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REVIEW PAPER

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Hypertension, heart failure, and frailty in older people: A common but unclear situation

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Abstract

Hypertension and heart failure are common conditions in older people. Comorbidity, together with aging, is commonly associated with frailty, which is a cause of a worse prognosis, more hospitalizations, increased dependency, and mortality. Despite being increasingly common conditions, data on the prevalence and influence of frailty in hypertensive older patients with HF are lacking. This may be due to the multidimensional aspects of frailty and the differing tools used to evaluate it. Nevertheless, in clinical practice, it is common to see frail hypertensive patients with HF but the specific characteristics of this group of patients, including multimorbidity and frailty, and the lack of data from registries or randomized clinical trials make the diagnosis and management of these patients more difficult than in those of other ages. This review focuses on what is known and on where future investigations should focus in this common but unclear situation.

1 | INTRODUCTION

Hypertension and heart failure are common diseases in older people, with an increasing prevalence according to age. The worldwide progressive increase in life expectancy is one reason why patients aged ≥80 years with hypertension and heart failure are frequently seen in our clinics. In the CARdiovascular disease–Living and Ageing in Halle (CARLA) cohort,[1] the prevalence of hypertension in people aged ≥75 years was 81.5% for men and 86.1% for women. More than 50% of patients hospitalized with heart failure are aged ≥75 years.[2]

In daily clinical practice, frail hypertensive patients with heart failure are common. However, the specific characteristics of this segment of the population, including multimorbidity and frailty, and the lack of data, either from registries or from randomized clinical trials, make the diagnosis and management more difficult than people of other ages. This review aims to summarize what is already known in this field and what should be the goal in future studies.

2 | DEFINITION AND EVALUATION OF FRAILTY

Life expectancy has increased worldwide over the past century,[3] reflecting changes in lifestyle and diet, as well as aging. However, older people have a greater likelihood of presenting multiple, and usually interacting, conditions.[4] This situation, known as multimorbidity, can lead to interactions between disorders and their treatments, affecting functionality, quality of life, and the risk of mortality. These interactions represent a greater risk than the sum of all individual effects expected from any disorder alone.[5]

Together, aging, underlying physiological changes, chronic diseases, and multimorbidity result in the so-called "geriatric syndromes,"[6] among which frailty is very common. Figure 1 shows the mechanisms leading to frailty. The prevalence of frailty in high-income countries is around 4% in persons aged 50-64 years and increases to 17% in people aged ≥65 years.[7]

However, what does frailty mean? As summarized in Figure 1, frailty has been defined as a state of reduced ability to recover from stress resulting from an age-related decline in reserves. Frailty involves several domains: physical, psychological, social, and others. Its importance lies in the fact that it confers an increased risk of adverse health outcomes such as falls, fractures, post-operative complications, disability, institutionalization, and mortality.[8] Therefore, a careful evaluation of frailty in older people is a better predictor of survival and other outcomes, than disease or the extent of comorbidities.[9]

How should we evaluate frailty? Frailty includes at least four domains: clinical, physical-functional, cognitive-psychological, and

social.[10] In addition, the tools available for its evaluation usually examine a partial aspect of this complex situation. For instance, Fried[11] proposed the frailty phenotype with five components: weakness, slowness, exhaustion, low activity, and weight loss. However, this only focuses on physical frailty, while there is a possible floor effect in heart failure patients, and unintentional weight loss is difficult to assess in patients taking diuretics. Another useful tool is the short physical performance battery,[12] which is a composite measure assessing walking speed, standing balance, and sit-to-stand performance. Again, it only focuses on physical frailty and also has a possible floor effect in heart failure patients. Another tool is the Frailty Index of Accumulative Deficits (FI-CD), also known as Rockwood's approach,[13] which assess frailty through the accumulation of health deficits across multiple domains including cognition, the activities of daily living, comorbidity, deficits in social relations and social support, and abnormal laboratory results. The main problem is that, for routine use, it is time consuming. These tools are summarized in Table 1.

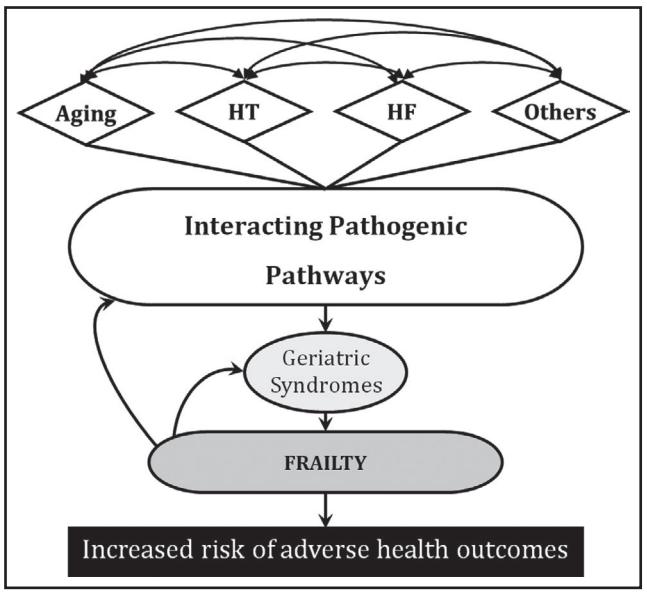

FIGURE 1 Pathway to frailty from aging, hypertension, heart failure, and other diseases. Aging, hypertension, heart failure, and other comorbidities may have an interaction which promotes development of other diseases in older people. For example, hypertension associated oxidative stress and Angiotensin II signaling appear to play an important role in the development of heart failure in the elderly. These, together with inflammatory response, promote collagen deposition. In this context, cardiomyocyte loss due to apoptosis and necrosis may also occur. Some of these pathophysiological pathways may also act at vascular level leading to various macro- and micro-vascular complications. The aforesaid shared factors, and their consequences, may lead to geriatric syndromes such as cognitive and functional decline, falls, delirium, and urinary incontinence. All these may lead to frailty, with feedback mechanisms enhancing risk factors and geriatric syndromes. Such pathways may result in increased risk of adverse health outcomes

TABLE 1 Most used instruments to identify and measure frailty

Frailty assessment instrument	Characteristics
Physical frailty	
Fried's frailty phenotype	Five physical components of frailty: weakness (handgrip dynamometer); slow walking speed (5 m gait speed); exhaustion; unintentional weight loss; and low physical activity
Short physical performance battery	Encompasses slowness, weakness, and balance measured by a series of three timed physical performance tests (gait speed, chair stand test, and tandem balance)
Multidimensional frailty	
Frailty Index of Accumulative Deficits (FI-CD) (Rockwood's approach)	Assessed through the accumulation of health deficits across multiple domains, such as cognition, activities of daily living, comorbid diseases, deficits of social relations and social support, or abnormal laboratory results

3 | HYPERTENSION IN OLDER PEOPLE

The prevalence of hypertension rises with age, especially isolated systolic hypertension. A recent systematic review[14] that included 135 population-based studies of 968 419 adults from 90 countries found that, in adults aged ≥70 years, the estimated prevalence of hypertension was 73.6% for men and 77.5% for women in high-income countries and 65.6% for men and 74.7% for women in low- and middle-income countries. In older people, hypertension is associated with other risk factors, including dyslipidemia, obesity, and diabetes, which increase the cardiovascular risk, cardiovascular mortality, and all-cause mortality in patients with hypertension.[15]

Although hypertension is very common in older people, current evidence on the efficacy and safety of blood pressure–lowering treatment in older patients with hypertension is far from being based on indisputable evidence. It is known that in the oldest old, blood pressure–lowering drugs have been shown to reduce the risk of stroke, cardiovascular events, and total mortality, according to some trials, such as the Hypertension in the Very Elderly Trial (HYVET) study.[16] Moreover, in the Systolic BP Intervention Trial (SPRINT) which included including 28.3% patients aged ≥75 years, a lower systolic blood pressure target (corresponding to a systolic blood pressure goal <120 mm Hg) resulted in lower rates of major cardiovascular events and any cause mortality. In the subgroup analysis, the authors found no differences between patients aged >75 years and those aged ≥75 years.[17] However, these results could reflect the benefit of more intensive blood pressure reduction in relatively healthy octogenarians, rather than the effect on frail hypertensive.

4 | HYPERTENSION AND FRAILTY

The association between hypertension and frailty syndrome in older patients is far from clear for various reasons including the definition of frailty and the tools used to measure it. This may originate a lack of information on the prevalence of hypertension in frail older patients. Likewise, there are no data on the relationship between hypertension and frailty. Therefore, whether a blood pressure–lowering treatment could result in a net benefit for frail older patients must be balanced against the safety risks which, in these patients, could be associated with drug treatment, including orthostatic hypotension, falls, and polypharmacy.

There are little data on the prevalence of hypertension in frail older people. A cross-sectional study of 619 older outpatients by Aprahamian[18] found that hypertension was more prevalent in the pre-frail (72.5%) and frail (83%) groups than among controls (51.7%), measuring frailty through the FRAIL scale. Kang[19] analyzed data from the 5th Korean National Health and Nutrition Examination Survey, including 4352 older adults (age ≥ 65 years). They measured frailty through a FI-CD based on 42 items. The prevalence of hypertension was higher in frail older people (67.8%) than pre-frail (60.8%) or robust older people (49.2%) ($P < .001$). Moreover, frail older people were more likely to be treated than pre-frail or robust older people ($P < .001$) but, interestingly, the proportion of patients whose blood pressure was controlled (<150/90 mm Hg) was lower in frail older people ($P = .005$).

More recently, a meta-analysis[20] analyzed the relationship between hypertension and frailty. With respect to the incidence of frailty according to baseline hypertension, two studies found that baseline hypertension did not significantly predict the incidence of frailty, but one found that hypertension was significantly associated with an increased incidence of pre-frailty and frailty, although there was no adjustment by confounders. Another study found an association between hypertension and incident frailty in the univariate analysis but this was not confirmed in the multivariate analysis. With respect to cross-sectional associations between frailty and hypertension, 13 studies found a significantly higher prevalence of frailty in patients with hypertension and 10 found no significant association. These data indicate that some subgroups of older patients with hypertension might be particularly fragile due to specific risk conditions and will require caution and strict monitoring during antihypertensive treatment.

With respect to relationship between blood pressure values and mortality, the Milan Geriatrics 75+ Cohort Study[21] was a longitudinal geriatric outpatient cohort that investigated the relationship between blood pressure and mortality in older adults by age, functional and cognitive status: 1587 outpatients (age ≥ 75 years) were included. The results showed a U-shaped relationship between systolic blood pressure and diastolic blood pressure and the mortality risk. However, although blood pressure, the Mini-Mental State Examination, and the Basic Activities of Daily Living were assessed at baseline, there was no specific assessment for frailty.

With respect to the efficacy of intensive blood pressure lowering, an exploratory subgroup analysis from the SPRINT trial[22] stratified by baseline frailty showed higher event rates with increasing frailty but significantly lower event rates in the intensive treatment group. The same results were found after stratifying by gait speed in favor of the intensive treatment group.

With respect to the safety of intensive blood pressure lowering in frail individuals, the Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population (PARTAGE) study[23] assessed all-cause mortality according to systolic blood pressure levels achieved (target systolic blood pressure <130 mm Hg) and the number of antihypertensive drugs in older residents of nursing homes. There was a higher risk of mortality in frail octogenarians who had lower systolic blood pressure but were on ≥2 antihypertensive agents compared with those on one or no medications.

5 | HYPERTENSION AND HEART FAILURE

It is known that elevated levels of diastolic blood pressure and, especially, systolic blood pressure are major risk factors for the development of heart failure. However, the association between systolic blood pressure and heart failure risk in older people is not completely defined. In a post hoc analysis using a 10-year follow-up of 4408 participants from the Cardiovascular Health Study and the Health Aging and Body Composition (ABC) Study, the authors found a continuous positive association between systolic blood pressure and heart failure risk in older people for levels of systolic blood pressure as low as <115 mm Hg; over half of incident HF events occur in individuals with systolic blood pressure <140 mm Hg. On the other hand, the long-term treatment of hypertension reduces the risk of heart failure by 30% in younger populations, by 50% in older people, and by almost 80% in older people with a history of myocardial infarction.[15,24]

With respect to the treatment of hypertension in patients with established heart failure, there are no compelling data to justify a single blood pressure target when treating hypertension in patients with established heart failure. Therefore, the optimal blood pressure target for the treatment of hypertension in patients with heart failure is not firmly established.

Guidelines[25] clearly establish that patients with previous or current symptoms of heart failure with reduced ejection fraction should be treated with diuretics, angiotensin-converting enzyme inhibitors (or Angiotensin receptor blockers if intolerant to angiotensin-converting enzyme inhibitors), β-blockers, and aldosterone receptor antagonists, which have been shown to improve outcomes for patients with HF and can lower blood pressure in hypertensive patients with heart failure with reduced ejection fraction. As for heart failure with preserved ejection fraction, there are no clear data on the BP goal or on which type of antihypertensive drug is preferable.

6 | FRAILTY, AGING, AND HEART FAILURE

Pathophysiological pathways in persons with heart failure and frailty sometimes coincide, as both appear to involve a multisystem cascade

that includes disorders and dysregulation in neurohormonal, metabolic, inflammatory, and immunologic pathways. This cascade leads to an enhanced catabolic state, energy failure, oxidative stress, and release of pro-inflammatory signals.[26,27] Therefore, as one of the most prevalent comorbid conditions in heart failure with preserved ejection fraction is hypertension, it could also contribute to a higher prevalence of frailty in hypertensive heart failure with preserved ejection fraction patients. Nevertheless, the clinical consequences and its impact on the prognosis are far from clear.

Available data on the prevalence are relatively scarce. Denfeld[28] in a systematic review and metanalysis of the prevalence of frailty in heart failure included 26 studies with 6896 heart failure patients and found a prevalence of frailty in heart failure of 44.5%. Using physical frailty measures, the prevalence was slightly lower (42.9%) and slightly higher when using multidimensional frailty measures (47.4%). No relationship between age, functional class, and the prevalence of frailty was found.

A study by Khan[29] assessed the association between physical and phenotypic frailty and the risk for heart failure in older adults in a cohort of 2825 participants from the Health ABC Study (community-dwelling patients, 70-79 years old). Compared with non-frail participants, those with physical or phenotypic frailty had a higher prevalence of heart failure.

Recently, Sze[30] analyzed the prevalence of frailty in 467 consecutive ambulatory heart failure patients and found it was higher in heart failure patients than in control patients (30%-52% vs 2%-15%, respectively). Frail patients tended to be older, have worse symptoms, higher natriuretic peptides (NTproBNP) levels, and more comorbidities.

However, once again the method of evaluating frailty is a key factor in determining the impact of frailty on heart failure outcomes. Regarding this aspect, a position paper of the Heart Failure Association of the European Society of Cardiology[31] has proposed a Heart Failure Association Frailty Score. With respect to the impact of treatment on frailty, current recommendations on treatment for heart failure which always include blood pressure–lowering drugs and proper blood pressure control should be followed.

However, given what we know, frailty is associated with aging, and comorbid conditions that are additive to the progressive age-related decline in physiological reserve. Therefore, although both frailty and heart failure are common in older adults, the prevalence of frailty in patients with heart failure is independent of age, as frailty may also be experienced by younger (<60 years) patients with heart failure. Thus, frailty, being more common in heart failure with preserved ejection fraction, could be related to the greater burden of cardiac and non-cardiac comorbidities typically experienced by patients with heart failure with preserved ejection fraction.[32]

7 | PENDING QUESTIONS

As the evidence shows, problems arise when it comes to the evaluation and treatment of frail patients with hypertension, and these difficulties are even greater in frail heart failure with preserved ejection fraction hypertensive patients.

In addition to the evaluation and measurement of frailty mentioned above, the type of blood pressure measurement is also important, as it is known that ambulatory blood pressure measurement is more reliable than office blood pressure measurement with respect to outcomes. However, very few studies are based on ambulatory blood pressure measurement.

Among those studies, a cross-sectional study by Bastos-Barbosa[33] in 77 frail, pre-frail, and non-frail older patients (according to Fried criteria) found that on ambulatory blood pressure measurement, frail patients had a higher systolic blood pressure and diastolic blood pressure levels at 24 hours and during sleep than the non-frail group.

As ambulatory physical activity is associated with daytime blood pressure, lower physical activity in frail older people causes lower daytime blood pressure, which often could result in non-dipper type of night-time blood pressure. In the elderly, non-dipping/reverse dipping may also be related to other factors such as poor sleep, impaired renal function, and others.[34-36] These conditions are associated with frailty.

Non-dipping patterns are, like riser pattern of nocturnal blood pressure, associated with an increased risk of heart failure in older people and with a poor prognosis, including cardiovascular events and the recurrence of hospitalized heart failure.[34,37-40]

The new ambulatory blood pressure measurement equipped with actigraphy could measure physical activity-associated blood pressure increases (Actisensitivity).[41,42] Hyper-actisensitivity and inverse actisensitivity are considered abnormal pathological conditions. Inverse actisensitivity (negative association between physical activity and daytime blood pressure) is associated with heart failure with a reduced ejection fraction. Responders may recover from inverse actisensitivity to adequate actisensitivity with medication.

Therefore, hypertension is significantly associated with frailty and is more prevalent in frail older patients. It also seems that intensive blood pressure control could influence the development of frailty, but there is scarce information to support this hypothesis, and it should be explored in future prospective clinical trials. As for intensive blood pressure lowering, it should not be forgotten that frail older patients may not tolerate blood pressure lowering in the same way as robust elderly patients with hypertension.

With respect to measuring clinical blood pressure or ambulatory blood pressure and their concordance, it should be remembered that white coat hypertension (WCH) represents a large percentage of our patients. In the HYVET study,[43] 50% of people aged >80 years had WCH and the authors found that very old patients with WCH may benefit from treatment, but as explained above, there was no frailty evaluation in HYVET. In another study, Pierdomenico[44] assessed the prognostic value of masked uncontrolled hypertension (MUCH) and white coat uncontrolled hypertension (WCUCH), respectively, in older treated patients with hypertension. They found that those with MUCH (34%) had a significantly higher risk and those with WCUCH (30%) have a slightly, non-significantly higher risk. Nevertheless, frailty was not evaluated in either of these studies.

To our knowledge, there are no studies evaluating blood pressure control through ambulatory blood pressure measurement together with frailty in heart failure with preserved ejection fraction patients, and therefore, the ABPM in HFpEF global registry[45] will aid understanding of this common but unclear situation.

8 | CONCLUSION

Older patients commonly have hypertension complicated with heart failure and frailty. However, our knowledge of this common situation is far from satisfactory. Hypertension and heart failure are more frequent at advanced ages, where frailty is also more frequent, but there are no validated tools to measure frailty in those patients. In addition, knowledge of the repercussions of frailty on hypertension and heart failure is very limited.

Taking this into account, and as current guidelines recommend,[25] individualized treatment strategies are indicated, considering the benefits of appropriate blood pressure control, as some studies have shown clinical benefits by reducing elevated blood pressure in "healthy" older people aged >80 years, but should frail older patients with multiple comorbidities and a reduced life expectancy be "overtreated" or rather, should the first goal to avoid harm and adverse effects in frail older patients? As part of this strategy, in older patients with hypertension, ambulatory blood pressure measurement and frailty evaluation should be part of routine clinical management.

As for treatment, there are little data available on the best blood pressure goal for frail or pre-frail patients with hypertension, and even less data about which class of blood pressure–lowering drug should preferably be used. Therefore, there is an urgent need to plan new studies in this group of patients, taking into account the possible need for patient-reported outcome measures, instead of traditional outcomes, and also the use of frailty measurement tools including different aspects of this common entity.

CONFLICT OF INTEREST

MC and KK have no conflicts of interest regarding the content of this review.

AUTHOR CONTRIBUTIONS

M Camafort and K Kario involved in conception and design of study, drafting the manuscript, revising the manuscript critically for important intellectual content, and approval of the version of the manuscript to be published (the names of all authors must be listed).

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