Hypertension in the Oldest Old, Beyond Guidelines

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Enrico Mossello, Giovambattista Desideri, and Andrea Ungar

8.1 Introduction

The importance of blood pressure (BP) assessment among oldest old is highlighted by several reasons. The most obvious one is represented by the steep increase of old age population share since 1960 and the even steeper increase forecasted during the next 30 years all over the world [1]. This increase will be multiplicative in the subgroup of subjects aged 80+, with an expected triplication by 2050 in Spain, Germany, and Japan and a seven-time increase in Korea and China [2]. The second reason of the importance and peculiarity of this population is linked to the incidence and prevalence of comorbidities, frailty, and loss of autonomy, which greatly increase among subjects aged 80+ [3]. Finally and most important, subjects in this age stratum have both highest cardiovascular risk and potentially severe adverse effects from BP treatment, with limited evidence from randomized clinical trials regarding risk and benefits of antihypertensive treatment.

E. Mossello (✉)
Division of Geriatric Medicine and Cardiology,
Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

Department of Experimental and Clinical Medicine,
University of Florence, Florence, Italy
e-mail: enrico.mossello@unifi.it

G. Desideri
Department of Life, Health and Environmental Sciences,
University of L'Aquila,
L'Aquila, Italy

A. Ungar
Hypertension Centre - Syncope Unit, Geriatrics Intensive Care Unit,
University of Florence and Azienda Ospedaliero Universitaria Careggi,
Florence, Italy
e-mail: aungar@unifi.it

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In fact, while the prevalence of high BP and the risk of vascular diseases are clearly associated with old age, the risk of syncope, falls, and fractures also increases with age, with low BP representing a major risk factor [4]. Orthostatic hypotension in particular seems to be associated both with antihypertensive treatment and with an increased fall risk [5] and was also found to increase the risk for mortality and cardiovascular events in a recent meta-analysis [6]. Of notice, in a large population-based study, older subjects showed a significant increase in hospitalizations for hip fracture over the 45 days after initiation of antihypertensive drug treatment [7]. Moreover hypotension-related events in old age are likely to be more common in real life than in clinical trials in which treatment is delivered by expert physicians, and patients are followed closely. Therefore, both the benefits (including preserving autonomy) and the risks of antihypertensive therapy should be considered before starting treatment in frail older population.

Finally, the data from randomized clinical trials seem somehow at an odd with observational studies, showing that in the very old population low BP values represent a risk factor for morbidity and mortality, at least as strong as high BP [8–10]. Although the possibility of reverse causality (i.e., more severe clinical conditions in subjects with lower BP) has been advocated for these data, a pathophysiologically founded hypothesis is that in frail very old subjects an impairment of the mechanisms preserving perfusion might critically decrease blood flow to vital organs (the heart, brain, kidney) [11]. Therefore the choice of most appropriate BP target in these subjects is still a matter of debate.

8.2 Epidemiology

Arterial hypertension (AH) represents the leading risk factor for global disease burden due to its great prevalence and deep impact on morbidity and mortality [12]. Overall the prevalence of AH appears to be around 30–45 % of the general population, presenting higher values in Europe (44 %) than in the United States (28 %) [13].

Although rise of BP values is not a normal part of aging, the prevalence of AH increases progressively with age, and thus most older subjects are hypertensive [14]. Data from the Framingham Heart Study in men and women free of AH at 55 years of age indicate that the remaining lifetime risks for development of AH until the age of 80 are 93 % and 91 %, respectively [15]. In other words, more than 90 % of individuals who are free of AH at 55 years of age will develop it during their remaining life-span. Several epidemiological surveys conducted in the United States and Europe conclude that AH prevalence in the elderly ranges between 53 and 72 % [16].

From the epidemiological standpoint, there are important subgroups with distinctive characteristics. AH prevalence is less in women than in men until 45 years of age, is similar in both genders from 45 to 64 years of age, and is much higher in women than men >65 years of age. Age-adjusted AH prevalence, both diagnosed and undiagnosed, from 1999 to 2002, was 78 % for older women and only 64 % for older men [17]. Both the prevalence and severity of AH increase markedly with advancing age in women, so that, after age 60 years, a majority of women (age 60–79 years: 48.8 %; age ≥80 years: 63 %) have stage 2 AH (BP ≥160/100 mmHg) or receive antihypertensive treatment [18]. Furthermore, BP control is difficult to achieve in elderly hypertensives [19]. Thus, although older patients with AH are

more likely to be aware of their condition and receiving treatment than middle-aged patients, BP control rates are lower in the elderly, especially after age 80 years [14].

AH in old age is commonly characterized by elevated systolic blood pressure (SBP), with often normal or even low diastolic blood pressure (DBP), which reflects a progressive increase in aortic stiffness during aging, in part related to increased collagen with cross-linking and degradation of elastin fibers [19]. Typically SBP rises gradually throughout adult life, while DBP peaks and plateaus in late middle age, declining slightly thereafter. The widened pulse pressure is a reflection of increased arterial stiffness [19]. Therefore, the proportion of hypertensive patients with isolated systolic hypertension increases with age, with this condition affecting 65 % of patients with AH >60 years of age and over 90 % >70 years of age [20]. The prevalence of isolated systolic hypertension is higher in women than in men, whereas the proportion of AH attributable to solely elevated SBP in older adults is similar across racial and ethnic groups [14].

White coat hypertension, a term reserved for those not on antihypertensive medications but with persistently elevated office BP (≥140/90 mmHg) together with a normal home BP or daytime ambulatory BP (≤135/85 mmHg), is also more common in the elderly and is more frequent among centenarians [21]. Masked hypertension, defined as normal office BP associated with high BP at home, is also frequent in the elderly and is associated with a high vascular risk profile [22]. Contrary to white coat hypertension, masked hypertension has been shown to be associated with an increased risk of cardiovascular events [23]. The frequency of non-dipping – defined as a nocturnal BP drop <10 % of daytime values – also increases with age [19]. As discussed below, these data should support the usefulness of home BP monitoring in elderly hypertensives.

In regard to treatment efficacy, resistant hypertension – defined as BP that remains above goal in spite of the concurrent use of three drugs at optimal dose amounts, one of whom should be a diuretic – has a substantial prevalence across all ages but is more frequent among older subjects [24].

AH is the most important risk factor for cardiovascular diseases in the elderly population, with estimates that 69 % of patients with incident myocardial infarction, 77 % with incident stroke, and 74 % with incident heart failure have antecedent AH. In addition, AH is a major risk factor for incident diabetes mellitus, as well as for atrial fibrillation and chronic kidney disease [14].

Therefore, the positive association of high BP with cardiovascular risk and mortality is maintained at higher age, although this association seems to loosen or even be reverted among very old, frail subjects [11]. Thus, despite the large body of evidence in middle-aged populations, the predictive value of high BP in the rapidly growing population of oldest old is still debated, as is the question of whether AH should be treated and if so, how intensively.

8.3 Clinical Assessment of BP in Older Subjects

8.3.1 Peculiar Aspects of BP Measurement

Recent guidelines reaffirm the need to obtain the BP measure in sitting position after 3–5 min of rest, repeating the measurement at least twice 1–2 min apart and

obtaining the measure on both sides at the first visit [13]. Specific aspects of BP measurement should be cared of in aged subjects. First, the age-associated increase of arterial stiffness, apart from being a main determinant on increased SBP values in old age, may affect the risk of *pseudohypertension*, which is quite common in old age and is defined as a falsely heightened SBP in comparison with the intra-arterial measurement [25]. This phenomenon is explained by the increased cuff insufflation pressure needed to obtain the collapse of brachial artery walls, due to the increased rigidity of the tunica media. The presence of pseudohypertension can be suspected with the Osler's maneuver, which is performed by assessing the palpability of the pulseless radial or brachial artery distal to the point of occlusion of the artery by cuff pressure [26]. While the Osler's maneuver is positive in about 10 % of older subjects, its ability to detect pseudohypertension has been questioned, and the measure of upper limb pulse wave velocity has been proposed as a more appropriate way of screening for this condition [27].

With a similar mechanism, arterial stiffness may be the cause of *auscultatory gap* phenomenon, which is defined by decrease or disappearance of Korotkoff sounds during BP measurement. The improper interpretation of this gap may lead to BP monitoring errors, namely, an underestimation of SBP and/or an overestimation of DBP. In order to correct for an auscultatory gap, the radial pulse should be monitored by palpation. Moreover, the examiner can avoid being confused by an auscultatory gap by always inflating a BP cuff to 20–40 mmHg higher than the pressure required to occlude the brachial pulse. The presence of an auscultatory gap has been associated with carotid atherosclerosis and increased arterial stiffness in hypertensive patients, independently of age, thus suggesting that it may have a prognostic relevance [28].

Among older subjects, BP should be measured in the sitting position, immediately after reaching the standing position, and again twice, when this position has been maintained for 1 and 3 min. Thus it is possible to detect orthostatic hypotension, defined as a decline of at least 20 mmHg of SBP and/or 10 mmHg of DBP in standing vs. the sitting position [13]. The detection of this condition is particularly important in older subjects, as it is particularly frequent and has been associated with falls, cardiovascular events, and total mortality [5, 6]. Therefore the choice of antihypertensive treatment should be based on orthostatic together with sitting BP values.

A critical point regarding BP measure in old age is represented by the discrepancy between office and out-of-office BP measures, including both home BP monitoring and 24-h ambulatory blood pressure monitoring (ABPM). In fact a meta-analysis of available studies shows that this discrepancy is age dependent, with office BP values increasing more steeply with age in comparison with daytime ABPM measures. In particular, office BP values tend to be higher than daytime ABPM ones after the age of 50 years for SBP and after the age of 45 years for DBP, while the reverse is true at younger ages [29]. This results in age-associated increases of "white coat hypertension" risk. This condition is defined as having elevated office BP without elevated daytime BP (or alternatively non-elevated 24-h BP) on ABPM in individuals not taking antihypertensive medication. White coat hypertension may

also refer to individuals taking antihypertensive medication. However, the preferred terms for this subset of patients is "treated white coat hypertension" or "white coat uncontrolled hypertension" [30].

The majority of studies regarding white coat hypertension have observed no increased cardiovascular risk for this condition in comparison with normotension. This has been confirmed in particular among older subjects with a clinical diagnosis of isolated systolic hypertension at clinical measurement and normal BP values at ABPM, whose 10-year risk of cardiovascular morbidity and mortality was similar to subjects with persistently normal BP values, both among treated and non-treated subjects [31]. Moreover, the phenomenon is highly prevalent among older disabled subjects: in a sample of older nursing home patients undergoing ABPM, it was detected in 33 % of the whole sample and in 70 % of those with high BP at office assessment [32].

The suspect of white coat hypertension is the first indication for ABPM cited in European guidelines [33]. Other indications include the suspect of masked hypertension, the detection of abnormal BP circadian rhythm (including "non-dipping" status, postprandial hypotension, and "morning surge"), and the assessment of response to treatment in complex cases (e.g., high BP variability and resistant hypertension). For all these reasons, ABPM is frequently useful among very old subjects. The superior prognostic ability of ABPM values compared with clinical ones in predicting the risk of mortality and cardiovascular events [34] represents a further reason to perform the assessment in conditions where prognostication is particularly challenging, such as complex geriatric patients. Although ABPM assessment is sometimes considered difficult to perform and poorly tolerated in older patients with cognitive impairment, this was found not to be the case for the vast majority of dementia patients in a memory clinic, with the only exception of those with severe behavioral disorders [35]. However, when ABPM is deemed as non-feasible, home BP measurements seem to be a reliable alternative [34].

8.3.2 The Role of Cognitive and Functional Status

Limitations in activities of daily living and cognitive impairment frequently occur during old age. Several longitudinal data have associated high BP with risk of disability onset [36]. This effect appears at least partly mediated by increased stroke risk [37], although higher BP has been associated with increased risk of motor impairment also in a cohort of older stroke-free subjects [38]. This association appears to be mediated by cognitive impairment onset and might be at least partly explained by the onset of microvascular cerebral lesions, such as white matter lesions, without acute cerebrovascular events [39]. Of notice, the extent of brain microvascular changes has been associated with extra-cerebral end-organ damages in AH, including chronic kidney damage [40], increased left ventricular mass [41], and retinal microvascular changes [42].

Moreover high BP at midlife has been associated with cognitive impairment and dementia in old age in several cohort studies [43]. Data are less consistent

regarding the effect of BP on risk of cognitive impairment among older subjects. In fact, while some studies have confirmed this association among older subjects [44], other studies could not confirm it and have observed just the opposite [45]. On the whole it seems that, while high BP is still associate d with increased risk of cognitive decline 10 years later among "young old" (age range 65–74), it might have a neutral effect between 75 and 84 and even act as a preventive factor among subjects aged 85+ [46]. On the other hand, it has repeatedly been shown that, while long-lasting high BP values are associated with increased dementia risk, dementia onset is associated with subsequent decline of BP values, possibly caused by an altered vascular control due to brain damage [47].

Finally, a poorer self-reported physical and mental health has been associated with lower BP values, not only among older subjects but also among younger adults with history of vascular disorders [48]. Therefore it is not surprising that lower BP is associated with lower grip strength, an objective measure of physical performance, among subjects aged 85 [49] and, similarly, with a worse cognitive and physical performance in centenarians [50].

Therefore, the assessment of cognitive and functional status in older hypertensives subjects has two different aims:

1. To have an indirect, easy obtainable estimate of brain end-organ damage associated with high BP.
2. To assess the prognostic role of BP values in the context of the biological age of the single subject. As it will be discussed below, target BP values might differ in old age according to "frailty status," which in turn can be estimated by validated and reproducible measures of cognitive and functional status.

Several short measures of cognitive status among older subjects exist and can be used in clinical practice. Among such measures, Mini Mental State Examination (MMSE) [51] is one of the best known and probably represents a "gold standard" for brief cognitive assessment, due to its widespread use both in clinical and in research setting all over the world, the ability to reliably identify dementia and stage its severity, and the possibility to follow up patients over time [52]. The administration of the test is 5–10 min long, depending on patient's cognitive status, and includes items testing orientation to space and time, memory, attention and calculation, word finding, phrase repetition, comprehension of spoken and written language, and constructional praxis. The total score is included between 0 and 30, with 24 being the most widely adopted cutoff for dementia. Locally validated rules exist to adjust the score for age and education. While this instrument is widely adopted in geriatric facilities, it will be probably felt as too time-consuming in a typical hypertension clinic. A suitable, less time-consuming alternative for cognitive screening is the Mini-Cog [53], which requests only a 2-min assessment, including the recall of the three words, similar to the MMSE, and the drawing of a clock. The scoring of the test is straightforward, as shown in Fig. 8.1.

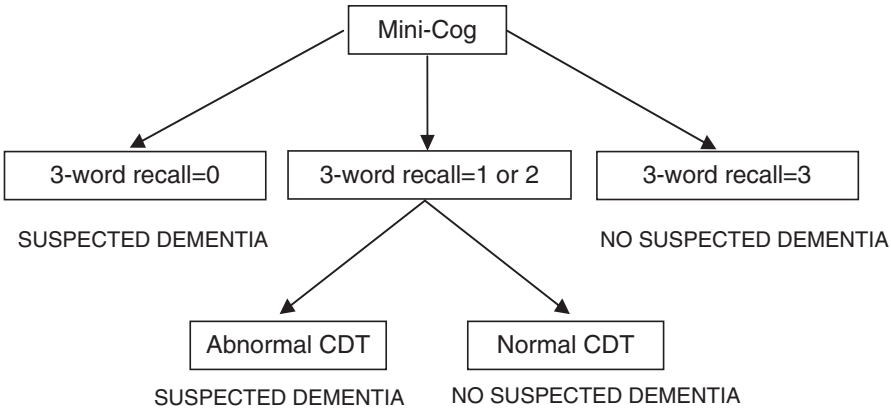

Fig. 8.1 Mini-Cog test (Borson et al. [53]): administration and scoring
- Ask the patient to repeat three semantically unrelated words.
- Ask the patient to draw a clock.
  - Draw a circle.
  - Add the numbers.
  - Set the time on 11:10.
- Ask the patient to recall the previously repeated words.

Clock Drawing Test (CDT) is normal if all numbers are present in the right sequence and position and clock's hands are in the right position.
Test is scored according to the following algorithm

To reduce the risk of false positives, it is recommended to corroborate the suspect of dementia, as resulting from Mini-Cog, with:

1. Report of cognitive impairment by the patient himself and/or relatives, according to accepted criteria for dementia and mild cognitive impairment [54]
2. Impairment in instrumental activities of daily living, especially use of telephone, handling medications, and finances, which appears to be fairly specific for dementia [55]

Lower extremity function measures are widely used in geriatric medicine as a measure of physical frailty, and several of them are usable as brief screener. The most validated single measure is represented by gait speed on a 4-m corridor, with speed <0.8 m/s (i.e., time to walk through 4 m >5 s) being a sensitive measure of physical frailty [56]. Gait speed is also included in more comprehensive physical performance tests, such as the short physical performance battery [57], which includes a balance test (measuring the ability to stand side by side, in semi-tandem, and in tandem), the abovementioned gait speed test, and the chair stand test, measuring the time needed to stand up for five times from a chair without using arms. Each subtest is scored from 0 to 4, with a total score ranging from 0 to 12 and values <10 indicating reduced physical performance and being associated with worse outcome, including higher risk of mortality, disability onset and progression,

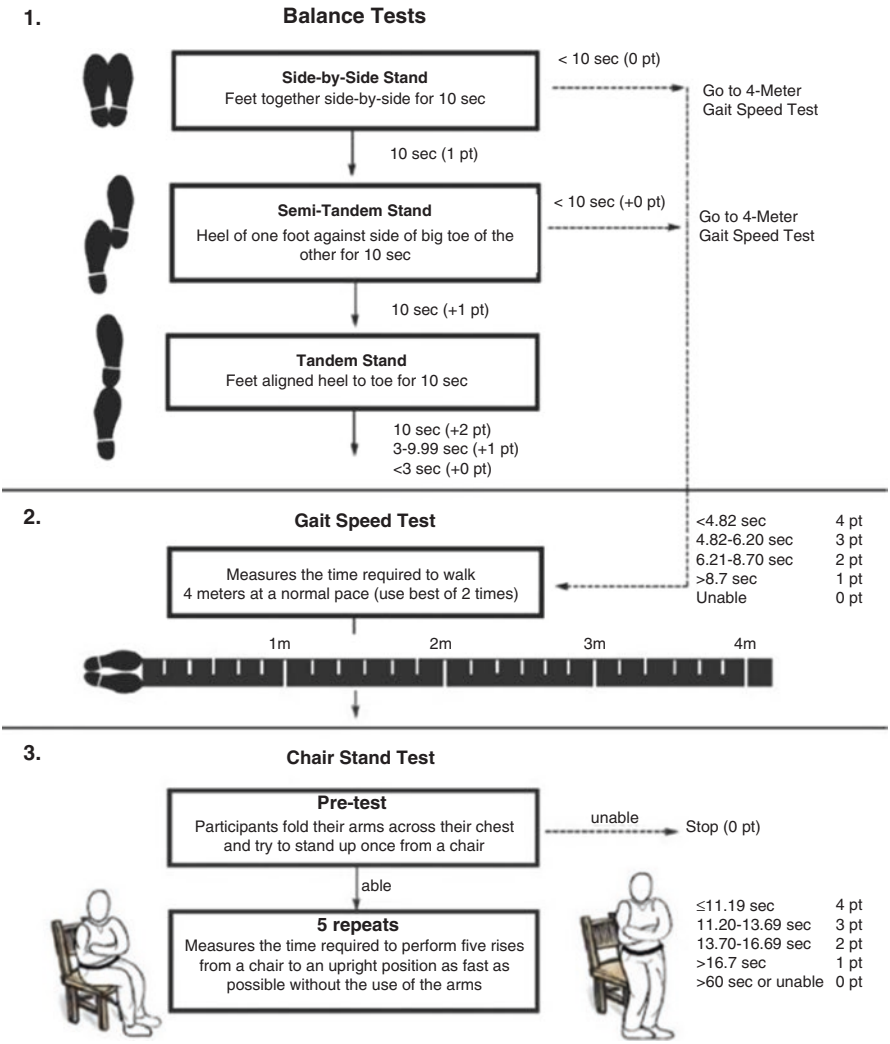

Fig. 8.2 Short physical performance battery: scoring sheet (Guralnik JM, Assesing Physical Performance in the Older Patient, National Institute on Aging)

hospitalization, and institutionalization [58, 59]. While this assessment is more comprehensive in comparison with gait speed only, as it includes measures of balance and lower extremity muscle strength, the predictive values of gait speed alone seem to be similar to the complete performance test [60] (Fig. 8.2).

Finally, the presence of overt disability in basic activities of daily living (ADL: washing, dressing, going to the toilet, transferring, eating) has to be identified in older subjects with AH, as it appears to have a strong prognostic role beyond the presence of associated comorbid conditions, including high BP [61]. This is evident for nursing homes patients, in whom the prognostic role of BP has been found

almost irrelevant in comparison with the presence of ADL disability and behavioral disorders [32], and possible beneficial effects of antihypertensive drugs have to be weighted carefully against the risk of brain hypoperfusion, falls, and fractures [7]. To screen for the presence of ADL disability, the single question regarding the ability to dress and undress oneself has been found to possess satisfactory accuracy to detect a significant impairment [62].

8.4 Treatment

8.4.1 Guidelines and Clinical Trials in the Oldest Old

Randomized clinical trials performed during last 20 years have clearly shown that the benefit of antihypertensive treatments on cardiovascular events is not significantly different at ages above rather than below 65 years, with a greater absolute benefit in the elderly because of the higher cardiovascular risk characterizing old age [63]. These results have been extended to very old age with Hypertension in the Very Elderly Trial (HYVET), which was prematurely terminated after the demonstration of a clear benefit of antihypertensive treatment in reducing total mortality, heart failure, and stroke in subjects aged 80+ [64].

Yet some points have not been clarified yet, one of the first being the effect of age on the cutoff and the target for antihypertensive treatment. Since 2013, European [13] and US [65] guidelines have acknowledged different cutoffs and target values for antihypertensive drugs treatment in old age (Table 8.1). This was mainly based on the critical reappraisal of previous guidelines, which clearly indicated that the treatment of grade I AH and the previously indicated cutoff of 140/90 mmHg were not evidence-based in the elderly [66]. In fact all randomized clinical trials including only subjects 65+ had SBP ≥160 mmHg as inclusion criterion, enrolled subjects showed a mean baseline SBP included between 166 and 196 mmHg, and generally did not attained a mean SBP <140 mmHg in the actively treated group. This is particularly true for subjects enrolled in HYVET, who were over 80, with no severe comorbidity, had mean BP values 173/91 mmHg at baseline and attained BP values of 144 and 159 mmHg at follow-up in active treatment and placebo group, respectively [64].

Only few intervention studies have addressed the issue of different BP targets among older subjects, with somehow conflicting results. In a subgroup analysis of the FEVER study, 3179 older Chinese patients randomized to more intense treatment (low-dose hydrochlorothiazide plus felodipine, achieved SBP 138 mmHg) had a lower risk of stroke, cardiovascular events, and total mortality compared to the ones randomized to less intense treatment (low-dose hydrochlorothiazide plus placebo, achieved SBP 142 mmHg) [67]. Yet it has to be acknowledged that this was a subgroup analysis and that "older subjects" group was 65+, with a mean age 69.5. Two other Japanese studies have specifically focused on different treatment targets for older subjects [68, 69]. In the VALISH study, 3260 patients aged 70–84 (mean age 76) were randomized to strict BP control (target SBP < 140 mmHg, achieved

SBP 137 mmHg) vs. moderate control (target SBP 140–150 mmHg, achieved SBP 142 mmHg). After 3 years the two groups did not differ for the primary composite end point neither for any of the secondary end points, including stroke, cardiac events, cardiovascular mortality, total mortality, and for incidence of adverse events [69]. Moreover, in the JATOS study, 4418 patients aged 65–85 (42 % over 75) were randomized to strict BP control (target SBP < 140 mmHg, achieved SBP 136 mmHg) vs. moderate control (target SBP 140–160 mmHg, achieved SBP 146 mmHg). After 2 years the two groups did not differ for the combined primary end point (stroke, cardiac events, renal failure) neither for total mortality nor for incidence of adverse events. Yet an interaction between age and treatment group was associated with primary end point, with the highest risk in the subgroup aged 75+ undergoing more strict control [68].

The abovementioned data are consistent with the results of a meta-analysis of data pertaining to subjects aged 80+ enrolled in different RCTs. In those subjects a significant effect of active treatment was confirmed for stroke, cardiovascular events, and heart failure, while no effect was observed for cardiovascular death and total mortality. In a meta-regression analysis, mortality risk was reduced in the treatment arm of trials that adopted a lower-intensity treatment and achieved the least BP reduction [70].

Moreover in observational studies of subjects aged 85+, SBP <140 mmHg has repeatedly been associated with higher mortality risk [8–10]. Yet this association might differ according to antihypertensive treatment status, as shown in an international study of home BP monitoring in older subjects aged 80+, aimed at identifying optimal BP targets in regard to mortality risk over a 5.5-year follow-up. In fact, cardiovascular mortality and morbidity showed a direct association with SBP among subjects non-treated with antihypertensives, with highest risk at values >152 mmHg, while it showed a curvilinear association with SBP in the subgroup receiving antihypertensive drugs, with an increased cardiovascular risk for SBP <127 mmHg [71]. Moreover the risk associated with low BP in old age appears to be greater among subjects with a history of AH at midlife, in regard both to survival [8] and to brain atrophy and cognitive decline [72].

On the whole the cited data raise a caveat for excessive SBP lowering among actively treated subjects in very old age, with a cutoff for increased risk around the age of 80, especially for those with a long-standing history of AH. On a pathophysiological ground, the observed epidemiological and clinical data might be explained by a small reduction of perfusion of vital organs coupled with an altered vascular autoregulation associated with chronic AH, possibly leading to critical hypoperfusion if associated with decreased BP [72]. This hypothesis has not been proven yet, as a recent study of the association between BP and cerebral blood flow of very old subjects with mild cognitive impairment was not able to show any correlation between lower BP values and cerebral hypoperfusion [73]. Moreover it should be remembered that low BP is often associated with more severe clinical, and especially cardiovascular, conditions and that at least part of the observed association might be confounded by comorbidities. For these and other reasons,

Table 8.1 Antihypertensive treatment in the elderly: synopsis of European and US guidelines and open issues

	ESH 2013 [13]	JNC VIII [65]	Open issues
General cutoff for treatment	SBP ≥160 mmHg	BP ≥150/90 mmHg	
Treatment target	140–150 mmHg	<150/90 mmHg	
Subgroups		Not specified	
Fit aged <80	Treat if SBP ≥ 140 mmHg and AHDs are well tolerated	–	*Is there a chronological age cutoff for different BP targets?*
Fit aged 80+	Treat if SBP ≥ 160 mmHg and AHDs are well tolerated	–	
Frail	Individualized choice, monitor AHDs effects	–	*Frailty indicators? Specific BP targets?*
AHDs discontinuation	Not advised after age 80 if well tolerated	Not advised for SBP < 140 mmHg if well tolerated	*Is there a lower limit to BP lowering?*

the so-called J-curve phenomenon regarding the prognostic role of BP has been widely debated [74].

The Systolic Blood Pressure Intervention Trial (SPRINT) [75] has strengthened the position of those supporting the preventive efficacy of aggressive BP treatment also among older subjects. In patients at high cardiovascular risk and already using antihypertensive drugs, a treatment strategy targeting a systolic BP of 120 mmHg resulted in lower incidence of major cardiovascular events and death from any cause compared to a less strict approach targeting a systolic BP of 140 mmHg; this result was also statistically significant in the subgroup (28 % of the entire sample, n=2636) of patients more than 75 years old. Yet, it has to be pointed out that patients with severe disability, living in nursing, affected by dementia, decompensated heart failure, previous stroke, or diabetes were excluded from the study. Conversely included subjects had a mean 20 % 10-year Framingham cardiovascular risk score and a mean BMI of 30. On the whole SPRINT results add relevant information regarding antihypertensive treatment of a significant part of the older population but seem to apply to high vascular risk patients without disability and abovementioned diseases, and therefore may not be unconditionally applied to the oldest old.

8.4.2 Frailty Detection and Antihypertensive Treatment Choices

Apart from chronological age, several studies in most recent years have pointed out at a role for "frailty" in increasing the risk associated with antihypertensive treatment among elderly subjects [11].

In geriatric research frailty is conceptualized as a physiological syndrome characterized by decreased functional reserve and diminished resistance to stressors, causing vulnerability to adverse health outcomes, including disability and death

[76]. While frailty should be reliably identified with a comprehensive geriatric assessment, identifying multiple physical, mental, and social impairments whose accumulation may ultimately lead to the increased vulnerability status [77], rapid screener for this condition is often needed in clinical practice due to time and resource constraints. Therefore simple clinical tools have been operationalized to detect frailty with sufficient sensitivity and specificity [56], instruments based on lower extremity performance being among the most useful for this purpose [59].

An analysis from the National Health and Nutrition Examination Survey (NHANES) supports a role for motor performance as a powerful modulator of BP-associated risk. In fact, in a cohort of 2340 older subjects (mean age 74), the association between BP and a 7-year mortality varied markedly among subjects, according to their ability to walk 6 m as fast walkers (≥0.8 m/s), slow walkers (<0.8 m/s), or unable to complete the task. In fact, while high SBP was associated with increased mortality among fast walkers, the association disappeared among slow walkers and was reverted among subjects unable to walk, who had a greater risk associated with low values of SBP and DBP [78].

In keeping with these data, a condition of overt disability in activities of daily living associated with low BP has been identified as a condition with a negative prognostic outcome among oldest old (age 85+), in terms of both increased risk of cognitive decline [45] and increased risk for stroke [79]. Moreover, in the vast group of disabled nursing home subjects, BP was found as unrelated to a 1-year mortality risk in one study [32] and inversely associated with increased 2-year mortality risk in another one [80]. Of notice, in the latter study the increased risk for mortality was restricted to subjects with SBP < 130 mmHg in combination with 2+ antihypertensive drugs, thus supporting the need of less intensive treatment in this highly impaired population.

Finally, subjects with cognitive impairment might represent a subpopulation at high risk for brain hypoperfusion. Yet in this condition the data are not clear-cut. In fact, one study of 1385 subjects with mild cognitive impairment (mean age 73.6, baseline MMSE 28/30) has found a faster progression of cognitive decline over 2 years among subjects with repeated detection of high BP (≥140/90 mmHg) [81]. In keeping with these data, subjects with mild cognitive impairment (mean age 67.8, baseline MMSE 26/30) have been found to have an increased risk of conversion to Alzheimer's disease after 5 years, while antihypertensive treatment reduced the risk [82]. Conversely a subsequent study conducted with ambulatory BP monitoring in a sample of 172 older subjects with dementia or mild cognitive impairment (mean age 79, MMSE 22/30) has observed an increased risk of cognitive decline after 9 months among subjects with lower mean daytime SBP (<129 mmHg) actively treated with antihypertensive drugs [83]. Another study of 141 subjects with mild cognitive impairment (mean age 74) has observed an independent association between orthostatic hypotension and increased risk for conversion to dementia after 2 years [84]. Therefore, the presence of mild cognitive impairment might be a caveat for possible detrimental effects of excessive BP lowering, at least among oldest old and for subjects with orthostatic hypotension and overt dementia. ABPM seems to be more useful than clinical measure in predicting the cognitive detrimental effects of low BP.

On the whole, the presence of functional disability, motor impairment, and cognitive impairment might be useful markers of increased vulnerability to antihypertensive treatment. These factors together with old age can suggest a more prudent approach to vascular risk factor prevention, including antihypertensive treatment [85]. A treatment discontinuation randomized trial of 385 older subjects 75+ with mild cognitive decline (mean age 81, MMSE 26/30) was recently published. Subjects were included if they took at least one antihypertensive drug, and SBP was ≤160 mmHg. After 16 weeks SBP went from 148.8 mmHg to 154.2 mmHg, but no positive effect was evident on cognitive function, psychological status, or daily functioning [86]. Further studies of treatment de-intensification are warranted, with the aim of identifying the role of different BP measures (clinical vs. ambulatory) and different BP targets for specific subgroups of frail older subjects.

Conclusion

Oldest old subjects represent a fast-rising share of world population who lacks firm indications regarding prognostic meaning of BP values and preventive or harmful effects of antihypertensive treatment. The need to differentiate antihypertensive treatment targets according to age and health status introduced by European guidelines represents an opportunity to personalize medical approach to this diverse population group. Observational and intervention studies published during the last years suggest that a strict BP control might be beneficial in some older subjects (as shown by SPRINT trial) but might harm other ones, probably the frailest. Comprehensive geriatric assessment is useful in detecting vulnerability indicators, and simple cognitive and functional measures should be used to screen for older subjects who need a more cautious approach. Future epidemiological and intervention studies targeting specific profiles of frailty are warranted, to support personalized antihypertensive treatment strategies for oldest old subjects.

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