A critical role for frailty?

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Online Data Supplement

An 88-year-old woman with chronic hypertension was seen in the internal/geriatric medicine outpatient clinic. She had been treated for high blood pressure (BP) for ≈20 years with a low-dose thiazide, to which an angiotensin-converting enzyme-inhibitor had been added 5 years ago. In addition, after a possible transient ischemic attack 10 years ago, aspirin, omeprazole, and simvastatin had been added. She is known with mild cognitive impairment, which is stable with a mini-mental state examination score of 25, and a mild depression for which fluoxetine has been prescribed. In addition, she experienced 2 falls in the past 2 years; calcium/vitamin D and alendronate were started for the management of osteoporosis. On physical examination, she appears vital with a normal fluent gait and no signs of hemiparesis. Her BP is 165/75 mm Hg in the sitting position. Immediately after standing up from her chair, she feels dizzy for ≈10 seconds, but after 1 and 3 minutes, no orthostatic hypotension is found. Estimated glomerular filtration rate is 50 mL/min per 1.73 m². Should antihypertensive treatment be intensified, left unaltered, or reduced?

The oldest old, that is, persons aged ≥80 years, will be the fastest growing segment of the population for the next 40 years. Despite longer life expectancy, the prevalence of various chronic diseases and functional impairment increases with age. As a result, populations of older individuals are often highly heterogeneous and individuals with same chronological age vary widely in health and functional ability. In other words, there is substantial heterogeneity in their biological age, and those at the higher end of biological age are often referred to as vulnerable or frail.

BP rises with age, and ≈80% of people in Western societies aged ≥80 years have hypertension. Their hypertension is characterized by elevated systolic BP, with often normal or even low diastolic BP. The widened pulse pressure (PP) is a reflection of increased arterial stiffness. Despite the large body of evidence in middle-aged populations, the predictive value of high BP in this rapidly growing older population is still debated, as is the question of whether hypertension should be treated, and if so, how intensively. Importantly, the current paradigm of lower is better may not apply to (untreated or treated) BP in the oldest old.

In this concise narrative review, we summarize evidence from observational studies and randomized clinical trials. We conclude that biological age/frailty is becoming an important criterion for treatment decisions. Finally, we address what we think are the most pressing research questions for the coming years.

Pathophysiology of BP Regulation in the Oldest Old

Although hypertension in the oldest old may reflect a long-standing condition, often it manifests itself as de novo abnormality. Data from the Framingham Heart Study indicate that the majority of patients in whom isolated systolic hypertension develops have not had an elevated diastolic pressure before. This suggests a different pathogenesis in older hypertensives with isolated systolic hypertension than in individuals with classic hypertension. The most conspicuous finding in isolated systolic hypertension, widening of PP, has its origin in arterial remodeling with progressive stiffening of the large arteries.

The mechanisms involved include fibrosis, hyperplasia, and hypertrophy of vascular smooth muscle cells, loss of contractility of vascular smooth muscle cells, deposition of collagen, fragmentation of the elastic lamina, endothelial dysfunction, and arterial calcification. Collectively, these vascular changes alter the pressure waveform of the aorta, which is composed of a forward traveling wave generated by cardiac contraction and a backwards traveling wave generated by reflection from peripheral arteries. The latter is generated at vascular bifurcations and at sites where elastic conduit arteries convert into muscular resistance arteries. Stiffening of arteries is associated with faster wave reflection, an augmented proximal aortic systolic pressure peak, and a highly pulsatile flow in the aorta and its branching arteries. The enhanced pulsatility is thought...
to damage sensitive target organs, as well as impair vascular function, and thereby to contribute to a vicious cycle of arterial remodeling. Blood flow becomes increasingly oscillatory with peaked systolic flows, as well as stasis and even flow reversal during diastole. The ensuing turbulence and locally alternating shear stress patterns cause endothelial dysfunction, manifested by impaired NO synthesis and upregulation of proinflammatory and proatherogenic factors, increased oxidative stress, and vasoconstriction. The high systolic load on the heart favors the development of left ventricular hypertrophy and stiffening of the heart. This, in turn, may impair diastolic relaxation and cause diastolic dysfunction. Eventually, this will lead to cardiac failure. Because diastolic ventricular filling becomes increasingly dependent on atrial contraction, it follows that the presence of atrial fibrillation, which is not uncommon in the oldest old, will accelerate the transition from a normal to a compromised circulatory pattern.

A problem for older patients with hypertension is that they cannot buffer pressure increases well. Because both the baroreceptor system and the kidney are involved in counteracting changes in pressure, it is likely that these systems are not functioning properly. Although baroreflex sensitivity tends to fall with age, in healthy individuals aged >80 years it does not differ much from that in middle-aged men. Conversely, there is abundant evidence that baroreflex sensitivity is blunted in hypertensives. Because baroreceptors do not respond directly to changes in intravascular pressure but rather to the mechanical deformation of the vessel wall, it is not surprising that increased arterial stiffness and calcification are associated with reduced baroreflex sensitivity. In most studies, baroreflex sensitivity has been assessed from the relationship between the changes in systolic BP and those in heart rate (or the R-R interval) during such maneuvers as Valsalva or the injection of vasoactive substances. This approach evaluates the cardiovasal component of the baroreflex system. Reduced cardiovasal baroreflex sensitivity may not only be related to the specific neural pathways but also to the number of functional β-adrenoceptors, which are diminished in older hypertensives. Recently, Okada et al described that in older people (mean age, 69 years) the sympathetic component of the reflex is also impaired. The latter was derived from muscle sympathetic nerve activity recordings. Sympathetic baroreflex sensitivity correlated inversely with carotid artery stiffness and to a lesser extent also with aortic stiffness. These data provide ≥1 explanation for the higher prevalence of hypertension in older persons. Reduced baroreflex sensitivity could also contribute to greater BP variability and the high prevalence of white-coat and masked hypertension in older patients. Finally, reduced baroreflex sensitivity may be responsible for the disappearance of the nocturnal decline in BP, for a greater morning surge, as well as for the frequent occurrence of orthostatic and postprandial hypotension in older persons. Orthostatic hypotension (defined as a fall in systolic pressure of ≥20 mm Hg or a drop in diastolic pressure of ≥10 mm Hg within 3 minutes of standing) occurred in as much as 8% of patients with hypertension >80 years who participated in the Hypertension in the Very Elderly Trial (HYVET), but higher prevalences have been reported in unselected (hypertensive) populations. Interestingly, a few studies showed that orthostatic intolerance is more prevalent during β-blocker treatment. This points to the neural pathway as the main responsible mechanism, at least in relatively stable patients. However, in a retrospective analysis of a presumably frail population of veterans attending a geriatric clinic, orthostatic hypotension was found more frequently when hydrochlorothiazide was used. Clinical experience tells us that the risk of orthostatic hypotension will be higher during volume depletion or in the course of acute illness. Therefore, all antihypertensive agents may cause or aggravate orthostatic hypotension depending on the clinical condition of the patient. Unfortunately, reliable data on this issue are lacking as patients with acute conditions have been excluded usually from analyses.

Kidney function also progressively falls with age, and more so in hypertensives. As a result of the decline in cortical blood flow (≥10% per decade) and subsequent atrophy of the cortex, the number of viable glomeruli is substantially reduced. Nevertheless, glomerular filtration rate is maintained for a relatively long period of time so that the filtration fraction (the ratio between glomerular filtration and perfusion rates) increases. Experimental data suggest that this is most likely because of an increase in intraglomerular pressure that, in turn, may contribute to further glomerular damage. Indeed, epidemiological observations show that the rate of decline in renal function with age is accelerated in hypertension and in patients >80 years hypertension is a particularly strong determinant of cystatin C estimated glomerular filtration rate. Although the term hypertensive nephrosclerosis has been used to denote this form of renal impairment, the usefulness of this term has been questioned as in many cases intrinsic renal disease takes primacy over hypertension. One of the functional characteristics of the aging kidney is a disturbed ability to adapt to changes in sodium intake. For instance, after a sudden reduction in dietary salt, older people need more time to attain a new balance during which they lose more sodium than younger individuals. Together with impaired reabsorption of sodium in the ascending part of Henle’s limb in old persons, this predisposes older patients with hypertension particularly to develop hyponatremia during a low-salt diet. At the same time this makes them more vulnerable to volume loss, which is unfortunate because plasma and extracellular volumes already tend to be reduced in hypertension. Low levels of renin and aldosterone further reinforce the tendency to volume loss, as well as to some increase in potassium concentrations. Aging in itself is associated with a progressive decline in renin, but high BP augments this trend. Only when (parts of) the kidneys become ischemic, renin may rise again.

In contrast to the situation in younger patients, the number of pathophysiological studies in very old patients with hypertension is small. Much of what we know about mechanisms in hypertension has been derived from young and middle-aged populations, and we can only extrapolate such findings to the very old. Nevertheless, it seems fair to state that the patients aged >80 years with hypertension are less able to maintain a stable BP level, largely because of defective neural pathways, and that such individuals may easily become volume depleted during acute illness with decreased intake of salt and water. To what extent renal function loss and volume control contribute to hemodynamic abnormalities at a high age has been less well investigated.
BP and Risk of Mortality and Morbidity in the Oldest Old

Risk of Cardiovascular Events and Mortality

The association between BP and cardiovascular disease and mortality has been the subject of numerous observational studies. Two conclusions from these studies are solid: (1) hypertension is associated with cardiovascular risk in the general population, and (2) there is no evidence of a clear association with noncardiovascular mortality, apart from end-stage renal disease. It is less clear, however, whether the association between BP and cardiovascular disease and mortality is different in the oldest old and, if so, what the determinants of such differences are. We will conclude that, in general, the positive association between BP and risk is maintained at higher age, but also that this association is probably lost or even inverted in old people who are frail.

Prospective cohort studies, and meta-analyses thereof, are crucial for clarification of the association between BP and associated morbidity and mortality. In 2002, the Prospective Studies Collaboration published the most comprehensive meta-analysis to date, including 1 million adults with no previous cardiovascular disease recorded at baseline in 61 prospective studies, with 12.7 million cumulative person-years at risk, and >55,000 cardiovascular deaths. Importantly, this meta-analysis also adjusted for time-dependent regression dilution effects, which become increasingly strong as the age of subjects increases. In short, the conclusions were that, as age increases, systolic and diastolic BP remain positively associated with risk of stroke (Figure 1) and ischemic heart disease. The association is less steep in the highest age categories, but there was no evidence of an inverse association.

Notwithstanding the quality of the Prospective Studies Collaboration meta-analysis, there is a striking discrepancy with several other high-quality prospective population-based cohort studies. In several of these studies, a sharply attenuated or even inverse association between BP and cardiovascular risk was found in the highest age groups. The age at which the association inverted in these studies is not unequivocal, but seems to be in the range of 75 to 85 years. In addition, a J-shaped association of diastolic BP with mortality and myocardial infarction was found in patients with cardiovascular disease, suggesting that excessive reduction of diastolic BP in these patients should be avoided. Why did the Prospective Studies Collaboration meta-analysis reach a different conclusion with respect to the impact of high BP in the oldest old than these studies? A recent analysis of the potential impact of frailty on the association between BP and mortality may provide an important clue. In 2340 persons, aged ≥65 years in the National Health and Nutrition Examination Survey, walking speed as a measure of frailty was assessed for a 20-ft distance and was used as a stratification variable for the association of hypertension with mortality. The results suggest that, among fast walkers, elevated systolic BP (>140 mmHg) is associated with increased mortality, just as in the general population. Among those who did not manage to complete the walking test, however, the association was inversed (Figure 2), even when they adjusted for potential confounders.

The results of the National Health and Nutrition Examination Survey study suggest that biological age, rather than chronological age, determines the nature of the association between BP and subsequent mortality risk. A recent similar analysis suggested that the same was true for stroke risk. Although biological aging/frailty as the main effect modifier of the association between BP and risk is an intriguing explanation for the discrepant study results noted above, several questions must still be addressed. First, it seems obvious that the average general health status of older persons that were included in the Prospective Studies Collaboration meta-analysis was better than of persons included in the separate cohort studies that

Figure 1. A and B, Stroke mortality rate in each decade of age vs usual blood pressure at the beginning of that decade. The figures for ischemic heart disease mortality run slightly less steep than those for stroke (not shown). CI indicates confidence interval.
found an inverse association between BP and risk. Indeed, the majority of the latter studies explicitly included older persons with high levels of comorbidity, frailty, activities of daily living dependency, or cognitive impairment.26–32 However, no study has systematically addressed the impact of general health status in the aggregate of the earlier cohort studies in an analysis similar to that performed by the Prospective Studies Collaboration. A second question that must be addressed is whether it would be possible to pinpoint the most appropriate way to assess general health/frailty in this particular context. Frailty is a state of increased vulnerability and is a consequence of cumulative decline in many interrelated physiological systems.37 Valid models of frailty have been developed. However, there is a lack of efficient methods to detect frailty and measure its severity in routine clinical practice. The frailty index is a clinically attractive way to assess frailty because it allows frailty to be regarded as gradable, rather than present or absent.37 Finally, the National Health and Nutrition Examination Survey analysis comprised total mortality as the outcome, and it is important to know whether frailty exerts its effects indeed via an effect on cardiovascular death, or whether other effects such as falling or hip fractures explain it, at least partly.

Diastolic BP, PP, and orthostatic hypotension deserve separate attention. Patients with diastolic BP <70 mm Hg were not separately analyzed in the Prospective Studies Collaboration meta-analysis, but several studies suggest that diastolic BP levels below this threshold are associated with a particularly strong increase in mortality risk.31,32 PP has not received the same level of attention, but most studies suggest that PP is a strong and independent risk predictor.38,39 Some evidence suggests that the predictive value of low diastolic BP is lost after adjustment for PP.40 Such analyses are statistically challenging because of strong collinearity but are important in that they can shed light on what might be the culprit in these associations. If diastolic hypotension is independently responsible for excess risk, impaired organ perfusion, particularly of the heart (which is perfused only in diastole) is a conceivable explanation. If, however, low diastolic BP would no longer predict risk after adjustment for PP, the increased risk associated with low diastolic BP is more likely because of increased arterial stiffness as a marker and, as discussed in the previous section, accelerator of vascular damage. These explanations, however, are not mutually exclusive, as increased stiffness is only partly reflected in PP, and stiffness also causally contributes to lower diastolic BP.

Orthostatic hypotension, both symptomatic and asymptomatic, has also been implicated as an independent risk factor for vascular death and events in older persons.41–42 However, in a recent analysis, this association was no longer significant after adjustment for frailty, suggesting that the latter is more important for survival.43

Risk of Functional Disabilities

As the number of older men and women continues to rise worldwide, their physical and cognitive independence is an important public health challenge. The inability to perform physical and cognitive tasks marks a serious decline in functional health, conferring an increased risk for hospitalization and death.44,45 As discussed above, frailty or functional disabilities may modify the relation between BP and cardiovascular disease and mortality. However, functional disabilities could also result from high BP, possibly through the development of cardiovascular disease or cerebrovascular pathology such as stroke or white matter lesions.46–49 This puts functional decline in a complex position; it may be a consequence of hypertension and cardiovascular disease and mortality. However, functional disabilities could also result from high BP, possibly through the development of cardiovascular disease or cerebrovascular pathology such as stroke or white matter lesions.46–49 This puts functional decline in a complex position; it may be a consequence of hypertension and cardiovascular disease and mortality. However, functional disabilities could also result from high BP, possibly through the development of cardiovascular disease or cerebrovascular pathology such as stroke or white matter lesions.46–49 This puts functional decline in a complex position; it may be a consequence of hypertension and cardiovascular disease and mortality.

With respect to cognitive function, most long-term observational studies report that hypertension during midlife increases risk for cognitive impairment later in life.50–53 Pooled analysis suggests that midlife hypertension is associated with a 60% increased risk of dementia.54 By contrast, the effects of late-life BP levels on cognitive function are complex and less clear.51,55 In fact, several studies, particularly in very old individuals, suggest that lower or decreasing BP levels contribute to more rapid cognitive decline and the severity of dementia.56,57 The age at which the association between BP and cognitive impairment inverses seems to be >75 years.58 Yet, lower BP levels could also be a consequence of the neurodegenerative disease process causing impaired BP autoregulation or behavioral changes, such as dietary changes and weight loss.59 Hypertension during midlife has detrimental effects on physical functioning (disability-adjusted life years) later in life.60 However, the relation between late-life BP levels and

Figure 2. Kaplan–Meier survival plots of persons with elevated systolic blood pressure (SBP) ≥140 mm Hg (A) and diastolic blood pressure (DBP) ≥90 mm Hg (B), stratified by walking speed, in National Health and Nutrition Examination Survey participants aged ≥65 years (1999–2002), followed up until December 31, 2006.26
physical functioning is less clear. Cross-sectional studies in older individuals have demonstrated a relation between high BP and poor physical function and physical disability as defined by lower gait speed, difficulty with activities of daily living, or reduced lower limb function.61-64 Results of longitudinal studies later in life are, however, inconsistent; in well-functioning older persons aged 70 to 80 years, high BP was related to physical decline (gait slowing)61,64 and disability,65 whereas in the oldest old low BP was related to physical decline66,66 and lower grip strength.67

Combined with systematic reviews from a life-course perspective reporting on the relation between BP and functioning,51,68 these findings suggest an age-dependent association of BP with risk of functional impairment: midlife hypertension causes cognitive and physical limitations later in life, but this relation seems to be inverted in certain subgroups of (biologically) older individuals. How do we identify these biologically older subjects? In line with the National Health and Nutrition Examination Survey analysis,35 a prospective study in the oldest old showed that the relation between low BP and cognitive decline was most pronounced in those who were physically frail.56 In addition, recent studies in a younger population (mean age, 60 years) with manifest cardiovascular disease demonstrated that low BP, particularly low diastolic BP, was associated with progression of brain atrophy and worse functioning.69,70 Such findings suggest that low systemic BP in certain subgroups of (biologically) older individuals, for example, as a result of a dysfunctional vascular system, may compromise perfusion of vital organs, including the brain. This can result in loss of brain tissue and subsequent decline in cognitive and physical functioning.51,72 Although evidence to support this hypothesis is limited, a recent study showed that patients with a combination of low BP and cerebral hypoperfusion had smaller brain volumes than those with either low BP or cerebral hypoperfusion.71

Orthostatic hypotension is not only associated with mortality and cardiovascular outcomes but has also been linked to falls and cognitive impairment.61,74 Although the relation between orthostatic hypotension and fall risk has been shown in several studies,75,76 studies on the relation between orthostatic hypotension and cognitive impairment are less consistent and causality is unclear.41,78 Also, whether there are differences between symptomatic and asymptomatic orthostatic hypotension with respect to risk of functional impairment is unknown and warrants further research.41 Furthermore, no studies of orthostatic hypotension have been done in a population selected for having hypertension. In particular, the role of antihypertensive treatment requires further study, as does the appropriate way of assessing orthostatic hypotension. A recent study identified initial (<1 minute) orthostatic BP drop as a potentially more relevant phenomenon than the traditional 1- to 3-minute drop after standing, at least in terms of complaints, falling risk, and frailty.79 However, the association of orthostatic hypotension with risk of cardiovascular events was mainly because of the delayed orthostatic BP drop.42

In conclusion, the bulk of the evidence suggests that, overall, increasing systolic and diastolic BP is associated with increasing cardiovascular risk and mortality. The picture is far less clear, however, in older individuals who are frail, as indicated, for example, by walking speed or comorbidity. In such individuals, the association between BP and risk might in fact be inverted. Why might high BP be a good sign in those aged >80 years? A considerable proportion of the oldest old with physical disabilities has widespread vascular alterations, ranging from atherosclerosis and arterial stiffness to microvascular rarefaction. In the presence of lower BP levels, regulatory mechanisms to preserve perfusion of vital organs may fail. Also, it has been shown that BP gradually decreases in the 3 years before death in the oldest old, suggesting that lower BP levels are a risk indicator of underlying comorbidity.80,81 Thus, high BP may be a compensatory mechanism to maintain organ perfusion, and therefore ultimately prevents morbidity and functional decline.

The role of diastolic BP <70 mm Hg, high PP, and orthostatic hypotension is complex, and future studies are required to show whether these are independent risk predictors, and whether their association with risk is modified by frailty indicators the same way as is systolic BP. Further research is also needed to determine whether frailty/biological age is a suitable instrument to select patients for antihypertensive treatment and, if so, which specific indicator of biological age or frailty is most appropriate.

### Antihypertensive Drug Treatment in the Oldest Old

Recent guidelines on antihypertensive treatment are cautiously optimistic about drug treatment in hypertensive older individuals, including those aged >80 years (Table 1).45 Importantly, however, all trials in older individuals have been conducted in patients with systolic BP ≥160 mm Hg, and there is little evidence that systolic BP levels <140 mm Hg are beneficial as compared with levels between 140 and 150 mm Hg. In addition, evidence that drug treatment is beneficial in fit individuals aged >80 years is based on a meta-analysis of trials43 (including the HYVET)16 that in total included <7000 patients (ie, is based on relatively few data). Most importantly, the generalizability of these trial data to clinical practice remains problematic and controversial. For example, the HYVET excluded individuals with heart failure, serum creatinine >150 μmol/L, dementia, receiving nursing care, or a standing systolic BP <140 mm Hg. In addition, treatment was limited to 2 drugs in low doses. Indeed, there is some evidence that more intensive treatment (ie, ≥2 antihypertensive drugs or BP reduction of >15–20 mm Hg) is associated with greater mortality.83 This raises the question of whether, in elderly individuals, clinicians should use a target systolic BP (eg, 140–150 or 140–160 mm Hg), a maximum number of antihypertensive drugs (eg, 2 or 3), or a target reduction in systolic BP (eg, 10–20 mm Hg).

Preservation of physical and cognitive abilities is a compelling outcome of therapeutic interventions in older populations. Treatment of hypertension has been shown to prevent disabling cardiovascular events in fit older adults, such as stroke, myocardial infarction, and congestive heart failure. The effectiveness of treatment on functioning has been scarcely studied, but the favorable effects of lowering BP in preventing cerebrovascular disease are not noticeably reflected in preservation of physical and cognitive functioning.51,67,84 Pooled data from the HYVET-cognitive function assessment and other trials have
Table 1. Selected Recommendations on Antihypertensive Treatment in Older Individuals, With Class of Recommendation and Level of Evidence (see Table S1 in the online-only Data Supplement), According to a Recent Guideline

1. In older patients with hypertension drug treatment is recommended when systolic BP is ≥160 mm Hg; there is solid evidence to recommend reducing systolic BP to between 150 and 140 mm Hg (Class I; Level of Evidence A).
2. In fit older patients aged <80 y drug treatment may also be considered when systolic BP is in the 140–159 mm Hg range with a target systolic BP <140 mm Hg provided that antihypertensive treatment is well tolerated (Class IIb; Level of Evidence C).
3. In individuals aged >80 y with an initial systolic BP ≥160 mm Hg, it is recommend to reduce systolic BP to between 150 and 140 mm Hg provided they are in good physical and mental conditions (Class I; Level of Evidence B).
4. In frail older patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, based on monitoring of the clinical effects of treatment and adapted to individual tolerability (Class I; Level of Evidence C).
5. Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian (Class IIa; Level of Evidence C).
6. All antihypertensive agents are recommended and can be used in older individuals although diuretics and calcium antagonists may be preferred in isolated systolic hypertension (Class I; Level of Evidence A).

Table 2. Selected Research Questions on Treatment of Hypertensive Individuals Aged >80 Years

1. Is a target reduction in systolic BP (eg, 10–20 mm Hg) more beneficial than a target level of systolic BP (eg, 140–150 mm Hg) and diastolic BP (eg, 70–75 mm Hg)?
2. Is the use of >2 antihypertensives safe and effective in fit individuals?
3. What are the preferred first and second line antihypertensive treatments?
4. Do surrogate end points exist that accurately predict beneficial effects of antihypertensive treatment?
5. What factor(s) related to frailty or biological age can most precisely predict the lack of clinical benefit of antihypertensive treatment?
6. What are the characteristics of those oldest old in whom higher BP levels are beneficial?
7. Is a severely reduced estimated GFR an argument in favor (to decrease the risk of end-stage renal disease) or against (to avoid adverse effects) drug treatment?
8. Why is antihypertensive treatment not beneficial in the very old?
9. Is reduction or withdrawal of antihypertensives beneficial in frail older patients, in patients exposed to polypharmacy, or in patients with diastolic BP <70 mm Hg or orthostatic hypotension?
10. Is reduction or withdrawal of antihypertensives beneficial when renal function worsens during such treatment (eg, a fall in estimated GFR >10%–20%)?
11. What parameter(s) of orthostatic hypotension is (are) most strongly related to clinically important outcomes?
12. Is either short-term BP variability as derived from 24-hour recordings or longer term variability such as expressed in visit-to-visit variability of blood pressure a risk factor in the oldest old?

BP indicates blood pressure.
*We consider systolic BP ≥180 mm Hg a reasonable alternative recommendation, and systolic BP ≥160 mm Hg only in truly fit older individuals.
†We consider this target too stringent.
‡We consider antihypertensive drug treatment in frail individuals, with some exceptions, contraindicated (see text).
§We consider drugs with an effect on the autonomic system (β-blockers, α-blockers, centrally acting agents) best avoided when a significant orthostatic blood pressure drop (assessed within 1 minute after standing) is observed.

suggested a marginally reduced risk of dementia associated with antihypertensive treatment. However, the Cochrane review of the randomized trials found no convincing evidence that antihypertensive treatment could reduce dementia risk, which is in line with another meta-analysis. In view of these uncertainties, guidelines appropriately stress the importance of clinical judgment (Table 1), but, except for tolerability, do not specify what factors the clinician should take into account. One study showed that, in patients taking active treatment, total mortality was increased in patients with lower treated systolic and diastolic BP levels, and that these patients were characterized by decreases in body weight and hemoglobin concentration, suggesting deterioration of general health. However, the question remains whether frailty/general physical and cognitive functioning affects the effect of antihypertensive treatment in the same way that it does on the observational association between BP and complications. In other words, can we use the same variables that seem to be important for how hypertension impacts on risk in older persons also for selection of patients to receive antihypertensive treatment and the desired intensity thereof? Stratification of trial populations according to frailty (or proxies thereof, such as polypharmacy) might shed some light on this, and we think such analyses could be useful in those trials that have suitable data.

Currently, the most important problem is the lack of robust data to guide clinicians, which suggests a research agenda (Table 2). Although, results of ongoing trials in older individuals studying the effect of intensive versus standard BP lowering on cardiovascular events (https://clinicaltrials.gov/ct2/show/NCT01835249) or functional decline (https://clinicaltrials.gov/ct2/show/NCT01650402) will help to fill in, at least in part, this lack of data, for now, we suggest the following. First, even in fit individuals aged >80 years, drug treatment should, as a rule, not exceed 2 drugs, as the safety and efficacy of using >2 drugs even in fit individuals aged >80 years have not been established. Severe hypertension (eg, systolic BP >180 mm Hg) may be an exception to this rule. Antihypertensives are an important contributor to polypharmacy (usually defined as use of ≥5 medications). Polypharmacy is extremely common in the very old, is associated with a substantial increase...
in the risk of adverse events and hospital admissions related to medications, and reduces quality of life, self-reliance, and cognitive functioning. It follows logically that reduction of antihypertensives in individuals treated with ≥3 drugs should be considered in the oldest old and when treated systolic BP is <140 mm Hg, but data on these issues are scarce (see below).

Second, antihypertensive drug treatment should, as a rule, not be started in frail individuals aged >80 years. Exceptions to this rule may be systolic BP >180 mm Hg, a recent stroke, and heart failure. Nevertheless, as discussed above, cohort data show that a high BP may not be associated with cardiovascular disease in frail older persons. In addition, there is no evidence that antihypertensive treatment reduces cardiovascular disease in the frail, and there is much evidence to suggest that such treatment is not safe. It follows that withdrawal of antihypertensive drugs should logically be considered in frail patients and when initially fit patients develop frailty. Unfortunately, it is unclear whether such an approach is safe. Withdrawal of antihypertensives in older persons (not specifically in the context of frailty or polypharmacy) generally has been associated with a return of hypertension without an increase in the incidence of cardiovascular disease.93–95 but these studies used liberal rules for reintitiatation antihypertensives and were thus underpowered. Withdrawal of diuretics has been shown to be associated with an increased risk of developing heart failure, especially in the first 4 weeks after withdrawal,92 and withdrawal of diuretics should therefore be accompanied by strict monitoring.

Third, antihypertensive drug treatment should be reconsidered or reduced in individuals aged >80 years (especially when frail) in the case of polypharmacy, when diastolic BP is repeatedly <70 mm Hg, and when there is orthostatic hypotension (systolic BP drop in the standing position >20 and <140 mm Hg, regardless of symptoms).

Fourth, we stress that the above recommendations present our subjective views, and are not based on firm evidence. Moreover, the criteria discussed above should not be seen as present or absent, as they in fact represent variables on continuous scales, and this should be taken into account when antihypertensive drug treatment is considered in the oldest old.

Finally, because of the dearth of solid data, weighing these criteria in the individual patient remains difficult. This is perhaps best illustrated by the fact that, in the patient presented above, 2 of the authors of this article would recommend leaving the antihypertensive treatment unchanged, whereas the other 2 would recommend a cautious reduction.

Conclusions

As the current paradigm of lower is better may not apply to BP levels and regulation in the entire population of older persons, specific guidelines for BP management dependent on the biological age or frailty status of older persons are needed. This review emphasizes that many key questions cannot be answered with currently available data (Table 2). Nevertheless, the increasing awareness of categorizing individuals based on biological instead of chronological age will facilitate personalized BP treatment for the aging hypertensive population, leading to a patient instead of a disease-based approach. Markers of biological age or frailty, such as gait speed, underlying comorbidities and polypharmacy, or a combined measure such as the frailty index could be used to understand the complex relationship between late-life BP levels and risk of clinical outcomes and to identify older individuals who are likely (not) to benefit from antihypertensive treatment. Clinicians need simple, accurate, and reliable methods to detect the biological age of an older person. Whether this should be based on a comprehensive geriatric assessment or whether a simple gait speed or even the clinicians’ gut-feeling suffices is unknown and warrants further research.95

Disclosures

None.

References


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TREATMENT OF HYPERTENSION IN THE OLDEST OLD:

A CRITICAL ROLE FOR FRAILTY?

Online Supplement

Running title: Treatment of hypertension in the oldest old

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Table S1. Classes of recommendations and levels of evidence.

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<th>Classes of recommendations</th>
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<td>I</td>
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<tr>
<td>II</td>
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<tr>
<td>III</td>
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<table>
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<th>Levels of evidence</th>
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<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
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