



Management of Hypertension in the Elderly and Frail Patient

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Abstract

Hypertension is a frequent finding in elderly patients. Hypertension in older age can be both associated with frailty and represent a risk factor for frailty. Hypertension is recognized as a main risk factor for cardiovascular diseases such as heart failure, atrial fibrillation, and stroke and the occurrence of these diseases may provoke a decline in health status and/or worsen the degree of frailty. Blood pressure targets in hypertensive older and frail patients are not completely defined. However, specific evaluations of individual patients and their co-morbidities and assessment of domains and components of frailty, together with weighted consideration of drug use, may help in finding the appropriate therapy.

Key Points

Frailty and hypertension are frequently found in the elderly and are closely interconnected.

A personalized approach is needed in the management of hypertension in older persons, focusing on hypotension, co-morbidities, and adherence/persistence to medical prescriptions, while considering the specific frailty deficits.

Pharmacogenetics might help in identifying (and preventing) frailty statuses associated with pharmacological treatments.

1 Frailty

The definition of frailty includes various aspects of patient evaluation and tends to capture the subject of vulnerability or the global risk of patients' inability to withstand potential acute stressors [1–5]. The classical domains that have been identified are the physical domain, the medical domain, the cognitive/depressive domain, and the social domain [6, 7]. Various deficits may combine to confer a frailty status to the patient.

For instance, among the medical domains, deficits could be related to multi-morbidity, polypharmacy, and nutrition, and these could be associated with deficits in other domains, thus increasing the degree of frailty (Fig. 1).

Although frailty is closely related with ageing and multi-morbidity, some components of frailty may change over time and even improve [8]. For instance, a patient could be particularly frail after an acute traumatic or ischemic vascular event, with the deleterious effects of hospitalization in older patients and the need for multidrug therapy. However, the same patient after some weeks of support focused on the main deficits evidenced by the subject may have improved health status and be completely recovered, thus returning to the same level of frailty as before the event (Fig. 2).

Traditionally the two models to approach frailty are the phenotype model and the cumulative deficit approach [9–12], identifying also minor degrees of frailty called pre-frailty. Moreover, the comprehensive geriatric assessment or multidimensional approaches are more representative of global complexity assessment, though time consuming [13–16]. Short multidimensional approaches such as the

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DOMAINS and COMPONENTS

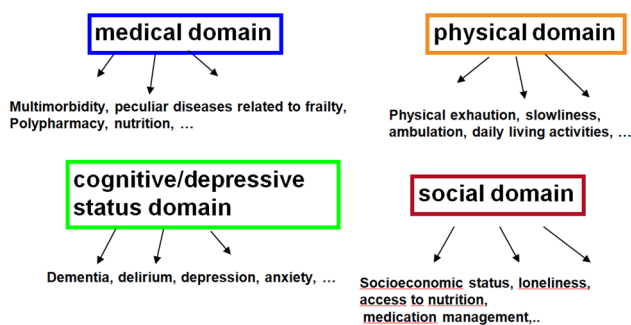


Fig. 1 The frailty domains and their components

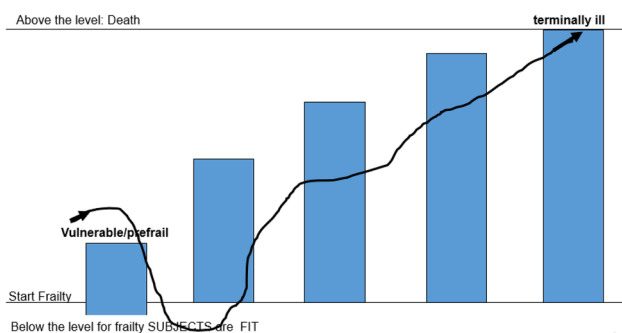


Fig. 2 The frailty trajectory from vulnerable/pre-frail to terminally ill (black arrows). Boxes indicate increasing degrees of frailty that these patients may experience towards end of life. During the trajectory, harmful health events may rapidly increase the degree of frailty. However, this increase can be reverted in some cases, due to appropriate targeting of frailty domains (e.g. introducing rehabilitation or social support)

Essential Frailty Toolset have been shown to have an additive predictive value in specific cardiovascular diseases such as aortic stenosis or cardiac surgery [17, 18] and are becoming popular, particularly in the general cardiology ambulatory setting, due to their feasibility.

2 Frailty in Cardiology

Increasing evidence points to a role of the immune system and inflammation in the atherosclerosis process, together with the classical risk factors including ageing, low-density lipoprotein cholesterol, hypertension, smoking habits, and diabetes mellitus [19]. The cellular and vascular changes are characterized by functional and morphological alterations of circulating immune cells and endothelial cells occurring early in the atherosclerosis development, and by obstructive lesions which may lead to downstream tissue ischemia and necrosis [19–21]. Frailty often begins with recognized

changes at molecular, cellular, and system levels with physiological impairment due to inflammation, sarcopenia and osteopenia, and neuroendocrine dysregulation [22, 23]. A shared pathophysiology between cardiovascular diseases risk and frailty has been suggested and both frailty and pre-frailty constitute independent risk factors for cardiovascular diseases and for cardiovascular mortality in older adults [24, 25]. Both cross-sectional and longitudinal findings show that frailty is closely related with cardiovascular diseases [25, 26]. In particular, frailty is more prevalent in patients with peripheral artery disease and heart failure whereas mainly heart failure was associated with incident frailty over time [26]. The identification of deficits and a screening for frailty provide the chance to highlight the potentially modifiable components of frailty, and, when identified, to provide a better definition of patient risk [7]. General support and management of frailty includes nutrition, exercise, and cognitive/emotional support, a multicomponent rehabilitation program when needed, focus on environmental aspects to reduce falls, a guarantee of social support, and targeting of inappropriate polypharmacy, while not denying appropriate treatments and reducing hospitalization periods when needed [7, 27]. Nutritional support before scheduled cardiac surgery has been suggested as a strategy to prevent frailty [28].

3 Hypertension and Frailty

The relationship between frailty and hypertension is difficult to interpret because hypertension could represent both a risk factor for the development of frailty [29] and a coexisting condition. In the cumulative deficit approach, which together with the Fried phenotype model constitutes the commonly used method for detecting frailty [9–11], hypertension is included in the accumulation of diagnoses and leads to a higher frailty score. The prevalence of hypertension is up to 80% in patients with frailty and appears to be significantly associated with lower cognitive performance and sedentary habits [30].

Patients with frailty may present with both low and high blood pressure (BP) values, with a typical U-shaped relationship [31, 32]. In a sub-study of the Systolic Blood Pressure Intervention Trial (SPRINT) [33], the state of frailty was characterized by the intake of a greater number of anti-hypertensive drugs. Other series showed lower BP values in frail patients with increased presence of comorbidities, malnutrition, and overtreatment [34, 35]. Frailty was associated with higher risk of non-dipping and reduced night-time systolic BP fall in a small study evaluating 24-h ambulatory BP, possibly indicating an effect of frailty on sleep quality and mobility, vascular endothelial dysfunction or impairment in the autonomic system [36]. However, differences in the BP pattern may simply reflect a selection bias of evaluated

patient populations; in particular, low BP would appear in the context of severely frail patients as a marker of reduced functional reserve and poor baseline health [37].

There is still insufficient evidence to establish a BP target in the elderly [38]; this population, especially patients with frailty, are often excluded from trials or are without precise identification in most studies, and thus suffer from the lack of recommendations. When participants of the SPRING trial were characterized according to frailty measures, the patients were found to have a similar degree of frailty compared with other large trials with ambulatory patients [33]. However, particular subgroups of frail older persons under-represented in clinical research are those who are institutionalized, requiring nursing, or with dementia, with a marked ‘gap in evidence’. In addition, most large trials on hypertension in older persons exclude patients with orthostatic hypotension, which is one major concern in treating older persons and the different domains and components of frailty are not disentangled, even in studies reporting frailty status. Moreover, in published literature, different age ranges are considered when studies on older persons are focussed on, making it difficult to compare results. Major guidelines suggest “individualized BP target” [39], “clinical judgement” [40], “determination of tolerance” [41], or “caution for intensive BP lowering” [42] without providing an indication as to what extent BP-lowering treatment benefits this patient population. This is probably due to accumulating evidence from several observational studies on neutral or adverse effects on mortality by targeting low BP values. The review by Todd et al. [43]—albeit limited by wide heterogeneity in frailty measures among considered studies—showed that in patients with frailty there was no difference in all-cause mortality between systolic BP < 140 mmHg and \geq 140 mmHg. In a large administrative database from the United Kingdom [44], an excess of all-cause mortality was recently found in patients with frailty who showed a systolic BP < 130 mmHg, without significant reduction in cardiovascular risk. This negative effect of low BP on mortality seems to be mostly related to those receiving antihypertensive drugs as compared with those presenting with spontaneous low BP [45]. In the HYPertension in the Very Elderly Trial (HYVET), targeting a BP of 150/80 mmHg in adults aged 80 years or older was associated with lower mortality also after adjustment for baseline frailty, with a 36% risk reduction of stroke and a 41% risk reduction of fatal and nonfatal cardiovascular events [46]. However, the prognostic role of BP on mortality and cardiovascular prognosis is probably not uniquely related to age, being better described by ‘non-chronological’ variables such as ‘vascular ageing’, the global functional capacity, and cognitive performance [47].

For these reasons, managing hypertension in frail patients cannot be reduced to a treat-to-target approach to improve cardiovascular prognosis, and needs to be integrated with

an individualized risk/benefit evaluation. This latter should include the comparison between the time-until-benefit of antihypertensive treatment and individual life expectancy, which often constitutes a missed estimation in most patients. Second, changes in pharmacokinetics induced by advanced age and the risk of drug–drug interactions should be taken into consideration with respect to the increased vulnerability to hypotension-related adverse events and a move towards deprescribing in selected cases.

4 Hypertension Drug Treatment and Frailty

4.1 Pharmacological Therapy of Hypertension

Pharmacological treatment of hypertension first of all includes agents such as diuretics (thiazide and thiazide-like diuretics), angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) and dihydropyridine calcium channel blockers (CCBs), alone or in combination. β -Blockers should be considered in the presence of cardiac conditions such as ischemic heart disease, atrial fibrillation or heart failure. Finally, current guidelines suggest the administration of triple-drug combinations, if the target BP is still unattained [39, 48].

Despite good efficacy and low frequency of side effects associated with antihypertensive therapy, achievement of adequate BP control is reported in only about half of treated patients [49–51].

4.2 Pharmacological Therapy of Hypertension in Frail Subjects

The relationship between frailty and hypertension includes two fundamental aspects. First of all, antihypertensive treatment may represent a risk factor for the development of frailty, in particular when double- or triple-drug combinations are employed [52–54]. On the other hand, frailty itself may increase the risk of treatment failure as well as of drug-induced side effects which, in a negative loop, result in increased patient frailty [55]. Moreover, specific adverse effects which need specific precautions may be associated with antihypertensive drugs in individuals aged 80+ years (for details see Table 3 of Benetos et al. 2019 [56]). Thus, an individualized approach is the best choice for the treatment of hypertension in patients with frailty. Nevertheless, older (and frailer) hypertensive patients have been shown to benefit from antihypertensive therapy [53, 57], as indicated by two large, randomized studies which included elderly and frail patients with a frailty distribution similar to that in the outpatient population. In these studies, antihypertensive treatment reduced coronary artery disease risk, heart failure,

stroke, and other causes of mortality in older patients, even in frail ones [58, 59].

However, as already mentioned above, antihypertensive treatment presents certain risks in frail older adults. In the SPRINT study, frail older adults receiving intensive antihypertensive treatment showed an increased risk of hypotension, syncope, electrolyte imbalance, and acute kidney injury [60]. Moreover, since participants included in the aforementioned studies were relatively robust and had a lower rate of comorbidity [46, 61], the assessment of the degree of frailty has been recommended before starting antihypertensive treatment in frail older adults [59].

The main risk associated with antihypertensive treatment in frail older adult patients is overtreatment [35], and observational studies on hypertension in the older population suggest that aggressive BP lowering may be one of the main causes of worsening of frail patients' conditions [52–54].

For this reason, current guidelines for hypertension recommend older hypertensive patients with frailty to be initially treated with monotherapy [61, 62]. Moreover, when systolic BP drops to or below 140 mmHg, antihypertensive administration should be reduced as much as possible, except in limited and special circumstances. Finally, no more than two antihypertensive drugs should be prescribed [63]. Concerning the choice of antihypertensive drugs in frail patients, no definitive evidence exists in frail patients supporting one class of antihypertensive drugs as safer compared with others. However, CCBs have been hypothesized to have a protective effect in frail older hypertensive patients [64] and ACEIs may prevent frailty by increasing muscle mass in lower limbs and muscle strength [65, 66].

4.3 Pharmacogenetics and Frailty in Antihypertensive Drug Therapy

The observation of a familial component in drug action opened the way to the idea of pharmacogenetics (PGx), defined as the study of inter-individual variations in DNA sequences related to drug response (EMA/CPMP/3070/01: Position paper on terminology in Pharmacogenetics) [107]. The goal of PGx is to associate a patient's genetic profile with his/her response to treatment, thus determining drug efficacy and toxicity before therapy initiation. This 'precision medicine' approach could allow a safer and more effective use of pharmacotherapy [67] and, in turn, reduce the patients' frailty condition.

Differences in patients' genetic profile are due to the presence of genetic polymorphisms which include insertion/deletion, copy number variations, mini- and micro-satellites, and single nucleotide polymorphisms (SNPs, i.e. DNA sequence variations occurring when a single nucleotide in the genome differs between paired chromosomes). SNPs are the most common type of genetic variations among people, and are

responsible alone for 90% of all genetic differences between individuals [68].

Genome-wide association studies (GWASs) led to the discovery of several genetic variants associated with both antihypertensive drug efficacy as well as drug-induced side effects [69, 70]. In Table 1 we summarize the most common polymorphisms in genes affecting antihypertensive drug response (for further details, see Rysz et al. 2020 [71]).

So far, there is no evidence for a direct relationship between subjects' genetic profile and frailty status in patients treated with antihypertensive drugs. However, patient's genotype has been suggested to contribute, together with other conditions (age, polypharmacy, co-morbidity, etc.), to frailty status in hypertensive patients in different ways by engaging in the pathophysiology of hypertension development, and by altering drug effects through modification of pharmacodynamic interactions between drugs and their targets. Moreover, drug responses might be affected by genetic polymorphisms both in genes encoding for drug-metabolizing enzymes/transporters or in pleiotropic genes participating in metabolic reactions and complex cascades [72, 73]. In any case, the relative role of specific genes and polymorphisms in frail subjects has been hypothesized to differ from non-frail people in terms of both therapy efficacy and drug-induced side effects.

For example, it is well known that falls cause a significant increase in morbidity and in turn in frailty status, especially in older persons [74]. Interestingly, older adults with uncontrolled hypertension (mainly due to drug therapy failure) and orthostatic systolic hypotension were shown to be at greater risk for falls than patients with good response to drug therapy [75]. Moreover, side effects induced by β -blockers (such as hypotension) were also associated with falls [76]. In the light of these results, it seems reasonable to assume that differences in patient's genetic profiles could both increase each subject's frailty state, in particular, when such state results from a therapy failure and/or side effects, and contribute to drug-induced side effects in patients with frailty compared with non-frail people.

In conclusion, the identification of genomic biomarkers for therapy outcome (i.e. effectiveness/ineffectiveness and drug-induced side effects) might help in identifying (and preventing) frailty statuses associated with pharmacological treatments.

5 Clinical Practice

When considering hypertension in older persons, our concern should focus on hypotension. Orthostatic hypotension affects the prognosis in older people not only by increasing the risk of syncope and falls, but also by increasing

Table 1 Selected gene polymorphisms affecting the clinical response to antihypertensive drugs

Drug	Gene	Polymorphisms	Effects	References
Thiazides and thiazide-like diuretics				
Hydrochlorothiazide	ACE	rs1799752	↑ response	[77]
		rs1799752	↑ response	[78]
	ADD1	rs4961	↑ response	[79]
	GNB3	rs5443	↑ response	[80]
	NEDD4L	rs4149601	↑ response	[81]
ARBs				
Losartan	NPHS1	rs3814995	↑ response	[82]
	CAMK1D	rs10752271	↑ response	[83]
Candesartan	SCNN1G	rs11649420	↑ response	[84]
	GPR83	rs3758785	↑ response	[84]
ACEis				
Enalapril	NOS3	rs3918226	↑ response	[85]
		rs3918188	↓ response	[85]
		rs2070744	↑ response	[86]
	PRKCA	rs16960228	↓ response	[85]
	BDKRB2	rs1799722	↑ response	[86]
DHP-CCBs				
Verapamil	KCNMB1	rs11739136	↑ response	[87]
	CACNA1C	rs1051375	↓ response	[88]
	CACNB2	rs2357928	↑ side effects	[88]
	CYP3A5	rs10264272	↑ response	[89]
Amlodipine	CYP3A4	rs2740574	↑ response	[90]
		rs2246709	↑ response	[90]
	CYP3A5	rs776746	↓ plasma conc.	[91]
	ABCB1	rs1045642	↑ oral clearance	[92]

ABCB1 ATP Binding Cassette Subfamily B Member 1, *ACE* angiotensin-converting enzyme, *ACEis* ACE inhibitors, *ADD1* Adducin, *ARBs* angiotensin II receptor blockers, *BDKRB2* Bradykinin Receptor B2, *CACNA1C* Calcium Voltage-Gated Channel Subunit Alpha1 C, *CACNB2* Calcium Voltage-Gated Channel Auxiliary Subunit Beta 2, *CAMK1D* Calcium/Calmodulin Dependent Protein Kinase, ID, *GNB3* G Protein Subunit Beta 3, *CYP3A5* Cytochrome P450 Family 3 Subfamily A Member 5, *CYP3A4* Cytochrome P450 Family 3 Subfamily A Member 4, *DHP-CCBs* dihydropyridine calcium channel blockers, *GPR83* G Protein-Coupled Receptor 83, *KCNMB1* Potassium Calcium-Activated Channel Subfamily M Regulatory Beta Subunit 1, *NEDD4L* Like E3 Ubiquitin Protein Ligase, *NOS3* Nitric Oxide Synthase 3, *NPHS1* Adhesion Molecule, Nephhrin, *PRKCA* Protein Kinase C Alpha, *SCNN1G* Sodium Channel Epithelial 1 Subunit Gamma

CV risk and all-cause mortality [7, 93–96]. Therefore, our main goal when treating hypertension in the elderly is to carefully titrate antihypertensive therapy, also in standing position, which should form part of the standard evaluation in elderly and in patients with frailty [7]. The current ESC guidelines suggest specific recommendations for these patients, that is, to maintain a 130–140 mmHg systolic target and 80–90 mmHg diastolic target, if tolerated, and to consider monotherapy as a first-line strategy in older and frail patients [41]. However, clinical judgement, based on biological age, remains the first fundamental step in complex medical contexts, especially when treating older persons with frailty [97].

Specific considerations should be made in patients with comorbidities such as atrial fibrillation [98]. A high prevalence of left ventricular hypertrophy was found in patients

with non-valvular atrial fibrillation, associated with older age, hypertension, and other factors such as female gender, diabetes, and previous myocardial infarction [99]. The correct stratification of cerebrovascular risk for patients with non-valvular atrial fibrillation requires the recognition of left ventricular hypertrophy [100]. Hypo- and hyper-thyroidism, including subclinical hyperthyroidism, are frequent diseases in elderly patients which are able to interfere with both BP values, antihypertensive treatments and cardiovascular health [101, 102]. Moreover, other conditions potentially worsening during hypotension, such as myocardial ischemia, stroke, worsening of hypotension in aortic stenosis, hypotension during meals, should be considered when treating hypertension in the elderly.

Critical steps during treatment are adherence, persistence, and the correct understanding of medication

schedules [103, 104]. These factors could limit the target achievement and/or influence potential adverse reactions to drugs in all hypertensive patients and particularly in the oldest ones. Shared decision making about a treatment plan includes initial acceptance and implementation, follow-up appointments, and adjustments in drug schedules [56]. Elderly patients with social frailty may be limited by difficulties measuring BP values, reaching the doctor's office, and filling drug prescriptions. Moreover, cognitive frailty and/or medical frailty such as the condition that can occur in patients with post-stroke disabilities may limit the correct timing and understanding of drug schedules.

Finally, the use of digital health technologies is rapidly expanding in the evaluation of hypertension and cardiac diseases, and this support to clinical practice seems to be particularly useful in the older population to facilitate telemedicine, teleconsults, interactions with caregivers, and adherence to medical prescriptions [105, 106].

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