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## Narrative Review

## Accounting for frailty when treating chronic diseases

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## ABSTRACT

Chronic diseases are considered to be major determinants of frailty and it could be hypothesized that their treatment may counteract the development of frailty. However, the hypothesis that intensive treatment of chronic diseases might reduce the progression of frailty is poorly supported by existing studies. In contrast, some evidence suggests that intensive treatment of chronic diseases may increase negative health outcomes in frail older adults. In particular, if treatment of symptoms related to chronic diseases (i.e. pain in osteoarthritis, dyspnoea in respiratory disease, motor symptoms in Parkinson disease) might potentially reverse frailty, the benefits related to preventive pharmacological treatment of chronic diseases (i.e. antihypertensive treatment) in patients with prevalent frailty is not certain. In particular, several factors might alter the risk/benefit ratio of a given treatment in persons with frailty. These include: exclusion of frail persons from clinical studies, reduced life expectancy in frail persons, increased susceptibility to iatrogenic events, and functional deficits associated with frailty. Therefore, frailty acts as an effect modifier, by modifying the risks and benefits of chronic disease treatments. This hypothesis must be considered and tested in future clinical intervention studies and clinical guidelines should provide specific recommendations for the treatment of frail people, underlining the pros and the cons of pharmacological treatment and possible targets for therapy in this population. Meanwhile, in older patients, the prescribing process should be individualized and flexible.

## 1. Introduction

The accumulation of biological deficits and dysfunctions occurring with age impairs the homeostatic balance of organisms, leading to a condition called “frailty”. Frailty is defined as a ‘progressive age-related decline in physiological systems, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health-outcomes’ [1]. Frailty is common in older adults, with a prevalence between 8% and 16% in community-dwelling older adults [2,3] and up to 85% among nursing home residents [4]. Frailty is associated with shorter survival, poor quality of life, and increased risk of disability, hospitalization, and institutionalization [5–7].

Chronic diseases are considered to be major determinants of frailty. According to the widely used frailty phenotype construct proposed by Fried et al. [8], the presence of chronic diseases has a central role in

initiating or worsening frailty. In addition, the frailty index proposed by Rockwood et al., which is based on a combination of different deficits, primarily includes chronic diseases as a criterion [9].

As chronic diseases have such a strong role in determining frailty, it could be hypothesized that treating these conditions may, in turn, counteract the development of frailty, eventually reducing any associated negative consequences [10]. However, the hypothesis that intensive treatment of chronic diseases might reduce the progression of frailty is poorly supported by existing studies. In contrast, some evidence suggests that intensive treatment of chronic diseases may increase negative health outcomes in frail older adults. For example, polypharmacy, anticholinergic and psychotropic medications have been associated with incident frailty and pre-frailty over two to five year follow-up periods [11].

The clinical picture of patients with chronic diseases is strongly

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**Table 1**

Clinical picture of frail and non-frail patients with chronic conditions (adapted from Rolfsen et al. Age aging. 2006 Sep; 35 [5]:526–9).

Characteristic/domain	Non-frail	Frail
Chronic diseases	Diabetes, hypertension	Diabetes, hypertension
Symptoms	None	Present (i.e. pain, dyspnea, dizziness)
Functional status	Physically active Independent in instrumental activities of daily, including managing finances and/or medications, use of transportation, housework, shopping, walking outside alone, preparing meals	Slow walking speed Need help in instrumental activities of daily living, including managing finances and/or medications, use of transportation, housework, shopping, walking outside alone, preparing meals
Cognition	Not impaired	Mild to moderate impairment
Social function	Availability social support (i.e. lives with spouse or relatives)	Poor social support (i.e. lives alone, limited support available from relatives or friends)
Continence	Continent	Urinary incontinence
Nutrition	Normal nutritional status	Obesity or malnutrition, recent weight loss
Mood	Normal	Depressive symptoms, sad or depressed

influenced by the presence of frailty features (see Table 1): presence of chronic disease might represent a limited part of the complexity of frail patients that usually present with multiple impairments in systems and organs and this complexity might influence the approach to pharmacological treatment and in particular the use of symptomatic and preventive medicines.

## 2. Symptomatic treatment of diseases in frailty

Symptoms related to chronic diseases might have a relevant role in the onset or worsening of frailty status, and the treatment of these symptoms might potentially reverse frailty. For example, it has been shown that pain is a strong determinant of frailty in patients with osteoarthritis and it was suggested that this condition could be considered as a component of the frailty phenotype [12]. Pain could impact on walking ability, speed, and strength and consequently cause a reduction in physical activity levels [13]. These parameters are all included among the criteria used to assess Fried's phenotype and can contribute to the development of frailty. In addition, pain might increase the risk of falls, cause depression, and worse quality of life and consequently precipitate frailty [14]. Based on this evidence it might be suggested that pharmacological treatment of pain might reverse frailty status.

Similarly, Parkinson's disease is often associated with frailty and its symptomatic treatment (for example by use of Levodopa) might have an impact on frailty status [15]. Medications used for symptomatic treatment of Parkinson's disease that have an impact on motor symptoms, improving walking ability and speed, may reduce exhaustion and falls, and might bring benefits in persons with frailty [16].

Another example is dyspnoea. This condition could lead to physical inactivity, loss of skeletal muscle strength, mobility problems (including walking deficits), and ultimately frailty [17]. For this reason it might be hypothesized that treatment of dyspnoea might reduce the progression of frailty.

Despite a beneficial effect of treatment of pain, motor symptoms of Parkinson's disease, and dyspnoea on frailty seems clinically obvious, studies proving evidence on this association are currently lacking.

## 3. Preventive treatment of diseases in frailty

Treatment of chronic diseases might have an impact on the onset of frailty by preventing the occurrence of negative health events. For example, it has been hypothesized that the pharmacological treatment of frail persons who experienced a bone fracture, may prevent the onset of new fractures and therefore reduce the risk of frailty and disability [18], but evidence suggests lack of benefit from treatment with bisphosphonates on fractures and mortality in frail women in nursing home [19]. Similarly, possible benefits related to preventive pharmacological treatment of hypertension on frailty onset are still being discussed.

In observational studies hypertension does not seem to have an

impact on frailty onset [20,21] and the negative effects of anti-hypertensive treatment seem to be more pronounced in patients with frailty [22,23]. In addition, the negative effects of hypertension on health outcomes might be reduced in the presence of frailty, suggesting a reverse epidemiology phenomenon in patients with frailty [24].

Results of observational studies were not confirmed in the SPRINT study, which is the only clinical trial exploring the efficacy of anti-hypertensive treatment in frail older people. SPRINT reported that, compared to standard blood pressure control, intensive control confers a benefit on cardiovascular morbidity and mortality both in frail and non-frail persons [25]. However, among frail participants those in the intensive blood pressure control group experienced a significantly higher rate of serious adverse events, including hypotension, syncope, bradycardia, electrolyte abnormalities, injurious falls, acute kidney injury, or acute renal failure. It is noteworthy, however, that the SPRINT study applied extensive exclusion criteria, to remove persons with various chronic diseases, cognitive impairment, psychiatric disorders, and those institutionalized or with poor medication adherence [26].

The example of hypertension could also apply to other chronic diseases, where the pros and the cons of intensive pharmacological treatment in frailty are still under debate, and any possible positive effects might be counterbalanced by an increased risk of negative effects. Indeed, treatment of chronic diseases in frail individuals may raise several concerns that might alter the risk/benefit ratio of a given treatment (Table 2).

### 3.1. Exclusion from studies

Frail older people are almost always excluded from randomized trials assessing the effects of treatments of chronic diseases. The main reasons might relate to barriers research clinics have that limit the possibility to perform assessments and examinations, or higher mortality rates that prevent having appropriate follow-up times [27]. This limits the generalizability of clinical trial findings and leads to difficulties in estimating efficacy and safety of treatments for chronic diseases in persons with frailty. Possible solutions may be to analyze larger datasets in order to perform comparative effectiveness analyses and answer questions that arise in clinical practice [28].

### 3.2. Limited life expectancy

Frailty is associated with limited life expectancy [29]; estimates from the SHARE study suggests that life expectancy for frail individuals at age of 70 years ranges between 0.1 and 1.8 years in men and between 0.4 and 5.5 years in women [30]. This clearly suggests that several preventive treatments for chronic disease might have limited benefits in persons with frailty, given that the time-until-benefit might exceed the actual life expectancy of the frail individual. In frail populations, it is essential to assess life expectancy, evaluate risk-benefit ratio of

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