Blood pressure and long-term mortality in older patients: results of the Fiesole Misurata Follow-up Study

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ORIGINAL ARTICLE

Blood pressure and long-term mortality in older patients: results of the Fiesole Misurata Follow-up Study

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Abstract

Background Optimal blood pressure (BP) control can prevent major adverse health events, but target values are still controversial, especially in older patients with comorbidities, frailty and disability.

Aims To evaluate mortality according to BP values in a cohort of older adults enrolled in the Fiesole Misurata Study, after a 6-year follow-up.

Methods Living status as of December 31, 2016 was obtained in 385 subjects participating in the Fiesole Misurata Study. Patients' characteristics were analysed to detect predictors of mortality. At baseline, all participants had undergone office BP measurement and a comprehensive geriatric assessment.

Results After a 6-year follow-up, 97 participants had died (25.2%). After adjustment for comorbidities and comprehensive geriatric assessment, mortality was significantly lower for SBP 140–159 mmHg as compared with 120–139 mmHg (HR 0.54, 95% CI 0.33–0.89). This result was also confirmed in patients aged 75 + (HR 0.49, 95% CI 0.29–0.85), and in those with disability (HR 0.36, 95% CI 0.15–0.86) or taking antihypertensive medications (HR 0.49, 95% CI 0.28–0.86).

Discussion An intensive BP control may lead to greater harm than benefit in older adults. Indeed, the European guidelines recommend caution in BP lowering in older patients, especially if functionally compromised, to minimize the risk of hypotension-related adverse events.

Conclusions After a 6-year follow-up, mortality risk was lower in participants with SBP 140–159 mmHg as compared with SBP 120–139 mmHg, in the overall population and in the subgroups of subjects aged 75 + , with a disability or taking antihypertensive medications.

Keywords Blood pressure · Mortality · Elderly · Hypertension

Introduction

Hypertension is one of the main risk factors for cardiovascular disease and mortality worldwide [1]. Therefore, achieving optimal blood pressure (BP) control is an important health care challenge. However, target BP values are still a matter of debate, especially in older patients.

In 2008, the "Hypertension in the Very Elderly Trial" (HYVET) demonstrated that antihypertensive treatment reduces the risk of stroke and mortality in subjects aged 80 or older with a systolic blood pressure (SBP) ≥ 160 mmHg [2]. More recently, the "Systolic Blood Pressure Intervention Trial" (SPRINT) showed that a SPB target less than 120 mmHg is associated with improved outcomes in patients at high cardiovascular risk but without diabetes,

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as compared with SBP between 120 and 140 mmHg. However, higher rates of adverse events were reported with an intensive BP control [3], particularly in patients aged 75 or older [4]. On the other hand, the "Action to Control Cardiovascular Risk in Diabetes" (ACCORD) trial reported that a SBP lower than 120 mmHg did not reduce the risk of fatal and nonfatal major cardiovascular events in patients with diabetes, as compared with a SBP lower than 140 mmHg [5]. Similarly, in the "Valsartan Antihypertensive Long-term Use Evaluation" (VALUE) trial a BP less than 130/80 mmHg was associated with a lower incidence of stroke, but the risk of other outcomes was similar or even greater than in patients with BP less than 140/90 mmHg [6]. Indeed, a recent review suggests that intensive BP lowering may increase the incidence of cardiovascular and renal events, disability and cognitive impairment, especially in older patients [7]. Moreover, a U-shaped correlation between BP and mortality has been reported in older adults, with higher SBP associated with increased survival in patients with functional and cognitive disability [8]. However, specific evidence referring to older people is scarce, particularly with regard to frail subjects with a high comorbidity burden. Therefore, the main international guidelines on hypertension do not define a precise BP target in this particular population [9–12].

The present study aimed at evaluating mortality according to BP values in a cohort of older subjects enrolled in the Fiesole Misurata Study, after a 6-year follow-up.

Methods

Design and methods of the "Fiesole Misurata" Study were described in detail in a previous publication [13]. Briefly, a list of all residents of the community of Fiesole (Tuscany, Italy) aged 65 years or more was obtained on May 1, 2010 from the City Registry Office and merged with the healthcare records obtained from the administrative archives of the Local Health Authority ($n = 2228$, claim dataset). All eligible subjects ($n = 2228$) were informed about the study and were asked for their participation in the face-to-face data collection. Three-hundred and eighty-five subjects aged 65 years or more living in the community of Fiesole City decided to participate ($n = 385$, the cross-sectional dataset) [13].

In the cross-sectional dataset, the socio-demographic status (i.e. years of education, marital status), the lifestyle habits (i.e. diet, alcohol consumption, smoking), the medication use and the medical history were investigated by means of a structured questionnaire [13]. In addition, office BP was measured and a comprehensive geriatric assessment was performed to assess the presence of disability (using the Instrumental and Basic Activities of Daily Living—IADL and BADL), cognitive impairment (using the Mini-Mental State Examination—MMSE) and depressive symptoms (using the Geriatric Depression Scale—GDS). BADL and IADL were categorized by grouping participants who had lost one or more activities against those who had lost none; disability was defined as the loss of at least one activity from BADL. The MMSE score, which decreases with cognitive impairment, and the GDS score, which increases with depressive symptoms, were dichotomized at 21 and 6, respectively.

Blood pressure was measured twice in each arm with the patient in the sitting position, after a 10-min rest period in a quiet room at a comfortable temperature. BP measurements were performed using a manual device, according to the traditional auscultatory method. A cuff larger than the standard was used when arm circumference exceeded 32 cm. The two sets of two BP measures were averaged and the mean values were considered as the reference systolic and diastolic BP. To investigate orthostatic hypotension (OH), BP was also measured during 3-min active standing. OH was defined as a fall in systolic BP $\geq$ 20 mmHg or diastolic BP $\geq$ 10 mmHg, or a decrease in systolic BP to $<$ 90 mmHg [14].

To analyze mortality, living status was assessed at December 31, 2016 by consulting the City Registry Office of the municipalities of residence.

The study was approved by the Local Ethic Committee. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Data are reported as mean $\pm$ standard deviation. The Fisher's exact test was used to compare the distribution of dichotomous variables; the Student's -test for unpaired data was used to compare mean values of continuous data. To compare mortality between different groups Kaplan–Meier curves were used and log-rank tests performed to test differences. Cox models were used to compare the survival curves for the different BP strata, with appropriate adjustment for those covariates with a significant relationship in this cohort to mortality. The hazard ratio (HR) was provided with its 95% confidence interval (CI). Analyses were performed using STATA version 14.0 (StataCorp, Texas, USA).

Results

The study population included 385 individuals aged 65 or more that agreed to participate in the face-to-face data collection (cross-sectional dataset); the mean age was 76.6 $\pm$ 7.6 years (range 65–98). The baseline clinical

features of the cross-sectional dataset have been described previously. As of December 31, 2016, 97 participants had died (25.2%, Table 1). Mortality increased with advancing age and it was higher in both underweight (BMI < 20 kg/m^2) and obese patients (BMI ≥ 30 kg/m^2, $p = 0.04$). The prevalence of diabetes and heart failure was lower among survivors (10.4% vs 22.7%, $p = 0.002$ and 3.1% vs 17.5%, $p < 0.0001$, respectively), whereas no significant differences were observed in the prevalence of coronary artery disease, stroke, hypertension and orthostatic hypotension (data not shown).

Mean SBP values were similar in the two groups ($p = 0.5$), whereas mean DPB was higher in survivors ($p = 0.002$). Pharmacological treatment with ACE-inhibitors and diuretics was more common in patients who died ($p = 0.003$ and $p < 0.0001$, respectively), while no significant differences were observed for other antihypertensive drugs (Table 1). After adjustment for comorbidities and comprehensive

Table 1 Patients` baseline characteristics according to living status

	Deceased, *n* (%)	Alive, *n* (%)	*p*-value
Fiesole Misurata Cohort ($n = 385$)	97 (25.2)	288 (74.8)	
Age (years)			< 0.0001
< 70	5 (5.2)	71 (24.7)	
70–74	8 (8.3)	84 (29.2)	
75–79	14 (14.4)	69 (23.9)	
80–84	29 (29.9)	45 (15.6)	
≥ 85	41 (42.3)	19 (6.6)	
Gender			0.007
Female	44 (45.4)	176 (61.1)	
Male	53 (54.6)	112 (38.9)	
BMI (Kg/m^2)			0.04
< 20	9/76 (11.8)	14/281 (4.9)	
20– < 25	34/76 (44.7)	118/281 (41.9)	
25– < 30	23/76 (30.3)	124/281 (44.1)	
≥ 30	10/76 (13.2)	25/281 (8.9)	
Missing	21/97	7/288	
SBP, mmHg ± SD	136.3 ± 19.1	137.7 ± 18.1	0.55
Missing	3	11	
DBP, mmHg ± SD	74.3 (11.5)	78.3 (10.4)	0.002
Missing	4	11	
Dyslipidemia	30 (30.9)	111 (38.5)	0.18
Diabetes/antidiabetic therapy	22 (22.7)	30 (10.4)	0.002
Ischemic heart disease	12 (12.4)	31 (10.8)	0.66
Heart failure	17 (17.5)	9 (3.1)	< 0.0001
Ischemic/hemorrhagic stroke	11 (11.3)	16 (5.6)	0.05
Hypertension	63 (64.9)	159 (55.2)	0.09
Orthostatic hypotension	11 (13.8)	37 (13.5)	0.96
Antihypertensive drugs	82 (84.5)	193 (67.0)	0.001
ACE-inhibitors	47 (48.5)	91 (31.6)	0.003
Diuretics	45 (46.4)	55 (19.1)	< 0.0001
ARB	23 (23.7)	50 (17.4)	0.17
Beta-blockers	24 (24.7)	61 (21.2)	0.46
CCBs-DHP	24 (24.7)	51 (17.7)	0.13
Central inhibitors	3 (3.1)	4 (1.4)	0.28
Alpha receptor blockers	9 (9.3)	23 (7.9)	0.69
CCBs not DHP	6 (6.2)	11 (3.8)	0.33
ACE inhibitors + Diuretics	24 (24.7)	56 (19.4)	0.27
ARB + Diuretics	18 (18.6)	48 (16.7)	0.67

ARB angiotensin receptor blockers, *BMI* Body Mass Index, *CCB* calcium−channel blockers, *DBP* diastolic blood pressure, *DHP* dihydropyridine, *SBP* systolic blood pressure, *SD* standard deviation

geriatric assessment, we observed that mortality was significantly lower in patients with SBP 140–159 mmHg as compared with SBP 120–139 mmHg (HR 0.54, 95% CI 0.33–0.89) (Table 2).

The Kaplan–Meier survival plot showed that patients with SBP lower than 120 mmHg had the highest mortality rate both in the overall population and in the subgroup taking antihypertensive medications (Fig. 1). In untreated participants, the lowest mortality rates were reported for SBP values < 120 mmHg and between 120 and 139 mmHg. Conversely, in the overall population and in the subgroup taking antihypertensive medications mortality was lower for SBP between 140 and 159 mmHg. The protective effect of SBP values 140–159 mmHg remained statistically significant in patients aged 75 or older (HR 0.49, 95% CI 0.29–0.85) and in those with disability (HR 0.36, 95% CI 0.15–0.86) or taking antihypertensive medications (HR: 0.49, 95% CI: 0.28–0.86) (Fig. 2).

Disability was identified in the 27.8% of our study population and was associated with higher mortality risk (HR 2.48, 95% CI 1.57–3.91); similar results were described for cognitive impairment (HR 3.79, 95% CI 2.07–6.96), whereas depressive symptoms were not associated with mortality (Table 2).

Discussion

The importance of antihypertensive treatment in reducing cardiovascular events and mortality in older patients has been clearly demonstrated [2, 15], however, appropriate BP targets are still controversial.

The present study provides 6-year follow-up data from a cohort of older subjects in Tuscany, Italy, and shows lower mortality in patients with SBP 140–159 mmHg as compared with SBP 120–139 mmHg. This result was also confirmed in patients aged 75 or older, in the subgroup of patients taking antihypertensive medications and in those with disability.

These results are consistent with the finding that older people have a higher susceptibility to the adverse events

Table 2 Relationship of mortality to blood pressure, disability, cognitive performance and depressive symptoms

	Deceased, *n* (%)	Alive, *n* (%)	HR (95% CI)
Fiesole Misurata Cohort (*n* = 385)	97 (25.2)	288 (74.8)	
SBP (*n*, %)			
< 120 mmHg (38, 10.2%)	11/94 (11.7)	27/277 (9.8)	0.94 (0.46–1.91)
120–139 mmHg (140, 37.7%)	40/94 (42.6)	100/277 (36.1)	1
140–159 mmHg (146, 39.4%)	30/94 (31.9)	116/277 (41.9)	0.54 (0.33–0.89)
≥ 160 mmHg (47, 12.7%)	13/94 (13.8)	34/277 (12.3)	0.7 (0.37–1.34)
Missing	3/97	11/288	
DBP (*n*, %)			
< 80 mmHg (170, 45.9%)	54/93 (58.1)	116/277 (41.9)	1.06 (0.64–1.75)
80–89 mmHg (135, 36.5%)	26/93 (27.9)	109/277 (39.4)	1
90–99 mmHg (47, 12.7%)	9/93 (9.7)	38/277 (13.7)	1.36 (0.63–2.96)
≥ 100 mmHg (18, 4.9%)	4/93 (4.3)	14/277 (5.1)	0.96 (0.32–2.09)
Missing	4/97	11/288	
Functional level (*n*, %)			
Lost BADL = 0 (267, 72.2%)	41/89 (46.1)	226/283 (80.4)	1
Lost BADL ≥ 1 (103, 27.8%)	48/89 (53.9)	55/283 (19.6)	2.48 (1.57–3.91)
Missing	8/97	5/288	
Cognitive performance (n, %)			
MMSE > 21 (348, 92.8%)	74/93 (79.6)	274/282 (97.2)	1
MMSE ≤ 21 (27, 7.2%)	19/93 (20.4)	8/282 (2.8)	3.79 (2.07–6.96)
Missing	4/97	6/288	
Depressive symptoms (*n*, %)			
GDS < 6 (294, 79.3%)	71/88 (80.7)	223/283 (78.8)	1
GDS ≥ 6 (77, 20.8%)	17/88 (19.3)	60/283 (21.2)	0.67 (0.38–1.19)
Missing	9/97	5/288	

BADL basic activities of daily living, *CI* confidence interval, *DBP* diastolic blood pressure, *GDS* geriatric depression scale, *HR* Hazard Ratio, *MMSE* mini−mental state examination, *SBP* systolic blood pressure

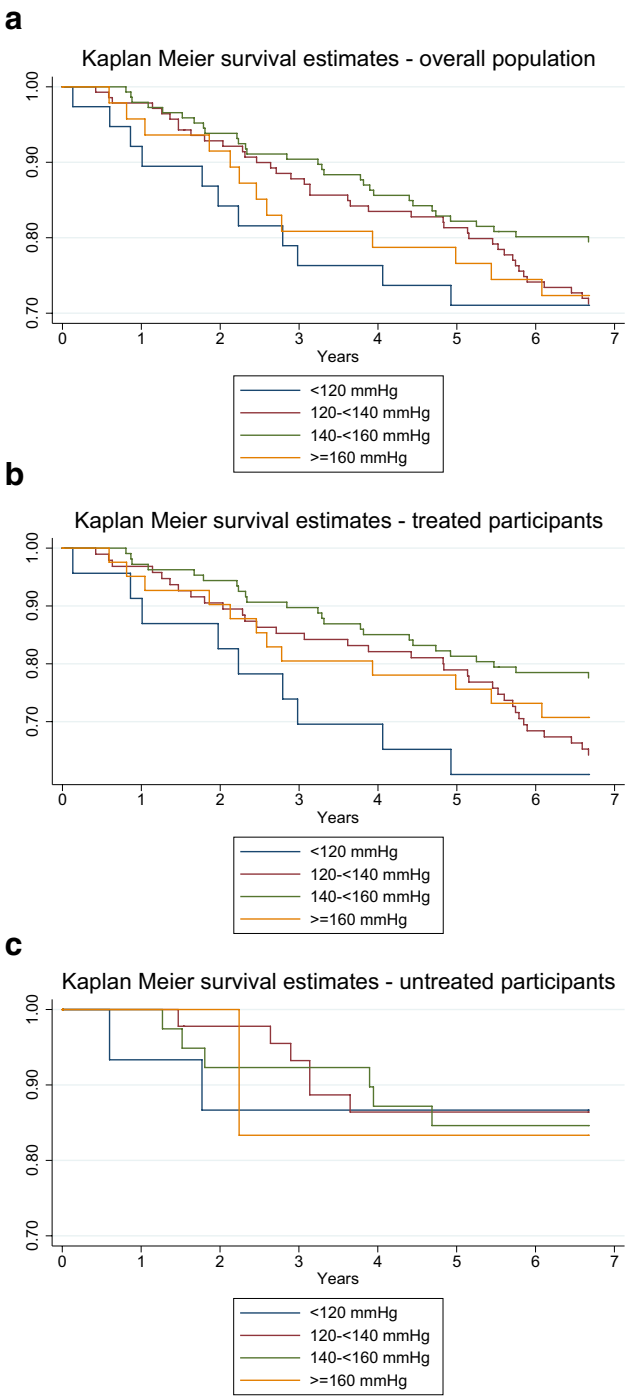

Fig. 1 Kaplan–Meier survival estimates depending on systolic blood pressure in the overall population (**a**), in treated (**b**) and untreated participants (**c**)

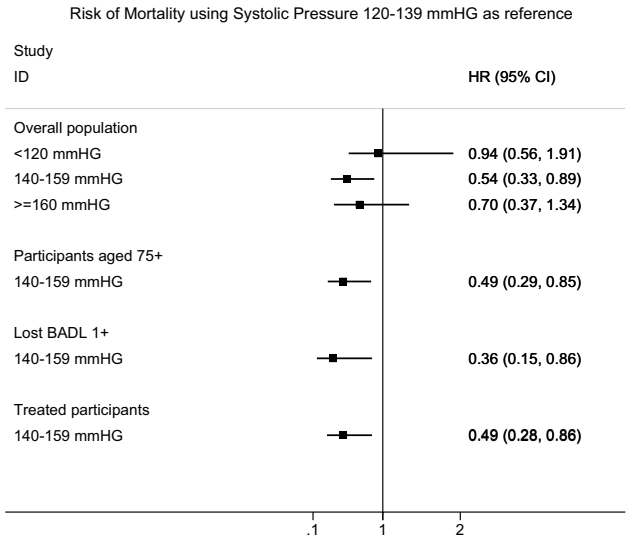

Fig. 2 Forest Plot of blood pressure values and mortality in the overall population and the subgroups of patients aged 75 or more, with disability and on antihypertensive treatment. Factors entered in the model: age (<70, 70–<75, 75–<80, 80–<85, 85+), gender, Body Mass Index, (<20, 20–<25, 25–<30, 30+), diabetes, heart failure, antihypertensive treatment. *BADL* basic activities of daily living, *CI* Confidence Interval, *HR Hazard Ratio*

associated with intensive BP control, such as syncope, falls and fractures. Indeed, these hypotension-related adverse events are common in geriatric patients, particularly if very old and frail, and the risk is further exacerbated by antihypertensive medications. In this regard, a recent document from a Working Group of the ESH/European Union Geriatric Medicine Society (EUGMS) has called attention to the risks of antihypertensive treatment and recommended caution in BP lowering in older patients, especially if functionally compromised [16].

Recently, the SPRINT and SPRINT-Senior studies have shown a clear reduction in mortality and cardiovascular disease targeting a SBP of less than 120 mmHg, including with regard to older patients [3, 4]. However, it should be highlighted that BP was measured with the patient being alone in a quiet room, and consequently it is problematic to compare these results to those reported in other clinical trials. This unattended measurement technique reduces the patient's alert reaction (white coat effect), making recorded values more similar to home rather than office BP. Indeed, some studies have demonstrated a significant difference between attended manual and unattended semiautomatic BP measurements [17, 18]. In addition, the SPRINT study mainly included patients with mild frailty [19], while subjects with orthostatic hypotension, disability and cognitive impairment were excluded. Consequently, SPRINT results seem to have limited transferability to the "real world", where these subgroups of patients are largely represented. This is a crucial issue since SPRINT participants randomized to intensive BP control showed a substantial increase in hypotension, syncope and renal failure and these adverse events are very likely to be accentuated in older patients, even more so if frail [16]. Consistently, in recent years observational studies have provided evidence that low BP is associated with

adverse outcomes including mortality in frail, older adults [8, 20–22], therefore, raising concerns about the safety of intensive BP lowering in more vulnerable geriatric subgroups. Nevertheless, SPRINT results have influenced the new Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults issued by the American College of Cardiology (ACC) and the American Heart Association (AHA). These guidelines redefine high and normal BP (< 120/80 mmHg) and recommend on-treatment SBP target values < 130 mmHg in older hypertensive too, even if suggesting caution in frail subjects and those with dementia or a high comorbidity burden [23]. This new classification of BP values implies that a higher percentage of patients would be classified as hypertensive, thus increasing the risk of over-treatment [24]. Moreover, targeting SBP < 130 mmHg may cause more harm than benefit in older patients due to the increased risk of hypotensive-related adverse effects, particularly in the presence of orthostatic hypotension [25].

The results of our study are consistent with the recent data suggesting a negative prognostic impact of low BP in older people. Frailty was not specifically assessed in our study population as compared with previous studies in the literature. Yet, the relationship between BP and mortality was specifically investigated in participants with a disability, confirming lower mortality in those with SBP 140–159 mmHg as compared with SBP 120–139 mmHg. Additionally, patients on antihypertensive treatment showed the highest mortality rate at SBP < 120 mmHg—even after adjustment for main comorbidities—which confirms the harmful effects of intensive BP control in older subjects. These results are consistent with the recommendations of the 2018 ESC/ESH Guidelines for the management of arterial hypertension, which indicate a SBP target of 130–140 mmHg in patients aged 65 or more and discourage SBP values < 120 mmHg [26].

An individualized approach to antihypertensive treatment seems to be reasonable in geriatric patients, driven by a comprehensive geriatric assessment evaluating functional status and comorbidities, particularly cognitive impairment and the risk of falls [8]. This strategy allows identification of the most appropriate BP target for each patient, minimizing the risk of hypotension-related adverse events that could hamper patients' quality of life, functional level and cognitive performance [16, 20, 27]. Moreover, hypotension and other drug-related adverse effects frequently induce treatment discontinuation, which may lead to a pronounced increase in cardiovascular risk [28, 29].

In our study population, DBP was < 80 mmHg in the majority of patients who died during the follow-up. This finding is consistent with several data in the literature describing an association between low DBP (< 60–70 mmHg) and the risk of ischaemic heart disease, renal impairment and mortality [30–34], and suggests more attention should be given to DBP when evaluating BP control in hypertensive patients.

Limitations and strengths

The main limitation of our study is related to self-reported diagnosis of comorbidities, which influence mortality and may have been underestimated in our population. Particularly, patients taking diuretics or ACE-inhibitors showed a higher mortality rate, which could reflect the risk associated with heart failure and/or diabetes. However, all estimates concerning both diseases and medication use were consistent with prior studies, as detailed previously [13]. The presence of sarcopenia was not assessed at baseline and we were unable to evaluate its impact on patients' prognosis. Indeed, sarcopenia is associated with an increased risk of multiple negative health outcomes in older people [35]. Additionally, given the relevant role of muscle mass in the blood pressure response to gravity stress [36, 37], sarcopenia may also increase the risk of low blood pressure and hypotension-related adverse events, thus further impacting on prognosis. Given the above, we cannot exclude that sarcopenia may have influenced mortality in our study, thus potentially confounding its association with blood pressure. Another limitation of our study is represented by the small sample size and the limited number of younger subjects included in the analysis, probably due to a self-selection of participants. The cross-sectional sample has not been randomly selected and it could be, therefore, affected by selection bias. Indeed, people aged 70 or more usually have more comorbidities and greater awareness of their cardiovascular health status, which may have favoured their participation in the cross-sectional dataset. Therefore, a selection bias cannot be excluded, but this could also be considered as a strength because it makes the study sample more representative of those subjects who are typically referred to our centers. Moreover, our study population also included participants with cognitive impairment and disability, for whom specific evidence is lacking as concerns the association between BP and mortality. For these reasons, this study provides a reliable picture of the "real world" and our results could be generalized to those patients that we meet in our daily ambulatory clinical practice. Finally, another strength of this study is represented by the prospective design and the 6-year follow-up, since only a few trials in the literature provide data on a long-term follow-up in geriatric populations.

Conclusions

After a 6-year follow-up, older patients with SBP 140–159 mmHg had lower mortality as compared with SBP 120–139 mmHg. This result was also confirmed in patients aged 75 or older, in the subgroup of patients with disability and in those taking antihypertensive medications. SBP values lower than 120 mmHg were associated with the highest mortality rate in patients on antihypertensive medications.

Author contribution Study conception and design by Andrea Ungar and Alessandro Mugelli. Material preparation, data collection and analysis were performed by Andrea Ungar, Ersilia Lucenteforte, Daniela Balzi, Matteo Bulgaresi, Nicola Nesti, Antonella Giordano, Martina Rafanelli, Niccolò Lombardi, Alfredo Vannacci, Alessandro Mugelli, Mauro Di Bari and Andrea Ungar. The first draft of the manuscript was written by Giulia Rivasi, Giada Turrin and Andrea Ungar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Comitato Etico AOU Careggi) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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