

1 **Antihypertensive treatment targets in older adults: an unsolved dilemma**

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14 Hypertension is highly prevalent among older adults, affecting approximately 60-80% of individuals
15 over the age of 65. Until the 1970s, hypertension was considered to be a physiological consequence of
16 aging and a compensatory mechanism developing at advanced age to overcome arterial stiffness. Over
17 the following decades, hypertension in older individuals clearly emerged as a major cardiovascular risk
18 factor, strongly associated with stroke, vascular disease, renal impairment, and mortality.

19 A number of epidemiological and observational studies have provided evidence on antihypertensive
20 treatment benefits at old age. In the 1990s, the randomized STOP-Hypertension and STOP-
21 Hypertension 2 trials first demonstrated that antihypertensive therapy significantly reduces
22 cardiovascular risk in hypertensive adults aged 70–84 years.^{1,2} A few years later, the Hypertension in the
23 Very Elderly Trial (HYVET) indicated that treatment benefits persist even in the oldest old, showing a
24 reduced risk of mortality, stroke and heart failure in treated hypertensive patients aged 80 or older
25 achieving a blood pressure (BP) target of 150/80 mmHg.³ More recent research has provided additional
26 data supporting BP lowering in older adults⁴ as would be expected based on cardiovascular risk profile,

1 that is typically high or very high at old age due to multiple risk factors and target-organ damage. Based
2 on this evidence, European guidelines explicitly state that advanced chronological age should not be
3 considered an exclusion criterion for antihypertensive therapy.⁵

4 In recent years, some studies have prompted more intensive BP control, also in older individuals. In the
5 Systolic Blood Pressure Intervention Trial (SPRINT), a systolic BP target <120 mmHg was associated
6 with lower rates of cardiovascular diseases and mortality as compared with a standard treatment
7 approach. Benefits of intensive antihypertensive treatment were also confirmed in older and frail
8 SPRINT participants.⁶ In the STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive
9 Patients) trial involving hypertensive individuals aged 60 to 80 years, BP lowering to a systolic BP
10 target of 110-130 mmHg resulted in a lower incidence of cardiovascular events compared to a standard
11 target of 130-150 mmHg.⁷ In the present issue, Deng and colleagues present a secondary analysis of
12 STEP based on systolic BP values achieved during the follow-up period.⁸ Their results show
13 significantly lower cardiovascular risk in participants achieving an intensive treatment target (mean
14 systolic BP 124.2 mmHg) compared to participants achieving a standard treatment target (mean
15 systolic BP 137.4/79.5 mmHg; adjusted hazard ratio [HR] for intensive treatment 0.61, 95%
16 confidence interval [CI] 0.46–0.80). Cardiovascular risk was twofold higher in intensively treated
17 participants failing to achieve target BP (mean achieved systolic BP 134.5 mmHg, HR 2.04, 95% CI
18 1.44–2.88). A J-shaped association emerged between mean achieved BP and risk of cardiovascular
19 events and all-cause mortality, with the nadir risk corresponding to a systolic BP of 126.9 mmHg and
20 129.1 mmHg, respectively.⁸

21 The study by Deng et al. reaffirms the prognostic relevance of BP lowering in old individuals, that
22 should not be excluded by age from treatment strategies representing the cornerstones of appropriate
23 cardiovascular prevention. Yet, it should be considered that the STEP trial enrolled young-older and
24 relatively healthy individuals, with low prevalence of comorbidities. As acknowledged by Deng and
25 colleagues, the trial results might have limited transferability to selected subgroups of the “real-world”
26 geriatric population with high levels of frailty and multimorbidity.

1 Frailty is a geriatric syndrome characterized by a decline in individuals' physiological functional
2 reserve, resulting in reduced homeostatic capacity and increased risk of adverse health outcomes such as
3 disability, hospitalization, institutionalization and mortality.⁹ Frail hypertensive patients represent a
4 vulnerable population commonly presenting with multimorbidity, impaired physical performance,
5 cognitive decline and disability, which suggest an increased predisposition to antihypertensive
6 treatment-related complications. As a higher incidence of hypotension has been reported in intensively
7 treated older patients,^{7,8,10} there is concern about the possible unfavourable consequences of intensive
8 antihypertensive treatment in frailer individuals.

9 Frailty and hypertension frequently coexist at old age, with 7 out of 10 frail adults being hypertensive.
10 Nevertheless, individuals with higher frailty levels are typically excluded from clinical trials, leading to
11 evidence gaps and lack of specific recommendations on hypertension management in this complex
12 subgroup. Over the last decades, a growing body of literature have provided observational data
13 suggesting a blunted association between high BP and adverse health outcomes in frailer individuals.
14 Indeed, current evidence clearly demonstrates that the association between BP and mortality varies
15 according to physical performance, cognitive status and disability, with low BP being associated with
16 higher mortality in older patients with poor health status.¹¹⁻¹³ A similar association has been reported
17 between BP and cognitive performance in individuals with cognitive impairment, showing accelerated
18 cognitive decline in the case of intensive BP control.¹⁴ Therefore, older hypertensive patients are likely
19 to benefit from an integrated decision-making based on a comprehensive geriatric assessment, aiming to
20 develop tailored treatment strategies customized to the individual's frailty and functional level.
21 However, at present mainly observational studies have investigated the prognostic role of severe frailty
22 and other geriatric conditions in the context of hypertension management. Moreover, existing data are
23 limited by heterogeneity of the study samples and lack of a standardised frailty assessment.¹⁵

24 In conclusion, current evidence indicates that the negative prognostic impact of hypertension is
25 maintained in young-older individuals with low levels of frailty and multimorbidity. This subgroup
26 deserves proper antihypertensive treatment and should be defended by an ageistic approach leading to
27 age-based a priori antihypertensive therapy withdrawal. By contrast, current evidence is insufficient to

1 support specific therapeutic indications in frail, oldest individuals and antihypertensive treatment targets
2 in this vulnerable population remain an unsolved dilemma.

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4 While the available literature reinforces recommendations on BP lowering in young-older individuals,
5 clinicians urge future research to develop randomized clinical trials supporting recommendations on
6 treatment targets in frailer geriatric subgroups.

ACCEPTED MANUSCRIPT

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