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

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

<sup>a</sup>Hypertension Clinic, Department of Geriatric and Intensive Care Medicine, Careggi Hospital and University of Florence, Florence, Italy

<sup>b</sup>SICGe – Società Italiana di Cardiologia Geriatrica, Via Matteotti 7, Firenze, Italy

<sup>c</sup>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 is 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  $\alpha$ -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 achieved 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

## REFERENCES

1. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA*. 2002; 287:1003–1010.
2. Yoon SS, Carroll MD, Fryar CD. Hypertension prevalence and control among adults: United States, 2011–2014. *NCHS Data Brief*. 2015; 220:1–8.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. 2015; 131(4):e29–322.
4. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ, American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011 Mar 1; 123(8):933-44.
5. Bavishi C, Goel S, Messerli FH. Isolated Systolic Hypertension: An Update After SPRINT. *Am J Med*. 2016 Dec; Sep, 129(12):1251-1258. Epub 2016 Sep 14. Erratum in: *Am J Med*. 2017 Sep; 130(9):1128. PMID: 27639873.
6. Muller M, Smulders YM, de Leeuw PW, et al. Treatment of hypertension in the oldest old: a critical role for frailty? *Hypertension*. 2014; 63(3):433–41.
7. O'Rourke MF, Mancia G. Arterial stiffness. *J Hypertens*. 1999; 17:1–4.
8. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation*. 2003; 107:2864–2869.
9. Mitchell GF, Lacourcière Y, Ouellet JP, Izzo JL Jr, Neutel J, Kerwin LJ, Block AJ, Pfeffer MA. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation*. 2003;108:1592–1598.
10. Oster JR, Materson BJ. Pseudohypertension: a diagnostic dilemma. *J Clin Hypertens*. 1986 Dec; 2(4):307-13. PMID:3543228.
11. Peeters LEJ, Kester MP, Feyz L, Van Den Bemt PMLA, Koch BCP, Van Gelder T, et al. Pharmacokinetic and pharmacodynamic considerations in the treatment of the elderly patient with hypertension. *Expert Opin Drug Metab Toxicol*. 2019; 15:287–297.
12. Rivasi G, Rafanelli M, Mossello E, Brignole M, Ungar A. Drug-Related Orthostatic Hypotension: Beyond Anti-Hypertensive Medications. *Drugs Aging*. 2020 Oct;37(10):725-738.
13. Monahan KD. Effect of aging on baroreflex function in humans. *Am J Physiol Regul Integr Comp Physiol*. 2007; 293:R3–R12.
14. Fedorowski A, Franceschini N, Brody J, et al. Orthostatic hypotension and novel blood pressure-associated gene variants: Genetics of Postural Hemodynamics (GPH) Consortium. *Eur Heart J*. 2012; 33:2331–234.

15. Ungar A, Galizia G, Morrione A, Mussi C, Noro G, Ghirelli L, et al. Two-year morbidity and mortality in elderly patients with syncope. *Age Ageing*. 2011; 40:696–702.
16. Gill TM, Murphy TE, Gahbauer EA, Allore HG. Association of injurious falls with disability outcomes and nursing home admissions in community-living older persons. *Am J Epidemiol*. 2013; 178:418–425.
17. Arik F, Soysal P, Capar E, Kalan U, Smith L, Trott M, Isik AT. The association between fear of falling and orthostatic hypotension in older adults. *Aging Clin Exp Res*. 2020 May 11.
18. Ceccofiglio, A., Peruzzi, G., Pecci, R. et al. Retrospective analysis of patients with dizziness evaluated in Syncope Unit: a real life experience. *Eur Geriatr Med*. 2018; 383–387 .
19. Freidenberg DL, Shaffer LE, Macalester S, Fannin EA. Orthostatic hypotension in patients with dementia: clinical features and response to treatment. *Cogn Behav Neurol*. 2013 Sep;26(3):105-20.
20. Romero-Ortuno R, Fouweather T, Jagger C. Cross-national disparities in sex differences in life expectancy with and without frailty. *Age Ageing*. 2014; 43:222–228.
21. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001; 56:M146–M156.
22. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet*. 2019; 394:1365–1375.
23. Kojima G, Liljas A, Iliffe S, Walters K. Prevalence of frailty in mild to moderate Alzheimer’s disease: a systematic review and meta-analysis. *Curr Alzheimer Res*. 2017; 14:1256–1263.
24. Kojima G. Prevalence of frailty in nursing homes: a systematic review and meta-analysis. *J Am Med Dir Assoc*. 2015; 16:940–945.
25. Afilalo J, Eisenberg MJ, Morin JF, Bergman H, Monette J, Noiseux N, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol*. 2010; 56:1668–1676.
26. Schoenenberger AW, Stortecky S, Neumann S, Moser A, Jüni P, Carrel T, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J*. 2013; 34:684–692.
27. Vetrano DL, Palmer KM, Galluzzo L, Giampaoli S, Marengoni A, Bernabei R, et al. Joint Action ADVANTAGE WP4 Group. Hypertension and frailty: a systematic review and meta-analysis. *BMJ Open*. 2018; 8:e024406.
28. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekblom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet*. 1991; 338:1281–1285.
29. Hansson L, Lindholm LH, Ekblom T, Dahlöf B, Lanke J, Scherstén B, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999; 354:1751–1756.
30. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015; 373:2103–2116.
31. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008; 358:1887–1898.
32. Briasoulis A, Agarwal V, Tousoulis D, Stefanadis C. Effects of antihypertensive treatment in patients over 65 years of age: a meta-analysis of randomised controlled studies. *Heart* 2014. 100:317–323.



33. Weiss J, Freeman M, Low A, Fu R, Kerfoot A, Paynter R, Motu'apuaka M, Kondo K, Kansagara D. Benefits and Harms of Intensive Blood Pressure Treatment in Adults Aged 60 Years or Older: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2017 Mar 21;166(6):419-429. doi: 10.7326/M16-1754. Epub 2017 Jan 17. Erratum in: *Ann Intern Med.* 2018 Jan 16;168(2):159. Erratum in: *Ann Intern Med.* 2018 Apr 3;168(7):529-530.
34. Warwick J, Falaschetti E, Rockwood K, Mitnitski A, Thijs L, Beckett N, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the Hypertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC Med.* 2015; 13:78.
35. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. SPRINT Research Group. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged  $\geq 75$  Years: A Randomized Clinical Trial. *JAMA.* 2016 Jun 28;315(24):2673-82.
36. Russo G, Liguori I, Aran L, Bulli G, Curcio F, Galizia G, et al. Impact of SPRINT results on hypertension guidelines: implications for 'frail' elderly patients. *J Hum Hypertens.* 2018; 32:633-63.
37. Molander L, Lövheim H, Norman T, Nordström P, Gustafson Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. *J Am Geriatr Soc.* 2008; 56:1853-1859.
38. Satish S, Freeman DH Jr, Ray L, Goodwin JS. The relationship between blood pressure and mortality in the oldest old. *J Am Geriatr Soc.* 2001; 49:367-374.
39. Charlesworth CJ, Peralta CA, Odden MC. Functional status and antihypertensive therapy in older adults: a new perspective on old data. *Am J Hypertens.* 2016; 29:690-695.
40. Todd OM, Wilkinson C, Hale M, Wong NL, Hall M, Sheppard JP, et al. Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis. *Age Ageing.* 2019; 48:627-635.
41. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults. *Arch Intern Med.* 2012; 172(15):1162-1168.
42. Sabayan B, Oleksik AM, Maier AB, van Buchem MA, Poortvliet RK, de Ruijter W, et al. High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus Study. *J Am Geriatr Soc.* 2012; 60:2014-2019.
43. Mossello E, Pieraccioli M, Nesti N, Bulgaresi M, Lorenzi C, Caleri V, et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. *JAMA Intern Med.* 2015; 175:578-585.
44. Rivasi G, Tortù V, D'Andria MF, Turrin G, Ceolin L, Rafanelli M, Mossello E, Ungar A. Hypertension management in frail older adults: a gap in evidence. *J Hypertens.* 2021 Mar 1;39(3):400-407.
45. Williams B, Mancia G, Spiering W, et al. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018; 39:3021-3104.
46. Rivasi G, Lucenteforte E, Turrin G, Balzi D, Bulgaresi M, Nesti N, et al. Blood pressure and long-term mortality in older patients: results of the Fiesole Misurata Follow-up Study. *Aging Clin Exp Res.* 2020.
47. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res.* 2008; 31:2115-2127.
48. Denardo SJ, Gong Y, Nichols WW, Messerli FH, Bavry AA, Cooper-Dehoff RM, et al. Blood pressure and outcomes in very old hypertensive coronary artery disease patients: an INVEST substudy. *Am J Med.* 2010; 123:719-26.

49. Rastas S, Pirttila T, Viramo P, Verkkoneimi A, Halonen P, Juva K, et al. Association between blood pressure and survival over 9 years in a general population aged 85 and older. *J Am Geriatr Soc.* 2006; 54:912–8.
50. Liang Y, Fratiglioni L, Wang R, Santoni G, Welmer AK, Qiu C. Effects of biological age on the associations of blood pressure with cardiovascular and noncardiovascular mortality in old age: a population-based study. *Int J Cardiol.* 2016; 220:508–513.
51. Benetos A, Labat C, Rossignol P, Fay R, Rolland Y, Valbusa F, et al. Treatment with multiple blood pressure medications, achieved blood pressure, and mortality in older nursing home residents: the PARTAGE study. *JAMA Intern Med.* 2015; 175:989–995.
52. Scott IA, Hilmer SN, Le Couteur DG. Going Beyond the Guidelines in Individualising the Use of Antihypertensive Drugs in Older Patients. 2019 Aug; 36(8):675-685. PMID: 31175614.
53. Leung AA, Daskalopoulou SS, Dasgupta K, et al. Hypertension Canada. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. *Can J Cardiol.* 2017; 33:557–576.
54. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:1269–1324.
55. Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA; Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians. Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med.* 2017 Mar 21;166(6):430-437.
56. Basile G, Catalano A, Mandraffino G, Maltese G, Alibrandi A, Ciancio G, et al. Relationship between blood pressure and frailty in older hypertensive outpatients. *Aging Clin Exp Res.* 2017; 29:1049–1053.
57. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, et al. Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: cohort study using electronic health records. *Circulation.* 2017; 135:2357–2368.
58. Ungar A, Rivasi G, Petrovic M, Schönerberger A, Martínez-Sellés M, Gasowski J, Bahat-Ozturk G, Bo M, Dallmaier D, Fumagalli S, Grodzicki T, Kotovskaya Y, Maggi S, Mattace-Raso F, Polidori MC, Rajkumar R, Strandberg T, Werner N, Benetos A. From the EuGMS Special Interest Group on Cardiovascular Medicine. Toward a geriatric approach to patients with advanced age and cardiovascular diseases: position statement of the EuGMS Special Interest Group on Cardiovascular Medicine. *Eur Geriatr Med.* 2020 Feb; 11(1):179-184.
59. Wu C, Smit E, Peralta CA, Sarathy H, Odden MC. Functional status modifies the association of blood pressure with death in elders: health and retirement study. *J Am Geriatr Soc.* 2017; 65:1482–1489.
60. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Sci World J.* 2001; 1:323–336.
61. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005; 173:489–495.
62. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton frail scale. *Age Ageing.* 2006; 35:526–529.

63. Minneci C, Mello AM, Mossello E, Baldasseroni S, Macchi L, Cipolletti S, et al. Comparative study of four physical performance measures as predictors of death, incident disability, and falls in unselected older persons: the Insufficienza Cardiaca negli Anziani Residenti a Dicomano Study. *J Am Geriatr Soc.* 2015; 63:136–141.
64. Volpato S, Cavalieri M, Guerra G, Sioulis F, Ranzini M, Maraldi C, et al. Performance-based functional assessment in older hospitalized patients: feasibility and clinical correlates. *J Gerontol A Biol Sci Med Sci.* 2008; 63:1393–1398.
65. Faller JW, Pereira DDN, de Souza S, Nampo FK, Orlandi DS, Matumoto S. Instruments for the detection of frailty syndrome in older adults: a systematic review. *PLoS One.* 2019; 14:e0216166.
66. Ungar A, Rivasi G. Increasing awareness on frailty in the management of hypertensive older adults. *J Hypertens.* 2020 Nov; 38(11):2148-2149.
67. Benetos A, Petrovic M, Strandberg T. Hypertension Management in Older and Frail Older Patients. *Circ Res.* 2019 Mar 29; 124(7):1045-1060.
68. Mallery LH, Allen M, Fleming I, et al. Promoting higher blood pressure targets for frail older adults: a consensus guideline from Canada. *Cleve Clin J Med.* 2014; 81(7):427–37.
69. Rivasi G, Brignole M, Rafanelli M, Bilo G, Pengo MF, Ungar A, Parati G. Blood pressure management in hypertensive patients with syncope: how to balance hypotensive and cardiovascular risk. *J Hypertens.* 2020 Dec;38(12):2356-2362.
70. Kuluski K, Gill A, Naganathan G, Upshur R, Jaakkimainen RL, Wodchis WP. A qualitative descriptive study on the alignment of care goals between older persons with multimorbidities, their family physicians and informal caregivers. *BMC Fam Pract.* 2013; 14:133.
71. Ishikawa J, Ishikawa Y, Edmondson D, Pickering TG, Schwartz JE. Age and the difference between awake ambulatory blood pressure and office blood pressure: a meta-analysis. *Blood Press Monit.* 2011; 16:159–167.
72. Mossello E, Pieraccioli MC, Zanieri S, Fedeli A, Belladonna M, Nesti N, et al. Ambulatory blood pressure monitoring in older nursing home residents: diagnostic and prognostic role. *J Am Med Dir Assoc.* 2012; 13:760.e1–760.e5.
73. Ward AM, Takahashi O, Stevens R, Heneghan C. Home measurement of blood pressure and cardiovascular disease: systematic review and meta-analysis of prospective studies. *J Hypertens.* 2012; 30:449–456.
74. Nesti N, Pieraccioli M, Mossello E, Sgrilli F, Bulgaresi M, Crescioli E, Biagini F, Caleri V, Tonon E, Cantini C, Biagini CA, Marchionni N, Ungar A. Tolerability of ambulatory blood pressure monitoring (ABPM) in cognitively impaired elderly. *Blood Press.* 2014 Dec; 23(6):377-80.
75. Gulla C, Flo E, Kjome RL, Husebo BS. Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure. *J Geriatr Cardiol.* 2018; 15:275–283.
76. Moonen JE, Foster-Dingley JC, de Ruijter W, van der Grond J, de Craen AJ, van der Mast RC. Effect of discontinuation of antihypertensive medication on orthostatic hypotension in older persons with mild cognitive impairment: the DANTE Study Leiden. *Age Ageing.* 2016; 45:249–255.
77. Ekblom T, Lindholm LH, Odén A, Dahlöf B, Hansson L, Wester PO, et al. A 5-year prospective, observational study of the withdrawal of antihypertensive treatment in elderly people. *J Intern Med.* 1994; 235:581–588.

78. Benetos A, Bulpitt CJ, Petrovic M, Ungar A, Agabiti Rosei E, Cherubini A, et al. An expert opinion from the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the Management of Hypertension in Very Old, Frail Subjects. *Hypertension*. 2016; 67:820-825.