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Biology of frailty: Implications for clinical pharmacology and drug therapy in frail older people

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ABSTRACT

Polypharmacy is very common in frail older people, although medications are rarely evaluated in this population. We conducted a narrative review of the effects of the biology of frailty on clinical pharmacology to inform the extrapolation of the results from clinical trials in robust people to the treatment of frail older people. Biological changes of frailty, such as changes in body composition, organ function and vulnerability to external stressors, are likely to impact on the pharmacokinetics and pharmacodynamics of drugs when used in frail older people. We considered whether these theoretical impacts were observed in the limited empirical data on pharmacokinetics in frail and robust older people. We applied what is known about the biology of frailty to interpret results of clinical trials that have conducted subgroup analyses of drug response by frailty status; and results of observational data on the safety of medications when used in frail older people. Synthesising the effects of the biology of frailty on clinical pharmacology is complicated by the use of different definitions of frailty, including a range of validated scales (that identify different people as frail), clinical judgement and residence in a nursing home.

1. Introduction

Frailty is characterised by a state of increased vulnerability to external stressors (Clegg et al., 2013). People who are frail have decreased functional and biological reserves across multiple organ systems (Fried et al., 2009; Rockwood and Mitnitski, 2007). Chronological age is not a reliable marker of physiological and functional status. There is increasing recognition that the concept of frailty helps to identify people who are at risk for adverse events, significant decompensation, increased morbidity and mortality (Fried et al., 2001a; Ensrud et al., 2009). The prevalence of frailty increases exponentially with age from 6.5% among adults aged 60–69 years to 65% in those aged ≥ 90 years (Gale et al., 2015). The incidence and prevalence of frailty are expected to increase as a result of improved life expectancy and an ageing population.

Older people are the main users of medications in our society, and polypharmacy (use of five or more medications) has become a major public health-care challenge over recent decades. Forty percent of adults aged ≥ 65 years and 50% of adults aged ≥ 80 years take five or more prescription medications (Charlesworth et al., 2015).

The relationship between frailty, multi-morbidity and polypharmacy is complex (Graphical Abstract). Polypharmacy often results from treating multi-morbidity (Farmer et al., 2016). It is not clear whether frailty is a cause or a consequence of multi-morbidity, with similar biological mechanisms proposed for ageing, frailty and many chronic diseases (Walston et al., 2017; Kennedy et al., 2014). Furthermore, polypharmacy and exposure to medications with anticholinergic and sedative effects appear to increase the risk of incident frailty (Gnjidic et al., 2012a). There is increasing recognition that biological changes of frailty affect pharmacokinetics and pharmacodynamics (Hilmer and Gnjidic, 2017; Hubbard et al., 2013).

Clinically, compared to young fit and healthy people, frail older people taking multiple medications pose significant therapeutic challenges due to increased risk of adverse drug events, drug-drug interactions, drug-disease interactions, functional decline, falls, hospitalisations and death (reduced time to benefit) (Hajjar et al., 2007; Hilmer and Gnjidic, 2009; Maher et al., 2014; Onder et al., 2018). Frail older people have been historically under-represented in major clinical trials. Most randomised clinical trials have either explicitly excluded frail people or only included relatively fit older people with few comorbidities or functional impairments. This leads to significant knowledge gaps in current evidence-based practice guidelines and precludes informed decision making when prescribing drugs to frail older people. As the global population ages and the prevalence of frailty increases, understanding the pathophysiological mechanisms of frailty and their impact on drug therapy is essential to inform extrapolation of clinical

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trial data from robust people and to facilitate prescribing of safe and effective treatment for this high-risk population.

2. Methods

The aim of this narrative review is to provide an overview of published studies to determine the interactions between biology of frailty and clinical pharmacology and therapeutics. The definition of clinical pharmacology encompasses all aspects of the relationship between drugs and humans, and here we focus on application of drugs as therapeutic agents and the beneficial and adverse effects of drugs in individuals and society (Birkett et al., 2010). We searched PubMed, focusing on studies published in English that examined the impact of frailty on pharmacokinetics, pharmacodynamics, drug use (including polypharmacy), safety and efficacy of therapeutic drugs. We included major randomised controlled drug trials that conducted subgroup analyses of outcomes in frail older people. We focused on studies with an objective definition of frailty. Where data using an objective definition was not available, we relied on the authors' definition, which usually was clinical impression or a care setting (eg nursing home). Where possible, we considered mechanistic factors related to the biology of frailty.

3. The impact of biology of frailty on pharmacokinetics and pharmacodynamics

Frailty has been defined as a 'state of vulnerability to poor resolution of homeostasis following a stress and…consequence of cumulative decline in multiple physiological systems'(1). Frailty is characterised by a number of physiological changes including increased sarcopaenia (Marzetti et al., 2017), increased adiposity (Buch et al., 2016), chronic inflammation (Soysal et al., 2016), decreased immune response, overactivation of the coagulation system (Walston et al., 2002) and decreased heart rate variability (Zaslavsky et al., 2013; Parvaneh et al., 2015). Characterisation of these changes requires a valid and consistent measure of frailty. Over the past decade, many objective measures have been validated, which generally align with two paradigms: the five-item frailty phenotype (self-reported exhaustion, low physical activity, slowness, unintentional weight loss and weakness (Fried et al., 2001b) and the frailty index, which views frailty as an accumulation of deficits corresponding to composite outcomes of multiple organ systems (e.g. diagnoses, mobility, strength, nutritional status and cognition) (Rockwood et al., 2005). These complementary approaches to measuring frailty do not identify exactly the same people as frail (Cigolle et al., 2009), and consequently the definition of frailty must be considered when synthesising the data on the biology of frailty and its impact on pharmacology.

The impact of frailty on drug disposition and effects is largely unknown. Of the few studies that have investigated this, many are underpowered. This is because the difficult feasibility of studying frail older people is compounded by their high degree of heterogeneity, resulting in highly variable pharmacokinetics and pharmacodynamics. For example, Groen, Horan (Groen et al., 1993) found higher inter-individual variability in the disposition of phenazone and theophylline in frail older women (defined by admission to a geriatrics service) compared to healthy older women. Recently developed mouse models of frailty have the potential to clarify how frailty impacts drug disposition and effects (Kane et al., 2017; Kane et al., 2016). The physiological changes of frailty, as distinct from ageing, are likely to influence pharmacokinetics and pharmacodynamics.

3.1. Pharmacokinetics (PK)

The impact of biological changes in ageing and frailty on pharmacokinetic parameters are described below and are summarised in Table 1. The changes predicted from first principles based on biology of frailty are frequently not observed in empirical studies. This may be due to underpowering of studies or because the frailty of the cohort has not been optimally characterised to detect the change.

3.1.1. Absorption

The extent of absorption of most drugs is not impacted by age (reviewed by Mangoni and Jackson, 2004), but may be impacted by frailty. Older people with the frailty phenotype have impaired gastric motility compared to older people without the frailty phenotype (Serra-Prat et al., 2013). As described below, impaired hepatic metabolism is also associated with frailty. Theoretically, these changes would result in delayed absorption and increased oral bioavailability of some orally administered drugs. Hughes, Lang (Hughes et al., 1992) found the bioavailability of oxybutynin to be greater among frail older individuals (frailty identified by expert opinion) compared to active older individuals, which may reflect increased absorption or reduced first pass metabolism.

3.1.2. Distribution

Distribution is altered in frail older people due to the greater increase in body fat and reductions in lean body mass (sarcopaenic obesity). In a study of 923 older people, Cesari and colleagues (Cesari et al., 2006) found frail older people had lower muscle mass and higher fat mass compared to their robust counterparts. Consequently, lipophilic drugs, which include most psychotropic drugs, have an increased volume of distribution leading to lower plasma concentrations and prolonged half-life in frail older people (Delafuente, 2008). This is the opposite for hydrophilic drugs such as digoxin and gentamicin. However, Hilmer and colleagues (Hilmer et al., 2011) found no difference in volume of distribution of gentamicin in frail older people identified by the Reported Edmonton Frail Scale (n = 14) compared to robust older people (n = 17). It is possible that using the frailty phenotype, which is likely to be more closely associated with body composition, could have led to a different result. Whilst hypoalbuminemia is minor and clinically insignificant in healthy older people, frail older people have significantly lower levels of serum albumin (Hubbard et al., 2009). This could result in higher concentrations of unbound drug in frail older people.

3.1.3. Metabolism

Age-related impairment of hepatic metabolism due to a decline in hepatic blood flow and in liver size (Le Couteur and McLean, 1998) is amplified in frailty (Tan et al., 2015). As a result, drugs with high extraction ratios (the clearance of which are largely determined by hepatic blood flow) have reduced clearance. Reduced hepatic metabolism also diminishes activation of pro-drugs, thereby decreasing or delaying their efficacy.

Phase I metabolism is somewhat impaired in frailty, although the data is conflicting. For example, in a study of 110 older people, significant reductions in plasma esterase activity were observed in frailer older people (Hubbard et al., 2008). Schwartz (2006) found that frail older people did not have reduced CYP3A4 and P-glycoprotein metabolism, according to erythromycin breath test results. Similarly, Hughes (Hughes et al., 1992) found that there was no reduced metabolism of N-desthyl oxybutynin in frailty. Opdam (Opdam et al., 2015) did not find a difference in CYP2D6 metabolism between frail and non-frail older people, although they were unable to achieve the desired sample size. Wynne (Wynne et al., 1989) observed no reduction in the clearance of acetanilide (oxidation) in frail older people compared to healthy older people.

Phase II metabolism is impaired in frail older people. For example, the glucuronidation of paracetamol was significantly more reduced in frail older people compared to their healthy counterparts (Wynne et al., 1990). Similarly, frail older people have reduced clearance of metoclopramide via sulfation (Wynne et al., 1993).

Table 1
Impact of biology of frailty on pharmacokinetics: theoretical and empirical data.

Pharmacokinetic parameter	Biological change in aging, which may be exaggerated in frailty	Impact of change on pharmacokinetic parameter	Direct empirical data comparing frail and non-frail older adults
Absorption	Reduced gastric motility and reduced hepatic metabolism	Delayed absorption and increased bioavailability of some orally administered drugs	Increased bioavailability of oxybutynin in frailty^ (Hughes et al., 1992)
Distribution	Sarcopaenia and increased relative body fat Reduced plasma albumin	Increased volume of distribution of lipophilic drugs and decreased volume of distribution of hydrophilic drugs Decreased protein binding of acidic drugs	No reduced volume of distribution of gentamicin in frailty* (Hilmer et al., 2011; Johnston et al., 2014)
Metabolism	Reduced hepatic volume and hepatic blood flow	Some reduced phase I clearance	No reduced CYP3A4 and P-glycoprotein metabolism in frailty according to erythromycin breath test results** (Schwartz, 2006) No reduced CYP2D6 metabolism in frailty** (Opdam et al., 2015) Reduced esterase activity in frailty ^(Hubbard et al., 2008) No reduced clearance of acetanilide in frailty ^(Wynne et al., 1989) No reduced metabolism of N-desthyl oxybutynin in frailty^ (Hughes et al., 1992)
		Reduced phase II clearance	Reduced clearance of metoclopramide via sulfation in frailty ^(Wynne et al., 1993) Reduced clearance of paracetamol in frailty via glucuronidation ^(Wynne et al., 1990)
Elimination	Reduced glomerular filtration rate	Reduced renal clearance	Reduced gentamicin clearance in frailty*(Hilmer et al., 2011; Johnston et al., 2014)

^ indicates studies that used a definition of frailty based on clinical impression and/or care setting.
* indicates studies that used an objective definition of frailty based on cumulative deficit model.
** indicates studies that used an objective definition of frailty based on phenotype model.

3.1.4. Elimination

The decline in renal function in old age has a major clinical impact as many drugs used by older people are predominately renally excreted (Delafuente, 2008). Frailty is associated with poorer renal function and reduced clearance of drugs such as gentamicin (Hilmer et al., 2011; Johnston et al., 2014). Impaired renal clearance, quantified by a reduction in glomerular filtration rate (GFR), is aggravated by the presence of comorbidities that are highly prevalent in old age and frailty, such as hypertension, heart failure and diabetes (Reeve et al., 2015). The use of serum creatinine (which is dependent on creatine load from skeletal muscle) or an equation to estimate renal function that does not adjust for body size, results in an overestimation of GFR in older people, particularly the frail. It is therefore paramount that the dose be adjusted to minimise the risk of toxicity caused by renally-cleared drugs. This is particularly important for drugs that are mostly excreted in urine unchanged and have a narrow therapeutic index such as digoxin (Currie et al., 2011) and dabigatran (Harper et al., 2012).

3.2. Pharmacodynamics (PD)

The literature investigating pharmacodynamic changes in ageing and frailty is very scarce and is summarised in Table 2. In general, older people are more sensitive to medications targeting the central nervous system (CNS) due in part to age-related deterioration of homeostatic mechanisms (Bowie and Slattum, 2007). For example, changes to benzodiazepine binding to the $GABA_A$ receptors result in increased sedation and confusion in older people taking benzodiazepines (Ng et al., 2018). Older people are also more likely to develop bleeding complications with oral anticoagulants and postural hypotension with antihypertensives (Turnheim, 2003). In frailty, magnified or dampened drug effects may be due to a reduction in resilience to external stressors and receptor function in presence of chronic inflammation. For example, frail older people experience increased sedation with metoclopramide (Wynne et al., 1993) and an increased risk of falls with CNS and cardiovascular medications (Bennett et al., 2014). Furthermore, changes in frailty may reduce the responsiveness of platelets to aspirin (Nguyen et al., 2016).

4. Polypharmacy and frailty

Recent experimental and population-based studies have demonstrated that polypharmacy is associated with the development of frailty. The pathophysiological mechanisms linking polypharmacy and frailty are complex and remain incompletely understood. Plausible explanations include adverse drug effects on multiple organs and systems, such as brain, heart, muscle, liver, kidneys, as well as immune, hormonal and metabolic systems (Fulop et al., 2010). Common biological mechanisms causing ageing, frailty and multimorbidity (which results in

Table 2
Impact of biology of frailty on pharmacodynamics: theoretical and empirical data.

Biological change in ageing which may be exaggerated in frailty	Impact of change on pharmacodynamics	Direct empirical data in frailty
Increased vulnerability to external stressors	Increased therapeutic or toxic effects	Greater sedation with intravenous metoclopramide in frailty (Wynne et al., 1993)^ Increased risk of falls with cardiovascular and psychoactive drugs in frailty (Bennett et al., 2014)*
Chronic inflammation leading to potentially reduced receptor function and activating platelets		Potentially reduced responsiveness of platelets to aspirin in frailty (Nguyen et al., 2016)*

^ indicates studies that used a definition of frailty based on clinical impression and/or care setting.
* indicates studies that used an objective definition of frailty based on cumulative deficit model.

polypharmacy) could also explain this association. Animal models can help understand causality of this relationship. Huizer-Pajkos et al. demonstrated short term exposure to polypharmacy (with therapeutic doses of a beta blocker, a statin, a proton pump inhibitor, a selective serotonin reuptake inhibitor and acetaminophen) resulted in impaired physical function in old C57BL/6 male mice (Huizer-Pajkos et al., 2016). Frailty assessment scores measured using the Mouse Clinical Frailty Index (deficit accumulation model) were not significantly worse in the polypharmacy group compared with the control (no drugs) group (Huizer-Pajkos et al., 2016). Studies of chronic exposure to polypharmacy, drug withdrawal (deprescribing) and mechanistic markers using this mouse model of frailty may help elucidate the causality of the relationship between frailty and polypharmacy.

In a population-based study, using long-term prospective data from a cohort of 4402 patients in the Osteoarthritis Initiative (OAI) with 8 years of follow-up, Veronese and colleagues identified polypharmacy as an important modifiable risk factor for frailty phenotype (Veronese et al., 2017). The association between polypharmacy and frailty was independent after adjustment for other risk factors such as comorbidities, age, sex, smoking and socioeconomic status (Veronese et al., 2017). Furthermore, the incidence of frailty nearly doubled in people taking 4–6 prescription medications compared to those taking 0–3 medications, and was six times higher in people taking 7 or more medications (Veronese et al., 2017). Each additional prescription medication used at the baseline increased the risk of developing frailty by 11% (Veronese et al., 2017).

In the Concord Health and Aging in Men Project (CHAMP), Gnjidic and colleagues studied the association between the number of regular prescription medications and outcomes such as frailty phenotype, disability, falls and mortality in a cohort of 1705 Australian community-dwelling men aged ≥ 70 years (Gnjidic et al., 2012b). Using receiver-operating characteristic analysis and the Youden Index, Gnjidic et al. demonstrated that the optimal discriminating number of medications associated with frailty was 6.5 medications. A threshold of 5.5 medications was associated with disability, and using 4.5 medications was associated mortality and incident falls in this cohort. In another study from the Concord Health and Aging in Men Project (CHAMP), Jamsen and co-workers examined the dynamic nature of frailty phenotype over time and the effects of number of prescription drugs and Drug Burden Index (DBI, a measure of exposure to medications with anticholinergic and sedative effects) on frailty transitions (progression and regression) (Jamsen et al., 2016). Specifically, the study demonstrated each additional medication was associated with a 22% greater risk of transitioning from the robust state to death. Every unit increment in DBI was found to confer an additional 73% risk of transitioning from the robust state to the prefrail state. However, there was no observed effect of medications on transitions between the prefrail state and the frail state.

As described above, frailty and polypharmacy often coexist. There is emerging evidence that polypharmacy has an adverse prognostic effect on frail people. In the Frailty and Dependence in Albacete (FRADEA) study, the investigators studied 773 institutionalised and community-dwelling people in whom frailty was assessed using the frailty phenotype (Bonaga et al., 2018). After a mean follow up of 2.9 years, polypharmacy (≥ 5 regular prescription medications) was associated with greater adjusted risk of mortality, incident disability and hospitalisation in frail and prefrail patients, compared with non-frail patients. Similarly, in a French study of 2350 people with a mean age of 83.3 ± 7.5 years, the risk of death was most notably increased by six-fold in patients with both frailty phenotype and hyperpolypharmacy (≥ 10 prescription medications) and three-fold in patients with both frailty and polypharmacy (5–9 prescription medications), compared with non-frail patients without polypharmacy (Herr et al., 2015). The underlying mechanisms for this phenomenon remain elusive. Whether polypharmacy causes an increased mortality or is a marker of more advanced frailty or more severe multimorbidity remains uncertain, but these findings suggest that frail older patients are very susceptible to detrimental effects associated with polypharmacy and hyperpolypharmacy.

Clinical practice guidelines on management of frailty, such as the Asia-Pacific Clinical Practice Guidelines for the Management of Frailty, also highlight the role of polypharmacy in the development of frailty (Dent et al., 2017). The guidelines recommend regular medication review in frail older people, and reducing inappropriate medications under the supervision of a healthcare professional. To date, there is a paucity of data on the outcomes of deprescribing polypharmacy in frail people (Ng et al., 2018; Avery and Bell, 2019). Biologically, frailty appears to be a dynamic state, so it is plausible that if adverse effects of medications contribute to development of frailty in a patient, it may be reversible with deprescribing. Polypharmacy is also associated with under-treatment. It is possible that medications that improve function, such as antiparkinsonian drugs in people with Parkinson's Disease, could improve some measures of frailty, although this has not been rigorously evaluated. However, the multifactorial nature of frailty is such that a single intervention may not have a significant impact. Future studies are needed to determine whether comprehensive medication review can attenuate the progression of frailty and/or improve function in frail older people.

5. Assessment of drug safety and efficacy in randomised controlled trials using frailty subgroup analysis

While frail older people are under-represented in most clinical trials, recent efforts have been made to measure drug effects according to baseline frailty in some randomised controlled trials, predominantly of cardiovascular drugs, with examples given below. Data synthesis and extrapolation to practice must consider the definition of frailty used, and the degree of frailty in the population. Hypotheses for the biological mechanisms of any changes seen with frailty are also discussed.

5.1. Aspirin in the primary prevention of cardiovascular disease in frail older people

The Aspirin in Reducing Events in the Elderly (ASPREE) trial was a large international multicentre randomised, placebo-controlled trial that examined the benefits and risks of aspirin in the primary prevention of cardiovascular disease in healthy community-dwelling people aged ≥ 70 years (McNeil et al., 2018a, b; McNeil et al., 2018c). The study screened 83,376 patients and randomised 19,114 patients across 50 centres in Australia and the United States to either aspirin (n = 9525) or placebo (n = 9589). The median age of the study population was 74 years, comprising 10,783 (56.4%) women. Frailty status was assessed using the Fried frailty phenotype, with at least 3 of 5 criteria required for a diagnosis of frailty and 1 or 2 criteria for classification as prefrail. At baseline, 421 (2.2%) of participants were frail, 7447 (39.0%) were prefrail and 11,246 (58.8%) were non-frail. Participants were followed-up for 4.7 years and primary endpoints included death, dementia or persistent physical disability. All-cause mortality was higher in the aspirin group compared with the placebo group (5.9% vs 5.2%; HR 1.14; CI 1.01–1.29) (McNeil et al., 2018c). Participants who were on aspirin also had more cancer-related death and major haemorrhagic events. There was no significant difference in the rates of cardiovascular disease (4.7% aspirin vs. 4.9% placebo HR 0.95; CI 0.83–1.08) (McNeil et al., 2018b). The investigators of the ASPREE trial concluded that aspirin as a primary prevention therapy resulted in a significantly increased risk of major bleeding and did not prolong disability-free survival in healthy older people. Furthermore, in the subgroup analysis of the ASPREE trial, frail patients treated with aspirin trended towards higher rates of all-cause mortality, compared with frail patients in the placebo group (McNeil et al., 2018a), although this finding did not reach statistical significance. The trend towards an increased risk of death in frail older people may be due to aspirin resistance in the presence of chronic inflammation of frailty, as suggested

in an observational study (Nguyen et al., 2016), or to an increased risk of haemorrhage in frailty which may reflect multi-morbidity and reduced resilience.

5.2. Management of hypertension in frail older people

The optimal blood pressure target in frail older people remains controversial. The Systolic Blood Pressure Intervention Trial (SPRINT) investigators examined the benefits and risks of intensive versus standard blood pressure control in people aged ≥ 50 years (Wright et al., 2015). Patients randomly assigned to the intensive treatment group with a systolic blood pressure target < 120 mmHg had a lower rate of major cardiovascular events (5.2% vs 6.8%; HR 0.75; CI 0.64-0.89; P < 0.001), and a lower rate of all-cause mortality (3.3% vs 4.5%; HR 0.73; CI 0.60-0.90; P < 0.003), compared with patients in the standard treatment group with a systolic blood pressure target < 140 mmHg. However, the prevalence of serious adverse events, such as hypotension, syncope, electrolyte abnormalities and acute kidney injury was significantly higher in the intensive treatment group than in the group with standard blood pressure control. In the subgroup analysis of the SPRINT trial (Williamson et al., 2016) by frailty status, defined using a frailty index, the benefits of intensive blood pressure control on cardiovascular disease outcomes and all-cause mortality were observed in people with and without frailty. However, the SPRINT trial excluded people with a history of type 2 diabetes or stroke and people living in nursing homes who were more likely to be very frail, functionally dependent and have multiple comorbidities. Therefore, the results of the SPRINT trial cannot be extrapolated to these vulnerable population groups who may be susceptible to side effects of antihypertensive medications such as postural hypotension and falls.

Complementary observational data on antihypertensive treatment in frailty comes from the Predictive Value of Blood Pressure and Arterial Stiffness in Institutionalised Very Aged Population (PARTAGE) study. This large, longitudinal observation study assessed the impact of antihypertensive therapy on all-cause mortality in older nursing home residents with a systolic blood pressure of < 130 mmHg (Benetos et al., 2015). The PARTAGE study recruited 1130 people, including 878 women living in French and Italian nursing homes. The prevalence of frailty in nursing homes is high but varies widely between nursing homes and therefore generalisability to other nursing home populations and applicability to patients defined with objective frailty measures is limited. All participants were at least 80 years old and over 91% of the study population were treated with antihypertensive medications. The main finding of the PARTAGE study was a higher risk of all-cause mortality in older institutionalised people with a systolic blood pressure of < 130 mmHg and older people taking two or more antihypertensive medications. The findings of the PARTAGE study raise concern for the potential for overtreatment of hypertension in frail older people. Frail older people may require a higher blood pressure to maintain adequate organ perfusion and a significant reduction in blood pressure may cause more harm due to impaired autoregulation, consistent with the ageing theory of adaptive senectitude, where changes in old age might be evolutionary adaptations to prolong life after reproduction (Le Couteur and Simpson, 2011).

Based on this combined evidence, current guidelines for management of arterial hypertension recommend a less aggressive blood pressure target in very frail older people (Williams et al., 2018). Further research is needed to determine the optimal blood pressure target in institutionalised and very frail people with hypertension.

5.3. Anticoagulation for stroke prevention in frail older people with atrial fibrillation

The decision to initiate or continue anticoagulation therapy for stroke prevention in older people with atrial fibrillation requires the treating clinician to assess the risks of stroke and bleeding. While advanced age is a major independent risk factor for stroke in patients with nonvalvular atrial fibrillation, studies have shown that age is also independently associated with underuse of oral anticoagulants in older people (Patti et al., 2017). This is in part explained by clinicians' concerns about the risks associated with frailty, falls and drug-drug interactions and non-adherence when prescribing anticoagulants in older people. In a meta-analysis of 20 studies involving 30,883 patients, Wilkinson and colleagues demonstrated frailty was common in patients with atrial fibrillation, with prevalence ranging from 3 to 38% (Wilkinson et al., 2018). Frailty was associated with increased incidence of stroke, all-cause mortality, symptom severity and length of hospital stay (Wilkinson et al., 2018). Frail older people are at high risk of bleeding due to falls, multimorbidity and variable adherence to therapy, particularly in those living with dementia.

The effects of oral anticoagulants in frail older people have not been comprehensively evaluated. The biology of frailty includes a pro-coagulant state. Observational data suggests that with anticoagulation using a vitamin K antagonist (warfarin), with the same INR, the effects on global measures of coagulation are similar in frail and non-frail older people (Nguyen et al., 2017). Similar evaluations have not been performed for the non-vitamin K antagonist oral anticoagulants. The ARISTOTLE, RE-LY and ROCKET AF trials demonstrated non-vitamin K antagonist oral anticoagulants reduced stroke or systemic embolism and were associated with lower haemorrhagic stroke and intracranial bleeding compared with warfarin (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011). However, although these trials included older people in the study population, it is not known how many of these people were frail, as the trials did not assess patients using frailty assessment tools.

Therefore, in the absence of strong empirical evidence to guide anticoagulation in frail older people, case-by-case clinical judgement, thorough assessment of patient's frailty status and bleeding risk, and frequent clinical monitoring and review, are essential in the management of frail older people with atrial fibrillation.

6. Conclusions

It is clinically important to consider frailty as one of many factors that influence drug use and response. Better understanding of the biology of frailty and more consistent identification and study of frailty in clinical and pre-clinical drug evaluation, will shed light on the effects of frailty on pharmacokinetics and pharmacodynamics. This will help guide safe and effective therapeutics in vulnerable, frail older people. Considering the effects of frailty on clinical pharmacology will also be important for future evaluation of the efficacy and safety of drugs targeting frailty, which are likely to be used initially in frail older people.

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