REVIEW

Risks associated with intensive blood pressure control in older patients

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ABSTRACT

Hypertension management forms a cornerstone of cardiovascular prevention. Strong evidence is available supporting the benefits of blood pressure (BP) lowering in older adults, and recent studies indicate that intensive BP control may provide additional advantages concerning cardiovascular and mortality risk, also at older ages. Yet, in older adults, the cardiovascular benefit of intensive treatment may come at the expense of an increase in adverse events. Indeed, advanced age and frailty may modify the risk/benefit ratio of BP lowering due to a greater predisposition to hypotension and more severe consequences deriving from treatment-related adverse effects. This mostly applies to individuals with poor health status and limited life expectancy, in whom aggressive BP lowering may not lead to cardiovascular benefits but rather increase the risk of short-term treatment-related complications. Furthermore, potential harms of intensive BP control might be underestimated in clinical trials due to exclusion criteria that preclude patients with frailty and multimorbidity from being eligible. Syncope and falls are the most frequently mentioned safety concerns related to antihypertensive treatment, but aggressive BP lowering may affect negatively also renal function, cognitive performance, quality of life, and survival. With the growing emphasis on intensive treatment strategies, raising the awareness of potential harms associated with aggressive BP lowering might help improve hypertension management in older adults and encourage implementation of clinical research on safety. Given these premises, we present a narrative review illustrating the most relevant risks associated with intensive BP control in older patients.

Key words: dementia, falls, hypertension, hypotension, mortality, renal function

INTRODUCTION

Hypertension is one of the most important modifiable risk factors for cardiovascular disease, and mortality and blood pressure (BP) management represents an essential pillar of cardiovascular prevention [1]. The prevalence of hypertension steadily rises with age, exceeding 60%–70% in individuals aged 60 years or older [2].

In Italian epidemiological studies involving individuals over the age of 65, the prevalence of hypertension varied from 65% up to over 80%, with higher rates reported in women [3]. Recent studies analyzing trends in hypertension prevalence in Polish older adults reported consistent data, with prevalence rates reaching 72%–75% in men and 79%–87% in women, and the highest prevalence observed in people over the age of 85 [4, 5]. Given the progressive increase in life expectancy and population aging, the prevalence of hypertension is expected to increase dramatically in the near future, especially in older individuals, which calls for greater attention to this condition in the geriatric population.

Over the last decades, several studies have provided compelling evidence that antihypertensive treatment substantially reduces cardiovascular morbidity and mortality in old and very old adults [6–8]. Consistently, the European Society of Cardiology guidelines advise not to consider age alone as a barrier to antihypertensive treatment [9]. More recent studies seem to support an intensive approach to BP lowering, targeting tight BP control [10]. In the STEP trial involving older adults aged 60–80 years, targeting systolic

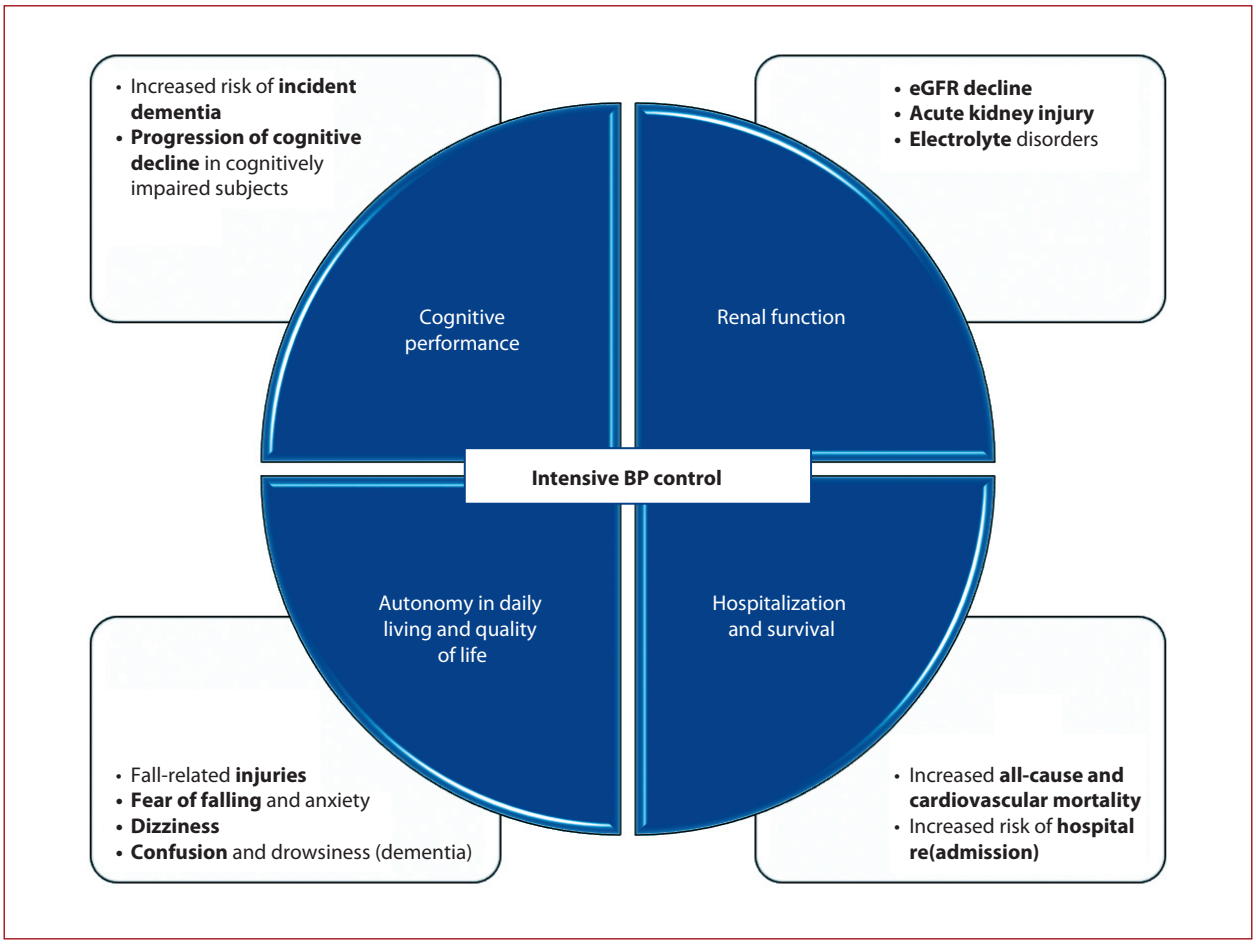

Figure 1. Potential risks of intensive blood pressure (BP) control in older adults
Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate

BP of 110–130 mm Hg reduced the risk of cardiovascular events compared with standard treatment targeting systolic BP of 130–150 mm Hg [11]. Similarly, data from the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that treating hypertensive adults to reach systolic BP <120 mm Hg reduced the number of cardiovascular events and deaths compared with a systolic BP target <140 mm Hg [12]. The benefits of intensive treatment were also confirmed in individuals aged 75 years or older [13], thus prompting a paradigm shift in hypertension guidelines from less intensive to more intensive BP targets for older adults [14, 15].

The cardiovascular benefits of intensive therapy may come at the expense of relevant drawbacks [16], particularly in older patients who typically present a higher risk of hypotension-related complications [17]. Indeed, multiple observational studies involving older individuals suggest increased potential for serious adverse effects in patients receiving intensive antihypertensive treatment, even more so if they are frail [18–23]. Many experts and analyses have thus argued against aggressive antihypertensive treatment in older patients, highlighting a discrepancy between clinical trials and the real world [24, 25]. Trial evidence that underpins guidelines usually includes patients with relatively good health status and no or mild frailty, who are more likely to benefit from long-term advantages of intensive BP control. By contrast, patients with higher levels of frailty and multimorbidity, who are particularly vulnerable to adverse events, are typically excluded [26, 27]. As a result, data from clinical trials may encourage the pursuit of aggressive BP control while potentially underestimating the risk of adverse events. As life expectancy and time available to experience long-term benefits of antihypertensive treatment decrease, attention should be given to avoiding early complications, including treatment-related adverse events.

Syncope and falls are the most frequently mentioned antihypertensive treatment-related safety concerns. However, aggressive BP lowering may negatively impact also renal function, cognitive performance, quality of life, and survival (Figure 1). The knowledge of potential harms associated with intensive BP lowering may be helpful to improve hypertension management in older adults while drawing attention to clinical research on safety. Therefore, this article presents a narrative review that outlines and discusses the risks of intensive BP control in older adults.

FALLS, FUNCTIONAL AUTONOMY, AND QUALITY OF LIFE

Hypotension represents the most common cause of syncope and falls in older adults [28–31]. Iatrogenic events related to drug-induced hypotension are especially common, particularly in frailer individuals receiving polypharmacy with hypotensive effects [32, 33]. Nevertheless, limited data are available on the association between intensive BP control and the risk of falls and injuries in older patients.

In the SPRINT cohort, including a subgroup of participants aged 75 years and older, intensive treatment was associated with increased risk of hypotension and syncope but not injurious falls, i.e., falls resulting in emergency department or hospital admissions [16]. Observational studies carried out in community-dwelling older adults describe a different scenario. Indeed, in a community-based cohort of subjects aged 75 years or older meeting the inclusion criteria for the SPRINT and undergoing a follow-up of comparable duration, rates of injurious falls and syncope were approximately 5-fold higher than in the standard care group in the SPRINT [25], suggesting limited generalizability of the trial results. Moreover, in a real-world sample including 477 516 treated hypertensive individuals at a mean age of 65 years, mean systolic BP <110 mm Hg carried a 50% higher risk of serious falls and syncope compared with mean systolic BP ≥110 mm Hg [34].

Fall risk seems to be especially relevant during the early phases of antihypertensive treatment. Indeed, introduction of antihypertensive medications was found to be associated with 69% and 94% increased risk of falls during the first 45 and 14 days of treatment initiation, respectively, independently of the drug class used [35]. Consistently, the risk of a serious fall injury was consistently and significantly increased in the 15 days after antihypertensive medication initiation and intensification in a large sample of older Medicare beneficiaries [36].

Although falls are recognized as possible adverse events related to antihypertensive treatment, their deleterious consequences on older patients' health and well-being are often overlooked. Fall-related injuries are usually more severe in older than in younger people and represent a significant cause of disability and mortality. A cohort study of 754 community-dwelling older adults investigating recovery from disability after serious fall-related injuries showed little or no recovery in 64% of participants. Moreover, 44%–59% of participants with no or mild-to-moderate pre-fall disability did not return to the pre-fall level of functioning [37]. Indeed, major injuries such as fractures and head traumas frequently lead to hospitalization, prolonged bed rest and deconditioning, impaired autonomy in daily living, and nursing home admission in more severe cases [38–40]. Falls that do not result in major injuries are also clinically important, potentially causing a "post-fall syndrome" characterized by fear of falling, anxiety, depression, restrictions in daily activities, and loss of functional autonomy [41–43]. Finally, falls represent the leading cause of injury-related deaths in persons aged ≥65 years [44].

Falls aside, aggressive BP lowering in older patients may be responsible for a number of symptoms such as dizziness, light-headedness, and unsteadiness, which impair quality of life and may lead to activity restriction.

Moreover, hypotension has been associated with mental fluctuations, confusion, and drowsiness in patients with dementia [45].

RENAL FUNCTION AND ELECTROLYTE BALANCE

High BP is a modifiable risk factor for chronic kidney disease and antihypertensive treatment is known to reduce the risk of renal function decline. However, uncertainties remain on the renal benefits of intensive BP control [46, 47].

In the SPRINT cohort, a >30% reduction in estimated glomerular filtration rate (eGFR) occurred in the 4% and 1.1% of participants in the intensive and standard treatment arms, respectively, and intensive treatment was associated with a significantly higher risk of a >30% reduction in eGFR (hazard ratio [HR], 3.69; 95% confidence interval [CI], 2.54–5.36) [48]. In a systematic review and meta-analysis assessing the efficacy and safety of intensive BP lowering in older adults, intensive treatment was consistently associated with a 2-fold increase in the risk of renal failure [10]. Moreover, a systematic review of clinical trials involving patients with non-diabetic chronic kidney disease demonstrated that intensive BP treatment does not slow renal function decline nor reduce the risk of renal outcomes, such as doubling of serum creatinine or a 50% reduction in GFR, although stricter BP control might be beneficial in selected subgroups of patients with higher levels of proteinuria [49].

In addition to unclear benefits for renal function and preventing renal disease progression, intensive BP lowering may also predispose to acute kidney injury (AKI) events. Data from primary care indicate that AKI is more likely to occur in older adults with low systolic BP values (i.e., <100 mm Hg) [50]. In the SPRINT study, the incidence of AKI events was 3.8% vs. 2.3% in the intensive and standard arms, respectively [51], and intensive treatment was identified as an independent predictor of AKI (adjusted HR, 1.83; 95% CI, 1.43–2.33) [48]. Although AKI events in the SPRINT participants were generally mild and largely reversible [51], they meaningfully raised the risk of cardiovascular events and all-cause death [48]. One may thus suppose that intensive BP lowering results in more pronounced alterations of intrarenal hemodynamics, leading to an increased probability of BP falling below the autoregulatory threshold for kidney perfusion. However, long-term follow-up data are needed to better evaluate the effects of intensive BP control strategies on worsening of renal function.

Electrolyte disorders also deserve mention although they are rarely assessed in detail in hypertension trials [10, 47]. In older adults participating in the SPRINT, severe

electrolyte disorders were significantly more common in the intensive treatment arm, with particular reference to hyponatremia [13]. Indeed, the risk of electrolyte disorders is especially high in older patients due to comorbidities, additional predisposing medications (e.g., benzodiazepines, antidepressants) [52], and a tendency for poor hydration. Diuretic therapy is recognized as the most important independent risk factor for electrolyte disorders, particularly hypokalemia, and hyponatremia [53]. Hyponatremia is most frequently associated with thiazide or thiazide-like agents, but it may occur also in patients receiving loop and potassium-sparing diuretics, particularly when different diuretic classes are combined [54]. Potassium-sparing diuretics also predispose to hyperkalemia, especially in patients with renal impairment, and/or receiving angiotensin system antagonists. By contrast, thiazide and loop diuretics predispose to hypokalemia, with higher risk at increased doses [53]. As electrolyte disorders are associated with several adverse outcomes including increased mortality [52], electrolyte monitoring is advisable during antihypertensive treatment intensification, particularly in older patients receiving diuretic therapy.

COGNITIVE PERFORMANCE

Numerous studies have shown that midlife hypertension is associated with increased risk of dementia in later life [55–58]. However, this association modifies with advancing age and high BP seems to no longer be a risk factor in older individuals [57, 59–61].

In a longitudinal observational study of over 8000 individuals, systolic BP ≥130 mm Hg at the age of 50 was associated with increased risk of dementia independently of cardiovascular disease, whereas no association was observed between high BP and incident dementia at the ages of 60 or 70 years [57]. The Rotterdam Study and the Leiden 85-plus Study [62] reported consistent results: in individuals aged 65–74 years, higher BP was associated with worse cognitive function in later life, while this association reversed in older participants — particularly in the oldest subgroup (age 85+ years) — in whom higher baseline BP was associated with better cognitive function. Van Dalen and colleagues [63] recently investigated the association between BP and dementia risk in 7 cohort studies involving a total of 17 286 participants: a non-linear association was reported in older participants that appeared to be U-shaped in groups aged 75 to 95 years, with the lowest risk points at systolic BP of approximately 160–170 mm Hg. In recent years, a relevant number of cohort studies have reported comparable findings, suggesting that the association between high BP and risk of incident dementia attenuates or even reverts at an advanced age [59, 60, 64, 65], particularly in treated hypertensive patients [66, 67]. Increasing evidence consistently suggests that aggressive BP lowering might not be beneficial or may even be harmful. In 8563 subjects included in the SPRINT MIND substudy (mean age 67 years), intensive BP control did not significantly reduce the incidence of probable dementia over a 5.1-year follow-up although potential benefits were reported on reducing the risk of mild cognitive impairment and of the composite outcome of mild cognitive impairment plus dementia, with a 15% risk reduction estimate [68]. In 1 626 individuals involved in the HOPE-3 cognitive substudy (mean age 74 years), the addition of antihypertensive treatment (candesartan plus hydrochlorothiazide) to standard treatment showed no beneficial effect on cognitive performance after a 5.7-year follow-up [69]. Moreover, in a subgroup analysis, a lower cognitive decline was observed in the placebo arm in subjects with lower baseline systolic BP (<133 mm Hg), with a significant blood pressure/treatment group interaction [69]. Similarly, the Sydney Memory and Aging Study [70] showed worse global cognition trajectories in a cohort of treated hypertensive patients aged 70–90 years with systolic BP values ≤120 mm Hg compared to those not receiving antihypertensive medications. Recent data from a large national population database [67] described an U-shaped association of BP with the risk of dementia and Alzheimer's disease, independently of antihypertensive use. By contrast, the risk of vascular dementia seems to differ by antihypertensive treatment. Indeed, in individuals not taking antihypertensive medications, the risk of vascular dementia was greater as SBP increased. In those taking antihypertensive treatment, the risk of vascular dementia was greatest at systolic SBP ≥160 mm Hg, lowest at systolic BP of 120–140 mm Hg, and increased at systolic BP of 100–120 mm Hg.

Based on the above, there seems to be a gradual shift with age from high BP being a risk factor for cognitive impairment to high BP potentially helping to preserve cognitive function in the oldest individuals. Whether low BP is causally related to dementia or the result of the dementia process remains unclear. It can be assumed that high BP values may help maintain adequate cerebral perfusion and normal cognition in the face of age-associated vascular changes [71]. However, some data indicate that BP declines in the years preceding dementia onset and further decreases over the disease course, with a more rapid decline compared to subjects with no diagnosis of dementia [59, 61, 72]. This may suggest an inverse association between BP and dementia risk, with lower BP values resulting from neurodegenerative processes in preclinical stages of dementia [73].

While a large body of literature has explored the association between BP and dementia risk, few studies provide information on BP control in patients with dementia, who are usually excluded from randomized clinical trials [8]. In the SPRINT study, a significant interaction between benefits from intensive treatment and cognitive performance was reported. Indeed, participants with higher baseline scores on the Montreal Cognitive Assessment derived strong benefits from intensive treatment, while no appreciable benefits were observed in participants with lower

cognitive function [74]. Consistently, in an Italian clinical sample of 172 patients with dementia or mild cognitive impairment (mean age 79 years), lower daytime systolic BP in ambulatory BP monitoring (mean daytime systolic BP <129 mm Hg) was associated with greater progression of cognitive decline at 9 months in patients receiving antihypertensive treatment [75].

In addition to uncertain benefits for cognitive function, individuals with cognitive impairment may be particularly liable to harms associated with antihypertensive treatment and may experience higher rates of adverse effects related to intensive BP control, particularly as regards falls [76]. On the whole, available data suggest that benefits of BP lowering may be attenuated in patients with coexisting cognitive impairment and recommend caution against excessive BP lowering in this subgroup.

HOSPITALIZATION AND MORTALITY

Over the last decades, several observational studies have provided evidence of an attenuated or even inverted relationship between BP and mortality in older individuals. Moreover, available evidence clearly demonstrates that physical performance, cognitive status, and functional level modulate the BP-mortality association in old age [77–79].

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 patients with preserved functional autonomy but not in those with disability [80]. In National Health and Nutrition Examination Survey (NHANES) participants aged 65 or older, BP was positively correlated with mortality in faster but not in slower walkers (gait speed <0.8 m/s), while BP was negatively associated with risk of death in those unable to complete the walk test [79]. In the Swedish population-based Swedish National Study on Aging and Care (SNAC-K) study involving 3 014 older subjects (mean age 73 years), systolic BP values <130 mm Hg were associated with the lowest mortality in "biologically young" participants, but with the highest mortality in "biologically older" participants, i.e., those with mobility limitations (gait velocity <0.8 m/sec) and/or cognitive impairment.

Based on this evidence, one might suppose that intensive BP control may not provide mortality benefits in older patients, particularly in frailer ones. Indeed, while the unfavorable prognostic impact of high BP tends to reduce with advancing age, low BP increasingly becomes a negative prognostic marker, especially in subjects with frailty or worse health status [81–83]. In agreement with this hypothesis, systolic BP <120 mm Hg was found to be associated with increased risk for mortality in nursing home residents [19, 84]. Moreover, observational studies indicate that also systolic BP <140 mm Hg may not be beneficial to older people. Six-year follow-up data from the Italian cohort study "Fiesole Misurata" showed lower mortality in community-dwelling older adults with systolic BP 140–159 mm Hg as compared with systolic BP 120–139 mm Hg (HR, 0.54; 95% CI, 0.33–0.89) [85]. Similarly, Oates and colleagues [86] reported reduced 5-year survival in hypertensive adults aged 80 or older with BP values <140/90 mm Hg (HR, 0.84; 95% CI, 0.78– 0.89, and HR, 0.91; 95% CI, 0.87–0.96, for each 10-point increase in SBP and DBP, respectively), while BP was not associated with survival in individuals with uncontrolled hypertension (HR, 1.01; 95% CI, 0.98–1.05; and HR, 0.89; 95% CI, 0.67–1.19, for each 10-point increase in systolic and diastolic BP ≥140/90 mm Hg, respectively). Finally, in a recent systematic review and meta-analysis, no mortality difference was observed between frail older people with systolic BP <140 mm Hg and those with higher BP values. Conversely, mortality was lower in non-frail individuals with systolic BP <140 mm Hg compared to those with higher systolic BP [87]. As regards diastolic BP, low values were found to predict all-cause mortality in older hypertensive outpatients [88].

A possible explanation of these findings is that older people have higher susceptibility to organ hypoperfusion due to vascular stiffness and impaired autoregulation, multimorbidity, and polypharmacy with hypotensive effects [32, 89, 90]. Therefore, in parallel with high cardiovascular risk, older people also show a significant predisposition to hypotension, which may diminish or even revert the potential benefits of intensive BP control due to increased vulnerability to treatment-related complications. Moreover, in frailer patients, the time-until-benefit of antihypertensive treatment might exceed the life expectancy due to coexisting conditions that substantially impact patients' prognosis and reduce the prognostic relevance of high BP [91]. However, reverse causality cannot be excluded, as low BP may represent an epiphenomenon of an overall decline in health status which would be responsible for the increased risk of mortality.

Uncertainties remain on the benefits of intensive BP control even in older patients with very high cardiovascular risk, e.g., those with previous cardiovascular events. In a secondary analysis of the INternational VErapamil SR-Trandolapril STudy (INVEST) including 22 576 hypertensive coronary artery disease patients, the systolic BP value corresponding to the nadir risk for the composite outcome of all-cause mortality, myocardial infarction and stroke increased with increasing age, being lowest (110 mm Hg) in participants <60 years and highest for those aged 80 years or older (140 mm Hg) [92]. In older patients with hypertension and coronary artery disease enrolled in the CLARIFY (ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) registry, BP values <120/70 mm Hg were consistently associated with higher all-cause mortality, myocardial infarction, and stroke [93]. In contrast to these studies, data from the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial suggest possible benefits of intensive BP control (systolic BP target <120 mm Hg) for the risk of disabling and fatal strokes in subjects older than 75 years with previous lacunar events [94].

In addition to mortality, hospitalization should also be considered as a possible complication related to intensive BP control. In a recent study involving older adults hospitalized for non-cardiac conditions, intensification of antihypertensive therapy on hospital discharge was not associated with reduced cardiac events or improved BP control within one year but was associated with increased risk of readmission and cardiovascular events in the short term [20]. These associations were not observed in patients with previously elevated BP but mostly applied to patients with well-controlled baseline BP, suggesting that the increased rate of adverse events may be at least partially explained by overtreatment [20]. Similarly, in hypertensive nursing home residents, increased intensity of antihypertensive treatment was significantly associated with a small increase in hospitalization risk although no significant association with mortality was reported [22].

CONCLUSIONS

With the growing emphasis on intensive BP control, attention should be given to the potential for treatment-related adverse events in the geriatric population. When considering intensive BP control in older hypertensive adults, clinicians need to individually weigh benefits against potential risks deriving from increased vulnerability to adverse events. Indeed, advanced age and frailty may modify the risk/benefit ratio of BP lowering due to an increased predisposition to hypotension and more severe consequences deriving from its complications. This mostly applies to individuals with poor physical performance, cognitive impairment, and disability, in whom aggressive BP lowering may not lead to cardiovascular benefits, but rather increase the risk of hypotension and treatment-related adverse events. In these patients, a more prudent BP lowering strategy seems to be advisable and a target range of 130–150 mm Hg systolic BP has been suggested to minimize the risk of hypotension-related adverse outcomes while providing adequate cardiovascular protection [19]. Additional trials are needed to thoroughly investigate the effects of intensive BP control and optimal BP targets in older adults.

Article information

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