Mortality Risk Associated With Resistant Hypertension Among Women: Analysis from Three Prospective Cohorts Encompassing the Spectrum of Women's Heart Disease

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Abstract

Background: Women are at greater risk of developing resistant hypertension (RH) than men, yet scarce data exist on RH-associated outcomes in women. We aimed to determine all-cause mortality risk associated with apparent RH (aRH) among women across the spectrum of underlying coronary disease.

Materials and Methods: We analyzed data from St. James Women Take Heart (WTH; women without coronary disease at baseline), Women's Ischemia Syndrome Evaluation (women with signs/symptoms of ischemia at baseline), and the International Verapamil-Trandolapril Study (INVEST; women with coronary artery disease and hypertension at baseline), totaling 15,108 adult women with no hypertension, non-RH (blood pressure [BP] $\geq 140/90$ mmHg on ≤ 2 drugs or BP $< 140/90$ mmHg on 1–3 drugs), or aRH (BP $\geq 140/90$ mmHg on ≥ 3 drugs or anyone on ≥ 4 drugs) at baseline. The primary outcome was all-cause mortality.

Results: Prevalence of aRH ranged from 0.4% (WTH) to 10.6% (INVEST). Women with aRH, compared to those without, were older, more often black, and more likely to be obese or diabetic. Pooling all cohorts, risk for all-cause death was greater in women with aRH than in women with non-RH (adjusted HR 1.40; 95% CI 1.27–1.55) and women without hypertension (adjusted HR 2.34; 95% CI 1.76–3.11) over a median follow-up of 14.3 years.

Conclusions: aRH prevalence in women varies according to underlying coronary disease, and aRH is associated with a substantial, early, and sustained increased risk of all-cause death. Additional research into early recognition and prevention strategies for RH are needed, especially in black and older women, and those with known cardiovascular risk factors.

Keywords: hypertension, resistant hypertension, women, mortality, INVEST, WISE

Introduction

AS AWARENESS AND MORE aggressive treatment of hypertension have increased over the past quarter-century,^{1–5} so too has the prevalence of resistant hypertension (RH), usually defined as uncontrolled blood pressure (BP) on ≥ 3 antihypertensive drugs or use of ≥ 4 antihypertensive drugs regardless of BP control.^{6–8} Data from the U.S. National Health and Nutrition Examination Survey (NHANES) suggest that the prevalence of RH has almost tripled in the last two decades, through which 21% of the adult U.S. population with treated hypertension had

RH between 2005 and 2008, increased from 8.8% between 1988 and 1994.⁶ Emerging evidence suggests that RH is associated with increased risk for major adverse cardiovascular (CV) events and mortality and worse health-related quality of life, compared with nonresistant hypertension (non-RH).^{9–16} Consequently, RH has been identified as a priority research area.^{7,17}

Multiple lines of empiric evidence suggest that women are at greater risk of developing RH than men: mean BP is demonstrably higher in postmenopausal women than age-matched men¹⁸; women are more likely than men to be treated with antihypertensive drugs, but less likely to achieve

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BP control^{1,6,19–22}; and female sex has been repeatedly identified as an independent predictor of RH.^{6,11–13,23,24} Yet, most studies of RH-associated outcomes have enrolled comparatively few women,¹⁷ consistent with CV studies in general.^{25–27} This lack of RH outcome data in women represents a major gap in knowledge. We recently observed a >7-fold increased risk of all-cause death in those with RH compared to normotensive women among a population of women with underlying ischemia.²⁸ To our knowledge, this study is the only previously published work focusing on RH in women, which represents a group at increased risk of developing RH, specifically. However, important questions remain, such as whether these findings can be replicated in larger, more diverse populations of women with long-term follow-up, what role ischemia plays in RH-associated risk of adverse outcomes, and whether such risk varies across differing levels of underlying coronary disease. A better understanding of these risk implications would help in optimally disseminating limited healthcare resources. To that end, we aimed to compare for the first time, the long-term risk for all-cause death associated with apparent RH (aRH) across three cohorts of women with and without underlying ischemia. Similar to other studies, we used the term aRH to encompass those with true RH and those with “pseudoresistant hypertension” in a single clinically useful definition that does not require adherence or out-of-office BP measurements. We hypothesized that aRH would portend greater risk for mortality in women, regardless of the presence of ischemia.

Materials and Methods

Study cohorts

We sought to include cohorts across the spectrum of women’s heart disease that rigorously assessed antihypertensive medication use, office BP, and coronary disease status. To that end, data were collected from three prospective observational cohorts of adult women with which the present study investigators have been previously involved: St. James Women Take Heart (WTH), Women’s Ischemia Syndrome Evaluation (WISE), and the INternational VERapamil-Trandolapril Study (INVEST). Their methods and primary outcomes have been published in detail.^{29–33} Briefly, the aim of WTH was to assess the implications of exercise stress testing in healthy, asymptomatic adult women who were able to walk on a treadmill at a moderate pace and did not have symptomatic coronary artery disease (CAD) or previous myocardial infarction. The WISE was a prospective, observational cohort study aimed at improving recognition, diagnosis, and understanding of pathophysiologic mechanisms underlying ischemic heart disease in women undergoing clinically indicated coronary angiography to further evaluate symptoms and/or signs of ischemia. The INVEST was a prospective, randomized, trial comparing outcomes among participants with clinically stable CAD and essential hypertension who were randomly assigned to a calcium antagonist-based (verapamil SR $\pm$ trandolapril) or β -blocker-based (atenolol $\pm$ hydrochlorothiazide) antihypertensive treatment strategy for BP control. To avoid bias associated with differences in practice patterns across the 14 countries participating in the INVEST,³⁴ only data from women cared for at U.S. sites were used in the present analysis.

Women in all three cohorts underwent baseline studies, including physical examination and BP measurement, using

standard clinical procedures.³⁵ Participants also provided data on demographics, lifestyle, and behavioral variables, as well as medical and medication history by self-administered questionnaires. Additional methodological details for each study are provided in the Supplement (Supplementary Data are available online at www.liebertpub.com/jwh).

Assembly of study cohort

For each cohort, participants were grouped into mutually exclusive categories according to hypertension status at baseline: no hypertension (among the WTH and WISE cohorts only: systolic BP [SBP] <140 mm Hg and diastolic BP [DBP] <90 mm Hg, no antihypertensive treatment, and no history of hypertension diagnosis), nonresistant hypertension (non-RH: SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg receiving two or fewer antihypertensive drug classes, or SBP <140 mm Hg and DBP <90 mm Hg receiving three or fewer antihypertensive classes), or aRH (SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg receiving three or more antihypertensive classes, or any patient on four or more antihypertensive classes, regardless of BP). We used baseline BP values, rather than study follow-up data, to determine hypertension status in the INVEST cohort to maintain consistency with the other cohorts, since follow-up BP and medication use data were unavailable from the WTH and WISE. In addition, we did not require diuretic use in the aRH definition since previous work by us¹² and others^{9,15} has indicated remarkably similar risk for adverse outcomes whether or not diuretic use is required to meet criteria for RH among patients using multiple antihypertensive drugs of different classes. Finally, because we had previously demonstrated an equivalent impact on outcomes and very similar effects on BP control between the treatment strategies,^{12,33} all U.S. women in INVEST were pooled, regardless of initial treatment randomization.

Study outcome

The primary outcome for this analysis was all-cause death, since this outcome is the most objective, unbiased endpoint of relevance to clinicians and patients. All-cause death was determined using the National Death Index. Possible matches were identified according to established National Death Index guidelines.³⁶ To be considered a confirmed death, we required at least four of five matches among Social Security number, name, date of birth, city, and state in the National Death Index.

Statistical analyses

Demographics and major events were summarized using mean $\pm$ standard deviation (SD) for continuous variables and *n* (%) for categorical variables. Unadjusted Kaplan–Meier survival curves were plotted for all-cause mortality. Cox regression was used to model the primary outcome of all-cause death and the proportional hazards assumption was met for hypertension status. Women from WTH, WISE, and INVEST were pooled together. Candidate variables for the full model included age (per 10-year increment), race (black vs. non-black), history of diabetes, history of dyslipidemia, obesity (body mass index $\geq$ 30 kg/m²), history of smoking, history of peripheral vascular disease (PVD), history of stroke or transient ischemic attack (TIA), presence of renal insufficiency (defined as serum creatinine concentration >1.5

FIG. 1. Flow diagram for cohort development. aRH, apparent resistant hypertension; INVEST, International Verapamil-Trandolapril Study; non-RH, nonresistant hypertension; WISE, Women's Ischemia Syndrome Evaluation; WTH, Women Take Heart.

but <4 mg/dL), presence of ischemia, and hypertension status. Sensitivity analyses were performed using a stratified Cox regression model for cohort effect, with presence of CAD (WISE and INVEST), but otherwise was unchanged from the primary model. For the analysis of all-cause death, data for women who did not appear in the National Death Index search were censored on the day that the search was completed for each cohort. Statistical significance was pre-defined as $p < 0.05$. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Results

A total of 15,108 women were included in the present analysis: of these, 4965 were from WTH, 927 were from WISE, and 9216 were from INVEST (Fig. 1). Combining all three cohorts, 7.1% of all women (8.8% of those with hypertension)

met criteria for aRH: the prevalence of aRH ranged from 0.4% (or 0.9% of women with hypertension) in WTH to 8.9% (10.4% of women with hypertension) in WISE and 10.6% in INVEST. Baseline demographic and clinical characteristics according to study cohort and hypertension status are summarized in Table 1. Mean $\pm$ SD age ranged from 52 ± 11 years in WTH to 58 ± 12 years in WISE, and 67 ± 10 years in INVEST. Non-Hispanic white women predominated in WTH (86%) and WISE (81%), whereas INVEST had comparatively fewer non-Hispanic white women (36%); black women comprised ~9% (WTH) to 17% (WISE, INVEST) of the individual study populations. Women with hypertension, compared to women without hypertension, were generally older, more frequently black, less frequently Hispanic, and had a higher prevalence of obesity, diabetes, and dyslipidemia. Notably, these trends were frequently more pronounced in women with aRH compared to those with non-RH.

TABLE 1. BASELINE CHARACTERISTICS OF WOMEN ACCORDING TO STUDY COHORT AND HYPERTENSION STATUS

Variable	WTH (N = 4965)			WISE (N = 927)			INVEST (N = 9216)	
	No HTN	Non-RH	aRH	No HTN	Non-RH	aRH	Non-RH	aRH
N	2690	2254	21	131	713	83	8242	974
Age, year, n (%)	49 $\pm$ 10	57 $\pm$ 11	60 $\pm$ 9	52 $\pm$ 11	59 $\pm$ 11	63 $\pm$ 11	67 $\pm$ 10	67 $\pm$ 10
<50	1576 (59)	649 (29)	1 (4.8)	56 (43)	165 (23)	8 (9)	0 (0)	0 (0)
50–60	693 (26)	670 (30)	10 (48)	47 (36)	212 (30)	24 (28)	2396 (29)	259 (27)
≥ 60	421 (16)	935 (41)	10 (48)	28 (21)	336 (47)	51 (61)	5846 (71)	715 (73)
Race/ethnicity, n (%)								
White	2341 (87)	1906 (85)	18 (86)	116 (89)	592 (83)	45 (54)	2880 (35)	404 (41)
Black	213 (7.9)	237 (11)	3 (14)	14 (11)	113 (16)	34 (40)	1310 (16)	302 (31)
Hispanic	78 (2.9)	55 (2.4)	0 (0)	1 (0.8)	3 (0.4)	1 (1.2)	3803 (46)	252 (26)
Other	58 (2.2)	56 (2.5)	0 (0)	0 (0)	5 (0.7)	3 (3.6)	249 (3.0)	16 (1.6)
BMI, kg/m ²	26 $\pm$ 5	29 $\pm$ 6	35 $\pm$ 7	28 $\pm$ 7	30 $\pm$ 7	30 $\pm$ 6	29 $\pm$ 6	32 $\pm$ 8
Obese, n (%)	471 (18)	876 (39)	18 (86)	40 (31)	294 (41)	40 (47)	3370 (41)	532 (55)
Systolic BP, mm Hg	120 $\pm$ 11	147 $\pm$ 16	159 $\pm$ 15	120 $\pm$ 12	137 $\pm$ 20	158 $\pm$ 21	148 $\pm$ 19	157 $\pm$ 18
Diastolic BP, mm Hg	77 $\pm$ 7	89 $\pm$ 8	94 $\pm$ 11	73 $\pm$ 8	77 $\pm$ 11	81 $\pm$ 13	85 $\pm$ 11	86 $\pm$ 12
History of hypertension, n (%)	0 (0)	781 (35)	21 (100)	0 (0)	469 (66)	80 (94)	8242 (100)	974 (100)
History of diabetes, n (%)	39 (1.5)	118 (5)	1 (4.8)	5 (4)	180 (25)	44 (52)	2361 (29)	437 (45)
History of dyslipidemia, n (%)	460 (17)	570 (25)	8 (38)	36 (27)	378 (53)	58 (70)	4238 (51)	589 (60)
Smoking history, n (%)	458 (17)	280 (12)	1 (4.8)	67 (51)	388 (54)	37 (45)	2558 (31)	310 (32)
History of PVD, n (%)	0 (0)	0 (0)	0 (0)	3 (2.3)	59 (8.5)	13 (16)	1027 (12)	160 (16)
History of stroke or TIA, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	529 (6.4)	109 (11)
Renal insufficiency, n (%)	11 (0.4)	28 (1.2)	1 (4.8)	0 (0)	16 (2.2)	8 (9.6)	91 (1.1)	43 (4.4)

Data are reported as mean $\pm$ SD or n (%). Obesity was defined as BMI ≥ 30 kg/m². History of hypertension, diabetes, and dyslipidemia was defined as a previous diagnosis of the respective condition, or taking antihypertensive, antidiabetic, or lipid-lowering medication, respectively. Stroke/TIA was an exclusion criteria for both WTH and WISE; likewise, history of PVD was an exclusion criteria for WTH. aRH, apparent resistant hypertension; BMI, body mass index; BP, blood pressure; HTN, hypertension; INVEST, International Verapamil-Trandolapril Study; Non-RH, nonresistant hypertension; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischemic attack; WISE, Women's Ischemia Syndrome Evaluation; WTH, Women Take Heart.

TABLE 2. BASELINE ANTIHYPERTENSIVE USE OF MAJOR ANTIHYPERTENSIVE CLASSES ACCORDING TO STUDY COHORT AND HYPERTENSION STATUS

Variable	WTH (N=4965)			WISE (N=927)			INVEST (N=9216)	
	No HTN	Non-RH	aRH	No HTN	Non-RH	aRH	Non-RH	aRH
N	2690	2254 (%)	21 (%)	131	713 (%)	83 (%)	8242	974
ACE inhibitor	—	166 (7)	14 (67)	—	182 (26)	58 (70)	3230 (39%)	698 (72%)
ARB	—	5 (0.2)	0 (0)	—	18 (3)	11 (13)	—	—
Diuretic	—	384 (17)	20 (95)	—	193 (27)	74 (89)	2477 (30%)	827 (85%)
Vasodilator	—	91 (4)	10 (48)	—	56 (8)	23 (28)	—	—
β -blocker	—	211 (9)	12 (57)	—	300 (42)	64 (77)	—	—
Calcium antagonist	—	161 (7)	10 (48)	—	207 (29)	51 (61)	2870 (35%)	730 (75%)
No. of antihypertensive medications, n (%)								
0	2690 (100)	1430 (63)	0 (0)	131 (100)	81 (11)	0 (0)	929 (11)	0 (0)
1	0 (0)	634 (28)	0 (0)	0 (0)	357 (50)	0 (0)	4163 (51)	0 (0)
2	0 (0)	186 (8.3)	0 (0)	0 (0)	228 (32)	0 (0)	2840 (34)	0 (0)
3	0 (0)	4 (0.2)	18 (86)	0 (0)	45 (6.3)	54 (65)	310 (3.8)	716 (74)
≥ 4	0 (0)	0 (0)	3 (14)	0 (0)	0 (0)	29 (35)	0 (0)	258 (26)

ACE, angiotensin converting enzyme; ARB, angiotensin (AT₂) receptor blocker.

BP and medication use

Mean $\pm$ SD baseline SBP was generally similar among women in WTH (133 ± 19 mm Hg), WISE (137 ± 21 mm Hg), and INVEST (135 ± 18 mm Hg); likewise, baseline DBP differed little between women in WTH (82 ± 10 mm Hg), WISE (77 ± 11 mm Hg), and INVEST (78 ± 10 mm Hg). Comparing groups within each cohort, mean SBP was higher in women with aRH compared to non-RH by 9–21 mm Hg; mean DBP was 1–5 mm Hg higher in those with aRH compared to those with non-RH (Table 1).

Antihypertensive medication use is summarized in Table 2. Among those with aRH in WTH, 86% were taking three antihypertensive drugs and 14% were taking ≥ 4 antihypertensive drugs, compared with 65% and 35%, respectively, in WISE, and 74% and 26%, respectively, in INVEST. Diuretics were the most commonly used agents in women with aRH across all three cohorts, followed by ACE inhibitors (WTH), β -blockers (WISE), or calcium antagonists (INVEST). Diuretic use was considerably more prevalent in women with aRH compared to those with non-RH in all three cohorts: in WTH, 95% of women with aRH used a diuretic compared to 17% of women with non-RH; in WISE, 89% of those with aRH used a diuretic compared to 27% of those with non-RH; and, in INVEST, 85% of those with aRH used a diuretic versus 30% of those with non-RH.

All-cause mortality

The results of Kaplan–Meier survival analysis for unadjusted all-cause death according to hypertension status and cohort are presented in Figure 2. Combining all three cohorts, 3668 women (24%) died from any cause over a median interquartile range [IQR] follow-up of 14.3 years (11.8, 16.2). All-cause death frequency and follow-up according to cohort and hypertension status are summarized in Table 3. Pooling data from all three cohorts, the risk of death from any cause was greater in women with aRH (adjusted HR 2.34; 95% CI 1.76–3.11) and non-RH (adjusted HR 1.67; 95% CI 1.28–2.17) compared to normotensive women. Risk of death from any cause was also greater in women with aRH compared to

women with non-RH (adjusted HR 1.40; 95% CI 1.27–1.55). The all-cause mortality rate was greatest in those with aRH (40.9 deaths/1000 patient-years), followed by those with non-RH (22.2 deaths/1000 patient-years); women without hypertension had the lowest rate (4.7 deaths/1000 patient-years). Figure 3 summarizes the factors independently associated with all-cause death. In addition to hypertension status, significant independent predictors of all-cause death were age (adjusted HR 2.00 per decade; 95% CI 1.92–2.07), history of diabetes (adjusted HR 1.70; 95% CI 1.58–1.83), history of smoking (adjusted HR 1.56; 95% CI 1.45–1.68), history of PVD (adjusted HR 1.11; 95% CI 1.01–1.23), history of stroke or TIA (adjusted HR 1.33; 95% CI 1.18–1.50), presence of renal insufficiency (adjusted HR 2.11; 95% CI 1.72–2.58), presence of ischemia (adjusted HR 1.10; 95% CI 1.01–1.19),

FIG. 2. Kaplan–Meier curve of all-cause mortality comparing hypertension status within each cohort. Data are truncated at 10 years in the figure. aRH, apparent resistant hypertension; HTN, hypertension; HR, hazard ratio; INVEST, International Verapamil-Trandolapril Study; non-RH, nonresistant hypertension; WISE, Women's Ischemia Syndrome Evaluation; WTH, Women Take Heart.

TABLE 3. ALL-CAUSE DEATH OCCURRENCE AND FOLLOW-UP ACCORDING TO STUDY COHORT AND HYPERTENSION STATUS

Variable	WTH (N=3286)			WISE (N=927)			INVEST (N=9216)	
	No HTN	Non-RH	aRH	No HTN	Non-RH	aRH	Non-RH	aRH
N	2690	2254	21	131	713	83	8242	974
All-cause death, n (%)	185 (6.9)	351 (16)	17 (81)	5 (3.8)	144 (20)	34 (41)	2524 (31)	421 (43)
Median (IQR)	9.0	9.1	9.2	9.4	9.3	8.8	8.3	8.2
follow-up, years	(8.8, 15.5)	(8.8, 15.5)	(8.9, 15.5)	(8.7, 10.2)	(8.2, 10.4)	(6.6, 9.7)	(7.8, 8.8)	(6.5, 8.8)

IQR, interquartile range.

and black race (adjusted HR 1.22; 95% CI 1.11–1.34). A sensitivity analysis, including CAD as a covariate instead of ischemia, revealed very similar results (data not shown).

Discussion

We assessed long-term risk of all-cause death in women without hypertension, with non-RH, and with aRH in three large cohorts with varying levels of underlying coronary disease. We observed a wide-ranging prevalence of aRH and, most importantly, a substantially increased risk of death in women with aRH and non-RH compared to those without hypertension. Interestingly, the increased risk of death from any cause was observed very early in the follow-up period and persisted over long-term follow-up. These data represent the largest study to date of aRH in women and some of the longest follow-up to date for any person with aRH. Moreover, this is one of the first studies in men or women, to our knowledge, to assess risks associated with resistant hypertension across the spectrum of underlying cardiac disease. Previous analyses have been largely limited to patients with high risk for CV events or to specific disease-based cohorts, for example, in those with underlying coronary artery disease,^{12,13} subclinical or clinical atherosclerotic disease,¹¹ or chronic kidney disease.¹⁰

The most important finding from this study is the very early emergence of and sustained increased risk of death associated with aRH, particularly in women with signs and symptoms of myocardial ischemia (from WISE) or CAD

(from INVEST). Pooling all-cause mortality data from the three cohorts, we observed a 1.4-fold increase in the risk for death from any cause in women with aRH compared to women with non-RH, and a 2.3-fold increase in risk among women with aRH compared to normotensive women, after adjusting for known CV risk factors. Although the magnitude of risk observed here was lower than that in a previous analysis in the WISE cohort,²⁸ our present results clearly demonstrate that women with aRH are at a substantially increased risk of dying compared to those without aRH. Importantly, the median follow-up time of >14 years in this study far surpasses the vast majority of previous analyses of RH-associated outcomes, which have typically had ≤5 years of follow-up.^{9–15} Finally, our findings are remarkably consistent with a recent analysis of ALLHAT data, in which RH (Vs. non-RH) was associated with a nearly 1.4-fold increased risk of all-cause mortality over ~5 years among a more homogenous group of women.⁹

The mechanisms underlying the association between aRH and death are not known, but it seems reasonable to presume that requiring a greater number of antihypertensive agents to achieve BP control reflects a combination of adverse underlying disease processes. These processes may include, for example, increased sympathetic nervous system activation, renin-angiotensin system activation, excess aldosterone production, increased arterial stiffness, or subclinical or clinical atherosclerotic diseases that are associated with elevated CV risk. Alternatively, it may be that women with aRH have had a greater lifetime BP burden, relative to those without aRH. However, previous work has found no association between adverse outcomes and duration of hypertension.¹⁵ Whatever the cause, the relatively simple definition of aRH used here (*i.e.*, requiring ≥4 antihypertensive drugs to achieve BP control), and elsewhere,⁷ clearly identifies a high-risk subpopulation of women with hypertension, regardless of the presence of microvascular disease.

Our results also reinforce previous suggestions that black women are at an especially increased risk for hypertension-related adverse outcomes³⁷ and extend this finding to women with aRH. These observations held true in our present analysis using data from cohorts that excluded patients with severe renal disease and other active comorbidities such as acute coronary syndrome. We also found that age (adjusted HR 2.00 per decade), history of smoking (adjusted HR 1.56), history of diabetes (adjusted HR 1.70), history of PVD (adjusted HR 1.11), history of stroke/TIA (adjusted HR 1.33), renal insufficiency (2.11), and presence of ischemia (adjusted HR 1.10) were independently associated with increased risk of all-cause mortality, consistent with previous studies of RH

FIG. 3. Full multivariate cox regression model for all-cause death. aRH, apparent resistant hypertension; HTN, hypertension; non-RH, nonresistant hypertension; PVD, peripheral vascular disease; TIA, transient ischemic attack.

in other populations.^{10,13,38} Adjusting for these risk factors did not obscure the strong relationship between aRH and mortality, suggesting that these factors do not lie in the pathway between aRH and death.

The major strengths of this study are its size (the largest to date in women with aRH), the inclusion of women with varying levels of underlying coronary disease at baseline thus increasing generalizability, and long follow-up. Moreover, we excluded women cared for outside of the United States because differences in clinical practice between countries are known to influence studies of CV disease.

Study limitations

All-cause mortality was ascertained through the National Death Index, which has inherent limitations, namely that deaths are likely underreported. Second, we used baseline BP and antihypertensive medication data to determine RH status, possibly resulting in misclassification of women with RH as having non-RH (*i.e.*, masking of RH due to undertreatment). Any such misclassification would be expected to bias toward an overestimation of the excess risk associated with non-RH, but toward conservative estimates associated with aRH. Along these lines, medication adherence data were unavailable. However, previous large studies using patient self-report or medication fill data have demonstrated that adherence is not appreciably different (and perhaps even greater) among patients with RH versus non-RH.^{39,40} Finally, this is a retrospective analysis of three cohorts of women with varying underlying CVD and must be taken with a degree of caution. Although our results in women are consistent with studies in other populations, we cannot exclude the possibility that unmeasured confounders impacted our results. Thus, these results should not be interpreted as definitive proof of a causal relationship between aRH and death.

Conclusions

This analysis of data from three large cohorts of clinically stable women suggests that aRH prevalence among older adult women varies substantially, according to cohort study design and possibly the severity of coronary disease. Furthermore, such women with aRH are at a significantly greater risk of dying relative to women without hypertension; particularly so for older women, black women, and those with additional CV risk factors. These observations have important implications for clinical practice and research. Future studies are needed to clarify the underlying pathophysiologic mechanism(s) associated with this increased mortality. Most importantly though, these findings reinforce the importance of early identification of women with aRH and instituting primary and secondary prevention strategies, which may reduce the risk of RH-associated adverse outcomes.⁴¹ Special attention should be paid to older women, blacks, and those with a history of smoking, diabetes, renal insufficiency, stroke or TIA, PVD, ischemia or CAD, all of whom are at increased risk of dying.

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Author Disclosure Statement

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