ORIGINAL RESEARCH



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# Cardiovascular and Mortality Risk of Apparent Resistant Hypertension in Women With Suspected Myocardial Ischemia: A Report From the NHLBI-Sponsored WISE Study

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***Background*—**Women are more likely than men to develop resistant hypertension, which is associated with excess risk of major adverse outcomes; however, the impact of resistant hypertension in women with ischemia has not been explicitly studied. In this Women's Ischemia Syndrome Evaluation (WISE) analysis, we assessed long-term adverse outcomes associated with apparent treatment-resistant hypertension (aTRH) among women with suspected myocardial ischemia referred for coronary angiography.

***Methods and Results*—**Women (n=927) were grouped according to baseline blood pressure (BP): normotensive (no hypertension history, BP <140/90 mm Hg, no antihypertensive drugs); controlled (BP <140/90 mm Hg and a hypertension diagnosis or on 1 to 3 drugs); uncontrolled (BP ≥140/90 mm Hg on ≤2 drugs); or aTRH (BP ≥140/90 mm Hg on 3 drugs or anyone on ≥4 drugs). Adverse outcomes (first occurrence of death [any cause], nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure or angina) were collected over 10 years of follow-up. Apparent treatment-resistant hypertension prevalence was 10.4% among those with hypertension. Women with aTRH had a greater incidence of adverse outcomes, compared with normotensive women (adjusted hazard ratio [HR], 3.25; 95% confidence interval [CI], 1.94 to 5.43), and women with controlled (HR, 1.77; 95% CI, 1.26 to 2.49) and uncontrolled (HR, 1.62; 95% CI, 1.15 to 2.27) hypertension; outcome differences were evident early in follow-up. Risk of all-cause death was greater in the aTRH group, compared to the normotensive women and women with controlled and uncontrolled hypertension.

***Conclusions*—**In this cohort of women with evidence of ischemia, aTRH was associated with a profoundly increased long-term risk of major adverse events, including death, that emerged early during follow-up. **(*J Am Heart Assoc*. 2014;3:e000660 doi: 10.1161/JAHA.113.000660)**

**Key Words:** hypertension • resistant hypertension • WISE • women



Hypertension (HTN) affects an estimated 1 billion adults globally and is a major modifiable risk factor for ischemic heart disease, stroke, heart failure, diabetes, and death.[1,2] An estimated 8% to 12% or more of those with HTN are believed to have resistant HTN,[3] usually defined as requiring ≥4 antihypertensive agents to achieve blood pressure (BP) control, and identified as a priority research area.[4] Previous studies have shown that resistant HTN, as compared with nonresistant HTN, is associated with an increased risk of major adverse cardiovascular (CV) events, all-cause mortality, or both, as well as lower health-related quality of life.[5–9] Furthermore, in a recent analysis, resistant HTN portended an increased risk of major adverse CV outcomes in patients with HTN and established coronary artery disease (CAD).[10] Yet, important questions remain, including whether the increased risk for adverse CV outcomes associated with resistant HTN is present in women specifically presenting for evaluation of symptoms and signs of ischemia and whether this risk remains over the long term.

Until recently, limited information was available regarding sex differences in HTN control and related outcomes. Overall prevalence of HTN appears to be similar among men and women, considering the entire age spectrum; however, more men than women have HTN at ages <45 years, whereas the

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reverse is true in those ≥65.[1,11] Women are more likely to be treated with antihypertensive drugs and prescribed a greater number of antihypertensive drugs, yet less likely to achieve BP control than age-matched men, particularly in aging populations.[11–18] Accordingly, several studies indicate that resistant HTN populations have a greater ratio of females to males than do nonresistant HTN populations and that female sex is an independent predictor of resistant HTN.[7,10,18,19] On the other hand, women with HTN in general have a lower risk for mortality and most adverse CV outcomes, compared to age-matched men with HTN.[20–22] This appears true even in older populations, where HTN is more prevalent and poorly controlled in women,[23] despite similar protection afforded both by antihypertensive therapies.[24] Thus, it would appear that women are less likely than men to experience adverse CV events, but more likely to develop resistant HTN. Whether resistant HTN portends increased risk of adverse outcomes in women has not been explicitly studied and risks associated with ischemia are unknown.

Therefore, the aim of this study was to ascertain the long-term risk of adverse outcomes associated with apparent treatment-resistant HTN (aTRH) in women with signs and symptoms of cardiac ischemia. We hypothesized that aTRH would be associated with an increased risk for adverse CV outcomes. To test this hypothesis, we analyzed data from the Women's Ischemia Syndrome Evaluation (WISE).



## Methods

### Study Design

The WISE study design and protocol details have been previously published.[25] Briefly, WISE is a National Heart, Lung and Blood Institute–sponsored observational cohort study aimed at improving recognition, diagnosis, and understanding of pathophysiologic mechanisms underlying ischemic heart disease in women. Women undergoing clinically indicated coronary angiography for symptoms and/or signs of ischemia were enrolled from September 1996 through March 2000 from four academic institutions, including the University of Alabama-Birmingham, University of Pittsburgh, University of Florida, and Allegheny General Hospital. Major exclusion criteria included comorbidities that compromised follow-up, pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, New York Heart Association class III to IV heart failure, recent myocardial infarction (MI), significant valvular or congenital heart disease, and language barrier to questionnaire testing. Each woman gave informed consent before enrollment. All clinical centers had institutional review board approval for inclusion of women in this cohort study as well as for collection of follow-up data.

### Baseline and Follow-up Procedures

Baseline evaluations included collection of demographics, medical history, symptom data, physical examination and blood sampling for lipids, reproductive hormones, and inflammatory markers, as described in detail elsewhere.[25] Blood pressure was measured in the clinic/office setting at centers very experienced in the treatment of HTN care and following routine clinical standards in line with what was outlined by JNC 6,[26] which was current during collection of the BP data described in this manuscript. Blood pressure was measured with women seated and after having rested for at least 5 minutes. Blood pressure values represented either antihypertensive-naïve or on-treatment BP if a baseline antihypertensive regimen was prescribed by a participant's primary physician. Coronary angiography analyses were performed by a core lab masked to all patient data, including symptoms and results of noninvasive testing. Any diameter stenosis ≥50% was considered obstructive CAD.[27] Outcome data used here were collected in two consecutive phases, as described previously.[28] During phase I (median duration, 6 years), women were contacted at 6 weeks and at 1-year intervals following enrollment. During telephone contact, a scripted interview was completed by an experienced nurse or physician at the respective center: Each patient (or a family member, for women who died or were lost to follow-up) was queried for occurrence of major adverse cardiac events or hospitalizations. For cases cared for at a WISE clinical center, patients' medical records were also reviewed. In the event of death, a death certificate and/or physician narrative was obtained. During the second phase, we conducted a National Death Index search to 10 years of median follow-up for those who were alive at last contact and had not withdrawn consent. All deaths were adjudicated as CV or non-CV by a committee of senior WISE investigators blinded to angiographic findings.

### Definition of HTN Groups and Assembly of Study Cohort

For this analysis, women were assigned to one of four groups according to baseline BP and antihypertensive use as follows: (1) normotensive, defined as no self-reported history of HTN, BP <140/90 mm Hg, and taking no antihypertensive drugs; (2) controlled HTN, defined as BP <140/90 mm Hg and either a self-reported previous HTN diagnosis (if taking no antihypertensive drugs) or use of 1 to 3 antihypertensive drugs irrespective of HTN diagnosis; (3) uncontrolled HTN, defined as BP ≥140/90 mm Hg using ≤2 antihypertensive drugs; and (4) aTRH, defined as BP ≥140/90 on ≥3 antihypertensive drugs or BP <140/90 mm Hg using ≥4 antihypertensive drugs. The normotensive group was the reference in all analyses.

## Outcomes

The primary outcome for this analysis was the first occurrence of death from any cause (including phase II data), nonfatal MI, nonfatal stroke, or hospitalization for heart failure or angina. All-cause death (including extended follow-up from phase II) was a secondary outcome.

## Statistical Analyses

Demographics and major events were summarized using mean±SD for continuous variables and n (%) for categorical variables. Comparisons across the four study groups were made using Fisher's exact test for categorical variables and Kruskal-Wallis' test for continuous variables. The log-rank test was used to test overall differences in outcomes among groups. Cox's regression models were fit to adjust covariates that were significantly different between groups. Candidate variables for the full models included age, race (nonwhite), history of diabetes, history of dyslipidemia, presence of obesity (defined as body mass index [BMI] >30 kg/m$^2$), history of smoking, presence of obstructive CAD, and family history of CAD. Models were developed using backward selection with age forced into the model; otherwise, only covariates with a $P$ value <0.10 remained in the final model. The proportional hazard assumption was checked by creating and adding time-dependent covariates in the model; no significant violation of the assumption was detected. A hazard ratio (HR) and 95% confidence intervals (CIs) were estimated for each variable. Unadjusted Kaplan-Meier survival curves were plotted for each outcome. Overall $P$ values ≤0.05 were considered significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

## Results

A total of 927 women with available BP, angiographic, and follow-up outcomes data were included in this analysis. At baseline, only 131 (14.1%) of these women were normotensive. Among the remaining 796 women with HTN, 390 (48.9%) had controlled HTN (BP <140/90 mm Hg), 323 (40.6%) had uncontrolled HTN, and 83 (10.4%) had aTRH according to our definitions. Pertinent baseline characteristics for the entire study cohort and the individual groups are summarized in Table 1. Women with HTN, as compared with normotensive women, were older, on average, and had a higher baseline prevalence of diabetes, dyslipidemia, obesity, and obstructive CAD. Notably, women with aTRH had the highest prevalence of each of these comorbidities. Additionally, almost half of the women with aTRH were nonwhite, whereas fewer than 1 in 5 of women in the normotensive, controlled HTN, and uncontrolled HTN groups were nonwhite.

## Baseline BP and Medication Use

Mean±SD baseline systolic BP was similar for the normotensive and controlled HTN groups (120±12 vs. 123±12 mm Hg, respectively) and for the uncontrolled HTN and aTRH groups (154±15 vs. 158±21 mm Hg, respectively). Corresponding mean±SD baseline diastolic BPs were 73±8 and 72±9 mm Hg for the normotensive and controlled HTN groups and 83±10 and 81±13 mm Hg for the uncontrolled and aTRH groups.

Self-reported antihypertensive medication use at baseline is summarized in Table 1. By definition, use of ≥1 agent from each antihypertensive class was considerably more common in women with aTRH than in those with controlled or uncontrolled HTN. In those with aTRH at baseline, diuretics were the most commonly used agents (89% of women), followed by β-blockers (77%) and angiotensin converting enzyme (ACE) inhibitors (70%). In both the controlled and uncontrolled HTN groups, β-blockers were the most commonly used agent (50% and 33% of women in each group, respectively). Diuretics were used by 28% of those with controlled HTN and 25% of those with uncontrolled HTN. No women used aldosterone antagonists.

## Adverse CV and Mortality Outcomes

Adverse CV and mortality outcome event frequencies are summarized in Table 2. Unexpectedly, nearly half of the 796 women with HTN had at least one of the following events: death from any cause, nonfatal MI, nonfatal stroke, or hospitalization for heart failure or angina. In the aTRH group, 69% experienced an event, compared with 46% in the uncontrolled HTN group and 44% in the controlled HTN group. Considerably fewer women in the normotensive group experienced an event (21%), relative to the HTN groups (overall log-rank, $P$<0.0001). These differences in adverse outcome frequency between groups were evident very early in follow-up (Figure 1).

In multivariable-adjusted analyses controlling for age, race, and available clinical characteristics, HTN of any type was associated with a higher risk of adverse outcome, relative to normotensive women. Specifically, we observed a graded association whereby excess risk (relative to normotensive women) was intermediate in those with controlled HTN (HR, 1.84; 95% CI, 1.19 to 2.84) and uncontrolled HTN (HR, 2.01; 95% CI, 1.29 to 3.13) and highest in the aTRH group (HR, 3.25; 95% CI, 1.94 to 5.43). Women with aTRH also had greater risk, compared with those in the controlled (HR, 1.77; 95% CI, 1.26 to 2.49; $P$=0.001) and uncontrolled HTN (HR, 1.62; 95% CI, 1.15 to 2.27; $P$=0.006) groups. No difference was observed in risk between controlled and uncontrolled HTN groups (HR, 0.91; 95% CI, 0.72 to 1.16; $P$=0.45).

**Table 1.** Baseline Characteristics According to Study Group and for the Cohort

| Variable | Overall (n=927) | Normotensive (n=131) | Controlled HTN (n=390) | Uncontrolled HTN (n=323) | Apparent Resistant HTN (n=83) | *P* Value* |
|---|---|---|---|---|---|---|
| Age, mean±SD | 58±12 | 52±11 | 57±12 | 61±11 | 63±11 | <0.0001 |
| Nonwhite, % | 19 | 12 | 15 | 19 | 46 | <0.0001 |
| HTN†, % | 59 | 0 | 61 | 72 | 97 | <0.0001 |
| Diabetes, % | 25 | 4 | 25 | 26 | 54 | <0.0001 |
| Dyslipidemia, % | 51 | 30 | 60 | 53 | 77 | <0.0001 |
| Obese, % | 40 | 31 | 39 | 44 | 48 | 0.019 |
| Obstructive CAD, % | 38 | 18 | 43 | 36 | 53 | <0.0001 |
| Family Hx of CAD, % | 64 | 63 | 70 | 64 | 63 | 0.17 |
| Hx of smoking, % | 53 | 51 | 58 | 50 | 45 | 0.044 |
| SBP (mm Hg), mean±SD | 137±21 | 120±12 | 123±12 | 154±15 | 158±21 | <0.0001 |
| DBP (mm Hg), mean±SD | 77±11 | 73±8 | 72±9 | 83±10 | 81±13 | <0.0001 |
| Antihypertensive drugs | | | | | | |
| ACE inhibitor, % | 26 | 0 | 29 | 22 | 70 | — |
| ARB, % | 3 | 0 | 2 | 3 | 13 | — |
| β-blocker, % | 39 | 0 | 50 | 33 | 77 | — |
| Diuretic, % | 29 | 0 | 28 | 25 | 89 | — |
| Vasodilator, % | 9 | 0 | 7 | 9 | 28 | — |
| CCB, % | 28 | 0 | 33 | 25 | 61 | — |
| Number of antihypertensive drugs | | | | | | |
| 0 drugs, % | 23 | 100 | 4 | 21 | 0 | — |
| 1 drug, % | 39 | 0 | 56 | 43 | 0 | — |
| 2 drugs, % | 25 | 0 | 28 | 37 | 0 | — |
| ≥3 drugs, % | 14 | 0 | 12 | 0 | 100 | — |

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; DBP, diastolic blood pressure; HTN, hypertension; Hx, history; SBP, systolic blood pressure.
**P* values represent comparison across the four study groups using Fisher's exact test for categorical variables and Kruskal-Wallis' test for continuous variables. No group comparisons were made for antihypertensive drugs and number of antihypertensive drugs because these variables were either 0% or 100% for normotensive patients by definition.
†Self-reported diagnosis of hypertension at baseline.

**Table 2.** Outcome Frequency by Study Group

| Outcome | Normotensive (n=131) | Controlled HTN (n=390) | Uncontrolled HTN (n=323) | Apparent Resistant HTN (n=83) | Total (n=927) |
|---|---|---|---|---|---|
| Primary outcome*, n (%) | 28 (21) | 170 (44) | 149 (46) | 57 (69) | 404 (44) |
| Individual components of primary outcome | | | | | |
| Nonfatal MI, n (%) | 1 (1) | 15 (4) | 12 (4) | 5 (6) | 33 (4) |
| Nonfatal Stroke, n (%) | 4 (3) | 17 (4) | 15 (5) | 6 (7) | 42 (5) |
| HF hospitalization, n (%) | 1 (1) | 16 (4) | 28 (9) | 17 (20) | 62 (7) |
| Angina hospitalization, n (%) | 21 (16) | 106 (27) | 91 (28) | 38 (46) | 256 (28) |
| All-cause death, n (%) | 5 (4) | 81 (21) | 63 (20) | 34 (41) | 183 (20) |

HF indicates heart failure; HTN, hypertension; MI, myocardial infarction.
*First occurrence of death from any cause (including extended follow-up), nonfatal MI, nonfatal stroke, or hospitalization for heart failure or angina.

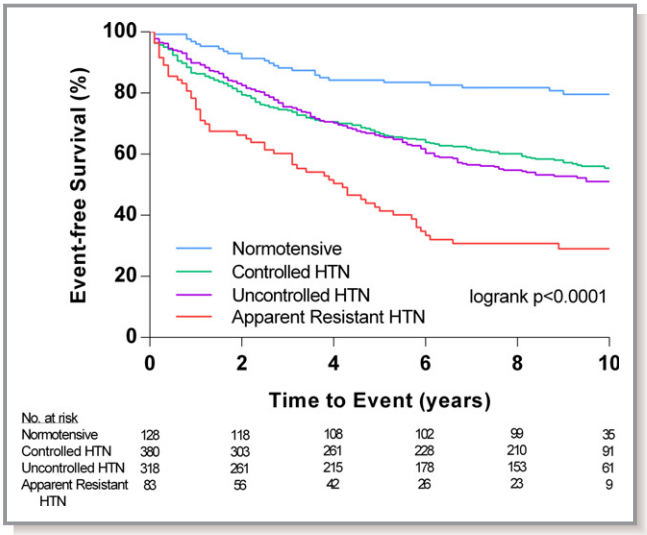


**Figure 1.** Kaplan-Meier curve for primary outcome event-free survival according to hypertension group. HTN indicates hypertension.

**Table 3.** Independent Predictors From Multivariate Cox Regression Model for First Occurrence of Death From Any Cause (Including Phase II Data), Nonfatal MI, Nonfatal Stroke, or Hospitalization for Heart Failure or Angina

| Parameter | HR (95% CI) | *P* Value |
|---|---|---|
| Age (per year) | 1.00 (0.99 to 1.01) | 0.45 |
| Non-white | 1.50 (1.15 to 1.95) | 0.003 |
| History of dyslipidemia (yes vs no) | 1.30 (1.04 to 1.63) | 0.021 |
| Obstructive CAD (yes vs no) | 1.93 (1.54 to 2.42) | <0.0001 |
| History of smoking (yes vs no) | 1.23 (0.99 to 1.52) | 0.06 |
| Normotensive (reference) | — | — |
| Controlled HTN | 1.84 (1.19 to 2.84) | 0.006 |
| Uncontrolled HTN | 2.01 (1.29 to 3.13) | 0.002 |
| Apparent resistant HTN | 3.25 (1.94 to 5.43) | <0.0001 |

CAD indicates coronary artery disease; CI, confidence interval; HR, hazard ratio; HTN, hypertension; MI, myocardial infarction.

In addition to HTN type, the presence of obstructive CAD, nonwhite race, and history of dyslipidemia also contributed significantly to higher risk of adverse outcome (Table 3).

Among those with HTN, nearly 1 in 4 women died during the 10-year mortality follow-up period (Table 2). The proportion of women dying from any cause was highest in the aTRH group (41%), whereas death occurred less frequently in the uncontrolled HTN (20%) and controlled HTN (21%) groups. Only 4% of women in the normotensive group died. The Kaplan-Meier curve for the unadjusted analysis of all-cause death is displayed in Figure 2. After adjustment, HTN of any type was associated with an increased risk of all-cause death. The greatest excess risk, relative to normotensive women, was observed in those with aTRH at baseline (HR, 7.36; 95% CI, 2.16 to 25.1), followed by those with controlled HTN (HR, 4.24; 95% CI, 1.31 to 13.7) and uncontrolled HTN (HR, 3.83; 95% CI, 1.17 to 12.5). Risk of all-cause death was also greater in women with aTRH, compared with controlled HTN (HR, 1.74; 95% CI, 1.07 to 2.81; *P*=0.03) and uncontrolled HTN (HR, 1.92; 95% CI, 1.17 to 3.15; *P*=0.01), whereas no difference in risk was observed between women with controlled versus uncontrolled HTN (HR, 1.11; 95% CI, 0.75 to 1.64; *P*=0.62). Hazard ratios from the full Cox regression model for all-cause death are summarized in Table 4.

## Discussion

Despite increasing awareness of CVD as the leading cause of mortality for women, relatively few studies have focused on women in relation to CVD and associated outcomes.[29] We tested the hypothesis that aTRH, defined in this study as baseline BP ≥140/90 mm Hg using ≥3 antihypertensive drugs or use of ≥4 antihypertensive drugs regardless of BP, portends an increased risk of adverse outcomes among adult women with signs or symptoms of myocardial ischemia. We show, for the first time, that women, referred to coronary angiography to evaluate symptoms/signs of ischemia, with aTRH have a profoundly increased risk of CV events and all-cause mortality, compared with normotensive women and those without aTRH. Moreover, we observed an association with both first occurrence of nonfatal stroke, nonfatal MI, hospitalization for angina or heart failure, or all-cause death, and all-cause death alone, whereby women with aTRH consistently had the greatest excess risk, followed by those with nonresistant HTN (regardless of BP control), whereas normotensive individuals had the lowest risk. Importantly, this pronounced increase in risk occurred early in follow-up, particularly for the primary outcome, and persisted over the long term for both the primary outcome and all-cause mortality.

The substantial and early excess risk of adverse outcomes among women with aTRH enrolled in WISE is noteworthy for several reasons. First, this is the only study, to our knowledge, that has quantified risk associated with aTRH in a female-only population. Compared to men, women are known to have more difficulty achieving BP control, thus requiring more aggressive therapy, and, consequently, are more likely to develop resistant HTN. Recent data also indicate that women with HTN have a significantly lower risk of most major adverse CV events, CV mortality, and all-cause mortality, when compared to age-matched men with HTN.[20–23] However, resistant HTN in women has not been explicitly studied previously and whether or not aTRH portends increased risk in women has not been clearly established. Thus, our findings highlight two key points regarding aTRH in women: (1) Regardless of any sex difference in CV or mortality risk in the

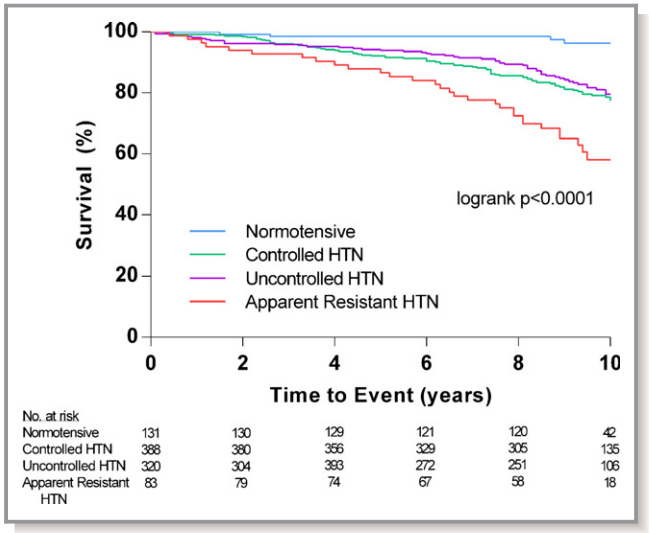


**Figure 2.** Kaplan-Meier curve for survival from all-cause death according to hypertension group. HTN indicates hypertension.

**Table 4.** Independent Predictors From Multivariate Cox Regression Model for All-Cause Death

| Parameter | HR (95% CI) | *P* Value |
|---|---|---|
| Age (per year) | 1.03 (1.02 to 1.05) | 0.0003 |
| History of diabetes (yes vs no) | 1.88 (1.31 to 2.72) | 0.0007 |
| History of smoking (yes vs no) | 1.85 (1.29 to 2.65) | 0.0009 |
| Obstructive CAD (yes vs no) | 1.83 (1.25 to 2.68) | 0.002 |
| Normotensive (reference) | — | — |
| Controlled HTN | 4.24 (1.31 to 13.7) | 0.017 |
| Uncontrolled HTN | 3.83 (1.17 to 12.5) | 0.026 |
| Apparent resistant HTN | 7.36 (2.16 to 25.1) | 0.001 |

CAD indicates coronary artery disease; HTN, hypertension.

overall hypertensive population, aTRH is associated with a profound increase in risk of adverse CV outcomes and death in women with symptoms/signs of ischemia, and (2) the association between aTRH and increased risk is independent of several traditional risk factors for adverse outcomes, including obstructive CAD, diabetes, dyslipidemia, and obesity. Second, the excess mortality risk associated with aTRH in the present study appears to persist for at least 10 years. To our knowledge, this is among the longest follow-up period reported in studies of resistant HTN. Most previous studies have included outcome assessment only up to 5 years.[6–8,10] Third, this substantial and long-term divergence in risk among the study groups was observed using only baseline clinic BP data. Almost assuredly, some of the women enrolled in WISE had pseudoresistant HTN, whereby baseline clinic BP (used in our definition of aTRH) was elevated, but 24-hour ambulatory BP would have been normal, had it been measured. Data from the Spanish Ambulatory Blood Pressure Monitoring (ABPM) registry suggest that as many as ≈40% of women with aTRH based on clinic BP would not be classified as having resistant HTN on the basis of 24-hour ABPM (ie, pseudoresistant HTN).[30] Unfortunately, precise estimates of pseudoresistant HTN prevalence in this population are unavailable and 24-hour ABPM was not performed in the WISE. Nevertheless, persons with isolated clinic BP elevations (aka a "white coat" effect) have a lower risk than those with elevated clinic and 24-hour ambulatory BP in unselected HTN populations[31,32] and, possibly, resistant HTN populations.[8] Thus, the excess risk attributable to aTRH in the present study is all the more impressive because, presumably, a significant proportion of these women likely had only isolated clinic BP elevations at baseline.

Few studies have examined predictors of adverse outcomes in patients with aTRH. Age, smoking, low-density lipoprotein cholesterol, left ventricular hypertrophy, and diabetes have been suggested as predictors for adverse outcomes (eg, MI, stroke, renal failure requiring dialysis, coronary or peripheral revascularization, or heart failure hospitalization).[5] Among patients with chronic kidney disease, predictors of adverse outcome (ie, CV death or nonfatal CV event requiring hospitalization) included only increasing age, male sex, decreasing glomerular filtration rate, history of CV events, and "true" resistant HTN (ie, as assessed by 24-hour ambulatory BP); BMI and diabetes were not significantly associated with the adverse outcome and race was not considered in the model because only whites were enrolled.[8] Although not directly comparable in terms of CV outcomes or patient populations assessed, we found that, in addition to aTRH, independent predictors of adverse outcomes in women in our study included nonwhite race, history of dyslipidemia, and obstructive CAD. We found no evidence of obesity or diabetes being independently associated with the adverse outcome. However, diabetes was independently associated with all-cause death, as were age, obstructive CAD, and smoking. The apparent differences, between predictors of adverse events in these studies, likely reflect differences in patient populations, as well as definitions of outcomes and resistant HTN. Nevertheless, these data, taken together, clearly demonstrate that the association between adverse outcomes and aTRH is not simply a reflection of the known risk of comorbidities (eg, obstructive CAD) found more often in those with resistant HTN. Rather, resistant HTN likely reflects a sicker patient population with underlying pathophysiologic changes, for example, increased arterial stiffness[33–35] and/or sympathetic nervous system activation resulting in altered vascular repair interacting to aggravate myocardial ischemia.[36–38]

A final point is that although women enrolled in WISE had a higher prevalence of HTN than the general female adult

population, the 10.4% prevalence of aTRH among only those with HTN is generally consistent with previous analyses of resistant HTN prevalence in unselected patients with HTN.[3] Furthermore, this prevalence is similar to that observed in the Reduction of Atherothrombosis for Continued Health registry, where 12.7% of adults ≥45 years of age with ≥3 atherosclerotic risk factors or established disease had resistant HTN based on baseline BP data and antihypertensive drug use.[7] However, not surprisingly, we observed a considerably lower prevalence in the present study, compared with INternational VErapamil SR-Trandolapril STudy (INVEST) participants, who all had HTN and established CAD at baseline, where approximately one third had resistant HTN.[10]

Our study has some noteworthy limitations. First, BP and antihypertensive use data were collected only at baseline and thus our study groups were defined accordingly. We cannot exclude the possibility that some women would have been classified differently based on data from later time points (eg, just before an event). However, in analyses of INVEST data, outcomes did not differ among those with controlled resistant HTN versus uncontrolled resistant HTN.[10] Thus, it is unclear whether achievement of BP control, or lack thereof, would substantially alter outcomes in the aTRH group. Unfortunately, the group sizes and outcome frequency were too small to adequately compare women with controlled aTRH versus uncontrolled aTRH in the present study. Second, medication adherence and secondary causes of HTN were not examined in WISE participants. Some of these women likely were nonadherent to antihypertensive therapy and we cannot exclude the possibility that nonadherence may have impacted adverse event rates in the hypertensive groups, especially those with aTRH. Third, our findings are applicable to women with signs or symptoms of myocardial ischemia of sufficient severity to prompt referral for angiography and should not be extrapolated to all adult women. Specifically, patients referred to the WISE study had signs and symptoms of ischemia based on a variety of different positive diagnostic tests; whether our findings would apply to a cohort of women without ischemia referral bias is not clear. Fourth, without a comparative male cohort, it is unknown whether our findings would apply to men. Unlike our women, more men undergoing angiography are identified with obstructive CAD[39,40] and therefore more intensely targeted for therapy to prevent atherosclerosis progression. Future investigation should be directed at testing these concepts in men. WISE centers may also have observed a higher percentage of women referred for coronary angiography without obstructive CAD as a result of tertiary care referral bias and publicized interest in heart disease among women. Fifth, although we controlled for baseline presence of several known risk factors for major adverse CV events, we cannot exclude the possibility that unmeasured confounders impacted our results. Moreover, our findings should not be construed as definitive proof of a causal relationship between aTRH and major adverse events. Sixth, nonfatal and fatal outcomes were verified by review of the medical records in all cases where records were available; however, we cannot exclude the possibility that some uncorroborated, patient-reported nonfatal outcomes may have been subject to misclassification. Finally, the WISE cohort had moderate rates of aspirin and statin medication use, both of which are known to reduce adverse outcomes in the absence of HTN. Use of these agents would have the potential to reduce risks and minimize relationships between the HTN groups and adverse outcomes and therefore lead to an underestimation of the observed relationships. Likewise, β-blocker and ACE inhibitor use were both greater in the aTRH group versus the nonresistant HTN groups, which would have the potential to result in underestimation of the relationship between aTRH and adverse outcomes in these women with evidence of myocardial ischemia.

In conclusion, this analysis confirms that aTRH is associated with a profound, early increase in risk of adverse outcomes among women with signs and symptoms of myocardial ischemia regardless of the presence of obstructive CAD. Furthermore, the risk of all-cause mortality associated with aTRH persists for at least 10 years from initial determination of resistant status. These findings fill a gap in the literature and have important implications for clinical practice and future research. Our observations reinforce the importance of recognizing women with, or at risk of developing, resistant HTN. Additionally, our findings highlight the need for future studies to clarify the pathophysiologic causes underlying increased CV risk in patients with aTRH and to determine appropriate risk reduction strategies, including pharmacologic and nonpharmacologic therapies.

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## Disclosures

None.

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