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Research Paper

Optimal systolic blood pressure and reduced long-term mortality in older hypertensive women with prior coronary events – An analysis from INVEST☆

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ABSTRACT

Background: Hypertension and coronary artery disease (CAD) are a prevalent combination in older women, however limited data are available to guide blood pressure (BP) management. We hypothesized that older women with hypertension and CAD may not derive long-term benefit by achieving systolic BP (SBP) < 130 mmHg.
Methods: We analyzed long-term all-cause mortality data from the International Verapamil SR/Trandolapril Study (INVEST), stratified by risk attributable to clinical severity of CAD (women with prior coronary events of myocardial infarction or revascularization considered high risk, all others at low risk) and by age group (50–64 or ≥65 years). The prognostic impact of achieving mean in-trial SBP <130 (referent group) was compared with 130–139 and ≥ 140 mmHg using Cox proportional hazards, adjusting for demographic and clinical characteristics.
Results: SBPs <130, 130–139, and ≥140 were achieved in 2960, 3024, and 3232 women, respectively. Among high-risk women aged ≥65 years, those achieving SBP 130–139 mmHg had lower mortality up to 16.7 years later than those with SBP <130 (hazard ratio [HR] 0.81, 95% CI 0.69–0.96). High-risk women aged 50–64 achieving SBP 130–139 had a similar mortality risk as those with SBP <130 (HR 1.21, 95% CI 0.87–1.68), while those achieving SBP ≥140 mmHg had a higher mortality risk than SBP < 130 (HR 1.92, 95% CI 1.37–2.68). A similar pattern was observed among low-risk women ≥65 and <65 years old.
Conclusion: Among women ≥65 years old with hypertension and prior coronary events, in-trial SBP between 130 and 139 mmHg was associated with lower mortality over the long term versus SBP <130 mmHg.

1. Introduction

The prevalence of hypertension and coronary artery disease (CAD) rises rapidly in aging populations, particularly among women. Although frequently overlooked, women have a higher prevalence of hypertension than men after age 65 [1]. However, data regarding optimal blood pressure (BP) for such women with CAD are limited. The 2017 American College of Cardiology/American Heart Association hypertension guideline recommended a systolic BP (SBP) < 130 mmHg in all patients with hypertension and CAD, regardless of age or sex [2]. However, these guidelines were informed by randomized controlled trials that under-enrolled women and included few CAD patients [2]. We and others have observed that excessive BP lowering may be detrimental in CAD patients [3,4], and of unclear benefit in women [5] and the elderly [6]. In contrast, the European hypertension guidelines recommend targeting SBP 130–139 mmHg in hypertensive patients with CAD aged ≥65 years, and 120–130 mmHg only in patients aged <65 years [7].

Accordingly, we hypothesized that older women with prior coronary events, defined as myocardial infarction or coronary revascularization, may not benefit from SBP<130 mmHg. We used data from the INternational VErapamil SR/Trandolapril STudy (INVEST) to explore the relationship between mean achieved in-trial systolic blood pressure and long-

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term, all-cause mortality.

2. Methods

The design and main findings of INVEST (NCT00133692) have been detailed previously [8]. INVEST targeted BP < 140/90 mmHg, except for patients with diabetes, chronic kidney disease (CKD) or heart failure, in whom the target was <130/85 mmHg. Intent to examine the influence of sex on outcomes was prespecified. Treatment strategies achieved similar BP and met the prespecified boundary for equivalence for the primary outcome, as well as all-cause mortality, thus treatment groups were combined into one cohort. This analysis was limited to women from the United States for whom long-term mortality data were available. We categorized baseline CAD-associated risk as high (defined as prior myocardial infarction or revascularization) or low (all others), and patient age at enrollment as ≥65 ("older adults" in current guidelines) or <65 years [2]. Mean achieved in-trial SBP (abbreviated hereafter as SBP) was calculated using all in-trial measurements except SBP recorded at baseline and visits preceding that when the woman experienced one of the components of the primary outcome. Mean achieved diastolic BP (DBP) and heart rate were calculated similarly. SBP was categorized as <130 (referent), between 130 and 139, and ≥140 mmHg. Cox proportional hazards models were used to assess the relationship between SBP category and long-term all-cause mortality (adjudicated in-trial and supplemented by the National Death Index search for 11.7 years after the trial termination). All models were adjusted for baseline risk: race, prior stroke/transient ischemic attack (TIA), heart failure, CKD, and diabetes as categorical variables, and mean in-trial DBP and heart rate as continuous variables. Categorical values were expressed as percentage and continuous variables were expressed as mean ± SD. $P < 0.05$ was considered statistically significant.

3. Results

In total, 9216 women were included, of whom 2945 (32%) died during 108,838 patient-years follow-up. Included women had an average age of 66.7 ± 10.3 years had a baseline SBP of 149 ± 19.5 mmHg, and a body mass index of 29.7 ± 6.5 kg/m^2. Baseline comorbidities included prior stroke or TIA (6.9%), heart failure (5.3%), CKD (1.5%), and diabetes (30.3%). Among these, 3011 (32.7%) met our high-risk criteria and 5202 (56.4%) were aged ≥65 years. Mean in-trial SBP of <130 mmHg was achieved in 2960 (32.1%) women, whereas 3024 (32.8%) achieved SBP of 130–139 mmHg, and 3232 (35.1%) achieved SBP ≥140 mmHg.

Fig. 1 summarizes the relationship between achieved SBP and mortality after stratifying by age and risk group. In high-risk women aged ≥65, achieving SBP 130–139 mmHg was associated with decreased risk of death when compared to <130 mmHg (HR 0.82, 95% CI 0.69–0.97, p = 0.018). High-risk women aged 50–64 had similar mortality risk when achieving SBP 130–139 versus <130 mmHg (HR 1.21, 95% CI 0.88–1.68, p = 0.25) and increased mortality risk at SBP ≥140 versus <130 mmHg (HR 1.92, 95% CI 1.37–2.68, p = 0.0001). Low-risk women from both age groups had similar mortality at SBP 130–139 versus <130 mmHg (≥65 years, HR 1.04, 95% CI 0.89–1.22, p = 0.63; 50–64 years, HR 1.06, 95% CI 0.81–1.39, p = 0.65) and increased mortality when achieving SBP ≥140 versus <130 mmHg (≥65 years, HR 1.42, 95% CI 1.21–1.68, p < 0.0001; 50–64 years, HR 1.74, 95% CI 1.30–2.32, p = 0.0002).

4. Discussion

Our data indicate that, among older hypertensive women at high-risk due to prior coronary events, achieving in-trial mean SBP 130–139 mmHg is associated with decreased long-term, all-cause mortality when compared with SBP<130 mmHg. When examining the association between achieving SBP 130–139 mmHg with age individually, we observed the mortality hazard favored decreased mortality in older women (HR 0.94, 95% CI 0.84–1.05, p = 0.27), albeit not statistically significant. By analyzing women aged ≥65 with prior coronary events, we have selected an endotype at very high risk of death, in which decrease of SBP to <130 mmHg was not associated with improved outcomes. Thus our results support recommendations of ESC/ESH Hypertension guidelines [7] to target SBP of 130–139 in patients ≥65 years old with hypertension and CAD, specifically in women with prior coronary events.

The link between SBP and all-cause mortality in CAD has been previously investigated in studies enrolling mainly men and with shorter-term follow-up. The CLARIFY registry investigators observed that in 22,672 stable CAD patients (75% men) with hypertension, SBP between 130–139 mmHg was associated with similar rates of all-cause death as SBP between 120-129 mmHg (HR 0.98, 95% CI 0.87–1.11, p = 0.7701) after median 5 years of follow-up [3]. The PROVE-IT TIMI 22 trial also

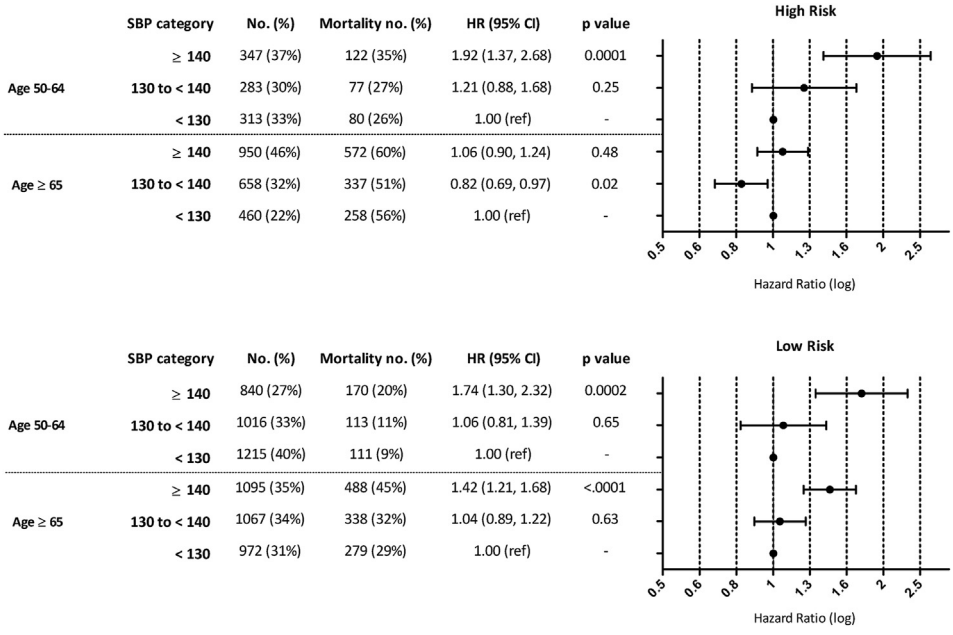

Fig. 1. Association between achieved systolic blood pressure and long-term mortality rates, stratifying by age and risk group. CI, confidence interval; HR, adjusted hazard ratio; No., number; SBP, systolic blood pressure.

suggests a slightly higher SBP is associated with survival benefit in patients with recent acute coronary syndrome [9]. In 4162 patients (78% men) enrolled within 10 days after an acute coronary syndrome, average SBP of 130–140 mmHg was associated with the lowest risk of death during an average follow-up of 24 months [9]. Our data extend these prior findings to a large cohort of older women with chronic CAD, and support the suggestion that achieved in-trial SBP continues to predict long-term mortality well over a decade into the future.

Mechanisms underlying the association between lower SBP and higher all-cause mortality in this endotype have not been completely elucidated. SBP lowering <140 mmHg may be associated with higher rates of renal failure [10,11]. Orthostatic hypotension, which is more frequent in women [14], may also contribute to worse outcomes. However, contemporary studies conducted in mainly male populations failed to support an association between lower BP targets and a higher incidence of orthostatic hypotension [12,13]. Reverse-causality, wherein patients with lower achieved SBP also have greater baseline cardiovascular risk, is less likely to have contributed to our findings, as we adjusted for baseline markers of more severe disease, including heart failure, prior stroke or TIA, diabetes, and CKD.

4.1. Limitations

The greatest strength of our study is that it included the largest cohort of women with hypertension and chronic CAD enrolled in a clinical trial to date; moreover women had high comorbidity burden, which is representative of the general population of older women with cardiovascular disease. It also had one of the longest follow-up periods for women, and intent to examine outcomes by sex and older age was prespecified. The major limitation is that after trial termination, data were not captured on medications, BP, or non-fatal clinical evolution. However, it is likely that INVEST women continued on a similar antihypertensive therapy after the trial, as site investigators were primary-care physicians and they were informed that BP control was the best reported at that time (~72%) and outcomes between the tested antihypertensive strategies were equivalent; furthermore the sponsor offered participants free drugs for at least 3 additional months after trial termination. Other limitations include the post-hoc nature of the analysis, the fact that SBP <130 was not a prespecified target for all INVEST patients, but only for those with diabetes or CKD, and that no adjustment was made for multiple testing.

5. Conclusion

In women with CAD and prior coronary events aged ≥65 years, achieving mean in-trial SBP of 130–139 mmHg during INVEST was associated with decreased long-term, all-cause mortality when compared with achieving SBP <130 mmHg.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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