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Andrea UNGAR, Giulia RIVASI, Antonio COSCARELLI, Alessandro BOCCANELLI, Niccolò MARCHIONNI, Paolo ALBONI, Samuele BALDASSERONI, Mario BO, Giuseppe PALAZZO, Renzo ROZZINI, Pierfranco TERROSU, Francesco VETTA, Giovanni ZITO, Giovambattista DESIDERI

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HYPERTENSION IN OLDER PERSONS: WHY ONE SIZE DOES NOT FIT ALL

Andrea Ungar[a,b], Giulia Rivasi[a], Antonio Coscarelli[a], Alessandro Boccanelli[b], Niccolò Marchionni[b], Paolo Alboni[b], Samuele Baldasseroni[b], Mario Bo[b], Giuseppe Palazzo[b], Renzo Rozzini[b], Pierfranco Terrosu[b], Francesco Vetta[b], Giovanni Zito[b], Giovambattista Desideri[b,c]

[a]Hypertension Clinic, Department of Geriatric and Intensive Care Medicine, Careggi Hospital and University of Florence, Florence, Italy

[b]SICGe – Società Italiana di Cardiologia Geriatrica, Via Matteotti 7, Firenze, Italy

[c]Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila.

Corresponding Author

Hypertension Clinic, Department of Geriatric and Intensive Care Medicine,

University of Florence and Azienda Ospedaliero Universitaria Careggi

Largo Brambilla 3, 50134, Florence, Italy

Phone: +39-055-2751820

email: aungar@unifi.it

Abstract

Over recent years, managing hypertension in older people has gained increasing attention, with particular reference to very old, frailer individuals. In these patients, hypertension treatment may be challenging due to a higher risk of hypotension-related adverse events which commonly overlaps with a higher cardiovascular risk. Additionally, frailer older adults rarely satisfy inclusion criteria of randomized clinical trials, which determines a substantial lack of scientific data. Although limited, available evidence suggests that the association between blood pressure and adverse outcomes significantly varies at advanced age according to frailty status. In particular, the negative prognostic impact of hypertension seems to attenuate or even revert in individuals with older biological age, e.g. patients with disability, cognitive impairment, and poor physical performance. Consequently, *one size doesn't fit all* and personalized treatment strategies are needed, customized to individuals' frailty and functional status. Similar to other cardiovascular diseases, hypertension management in older people should be characterized by a geriatric approach based on

biological rather than chronological age and a geriatric comprehensive evaluation including frailty assessment is required to provide the most appropriate treatment, tailored to patients' prognosis and health care goals. This review illustrates the importance of a patient-centered geriatric approach to hypertension management in older people with the final purpose to promote a wider implementation of frailty assessment in routine practice.

INTRODUCTION

Older people represent a very heterogeneous population in terms of cognitive function, physical performance, functional autonomy and life expectancy. This implies very different treatment goals, which also applies to antihypertensive treatment. Furthermore, this age group requires special attention due to the presence of multiple comorbidities and frailty, which determine an increased vulnerability to adverse events. A careful risk-benefit assessment is thus needed, also in the context of hypertension management. In particular, potential benefits of antihypertensive therapy must be balanced against the increased predisposition to treatment-related complications, such as syncope, falls and injuries, electrolyte imbalances and renal dysfunction.

Literature on hypertension management in frail older people is scarce and inconsistent. To date, only two randomized controlled trials have taken into consideration frailty status while assessing the prognostic impact on antihypertensive treatment in the geriatric population. Both these studies have provided data supporting blood pressure lowering in frail older adults, but their results have limited transferability to the "real world", with particular reference to frailer people (1) (2). By contrast, over recent years some studies have provided observational data suggesting that blood pressure targets should be considerably higher in frailer people, such as patients with cognitive impairment or physical disability. Although very limited, available evidence indicates that hypertension management in older people represents a clinical challenge, where *one size doesn't fit all*. Treatment strategies should not be standardized but rather tailored based on patient's biological age. It follows that, in the geriatric population, the clinical assessment of hypertension cannot be separated from a comprehensive geriatric assessment aimed to define frailty status, patients' prognosis and treatment goals. This narrative review illustrates the clinical challenge of hypertension management in older people through the discussion of the available literature that prompts a patient-centred treatment approach.

Hypertension in older people

Hypertension is highly prevalent in the general population and even more so in older people. According to the Framingham Study, (3) people aged 55-65 years have a lifetime risk of more than 90% of developing hypertension. In the geriatric population, approximately two thirds of people are hypertensive, with prevalence rates reaching 90% in individuals aged 75 years or more (4). Hypertension is recognized as one

of the major modifiable risk factors, being associated with an increased risk of stroke, renal disease, coronary syndromes, peripheral arterial disease and dementia (5). Given the progressive increase in life expectancy and the growing ageing population, the prevalence of hypertension is expected to rise dramatically over the next decades, especially in older individuals (6), thus imposing ever greater attention to this condition.

Hypertension in older adults people more commonly presents as isolated systolic hypertension (7), i.e. high systolic blood pressure values associated with normal diastolic blood pressure. The high prevalence of isolated systolic hypertension has a pathophysiological explanation, which is mainly related to increased arterial stiffness. Arterial stiffness can be defined as a reduced distensibility of the arterial wall deriving from vascular aging and exposure to cardiovascular risk factors such as hypertension and diabetes, which cause atherosclerosis, arterial calcifications, endothelial dysfunction, fibrosis of the vascular muscular tunica (8). Arterial stiffening is accompanied by an increase in the velocity at which pressure waves generated by the heart propagate along the arterial vessels, resulting in increased left ventricular load and predisposing to cardiac remodeling (9). In parallel, diastolic arterial pressure tends to reduce, which determines an increase in pulse pressure (10) (11).

Arterial stiffness is responsible for pseudo-hypertension, a phenomenon which is characterized by falsely elevated blood pressure values at non-invasive measurements (using sphygmomanometer) and normal blood pressure values at intra-arterial measures. Pseudo-hypertension manifests in patients with marked arterial stiffness and vascular calcifications, that do not allow vessels to be compressed during non-invasive blood pressure measurements, thus leading to falsely elevated blood pressure estimates. Pseudo-hypertension can be suspected if the radial artery remains palpable during cuff inflation ("Osler sign") or in the case vascular calcifications are detected on X-rays. Pseudo-hypertension is a condition of great clinical relevance as it may potentially result in overtreatment, hypotension, syncope and falls (12).

Indeed, it widely recognized that older people have a significant predisposition to hypotension, due to the overlap of several risk factors with an age-related prevalence increase. These include a tendency to poor hydration, polypharmacy and multimorbidity, as well as age-related changes in pharmacodynamics and pharmacokinetics which determine an increased risk of drug adverse events and interactions (13).

In addition, orthostatic hypotension is highly prevalent in the geriatric population, due to cardiovascular autonomic ageing and reduced baroreceptor sensitivity. Iatrogenic drug-related orthostatic hypotension may

also coexist, particularly in patients receiving polypharmacy (14). Finally, neurogenic orthostatic hypotension frequently manifests in patients with neurodegenerative diseases that affect the autonomic nervous system, such as diabetes and Parkinson's disease (15) (16). In the geriatric population, hypotension may severely impact individuals' prognosis, functional autonomy and survival (17) (18). Hypotension is the main cause syncope and falls in older people, potentially leading to severe injuries, hospitalization and disability. Additionally, it may be responsible for symptoms such as dizziness, balance impairment, and fear of falling, which also impair daily quality of life and functional autonomy (19) (20). Finally, hypotension may cause mental fluctuations, confusion, and drowsiness, particularly in patients with dementia (21).

In parallel with a high risk of hypotension, older people also present an increased risk of cardiovascular events, due to the coexistence of multiple cardiovascular risk factors and target-organ damage. This might suggest that antihypertensive therapy could be of great benefit in geriatric patients. Yet, it should be considered that concomitant conditions of the advanced age may influence patients' prognosis and reduce the prognostic relevance of high blood pressure (22). This applies mainly to frailer patients with poor physical performance, cognitive impairment, multimorbidity and disability.

Frailty is a geriatric syndrome, characterized by a decline in physiological functional reserve and a worsening in the ability to withstand stressful events, leading to an increased risk of adverse outcomes such as disability, hospitalization, institutionalization and mortality (23). According to the literature, the prevalence of frailty varies from 4% to 59% depending on different study populations and frailty measures (24), with higher rates reported in patients with dementia and in long-term care residents (25) (26). Frailty is known to significantly influence the outcomes of cardiovascular diseases (27) (28). Similarly, recent literature demonstrate that frailty is highly prevalent in hypertensive patients (29) and clinical management of hypertension cannot disregard an accurate assessment of frailty.

Prognostic role of hypertension in older people

For a long time, older adults have been denied antihypertensive therapy due to concerns on treatment tolerability. In the nineties, the randomized STOP-Hypertension and STOP-Hypertension 2 trials first demonstrated that antihypertensive therapy significantly reduces cardiovascular risk in hypertensive adults aged 70–84 years (30) (31). Over the last decades, several studies have provided additional, strong evidence of cardiovascular benefits deriving from blood pressure lowering in older people and have clarified that

advanced chronological age should not be considered as an exclusion criterion for antihypertensive therapy (32) (33) (34) (35). More recently, two major randomized clinical trials also investigated the effects of frailty on antihypertensive treatment benefits. In participants from the HYpertension in the Very Elderly Trial (HYVET), no significant interaction was reported between frailty level and antihypertensive treatment on risk of stroke, mortality and cardiovascular events, implying that beneficial effects of antihypertensive treatment also apply to frailer patients (1). Yet, patients with more severe frailty, e.g. with dementia and disability, were excluded from the HYVET. Moreover, study participants had baseline systolic blood pressure values higher than 160 mmHg, and it remained unclear whether the study results can be extended to those with grade 1 hypertension (systolic blood pressure 140 - 160 mmHg). Similarly, in the Systolic Blood Pressure Intervention Trial (SPRINT) (2), frailty as measured using both the Frailty Index and gait speed did not modify treatment benefits in participants aged 75 or older. Yet, participants' characteristics were suggestive of mild frailty, and study results had limited transferability to the real world frailer geriatric subgroups (36).

In contrast with HYVET and SPRINT data, a number of studies has pointed out an inverse relationship between blood pressure and adverse events in older people, with particular reference to frailer individuals. Indeed, the negative prognostic role of hypertension seems to attenuate or even revert with advancing age, especially in biologically older people (37) (38). In a post-hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP), antihypertensive treatment was associated with a lower rate of mortality and myocardial infarction in fit patients but not in those with disability (39). In a recent systematic review and meta-analysis, mortality was similar in frail older people with systolic blood pressure less than 140mmHg and in those with higher blood pressure values. Conversely, mortality was lower in fit individuals with systolic blood pressure less than 140mmHg compared with those with systolic blood pressure more than 140mmHg (40). Consistently, Odden et al. showed that the correlation between blood pressure and mortality is significantly influenced by gait speed (41).

Ageing does not only modify the predictive role of hypertension for cardiovascular events, but also significantly influences its impact on cognitive outcomes. Indeed, in the Leiden-85 plus Study, higher systolic blood pressure values were independently associated with lower cognitive decline (42). Moreover,

hypertensive older adults with Mild Cognitive Impairment or dementia showed greater progression of cognitive decline in the case of lower blood pressure levels (43).

Of notice, the influence of frailty, functional level and physical or cognitive disability on the prognostic role of hypertension has only been assessed in observational studies. Indeed, frailer individuals hardly fit the inclusion criteria of randomized controlled trials and are underrepresented in study populations (44). Therefore, no major evidence exists to guide the therapeutic management of older frail hypertensive patients (45).

Treatment targets in older patients with hypertension

Due to the above mentioned lack of evidence, there is currently no agreement on which blood pressure targets are most appropriate in older hypertensive patients, even more so if frail.

A recent study including community-dwelling older adults showed lower mortality in patients with systolic blood pressure between 140 and 159 mmHg than in those with systolic blood pressure between 120 mmHg and 139 mmHg (46). The JATOS study shows that intensive blood pressure control does not improve prognosis in the older adults, and blood pressure reduction below 146 mmHg was sufficient to decrease cardiovascular risk (47). Similarly, some authors suggest that the correlation between blood pressure and cardiovascular risk is U- or J-shaped in older people, with increased risk at extreme blood pressure values and risk nadir at 140/80 mmHg (48) (49). As frailty has been proven to significantly influence the association of blood pressure with adverse outcomes, it can be expected that treatment targets vary according to frailty status. In the SNAC-K study, systolic blood pressure values below 130 mmHg were associated with lower mortality in the fit older adults (with younger “biological age”), while similar blood pressure values were associated with increased mortality in the frailer adults with impaired cognitive or physical performance (older “biological age”) (50). Consistent data are reported by the PARTAGE study, which demonstrated a correlation between systolic blood pressure levels below 130 mmHg and increased mortality in nursing home residents taking two or more antihypertensive drugs (51).

As available evidence is limited, especially as regards frailer individuals, conflicting indications are provided by international guidelines (52). The 2017 Canadian guidelines indicate a systolic blood pressure target of less than 120 mmHg in people aged 75 years or older (53), while the 2017 American College of Cardiology/American Heart Association guidelines propose a target values of less than 130/80 mmHg in

people aged 65 years or older (54). The 2017 American College of Physicians/American Association of Family Physicians guidelines propose a target of less than 150/90 mmHg (55). Finally, the 2018 European Society of Cardiology / European Society of Hypertension guidelines (45) indicate a blood pressure target of 130-139/70-79 mmHg in fit older people (aged 65 or older), provided that antihypertensive treatment is tolerated, and they clearly recommend that lower blood pressure values are avoided due to an increase risk of hypotension. As concerns frailer individuals, European guidelines acknowledge that evidence is lacking and therapeutic decisions mainly rely on clinical judgement (45).

A possible explanation of the reported association between low blood pressure and adverse health outcomes is that frail older people have higher susceptibility to reduced organ perfusion due to arterial stiffness and impaired blood flow autoregulation. High blood pressure may thus develop as a compensatory mechanism to overcome vascular stiffness and preserve organ perfusion (44). An alternative hypothesis is that increased mortality risk derives from underlying condition which determine low blood pressure values. If that was the case, low blood pressure would not be a risk factor for mortality, but it would rather represent an epiphenomenon of poor health status. Low blood pressure could thus represent both a cause or a consequence of frailty (44). In the former case, low blood pressure would reduce organ perfusion and act as a contributing factor of frailty. In the latter case, low blood pressure would develop in the context of the reduced functional reserve that characterizes frailty, which also involves impaired blood pressure control. Finally, it cannot be excluded that overtreatment contributes to hypotension in frail people (56) (57). As reverse causality may confound the association between blood pressure and adverse events, there is a need for randomized studies including frail older adults to clarify this association.

The importance of frailty in the clinical evaluation of older hypertensive patients

Against the above background, managing hypertension in older people cannot be separated from an accurate assessment of frailty and biological age. Such assessment is indeed a precondition for optimal treatment, characterized by personalized blood pressure targets based on individual's hypotension/cardiovascular risk ratio. This therapeutic approach agrees with the invitation of the European Geriatric Medicine Society to promote a geriatric attitude to cardiovascular medicine, implying a patient-centred care customized to individuals' frailty and functional status (58). Stratification of older patients on the basis of frailty status has

been shown to predict adverse outcomes in patients with cardiovascular diseases (27) (28), including hypertension (59).

Several frailty measure tools have been proposed over the last decades, the most widely known including the Fried Frailty Phenotype (23), the Frailty Index (60), the Clinical Frailty Scale (61), and the Edmonton Frail Scale. (62) Physical performance tests such as the Short Physical Performance Battery or walking speed can also be used to investigate and quantify frailty (63) (64). Each single frailty measure has different peculiarities that make it more suitable for a different clinical context (65), but no gold standard instrument for frailty assessment has been identified to date. Most widely used frailty measures include the Fried Frailty Phenotype and the Frailty Index. The former mainly assesses physical signs of frailty, such as weight loss, low physical activity, exhaustion, slowness and weakness, with frailty corresponding to the presence of at least three markers (23). The second takes count of more than 30 symptoms, diseases, disabilities and other health deficits that contribute to determine frailty, with a greater number of deficits indicating a higher level of frailty (60).

As concerns hypertensive patients, the European Society of Hypertension and the European Geriatric Medicine Society suggests that frailty assessment is carried out according to the Fried Frailty Phenotype, which is rapid and easy to use in routine practice (66). The Clinical Frailty Scale has also been suggested for use in the context of hypertension management (67), while the Frailty Index has been frequently applied in the research setting (1) (36).Anyway, the assessment of frailty in hypertensive individuals is still limited in routine practice.

Frailty-based blood pressure management strategies

Different blood pressure targets have been proposed for older hypertensive adults based on frailty levels. Scott et al. suggest a systolic blood pressure target not inferior to 130 mmHg in fit older adults with high cardiovascular risk i.e. established cardiovascular disease or risk of cardiovascular events exceeding 20% at 10 years, previous cerebrovascular events, heart failure, advanced chronic renal disease. On the other hand, a target systolic blood pressure of 140-160 mmHg is considered more appropriate in people aged 80 or older with no cardiovascular disease, moderate-severe frailty, cognitive impairment or functional limitations, as well as in patients with orthostatic hypotension or previous syncope episodes, and in people with poor prognosis and life expectancy of less than 12 months (52). Mallery et al. propose a more conservative

approach targeting a systolic blood pressure range of 140 - 160 mmHg. In very frail people with reduced life expectancy a target range of 160-190 mmHg is considered to be more reasonable (68). In agreement with these expert opinions, Benetos et al. recommend that older hypertensive patients and treatment strategies are stratified according to their autonomy and function. In older adults with preserved autonomy, the approach to antihypertensive treatment should be similar to that of younger adults, in accordance with international guidelines. Older adults with cognitive or functional impairment, loss of autonomy, significant frailty and limited life expectancy, a target blood pressure of 150 mmHg is proposed and deprescribing should be considered in presence of lower blood pressure values, especially in patients with systolic blood pressure below 130 mmHg and/or orthostatic hypotension. In patients who show only moderate functional decline, a more detailed geriatric assessment is desirable to better define the risks and benefits of the available treatment options (67).

In addition to frailty-based customized treatment targets, additional strategies allow a more cautious approach to blood pressure lowering in older people, especially in patients with previous hypotensive episodes. It may be appropriate to start treatment with monotherapy and gradually potentiate it under close monitoring (45). Antihypertensive polypharmacy, e.g. more than 3 antihypertensive medications, should be preferably avoided (67). Drug choice should aim to avoid higher risk drug classes, i.e. those associated with an increased risk of hypotension-related adverse events. These include diuretics and vasodilating agents such as α-adrenergic receptor antagonists, but also beta-blockers that may predispose to orthostatic hypotension due to their negative inotropic and chronotropic effects (14). Conversely, ACE-inhibitors and angiotensin receptor antagonists carry a very low risk of orthostatic hypotension and should be preferred as first line therapy. Bedtime administration of antihypertensive medications can be considered to minimise the risk of daytime hypotension, although limited evidence is available to support this strategy (69).

It is important to consider that, in older people, clinicians should not consider prolonging survival as the only priority of health care, as it is for younger patients. Indeed, one of the main goal of health in older people is quality of life and functional autonomy in daily life activities, which may be even more relevant to the individual than survival (70). While assessing risk and benefits of blood pressure lowering, clinicians should thus take into account these geriatric treatment goals as well as patients' preferences, i.e. considering the risk

of short-term hypotension-related versus long-term hypertension related adverse outcomes and their implications on prognosis and treatment.

The European guidelines recommend that treatment tolerability is regularly assessed in older people, and suggest ambulatory blood pressure monitoring (ABPM) as a useful diagnostic tool to check for hypotension, when suspected (45). Indeed, white coat effect is frequently observed in older people (71) (72) and may lead to overtreatment in case falsely elevated office blood pressure prompts treatment increase. Therefore, preference should be given to out-of-office measurement techniques, including ABPM and home blood pressure monitoring. Both ABPM and home blood pressure monitoring were found to better correlate with target organ damage and cardiovascular risk as compared to office blood pressure (45) (73). Although both testing may be difficult to perform in patients with dementia, ABPM has proven to have good tolerability in cognitively impaired older patients (74). Obviously, cuffs of appropriate size should be used and child sized cuff should be considered in patients with severe sarcopenia (67).

When hypotension or overtreatment are detected in older people, with blood pressure values being below the target range, deprescribing should be carried out. Although evidence on the topic is still very limited, available data indicate that deprescribing can be safely performed in older adults. A recent multicentre controlled trial involving nursing home residents investigated the effect of a systematic review of antihypertensive medications showing no relevant changes in systolic blood pressure, and a significantly higher number of hospitalizations in the control group (75). In the DANTE study (76), deprescribing of antihypertensive medications in hypertensive older people with mild cognitive impairment (mean blood pressure values 149/82 mmHg) determined a 45% increased probability of recovery from orthostatic hypotension. Additionally, antihypertensive discontinuation was not found to increase the risk of mortality and cardiovascular events (77). Yet, blood pressure values and conditions that should prompt deprescribing remain doubtful, and only expert opinions are available to guide clinical decisions. According to the European Society of Hypertension and the European Union Geriatric Medicine Society (78), in very old and frail individuals, antihypertensive therapy should target a systolic blood pressure “safety range” of 130–150 mmHg and should be reduced at systolic blood pressure less than 130 mmHg. This approach is expected to minimize the risk of hypotension-related adverse outcomes, while achieving adequate cardiovascular risk reduction. Again, deprescribing should not be carried out based on chronological age alone, but it should be

considered when blood pressure lowering is likely no longer necessary or even harmful, with particular reference to patients with older biological age.

Conclusions

Managing hypertension in older people cannot be achieving using a standardized treatment approach, as *one size doesn't fit all*. Indeed, older people represent an extremely heterogeneous population, with different functional autonomy, frailty status, life expectancy and treatment goals. A geriatric evaluation including frailty assessment is needed in older hypertensive adults, to balance treatment benefits and risk and develop personalized treatment strategies, customized according to individuals' frailty and functional status. Similar to other cardiovascular diseases, hypertension therapeutic management should be characterized by a geriatric approach based on biological rather than chronological age. This approach is expected to provide the most appropriate treatment, tailored to patients' prognosis and health care goals. As frailty is still poorly investigated in daily clinical practice, particularly in hypertension clinics, we hope that this literature overview may help to promote a wider implementation of frailty assessment in routine activity.

Authors' contribution

• Study concept and design: Ungar A, Rivasi G, Desideri G.

• Analysis and interpretation of data: Ungar A, Rivasi G, Coscarelli A, Desideri G.

• Drafting of the manuscript: Ungar A, Rivasi G, Coscarelli A, Desideri G.

• Critical revision of the manuscript for important intellectual content: all authors.

All authors read and approved the final version of the manuscript

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