
DDI17	Bleeding	1	0	DDI49	Carbamazepine toxicity Decreased macrolide efficacy	0	0
DDI18	Bleeding	2	1	DDI50	Bradycardia	2	0
DDI19	Bleeding	6	0	DDI51	Theophylline toxicity	0	0
DDI20	Bleeding, gastrointestinal bleeding and toxicity (i.e. inflammation, ulceration and perforation) With aspirin, decreased cardioprotective effect	7	3	DDI52	Theophylline toxicity	0	0
DDI21	Hyperkalaemia	19	0	DDI53	Theophylline toxicity	0	0
DDI22	Hyperkalaemia	0	0	DDI54	Theophylline toxicity	0	0
DDI23	Deterioration of renal function and hyperkalaemia Altered blood pressure control	8	2	DDI55	Azathioprine toxicity	0	0
DDI24	Deterioration of renal function, hyperkalaemia and congestive heart failure. Altered blood pressure control	8	3	DDI56	Gastrointestinal ulceration or bleeding	0	0
DDI25	Severe myopathy and rhabdomyolysis which may lead to acute renal failure and death	0	0	DDI57	Anticholinergic effects including cognitive decline	7	2
DDI26	Severe myopathy and rhabdomyolysis which may lead to acute renal failure and death	1	0	DDI58	Organ rejection	0	0

DDI27	Severe myopathy and rhabdomyolysis which may lead to acute renal failure and death	4	1	DDI59	Ergot toxicity	0	0
DDI28	Severe myopathy and rhabdomyolysis which may lead to acute renal failure	4	0	DDI60	Potentially fatal methotrexate toxicity	0	0
DDI29	Severe myopathy and rhabdomyolysis which may lead to acute renal failure	3	0	DDI61	Severe hypotension, myocardial ischemia	0	0
DDI30	Increased effects of calcium channel blockers	0	0	DDI62	Bleeding	0	0
DDI31	Hypoglycaemic coma, QT prolongation, torsade de pointes, heart block and ventricular fibrillation	0	0	DDI63	Ventricular arrhythmias, torsade de pointes and sudden death	1	0
DDI32	Potentially serious cardiovascular adverse effects including congestive heart failure, severe hypotension, exacerbation of angina, ventricular asystole, sinus arrest, heart block	0	0	DDI64	Reduced effectiveness of tamoxifen	0	0
DDI33	(Exacerbation of pre-existing) arrhythmias and QT prolongation	0	0	DDI65	Hypokalaemia, QT prolongation and torsade de pointes	21	2
DDI34	Cardiac adverse effects including QT prolongation, torsade de pointes, cardiac arrest	0	0	DDI66	Hyponatraemia, orthostatic hypotension	16	3

Daily admission medications were screened using Stockley's interactions checker, 16 seriously life-threatening interactions were identified and 229 participants (61.3%) had at least one potential DDI. In contrast to the older adults DDI list, there was a median of 1 DDI (min = 0, max = 3, IQR =3) and a mean (SD) DDI prevalence of 2 (±2.81) present at admission.

4.3.4 Association between frailty and Drug-Drug Interactions

A Mann-Whitney *U* Test revealed no significant difference in the number of potentially clinically significant DDIs at admission between non-frail (CFS <4) participants (Md=0, n=94) and frail (CFS ≥4) participants (Md=0, n=279) (*U*=12427, *z*= -.702, p = .48, r = 0.03). In addition, no significant difference was demonstrated between the number of new DDIs during admission and new DDIs on discharge between the non-frail and frail participants.

An independent sample t-test was conducted to compare the number of daily admission medications in robust and frail older people. There was a significant difference in the mean number of daily medications between robust participants (M = 6.73, SD = 3.35) and frail participants (M = 8.53, SD = 3.37, *t (*373) = 3.37, *p* = .01 two-tailed). While at admission robust people were prescribed fewer daily medications, their mean number of discharge medications was greater. Again, there was a difference in the number of daily medications with robust participants prescribed a mean (SD) 9.23 medications (3.36) at discharge compared to a mean (SD) of 8.60 (3.36) daily medications in frail participants at discharge but this was not statistically significant (*t* (325) =-1.47, p = 0.14 two-tailed).

The relationship between the number of daily medications at admission and the number of daily DDIs was investigated using Spearman's rank correlation test. A significant correlation was not found. However, there was a significant positive correlation between the number of discharge medications and the number of discharge DDIs (r = 0.324, n = 336, p < 0.01).

4.4 Discussion

This is the first prospective observational study to be carried out using a recently validated, international consensus list of potentially clinically significant drug-drug interactions (DDIs) in older people (184). The primary aim of the study was to assess the prevalence of potentially clinically relevant DDIs in older adults presenting acutely to a model 4 tertiary referral hospital (i.e. major teaching hospital) in the south of Ireland. The majority of the 373 participants recruited to the study were living with frailty and polypharmacy with a mean (SD) CFS score of 4.7 (1.77) and were taking an average (SD) of 8.08 (3.45) daily medications on admission. The study participants were, in general, also living with a high level of co-morbidity. There was a relatively high prevalence of DDIs detected in the cohort, with 38.9% of participants experiencing at least one DDI at admission to hospital. There was no significant difference in DDI prevalence between frail and non-frail participants. It has been well established that polypharmacy at discharge from hospital is associated with increased mortality and higher re-admission rates (188-191). Perhaps surprisingly, I found that while the mean number of medications at discharge increased to more than 8 (i.e. 8.74+/-3.34), there was a statistically significant *reduction* in the number of potential DDIs in contrast to previous studies (192).

The prevalence of DDIs in the present study cohort was lower than that in a previous observational study by Ocovska et al. (2023) which found a DDI prevalence of 46% in older adults aged ≥ 65 years. It was also lower than the prevalence of DDIs detected in a sub-study of the OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) clinical trial (54%) (185) involving multimorbid older patients with associated polypharmacy presenting to 4 large medical centres in Europe. In contrast to the present study, DDI prevalence in

OPERAM increased significantly from baseline to discharge but in the control group only ($P < 0.001$).

One of the areas for concern demonstrated by the present study is the number of older people that were using greater than three centrally acting medications who were admitted with possible ADR harm related to this DDI. One in 10 study participants

was exposed to this potential DDI with 30.1% of those exposed to the DDI presenting with a fall or new-onset confusion. This observation indicates a particular need for increased vigilance to identify and deprescribe these potentially harmful centrally-acting medications. This DDI was also identified as one of the five most frequent DDIs by both of the previous sub-studies.

The findings from the present study align with those reported by Zerah et al. (2021), in that four of the most prevalent DDIs are the same in both studies (Table 4.9). There was also agreement across the 3 studies relating to the DDIs that contribute most often to acute hospital admission i.e. centrally-acting drugs, drugs affecting renal function/serum potassium and drugs contributing to bleeding risk.

Table 4.9 Five most frequently encountered DDIs in OPERAM sub-study and current study

Zerah et al., 2021	**Current Study**
DDI 65 (prescription of ≥2 drugs that reduce potassium)	DDI 36 (prescription of ≥3 centrally-acting drugs)
DDI 36 (prescription of ≥3 centrally-acting drugs)	DDI 65 (prescription of ≥2 drugs that reduce potassium)
DDI 21 (prescription of ≥2 potassium-sparing drugs)	DDI 21 (prescription of ≥2 potassium-sparing drugs)
DDI 12 (oral anticoagulant and antiplatelet)	DDI-66 SSRI + loop or thiazide diuretic
DDI 39 (oral non-steroidal anti-inflammatory drug and selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor)	DDI 12 (oral anticoagulant and antiplatelet)

4.4.1 Potential Limitations of this study

One limitation of the present study is that it was single-centre and smaller scale than that of Zerah et al. In addition, recruitment for this study was carried out during the Covid-19 pandemic and was limited by contemporaneous infection control protocols and visiting restrictions that may have influenced the frailty profile of those patients recruited to the study.

4.4.2 Conclusion

Previous studies have highlighted a risk that potential DDIs could be over-estimated in comparison actual DDI-related harm, leading to some potentially beneficial medications not being prescribed for older adults (194, 195) . Use of an explicit DDI list validated for older adults could, in theory, reduce this risk. Thirty-nine of the consensuses validated 66 DDIs were not identified in the study cohort at either

admission or discharge. When the prevalence of DDIs was assessed using Stockley's drug interaction database, not surprisingly a greater prevalence of interactions was identified, however many of these interactions required close monitoring or dose adjustment rather than drug discontinuation i.e. some drugs were not absolutely contraindicated or subjecting study participants to life-threatening interactions. Frailty did not affect the prevalence or risk of DDIs for the study participants, highlighting the importance of vigilance for DDI's when prescribing for all older adults, regardless of frailty status.

CHAPTER 5

A Novel Screening Tool to Detect Potentially Clinically Relevant Prescribing Cascades in Older Adults: STOPPCascade

5.1 Introduction

Since the concept was first introduced by Rochon and Gurwitz over two decades ago, prescribing cascades have gained increasing recognition as a cause of potentially inappropriate polypharmacy. Prescribing cascades occur when an adverse drug event (ADE) is misinterpreted as a new symptom or medical condition, with the subsequent prescription of another, potentially inappropriate drug to treat that new symptom or medical condition (84, 194). Prescribing cascades as a form of inappropriate prescribing represent a potentially important public health problem as they lead to unnecessary and excessive cost to healthcare systems, can lead to adverse clinical outcomes and may result in reduced quality of life for multi-morbid older people (85, 86). With polypharmacy comes increased risk of drug-drug and drug-disease interactions (88, 89). Adverse Drug Events in older adults can be misinterpreted as worsening frailty or the onset of new geriatric syndromes due to non-specific symptoms. Historically, ADEs in older people have been under-reported in drug trials where older people are often underrepresented (90-93) .

A recently published systematic review which examined 101 studies of prescribing cascades in community based adults found that the most commonly described prescribing cascades were (i) calcium channel blockers (CCBs) → loop diuretics to treat peripheral oedema, (ii) amiodarone → thyroxine to treat hypothyroidism, (iii) inhaled corticosteroids → topical antifungal to treat oral candidiasis, (iv) antipsychotics → levodopa to treat Parkinsonism, and (v) acetylcholinesterase inhibitors → antimuscarinics to treat urinary frequency (94). While this study specifically looked at cascades in all adults over 18, excluding studies conducted solely in nursing homes, residential care, inpatient settings or emergency departments

and case reports, it demonstrates a tendency for the most widely known cascades to be the most frequently assessed and measured.

The true overall prevalence of prescribing cascades in multimorbid older people is unknown, although individual cascades, evaluated using population database information and cohort studies, suggest that cascades occur with relatively high frequency particularly in older adults. (95-97). Prescription sequence symmetry analysis (PSSA) studies have gained increasing momentum as a detection method in pharmacovigilance to rapidly detect and evaluate potential prescribing cascade signals. When potential cascade signals are detected, they can serve as a prompt for clinical review and clinical process mapping. Such a process has been described as a method to screen for cascades when older people presenting with new symptoms that might result from cascades (99) (100). At present, the overall extent of prescribing cascades as both a clinical problem and as a public health hazard is likely underestimated.

Another challenge that prescribers face is how to intervene when a potential prescribing cascade is detected as comprehensive explicit cascade criteria are currently lacking. Practical approaches to cascade detection include implicit algorithms that can be applied during routine medication review. More recently, an explicit prescribing cascades list called ThinkCascades has been published (101). ThinkCascades is a concise, a 9-item, international consensus-based list of clinically important prescribing cascades which was developed to enhance awareness and clinicians' recognition of common prescribing cascades that may represent inappropriate prescribing during routine medication review (101). While this tool may serve to alert prescribers to more common prescribing cascades, sceptics may consider the list too narrow spectrum to

be of practical clinical value since many other potentially problematic cascades could be overlooked.

In the present study, my primary aim was to develop a broader explicit list of clinically relevant prescribing cascades in older adults (called STOPPCascade) in order to facilitate their detection during medication review while simultaneously serving as a tool that could be applied easily to population databases or electronic medication records to screen for the overall prevalence of prescribing cascades. The secondary aim of this study was to determine the prevalence of potential prescribing cascades in older patients presenting to hospital with acute illness using the STOPPCascade list.

5.2 Methods

5.2.1 Literature Search

A structured literature search was carried out of the PubMed, CINAHL and Google Scholar databases. The search used the following search terms: Prescribing Cascades OR Cascades OR Cascade AND Older Adults OR Adults Over 65 OR Older People OR Gero* OR Geri*. All study designs, without limitations, including reviews, experimental and observational studies, case series, and case reports were included. I also considered published abstracts from scientific meetings in the literature review. The initial literature search was designed to be as broad as possible to include as many potential prescribing cascades described in the literature as possible. Studies that did not include prescribing cascades in the title or the abstract, studies without access to the full text article or without access to an English version of the article and studies exclusively describing patients aged under 65 years were excluded. The specified patient population was adults aged ≥65 years, included in community-based, hospital-

based, or residential care-based studies. I also included studies where age was not specifically described in the initial literature review.

Abstracts were screened for articles that did not describe evidence-based cascades in older adults and were excluded. Full text articles were subsequently reviewed for cascades using inclusion criteria. Clinically relevant cascade criteria that were required were:

- ➢ Drug A prescribed.
- ➢ Adverse drug event/reaction occurs following introduction of Drug A and is misinterpreted as a new medical condition.
- ➢ Drug B prescribed to treat the misdiagnosed 'new medical condition' (i.e. the adverse drug event/reaction).

According to these criteria, a long-list of potential cascades was created and organized according to physiological systems as per the STOPP/START criteria for potentially inappropriate prescribing (64, 195, 196) using Drug A as the index drug and Drug B as the possible cascade response drug presented in an Excel file format with a Likert scale. A data file with the source reference material and references was compiled also.

5.2.2 Adjudication:

Three academic clinical reviewers with expertise in geriatric pharmacotherapy evaluated each individual drug cascade and the associated published evidence to support it. The short list was provided to each panellist individually as an Excel® file. Taking into account the requirement for standardised quantification of the construct of interest, a 5-point Likert scale was utilised to evaluate each cascade for inclusion/exclusion in the final list.

Each reviewer was asked to consider each individual potential cascade and the accompanying evidence along with their own clinical judgement and to score the possible cascade from 1 (i.e., strongly disagree) to 5 (i.e. strongly agree) on the Likert scale. The question presented to the reviewers relating to each potential cascade was:

> "Do you agree that this Drug A/ADE/Drug B represents a potentially problematic cascade?".

The panellists were requested to score the potential cascades individually, without influence from the other two panellists. Subsequently, each cascade and the Likert scale scores were presented at a series of 3 consensus meetings. Potential cascades where two or all three reviewers assigned a Likert score of 4 or more were included in the final list for STOPPCascade. Where there was disagreement or a need for clarification regarding a cascade, the British National Formulary volume 81 (March – September 2021) and drug A's individual Summary of Product Characteristics (SPC) were consulted to assess whether the ADE was known to be associated with that drug and therefore clinically plausible. Potential cascades that did not reach the threshold for inclusion in the final list are shown in Appendix 4.

5.2.3 Determining the Prevalence of Potential Prescribing Cascades

The STOPPCascade list of potential prescribing cascades was applied to the database of prescribed drugs from the potentially clinically relevant drug-drug interactions in older people project. The methodology for data collection is described in detail in Chapter 4. Medication lists were assessed at 3 time points;

1. Within 48 hours of admission to hospital
2. During the first 5 days of admission
3. At discharge.

The index drug A was colour coded based on initial timepoint where it was first present. In the case of the admission medication list, a prescribing cascade was possible if Drug A and Drug B were co-prescribed on admission. For inpatient and discharge cascades, a possible cascade was detected if Drug B was prescribed after Drug A ('cascade positive'). If Drug B was present at a timepoint before Drug A was prescribed it was ruled out as a possible cascade ('cascade negative').

5.3 Results

5.3.1 Literature Search

The initial database search identified 2999 records, 174 records were screened criteria after duplicates (64) and ineligible records were removed (1262, refereed to non-medication related cascades such as coagulation cascades, therapeutic cascades in TB/HIV treatment and signalling cascades). 132 full text articles were sought for review, of which 119 were available. Full text articles and conference presentation abstracts were screened using the inclusion/exclusion criteria with 113 publications being used to compile the initial long list of potential prescribing cascades. The structured literature search is described in the PRISMA diagram (see **Figure 5.1**).

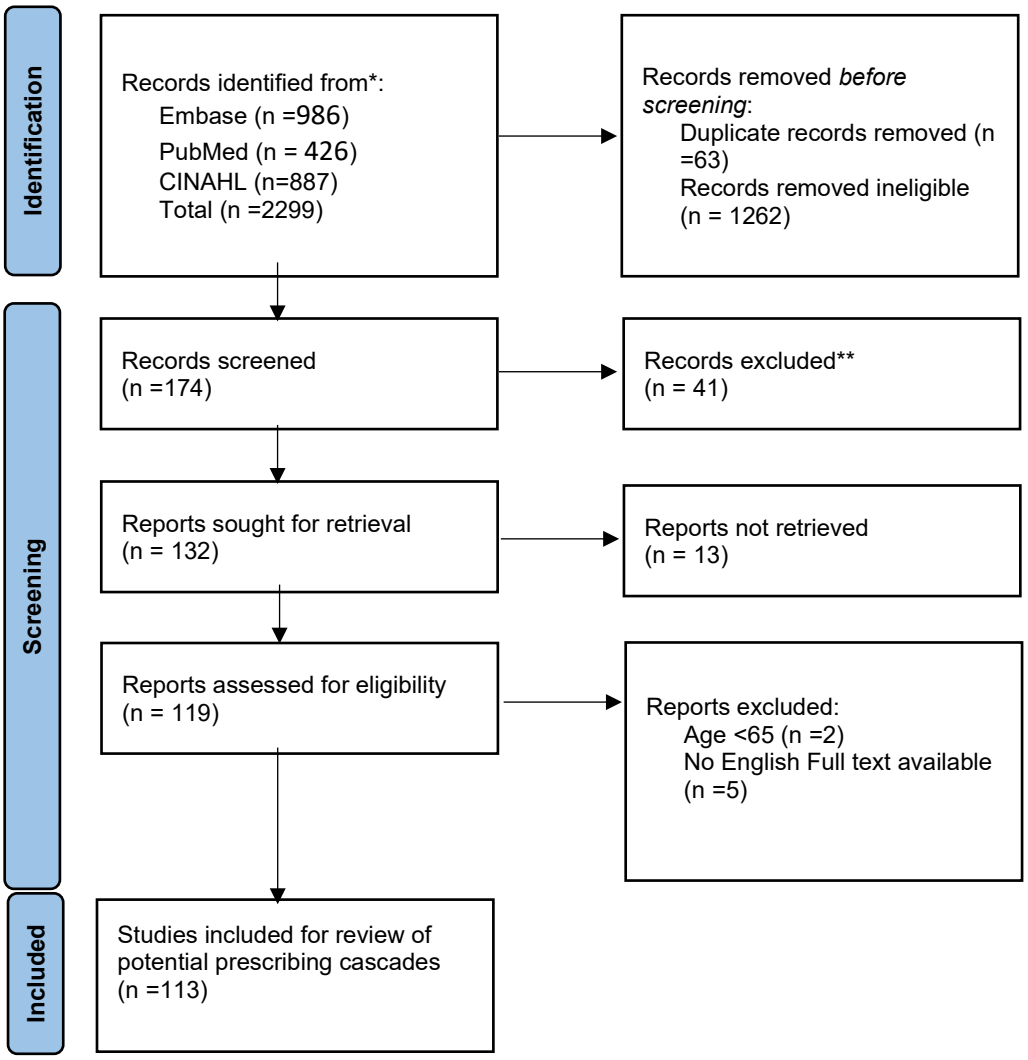


Figure 5.1. PRISMA Diagram of Structured Literature Search Results(197)

5.3.2 Short-List Development

The 113 publications identified in the literature search were assessed and individual prescribing cascades were listed. In total, 283 individual prescribing cascades were described in these 113 articles. Some prescribing cascades were described multiple times as some of the publications were review articles citing included cascades. For example, the calcium channel blocker -> pedal oedema -> diuretic prescribing cascade was described in 22 individual articles. In some cases, an individual calcium channel blocker was described (mostly amlodipine), in others the drug class was described

(mostly dihydropyridines). Duplicate articles were removed. The list of references for the included cascades is provided in Appendix 4. Where a drug class and individual drug from that class were described as contributing to the same cascade, consolidation into the drug class was made according to Anatomical Therapeutic Classification (ATC) code unless the cascade was drug-specific rather that a class effect. The resulting short list of 131 prescribing cascades with a supporting literature file was then presented to the 3 members of the adjudication panel.

5.3.3 Final Cascades List

A physiological systems-based draft short-list of 131 potential cascades was adjudicated by the panel, system-by-system. Seventy-one individual potential prescribing cascades met the Likert scale threshold for inclusion and were accepted for the STOPPCascade list, involving 40 drugs/drug classes (**Table 5.1**). In the case of some drug classes, multiple prescribing cascades occurred, for example non-steroidal anti-inflammatory drugs (NSAIDs) were associated with 5 individual potential cascades:

(i) NSAIDs -> Hypertension -> Antihypertensives

(ii) NSAIDs -> Heartburn -> Proton pump inhibitors

(iii) NSAIDs -> Nausea -> Metoclopramide/Antiemetics

(iv) NSAIDs -> Lower Limb Oedema -> Diuretic

(v) NSAIDs -> Dizziness ->Labyrinthine sedatives.

The potential prescribing cascades were not present in all physiological system categories as in the STOPP/START criteria following review. The physiological systems with ≥ 1 cascade included Cardiovascular System, Central Nervous System,

Gastrointestinal System, Respiratory System, Musculoskeletal system, and Endocrine system. As per the presentation of STOPP/START criteria, analgesic drugs and anticholinergic/antimuscarinic drugs were included with a further section added for antimicrobial drugs, not previously part of the original STOPP/START list.

Additionally, after some discussion, the adjudication panel expanded the list of potential drug B's (the drug/drug class arising from the prior side-effects of the causative drug A's) in some cases to standardise the cascades. This is illustrated in the antipsychotic -> tremor/movement disorder -> antiparkinsonian drug cascade. The list of potential drugs Bs represent all possible drugs that may be prescribed to treat the drug-induced parkinsonism ADE. They include the drug classes used in the treatment of parkinsonism i.e. dopamine agonists (bromocriptine, pergolide, ropinirole, rotigotine, cabergoline), dopamine derivatives (levodopa), amantadine, monoamine oxidase B derivatives (selegiline, rasagiline), and anti-cholinergic agents (biperiden, procyclidine). This standardised list of drug B's is applied wherever the ADE is tremor/movement disorder. Suggested appropriate clinical actions are also included in STOPPCascade to assist clinicians once a prescribing cascade is detected.

Table 5.1 STOPPCascade list of potential Prescribing Cascades in Older Adults

1. This list serves as a guide to potential prescribing cascades that may occur older adults, it is not intended to replace clinician judgement.
2. Patient care goals and wishes along with potential drug-drug interactions and drug-disease interactions should be taken into account on an individual basis when prescribing or de-prescribing medications
3. New medications should be commenced at the lowest possible dose and titrated slowly to minimise the risk of adverse reactions.
4. If patients report new symptoms after commencing a new drug or recent dose change, consider the potential for an adverse drug reaction and carefully consider the benefits of continuing therapy with the first medicine.

Cardiovascular System

	Drug A	ADE	Drug B	Suggested Action
1.a	C09AA **Angiotensin-converting enzyme inhibitors** e.g., captopril, enalapril, lisinopril, perindopril, ramipril	Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Monitor blood pressure for hypotension and orthostatic hypotension. Consider dose reduction.
1.b		Cough	Cough Suppressant Inhalers (without diagnosis of asthma) Antibiotic	Consider reducing dose or switching to alternative antihypertensive such as an Angiotensin II Receptor Blocker.
2.a	C07A **Beta-Blocking Agents** e.g., metoprolol, atenolol, bisoprolol, nebivolol, timolol, sotalol, propranolol)	Depression	Antidepressants	Review initial indication for B-Blocker and duration of treatment
2.b		Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Monitor heart rate and blood pressure, review initial indication and duration of treatment. Consider reducing dose if bradycardia or hypotension present
2.c		Sexual Dysfunction	Phosphodiesterase Inhibitors	Consider switch to 3rd. generation B-Blocker such as Nebivolol
3.a	C08CA **Dihydropyridine Calcium Channel Blockers** e.g., Amlodipine, nifedipine, nimodipine, lercanidipine, felodipine	Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Monitor blood pressure for hypotension and orthostatic hypotension. Consider dose reduction.
3.b		Lower Limb Oedema	Diuretic	Consider switching to alternative antihypertensive therapy
4	C01AA05 **Digoxin**	Nausea	Antiemetics	Check serum digoxin level

5.a	C03C **High Ceiling (Loop) Diuretics**	Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Monitor blood pressure for hypotension and orthostatic hypotension. Consider dose reduction. May need to discontinued if evidence of ototoxicity.
5.b		LUTS/Incontinence	Antimuscarinic/B-agonist/Alpha-blocker	Once exacerbation of heart failure is ruled out, consider tapering dose and adjusting administration time.
5.c		Nausea	Antiemetics	Check serum electrolyte levels (Mg, Ca, K)
5.d		Nocturnal leg cramps	Quinine Sulphate	Check serum electrolyte levels (Mg, Ca, K)
6.a	C03A **Thiazide Diuretics**	Hyperglycaemia	Oral Hypoglycaemics	Check Serum K, consider whether switch to thiazide-like diuretic or alternative diuretic/antihypertensive depending on initial indication
6.b		Gout/Hyperuricaemia	Gout Treatment Allopurinol/Colchicine/Febuxostat	Treatment for asymptomatic hyperuricemia not indicated, consider dose reduction or alternative antihypertensive if active gout
7	C10AB **Fibrates**	Nausea/vomiting	Antiemetics	Check initial indication (hypertriglyceridemia>4.5mmol/l, pancreatitis or CHD), slow titration, take with main meal. Check LFTs and Renal function
8	H02AA **Mineralocorticoids** e.g., Fludrocortisone	Hypertension	Antihypertensives	Assess initial indication for mineralocorticoid and timing of medication
9.a	C01D **Vasodilators used in cardiac disease** e.g., nitrates	Nausea	Antiemetics	Monitor blood pressure for hypotension and orthostatic hypotension. Consider dose reduction.
9.b		Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Monitor blood pressure for hypotension and orthostatic hypotension. Consider dose reduction.
10	C02CA01 Alpha-adrenoreceptor Antagonist e.g. Prazosin	Urinary Incontinence	Oxybutynin	Consider switching to alternative antihypertensive therapy
11.a	C10AA **HMG-CoA Reductase Inhibitors** (Statins)	Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Check LFTs and CK, consider dose reduction.
11.b		Nocturnal leg cramps	Quinine Sulphate	Check LFTs and CK, consider dose reduction or challenge/rechallenge/rechallenge. If statin required consider Pravastatin or Fluvastain

Central Nervous System

	Drug A	ADE	Drug B	Suggested Action
12.a	N06DA **Anticholinesterases**, e.g., Donepezil, Rivastigmine, Galantamine	Agitation/aggression/sleep disturbance	Antipsychotic	Careful history/collateral history regarding symptoms and recent initiation/dose increase, administer with meals to avoid peak blood levels during sleep.
		GI Disturbance (Nausea/Diarrhoea)	PPI/Pro-kinetic/Acid Lowering therapy	Consider administering with meals, slow titration of Anticholinesterase
12.b			Anticholinergic anti-diarrhoeal Anticholinergic Antiemetic	
12.c		Rhinorrhoea	Rhinorrhoea Medications: First generation histamine1 (H1)-blockers, second-generation H1 blockers, nasal anticholinergics, nasal glucocorticoids, and montelukast, a leukotriene antagonist	Consider dose reduction of Anticholinesterase
12.d		Urinary Incontinence	Anticholinergic/Antimuscarinic/Mirabegron	Careful history regarding timing of urinary symptoms, avoid anticholinergic medications
13.a	N06DA **Selective Serotonin Reuptake Inhibitors** e.g., Fluoxetine, citalopram, sertraline, escitalopram	Gi Disturbance	PPI	Consider lowest effect dose with small amount of food. If ongoing consider switch to alternative antidepressant
13.b		Tremor	Benzodiazepine/Anti-Parkinson Drugs e.g., Dopamine agonists (bromocriptine, pergolide, ropinirole, rotigotine, cabergoline), Dopamine derivatives (Levodopa), Amantadine, Monoamine oxidase B derivatives (selegiline, rasagiline), Anti-cholinergic agents (biperiden, procyclidine), Propranolol	Assess polypharmacy and other causes of tremor. Use lowest effective dose.

14.a	N06AX **Selective Noradrenaline Reuptake inhibitors** e.g., Duloxetine, Venlafaxine	Hypertension	Antihypertensives	Evaluate risk/benefit of SNRI in context of cardiovascular and cerebrovascular risks, consider alternative class of antidepressant if appropriate
14.b		Tremor	Benzodiazepine/Anti-Parkinson Drugs e.g., Dopamine agonists (bromocriptine, pergolide, ropinirole, rotigotine, cabergoline), Dopamine derivatives (Levodopa), Amantadine, Monoamine oxidase B derivatives (selegiline, rasagiline), Anti-cholinergic agents (biperiden, procyclidine), Propranolol	Assess polypharmacy and other causes of tremor. Use lowest effective dose.
14.c		Migraine	Analgesia	
15.a	N06AA **Tri-cyclic antidepressants**, e.g., Amitriptyline/Nortriptyline/Doxepin	Constipation	Laxatives	Evaluate initial indication for Tri-cyclic antidepressant. Consider down titration if possible. Increase activity level, fluid intake and dietary fibre intake
15.c		Urinary Retention	Tamsulosin	Evaluate initial indication for Tri-cyclic antidepressant. Consider down titration if possible or switch to alternative antidepressant.
15.d		Cognitive impairment	Cholinesterase inhibitor	Evaluate initial indication for Tri-cyclic antidepressant. Consider down titration if possible.
16	N06AX12 **Bupropion**	Insomnia	Mirtazapine/Hypnotics	Consider morning administration and switch to sustained release or extended-release formulations.
17	N06AX05 **Trazodone**	Hypertension	Antihypertensives	Evaluate initial indication. Consider slow down titration and switch to alternative if appropriate.
18	N03AG01 **Valproic Acid**	Tremor	Anti-Parkinson Drugs e.g., dopamine agonists (bromocriptine, pergolide, ropinirole, rotigotine, cabergoline), dopamine derivatives (Levodopa), amantadine, monoamine oxidase B derivatives (selegiline, rasagiline), anti-cholinergic agents (biperiden, procyclidine), beta-blockers, primidone, gabapentin	Tremor can worsen with longer duration of therapy and higher doses, if withdrawal not appropriate, consider minimum effective dose or switch to alternative anti-epileptic, levetiracetam or carbamazepine.

19.a	N05A **Antipsychotics** e.g., haloperidol, phenothiazines, olanzapine, quetiapine risperidone, Levosulpride)	Extrapyramidal Symptoms, Parkinsonism, Movement Disorder, tremor	Anti-Parkinson Drugs e.g., dopamine agonists (bromocriptine, pergolide, ropinirole, rotigotine, cabergoline), dopamine derivatives (Levodopa), amantadine, monoamine oxidase B derivatives (selegiline, rasagiline), anti-cholinergic agents (biperiden, procyclidine)	Evaluate initial indication for antipsychotic. Consider dose reduction or switch to atypical antipsychotic/antipsychotic with lower risk.
19.b		Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Evaluate initial indication for antipsychotic. Monitor lying/standing blood pressure. Check for QTc prolongation. If Orthostatic Hypotension present, consider dose adjustment, timing adjustment and maintain adequate hydration.
20	N04BC **Dopamine Agonists**	Lower Limb Oedema	Diuretic	Consider dose reduction and compensatory increase in L-Dopa
21	N04 **Anti-Parkinson Drugs** e.g., dopamine agonists (bromocriptine, pergolide, ropinirole, rotigotine, cabergoline), dopamine derivatives (Levodopa), amantadine, monoamine oxidase B derivatives (selegiline, rasagiline), anti-cholinergic agents (biperiden, procyclidine)	Behavioural Disturbance/Psychosis	Antipsychotics	Consider stopping anticholinergic agents, dose reduction of dopaminergic agents to lowest effective dose of L-Dopa.
22	N05C **Hypnotics/Sedatives** (Z-drugs/benzodiazepines)	Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Consider reducing dose or stopping sedative/hypnotic. Monitor supine and standing blood pressure.
23	N05AN **Lithium**	Tremor	Anti-Parkinson Drugs e.g., dopamine agonists (bromocriptine, pergolide, ropinirole, rotigotine, cabergoline), dopamine derivatives (Levodopa), amantadine, monoamine oxidase B derivatives (selegiline, rasagiline), anti-cholinergic agents (biperiden, procyclidine)	Check serum lithium level, assess drugs that interact with lithium. Consider dose reduction of withdrawal if appropriate.

Gastrointestinal System

	Drug A	ADE	Drug B	Suggested Action
24.a	A03FA01/N05AB04 **Metoclopramide/Prochlorperazine**	Extrapyramidal symptoms/movement disorder/parkinsonism	Anti-Parkinson Drugs e.g., dopamine agonists (bromocriptine, pergolide, ropinirole, rotigotine, cabergoline), dopamine derivatives (Levodopa), amantadine, Monoamine oxidase B derivatives (selegiline, rasagiline), anti-cholinergic agents (biperiden, procyclidine, benztropine, trihexylphenadine), Levodopa, dopamine agonists	Consider stopping or changing to serotonin antagonist such as ondansetron.
24.b		Diarrhoea	Loperamide	
25.a	A02BC **Proton Pump Inhibitors** e.g., Pantoprazole, esomeprazole, omeprazole, rabeprazole, pantoprazole, lansoprazole	Hypomagnesemia	Magnesium replacement therapy	Evaluate initial indication for PPI, consider stopping or dose reduction, re-check serum magnesium post-cessation.
25.b		Vit B12 deficiency	Vit B12 replacement therapy	Evaluate initial indication for PPI, consider stopping or dose reduction, re-check serum B12 post-cessation
26	A06A **Drugs for Constipation**	Diarrhoea	Loperamide	Assess for overflow diarrhoea, stop drugs for constipation/reduce frequency

Respiratory System

	Drug A	ADE	Drug B	
27	R03DA **Methylxanthines** e.g., theophylline	Nausea	Metoclopramide/Antiemetics	Check serum theophylline level. Consider dose reduction/withdrawal of theophylline.
28	R03AC **Long-Acting Beta-Agonist**	Nocturnal Leg Cramps	Quinine sulphate	Check serum potassium levels, consider reduction, substitution, or discontinuation.

Musculoskeletal System

	Drug A	ADE	Drug B	
29.a	M01A **non-steroidal anti-inflammatory drugs**	Hypertension	Antihypertensives	Evaluate initial indication for NSAID, consider substitution or discontinuation on those with high cardiovascular or cerebrovascular risk.
29.b		Heartburn	PPI	Stop NSAID, if symptoms ongoing consider further investigation.
29.c		Nausea	Metoclopramide/Antiemetics	If drug cannot be reduced or discontinued try taking with water or food.
29.d		Lower Limb Oedema	Diuretic	In absence of heart failure, oedema is generally mild and tends to resolve on discontinuation of NSAID.
29.e		Dizziness	Labyrinthine sedatives (prochlorperazine/ betahistine/hyoscine/cinnarizine), antihistamines or metoclopramide	Stop NSAID, assess for evidence of ototoxicity.
30	N02BF **Gabapentinoid,** e.g., gabapentin, pregabalin	Lower Limb Oedema	Diuretic	Evaluate initial indication for Gabapentinoid, consider reducing dose, discontinuation or substitution.

31.a	H02AB **Glucocorticoids** e.g., prednisolone, hydrocortisone, dexamethasone	Uncontrolled hypertension	Antihypertensives	Use smallest effective dose of steroid at shortest duration. Consider steroid sparing agents if appropriate.
31.b		Dyspepsia	PPI	Consider drug discontinuation and investigation of underlying pathology.
31.c		Nausea	Metoclopramide/antiemetics	If drug cannot be reduced or discontinued try taking with water or food.
31.d		Psychosis	Antipsychotics	Use smallest effective dose for shortest duration possible if steroids cannot be discontinued.
31.e		Hyperglycaemia	Anti-diabetics	Monitor glucose levels/HbA1c once to steroids have stopped as antidiabetics may require down titration.
32	M05BA08 **Zoledronic Acid**	Fever	Antibiotics	Patient reassurance and education pre-administration, paracetamol if discomfort.

Endocrine System

	Drug A	**ADE**	**Drug B**	
33	A10BA02 **Metformin**	Vit B12 deficiency	Vit B12	Discontinuation of Metformin in refractory cases non- responsive to intramuscular or crystalline cobalamin may be required.

Analgesic Drugs

	Drug A	ADE	Drug B	
34.a	N02A **Opioid Analgesics**	Confusion/sedation	Rivastigmine	Reduce or discontinue opioid analgesic, ensure adequate hydration.
34.b		Urinary Retention	Tamsulosin	Assess for constipation, consider reducing or discontinuing opioid.
34.c		Delirium	Antipsychotic	Reduce or discontinue opioid analgesic, ensure adequate hydration.
35	N02BF02 **Pregabalin**	Confusion/Sedation	Rivastigmine	Review initial indication. Monitor renal function, consider reducing dose or discontinuing pregabalin.
36	N02AX02 **Tramadol**	Dizziness	Labyrinthine sedatives e.g., metoclopramide/prochlorperazine/antihistamines	Stop tramadol. Consider alternative analgesic.

Antimuscarinic/Anticholinergic Drug Burden

	Drug A	ADE	Drug B	
37	Anticholinergics*	GI disturbance	Proton pump inhibitors	Avoid strongly anticholinergic medications in older adults.
38	R06AE03/A03FA01/R06AE02 **Anticholinergic Antiemetics**	Urinary retention	Alpha blockers	Avoid strongly anticholinergic medications in older adults.

Antimicrobial Drugs

	Drug A	ADE	Drug B	
39.a	J01 **Antibiotics for systemic use**	Diarrhoea	Dicyclomine/antidiarrheal drug (e.g. loperamide, codeine phosphate)	If antiemetics are necessary, ensure drugs are not continued beyond antibiotic course duration.
39.b		Nausea	Antiemetic/metoclopramide	If antiemetics are necessary, ensure drugs are not continued beyond antibiotic course duration.
40	J01DH **Carbapenem antibiotics**	Seizure	Lorazepam/anti-epileptics	Consider switching to alternative antibiotic if appropriate. Ensure antiepileptic medications are not continued beyond antibiotic course duration.
*Anticholinergics were defined using list published by Duran et al. (2013) (198)				

5.3.4 Prevalence of Prescribing Cascades

The STOPPCascade criteria were applied to the medication lists of the 373-patient cohort described in detail in Chapter 4 of this thesis. These patients were older, multimorbid and experiencing polypharmacy and presenting to hospital with unselected acute illnesses of various kinds. A total of 70.85% percent of these participants (265 patients) were exposed to at least one potential prescribing cascade as defined by the STOPPCascade list during their admission. The median number of potential prescribing cascades per patient was 1 (Min 0, Max 13, IQR=3). 662 potential prescribing cascades were identified among these 373 patients. 125 new potential prescribing cascades occurred during the initial 72 hours of admission and 537 new potential prescribing cascades were detected in the discharge medication lists. **Table 5.2** provides specific details of the various STOPPCascade-defined potential prescribing cascades identified in this patient cohort.

The prevalence of each individual potential prescribing cascade , during admission and on discharge are shown in **Table 5.2**. The most frequently encountered potential cascade at was anticholinergics -> gastrointestinal disturbance -> proton pump inhibitor (16.06%), the most common new cascade on discharge was glucocorticoids ->uncontrolled hypertension -> new antihypertensive(s). The most frequently identified potential prescribing cascades across both timepoints are detailed in **Table 5.3.** At admission, there were 492 incidences of co-prescribing where STOPPCascade defined index drug a and drug b were co-prescribed. As the temporal relationship of drug, a and b prescription was not available at this timepoint, these could not be adjudicated as potential prescribing cascade.

Table 5.2 Prevalence of STOPPCascade defined cascades in older adults admitted acutely to hospital.

Cascade Number		New During Admission N=355	%	New on Discharge N=336	%
1.a	Angiotensin-converting enzyme inhibitors → Dizziness → Labyrinthine sedatives), antihistamines or metoclopramide	4	1.00%	7	2.00%
1.b	Angiotensin-converting enzyme inhibitors → Cough → Cough Suppressant/Inhalers/Antibiotics	16	4.00%	11	3.00%
2.a	Beta-Blocking Agents → Depression → Antidepressants	1	0.00%	46	12.00%
2.b	Beta-Blocking Agents → Dizziness → Labyrinthine sedatives antihistamines or metoclopramide	11	3.00%	12	3.00%
2.c	Beta-Blocking Agents →Sexual Dysfunction → Phosphodiesterase Inhibitors	0	0.00%	0	0.00%
3.a	Dihydropyridine Calcium Channel Blockers → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	4	1.00%	6	2.00%
3.b	Dihydropyridine Calcium Channel Blockers → Lower Limb Oedema → Diuretics	7	2.00%	26	7.00%
4	Digoxin → Nausea → Antiemetics	0	0.00%	1	0.00%
5.a	High Ceiling (Loop) Diuretics → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	6	2.00%	6	2.00%
5.b	High Ceiling (Loop) Diuretics → LUTS/Incontinence → Antimuscarinic/B-agonist/Alpha-blocker	0	0.00%	21	6.00%
5.c	High Ceiling (Loop) Diuretics → Nausea→ Antiemetics	1	0.00%	2	1.00%
5.b	High Ceiling (Loop) Diuretics → Nocturnal leg cramps → Quinine Sulphate	0	0.00%	4	1.00%
6.a	Thiazide Diuretics → Hyperglycaemia → Oral Hypoglycaemics	0	0.00%	4	1.00%
6.b	Thiazide Diuretics → Gout/Hyperuricaemia → Gout Treatment	0	0.00%	5	1.00%
7	Fibrates → Nausea/Vomiting → Antiemetics	0	0.00%	0	0.00%
8	Mineralocorticoids → Hypertension → Antihypertensives	0	0.00%	0	0.00%
9.a	Vasodilators used in cardiac disease → Nausea → Antiemetics	0	0.00%	1	0.00%
9.b	Vasodilators used in cardiac disease → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	2	1.00%	0	0.00%
10	Alpha-adrenoreceptor Antagonist → Urinary Incontinence → Oxybutynin	0	0.00%	0	0.00%
11.a	HMG CoA Reductase Inhibitors → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	9	2.00%	11	3.00%
11.b	HMG CoA Reductase Inhibitors → Nocturnal leg cramps → Quinine Sulphate	0	0.00%	6	2.00%
12.a	Anticholinesterases → Agitation/Aggression/Sleep disturbance → Antipsychotic	1	0.00%	0	0.00%
12.b	Anticholinesterases → GI Disturbance (Nausea/Diarrhoea) → PPI/Pro-kinetic, Acid lowering therapy, Anticholinergic anti-diarrhoeal, Anticholinergic antiemetic	0	0.00%	3	1.00%
12.c	Anticholinesterases → Rhinorrhoea → Rhinorrhoea Medications	0	0.00%	4	1.00%
12.d	Anticholinesterases → Urinary Incontinence → Anticholinergic/Antimuscarinic/Mirabegron	0	0.00%	1	0.00%
13.a	Selective Serotonin Reuptake Inhibitor → Gi Disturbance → PPI	0	0.00%	19	5.00%
13.b	Selective Serotonin Reuptake Inhibitor → Tremor → Benzodiazepine/Anti-Parkinson Drugs, Anti-cholinergic agents, Propranolol	0	0.00%	20	5.00%
14.a	Selective Noradrenaline Reuptake inhibitors → Hypertension → Antihypertensives	3	1.00%	31	8.00%
14.b	Selective Noradrenaline Reuptake inhibitors → Tremor → Benzodiazepine/Anti-Parkinson Drugs/ Anti-cholinergic agents or Propranolol	4	1.00%	26	7.00%
14.c	Selective Noradrenaline Reuptake inhibitors → Migraine → Analgesia	7	2.00%	18	5.00%
15.a	Tri-cyclic antidepressants →Constipation → Laxatives	2	1.00%	10	3.00%
15.b	Tri-cyclic antidepressants → Tremor → Benzodiazepine/Anti-Parkinson Drugs/ Anti-cholinergic agents or Propranolol	0	0.00%	1	0.00%
15.c	Tri-cyclic antidepressants → Migraine → Analgesia	0	0.00%	2	1.00%
16	Bupropion → Insomnia → Mirtazapine/Hypnotics	0	0.00%	0	0.00%
17	Trazodone → Hypertension → Antihypertensives	0	0.00%	0	0.00%

18	Valproic Acid →Tremor→ Anti-Parkinson Drugs, anti-cholinergic agents, propranolol, primidone, gabapentin	0	0.00%	3	1.00%
19.a	Antipsychotics → Extrapyramidal Symptoms, Parkinsonism or Tremor → Anti-Parkinson Drugs, Anti-cholinergic agents, Propranolol	0	0.00%	5	1.00%
19.b	Antipsychotics → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	1	0.00%	4	1.00%
20	Dopamine Agonists → Lower Limb Oedema → Diuretic	0	0.00%	3	1.00%
21	Anti-Parkinson Drugs → Behavioural Disturbance/Psychosis → Antipsychotics	0	0.00%	1	0.00%
22	Hypnotics/Sedatives → Dizziness → Labyrinthine sedatives, Antihistamines or Metoclopramide	2	1.00%	2	1.00%
23	Lithium → Tremor → Anti-Parkinson Drugs or anti-cholinergic agents	0	0.00%	0	0.00%
24.a	Metoclopramide/Prochlorperazine → Diarrhoea → Loperamide	0	0.00%	1	0.00%
24.b	Metoclopramide/Prochlorperazine → Extrapyramidal symptoms/Movement disorder/Parkinsonism → Anti-Parkinson Drugs or Anti-cholinergic agents	0	0.00%	0	0.00%
25.a	Proton Pump Inhibitors → Hypomagnesemia → Magnesium replacement therapy	4	1.00%	6	2.00%
25.b	Proton Pump Inhibitors → Vit B12 deficiency →Vit B12 replacement therapy	2	1.00%	14	4.00%
26	Drugs for Constipation →Diarrhoea →Loperamide	0	0.00%	1	0.00%
27	Methylxanthines →Nausea →Metoclopramide/Antiemetics	0	0.00%	0	0.00%
28	Long-Acting Beta-Agonist →Nocturnal Leg Cramps →Quinine sulphate	0	0.00%	1	0.00%
29.a	Non-steroidal anti-inflammatory drugs → Hypertension →Antihypertensives	2	1.00%	8	2.00%
29.b	Non-steroidal anti-inflammatory drugs →Heartburn →PPI	2	1.00%	10	3.00%
29.c	Non-steroidal anti-inflammatory drugs → Nausea →Metoclopramide/Antiemetics	0	0.00%	0	0.00%
29.d	Non-steroidal anti-inflammatory drugs →Lower Limb Oedema →Diuretic	3	1.00%	5	1.00%
29.e	Non-steroidal anti-inflammatory drugs → Dizziness →Labyrinthine sedatives, antihistamines or metoclopramide	0	0.00%	0	0.00%
30	Gabapentinoid →Lower Limb Oedema →Diuretic	3	1.00%	9	2.00%
31.a	Glucocorticoids →Uncontrolled hypertension →Antihypertensives	3	1.00%	52	14.00%
31.b	Glucocorticoids →Dyspepsia →PPI	2	1.00%	20	5.00%
31.c	Glucocorticoids →Nausea →Metoclopramide/antiemetics	3	1.00%	2	1.00%
31.d	Glucocorticoids → Psychosis →Antipsychotics	1	0.00%	4	1.00%
31.e	Glucocorticoids →Hyperglycaemia →Anti-diabetics	0	0.00%	0	0.00%
32	Zoledronic Acid →Fever →Antibiotics	0	0.00%	0	0.00%
33	Metformin →Vit B12 deficiency →Vit B12	1	0.00%	3	1.00%
34.a	Opioid Analgesics →Confusion/sedation →Rivastigmine	1	0.00%	4	1.00%
34.b	Opioid Analgesics →Urinary Retention →Tamsulosin	0	0.00%	11	3.00%
34.c	Opioid Analgesics →Delirium →Antipsychotic	0	0.00%	9	2.00%
35	Pregabalin →Confusion/Sedation →Rivastigmine	0	0.00%	1	0.00%
36	Tramadol→ Dizziness →Labyrinthine sedatives, antihistamines or metoclopramide	1	0.00%	0	0.00%
37	Anticholinergics → GI disturbance →PPI	10	3.00%	50	13.00%
38	Anticholinergic Antiemetics →Urinary retention →Alpha blocker	0	0.00%	2	1.00%
39.a	Antibiotics for systemic use →Diarrhoea →Dicyclomine/antidiarrheal	0	0.00%	2	1.00%
39.b	Antibiotics for systemic use → Nausea →Antiemetic/metoclopramide	6	2.00%	1	0.00%
40	Carbapenem antibiotics →Seizure →Lorazepam/anti-epileptics	0	0.00%	1	0.00%
Total Number of Potential Cascades		**125**		**537**	

Table 5.3 Most frequent prescribing cascades as defined by the STOPPCascade list

New During Admission (up to day 5)		
Cascade Number	N	%
1.b Angiotensin-converting enzyme inhibitors → Cough → Cough Suppressant/Inhalers/Antibiotics	16	4%
2.b Beta-Blocking Agents → Dizziness → Labyrinthine sedatives antihistamines or metoclopramide	11	3%
37 Anticholinergics → GI disturbance →PPI	10	3%
11.a HMG CoA Reductase Inhibitors → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	9	2%
3.b Dihydropyridine Calcium Channel Blockers → Lower Limb Oedema → Diuretics	7	2%
14.c Selective Noradrenaline Reuptake inhibitors → Migraine → Analgesia	7	2%
5.a High Ceiling (Loop) Diuretics → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	6	2%
39.b High Ceiling (Loop) Diuretics → LUTS/Incontinence → Antimuscarinic/B-agonist/Alpha-blocker	6	2%
1.a Angiotensin-converting enzyme inhibitors → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	4	1%
3.a Dihydropyridine Calcium Channel Blockers → Dizziness → Labyrinthine sedatives, antihistamines or metoclopramide	4	1%
On Discharge		
Cascade Number	N	%
31.a Glucocorticoids →Uncontrolled hypertension →Antihypertensives	52	14%
37 Anticholinergics → GI disturbance →PPI	50	13%
2.a Beta-Blocking Agents → Depression → Antidepressants	46	12%
14.a Selective Noradrenaline Reuptake inhibitors → Hypertension → Antihypertensives	31	8%
3.b Dihydropyridine Calcium Channel Blockers → Lower Limb Oedema → Diuretics	26	7%
14.b Selective Noradrenaline Reuptake inhibitors → Tremor → Benzodiazepine/Anti-Parkinson Drugs/ Anti-cholinergic agents or Propranolol	26	7%
5.b High Ceiling (Loop) Diuretics → LUTS/Incontinence → Antimuscarinic-agonist or Alpha-blocker	21	6%
13.b Selective Serotonin Reuptake Inhibitor → Tremor→ Benzodiazepine, Anti-Parkinson Drugs, Anti-cholinergic agents, Propranolol	20	5%
31.b Glucocorticoids →Dyspepsia →PPI	20	5%
13.a Selective Serotonin Reuptake Inhibitor → Gi Disturbance → PPI	19	5%

The 5 most prevalent prescribing cascades involved 5 index drugs; anticholinergics, glucocorticoids, beta-blockers, selective-noradrenaline reuptake inhibitors and calcium channel blockers.

5.5 Discussion

To detect and quantify the overall prevalence and severity of prescribing cascades, a less well-known form of potentially inappropriate prescribing, a detection tool based on published explicit prescribing cascades was needed. The STOPPCascade list attempts to address this need. We anticipated that by applying this tool prospectively, some insight into the prevalence of individual cascades among older multimorbid people in hospital would be gained, resulting in some cascades being excluded in favour of more prevalent novel cascades over time. The overall prevalence of STOPPCascade-defined potential prescribing cascades was unexpectedly high. By applying STOPPCascade criteria, 7 out of 10 older adults studied were exposed at least one potential prescribing cascade on presentation or during their hospital admission.

5.5.1 Potential Limitations in this Study

In relation to some cascades, although noted from clinical experience, they did not have any published supporting case studies and were therefore excluded based on the methodology used for this list. There is the potential that some clinically relevant prescribing cascades could be underreported in this project. This highlights the importance of clinicians identifying and publishing case reports to highlight emerging potential prescribing cascades. By including a wide literature base, the low quality of evidence for some cascades is acknowledged. Also acknowledged is the fact that the patient sample size was not specifically powered for detection of prescribing cascades, but rather for detection of drug-drug interactions. However given the relatively low overall quantity and quality of publications detailing individual prescribing cascades,

the initial evidence base examined was purposefully as broad as possible. Finally, as the cascade list was applied to a pre-existing database, the number of patients in the prevalence study was not specifically powered for the detection of cascades.

5.6 Conclusions

In the present study, I focused on potentially inappropriate and clinically relevant cascades (199). With STOPPCascade criteria, my aim was to produce a potential prescribing cascades screening tool to help clinicians to identify potential cascades in older patients' medication lists both at transitions of care and during routine medication review. I also anticipate that STOPPCascade could be used to screen large populations retrospectively for cascades and could form the basis for prospective longitudinal cohort studies where cause and effect can be more clearly adjudicated.

Given that lists of explicit prescribing cascades have been absent from the literature until recently, comparisons will inevitably be drawn between STOPPCascade and the recently published ThinkCascades tool (101). However, STOPPCascade should be seen as a companion tool that can be utilised when more in-depth exploration of cascades is required. The intention is that explicit cascades list like STOPPCascade are applied during medication review in multimorbid older people with associated polypharmacy as a means of detection of potential cascades which then require further careful analysis of prescribing sequence, drug B indication and careful consideration of drug B deprescribing, if appropriate and safe to do so.

Identification and deprescribing of potentially inappropriate medications have been shown to provide clinical benefit for affected patients through reduction in pill burden and potentially deleterious drug-drug interactions. Appropriate deprescribing of adverse medication also has an economic benefit by reducing iatrogenic morbidity and excess healthcare utilization (200-202). Given that the median number of STOPPCascade-defined potential prescribing cascades per patient was 3 in the present study, there appears to be a real clinical need to screen not only for potential adverse drug-drug interactions and excessive polypharmacy but also for potential adverse inappropriate cascades as a way of improving the safety of polypharmacy in older people with multimorbidity. It must be noted that only one of the most prevalent potential prescribing cascades identified using STOPPCascade would have been detected using ThinkCascades i.e. calcium channel blocker > pedal oedema > diuretic.

The STOPPCascade list consists of 71 explicit potential prescribing cascades in older adults. This list aims to serve as a guide to detection of true, inappropriate prescribing cascades that may occur older adults, particularly those with multimorbidity and associated polypharmacy. However, as with all explicit prescribing criteria, it is not intended to replace clinical judgement. Individual patient care goals and preferences along with potential drug-drug interactions and drug-disease interactions should be taken into account when prescribing or de-prescribing medications that may possibly represent prescribing cascades. If patients report new symptoms after commencing a new drug or recent dose change, prescribers should consider the possibility of an adverse drug reaction and carefully consider the benefits and potential hazards of

continuing therapy with the first drug before prescribing a new medication to treat the new symptoms.

CHAPTER 6

Summary & Conclusions

The work described in this thesis focused on the relationship between frailty and potentially inappropriate prescribing in older adults, acknowledging that pharmacotherapy in older people requires an understanding of the pharmacokinetic and pharmacodynamic changes that accompany the aging process. It also demands awareness of the physiological changes that could be attributed to frailty and that may predispose to adverse medication-related outcomes. For the purposes of this body of work, I expanded the definition of potentially inappropriate prescribing to include drug-drug interactions, falls risk-increasing drug (FRID) exposure and potential prescribing cascades. In total, 936 participants were studied for this thesis across three prospective, prevalence studies.

In Chapter 1, I explored the definitions of frailty and critically assessed the models and concepts of frailty in the published literature that can be used to understand and measure frailty in late life. I concluded that identification of frailty by clinicians should be seen as an important trigger for structured medication review to guide both prescriber and patient towards greater focus on individual treatment goals. I proposed that changes in frailty status or accumulation of new deficits may be attributable to medication use and should trigger further analysis of patients' pharmacotherapy including long term medications that may no longer be necessary or appropriate as a patient loses physiological reserve.

In Chapter 2, I examined the association between frailty and potentially inappropriate prescribing (PIP) as defined by STOPP/START Version 2 criteria in a population of acutely hospitalised older adults. In Chapter 3, I explored the prevalence of falls risk increasing drug (FRID) use in older people who have experienced a fall in the previous

12 months. As part of the expanding the definition of PIP in Chapter 4, I evaluated the prevalence of potential DDIs in a cohort of acutely hospitalised older adults. Finally, in Chapter 5, I described the development of an explicit list of prescribing cascades based on the published literature and expert opinion and applied this explicit cascade list to investigate the prevalence of potential cascades at admission and discharge from hospital in multimorbid older people hospitalized with acute illness. Based on the findings from the work completed in this thesis, I concluded that measured frailty is an important factor when considering new medication choices, when reviewing existing medications and when considering deprescribing decisions in older adults with limited life expectancy.

6.1 Frailty

Measured frailty was highly prevalent across all 3 prospective observational studies. Frailty was measured using the Frail-VIG index, Clinical Frailty Scale (CFS) Version 1 and Clinical Frailty Scale Version 2 (186, 203, 204). The core difference between CFS version 1 and CFS version 2 was the recategorization of CFS level 4 from "vulnerable" to "living with mild frailty", this had the effect of increasing the prevalence of frailty across the population of older adults in the final study where CFS version 2 was used to identify frailty. There were also some variabilities in the prevalence of frailty and severe frailty depending on whether the CFS or the Frail-VIG index was used in Chapter 2. The prevalence of frailty varied from 52.6% (Frail-VIG, Chapter 2) to 74.8% in Chapter 4 (CFS Version 2). There was a significant variation in the prevalence of severe frailty across the studies, with a range of 2.3% (Frail-VIG)

to 14.2% (CFS, drug-drug interactions study). This may possibly be explained by a change in infection control restrictions observed in the latter study, allowing the recruitment of frailer participants if a proxy was available to provide consent to participation. It does however highlight the importance of selecting a frailty measurement tool that has adequate sensitivity to identify severely frail people for the purpose of guiding deprescribing decisions.

Table 6.1. Prevalence of frailty across the three studies included in this thesis.

Study Name	**Frailty Prevalence Frail-VIG Index**	**Frailty Prevalence CFS**
Measured Frailty as a Predictor of Potentially Inappropriate Prescribing in Hospitalised Older Adults	52.6%	64.1%
Falls Risk Increasing Drugs in Frail Older Adults Experiencing Falls		55.9%
Potentially Clinically Relevant Drug-Drug Interactions in Older People		74.8%*

*CFS Version 2 used with CFS category 4 taken as threshold for very mild frailty.

Applying the CFS to a nationally representative sample of community dwelling older adults from the TILDA study, O'Halloran et al. (2021) found 73.6% of adults aged 65 years and over were classified as very fit, fit or managing well, while 16% were considered vulnerable or living with very mild frailty. The remaining 10.5% were classified as having some degree of frailty; within the latter, mild frailty was most

prevalent (5.5%), followed by moderate frailty (4.3%) and severe frailty (0.7%). This study did not identify any participants that were classified as severely frail or terminally ill.

Another study focusing on frailty in all adult patients admitted to an acute hospital in Ireland demonstrated a frailty prevalence of 60% in patients over 65 years (205). These results aligned with a pooled prevalence estimate of 47.4% in an international systematic review and meta-analysis of hospitalised adults aged ≥ 65 years of age (206).

The contrasting levels of frailty prevalence between community dwelling older adults and those who have been admitted acutely to hospital demonstrates the need for developing capacity within the acute services that is attuned to older people to prevent transitions to higher levels of frailty and dependence post-admission. This capacity could be developed by using 'front door' emergency department frailty teams and rapid direct access to specialist geriatric wards.

6.2 Polypharmacy

As predicted from my review of previous literature, there was a high prevalence of polypharmacy within all three patient populations studied in this thesis.

In chapter 2, polypharmacy was highly prevalent in the sample with a mean of 8.90 medications prescribed daily (SD ± 3.92). Not surprisingly, 92.7% to 97.0% of frail participants (as defined by CFS or -Frail-VIG) were prescribed 5 or more daily medications on admission to hospital. The exposure of older hospitalised adults to polypharmacy (≥5 daily medications) and hyperpolypharmacy (≥10 daily

medications) was also highly prevalent: 50% of patients assessed were prescribed 5-9 daily medications and 38% of patients were prescribed ≥10 daily medications in the overall sample. Polypharmacy was shown to be significantly associated with increased risk of potentially inappropriate prescribing, consistent with previous published studies.

Over half of the participants studied in chapter 3 (51.4%) experienced polypharmacy defined as ≥5 daily medications and over a third (37.4%) of participants were taking ≥10 daily medications.

There was also a high prevalence of polypharmacy among the participants described in chapter 4, with an average (SD) of 8.08 (3.45) medications per participant at admission and 8.74 (3.34) long-term daily medications prescribed on discharge. Overall, 318 of the 373 participants (85.3%) experienced polypharmacy (≥5 daily medications) and 114 participants (30.6%) were taking ≥10 daily medications i.e. hyper-polypharmacy.

Polypharmacy is the direct pharmacotherapeutic consequence of multimorbidity and frailty with a bidirectional relationship being described previously along with increased risk of death, falls, hospitalisation and cognitive decline (208-210). Previous meta-analysis has demonstrated a wide ranging prevalence of polypharmacy (2-6% to 86-6%) (211) with trends of increasing polypharmacy and hyperpolypharmacy in evident in primary care (212) . Based on the findings of this thesis, I propose that regular (such as 3- to 6-monthly) focused medication review and careful re-assessment of indication, therapeutic value and appropriateness of all prescriptions should be

undertaken in all older people with multimorbidity and associated polypharmacy. Changes in frailty status should, I propose, serve as a trigger to further interspersed medication review.

6.3 Potentially inappropriate prescribing: PIMs, PPOs and DDIs

From my assessment of potentially inappropriate prescribing using various tools, it is clearly an ongoing issue for older adults presenting to hospital with acute unselected illness. Potentially inappropriate medication (PIM) use continues to affect a substantial proportion of the older people included in this thesis. According to STOPP/START Version 2 criteria, (195) one or more PIMs were identified in 76% of patients in my study, with just under half of patients (49%) having 2 or more STOPP-defined PIMs. Applying START Version 2 criteria, almost half (48.4%) of all participants were found to have ≥1 potential prescribing omission (PPO). Not surprisingly, the median numbers of PIMs and PPOs were significantly higher in the frailer patients. A significant, positive correlation between Frail-VIG score and number of PIMs was demonstrated, this correlation was maintained when controlling for number of medications, age and co-morbidities. Frailty measured using the CFS also had a significant positive association with PIMs, PPOs and total PIP after adjustment for confounders.

In Chapter 3, one hundred and forty-six patients (81.6% of the total cohort studied) who had a fall in the previous 12 months were taking at least one STOPPFall-defined FRID. One in 10 older adults experiencing a fall was using four or more FRIDs. Once again, it was noted that frailer older adults were exposed to more FRIDs than non-frail

patients. Evaluating the prevalence of potentially relevant drug-drug interactions, I found that over one third (38.9%) of acutely hospitalized older patients were exposed to ≥1 potentially relevant DDIs based on the validated list of DDIs in older adults. At discharge, there was a reduction in potential DDI prevalence to 27.13%.

The cost of avoidable healthcare PIP-related expenditure has previously been reported to range from €18.66-€1449.05 per year. Also, older adults taking STOPP criteria-defined PIMs have more frequent healthcare utilisation and greater overall healthcare costs than age-matched adults who were not prescribed STOPP criteria PIMs. In one study, this difference was estimated at €1958 (€1428–€2616) vs €881 (€817–€1167), p=0.002) per annum (104). Consequently, cost-effective structured screening for PIP in all its manifestations should be implemented at admission, discharge and when a change in frailty status is identified.

6.4 Potential Harm

When I compared the common PIMs encountered across all 3 prospective studies, a particular pattern of adverse medication was evident relating to psychotropic drugs. The most frequently encountered STOPP version 2 PIMs were (i) the prescription of any drug without documented evidence-based clinical indication, (ii) the use of hypnotic z-drugs that may increase the risk of falls in older people, (iii) benzodiazepine use beyond 4 weeks, (iv) drug prescription beyond recommended duration, and (v) neuroleptic antipsychotics as hypnotics, unless sleep disorder is due to psychosis or dementia. The most frequently prescribed FRID class was antidepressants with a prevalence of 35.75%. Therefore, careful focused review of

psychotropic medication indication and dose are particularly important in older people, particularly those who present with falls either in primary care or in hospital.

Although I did not detect a significant difference in FRIDs prevalence among non-frail fallers compared to frail fallers as two categorical patient groups, severely frail patients as a subgroup had 12-fold increased odds of being prescribed one or more FRIDs compared to non-frail patients.

The most frequently encountered DDI at admission (based on an international consensus list of potentially clinically significant drug-drug interactions in older people (213)) was the concomitant use of ≥ 3 centrally acting drugs in 46 patients, (12.3%), decreasing to 8.6% on discharge. DDIs involving drugs that may adversely affect serum potassium were the next most prevalent interactions at admission. There were 36 admissions (9.6%) possibly attributable to a potential harm from an interaction identified using the DDI list. The most frequent medication-related reason for acute hospitalization was a fall, fracture or impaired cognition linked to ≥3 centrally acting drugs. Out of 46 cases where DDIs were identified, fourteen could possibly be attributed to an International Consensus List-defined DDI. Three admissions could be attributed to the concomitant use of an SSRI and a thiazide or loop diuretic and three more admissions to deterioration of renal function, hyperkalaemia and congestive heart failure in the context of concomitant diuretic and oral NSAID use. However, potential DDIs that could lead to hyperkalaemia, while prevalent, did not appear to lead directly to acute admissions.

One of the areas for concern generated by this thesis is the high utilisation of centrally acting drugs, antidepressants, benzodiazepine and hypnotic drugs.

It is widely acknowledged that compared to robust older adults, frailer individuals are exposed to greater levels of polypharmacy and have greater exposure to high-risk medication regimes leading to an increased risk of prescribing cascades (80, 87). That being said, there is a general lack of evidence regarding to overall prevalence of prescribing cascades. I propose that by applying the STOPPCascade tool prospectively, greater insight into the prevalence of the avoidable prescribing cascades and resultant inappropriate polypharmacy will accrue. Prospective application of explicit prescribing criteria for older patients and routine medication review at every healthcare interaction could have the potential to reduce medication related harm.

6.5 The Impact of COVID-19 on this research

This research was commenced in July 2020 when Ireland was experiencing the first wave of the Covid-19 pandemic. On the week this research was commenced, the Irish Government postponed the easing of Covid-19 restrictions to level 4 (bars, hotels, nightclubs and casinos would remain closed with food serving establishments allowed to remain open to 11pm). Face coverings were mandatory in all healthcare settings and shortly afterwards would become mandatory in all shops and shopping centres, public transport. UCC had instituted a work-from-home policy. Ethics applications were changed to electronic version and meetings held remotely.

By the time recruitment began for the studies described in this thesis, Covid-19 numbers and deaths had begun to increase despite government restrictions. After a risk assessment was carried out in Cork University Hospital, permission was granted by hospital management to continue research and patient recruitment. At various time points during my thesis studies, infection control restrictions meant that family members of delirious patients and those with dementia were not permitted to accompany them to hospital. Recruitment was also suspended on two occasions when Covid-19 outbreaks within the hospital resulted in ward closures and halted the safe recruitment of patients for the studies described in this thesis.

The impact of Covid-19 infection itself, along with the unintended consequences of lockdowns and restrictions of movement are better understood in the pandemic's aftermath. While it stands to reason that transitions in frailty status have been well-recognized in older people who survived Covid-19 infection and hospitalisation (214, 215), evidence is now emerging about the impact of reduced social interaction and restrictions of movement resulting in increasing frailty prevalence compared to pre-pandemic years (216). A meta-analysis of 8 studies showed that increases in CFS rating was associated with increases in mortality in a linear fashion i.e. each 1-point increase in CFS associated with a 12% increase in mortality (OR 1.12 (1.04, 1.20), p = 0.003; I^2: 77.3%) (217)

Sadly, some of the participants included in the studies described in this thesis died from Covid-19 during their index acute admission. Many staff who were involved in the care of patients also contracted Covid-19 infection.

6.6 Limitations of This Work

There are some limitations to the studies described in this thesis. As previously discussed, participant recruitment for all three observational studies was carried out during the Covid-19 pandemic. I was concerned that this could have led to potential bias in the degree of frailty observed amongst enrolled participants. Infection control guidelines affecting access to potential participants and limitations of next of kin or potential proxies could have caused a degree of skew in the levels of frailty observed towards less frail participants than are usually encountered among unselected acutely ill patients presenting to hospital. Furthermore, there was a global reduction in the number of older people presenting to Emergency Departments during the pandemic (218, 219). Nevertheless, when I compared the mean level of frailty within the enrolled patient cohorts, they were comparable to the frailty levels observed in previous studies (136). As previously noted, most of the data collections in these studies (with the exception of Chapter 3) were carried out by a single researcher, and formal data validation was not performed. This leads to the potential for researcher bias. To mitigate this potential bias, data collection was carried out using standardised data collection proforma sheets. Future research should include data validation using a sample of participants' data collected by 2 researchers independently. Another potential limitation of these studies is that they were carried out in the same geographical region, with all enrolment sites affiliated with the same large-scale level 4 hospital. Consequently, trends in prescribing observed might not be fully generalisable to other locations or centres. In addition, the observational nature of

these studies means that whilst associations have been demonstrated, causal relationships cannot necessarily be inferred.

Finally, in comparison to other explicit deprescribing lists such as STOPP/START, STOPPFrail and STOPPFall, I did not apply a conventional Delphi methodology in the development of the STOPPCascade list. Instead, the list was based on the expert consensus opinion of three experienced clinicians in relation to published cascades leaving greater room for potential adjudicator bias.

6.7 Directions for Future Research

Structured medication review has been shown to lead to reduced inappropriate medication and ADRs in older people and is likely to be cost effective (220-222). Based on the findings of this thesis, it is clear that further studies are required to investigate the effect of deprescribing of falls risk increasing drugs (FRIDs), focusing on severely frail fallers in particular with longitudinal follow up, applying a randomised controlled trial methodology. While deprescribing should be included as part of a structured multi-faceted intervention to reduce falls in all older adults, a previous meta-analysis has shown that severely frail older adults may benefit the most from medication review even as a single time point intervention (223).

There is also scope for further longitudinal studies measuring progressions in frailty status in multimorbid older people who are exposed to varying levels of polypharmacy with inherent risks of PIMs. Ongoing measurement of frailty at times of onset of new frailty syndromes (e.g. delirium new onset of incontinence, recent falls) would allow researchers to develop greater understanding into which specific PIMs lead directly to

increased frailty. Another recent meta-analysis has shown a greater association between neurological system PIMs and increased frailty in older people (224). These PIMs were highly prevalent across all three point-prevalence studies included in this thesis. Longitudinal follow up study of emergent frailty in pre-frail and non-frail older patients who are exposed to polypharmacy, DDIs, FRIDs and cascades versus those who are not exposed is indicated.

In addition, further assessment of the STOPPCascade list inter-rater reliability is warranted as well as evaluation of the performance of the tool across diverse clinical settings such as primary care and long stay/residential settings and in different geographical areas.

Another potential direction for further research would be to assess the effect of deprescribing interventions targeted at the level of the prescriber. To date, deprescribing trials have not shown improvement in participant outcomes such as hospital admissions or ADRs (225, 226). There is a need for a well-designed randomized trial of a prescriber-level intervention to assess whether randomizing prescribers to a structured deprescribing education programme compared to current standard pharmaceutical care results in a reduced number of key adverse clinical outcomes such as falls, frailty status, incident ADRs and unscheduled hospital admissions.

Based on the findings of this thesis, I recommend formal frailty screening in all older adults presenting to acute hospitals and heightened vigilance for ADRs which may overlap with or mimic frailty syndromes. This work has shown a clinically important

effect of frailty on potentially inappropriate prescribing. This finding has the potential to provide better pharmaceutical care of multimorbid older patients. In the context of rapid and major demographic change in all populations globally, the avoidance of adverse pharmacotherapy in multimorbid older people will become increasingly important for valid clinical and economic reasons in the coming decades.

References

1. He W, Goodkind D, Kowal P. An Aging World Washington: United States Cenus Bureau; 2015 [Available from: https://www.census.gov/library/publications/2016/demo/P95-16-1.html.
2. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62-7.
3. Aisling O'Halloran CM, Siobhan Scarlett, Lorna Roe,, Kenny RR-OaRA. TILDA Report on Population Estimates of Physical Frailty in Ireland to Inform Demographics for Over 50s in Ireland during the COVID-19 Pandemic. Dublin; 2020.
4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older Adults: Evidence for a Phenotype. The Journals of Gerontology: Series A. 2001;56(3):M146-M57.
5. Fried TR, Mor V. Frailty and Hospitalization of Long-Term Stay Nursing Home Residents. Journal of the American Geriatrics Society. 1997;45(3):265-9.
6. Liu X, Ng DH-M, Seah JW-T, Munro YL, Wee S-L. Update on Interventions to Prevent or Reduce Frailty in Community-Dwelling Older Adults: a Scoping Review and Community Translation. Current Geriatrics Reports. 2019;8(2):72-86.
7. Apóstolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, et al. Predicting risk and outcomes for frail older adults: an umbrella review of frailty screening tools. JBI Database System Rev Implement Rep. 2017;15(4):1154-208.
8. Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial. Am J Med. 2015;128(11):1225-36.e1.
9. Cohen HJ, Feussner JR, Weinberger M, Carnes M, Hamdy RC, Hsieh F, et al. A controlled trial of inpatient and outpatient geriatric evaluation and management. N Engl J Med. 2002;346(12):905-12.
10. Gené Huguet L, Navarro González M, Kostov B, Ortega Carmona M, Colungo Francia C, Carpallo Nieto M, et al. Pre Frail 80: Multifactorial Intervention to Prevent Progression of Pre-Frailty to Frailty in the Elderly. J Nutr Health Aging. 2018;22(10):1266-74.
11. Mekonnen AB, Redley B, de Courten B, Manias E. Potentially inappropriate prescribing and its associations with health-related and system-related outcomes in hospitalised older adults: A systematic review and meta-analysis. British Journal of Clinical Pharmacology. 2021;87(11):4150-72.
12. Xue L, Boudreau RM, Donohue JM, Zgibor JC, Marcum ZA, Costacou T, et al. Persistent polypharmacy and fall injury risk: the Health, Aging and Body Composition Study. BMC Geriatrics. 2021;21(1):710.
13. Davies LE, Spiers G, Kingston A, Todd A, Adamson J, Hanratty B. Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews. Journal of the American Medical Directors Association. 2020;21(2):181-7.
14. Turner G, Clegg A. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. Age and Ageing. 2014;43(6):744-7.

15. Wong YG, Hang J-A, Francis-Coad J, Hill A-M. Using comprehensive geriatric assessment for older adults undertaking a facility-based transition care program to evaluate functional outcomes: a feasibility study. BMC Geriatrics. 2022;22(1):598.
16. McIsaac DI, MacDonald DB, Aucoin SD. Frailty for Perioperative Clinicians: A Narrative Review. Anesthesia & Analgesia. 2020;130(6):1450-60.
17. Engel JS, Tran J, Khalil N, Hladkowicz E, Lalu MM, Huang A, et al. A systematic review of perioperative clinical practice guidelines for care of older adults living with frailty. British Journal of Anaesthesia. 2023;130(3):262-71.
18. Ruiz JG, Dent E, Morley JE, Merchant RA, Beilby J, Beard J, et al. Screening for and Managing the Person with Frailty in Primary Care: ICFSR Consensus Guidelines. The journal of nutrition, health & aging. 2020;24(9):920-7.
19. Moloney E, O'Donovan MR, Carpenter CR, Salvi F, Dent E, Mooijaart S, et al. Core requirements of frailty screening in the emergency department: an international Delphi consensus study. Age and Ageing. 2024;53(2).
20. Muscedere J, Waters B, Varambally A, Bagshaw SM, Boyd JG, Maslove D, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Medicine. 2017;43(8):1105-22.
21. Zampieri FG, Iwashyna TJ, Viglianti EM, Taniguchi LU, Viana WN, Costa R, et al. Association of frailty with short-term outcomes, organ support and resource use in critically ill patients. Intensive Care Medicine. 2018;44(9):1512-20.
22. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. CA: A Cancer Journal for Clinicians. 2017;67(5):362-77.
23. Hamlyn J, Lowry C, Jackson TA, Welch C. Outcomes in adults living with frailty receiving cardiopulmonary resuscitation: A systematic review and meta-analysis. Resusc Plus. 2022;11:100266.
24. Sezgin D, Liew A, O'Donovan MR, O'Caoimh R. Pre-frailty as a multi-dimensional construct: A systematic review of definitions in the scientific literature. Geriatric Nursing. 2020;41(2):139-46.
25. Walters K, Frost R, Kharicha K, Avgerinou C, Gardner B, Ricciardi F, et al. Home-based health promotion for older people with mild frailty: the HomeHealth intervention development and feasibility RCT. Health Technology Assessment (Winchester, England). 2017;21(73):1.
26. Salive ME. Multimorbidity in older adults. Epidemiologic reviews. 2013;35(1):75-83.
27. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal. 2005;173(5):489.
28. Darvall JN, Loth J, Bose T, Braat S, De Silva A, Story DA, et al. Accuracy of the Clinical Frailty Scale for perioperative frailty screening: a prospective observational study. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2020;67(6):694-705.
29. Ko FC. Preoperative Frailty Evaluation: A Promising Risk-stratification Tool in Older Adults Undergoing General Surgery. Clin Ther. 2019;41(3):387-99.
30. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323-36.
31. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatrics. 2008;8(1):24.

32. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. The journal of nutrition, health & aging. 2012;16(7):601-8.
33. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age and ageing. 2006;35(5):526-9.
34. Raîche M, Hébert R, Dubois M-F. PRISMA-7: A case-finding tool to identify older adults with moderate to severe disabilities. Archives of Gerontology and Geriatrics. 2008;47(1):9-18.
35. Jones DM, Song X, Rockwood K. Operationalizing a Frailty Index from a Standardized Comprehensive Geriatric Assessment. Journal of the American Geriatrics Society. 2004;52(11):1929-33.
36. Steverink N. Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator). The gerontologist. 2001;41:236.
37. Amblàs-Novellas J, Martori JC, Espaulella J, Oller R, Molist-Brunet N, Inzitari M, et al. Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. BMC Geriatrics. 2018;18(1):29.
38. Faller JW, Pereira DdN, de Souza S, Nampo FK, Orlandi FdS, Matumoto S. Instruments for the detection of frailty syndrome in older adults: A systematic review. PLoS One. 2019;14(4):e0216166-e.
39. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019;394(10206):1376-86.
40. O'Caoimh R, Sezgin D, O'Donovan MR, Molloy DW, Clegg A, Rockwood K, et al. Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. Age and ageing. 2021;50(1):96-104.
41. O'Caoimh R, Galluzzo L, Rodríguez-Laso Á, Van der Heyden J, Ranhoff AH, Lamprini-Koula M, et al. Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: a systematic review and meta-analysis. Annali dell'Istituto superiore di sanita. 2018;54(3):226-38.
42. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue Q-L, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. Ageing Research Reviews. 2016;26:53-61.
43. Andrew Clegg, Kenneth Rockwood, Roman Romero-Ortuno, Conal Cunningham. Friailty. 2021. In: British Geriatrics Society, Silver Book II [Internet]. British Geriatrics Society. Available from: https://www.bgs.org.uk/resources/silver-book-ii-frailty.
44. Rockwood K, Mitnitski AB, MacKnight C. Some mathematical models of frailty and their clinical implications. Reviews in Clinical Gerontology. 2002;12(2):109.
45. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and ageing. 2016;45(3):353-60.
46. Torné A, Puigoriol E, Zabaleta-del-Olmo E, Zamora-Sánchez J-J, Santaeugènia S, Amblàs-Novellas J. Reliability, Validity, and Feasibility of the Frail-VIG Index. International Journal of Environmental Research and Public Health. 2021;18(10):5187.
47. León-Ramón S, Navarro-Flores E, Losa-Iglesias ME, Becerro-de-Bengoa-Vallejo R, Jiménez-Cebrián AM, Romero-Morales C, et al. Reliability of Frail and Barthel Tests for Detecting Frailty in Palliative Oncological Patients in a Home Hospitalization Unit: A Comparative Study. Life. 2022;12(2):286.

48. Kaeppeli T, Rueegg M, Dreher-Hummel T, Brabrand M, Kabell-Nissen S, Carpenter CR, et al. Validation of the Clinical Frailty Scale for Prediction of Thirty-Day Mortality in the Emergency Department. Ann Emerg Med. 2020;76(3):291-300.
49. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the Clinical Frailty Scale. BMC Geriatrics. 2020;20(1):393.
50. Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. Can Geriatr J. 2020;23(3):210-5.
51. González-Vaca J, de la Rica-Escuín M, Silva-Iglesias M, Arjonilla-García MD, Varela-Pérez R, Oliver-Carbonell JL, et al. Frailty in INstitutionalized older adults from ALbacete. The FINAL Study: rationale, design, methodology, prevalence and attributes. Maturitas. 2014;77(1):78-84.
52. Dorner T, Luger E, Tschinderle J, Stein K, Haider S, Kapan A, et al. Association between nutritional status (MNA®-SF) and frailty (SHARE-FI) in acute hospitalised elderly patients. The journal of nutrition, health & aging. 2014;18(3):264-9.
53. Peters LL, Boter H, Buskens E, Slaets JPJ. Measurement Properties of the Groningen Frailty Indicator in Home-Dwelling and Institutionalized Elderly People. Journal of the American Medical Directors Association. 2012;13(6):546-51.
54. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review. Journal of the American Geriatrics Society. 2012;60(8):1487-92.
55. Martínez-Velilla N, Herce PA, Herrero ÁC, Gutiérrez-Valencia M, Sáez de Asteasu ML, Mateos AS, et al. Heterogeneity of Different Tools for Detecting the Prevalence of Frailty in Nursing Homes: Feasibility and Meaning of Different Approaches. Journal of the American Medical Directors Association. 2017;18(10):898.e1-.e8.
56. Ofori-Asenso R, Chin KL, Mazidi M, Zomer E, Ilomaki J, Zullo AR, et al. Global Incidence of Frailty and Prefrailty Among Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. JAMA Network Open. 2019;2(8):e198398-e.
57. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research Agenda for Frailty in Older Adults: Toward a Better Understanding of Physiology and Etiology: Summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. Journal of the American Geriatrics Society. 2006;54(6):991-1001.
58. Fried LF, Lee JS, Shlipak M, Chertow GM, Green C, Ding J, et al. Chronic kidney disease and functional limitation in older people: health, aging and body composition study. Journal of the American Geriatrics Society. 2006;54(5):750-6.
59. Montesanto A, De Rango F, Berardelli M, Mari V, Lattanzio F, Passarino G, et al. Glomerular filtration rate in the elderly and in the oldest old: correlation with frailty and mortality. AGE. 2014;36(3):9641.
60. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Current medicinal chemistry. 2010;17(6):571-84.
61. Gnjidic D, Hilmer SN. Potential contribution of medications to frailty. Journal of the American Geriatrics Society. 2012;60(2):401-.
62. Hilmer SN, Kirkpatrick CMJ. New Horizons in the impact of frailty on pharmacokinetics: latest developments. Age Ageing. 2021;50(4):1054-63.

63. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and ageing. 2014;44(2):213-8.
64. O'Mahony D, Cherubini A, Guiteras AR, Denkinger M, Beuscart J-B, Onder G, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. European Geriatric Medicine. 2023;14(4):625-32.
65. Lavan AH, Gallagher P, Parsons C, O'Mahony D. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age and Ageing. 2017;46(4):600-7.
66. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit Criteria for Determining Inappropriate Medication Use in Nursing Home Residents. Archives of Internal Medicine. 1991;151(9):1825-32.
67. American Geriatrics Society Beers Criteria Update Expert Panel, Fick DM, Semla TP, Steinman M, Beizer J, Brandt N, et al. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society. 2019;67(4):674-94.
68. Panel BtAGSBCUE. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society. 2023;71(7):2052-81.
69. Laroche M-L, Charmes J-P, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. European Journal of Clinical Pharmacology. 2007;63(8):725-31.
70. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. European Journal of Clinical Pharmacology. 2015;71(7):861-75.
71. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. Journal of Clinical Epidemiology. 1992;45(10):1045-51.
72. Lewis T. Using the NO TEARS tool for medication review. BMJ. 2004;329(7463):434.
73. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230-.
74. Kennel PJ, Kneifati-Hayek J, Bryan J, Mehta K, Banerjee S, Sobol I, et al. Prevalence and Determinants of Hyperpolypharmacy in Adults with Heart Failure. Journal of Cardiac Failure. 2018;24(8, Supplement):S33.
75. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. Journal of the American Medical Directors Association. 2015;16(6):535. e1-. e12.
76. Hammond T, Wilson A. Polypharmacy and falls in the elderly: a literature review. Nursing and midwifery studies. 2013;2(2):171.
77. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert opinion on drug safety. 2014;13(1):57-65.
78. Gómez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-León J. Polypharmacy in the elderly: a marker of increased risk of mortality in a population-based prospective study (NEDICES). Gerontology. 2015;61(4):301-9.
79. Jyrkkä J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs & aging. 2009;26:1039-48.

80. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. Journal of Clinical Epidemiology. 2012;65(9):989-95.
81. Milton JC, Hill-Smith I, Jackson SHD. Prescribing for older people. BMJ. 2008;336(7644):606-9.
82. Duerden M, Avery T, Payne R. The Kings Fund. Polypharmacy and medicines optimisation. Making it safe and sound. 2013.
83. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. BMJ. 1997;315(7115):1096-9.
84. Rochon PA, Gurwitz JH. The prescribing cascade revisited. The Lancet. 2017;389(10081):1778-80.
85. Cahir C, Fahey T, Teeling M, Teljeur C, Feely J, Bennett K. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. Br J Clin Pharmacol. 2010;69(5):543-52.
86. Black CD, Thavorn K, Coyle D, Bjerre LM. The Health System Costs of Potentially Inappropriate Prescribing: A Population-Based, Retrospective Cohort Study Using Linked Health Administrative Databases in Ontario, Canada. Pharmacoecon Open. 2020;4(1):27-36.
87. Bennett A, Gnjidic D, Gillett M, Carroll P, Matthews S, Johnell K, et al. Prevalence and impact of fall-risk-increasing drugs, polypharmacy, and drug–drug interactions in robust versus frail hospitalised falls patients: a prospective cohort study. Drugs & aging. 2014;31:225-32.
88. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. British Medical Journal Publishing Group; 2015.
89. Sharifi H, Hasanloei M, Mahmoudi J. Polypharmacy-induced drug-drug interactions; threats to patient safety. Drug research. 2014;64(12):633-7.
90. Crome P, Lally F, Cherubini A, Oristrell J, Beswick AD, Clarfield AM, et al. Exclusion of Older People from Clinical Trials. Drugs & Aging. 2011;28(8):667-77.
91. Konrat C, Boutron I, Trinquart L, Auleley G-R, Ricordeau P, Ravaud P. Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. PloS one. 2012;7(3):e33559.
92. van Marum RJ. Underrepresentation of the elderly in clinical trials, time for action. British Journal of Clinical Pharmacology. 2020;86(10):2014.
93. Veronese N, Petrovic M, Benetos A, Denkinger M, Gudmundsson A, Knol W, et al. Underrepresentation of older adults in clinical trials on COVID-19 vaccines: a systematic review. Ageing Research Reviews. 2021;71:101455.
94. Doherty AS, Shahid F, Moriarty F, Boland F, Clyne B, Dreischulte T, et al. Prescribing cascades in community-dwelling adults: A systematic review. Pharmacology Research & Perspectives. 2022;10(5):e01008.
95. Read SH, Giannakeas V, Pop P, Bronskill SE, Herrmann N, Chen S, et al. Evidence of a gabapentinoid and diuretic prescribing cascade among older adults with lower back pain. J Am Geriatr Soc. 2021;69(10):2842-50.
96. Savage RD, Visentin JD, Bronskill SE, Wang X, Gruneir A, Giannakeas V, et al. Evaluation of a Common Prescribing Cascade of Calcium Channel Blockers and Diuretics in Older Adults With Hypertension. JAMA Intern Med. 2020;180(5):643-51.

97. Gill SS, Mamdani M, Naglie G, Streiner DL, Bronskill SE, Kopp A, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. Arch Intern Med. 2005;165(7):808-13.
98. Hallas J. Evidence of Depression Provoked by Cardiovascular Medication: A Prescription Sequence Symmetry Analysis. Epidemiology. 1996;7(5).
99. Piggott KL, Mehta N, Wong CL, Rochon PA. Using a clinical process map to identify prescribing cascades in your patient. Bmj. 2020;368:m261.
100. Morris EJ, Hollmann J, Hofer A-K, Bhagwandass H, Oueini R, Adkins LE, et al. Evaluating the use of prescription sequence symmetry analysis as a pharmacovigilance tool: A scoping review. Research in Social and Administrative Pharmacy. 2021.
101. McCarthy LM, Savage R, Dalton K, Mason R, Li J, Lawson A, et al. ThinkCascades: A Tool for Identifying Clinically Important Prescribing Cascades Affecting Older People. Drugs Aging. 2022;39(10):829-40.
102. Cahir C, Fahey T, Teeling M, Teljeur C, Feely J, Bennett K. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. British Journal of Clinical Pharmacology. 2010;69(5):543-52.
103. Mucherino S, Casula M, Galimberti F, Guarino I, Olmastroni E, Tragni E, et al. The Effectiveness of Interventions to Evaluate and Reduce Healthcare Costs of Potentially Inappropriate Prescriptions among the Older Adults: A Systematic Review. International Journal of Environmental Research and Public Health. 2022;19(11):6724.
104. Robinson EG, Hedna K, Hakkarainen KM, Gyllensten H. Healthcare costs of adverse drug reactions and potentially inappropriate prescribing in older adults: a population-based study. BMJ Open. 2022;12(9):e062589.
105. Organization WH. International drug monitoring: the role of national centres, report of a WHO meeting [held in Geneva from 20 to 25 September 1971]: World Health Organization; 1972.
106. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. The Lancet. 2000;356(9237):1255-9.
107. Parliament E, December Co. Directive 2010/84/EU of The European Parliament and of the Council of 15 December 2010, amending, as regards to pharmacovigilance, Directive 2001/83/EC on the Community Code relating to medicinal products for human use. 2010.
108. Davies EA, O'Mahony MS. Adverse drug reactions in special populations – the elderly. British Journal of Clinical Pharmacology. 2015;80(4):796-807.
109. Corsonello A, Pedone C, Lattanzio F, Onder G, Incalzi RA. Association between Glomerular Filtration Rate and Adverse Drug Reactions in Elderly Hospitalized Patients. Drugs & Aging. 2011;28(5):379-90.
110. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PloS one. 2014;9(7):e102149.
111. Corsonello A, Pedone C, Corica F, Incalzi RA. Polypharmacy in elderly patients at discharge from the acute care hospital. Therapeutics and clinical risk management. 2007;3(1):197.
112. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Medicine. 2015;13(1):74.
113. Johnell K, Klarin I. The Relationship between Number of Drugs and Potential Drug-Drug Interactions in the Elderly. Drug Safety. 2007;30(10):911-8.

114. Aapro MS, Köhne C-H, Cohen HJ, Extermann M. Never Too Old? Age Should Not Be a Barrier to Enrollment in Cancer Clinical Trials. The Oncologist. 2005;10(3):198-204.
115. Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquín B, Sánchez-Castellano C, Sánchez-García E. Exclusion of Older Adults from Ongoing Clinical Trials About Type 2 Diabetes Mellitus. Journal of the American Geriatrics Society. 2013;61(5):734-8.
116. Bergen G, Stevens MR, Burns ER. Falls and Fall Injuries Among Adults Aged ≥65 Years - United States, 2014. MMWR Morb Mortal Wkly Rep. 2016;65(37):993-8.
117. CDC. Injury Prevention & Control. Keep on your feet-Preventing Older Adult Falls.
118. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. Journal of the American Medical Directors Association. 2018;19(4):371.e1-.e9.
119. Seppala LJ, van de Glind EM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink AM, et al. Fall-risk-increasing drugs: a systematic review and meta-analysis: III. Others. Journal of the American Medical Directors Association. 2018;19(4):372. e1-. e8.
120. Seppala LJ, Wermelink AM, de Vries M, Ploegmakers KJ, van de Glind EM, Daams JG, et al. Fall-risk-increasing drugs: a systematic review and meta-analysis: II. Psychotropics. Journal of the American Medical Directors Association. 2018;19(4):371. e11-. e17.
121. Andersen CU, Lassen PO, Usman HQ, Albertsen N, Nielsen LP, Andersen S. Prevalence of medication-related falls in 200 consecutive elderly patients with hip fractures: a cross-sectional study. BMC geriatrics. 2020;20:1-9.
122. Beunza-Sola M, Hidalgo-Ovejero ÁM, Martí-Ayerdi J, Sánchez-Hernández JG, Menéndez-García M, García-Mata S. Study of fall risk-increasing drugs in elderly patients before and after a bone fracture. Postgraduate Medical Journal. 2018;94(1108):76-80.
123. Milos V, Bondesson Å, Magnusson M, Jakobsson U, Westerlund T, Midlöv P. Fall risk-increasing drugs and falls: a cross-sectional study among elderly patients in primary care. BMC Geriatrics. 2014;14(1):40.
124. Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age and Ageing. 2022;51(9).
125. Centre for Clinical Practice at N. National Institute for Health and Care Excellence: Clinical Guidelines. Falls: Assessment and Prevention of Falls in Older People. London: National Institute for Health and Care Excellence (UK) Copyright © National Institute for Health and Care Excellence, 2013.; 2013.
126. HSE. Strategy to Prevent Falls and Fractures in Ireland's Ageing Population: Report of the National Steering Group on the Prevention of Falls in Older People and the Prevention and Management of Osteoporosis throughout Life. In: Health Do, editor. Dublin2008.
127. Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing. 2022;51(9).
128. Seppala LJ, Petrovic M, Ryg J, Bahat G, Topinkova E, Szczerbińska K, et al. STOPPFall (Screening Tool of Older Persons Prescriptions in older adults with high fall risk): a Delphi study by the EuGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Age and ageing. 2020.
129. de Vries OJ, Peeters GMEE, Lips P, Deeg DJH. Does frailty predict increased risk of falls and fractures? A prospective population-based study. Osteoporosis International. 2013;24(9):2397-403.

130. Cheng M-H, Chang S-F. Frailty as a Risk Factor for Falls Among Community Dwelling People: Evidence From a Meta-Analysis. Journal of Nursing Scholarship. 2017;49(5):529-36.
131. Gilmartin D, O'Mahony D, editors. Polypharmacy and Potentially Inappropriate Prescribing in Hospitalised Older Irish Adults. British Geriatric Society Annual Scientific Meeting; 2012: Age and Aging.
132. Hughes JE, Waldron C, Bennett KE, Cahir C. Prevalence of Drug-Drug Interactions in Older Community-Dwelling Individuals: A Systematic Review and Meta-analysis. Drugs Aging. 2023;40(2):117-34.
133. de Oliveira LM, Diel JdAC, Nunes A, da Silva Dal Pizzol T. Prevalence of drug interactions in hospitalised elderly patients: a systematic review. European Journal of Hospital Pharmacy. 2021;28(1):4.
134. Becker ML, Kallewaard M, Caspers PW, Visser LE, Leufkens HG, Stricker BH. Hospitalisations and emergency department visits due to drug–drug interactions: a literature review. Pharmacoepidemiology and Drug Safety. 2007;16(6):641-51.
135. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-62.
136. Cullinan S, O'Mahony D, O'Sullivan D, Byrne S. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. Age and ageing. 2016;45(1):115-20.
137. Dalleur O, Spinewine A, Henrard S, Losseau C, Speybroeck N, Boland B. Inappropriate Prescribing and Related Hospital Admissions in Frail Older Persons According to the STOPP and START Criteria. Drugs & Aging. 2012;29(10):829-37.
138. Hanlon JT, Artz MB, Pieper CF, Lindblad CI, Sloane RJ, Ruby CM, et al. Inappropriate Medication Use Among Frail Elderly Inpatients. Annals of Pharmacotherapy. 2004;38(1):9-14.
139. Récoché I, Lebaudy C, Cool C, Sourdet S, Piau A, Lapeyre-Mestre M, et al. Potentially inappropriate prescribing in a population of frail elderly people. International Journal of Clinical Pharmacy. 2017;39(1):113-9.
140. Muhlack DC, Hoppe LK, Saum K-U, Haefeli WE, Brenner H, Schöttker B. Investigation of a possible association of potentially inappropriate medication for older adults and frailty in a prospective cohort study from Germany. Age and ageing. 2019;49(1):20-5.
141. Gutiérrez-Valencia M, Izquierdo M, Lacalle-Fabo E, Marín-Epelde I, Ramón-Espinoza MF, Domene-Domene T, et al. Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes. European journal of clinical pharmacology. 2018;74(7):961-70.
142. Maclagan LC, Maxwell CJ, Gandhi S, Guan J, Bell CM, Hogan DB, et al. Frailty and Potentially Inappropriate Medication Use at Nursing Home Transition. Journal of the American Geriatrics Society. 2017;65(10):2205-12.
143. Bolina AF, Gomes NC, Marchiori GF, Pegorari MS, Tavares DMdS. Potentially inappropriate medication use and frailty phenotype among community-dwelling older adults: A population-based study. Journal of Clinical Nursing. 2019;28(21-22):3914-22.
144. Cesari M. How polypharmacy affects frailty. Expert Review of Clinical Pharmacology. 2020;13(11):1179-81.
145. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. British Journal of Clinical Pharmacology. 2018;84(7):1432-44.

146. Peklar J, O'Halloran AM, Maidment ID, Henman MC, Kenny RA, Kos M. Sedative load and frailty among community-dwelling population aged ≥65 years. J Am Med Dir Assoc. 2015;16(4):282-9.
147. Ritt M, Ritt JI, Sieber CC, Gaßmann KG. Comparing the predictive accuracy of frailty, comorbidity, and disability for mortality: a 1-year follow-up in patients hospitalized in geriatric wards. Clin Interv Aging. 2017;12:293-304.
148. Kathryn Richardson PM, Jure Peklar, Rose Galvin, Kathleen Bennett and Rose Anne Kenny. Polypharmacy in adults over 50 in Ireland: Opportunities for cost saving and improved healthcare. Dublin: The Irish Longitudinal Study of Aging; 2012.
149. Gómez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-León J. Polypharmacy in the Elderly: A Marker of Increased Risk of Mortality in a Population-Based Prospective Study (NEDICES). Gerontology. 2015;61(4):301-9.
150. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57-65.
151. Jyrkkä J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging. 2009;26(12):1039-48.
152. Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. European Journal of Clinical Pharmacology. 2015;71(12):1415-27.
153. Gallagher P, Lang PO, Cherubini A, Topinková E, Cruz-Jentoft A, Montero Errasquín B, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. European Journal of Clinical Pharmacology. 2011;67(11):1175.
154. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. New England Journal of Medicine. 2011;365(21):2002-12.
155. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clinical Practice. 2012;120(4):c179-c84.
156. Blanc B. Nutritional anemias. Report of a WHO scientific group. WHO Tech Rep Ser. 1968;405:1-40.
157. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013;35(2):121-6.
158. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. European Journal of Internal Medicine. 2016;31:3-10.
159. Gordon EH, Reid N, Khetani IS, Hubbard RE. How frail is frail? A systematic scoping review and synthesis of high impact studies. BMC Geriatrics. 2021;21(1):719.
160. O'Mahony D, O'Sullivan D, Byrne S, O'Connor M, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. Age and ageing. 2014;44.
161. Doody P, Asamane EA, Aunger JA, Swales B, Lord JM, Greig CA, et al. The prevalence of frailty and pre-frailty among geriatric hospital inpatients and its association with economic prosperity and healthcare expenditure: A systematic review and meta-analysis of 467,779 geriatric hospital inpatients. Ageing Research Reviews. 2022;80:101666.
162. Wallis SJ, Wall J, Biram RWS, Romero-Ortuno R. Association of the clinical frailty scale with hospital outcomes. QJM: An International Journal of Medicine. 2015;108(12):943-9.

163. O'Mahony D, Cherubini A, Guiteras AR, Denkinger M, Beuscart J-B, Onder G, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. European Geriatric Medicine. 2023.
164. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age and ageing. 2008;37(6):673-9.
165. Fabbietti P, Ruggiero C, Sganga F, Fusco S, Mammarella F, Barbini N, et al. Effects of hyperpolypharmacy and potentially inappropriate medications (PIMs) on functional decline in older patients discharged from acute care hospitals. Archives of Gerontology and Geriatrics. 2018;77:158-62.
166. Molist-Brunet N, Sevilla-Sánchez D, Puigoriol-Juvanteny E, Espaulella-Ferrer M, Amblàs-Novellas J, Espaulella-Panicot J. Factors Associated with the Detection of Inappropriate Prescriptions in Older People: A Prospective Cohort. International Journal of Environmental Research and Public Health. 2021;18(21):11310.
167. Pazan F, Petrovic M, Cherubini A, Onder G, Cruz-Jentoft AJ, Denkinger M, et al. Current evidence on the impact of medication optimization or pharmacological interventions on frailty or aspects of frailty: a systematic review of randomized controlled trials. European Journal of Clinical Pharmacology. 2021;77(1):1-12.
168. Altman DG. Practical statistics for medical research: Chapman and Hall/CRC; 1990.
169. McMahon CG, Cahir CA, Kenny RA, Bennett K. Inappropriate prescribing in older fallers presenting to an Irish emergency department. Age and Ageing. 2014;43(1):44-50.
170. Hart LA, Phelan EA, Yi JY, Marcum ZA, Gray SL. Use of Fall Risk-Increasing Drugs Around a Fall-Related Injury in Older Adults: A Systematic Review. Journal of the American Geriatrics Society. 2020;68(6):1334-43.
171. Regan CO, Kearney PM, Savva GM, Cronin H, Kenny RA. Age and sex differences in prevalence and clinical correlates of depression: first results from the Irish Longitudinal Study on Ageing. International journal of geriatric psychiatry. 2013;28(12):1280-7.
172. Briggs R, Tobin K, Kenny RA, Kennelly SP. What is the prevalence of untreated depression and death ideation in older people? Data from the Irish Longitudinal Study on Aging. International psychogeriatrics. 2018;30(9):1393-401.
173. Hu T, Zhao X, Wu M, Li Z, Luo L, Yang C, et al. Prevalence of depression in older adults: A systematic review and meta-analysis. Psychiatry Research. 2022;311:114511.
174. van Poelgeest EP, Pronk AC, Rhebergen D, van der Velde N. Depression, antidepressants and fall risk: therapeutic dilemmas—a clinical review. European Geriatric Medicine. 2021;12(3):585-96.
175. Bennett A, Gnjidic D, Gillett M, Carroll P, Matthews S, Johnell K, et al. Prevalence and Impact of Fall-Risk-Increasing Drugs, Polypharmacy, and Drug–Drug Interactions in Robust Versus Frail Hospitalised Falls Patients: A Prospective Cohort Study. Drugs & Aging. 2014;31(3):225-32.
176. Van Der Velde N, Stricker BHC, Pols HAP, Van Der Cammen TJM. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. British Journal of Clinical Pharmacology. 2007;63(2):232-7.
177. Boyé NDA, van der Velde N, de Vries OJ, van Lieshout EMM, Hartholt KA, Mattace-Raso FUS, et al. Effectiveness of medication withdrawal in older fallers: results from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) trial. Age and Ageing. 2016;46(1):142-6.

178. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age Ageing. 2021;50(2):465-71.
179. Dumbreck S, Flynn A, Nairn M, Wilson M, Treweek S, Mercer SW, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. BMJ : British Medical Journal. 2015;350:h949.
180. Hilmer SN, Wu H, Zhang M. Biology of frailty: Implications for clinical pharmacology and drug therapy in frail older people. Mechanisms of Ageing and Development. 2019;181:22-8.
181. Hines LE, Murphy JE. Potentially Harmful Drug–Drug Interactions in the Elderly: A Review. The American Journal of Geriatric Pharmacotherapy. 2011;9(6):364-77.
182. Bucşa C, Farcaş A, Cazacu I, Leucuta D, Achimas-Cadariu A, Mogosan C, et al. How many potential drug–drug interactions cause adverse drug reactions in hospitalized patients? European journal of internal medicine. 2013;24(1):27-33.
183. Dechanont S, Maphanta S, Butthum B, Kongkaew C. Hospital admissions/visits associated with drug–drug interactions: a systematic review and meta-analysis. Pharmacoepidemiology and Drug Safety. 2014;23(5):489-97.
184. Anrys P, Petit AE, Thevelin S, Sallevelt B, Drenth C, Soiza RL, et al. An International Consensus List of Potentially Clinically Significant Drug-Drug Interactions in Older People. J Am Med Dir Assoc. 2021.
185. Zerah L, Henrard S, Wilting I, O'Mahony D, Rodondi N, Dalleur O, et al. Prevalence of drug-drug interactions in older people before and after hospital admission: analysis from the OPERAM trial. BMC geriatrics. 2021;21:1-11.
186. Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. Can Geriatr J. 2020;23(3):210-5.
187. Society RP. Stockley's Interaction Checker London: Royal Pharmaceutical Society; 2023 [Available from: https://www.medicinescomplete.com/#/interactions/stockley.
188. Alhumaidi RM, Bamagous GA, Alsanosi SM, Alqashqari HS, Qadhi RS, Alhindi YZ, et al. Risk of Polypharmacy and Its Outcome in Terms of Drug Interaction in an Elderly Population: A Retrospective Cross-Sectional Study. Journal of Clinical Medicine. 2023;12(12):3960.
189. Chang TI, Park H, Kim DW, Jeon EK, Rhee CM, Kalantar-Zadeh K, et al. Polypharmacy, hospitalization, and mortality risk: a nationwide cohort study. Scientific Reports. 2020;10(1):18964.
190. Doumat G, Daher D, Itani M, Abdouni L, El Asmar K, Assaf G. The effect of polypharmacy on healthcare services utilization in older adults with comorbidities: a retrospective cohort study. BMC Primary Care. 2023;24(1):120.
191. Sganga F, Landi F, Ruggiero C, Corsonello A, Vetrano DL, Lattanzio F, et al. Polypharmacy and health outcomes among older adults discharged from hospital: Results from the CRIME study. Geriatrics & Gerontology International. 2015;15(2):141-6.
192. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Prevalence of drug–drug interactions at hospital entry and during hospital stay of patients in internal medicine. European journal of internal medicine. 2008;19(6):413-20.
193. Očovská Z, Maříková M, Vlček J. Potentially clinically significant drug-drug interactions in older patients admitted to the hospital: A cross-sectional study. Frontiers in Pharmacology. 2023;14.
194. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: The prescribing cascade. British Medical Journal. 1997;315(7115):1096-9.

195. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213-8.
196. O'Mahony D, Gallagher P, Ryan C, Byrne S, Hamilton H, Barry P, et al. STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age. European Geriatric Medicine. 2010;1(1):45-51.
197. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj. 2021;372.
198. Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. European Journal of Clinical Pharmacology. 2013;69(7):1485-96.
199. McCarthy LM, Visentin JD, Rochon PA. Assessing the Scope and Appropriateness of Prescribing Cascades. Journal of the American Geriatrics Society. 2019;67(5):1023-6.
200. Romano S, Figueira D, Teixeira I, Perelman J. Deprescribing Interventions among Community-Dwelling Older Adults: A Systematic Review of Economic Evaluations. PharmacoEconomics. 2022;40(3):269-95.
201. Halli-Tierney A, Scarbrough C, Carroll DG. Polypharmacy: evaluating risks and deprescribing. American family physician. 2019;100(1):32-8.
202. Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA internal medicine. 2015;175(5):827-34.
203. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. Cmaj. 2005;173(5):489-95.
204. Amblàs-Novellas J, Martori JC, Espaulella J, Oller R, Molist-Brunet N, Inzitari M, et al. Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. BMC geriatrics. 2018;18:1-12.
205. O'Caoimh R, Morrison L, Costello M, Flannery A, Small C, O'Reilly L, et al. Frailty in an Adult Acute Hospital Population: Predictors, Prevalence, and Outcomes. International Journal of Environmental Research and Public Health. 2024;21(3):273.
206. Doody P, Asamane EA, Aunger JA, Swales B, Lord JM, Greig CA, et al. The prevalence of frailty and pre-frailty among geriatric hospital inpatients and its association with economic prosperity and healthcare expenditure: A systematic review and meta-analysis of 467,779 geriatric hospital inpatients. Ageing Res Rev. 2022;80:101666.
207. O'Halloran AM, Hartley P, Moloney D, McGarrigle C, Kenny RA, Romero-Ortuno R. Informing patterns of health and social care utilisation in Irish older people according to the Clinical Frailty Scale. HRB Open Res. 2021;4:54.
208. Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. European Geriatric Medicine. 2021;12(3):443-52.
209. Khezrian M, McNeil CJ, Murray AD, Myint PK. An overview of prevalence, determinants and health outcomes of polypharmacy. Ther Adv Drug Saf. 2020;11:2042098620933741.
210. Palmer K, Villani ER, Vetrano DL, Cherubini A, Cruz-Jentoft AJ, Curtin D, et al. Association of polypharmacy and hyperpolypharmacy with frailty states: a systematic review and meta-analysis. Eur Geriatr Med. 2019;10(1):9-36.

211. Nicholson K, Liu W, Fitzpatrick D, Hardacre KA, Roberts S, Salerno J, et al. Prevalence of multimorbidity and polypharmacy among adults and older adults: a systematic review. The Lancet Healthy Longevity. 2024;5(4):e287-e96.
212. Moriarty F, Hardy C, Bennett K, Smith SM, Fahey T. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: a repeated cross-sectional study. BMJ Open. 2015;5(9):e008656.
213. Anrys P, Petit AE, Thevelin S, Sallevelt B, Drenth C, Soiza RL, et al. An International Consensus List of Potentially Clinically Significant Drug-Drug Interactions in Older People. J Am Med Dir Assoc. 2021;22(10):2121-33.e24.
214. Ferrara MC, Zarcone C, Tassistro E, Rebora P, Rossi E, Luppi F, et al. Frailty and long-COVID: is COVID-19 responsible for a transition in frailty status among older adults who survived hospitalization for COVID-19? Aging Clinical and Experimental Research. 2023;35(2):455-61.
215. Ilena M, Marco M, Anja R, Pierre-Olivier B, Martin HB, Christian C, et al. Frailty assessment for COVID-19 follow-up: a prospective cohort study. BMJ Open Respiratory Research. 2022;9(1):e001227.
216. Hirose T, Sawaya Y, Ishizaka M, Hashimoto N, Kubo A, Urano T. Frailty under COVID-19 pandemic in Japan: changes in prevalence of frailty from 2017 to 2021. Journal of the American Geriatrics Society. 2023;71(5):1603-9.
217. Pranata R, Henrina J, Lim MA, Lawrensia S, Yonas E, Vania R, et al. Clinical frailty scale and mortality in COVID-19: A systematic review and dose-response meta-analysis. Arch Gerontol Geriatr. 2021;93:104324.
218. Bardin A, Buja A, Barbiellini Amidei C, Paganini M, Favaro A, Saia M, et al. Elderly People's Access to Emergency Departments during the COVID-19 Pandemic: Results from a Large Population-Based Study in Italy. J Clin Med. 2021;10(23).
219. Howley F, Lavan A, Connolly E, McMahon G, Mehmood M, Briggs R. Trends in emergency department use by older people during the COVID-19 pandemic. European Geriatric Medicine. 2021;12:1159-67.
220. Gallagher J, O'Sullivan D, McCarthy S, Gillespie P, Woods N, O'Mahony D, et al. Structured Pharmacist Review of Medication in Older Hospitalised Patients: A Cost-Effectiveness Analysis. Drugs & Aging. 2016;33(4):285-94.
221. Khera S, Abbasi M, Dabravolskaj J, Sadowski CA, Yua H, Chevalier B. Appropriateness of Medications in Older Adults Living With Frailty: Impact of a Pharmacist-Led Structured Medication Review Process in Primary Care. Journal of Primary Care & Community Health. 2019;10:2150132719890227.
222. Klopotowska JE, Kuks PFM, Wierenga PC, Stuijt CCM, Arisz L, Dijkgraaf MGW, et al. The effect of structured medication review followed by face-to-face feedback to prescribers on adverse drug events recognition and prevention in older inpatients – a multicenter interrupted time series study. BMC Geriatrics. 2022;22(1):505.
223. Seppala LJ, Kamkar N, van Poelgeest EP, Thomsen K, Daams JG, Ryg J, et al. Medication reviews and deprescribing as a single intervention in falls prevention: a systematic review and meta-analysis. Age and Ageing. 2022;51(9).
224. Ma W, Wang H, Wen Z, Liu L, Zhang X. Potentially inappropriate medication and frailty in older adults: A systematic review and meta-analysis. Archives of Gerontology and Geriatrics. 2023;114:105087.
225. O'Mahony D, Gudmundsson A, Soiza RL, Petrovic M, Cruz-Jentoft AJ, Cherubini A, et al. Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity

and polypharmacy: the SENATOR* randomized controlled clinical trial. Age Ageing. 2020;49(4):605-14.
226. Blum MR, Sallevelt B, Spinewine A, O'Mahony D, Moutzouri E, Feller M, et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial. Bmj. 2021;374:n1585.

Appendix 1: Frail-VIG Index.

Table 1 Description and characteristics of the Frail-VIG index

Domain		Variable	Description		Points
Functional	IADLs	Money management	*Needs help managing financial matters (bank, shops, restaurants)*	Yes	1
				No	0
		Telephone use	*Needs help using the telephone*	Yes	1
				No	0
		Medication management	*Needs assistance in preparing or administering medications*	Yes	1
				No	0
	ADLs	Barthel index (BI)	*No dependency (BI ≥ 95)*		0
			Mild-moderate dependency (BI 90–65)		1
			Moderate-severe dependency (BI 60–25)		2
			Absolute dependency (BI ≤ 20)		3
Nutritional		Malnutrition	*Weight loss ≥ 5% in the last 6 months*	Yes	1
				No	0
Cognitive		Degree of cognitive impairment	*No cognitive impairment*		0
			Mild-moderate cognitive impairment (equivalent to GDS ≤ 5)		1
			Severe-very severe cognitive impairment (equivalent to GDS ≥ 6)		2
Emotional		Depressive syndrome	*Need for antidepressant medication*	Yes	1
				No	0
		Insomnia/anxiety	*Frequent need for benzodiazepines or other psychiatric drugs with a sedative effect for insomnia/anxiety*	Yes	1
				No	0
Social		Social vulnerability	*Do health care professionals perceive the presence of social vulnerability?*	Yes	1
				No	0
Geriatric syndromes		Delirium	*Presence of delirium and/or behaviour disorder requiring antipsychotic drugs in the last 6 months.*	Yes	1
				No	0
		Falls	*In the last 6 months, ≥2 falls or hospitalization due to a fall*	Yes	1
				No	0
		Ulcers	*Presence of ulcer (pressure or vascular, any grade)*	Yes	1
				No	0
		Polypharmacy	*Taking ≥ 5 drugs*	Yes	1
				No	0
		Dysphagia	*Difficulty swallowing when eating or drinking? Presence of aspiration respiratory infections during the last 6 months?*	Yes	1
				No	0
Severe symptoms		Pain	*Need for ≥ 2 conventional analgesics and/or strong opioids for pain control*	Yes	1
				No	0
		Dyspnea	*Basal dyspnea impeding the ability to leave the house and/or opioids are frequently needed*	Yes	1
				No	0
Diseases (+)		Cancer	*Active cancer*	Yes	1
				No	0
		Respiratory	*Presence of any type of chronic respiratory disease (COPD, restrictive lung disease...)*	Yes	1
				No	0
		Cardiac	*Presence of any type of chronic heart disease (heart failure, ischemic cardiomyopathy, arrhythmia)*	Yes	1
				No	0
		Neurological	*Presence of any type of neurodegenerative disease (Parkinson, ALS...) or a history of stroke (ischemic or hemorrhagic).*	Yes	1
				No	0

Appendix 2: Permission to reproduce Clinical Frailty Scale Versions 1 and 2.

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Appendix 3: STOPP/START Version 2 criteria.

Screening Tool of Older Persons' Prescriptions (STOPP) version 2.

The following prescriptions are potentially inappropriate to use in patients aged 65 years and older.

Section A: Indication of medication

1. Any drug prescribed without an evidence-based clinical indication.

2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined.

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

Section B: Cardiovascular System

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).

2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).

3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).

4. Beta blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).

5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem).

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

7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).

8. Thiazide diuretic with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).

9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).

10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).

11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.

12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).

13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse).

<u>Section C: Antiplatelet/Anticoagulant Drugs</u>

1. Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).

2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).

3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).

4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has

a high-grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).

5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin)

6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (No added benefit from dual therapy).

7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).

8. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).

9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).

10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).

11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease).

Section D: Central Nervous System and Psychotropic Drugs

1. Tricyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).

2. Initiation of Tricyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).

3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects

(Chlorpromazine, clozapine, flupentixol, fluphenazine, pipotiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).

4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).

5. Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).

6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy

Body Disease (risk of severe extra-pyramidal symptoms).

7. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),

8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation

of cognitive impairment).

9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).

10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).

11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).

12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of

persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).

13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)

14. First-generation antihistamines (safer, less toxic antihistamines now widely available).

Section E: Renal System. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)

1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m2 (risk of digoxin toxicity if plasma levels not measured).

2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m2 (risk of bleeding).

3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2 (risk of bleeding).

4. NSAID's if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function).

5. Colchicine if eGFR < 10 ml/min/1.73m2 (risk of colchicine toxicity).

6. Metformin if eGFR < 30 ml/min/1.73m2 (risk of lactic acidosis).

Section F: Gastrointestinal System

1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).

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

3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where nonconstipating alternatives are available (risk of exacerbation of constipation).

4. Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day; no evidence of enhanced iron absorption above these doses).

Section G: 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-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).

3. Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).

4. Non-selective beta-blocker (whether oral or topical for glaucoma) with a history of asthma

requiring treatment (risk of increased bronchospasm).

5. Benzodiazepines with acute or chronic respiratory failure i.e. $pO2 < 8.0$ kPa ± $pCO2 > 6.5$ kPa (risk of exacerbation of respiratory failure).

Section H: Musculoskeletal System

1. Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).

2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).

3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).

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

5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).

6. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no

contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine oxidase inhibitors are first choice prophylactic drugs in gout).

7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).

8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease).

9. Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture).

Section I: Urogenital System

1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).

2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).

Section J. Endocrine System

1. Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).

2. Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure).

3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).

4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).

5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).

6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).

Section K: Drugs that predictably increase the risk of falls in older people

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

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

3. Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (risk of syncope, falls).

4. Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

Section L: Analgesic Drugs

1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).

2. Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).

3. Long-acting opioids without short-acting opioids for break-through pain (risk of persistence
of severe pain).

Section N: Antimuscarinic/Anticholinergic Drug Burden

Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity).

Screening Tool to Alert to Right Treatment (START), version 2.

Unless an elderly patient's clinical status is end-of-life and therefore requiring a more palliative

focus of pharmacotherapy, the following drug therapies should be considered where omitted for no valid clinical reason(s). It is assumed that the prescriber observes all the specific contraindications to these drug therapies prior to recommending them to older patients.

Section A: Cardiovascular System

1. Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
2. Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.
4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.
5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.
6. Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.
7. Beta-blocker with ischaemic heart disease.
8. Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.

Section B: Respiratory System

1. Regular inhaled alpha-2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.

2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.

3. Home continuous oxygen with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%).

Section C: Central Nervous System& Eyes

1. L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.

2. Non-TCA antidepressant drug in the presence of persistent major depressive symptoms.

3. Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).

4. Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.

5. Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.

6. Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.

Section D: Gastrointestinal System

1. Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.

2. Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation.

Section E: Musculoskeletal System

1. Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.

2. Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.

3. Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).

4. Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).

5. Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).

6. Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.

7. Folic acid supplement in patients taking methotrexate.

Section F: Endocrine System

1. ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.

Section G: Urogenital System

1. Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.

2. 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.

3. Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.

Section H: Analgesics

1. High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency

opioids are not appropriate to the pain severity or have been ineffective.

2. Laxatives in patients receiving opioids regularly.

Section I: Vaccines

1. Seasonal trivalent influenza vaccine annually

2. Pneumococcal vaccine at least once after age 65 according to national guidelines

Appendix 4: Prescribing cascades source reference list.

1. Poirier R, Sturrock J, Cossette B, Morel N, Mallet L. 5 prescription cascades, 5 hospitalizations in a 93 year old man. Journal of the American Geriatrics Society. 2020;68(SUPPL 1):S24.

2. Gill SS, Mamdani M, Naglie G, Streiner DL, Bronskill SE, Kopp A, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. Arch Intern Med. 2005;165(7):808-13.

3. Mohammad D, Chan P, Bradley J, Lanctôt K, Herrmann N. Acetylcholinesterase inhibitors for treating dementia symptoms - a safety evaluation. Expert Opinion on Drug Safety. 2017;16(9):1009-19.

4. Caughey G, Roughead E, Pratt N, Shakib S, Vitry A, Gilbert A. Adverse outcomes associated with potential prescribing cascades. Pharmacoepidemiology and Drug Safety. 2010;19:S130-S1.

5. Vouri SM, van Tuyl JS, Olsen MA, Xian H, Schootman M. An evaluation of a potential calcium channel blocker–lower-extremity edema–loop diuretic prescribing cascade. Journal of the American Pharmacists Association. 2018;58(5):534-9.e4.

6. Trenaman SC, Bowles SK, Kirkland S, Andrew MK. An examination of three prescribing cascades in a cohort of older adults with dementia. BMC Geriatr. 2021;21(1):297.

7. Huisman L, Dijkstra H, Vegter S. Antagonistic drug prescribing: Cholinesterase inhibitors and anticholinergics. Value in Health. 2012;15(7):A333.

8. Singh S, Cocoros NM, Haynes K, Nair VP, Harkins TP, Rochon PA, et al. Antidopaminergic-Antiparkinsonian Medication Prescribing Cascade in Persons with Alzheimer's Disease. Journal of the American Geriatrics Society. 2021;69(5):1328-33.

9. Anderson TS, Steinman MA. Antihypertensive Prescribing Cascades as High-Priority Targets for Deprescribing. JAMA Intern Med. 2020;180(5):651-2.

10. Masurkar PP, Chatterjee S, Sherer JT, Aparasu RR. Antimuscarinic Cascade Across Individual Cholinesterase Inhibitors in Older Adults with Dementia. Drugs & Aging. 2021;38(7):593-602.

11. Stout NL, Wagner SS. Antineoplastic therapy side effects and polypharmacy in older adults with cancer. Topics in geriatric rehabilitation. 2019;35(1):15.

12. McCarthy LM, Visentin JD, Rochon PA. Assessing the Scope and Appropriateness of Prescribing Cascades. Journal of the American Geriatrics Society. 2019;67(5):1023-6.

13. Vouri SM, Jiang X, Pepine C, Solberg L, Malone DC, Winterstein A. Assessment of the calcium channel blocker, lower extremity edema, loop diuretic prescribing cascade: A prescription sequence symmetry analysis. Pharmacoepidemiology and Drug Safety. 2019;28:398.

14. Pradhan R, Liu W, Gurwitz J, Yu H. Automatically identifying prescribing cascades in clinical notes using natural language processing. Pharmacoepidemiology and Drug Safety. 2018;27:464.

15. Visentin JD, Savage RD, Gatley JM, Stall N, Herrmann N, Gruneir A, et al. Calcium channel blockers and diuretics: A retrospective cohort study exploring a prescribing cascade. Journal of Population Therapeutics and Clinical Pharmacology. 2018;25(2):e55.

16. Woodford HJ. Calcium Channel Blockers Co-prescribed with Loop Diuretics: A Potential Marker of Poor Prescribing? Drugs and Aging. 2020;37(2):77-81.

17. Alagiakrishnan K, Mah D, Padwal R. Classic challenges and emerging approaches to medication therapy in older adults. Discov Med. 2018;26(143):137-46.

18. Salazar JA, Poon I, Nair M. Clinical consequences of polypharmacy in elderly: expect the unexpected, think the unthinkable. Expert Opin Drug Saf. 2007;6(6):695-704.

19. Huang ST, Chen Y, Hsu TC, Peng LN, Hsiao FY, Chen LK. Comparisons of effect estimates of 12 prescribing cascades using prescription sequence symmetry analysis. Pharmacoepidemiology and Drug Safety. 2021;30(SUPPL 1):183-4.

20. Gromek KR, Thorpe CT, Aspinall S, Hanson L, Niznik JD. Co-prescribing of anticholinergics and cholinesterase inhibitors: A potential deprescribing cascade. Journal of the American Geriatrics Society. 2021;69(SUPPL 1):S261.

21. Hoang T, Liu J, Pratt N, Zheng VW, Chang KC, Roughead E, et al. Detecting signals of detrimental prescribing cascades from social media. Artificial Intelligence in Medicine. 2016;71:43-56.

22. Morris EJ, Brown JD, Manini TM, Vouri SM. Differences in Health-Related Quality of Life Among Adults with a Potential Dihydropyridine Calcium Channel Blocker–Loop Diuretic Prescribing Cascade. Drugs & Aging. 2021:1-8.

23. Largeau B, Cracowski JL, Lengellé C, Sautenet B, Jonville-Béra AP. Drug-induced peripheral oedema: An aetiology-based review. British Journal of Clinical Pharmacology. 2021;87(8):3043-55.

24. Savage RD, Visentin JD, Bronskill SE, Wang X, Gruneir A, Giannakeas V, et al. Evaluation of a Common Prescribing Cascade of Calcium Channel Blockers and Diuretics in Older Adults With Hypertension. JAMA Intern Med. 2020;180(5):643-51.

25. Morris EJ, Jiang X, Pepine CJ, Smith SM, Vouri SM. Evaluation of the beta blocker-edema-loop diuretic prescribing cascade among adults: A prescription sequence symmetry analysis. Pharmacoepidemiology and Drug Safety. 2020;29(SUPPL 3):475.

26. Vouri SM, Smith SM, Jiang X, Morris EJ, Usmani SA, Manini T, et al. Evaluation of the hydralazine-anxiousness-benzodiazepine prescribing cascade among older adults. Journal of the American Geriatrics Society. 2020;68(SUPPL 1):S223.

27. Vouri SM, Morris EJ, Usmani SA, Reise R, Jiang X, Pepine CJ, et al. Evaluation of the key prescription sequence symmetry analysis assumption using the calcium channel

blocker: Loop diuretic prescribing cascade. Pharmacoepidemiology and Drug Safety. 2022;31(1):72-81.

28. Vouri SM, Smith SM, Jiang X, Morris EJ, Usmani SA, Manini T, et al. Evaluation of the non-dihydropyridine calcium channel blocker-edema-loop diuretic prescribing cascade among older adults. Journal of the American Geriatrics Society. 2020;68(SUPPL 1):S223.

29. Vouri SM, Possinger MC, Usmani S, Solberg LM, Manini T. Evaluation of the Potential Acetylcholinesterase Inhibitor-Induced Rhinorrhea Prescribing Cascade. J Am Geriatr Soc. 2020;68(2):440-1.

30. Read SH, Giannakeas V, Pop P, Bronskill SE, Herrmann N, Chen S, et al. Evidence of a gabapentinoid and diuretic prescribing cascade among older adults with lower back pain. J Am Geriatr Soc. 2021;69(10):2842-50.

31. Peddagovindu B, Oleson E, DuBeau C. Fever of unknown origin in women with osteoporosis. Journal of the American Geriatrics Society. 2012;60:S74.

32. Onder G, Bonassi S, Abbatecola AM, Folino-Gallo P, Lapi F, Marchionni N, et al. High Prevalence of Poor Quality Drug Prescribing in Older Individuals: A Nationwide Report From the Italian Medicines Agency (AIFA). The Journals of Gerontology: Series A. 2013;69(4):430-7.

33. Singh S, Cocoros NM, Haynes K, Nair VP, Harkins TP, Rochon PA, et al. Identifying prescribing cascades in Alzheimer's disease and related dementias: The calcium channel blocker-diuretic prescribing cascade. Pharmacoepidemiol Drug Saf. 2021;30(8):1066-73.

34. Taylor Touré J, Brandt NJ, Rhona Limcangco M, Briesacher BA. Impact of second-generation antipsychotics on the use of antiparkinson agents in nursing homes and assisted-living facilities. American Journal Geriatric Pharmacotherapy. 2006;4(1):25-35.

35. Pasina L, Novella A, Elli C, Nobili A, Ianes A. Inappropriate use of antiplatelet agents for primary prevention in nursing homes: An Italian multicenter observational study. Geriatrics & Gerontology International. 2020;20(9):828-32.

36. Caughey GE, Roughead EE, Pratt N, Shakib S, Vitry AI, Gilbert AL. Increased risk of hip fracture in the elderly associated with prochlorperazine: Is a prescribing cascade contributing? Pharmacoepidemiology and Drug Safety. 2010;19(9):977-82.

37. Elli C, Novella A, Nobili A, Ianes A, Pasina L. Laxative Agents in Nursing Homes: An Example of Prescribing Cascade. Journal of the American Medical Directors Association. 2021;22(12):2559-64.

38. Mangin D, Lawson J, Cuppage J, Shaw E, Ivanyi K, Davis A, et al. Legacy Drug-Prescribing Patterns in Primary Care. Ann Fam Med. 2018;16(6):515-20.

39. Hickner J. Let's put a stop to the prescribing cascade. Journal of Family Practice. 2012;61(11):645-6.

40. Marras C, Herrmann N, Fischer HD, Fung K, Gruneir A, Rochon PA, et al. Lithium Use in Older Adults is Associated with Increased Prescribing of Parkinson Medications. American Journal of Geriatric Psychiatry. 2016;24(4):301-9.

41. Vouri SM, Jiang X, Manini TM, Solberg LM, Pepine C, Malone DC, et al. Magnitude of and Characteristics Associated With the Treatment of Calcium Channel Blocker–Induced Lower-Extremity Edema With Loop Diuretics. JAMA Network Open. 2019;2(12):e1918425-e.

42. Herrmann N, Marras C, Fischer HD, Wang X, Anderson GM, Rochon PA. Management of Neuropsychiatric Symptoms in Long-Term Care Residents with Parkinson's Disease: A Retrospective Cohort Study. Drugs & Aging. 2013;30(1):19-22.

43. Tannenbaum C, Johnell K. Managing therapeutic competition in patients with heart failure, lower urinary tract symptoms and incontinence. Drugs Aging. 2014;31(2):93-101.

44. Lucas C, Byles J, Martin JH. Medicines optimisation in older people: Taking age and sex into account. Maturitas. 2016;93:114-20.

45. Huh Y, Kim DH, Choi M, Park JH, Kwon DY, Jung JH, et al. Metoclopramide and Levosulpiride Use and Subsequent Levodopa Prescription in the Korean Elderly: The Prescribing Cascade. J Clin Med. 2019;8(9).

46. McLendon A, Shelton P. New Symptoms in Older Adults: Disease or Drug? Generations. 2011;35(4):25-30.

47. Garrison SR, Dormuth CR, Morrow RL, Carney GA, Khan KM. Nocturnal Leg Cramps and Prescription Use That Precedes Them: A Sequence Symmetry Analysis. Archives of Internal Medicine. 2012;172(2):120-6.

48. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. BMJ. 1997;315(7115):1096-9.

49. Farrell BJ, Jeffs L, Irving H, McCarthy LM. Patient and provider perspectives on the development and resolution of prescribing cascades: a qualitative study. BMC Geriatr. 2020;20(1):368.

50. Rege S, Holmes H, Aparasu R. PMH20 Antimuscarinic Prescribing Cascade with Acetylcholinesterase Inhibitor Use Among a National Cohort of Older Adults with Alzheimer's Disease. Value in Health. 2021;24:S131.

51. Masurkar P, Chatterjee S, Sherer JT, Aparasu R. PND60 ACETYLCHOLINESTERASE INHIBITOR - ASSOCIATED ANTIPSYCHOTIC PRESCRIBING CASCADE AMONG OLDER ADULTS WITH DEMENTIA. Value in Health. 2020;23:S270.

52. Sharp CN, Linder MW, Valdes R. Polypharmacy: a healthcare conundrum with a pharmacogenetic solution. Critical Reviews in Clinical Laboratory Sciences. 2020;57(3):161-80.

53. Testman JA. The prescribing cascade game: Applying geriatric pharmacotherapy principles in the classroom. Currents in Pharmacy Teaching and Learning. 2014;6(5):646-51.

54. Liu PT, Argento VS, Skudlarska BA. Prescribing cascade in an 80-year-old Japanese immigrant. Geriatrics & gerontology international. 2009;9(4):402-4.

55. Nguyen PVQ, Spinelli C. Prescribing cascade in an elderly woman. Canadian Pharmacists Journal. 2016;149(3):122-4.

56. Ponte ML, Wachs L, Wachs A, Serra HA. Prescribing cascade. A proposed new way to evaluate it. Medicina (Argentina). 2017;77(1):13-6.

57. Bloomstone S, Anzuoni K, Cocoros N, Gurwitz JH, Haynes K, Nair VP, et al. Prescribing cascades in persons with Alzheimer's disease: engaging patients, caregivers, and providers in a qualitative evaluation of print educational materials. Ther Adv Drug Saf. 2020;11:2042098620968310.

58. Nunnari P, Ceccarelli G, Ladiana N, Notaro P. Prescribing cascades and medications most frequently involved in pain therapy: A review. European Review for Medical and Pharmacological Sciences. 2021;25(3):1034-41.

59. Sternberg SA, Guy-Alfandary S, Rochon PA. Prescribing cascades in older adults. CMAJ. 2021;193(6):E215-E.

60. Marzolini C, Livio F. Prescribing issues in elderly individuals living with HIV. Expert Rev Clin Pharmacol. 2019;12(7):643-59.

61. Hofmann A, Khalid A, Mao YH, Al-Nakeeb S, Obi I, Essem J, et al. Prescribing cascade in mental health: the older person at risk. Progress in Neurology and Psychiatry. 2020;24(2):17-20.

62. Vouri SM, Van Tuyl J, Olsen MA, Xian H, Schootman M. Prevalence and factors associated with a potential calcium channel blocker-lower extremity edema-loop diuretic prescribing cascade. Journal of the American Geriatrics Society. 2018;66:S136-S7.

63. Vitarello J, Fitzgerald C. Prevalent use of blood pressure raising medications among us adults with hypertension: National cross-sectional study. Journal of General Internal Medicine. 2021;36(SUPPL 1):S25.

64. Rababa M. Proton Pump Inhibitors and the Prescribing Cascade. Journal of Gerontological Nursing. 2016;42(4):23-31.

65. Trenaman SC, Bowles SK, Kirkland S, Andrew MK. Proton pump inhibitors following strongly anticholinergic medications: A novel prescribing cascade. Pharmacoepidemiology and Drug Safety. 2020;29(SUPPL 3):292.

66. Vouri SM. Rhinorrhea as a Result of Alzheimer's Disease Treatment. Sr Care Pharm. 2020;35(4):148-9.

67. Masurkar P, Chatterjee S, Sherer JT, Aparasu R. PND58 RISK OF ACETYLCHOLINESTERASE INHIBITOR - ASSOCIATED ANTIMUSCARINIC

PRESCRIBING CASCADE AMONG OLDER ADULTS WITH DEMENTIA: A NESTED CASE-CONTROL STUDY. Value in Health. 2020;23:S270.

68. Kalisch Ellett LM, Pratt NL, Barratt JD, Rowett D, Roughead EE. Risk of Medication-Associated Initiation of Oxybutynin in Elderly Men and Women. Journal of the American Geriatrics Society. 2014;62(4):690-5.

69. Hume AL. Safe and effective drug therapy in older adults. Rhode Island Medical Journal. 2005;88(1):15.

70. Vouri SM, Chung JM, Binder EF. Successful intervention to mitigate an acetylcholinesterase inhibitor-induced rhinorrhea prescribing cascade: a case report. Journal of Clinical Pharmacy and Therapeutics. 2017;42(3):370-1.

71. Vegter S, de Boer P, van Dijk KW, Visser S, de Jong-van den Berg LT. The effects of antitussive treatment of ACE inhibitor-induced cough on therapy compliance: a prescription sequence symmetry analysis. Drug Saf. 2013;36(6):435-9.

72. Kalisch LM, Caughey GE, Roughead EE, Gilbert AL. The prescribing cascade. The Australian Prescriber. 2011.

73. Rochon PA, Gurwitz JH. The prescribing cascade revisited. The Lancet. 2017;389(10081):1778-80.

74. Rosenberg J, Rochon PA, Gill SS. Unveiling a prescribing cascade in an older man. Journal of the American Geriatrics Society. 2014;62(3):580-1.

75. Vouri SM, Jiang X, Brumback B, Winterstein AG. Use of negative controls in a prescription sequence symmetry analysis used to mitigate time-varying bias. Pharmacoepidemiology and Drug Safety. 2020;29(SUPPL 3):390-1.

76. Piggott KL, Mehta N, Wong CL, Rochon PA. Using a clinical process map to identify prescribing cascades in your patient. Bmj. 2020;368:m261.

77. Walia R, Mangini L, Ang S, Leahy E. When the solution becomes the problem: The dangers of a prescribing cascade. Journal of the American Geriatrics Society. 2018;66:S104.

78. Nichols S, McCall K, Centanni N, Ki MJC, Stewart D, Piper B. Antagonistic psychotropic polypharmacy: Concomitant sedative and stimulant prescriptions. Pharmacotherapy. 2016;36(12):e271.

79. Page A, Hyde Z, Smith K, Etherton-Beer C, Atkinson DN, Flicker L, et al. Potentially suboptimal prescribing of medicines for older Aboriginal Australians in remote areas. Medical Journal of Australia. 2019;211(3):119-25.

Excluded Prescribing Cascades Post Adjudication (Highlighted in Red)

Rater 1	Rater2	Rater 3		Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree		Drug A	ADE	Drug B	Reference								
5	5	4	1	☑	☐	☐	☐	☐	1	Angiotensin-converting enzyme (ACE) inhibitors	Dizziness	Prochlorprazine	[36] [72]								
5	5	5																			
			2	☑	☐	☐	☐	☐	2		Cough	Cough Suppressant	[9] [54]								
												Inhalers(without diagnosis of asthma)									
												Antibiotic	[60], [71]								
5	2	3	3	☑	☐	☐	☐	☐	3		Nausea	Metoclopromide	[72]								
3	2	2	4	☐	☐	☑	☐	☐	4		Urinary Incontinence	Oxybutinin	[68]								
2	2	2	5	☐	☐	☐	☑	☐	5	Amiodarone	Hypothyroidism	levothyroxine	[56]								
										C01B											
5	5	4	6	☑	☐	☐	☐	☐	6	Angiotensin II receptor blockers (AR2Bs)	Dizziness	Prochlorprazine	[36]								
3	2	2	7	☐	☐	☑	☐	☐	7		Urinary Incontinence	Oxybutinin	[68]								
5	1	1	8	☑	☐	☐	☐	☐	8	Antihypertensive	Dizziness	Antihistamine/Betahistine/Benzodiazep	[9]								
5	4	4	9	☑	☐	☐	☐	☐	9	Beta-Blocker	Depression	Antidepressant	[60]								
4	4	4	10	☐	☑	☐	☐	☐	10		Dizziness	Prochlorprazine	[36]	[72]							
4	2	2	11	☐	☑	☐	☐	☐	11		Lower Limb Odema	Diuretic	[25]								
3	2	2	12	☐	☑	☑	☐	☐	12		LUTS/Incontinence	Antimuscarinic/B-agonist	[44]								
5	5	5	13	☑	☐	☐	☐	☐	13		Sexual Dysfunction	Phosphrodiesterase Inhibitor	[9]								
4	4	4	14	☑	☐	☐	☐	☐	14	Calcium channel block	Dizziness	Prochlorprazine	[36]	[72]							
5	5	5	15	☑	☐	☐	☐	☐	15		Lower Limb Odema	Diuretic	[62]	[13]	[9]	[6]	[5]	[55]	[60]	[16]	[14]
													[49]	[52]	[59]	[57]	[15]	[24]	[22]	[27]	[33]
													[41]	[75]	[28]						
3	1	2	16	☐	☐	☑	☐	☐	16		Urinary Incontinence	Oxybutinin	[68]								
3	2	2	17	☐	☐	☑	☐	☐	17	Diltiazem	Lower Limb Odema	Chlorthalidone	[49]								
5	5	5	18	☑	☐	☑	☐	☐	18	Digoxin	Nausea	Metoclopromide	[72]								
5	4	4	19	☑	☐	☐	☐	☐	19	Diuretics	Dizziness	Prochlorprazine	[72]	[36]	[4]						
5	2	2	20	☑	☐	☐	☐	☐	20		Hypomagnesemia	Mg	[17]								
5	4	4	21	☑	☐	☐	☐	☐	21		LUTS/Incontinence	Antimuscarinic/B-agonist/Alpha-blocke	[43]	[45]	[52]	[9]	[49]	[55]			
5	4	4	22	☑	☐	☐	☐	☐	22		Nausea	Metoclopromide	[72]								
4	4	4	23	☐	☑	☐	☐	☐	23		Nocturnal leg cramps	Quinine Sulphate	[47]								
4	4	4	24	☑	☐	☐	☐	☐	24	Chlorthalidone	Hyperglycaemia	Glyburide	[49]								
4	5	5	25	☑	☐	☐	☐	☐	25	Thiazide Diuretic	Gout/Hyperurecaemia	Gout Treatment Allopurinol/Colchicine	[46]	[48]	[49]	[72]	[60]				
4	4	4	26	☐	☑	☐	☐	☐	26	Fibrate	Nausea/vomiting	Metoclopromide	[56]								
5	5	5	27	☐	☐	☑	☐	☐	27	Fludrocortisone	Hyptertension	Antihypertensives	[46]								
3	2	2	28	☐	☐	☑	☐	☐	28	Hydralazine	Anxiety	Benzodiazapine	[26]								

4	4	4	29	☐	☑	☐	☐	☐	29	Nitrates	Nausea	Metoclopromide	[72]	
4	4	4	30	☐	☑	☐	☐	☐	30	Prazosin	Urinary Incontinence	Oxybutinin	[68]	
4	4	4	31	☑	☐	☐	☐	☐	31	Statins	Dizziness	Prochlorprazine	[72]	
4	4	2	32	☐	☑	☐	☐	☐	32	Statins	Nocturnal leg cramps	Quinine Sulphate	[47]	
5	4	5	33	☑	☐	☐	☐	☐	33	Vasodilators	Dizziness	Prochlorprazine	[72]	

Section C: Antiplatelet/Anticoa

				Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree		Drug A	ADE	Drug B	Reference
			34	☐	☐	☐	☑	☐	34	Aspirin (Primary Prevention)		PPI	[35]

Section D: Central Nervous System and Psychotropic Drugs

				Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree		Drug A	ADE	Drug B	Reference
4	4	4	35	☑	☐	☐	☐	☐	35	Acetylcholinesterase inhibitor (Donepezil, Galantamine, Rivastigmine)	BPSD	Antipsychotic	[51]
4	4	4	36	☐	☑	☐	☐	☐	36		GI Disturbance (Nausea/Diarrhoea)	Bismuth Sub-salicylate	[60]
												Anticholinergic anti-diarrhoeal	[76]
												Anticholinergic Antemetic	[73] [74] [18] [47]
4	4	4	37	☐	☑	☐	☐	☐	37		Rhinorrhea	Rhinorrhoea Medications: First generation histamine1 (H1)-blockers, second-generation H1 blockers, nasal anticholinergics, nasal glucocorticoids, and montelukast, a leukotriene antagonist	[29] [60] [70] [66]
4	4	4	38	☐	☑	☐	☐	☐	38		Urinary Incontinence	Anticholinergic/Antimuscarinic	[60] [2] [3] [46] [49] [10] [72] [50] [6] [7] [12] [20] [53]
2	1	1	39	☐	☐	☑	☐	☐	39	Amitriptyline	Cough	Salbutamol	[58]
4	5	5	40	☐	☑	☐	☐	☐	40		Cognitive decline	Donepezil	[58]
4	4	4	41	☐	☑	☐	☐	☐	41		Urinary Retention	Tamsulosin	[1]
			42	☐	☑	☐	☐	☐	42	Antidepressants	Constipation	Laxitives	[39]
			43	☐	☑	☐	☐	☐	43		Extrapyramidal Symptoms	Parkinsons Meds	[58]
			44	☐	☐	☑	☐	☐	44		Hypotension	Prochlorprazine	[60]
			45	☐	☑	☐	☐	☐	45		Tremor	Beta-Blockers	[58]
												Gabapentin	[58]
				☐								Primadone	[58]
			46	☐	☑	☐	☐	☐	46		Uncontrolled hypertension	Antihypertensive	[63]
			47	☐	☑	☐	☐	☐	47	SSRI/SNRI	Tremor	Benzodiazapine	[60]

			47	☐	☑	☐	☐	☐	47	SSRI/SNRI	Tremor	Benzodiazapine	[60]									
			48	☐	☑	☐	☐	☐	48	SSRI	GI Disturbance	PPI	[58]									
			49	☐	☐	☐	☐	☑	49	Citalopram	PE	Warfarin	[58]									
			50	☐	☑	☐	☐	☐	50	Paroxetine	Tremor	Parkinsons Meds	[49]	[58]	[72]							
1	1	1	51	☐	☐	☐	☑	☐	51	Mirtazipine	Akathesia (Secondary to se	Escitalopram, Trazadone, olanzapine, lo	[77]									
3	2	3	52	☐	☐	☑	☐	☐	52	Duloxetine	Headache	Topiramate	[49]									
2	1	1	53	☐	☐	☐	☑	☐	53	Venlefaxine	Arthritis	NSAID	[58]									
4	5	5	54	☐	☑	☐	☐	☐	54		Hypertension	Lisinopril	[58]									
1	1	1	55	☐	☐	☐	☑	☐	55		MI	Statin	[58]									
4	5	5	54a	☐	☑	☑	☑	☐	54		Migraine	Aspirin	[58]									
1	1	1	55a	☐	☐	☐	☑	☐	55		Stroke	Atorvastatin	[58]									
3	5	5	56	☐	☐	☑	☐	☐	56		Tremor	Benzodiazapine	[58]									
4	4	2	57	☐	☑	☐	☐	☐	57	Tri-cyclic antidepressa	Constipation	Laxitives	[40]	[60]								
4	5	5	58	☐	☑	☐	☐	☐	58		Cognitive impairment	Cholinesterase inhibitor	[60]									
4	4	4	59	☐	☑	☐	☐	☐	59	Bupropion	Insomnia	Mirtazipine	[58]									
4	4	4	60	☐	☑	☐	☐	☐	60	Levosulpride	Extrapyramidal Symptoms	Parkinsons Meds	[58] change to antipsychotics section									
4	4	4	61	☐	☑	☐	☐	☐	61	Trazadone	Hypertension	Prazosin	[58]									
4	2	2	62	☐	☑	☐	☐	☐	62	Anti-epileptics	Nausea	Metoclopromide	[58]									
												Prochlorprazine	[58]									
												Domperidone	[72]									
4	2	2	63	☐	☑	☐	☐	☐	63		Rash	Topical corticosteroids	[72]									
4	2	2	64	☐	☑	☐	☐	☐	64	Valporic Acid	Agitation	Benzodiazapine	[61]									
4	5	5	65	☐	☑	☐	☐	☐	65		Tremor	Parkinsons Meds	[58]									
												Beta-Blocker	[58]									
												Primadone	[58]									
												Gabapentin	[58]									
5	5	5		☑	☐	☐	☐	☐	66	Antipsychotic	Extrapyramidal Symptoms, F	Parkinsons Meds, Anticholinergics	[60]	[49]	[58]	[72]	[46]	[57]	[8]	[32]	[34]	
													[58]	[49]	[42]							
4	4	4	67	☐	☑	☐	☐	☐	67	Haloperidol	Dizziness	Metoclopromide	[58]									
2	1	1	68	☐	☐	☐	☑	☐	68	Quetiapine	Arthritis	Meloxicalm	[58]									
3	1	2	69	☐	☐	☑	☐	☐	69	Benzodiazapines	Constipation	Laxitives	[37]									
3	1	1	70	☐	☐	☑	☐	☐	70		Incontinence	Oxybutinin	[68]	[58]								
1	1	1	71	☐	☐	☐	☑	☐	71		Sleepiness	Caffeine	[58]									
4	4	4	72	☐	☑	☐	☐	☐	72	Dopamine Agonist	Lower Limb Odema	Diuretic	[23]									
4	5	5	73	☐	☑	☐	☐	☐	73	Parkinsons Meds	Behavioural Disturbance	Antipsychotic	[32]									
3	1	2	74	☐	☐	☑	☐	☐	74		Constipation	Laxitives	[38]									
4	4	4	75	☐	☑	☐	☐	☐	75	Hypnotics/Sedatives	Dizziness	Prochlorprazine	[58]	[72]	[4]							
1	1	1	76	☐	☐	☐	☑	☐	76		Not Specified	Stimulant	[78]									

1	1	1	76	☐	☐	☐	☑	☐	76		Not Specified	Stimulant	[78]										
4	5	5	77	☐	☑	☐	☐	☐	77	Lithium	Tremor	Propanolol	[60]										
												Antipsychotic	[34]	Abstract only									
1	1	1	78	☐	☐	☐	☑	☐	78	Stimulants*	Uncontrolled hypertension	Antihypertensive	[63]										
										Section F: Gastrointestinal System													
				Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree		**Drug A**	**ADE**	**Drug B**	**Reference**										
4	4	4	79	☐	☑	☐	☐	☐	79	Antiemetic	Movement disorder	Parkinsons Meds	[57]										
				☐	☐	☐	☐	☐		(Metoclopromide)		Lorazepam	[56]	[58]									
				☐	☐	☐	☐	☐			Extrapyramidal Symptoms/N	Parkinsons Meds	[46]	[48]	[49]	[58]	[60]	[53]	[72]	[6]	[8]		
4	4	4	80						80		Diarrhoea	Loperemide	[58]										
												Benzotropine	[58]										
												Trihexylphenadine	[58]										
												Biperiden	[58]										
2	2	1	82	☐	☑	☐	☐	☐	82		Seizure	Lorazepam/anti-epileptics	[56]										
4	4	4	83	☐	☑	☐	☐	☐	83	PPI	Hypomagnesemia	Mg Replacement	[58]										
4	4	4	84	☐	☑	☐	☐	☐	84		Vit B12 defficency	Vit B12	[58]	[49]									
2	2	2	85	☐	☐	☐	☑	☐	85		MI	Simvastatin	[58]										
2	2	2	86	☐	☐	☐	☑	☐	86	PPI/Abx	Diarrhoea	Dicyclomine	[70]										
3	4	4	87	☐	☐	☑	☐	☐	87	Senna	Diahorrea	Loperamide	[58]										
										Section G: Respiratory System													
				Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree		**Drug A**	**ADE**	**Drug B**	**Reference**										
4	5	5	88	☐	☑	☐	☐	☐	88	Methylxanthines (e.g. th	Nausea	Metoclopromide	[72]										
3	1	1	89	☐	☐	☑	☐	☐	89	Pseudophenidrine	Insomnia	Diphenhydramine	[53]										
2	2	2	90	☐	☐	☐	☑	☐	90	Beta-Agonist	Not Specified	Beta-blocker*	[79]										
4	4	4	91	☐	☑	☐	☐	☐	91	Long Acting Beta-Ago	Nocturnal Leg Cramps	Quinine Sulphate	[47]										
										Section H: Musculoskeletal System													
				Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree		**Drug A**	**ADE**	**Drug B**	**Reference**										
4	5	5	92	☐	☑	☐	☐	☐	92	NSAIDS	Hypertension	Antihypertensives	[63]	[58]	[53]	[21]	[49]	[48]	[46]	[60]	[72]		
4	4	4	93	☐	☑	☐	☐	☐	93		Heartburn	PPI	[49]	[58]	[72]	[17]	[58]						
4	4	4	94	☐	☑	☐	☐	☐	94		Nausea	Metoclopromide	[58]	[72]									
4	4	4	95	☐	☑	☐	☐	☐	95		Lower Limb Odema	Diuretic	[17]										
4	4	4	96	☐	☑	☐	☐	☐	96		Dizziness	Prochlorprazine	[36]										

Antimicrobial Drugs

			Strongly Agr	Agree	Neutral	Disagree	Strongly Disagree		Drug A	ADE	Drug B	Reference
5	4	125	☐	☐	☐	☑	☐	**125**	Antibiotics for system	Diarrhoea	Dicyclomine	[58]
5	4	126	☐	☐	☐	☑	☐	**126**	Antibiotics	Nausea	Metoclopromide	[72]
4	4	127	☐	☑	☐	☐	☐	**127**	Carbapenem abx	Seizure	lorazepam/anti-epileptics	[56]
2	1	128	☐	☑	☐	☐	☐	**128**	Erythromycin	Arrythmia	Antiarrythmic	[60] [72]
1	1	129	☐	☐	☐	☑	☐	**129**	Imipenem	Fever	antibiotic escalation	[56]
1	1	130	☐	☐	☐	☑	☐	**130**	Levofloxacin	Pseudomembranous colitis	Metronidazole	[54]
2	2	131	☐	☑	☐	☐	☐	**131**	Quinolone	Delirium	Anti-Psychotics	[60]

Appendix 5: Ethical approval for research carried out in this thesis.

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (f) 20/10/2020
& ECM 3 (n) 10/11/2020

Date: 29th October 2020

Professor Denis O' Mahony
Senior Lecturer in Medicine/Consultant Geriatrician
Department of Geriatric Medicine
Cork University Hospital
Wilton
Cork

Study Title: Measured Frailty as a Predictor of Potentially Inappropriate Prescribing in Multimorbid Older Patients based on STOPP/START Version 2 and the Medication Appropriateness Index: A Prospective Observational Study.

Dear Professor O'Mahony

The following documents have been approved:

- Proof of Insurance (UCC)
- Participant Information Leaflet Version 3 dated October 2020
- Consent Form Version 3 dated October 2020.

Full approval is now granted to carry out the above study. The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes. The study must be carried out in accordance with General Data Protection Regulation and Health Research Regulation 2018.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter). **We would encourage you to keep note of this date as the CREC will not issue a reminder.**
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (u) 1/6/2021
& ECM 3 (v) 19/10/2021

Date: 20th September 2021

Professor Denis O' Mahony
Department of Geriatric Medicine
Cork University Hospital
Wilton
Cork

Study Title: Potentially Clinically Relevant Drug-Drug Interactions in Older People: An Observational Study

Dear Professor O'Mahony

The following document has been approved:

- Signed Application Form.

Full approval is now granted to carry out the above study. The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes. The study must be carried out in accordance with General Data Protection Regulation and Health Research Regulation 2018.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter). **We would encourage you to keep note of this date as the CREC will not issue a reminder.**
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (oo) 09/03/2021
& ECM 3 (h) 16/11/2021

Date: 28th October 2021

Professor Denis O'Mahony
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Study Title: Falls-Risk Increasing Drugs in Older Adults Attending a Specialist Falls Service: An Observational Study.

Dear Professor O'Mahony

The following amendment has been approved:

- Amendment Application Form signed 21st October 2021
- Addition of Dr Elizabeth (Jenny) Gannon, Specialist Registrar Geriatric Medicine, Cork University Hospital/St. Finbarr's Hospital and Ms Natasha Lewis, Clinical Nurse Manager & Falls Coordinator, Assessment and Treatment Centre, St. Finbarr's Hospital.

Yours sincerely

_____
Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Appendix 6: Data collection sheets used for studies described in this thesis.

Study ID_____

DATA COLLECTION PROFORMA

Measured Frailty as a Predictor of Potentially Inappropriate Prescribing in Multimorbid Older Patients based on STOPP/START Version 2 and the Medication Appropriateness Index: A Prospective Observational Study

Study ID: _____

Inclusion Criteria	Yes	No	Exclusion criteria	Yes	No
≥65 Years		Not Eligible	<~~65 Years~~	Not Eligible	
Acute Admission <72 hours		Not Eligible	Actively Dying/Palliative Admission	Not Eligible	
Expected Length of stay >24 hours		Not Eligible	Direct Admission to ICU	Not Eligible	
			~~Non Consent~~	Not Eligible	
			Isolation	Not Eligible	

Consent	□ Self	□ Proxy

Study ID_____

Date of Admission: _____ **Date of Discharge:** _____ **PDD:**_____
ALOS:_____

Sociodemographic Demographic Data:

Gender: Male □ Female □

Age in Years: _____ **Place of Residence:** Own Home □
Relatives Home □
Nursing Home □
Other □ _____

Primary Carer: Self □ Spouse □ Relative □ Other □

Lives With: _____

Brief Clinical Summary :

Reason for Admission/Current Diagnoses:	**Falls in the last Year:**	**Number of Hospital Admissions in the last year:**
_____ _____ _____ _____ _____ _____ _____	□ Yes □ No Total No. of Falls: _____ **Previous ADRs:** □ Yes □ No **ADLS Support:** □ Yes □ No _____	_____ **Admitting Speciality:** □ **Medical** □ **Surgical** _____

Study ID_____

Admission Medication:

	Drug	Dose	Frequency	Route	
1.					
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3.					
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Medical History	
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Clinical/Laboratory results:

Date:					**Date:**				
Hb:					**Alk Phos:**				
WBC:					**Bili:**				
Na:					**Other::**				
Creat:					**Hr**				
Ca2+:					**BP:**				
Alt:					**HR**				

Study ID_____

Medication Changes During Admission:

Date:	Drug:	Change:	Reason:

Clinical Frailty Scale:

□ 1. Very Fit: People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age

□ 2. Well: People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally

□ 3. Managing: People whose medical problems are well controlled, but are not regularly active beyond routine walking.

□ 4. Vulnerable: While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day

□ 5. Mild: These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

□ 6. Moderate: People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

□ 7. Severe: Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months)

□ 8. Very Severe: Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness

□ 9. Terminal: Approaching the end of life. This category applies to people with a life expectancy less than 6 months but otherwise not frail.

Study ID_____

Frail-VIG Frailty Index:

Domain		Variable	Description		Point
Functional	IADLs	Money management	Needs help managing financial matters (bank, shops, restaurants)	Yes	1
				No	0
		Telephone use	Needs help using the telephone	Yes	1
				No	0
		Medication management	Needs assistance in preparing or administering medications	Yes	1
				No	0
	ADLs	Barthel index (BI)	No dependency (BI ≥ 95)		0
			Mild-moderate dependency (BI 90–65)		1
			Moderate-severe dependency (BI 60–25)		2
			Absolute dependency (BI ≤ 20)		3
Nutritional		Malnutrition	Weight loss ≥ 5% in the last 6 months	Yes	1
Cognitive		Degree of cognitive impairment	No cognitive impairment		0
			Mild-moderate cognitive impairment (equivalent to GDS ≤ 5)		1
			Severe-very severe cognitive impairment (equivalent to GDS ≥ 6)		2
Emotional		Depressive syndrome	Need for antidepressant medication	Yes	1
				No	0
		Insomnia/anxiety	Frequent need for benzodiazepines or other psychiatric drugs with a sedative effect for insomnia/anxiety	Yes	1
				No	0
Social		Social vulnerability	Do health care professionals perceive the presence of social vulnerability?	Yes	1
				No	0
Geriatric syndromes		Delirium	Presence of delirium and/or behaviour disorder requiring antipsychotic drugs in the last 6 months.	Yes	1
				No	0
		Falls	In the last 6 months , ≥2 falls or hospitalization due to a fall	Yes	1
				No	0
		Ulcers	Presence of ulcer (pressure or vascular, any grade)	Yes	1
				No	0
		Polypharmacy	Taking ≥ 5 drugs	Yes	1
				No	0
		Dysphagia	Difficulty swallowing when eating or drinking? Presence of aspiration respiratory infections during the last 6 months ?	Yes	1
				No	0
Severe symptoms		Pain	Need for ≥ 2 conventional analgesics and/or strong opioids for pain control	Yes	1
				No	0
		Dyspnea	Basal dyspnea impeding the ability to leave the house and/or opioids are frequently needed	Yes	1
				No	0
Diseases (+)		Cancer	Active cancer	Yes	1
				No	0
		Respiratory	Presence of any type of chronic respiratory disease (COPD, restrictive lung disease...)	Yes	1
				No	0
		Cardiac	Presence of any type of chronic heart disease (heart failure, ischemic cardiomyopathy, arrhythmia)	Yes	1
				No	0
		Neurological	Presence of any type of neurodegenerative disease (Parkinson, ALS,..) or a history of stroke (ischemic or hemorrhagic).	Yes	1
				No	0
		Digestive	Presence of any type of chronic digestive disease (chronic liver disease, cirrhosis, chronic pancreatitis, inflammatory bowel disease,...)	Yes	1
				No	0
		Renal	Presence of chronic renal failure (GFR < 60)	Yes	1
				No	0
			Frail-VIG index =		X / 25

Study ID_____

Potential ADE:

□ Yes

□ No

Brief Clinical Summary of Event(s):

Drug Class/Name	Summary of event	Investigations	Changes to Medication

Drug Class/Name	Summary of event	Investigations	Changes to Medication

DATA COLLECTION PROFORMA

Falls-Risk Increasing Drugs in Older Adults Attending a Specialist Falls Service: An Observational Study

Study ID: _____

Inclusion Criteria	Yes	No	Exclusion criteria	Yes	No
≥65 Years		Not Eligible	<~~65 Years~~	Not Eligible	
Falls within the last 12 months		Not Eligible	Non consent	Not Eligible	

Consent	□ Self	□ Legal Representative

Study ID_____

Sociodemographic Demographic Data:

Gender: Male □ Female □

Age in Years: _____ **Place of Residence:** Own Home □

Relatives Home □

Nursing Home □

Other □ _____

Primary Carer: Self □ Spouse □ Relative □ Home Help □ Other □

ADLS Support: Yes □ No □ **Type/Frequency of ADLS Support:** _____

Diagnosis of Cognitive Impairment: Yes □ No □

Falls History :

Reason for Referral to Falls Service/Type of Falls:	**Falls in the last Year:**	**Number of Hospital Admissions in the last year:**
_____ _____ _____ _____ _____ _____ _____	□ Yes □ No Total No. of Falls: _____ **Mobility Aid:** □ Yes □ No _____ **Weekly Alcohol Intake:** _____	_____ **Number of Admissions due to falls in last year:** _____ **Previous Medication changes due to Falls:** _____ _____ _____

Medications (including recent changes if applicable):

	Drug	Dose	Frequency	Route	
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Medical History	
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Clinical/Laboratory results:

Date:					**Date:**				
Hb:					**K:**				
WBC:					**eGFR:**				
Na:					**Bp: (L/S)**				
Creat:					**Hr:**				

Frailty Measurement:

Clinical Frailty Scale:

□ 1. Very Fit: People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age	□ 2. Well: People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally
□ 3. Managing: People whose medical problems are well controlled, but are not regularly active beyond routine walking.	□ 4. Vulnerable: While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day
□ 5. Mild: These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.	□ 6. Moderate: People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
□ 7. Severe: Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months)	□ 8. Very Severe: Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness
□ 9. Terminal: Approaching the end of life. This category applies to people with a life expectancy less than 6 months but otherwise not frail.	

STOPPFall Falls risk increasing drugs List:

Drug Type	Yes	No
Benzodiazepine related Drugs		
Benzodiazepines		
Antipsychotics		
Opioids		
Antidepressants		
Antiepileptics		
Diuretics		
Alpha Blockers (As anti-hypertensives)		
Alpha Blockers (For prostatic hyperplasia)		
Centrally acting antihypertensives		
Sedative Antihistamines		
Vasodilators in cardiac disease		
Overactive bladder medications		
Anticholinergics		

DATA COLLECTION PROFORMA

POTENTIALLY CLINICALLY RELEVANT DRUG-DRUG INTERACTIONS IN OLDER PEOPLE: A PROSPECTIVE OBSERVATIONAL STUDY

Study ID: _____

Inclusion Criteria	Yes	No	Exclusion criteria	Yes	No
≥65 Years		Not Eligible	<~~65 Years~~	Not Eligible	
Admission <72 hours		Not Eligible	Actively Dying/Palliative Admission	Not Eligible	
Expected Length of stay >24 hours		Not Eligible	Direct Admission to ICU	Not Eligible	
Taking 2 or more medications		Not Eligible	~~Non Consent~~	Not Eligible	
			Isolation	Not Eligible	

Consent	□ Self	□ Legal Representative

Study ID_____

Sociodemographic Demographic Data:

Gender: Male □ Female □

Age in Years: _____ **Place of Residence:** Own Home □

Relatives Home □

Nursing Home □

Other □ _____

Primary Carer: Self □ Spouse □ Relative □ Home Help □ Other □_____

Lives With: _____

Brief Summary of Admission :

Reason for Admission/Current Diagnoses:	**Falls in the last Year:**	**Number of Hospital Admissions in the last year:**
_____ _____ _____ _____ _____ _____ _____	□ Yes □ No Total No. of Falls: _____ **Previous ADRs:** □ Yes □ No **ADLS Support:** □ Yes □ No	_____ **Admitting Speciality:** □ Medical □ Surgical _____

Study ID_____

Medications (including recent changes if applicable):

	Drug	Dose	Frequency	Route	
1.					
2.					
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Medical History	
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Clinical/Laboratory results:

Date:					**Date:**				
Hb:					**K:**				
WBC:					**Alk Phos**				
Na:					**Ast**				
AdjCa2+					**Alt**				
eGFR:					**Bp: (L/S)**				
Creat:					**Hr:**				

Study ID_____

Frailty Measurement:

Clinical Frailty Scale:

□ 1. Very Fit: People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age	□ 2. Well: People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally
□ 3. Managing: People whose medical problems are well controlled, but are not regularly active beyond routine walking.	□ 4. Vulnerable: While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day
□ 5. Mild: These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.	□ 6. Moderate: People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
□ 7. Severe: Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months)	□ 8. Very Severe: Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness
□ 9. Terminal: Approaching the end of life. This category applies to people with a life expectancy less than 6 months but otherwise not frail.	

Medication Changes During Admission:

Date:	Drug:	Change:	Reason:

Potentially Clinically Relevant Drug-Drug Interactions:

Drug Name	DDI Number	Potential ADE?	Summary of Event
		□ Yes □ No	
		□ Yes □ No	
		□ Yes □ No	
		□ Yes □ No	
		□ Yes □ No	

Appendix 7: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

1

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 8: Peer reviewed publications arising from this thesis to date.

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CURRENT OPINION

Frailty and Potentially Inappropriate Prescribing in Older People with Polypharmacy: A Bi-Directional Relationship?

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Abstract
Frail older adults commonly experience multiple co-morbid illnesses and other risk factors for potentially inappropriate prescribing. However, determination of frailty varies depending on the frailty instrument used. Older people's degree of frailty often influences their care and treatment priorities. Research investigating the association between frailty and potentially inappropriate prescribing is hindered by a wide variety of frailty definitions and measurement tools. We undertook a narrative review of selected articles of PubMed and Google Scholar databases. Articles were selected on the basis of relevance to the core themes of frailty and potentially inappropriate prescribing. We identified observational studies that clearly link potentially inappropriate prescribing, potential prescribing omissions, and adverse drug reactions with frailty in older adults. Equally, the literature illustrates that measured frailty in older adults predisposes to inappropriate polypharmacy and associated adverse drug reactions and events. In essence, there is a bi-directional relationship between frailty and potentially inappropriate prescribing, the underlying substrates being multimorbidity and inappropriate polypharmacy. We conclude that there is a need for consensus on rapid and accurate identification of frailty in older people using appropriate and user-friendly methods for routine clinical practice as a means of identifying older multimorbid patients at risk of potentially inappropriate prescribing. Detection of frailty should, we contend, lead to structured screening for inappropriate prescribing in this high-risk population. Of equal importance, detection of potentially inappropriate prescribing in older people should trigger screening for frailty. All clinicians undertaking a medication review of multimorbid patients with associated polypharmacy should take account of the important interaction between frailty and potentially inappropriate prescribing in the interest of minimizing patient harm.

1 Introduction

Medication management in older people experiencing multimorbidity is often challenging. As multimorbidity increases, the number of prescription medications increases in parallel, exposing patients to greater degrees of polypharmacy, thereby heightening the risk of potentially inappropriate prescribing (PIP) and adverse drug events (ADEs) [1].

Observational studies show that potentially inappropriate medications (PIMs), potential prescribing omissions (PPOs), and adverse drug reactions are highly prevalent in frail older adults [2–4]. Consequently, geriatricians recognize the importance of medication review and optimization as part of a routine comprehensive geriatric assessment. However, most multimorbid older adults managed in the community or undergoing unscheduled hospital attendance are not reviewed by specialist geriatricians. Furthermore, there are knowledge deficits about the factors that predispose some patients more than others to ADEs, which often cause geriatric syndromes such as falls, cognitive impairment, and incontinence. Although an international consensus on the operational definition of frailty is still lacking, it is generally recognized as an age-related state of decreased physiological reserve characterized by a weakened response to stressors and an increased risk of poor clinical outcome following acute illness [5, 6]. These characteristics predispose frail older adults to adverse outcomes from PIP compared with

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Key Points

Susceptibility to medication adverse effects is an intrinsic part of the frailty syndrome.

Potentially inappropriate prescribing and related adverse drug reactions may cause or exacerbate other features of frailty such as cognitive decline, falls, and incontinence and lead to a reduced physiological reserve.

Consensus around the measurement of frailty and how it may be linked to potentially inappropriate prescribing assessment tools is needed.

their age-matched non-frail counterparts. As age-related frailty is associated with adverse outcomes including functional decline, falls, hospitalization, and death in older people, it is essential for prescribers to identify frailty in order to optimize their care [6]. However, the prevalence of frailty varies widely depending on the frailty measurement instrument used [7, 8]. Additionally, the degree of patients' frailty often influences their care goals and treatment priorities [9–11].

In pre-frail and robust older people, certain medications may prevent the development or exacerbation of frailty syndromes. For severely frail older people with a short life expectancy, it is generally accepted that treatment choices should be focused on symptom management and quality of life rather than disease-based guidelines or long-term prevention. In their systematic review of unnecessary medication use and its avoidance in frail older adults, Tjia et al. concluded that the synthesis of overall effect sizes was difficult because of the heterogeneity of frailty measures, outcomes, and study designs, in line with more recent systematic reviews of frailty prevalence [12, 13].

In this narrative review, our aim was to explore the relationship between frailty and PIP and the various ways in which frailty may be exacerbated by PIP and may predispose older adults to PIP exposure. We also aimed to examine whether a practical and clinically applicable method of assessing frailty and PIP could be used to optimize prescribing decisions for older adults and correspondingly whether identification of PIP should act as a trigger for frailty assessment.

For this purpose, a literature search of PubMed and Google Scholar databases was undertaken. Search terms included: Frailty OR Measured Frailty, Frailty OR Measured Frailty AND Potentially Inappropriate Prescribing OR Potentially Inappropriate Medication Use OR Potential Prescribing Omissions OR Medication Underuse. We included articles involving adults aged ≥ 65 years in all settings, i.e., community, hospital, and residential care. Studies with no access to the full-text article or English version of the article and studies exclusively describing patients aged < 65 years were excluded. We also performed reference searching for appropriate articles.

The following clinical vignette illustrates the need for a simple reliable definition of frailty that is related to clinical outcomes. It also shows how frailty detection should prompt an individualized medication assessment, using the individual components of the frailty syndrome or a cumulative deficit model as a guide to deprescribing, and why the presence of PIP should prompt an assessment of frailty.

Clinical Vignette

D.A. is an 81-year-old female who lives alone in her own home. Her past medical history includes hypertension, hyperlipidaemia, hypothyroidism and fragility fracture of her left wrist 3 years previously. She does not have any known cognitive impairment. Her current medications include ramipril, aspirin, levothyroxine, amlodipine and pantoprazole. She also takes paracetamol as required for episodic residual wrist pain. She is independent with her personal activities of daily living, though she receives assistance from her son for weekly shopping and pension collection. She was recently commenced on furosemide for dependant lower limb oedema. Subsequently, she has experienced nocturia and disturbed sleep. She attends her doctor about the sleep problem and is prescribed zopiclone. Within 2 weeks of starting zopiclone, she develops new onset nocturnal incontinence. With a presumptive diagnosis of overactive bladder, she is subsequently prescribed tolterodine. Unfortunately, her sleep problem does not improve and on follow-up with her doctor, she complains of feeling increasingly drowsy during the daytime. Her son notices she has become increasingly forgetful and disoriented and on one particular day finds her lying on the floor of her bedroom, confused and unable to move due to pain. She is admitted to hospital and is found to have a fractured neck of femur, delirium and acute renal failure. Her hospital admission is complicated by pneumonia and prolonged delirium. Following corrective hip surgery, she fails to regain her independent mobility and consequently is discharged to a nursing home for extended care.

Table 1 Selection of frailty assessment tools and a summary of their threshold scores for defining frailty and pre-frailty

Frailty instrument	Components	Classification	Pre-frailty	Medications assessed
(Physical/Fried) Frailty Phenotype [15]	Five items: weight loss, low physical activity, exhaustion, slowness, weakness	Frailty: ≥ 3 present, pre-frailty: 1–2 items, robust: 0 items	Yes	No
Cumulative Deficit Frailty Index [25, 26]	Minimum of 30 accumulated health deficits. Dichotomous yes/no. Index scores 0 (none present) to 1 (all present)	Frailty: > 0.25	No	If included in construction of index
Clinical Frailty Scale [17]	Nine graded pictures on visual or written chart. 1 = very fit to 9 = terminally ill	Frailty: ≥ 5	Yes	No
FRAIL Scale [51]	Self-rated scale, five items: fatigue, resistance, ambulation, illnesses, loss of weight (i.e., 1 point for each component; 0 = best to 5 = worst) and represent frail (3–5), pre-frail (1–2), and robust (0) health status	Frailty: ≥ 3, pre-frailty: 1–2, robust: 0	Yes	No
Edmonton Frailty Scale [52]	Nine questions: cognition, general health, self-described health, functional independence, social support, medication use, nutrition, mood, continence, functional performance	Frailty: ≥ 7, pre-frailty: 5–6, robust: ≤ 4	Yes	Yes
PRISMA-7 [53]	Seven self-reported items: age 85 years, male, social support, activities of daily living	Frailty score ≥ 3	No	No
FI-CGA [54]	Ten items: cognition, mood, communication, mobility, bowel function, balance, pADL/iADL, nutrition, social resources. Each domain scored 0 (no problem) to 2 (major problem)	Mild frailty = 0–7, moderate = 7–13, severe > 13	No	No
Groningen Frailty Indicator [55]	Fifteen self-reported items across four domains: physical, cognitive, social, psychological	Frailty score ≥ 4	No	No
Frail-VIG [56]	Twenty-five question frailty index assessing 22 domains: developed from CGA and designed for clinical use. No deficit = 0, deficit = 1	Frailty: > 0.25	No	Yes

CGA Comprehensive Geriatric Assessment, *CHSA-92* Canadian Study of Healthy Aging in 1992, *FI* Frailty Index, *iADL* instrumental activities of daily living, *pADL* personal activities of daily living

2 Frailty

Frailty is a common clinical syndrome that becomes more prevalent with advancing age. Despite its high prevalence, there is no universally accepted method to confirm a diagnosis of frailty [5]. Frailty is defined as "a progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes" [14]. The terms frail, pre-frail and robust have emerged as descriptive categories with varying risks of adverse outcomes [15]. Although it is associated with multimorbidity, frailty is not in itself a surrogate for disease burden, i.e., a person may have multimorbidity and not be frail [16].

Over the last 20 years, various methods of accurately screening for and assessing frailty have been devised to identify those most at risk of adverse outcomes in the community, in healthcare settings and in hospital peri-operative situations [17–19]. The choice of frailty instruments may also be determined by the time available, location of assessment, space, and equipment required to carry out the assessment. A selection of commonly used frailty instruments is shown in Table 1, with a specific focus on their relationship with the assessment of medication use. This is not an exhaustive list; instruments were selected to demonstrate the numerous methods of quantifying frailty from identifying a phenotype to self-reported items.

In 2016, Buta et al. identified 67 frailty tools cited in the literature [17], of which nine had more than 200 citations. The most commonly cited were the Physical Frailty Phenotype and the Cumulative Deficit Frailty Index. A further systematic review in 2018 found that of the 51 instruments presented, 23 had the capacity to identify pre-frailty [20]. Most frailty assessment instruments can be broadly divided into frailty phenotype or frailty index/cumulative deficit categories. Both categories have been internationally validated for use in identifying older people at a high risk for adverse outcomes relating to frailty compared to other non-frail people of similar age.

The Frailty Phenotype was developed by Fried et al. in 2001 [15]. It includes five variables: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. People categorized as frail (three or more variables present) had higher rates of falls, impaired function, and death compared with people categorized as robust (0 variables) or pre-frail (one to two variables). Validated in the community, long-term care, and hospital in-patient settings [13, 21, 22], the Frailty Phenotype is the most commonly cited frailty measurement in the literature. However, it has some limitations [23], including the substantial time required to translate the five variables into clinical practice, the narrow focus on physical characteristics, the requirement for measurement equipment, and the variable effect of acute illness on the frailty variables. These limitations are potential obstacles to its routine clinical application [24].

Mitnitski et al. utilized a cumulative deficit model to create the frailty assessment tool. Using a holistic and multidimensional construct of frailty, they proposed that frailty is caused by the lifelong accumulation of deficits such as falls, cognitive impairment, co-morbidities, and abnormal laboratory variables. The greater number of deficits present results in greater levels of frailty [25]. A published standard procedure for the development of a frailty index using a minimum of 30 deficits allows the cumulative deficit model to be applied to different sets of data and has led to the development of further indices such as the Electronic Frailty Index based on primary care electronic health record data. The use of a graded frailty index also discriminates moderate frailty from severe frailty and although it does not identify pre-frailty, it has been validated across multiple clinical settings [21, 26].

Following from the Frailty Index, Rockwood et al. later developed a 7-point Clinical Frailty Scale (CFS) The outcomes of institutionalization and mortality were highly correlated with a 7-point CFS range ($r = 0.80$) and with the original Frailty Index. Each category increment of the CFS significantly increased the medium-term risks of death (21.2%, 95% confidence interval [CI] 12.5–30.6) and institutionalization (23.9%, 95% CI 8.8–41.2) in multivariable models that adjusted for age, sex, and education [17]. The CFS is highly dependent on the clinical judgment of the user, nevertheless, it is quick and easy to use and has been validated in primary care, hospital, and long-term care settings. The second version of the CFS includes nine grades in which the category of 'vulnerable' was replaced with 'living with very mild frailty' [27]. The creators of the CFS have expressed caution regarding the use of this judgment-dependent instrument by those inexperienced in frailty evaluations [27].

A meta-analysis of studies has shown an average pooled frailty prevalence of 18% across all clinical settings, with the highest prevalence encountered in the hospital in-patient and nursing home settings (54.1–54.2% and 62.1–68.8%) [22]. Based on a systematic review and meta-analysis of data involving over 61,500 patients, Collard et al. found that, on average, 10.7% of community-dwelling older persons are overtly frail and 41.6% are pre-frail. However, the reported prevalence differed substantially within the included studies, with a range from 4.0 to 59.1%, reflecting the different instruments used to measure frailty [28]. A large multinational meta-analysis confirms this variance, producing a pooled estimate of 12% (11–13%) for physical frailty and 24% (22–26%) for the deficit accumulation model [13].

In nursing home residents, frailty prevalence ranged from 36.4% (95% CI 23.8–51.1) using the Fried Phenotype to 71.8% (95% CI 62.8–79.5) using the CFS [29].

This variability in reported prevalence in frailty according to the measurement tool and setting is readily reflected in practice if one applies the different frailty tools to our clinical vignette. For example, using the CFS, Mrs DA would be considered to have mild frailty (CFS < 5), she would not be classified as frail on the Edmonton Frail Scale or FrailVig Index, and the Frailty Phenotype would require further examinations of grip strength that may not be practical or accurate in the emergency department but would be feasible in the primary care setting. The Frailty Phenotype would be affected the most by her intercurrent acute illness while collateral histories would be required to complete the Frailty Indices.

3 Potentially Inappropriate Prescribing

Potentially inappropriate prescribing occurs where there is a lack of evidence or indication for a medication, where there is avoidable adverse drug–disease or drug–drug interaction exposure, where the risks of medications outweigh their benefits, or where the time to benefit from treatment exceeds individual life expectancy. Potentially inappropriate prescribing also encompasses omission of potentially beneficial medications that are clinically indicated for the treatment or prevention of a disease, mis-prescribing, and prescribing cascades [30–32]. We refer to the term PIP to include the prescription of PIM, potential prescribing omissions, or both.

Potentially inappropriate prescribing is associated with reduced health-related quality of life, excess adverse drug events, increased hospitalization, re-hospitalization, and increased mortality [33]. To minimize exposure of frail older adults to PIP, a structured medication review with appropriate deprescribing is a logical approach. Several tools have been developed to help identify PIP. A recent systematic review that included 42 prescribing assessment tools found that only 13 had been externally validated, with hospitalization being the most commonly measured patient-related outcome [34]. Deprescribing tools are classified as explicit, implicit, or a combination of both. Explicit criteria tools such as Beers criteria, LaRoche criteria, EU-7 criteria, and STOPP/START criteria typically contain lists of drugs or drug classes that are known to expose older adults to potential harms that outweigh their benefits [35–38]. In the STOPP/START criteria, there is also a list of 'potential prescribing omissions', i.e., drugs that probably should be prescribed in older people but are not for various inappropriate reasons, including perceived high-level frailty. Implicit PIP assessment tools such as the Medication Appropriateness Index require knowledge of individual treatment goals and comorbidities in the context of each prescribed drug [39]. While the Medication Appropriateness Index is patient centred, it is time consuming to apply to older adults with polypharmacy and hyper-polypharmacy and requires comprehensive knowledge of the prescribed drugs.

Given the number and range of methods for measuring PIP, it is unsurprising that PIP prevalence, like frailty, varies greatly depending on which assessment tool is used and the patient population studied. A wide range of PIP prevalence (22–79%) has been reported in studies with the wide variance attributed to the different patient populations being assessed and the PIP assessment tool used [40, 41]. Returning to Mrs. DA's medications, one can discern several instances of PIP using both explicit tools and implicit tools. Applying STOPP/START criteria, her initial medications of aspirin with no clear indication for primary cardiovascular prevention and a proton pump inhibitor to minimize gastrointestinal side effects of aspirin are potentially inappropriate. Subsequent addition of a loop diuretic for lower limb edema in the absence of heart failure and a further inappropriate addition of a bladder antimuscarinic and a hypnotic may have caused her confusion and injurious fall. This would likely be reflected in a high Medication Appropriateness Index score. Beers criteria would have identified zopiclone as a drug to avoid in this case with previous falls and aspirin as a drug to use with caution for primary prevention; the high anticholinergic burden of tolterodine would also be detected. There are also multiple avoidable prescribing cascades representing another form of PIP in Mrs DA's medications, such as amlodipine causing the misdiagnosed drug-induced lower limb edema and subsequent inappropriate introduction of a diuretic. Prescribing cascades represent an important, often under-recognized, element of problematic polypharmacy. Cascades occur when an ADE is misinterpreted as a new medical condition, with the subsequent prescription of another, potentially inappropriate drug [42]. With Mrs DA, she is subsequently prescribed a sedative and anticholinergic medicine to treat unrecognized adverse events of the diuretic.

4 Frailty and Potentially Inappropriate Prescribing

There is growing interest in the relationship between PIP and frailty. Physiological systems associated with susceptibility to impaired homeostasis in the context of frailty include the central nervous system, the sympathetic nervous system, the endocrine system (particularly pituitary and adrenal glands), and the immune system [43]. With attenuated physiological reserve in other systems including the cardiovascular, respiratory, and renal systems, an overtly frail individual with

Table 2 Selection of studies exploring the association between potentially inappropriate prescribing and frailty

Study (year)	Type of study	Population characteristics	Frailty criteria	Medication appropriateness measurement	Main findings
Cullinan et al. (2016) [46]	Retrospective analysis of randomized controlled trial database	n = 711 Sex = not reported Age = not reported Acute hospital inpatients	Novel 34-item FI developed using variables available in the database	STOPP/START	The mean FI score above which patients experienced at least one instance of PIP was 0.16. Patients above this threshold were twice as likely to experience PIP [OR = 2.6 (2.0–3.6); p< 0.0001] and to develop an ADR [OR = 2.1, p < 0.0001]. Patients taking more than six medications were three times more likely to experience PIP
Dalleur et al. (2012) [57]	Cross-sectional study	n = 302 Female = 62.6% (189) Median age [P25–P75] = 84 years [81–88 years] Acute hospital inpatients	Identification of Seniors At Risk	STOPP/START	PIMs were found in 144 of the 302 frail older adults (prevalence 47.7%), with the following distribution: 1 PIM (29%), 2 PIMs (16%), and ≥ 3 PIMs (3%). The prevalence of PPOs was 62.9% (190/302), with the following distribution: 1 PPO (29%), 2 PPOs (19%), and 3 PPOs (15%)
Hanlon et al. (2004) [58]	Cross-sectional, secondary analysis of data from a randomized controlled trial	n = 397 Female = 2.8% (11) Age ≥ 75 years = 184 (46.4%), 65–74 years = 213 (53.6%) Acute hospital inpatients[a]	> 2 of 10 frailty criteria	MAI	365 (91.9%) patients had ≥ 1 medications with ≥ 1 MAI criteria rated as inappropriate
Récoché et al. (2017) [4]	Cross-sectional study	n = 229 Female = 156 (68.1%) Age (SD) = 82.14 (6.22) years Day hospital patients	Gerontopole Frailty Screening Tool Fried Phenotype	Criteria based on Laroche list and STOPP/START	Among the 229 frail patients included, 163 (71.2%) had ≥ 1 instance of PIP
Muhlack et al. (2020) [3]	Longitudinal cohort study	n = 2865 Female = 1480 (51.7%) Age (SD) = 70.2 (5.9) years Community-dwelling older adults	Fried Phenotype	2015 Beers criteria 2015 Beers dementia sub-list PRISCUS EU(7)-PIM list	At baseline, 32.1% (919) participants were classified as robust, 58.8% (1685) were pre-frail, and 9.1% (261) were frail. The baseline PIM prevalence varied between 9.2% (Beers dementia PIM) and 37.5% (EU(7) PIM). 21% of participants became frail during the follow-up. All PIM criteria were significantly associated with incident frailty in the unadjusted and in the age-adjusted and sex-adjusted analyses; however, not significant after adjustment for a number of medicines and propensity scores
Gutiérrez-Valencia et al. (2018) [2]	Cross-sectional analysis from a concurrent cohort study	n = 110 Female = 79 (71.8%) Age (SD) = 86.3 (7.3) years Nursing home residents	Fried Phenotype, Imputed Fried Frailty Criteria, Rockwood Frailty Scale, and FRAIL in nursing home scales	STOPP/START	Prevalence of frailty was 71.8%, 42.7%, and 36.4% according to the Rockwood CFS, FRAIL-NH, and FRIED Index, respectively. (Fried Phenotype was only assessed in 40% of participants). Under-prescription was more prevalent in frail participants but only reached significance when Fried criteria were used
Maclagan et al. (2017) [47]	Retrospective cohort study	n = 41,351 Female = 26,748 (64.7%) Age range: 65–74 years = 3691 (8.9%), 75–84 years = 15,130 (36.6%), ≥ 85 years = 22,530 (54.5%) Newly admitted to nursing homes with a history of cognitive impairment or dementia	72-Item FI	Beers criteria 2015	44% of patients were frail at admission, 36.9% were pre-frail, and 19.1% were non-frail 44.3% of the cohort had at least one PIM. PIMs were most prevalent among frail residents across the age cohorts, i.e., 48.1% vs 42.7% vs 38.7% ($p \leq 0.001$). After adjustment for potential confounders, frail residents were also significantly more likely to be newly prescribed PIMs

Table 2 (continued)

Study (year)	Type of study	Population characteristics	Frailty criteria	Medication appropriateness measurement	Main findings
Bolina et al. (2019) [40]	Cross-sectional study as part of a longitudinal study	n = 1607 Female = 1036, (64.5%) Age range: 60–70 years = 611 (38.0%), 70–80 years = 707 (44.0%), 80 years or more = 289 (18.0%) Community-dwelling older adults[b]	Fried Frailty Phenotype components	Beers criteria 2012	Prevalence of frailty was 13.6% and pre-frailty was 51.1%. PIM use was 51.1% for the frail group, 33.2% for the pre-frail group, and 17.0% in the non-frail group

ADR adverse drug reaction, *FI* Frailty Index, *MAI* Medication Appropriateness Index, *OR* odds ratio, *PIM* potentially inappropriate medication, *PIP* potentially inappropriate prescribing, *PPO* potential prescribing omission, *SD* standard deviation, *START* Screening Tool to Alert doctors to Right Treatments, *STOPP* Screening Tool of Older Persons' potentially inappropriate Prescriptions

[a]Patients were excluded if they were admitted from a nursing home, were already receiving care at an outpatient clinic for geriatric evaluation and management, had previously been hospitalized in an inpatient unit for geriatric evaluation and management, were currently enrolled in another clinical trial, had a severe disabling disease or terminal condition, or severe dementia

[b]Those with cognitive decline and unable to undergo a physical assessment were excluded

compromised reserve in one or more systems is more susceptible than non-frail or pre-frail persons to physiological stress arising from adverse medications. Medications may also play a role in worsening measured variables that characterize frailty. Delirium, falls, anorexia, functional impairment, cognitive impairment, renal impairment, and impaired balance are recognized commonly occurring ADEs that may be attributed incorrectly to irreversible aspects of age-related frailty. In our vignette patient, as a consequence of inappropriate prescribing, she experiences incontinence, new-onset cognitive decline, and falls. Several studies have examined the relationship between frailty and PIP in hospital, community, and institutional settings. Table 2 summarizes a selection of these studies and briefly summarizes the variable methods of assessment.

5 Frailty and the Associated Risk of Potentially Inappropriate Prescribing

Frail older adults are exposed to higher levels of polypharmacy and hyper-polypharmacy, established independent risk factors for PIP [41]. Frail older people are more likely to experience increased clinical complexity, extreme vulnerability to stressors, and reduced physiological reserve. Frail older people are also commonly excluded from drug trials [42]. With increased multimorbidity, a related increase in the number of physician consultations often follows, resulting in a higher risk of drug–drug and drug–disease interactions [44]. The association between frailty and polypharmacy has been established, though a meta-analysis in this area has also been hampered by a lack of homogeneity in the definition of frailty [45]. Cullinan et al. applied a novel frailty index as a means of investigating the association between frailty and PIP defined by STOPP/START criteria in older hospitalized patients with multimorbidity and polypharmacy. Though limited by the database variables available, a significant correlation between frailty, adverse drug reaction, and STOPP/START criteria breaches was found [46]. Gutiérrez-Valencia et al. have reported that frail institutionalized older people had a significantly higher average number of START criteria PPOs compared with non-frail institutionalized age-matched control subjects, independent of polypharmacy (1.9 vs 1.0, $p = 0.017$) [2]. Another study designed to estimate the prevalence of PIMs among older adults with cognitive impairment and dementia in long-term care found that after adjustment for potential confounders, frail residents were more likely to be prescribed benzodiazepines, antipsychotics, and anticholinergics [47]. Using a 72-item frailty index and 2015 Beers criteria, Maclagan et al. found PIMs were most prevalent among frail residents across the age cohorts, i.e., 48.1% versus 42.7% versus 38.7% ($p \leq 0.001$) in frail, pre-frail, and robust adults, respectively [47]. In a sample

of ambulatory patients, Récoché et al., assessing for frailty using the Gerontopole Frailty Screening tool and Fried's Phenotype, demonstrated a prevalence of 71.2% of participants with at least one identified STOPP/START or Laroche list-defined PIP [4]. Frailer older adults experience a greater sedative medication load compared with non-frail age-matched counterparts, which increased in proportion to greater levels of frailty [48]. This predisposes to impaired psychomotor function, falls, and cognitive impairment in frail older people.

6 Potentially Inappropriate Prescribing Increasing the Risk of Frailty/Associations

While there are fewer studies investigating the association between PIP and the risk of frailty, a study of community-dwelling older people by Bolina et al. found that PIP (Beers criteria) was associated with a higher incidence of frailty and pre-frailty (Fried's Phenotype) [49]. Similarly, Muhlack et al. [3] demonstrated that PIMs (Beers criteria) were significantly associated with incident frailty (Fried's Phenotype) in both the unadjusted and age-adjusted and sex-adjusted analyses, though not significantly associated after adjustment for the number of daily drugs, concluding that incident frailty was restricted to drugs that could induce frailty syndromes. Pazan et al., examining the effects of medication optimization and pharmacological interventions for frailty, concluded that evidence for a direct causal relationship between medications and frailty was inconclusive and emphasized the need for further research using an internationally consistent and reproducible measure of frailty.

7 Challenges in Measuring and Reducing the Risks of Potentially Inappropriate Prescribing

There is notable heterogeneity both in the frailty measurement tools and also in the criteria utilized to assess medication appropriateness, leading to some difficulty with applying research study findings to a clinical case such as Mrs. DA. This patient could be classified as frail or robust depending on the frailty assessment tool used and its time of application. Current research on the effects of medication optimization is limited to studies on the effect of a single drug adjustment accompanied by multi-component interventions for frailty, and there are no studies assessing the negative effects of drugs on frailty. In their recent systematic review, Pazan et al. concluded that there is a clear need for randomized controlled trials to examine the impact of medication optimization or pharmacological interventions on frailty or aspects of frailty based on a comprehensive and reproducible concept of frailty assessment [50].

8 Conclusions

Pharmacotherapy in frail older people requires an understanding not only of age-related physiological, pharmacokinetic, and pharmacodynamic changes but also frailty-related physiological changes, which predispose to adverse medication-related outcomes. Many studies investigating PIP in older adults focus on age alone as a prompt for medication review. We propose measured frailty as the more important prompt for a structured medication review to guide individual treatment goals. Not only should the presence of frailty prompt a structured medication review but patients who are identified as pre-frail may benefit from judicious prescribing to avoid PIP. Changes in frailty status or the accumulation of new deficits may be attributable to medication use and should trigger a further analysis of medications including long-term medications that may no longer be appropriate. Overall, different frailty measurement tools may be appropriate for different settings and different groups of patients, and having a baseline assessment and identifying changes in vulnerability may assist the clinician in preventing medication-related morbidity. We conclude that different frailty assessment tools may have been more appropriate for Mrs. DA at different stages in her protracted illness. The physical phenotype model may have been suitable to identify vulnerability when she was not experiencing any disability in the community setting but she possibly had underlying pre-frailty. When she was admitted to hospital, a collateral history and frailty index might have identified the forthcoming rapid decline in physical and cognitive function.

Measured frailty should be an important factor when considering new medication choices and when reviewing existing medications as well, as when considering deprescribing decisions in older adults with limited life expectancy. There is a need for further research on the role of inappropriate prescribing in those at risk of developing frailty syndromes such as falls, incontinence, cognitive decline, weight loss, and lethargy. Use of established PIP assessment tools such as STOPP/START criteria, STOPPFrail criteria, or Beers criteria may assist in deprescribing once the degree of frailty has been identified.

Declarations

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References

1. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging. 2014;9:2079–86.
2. Gutiérrez-Valencia M, Izquierdo M, Lacalle-Fabo E, Marín-Epelde I, Ramón-Espinoza MF, Domene-Domene T, et al. Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes. Eur J Clin Pharmacol. 2018;74(7):961–70.
3. Muhlack DC, Hoppe LK, Saum K-U, Haefeli WE, Brenner H, Schöttker B. Investigation of a possible association of potentially inappropriate medication for older adults and frailty in a prospective cohort study from Germany. Age Ageing. 2019;49(1):20–5.
4. Récoché I, Lebaudy C, Cool C, Sourdet S, Piau A, Lapeyre-Mestre M, et al. Potentially inappropriate prescribing in a population of frail elderly people. Int J Clin Pharm. 2017;39(1):113–9.
5. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62–7.
6. Vermeiren S, Vella-Azzopardi R, Beckwée D, Habbig AK, Scafoglieri A, Jansen B, et al. Frailty and the prediction of negative health outcomes: a meta-analysis. J Am Med Dir Assoc. 2016;17(12):1163.e1-17.
7. Lim YJ, Ng YS, Sultana R, Tay EL, Mah SM, Chan CHN, et al. Frailty assessment in community-dwelling older adults: a comparison of 3 diagnostic instruments. J Nutr Health Aging. 2020;24(6):582–90.
8. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci. 2007;62(7):738–43.
9. Lacas A, Rockwood K. Frailty in primary care: a review of its conceptualization and implications for practice. BMC Med. 2012;10(1):4.
10. Curtin D, Jennings E, Daunt R, Curtin S, Randles M, Gallagher P, et al. Deprescribing in older people approaching end of life: a randomized controlled trial using STOPPFrail criteria. J Am Geriatr Soc. 2020;68(4):762–9.
11. Pulignano G, Del Sindaco D, Di Lenarda A, Tarantini L, Cioffi G, Gregori D, et al. Usefulness of frailty profile for targeting older heart failure patients in disease management programs: a cost-effectiveness, pilot study. J Cardiovasc Med. 2010;11(10):739–47.
12. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs Aging. 2013;30(5):285–307.
13. O'Caoimh R, Sezgin D, O'Donovan MR, Molloy DW, Clegg A, Rockwood K, et al. Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. Age Ageing. 2021;50(1):96–104.
14. WHO Clinical Consortium on Healthy Ageing. Topic focus: frailty and intrinsic capacity. Report of consortium meeting 1–2 December 2016 in Geneva, Switzerland. Geneva: WHO; 2017.
15. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–57.
16. Salive ME. Multimorbidity in older adults. Epidemiol Rev. 2013;35(1):75–83.
17. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. Can Med Assoc J. 2005;173(5):489.
18. Darvall JN, Loth J, Bose T, Braat S, De Silva A, Story DA, et al. Accuracy of the Clinical Frailty Scale for perioperative frailty screening: a prospective observational study. Can J Anaesth. 2020;67(6):694–705.
19. Ko FC. Preoperative frailty evaluation: a promising risk-stratification tool in older adults undergoing general surgery. Clin Ther. 2019;41(3):387–99.
20. Faller JW, Pereira DN, de Souza S, Nampo FK, Orlandi FS, Matumoto S. Instruments for the detection of frailty syndrome in older adults: a systematic review. PLoS ONE. 2019;14(4): e0216166.
21. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019;394(10206):1376–86.
22. O'Caoimh R, Galluzzo L, Rodríguez-Laso Á, Van der Heyden J, Ranhoff AH, Lamprini-Koula M, et al. Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: a systematic review and meta-analysis. Ann Ist Super Sanita. 2018;54(3):226–38.
23. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue Q-L, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016;26:53–61.
24. Clegg A, Rockwood K, Romero-Ortuno R, Cunningham C. Frailty. 2021. In: British Geriatrics Society. Silver Book II. https://www.bgs.org.uk/resources/silver-book-ii-frailty. Accessed 7 June 2022.
25. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323–36.
26. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8(1):24.
27. Rockwood K, Theou O. Using the Clinical Frailty Scale in allocating scarce health care resources. Can Geriatr J. 2020;23(3):210–5.
28. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc. 2012;60(8):1487–92.

29. Martínez-Velilla N, Herce PA, Herrero ÁC, Gutiérrez-Valencia M, de Asteasu MLS, Mateos AS, et al. Heterogeneity of different tools for detecting the prevalence of frailty in nursing homes: feasibility and meaning of different approaches. J Am Med Dir Assoc. 2017;18(10):898.e1-8.
30. Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation. Making it safe and sound. London: The King's Fund; 2013.
31. O'Connor MN, Gallagher P, O'Mahony D. Inappropriate prescribing. Drugs Aging. 2012;29(6):437–52.
32. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. BMJ. 1997;315(7115):1096–9.
33. Counter D, Millar JWT, McLay JS. Hospital readmissions, mortality and potentially inappropriate prescribing: a retrospective study of older adults discharged from hospital. Br J Clin Pharmacol. 2018;84(8):1757–63.
34. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. Tools for assessment of the appropriateness of prescribing and association with patient-related outcomes: a systematic review. Drugs Aging. 2018;35(1):43–60.
35. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (screening tool of older person's prescriptions) and START (screening tool to alert doctors to right treatment): consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72.
36. Panel AGSBCUE, Fick DM, Semla TP, Steinman M, Beizer J, Brandt N, et al. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674–94.
37. Laroche M-L, Charmes J-P, Nouaille Y, Fourrier A, Merle L. Impact of hospitalisation in an acute medical geriatric unit on potentially inappropriate medication use. Drugs Aging. 2006;23(1):49–59.
38. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015;71(7):861–75.
39. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45(10):1045–51.
40. Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. Eur J Clin Pharmacol. 2015;71(12):1415–27.
41. Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. J Clin Pharm Ther. 2013;38(5):360–72.
42. Rochon PA, Gurwitz JH. The prescribing cascade revisited. Lancet. 2017;389(10081):1778–80.
43. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62.
44. Cesari M. How polypharmacy affects frailty. Expert Rev Clin Pharmacol. 2020;13(11):1179–81.
45. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: a systematic review. Br J Clin Pharmacol. 2018;84(7):1432–44.
46. Cullinan S, O'Mahony D, O'Sullivan D, Byrne S. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. Age Ageing. 2016;45(1):115–20.
47. Maclagan LC, Maxwell CJ, Gandhi S, Guan J, Bell CM, Hogan DB, et al. Frailty and potentially inappropriate medication use at nursing home transition. J Am Geriatr Soc. 2017;65(10):2205–12.
48. Peklar J, O'Halloran AM, Maidment ID, Henman MC, Kenny RA, Kos M. Sedative load and frailty among community-dwelling population aged ≥65 years. J Am Med Dir Assoc. 2015;16(4):282–9.
49. Bolina AF, Gomes NC, Marchiori GF, Pegorari MS, Tavares DMS. Potentially inappropriate medication use and frailty phenotype among community-dwelling older adults: a population-based study. J Clin Nurs. 2019;28(21–22):3914–22.
50. Pazan F, Petrovic M, Cherubini A, Onder G, Cruz-Jentoft AJ, Denkinger M, et al. Current evidence on the impact of medication optimization or pharmacological interventions on frailty or aspects of frailty: a systematic review of randomized controlled trials. Eur J Clin Pharmacol. 2021;77(1):1–12.
51. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012;16(7):601–8.
52. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing. 2006;35(5):526–9.
53. Raîche M, Hébert R, Dubois M-F. PRISMA-7: a case-finding tool to identify older adults with moderate to severe disabilities. Arch Gerontol Geriatr. 2008;47(1):9–18.
54. Jones DM, Song X, Rockwood K. Operationalizing a Frailty Index from a standardized comprehensive geriatric assessment. J Am Geriatr Soc. 2004;52(11):1929–33.
55. Steverink N. Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator). Gerontologist. 2001;41:236.
56. Amblàs-Novellas J, Martori JC, Espaulella J, Oller R, Molist-Brunet N, Inzitari M, et al. Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. BMC Geriatr. 2018;18(1):29.
57. Dalleur O, Spinewine A, Henrard S, Losseau C, Speybroeck N, Boland B. Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. Drugs Aging. 2012;29(10):829–37.
58. Hanlon JT, Artz MB, Pieper CF, Lindblad CI, Sloane RJ, Ruby CM, et al. Inappropriate medication use among frail elderly inpatients. Ann Pharmacother. 2004;38(1):9–14.