82424_Auto_Edited.docx

WORD COUNT	4063	TIME SUBMITTED	07-APR-2023 10:59PM
		PAPER ID	98472738

Name of Journal: *World Journal of Cardiology*
Manuscript NO: 82424
Manuscript Type: ORIGINAL ARTICLE

Observational Study

Pharmacoepidemiologic Study of Association between Apparent Treatment Resistant Hypertension, Cardiovascular Disease and Interaction Effect by Sex and Age

Resistant hypertension; Cardiovascular risk

Julianne Theresa Nelson, Longjian Liu

Abstract

BACKGROUND

A Limited number of studies have been conducted to test the magnitudes of the association between apparent treatment resistant hypertension (aTRH) and risk of cardiovascular disease (CVD).

AIM

To investigate the association between aTRH and risk of CVD and examine whether sex and age modify this association.

METHODS

We applied an observational analysis study design using data from the US Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT recruited participants (n = 25,516) from 625 primary care settings throughout the United States (U.S.), Canada, Puerto Rico, and U.S. Virgin Islands, aged 55 and older with hypertension and at least one additional risk factor for heart disease. aTRH was assessed from the year 2 visit. CVD event was defined as one of the following from the year 2 follow-up visit: fatal or non-fatal myocardial infarction (MI), coronary revascularization, angina, stroke, heart failure (HF), or peripheral artery disease (PAD). Cox proportional hazards regression was used to examine the effect of aTRH on CVD risk. Potential modifications of sex and age on this association were examined on the multiplicative scale by interaction term and additive scale by joint effects and relative excess risk for interaction (RERI)

RESULTS

Of the total study participants (n = 25,516), 5,030 experienced a CVD event during a mean of 4.7 years follow-up. aTRH was associated with a 30% increase in risk of CVD compared to non-aTRH (Hazards ratio, HR=1.3, 95%CI: 1.19-1.42). Sex and age modified this relationship on both multiplicative and additive scales independently.

Stratified by sex, aTRH was associated with a 64% increase in risk of CVD (HR=1.64, 95%CI: 1.43 – 1.88) in women, and a 13% increase in risk of CVD (HR=1.13, 95%CI: 1.01 – 1.27) in men. Stratified by age, aTRH had a stronger impact on the risk of CVD in participants aged <65 (HR= 1.53, 95%CI: 1.32 – 1.77) than it did in those aged ≥65 (HR=1.18, 95%CI: 1.05 – 1.32). Significant two-way interactions of sex and aTRH, and age and aTRH on risk of CVD were observed ($p<0.05$). The observed joint effect of aTRH and ages ≥ 65 years (HR=1.85, 95%CI: 1.22 – 2.48) in males was less than what was expected for both additive and multiplicative models (HR=4.10, 95%CI: 3.63 – 4.57 and 4.88, 95%CI: 3.66 – 6.31), although three-way interaction of sex, age, and aTRH on the risk of CVD and CHD did not reach a statistical significance ($P>0.05$).

CONCLUSION

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age. Further studies are warranted to test these mechanisms.

Key Words: Apparent treatment resistant hypertension; Cardiovascular disease outcomes

Nelson JT, Liu L. Pharmacoepidemiologic Study of Association between Apparent Treatment Resistant Hypertension, Cardiovascular Disease and Interaction Effect by Sex and Age. *World J Cardiol* 2023; In press

Core Tip: Apparent treatment resistant hypertension increased the risk of a cardiovascular event by 30%. This association varied by sex and age, with a stronger impact in women and in younger adults. These findings highlight the importance of controlling aTRH among those with excess risk of cardiovascular disease.

INTRODUCTION

Hypertension has long been a serious public health concern. Its impact on cardiovascular health and long-term outcomes has been well studied.[1] In the U.S. approximately 121.5 million (47.3%) adults suffer from hypertension leading to an added economic burden costing up to $51.1 billion per year.[2] One of the significant challenges in control of hypertension is the appearance of treatment resistant hypertension.

Treatment resistant hypertension is defined as having blood pressure (BP) that remains uncontrolled (systolic (SBP) ≥ 140 mmHg or diastolic (DBP) ≥ 90 mmHg) while a patient is on ≥ 3 different antihypertensive medications. Additionally, those who are on 4 or more different classes of antihypertensive medications, regardless of BP are also classified as treatment resistant hypertension. Individuals with diabetes or chronic kidney disease (CKD) have an altered definition, these patients with SBP/DBP ≥ 130/80 mmHg are classified as treatment resistant hypertension.[3-5] In addition to the number of antihypertensive medications and blood pressure readings, ideally at least one of the medications should be a diuretic.[6] Apparent treatment resistant hypertension (aTRH) is used to define observed treatment resistant hypertension when factors relating to pseudoresistance (adherence to regimen, sufficient dose for therapy, *etc.*) are unknown.[7]

It is estimated that 19.7% of patients on antihypertensive medication have aTRH, a 2% increase within the recent decade.[3-5] While it is known that treatment of hypertension can reduce the risk of cardiovascular events and mortality, little research has been done on outcomes of those with resistant hypertension.[3,8] Several cross-sectional studies have found relationships between aTRH and CVD, however, longitudinal studies remain sparse.[3,9] What has been observed is that aTRH is associated with higher rates of cardiovascular and renal diseases, including: coronary heart disease (CHD), peripheral artery disease (PAD), stroke, heart failure (HF), end-stage renal disease (ESRD), and all-cause mortality. Of particular note is that aTRH increased the risk of CHD by 44% and the risk of death by 30% compared to non-aTRH.[9,10]

Men and women experience differing rates of hypertension and CVD.[11,12] However, findings of sex-specific aTRH studies remain inconsistent.[3,5,13-15] Women experience an increase in risk of hypertension post-menopause indicating a possible impact of sex and age on the risk of aTRH and CVD outcomes.[12]

Of the many risk factors for CVD, age is one of the most important factors as age is an independent risk factor for the development of atherosclerosis.[5,11,16,17] However, the degree of this effect does not impact men and women in the same way neither in the risk of incident hypertension nor in the progress of hypertension in clinical treatment.[11,18] Several studies have observed that age is significantly and independently associated with risk of aTRH.[3-5,14] However, studies of the potential modification effects of sex and age on the association between aTRH and risk of CVD are limited. In this study, we hypothesized that sex and age play an important role both independently and together in the risk of aTRH for CVD outcomes. To test this hypothesis, we examined the independent and additive effects of sex and age on aTRH and risk of CVD, and whether sex and age modify the association between aTRH and CVD risk.

MATERIALS AND METHODS

Study Sample

We analyzed data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In ALLHAT, a total of 42,418 participants aged 55 and older were recruited from 625 primary care settings throughout the United States (U.S.), Canada, Puerto Rico, and U.S. Virgin Islands. Participants were randomly assigned into four groups and then received one of four antihypertensive treatment arms: chlorthalidone, amlodipine, lisinopril, and doxazosin. Participants who received doxazosin are excluded in the analysis because this group was discontinued early. All participants had hypertension and at least one additional risk factor for CHD. Participants were followed for an average of 6 years.[19-21] The study design and process of ALLHAT have been published in detail elsewhere.[21]

This study, using de-identified data from the National Heart, Lung, and Blood Institute, has been approved by Drexel University Institutional Review Board (# 1608004781).

Measures

Exposure (aTRH): In ALLHAT the recruited participants were initially randomized to one of 4 first-line antihypertensive drugs. Additional anti-hypertensive medications were added on to therapy over the course of follow-up visits, thus, aTRH was determined at the year 2 visit to allow time for additional medications to be added, consistent with follow-up studies.[10,21] aTRH was defined as BP ≥ 140/90 while on 3 antihypertensive medications, or being on 4 antihypertensive medications regardless of BP at the year 2 visit. For subjects with either type II diabetes or CKD (assessed by glomerular filtration rate, eGFR < 60 mL/min), the cut-offs of SBP/DBP were set at ≥ 130/80 mmHg. Due to subjects being randomized to first-line anti-hypersensitive treatment, the condition that one medication be a diuretic for aTRH classification could not be applicable in the study.

Outcome (CVD): Subjects were classified as having had a CVD event if they experienced one of the following after the year 2 follow-up visit: fatal or non-fatal myocardial infarction (MI), coronary revascularization, angina, stroke, HF, or PAD. These events were ascertained from follow-up visits and medical recording during the course of the trial.[10]

Covariates: Covariates were selected based on their independent associations with both the exposure (aTRH) and outcome (CVD), existing literature, and use of a directed acyclic graph (DAG).[10] All covariates were measured at baseline of ALLHAT. They included: race (white, African American, American Indian/Alaskan Native, Asian/Pacific Islander, other), ethnicity (Hispanic), geographic region (East, Midwest, South, West, Canada, Puerto Rico/Virgin Islands), measures of GFR, SBP and DBP at

baseline, and history of CHD, history of MI or stroke, history of coronary revascularization, previous use of BP medication, smoking status (current, former, never), history of left ventricular hypertrophy (LVH), estrogen use (in women subgroup analysis only), aspirin use, and enrollment in concurrent lipid lowering trial (LLT).

Statistics

Univariate analysis was conducted to describe the baseline characteristics of participants by aTRH status. Student's t test was used to examine mean difference in continuous variables, and Chi-square tests to examine rate and proportion differences in categorical variables. We used Cox Proportional Hazards regression models to examine the association between aTRH and CVD risk with adjusting covariates. Assumptions of the proportional hazards in Cox model were tested graphically by log-log survival curves. To test potential modification effects of sex (men vs. women) and age (<65 vs. ≥65) on the association between aTRH and CVD risk, we assessed potential multiplicative interaction (e.g., aTRH*modifier) on CVD risk. We also assessed potential additive interaction effects on CVD risk by estimating the joint effects and calculating the relative excess risk for interaction (RERI).[22] If the RERI ≠ 0 then there is evidence that the observed additive risk of our exposures is different (more or less depending on the direction of the RERI) than what was expected. The methods of the calculations and hypothesis tests for the RERI have been discussed and published in detail elsewhere.[23] To test the overall interaction effect of sex and age and aTRH on CVD risk, we tested three-way interaction through a product interaction term (e.g., aTRH*sex*age) in Cox models. Observed joint effects were compared to expected for both additive and multiplicative models to determine presence of effect modification and subgroup analyses were performed.

Sensitivity Analyses: To avoid overfitting attributable to multiple control covariates, we applied a propensity score analysis technique.[24] A propensity score for the probability of aTRH was estimated utilizing all confounders and created using the boosted CART

method in the "twang" package in R software. [25-27] Extreme weights were trimmed and inverse probability weighting (IPW) was used to weight observations by the propensity score.[24,28] Second, in the ALLHAT study, missing data in BP measures occurred at year 2 visit. We conducted a sensitivity analysis using Markov Chain Monte Carlo method for multiple imputation based on the randomness of the missing values.[29] Third, because of the pathophysiologic differences between hemorrhagic and ischemic stroke, we conducted a subgroup of CVD analysis by strokes and CHD (fatal CHD or nonfatal MI, coronary revascularization, or hospitalized angina). Fourth, to control the effects attributable to the conclusion of patients who had uncontrolled hypertension (BP ≥ 140/90) but with < 3 medications (n = 11,223), on the estimate of HR for CVD risk, we excluded this group of patients in the final sensitivity analysis.

Data analyses were conducted using SAS software (Version 9.4, SAS Institute Inc., Cary, NC, USA). Statistical significance as set up at a two-sided P<0.05.

RESULTS

From the original sample of 42,418 subjects in ALLHAT, those on the doxazosin treatment arm (9,061) were removed early for safety reasons. After excluding subjects with CVD events or death prior to year 2, and those missing year 2 visit information we had an analytic study sample of 25,516. During the follow-up (average 4.7 years), 5030 (19.7%) participants had a CVD event. Table 1 shows baseline characteristics of the participants.

Overall subjects were more likely male (53.3%), from the South (41.6%), white (60.3%), and previously treated for hypertension (90.3%). Over a third (35.2%) had type 2 diabetes (T2DM), and 40.7% were former smokers. While over 40% of subjects were obese, the average BMI was 29.7 (SD 5.92). The average age was 66 years, and average GFR 78 mL/min. The rate of aTRH was 9.1% (n = 2329) in the total sample, 9.8% in men, 8.4%% in women, and 9.1% in those aged 65 and older. Subjects with aTRH were predominantly more likely to be African American, male, BMI >=30 kg/m^2, and T2DM than their corresponding counterparts.

Table 2 shows that after adjustment for covariates, aTRH remained significantly associated with risk of CVD (HR 1.30, 95%CI 1.19 – 1.42, p-value < 0.0001).

Sensitivity analyses of propensity score for adjusting multi-covariates and multiple imputation for estimates of missing values produced similar results as did the analysis involving exclusion of participants with uncontrolled BP on < 3 medications. When CHD was examined as the endpoint instead of CVD, the overall risk associated with aTRH was stronger (HR 1.56, 95%CI 1.29 – 1.89).

Table 3 shows individual and joint effects. Among women, aTRH was associated with a 64% increase in risk of CVD event (95%CI 1.43 – 1.88), and a 13% increase in risk of CVD (95%CI 1.01 – 1.27) among men. aTRH had a stronger impact on risk of CVD among younger subjects than it did among older (HR 1.53, 95%CI: 1.32 – 1.77 In those aged <65, and HR 1.18, 95%CI: 1.05 – 1.32 in those aged 65 and older). All HRs were statistically significant and the two-way multiplicative interaction terms of sex*aTRH, and age*aTRH and RERIs on risk of CVD were statistically significant ($p<0.05$).

Results stratified by aTRH, age, and sex can be found in Table 4 and Figure 1. Females aged 65 and older with aTRH had the highest risk of CVD (HR 2.61, 95%CI 2.20 – 3.01), followed by men < 65 years with aTRH (HR 2.17, 95%CI 1.76 – 2.58). The observed joint effect (HR 1.85 95%CI: 1.22 – 2.48) was less than expected for both additive and multiplicative models (HRs 4.10 95%CI 3.63 – 4.57 and 4.88 95%CI 3.66 – 6.31 respectively). However, the three-way interaction term for sex, age and aTRH was not significant for CVD ($P = 0.28$), and CHD ($P = 0.42$).

DISCUSSION

The overall findings of the present study indicate that there is a positive association between aTRH and risk of CVD. Based on statistically significant two-way interactions of sex with aTRH, and age with aTRH, heterogeneous strata results, statistically significant relative excess risk for interactions (RERIs), and differing observed and expected joint effects, this study highlights that the association between

aTRH and risk of CVD is modified independently by sex and age on both the additive and multiplicative scales.

Although it appeared there was a potential three-way interaction such that sex may modify the interaction of age and aTRH, and vice versa that age may modify the interaction of sex and aTRH on CVD risk, testing for these three-way interactions were not statistically significant. The results suggest that the interaction of sex and aTRH, or of age and aTRH did not depend on the third factor. This finding adds new insights into the body of the literature, that sex and age independently modify the association between aTRH and CVD.

Treating blood pressure becomes more difficult as a patient ages and is complicated by differing blood pressure goals by age and a possible U-shaped relationship between blood pressure (SBP) and mortality among the elderly. Among this population also exists the risk of over-correcting and lowering blood pressure too much which can cause other health concerns including dizziness and falls.[2,30,31] However, 2017 ACC/AHA changes to the guidelines no longer specify a different target BP for those ≥ 60 and the SPRINT study of older Americans indicated better health outcomes among those with more aggressive BP lowering targets (SBP 120 *vs* 140 mmHg).[32,33] This area remains a topic of debate with more research needed on this unique population.

Research has shown that older women are more likely to adhere to medications and more likely to have their blood pressure taken regularly, yet they appear to experience higher rates of uncontrolled hypertension.[15] Multiple mechanisms are believed to contribute to this increase in hypertension and uncontrolled hypertension in aging women including: activation of the renin angiotensin system (RAS), obesity, activation of sympathetic nervous system, and decline in estrogen levels.[15,17,34]. Stress on the body due to hypertension is believed to be more severe in women than in men.[35] Coupled with gender biases in treatment and management of CVD symptoms and events, we can envision how uncontrolled hypertension and aTRH would lead to more adverse health outcomes in women than men, especially in an aging

population.[36,37] The pathophysiology of aTRH is believed to be linked to blood volume and salt, and salt-sensitive hypertension increases in women post-menopause thus we would expect aTRH to be more prevalent among post-menopausal women.[18,38,39]

Very few studies have examined potential effect modifiers on the relationship between aTRH and CVD. Our findings are consistent with existing research in that aTRH is positively associated with CVD and both sex and age independently can modify the association between aTRH and CVD.[3-5,9,10] However, these studies only examined relative measures of association. Our study both confirmed presence of two-way interaction on the multiplicative scale and also identified that this modification is present on the additive scale. Epidemiologists have noted that additive interaction is most important for public health as it indicates an absolute number of cases which would be prevented if the modifier were removed.[22,40]

No study to date has examined potential three-way interaction with aTRH. With health effects of sex and age linked it is important to examine how these gender disparities in cardiovascular outcomes of patients with aTRH differ between subgroups of age.[11,12] Public health programs aimed at improving awareness of aTRH should make specific effort to target women and informing them of the dangerous health consequences associated. This study suggests that physicians should take special note in their treatment considerations when female patients are experiencing uncontrolled hypertension and understand the serious cardiovascular risks associated with developing aTRH. For example, because the interaction of age and aTRH on CVD did not change by sex, we would still endorse applying these recommendations to vigorously control aTRH in women of all ages instead of focusing on the older group only.

This study has several strengths. ALLHAT provides us with one of the largest datasets to test the impact of aTRH on CVD risk. Sample size is particularly important when analyzing effect modification as it utilizes subgroup analyses. We also deployed two methods (propensity score weighting and multiple imputation) to conserve power in our analyses. Similar findings from our original analysis and both sensitivity

analyses indicate our study is adequately powered. Another strength provided by use of ALLHAT is in our classification of aTRH. Blood pressure was taken twice from a seated position and averaged for each study visit, medication adherence was maintained through pill counts at each study visit, and doses of antihypertensive medications were appropriately titrated up to the maximum tolerated dose prior to adding on an additional medication. All of these factors allow for accurate ascertainment of aTRH status and reduce the likelihood of false positives due to pseudoresistance.[2-5]

While a strong study, there are also several limitations. As this study is limited to its analysis of variables collected in ALLHAT only, additional data could be included in the analysis. For example, dietary salt intake was not measured in ALLHAT, thus we could not adjust for this in multivariate models as it is suggested that aTRH is influenced by blood volume and salt intake.[38,39] However, because ALLHAT is a randomized clinical trial, potential unmeasured factors are balanced among the participants. The clinical trial nature of our data source, while a strength for validity of aTRH classification, is also a limitation as subjects were selected based on pre-determined criteria best fit for the goals of ALLHAT and thus further studies are needed to confirm the results among different study populations. The study participants consisted of older adults (≥ 55) and thus findings of the study in women should also be evaluated in women aged 55 and older, instead of interpretating the results to those aged <55. Additionally, the impact of pseudoresistance can never be completely removed and "white coat" effect is always a possibility when examining blood pressure readings.

aTRH increases the risk of CVD in patients with hypertension and this relationship is modified by age and sex independently on both the relative (multiplicative) and absolute (additive) scales. More research is needed to shed further light on these gender differences, especially with regard to women both pre and post menopause. Future research should focus on these sex and age differences and how it might impact treatment and control of aTRH as there is still much unknown about this

specific relationship. Management of aTRH should take a patient's age and sex into consideration and more preventive interventions should be aimed at aging women as they represent the subgroup of aTRH patients with the highest combined risk of CVD.

CONCLUSION

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age. Further studies are warranted to test these mechanisms.

ARTICLE HIGHLIGHTS

Research background

A Limited number of studies have been conducted to test the magnitudes of the association between apparent treatment resistant hypertension (aTRH) and risk of cardiovascular disease (CVD).

Research motivation

aTRH is significantly associated with the risk of CVD. It is important to understand whether age and sex significantly modify this association. Findings of the study could add new evidence to the body of literature, and provide new insights into further mechanism studies.

Research objectives

To investigate the association between aTRH and risk of CVD and examine whether sex and age modify this association.

Research methods

We applied an observational analysis study design using data from the US Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

(ALLHAT). ALLHAT recruited participants (n = 25,516) from 625 primary care settings throughout the United States (U.S.), Canada, Puerto Rico, and U.S. Virgin Islands, aged 55 and older with hypertension and at least one additional risk factor for heart disease. aTRH was assessed from the year 2 visit. CVD event was defined as one of the following from the year 2 follow-up visit: fatal or non-fatal myocardial infarction (MI), coronary revascularization, angina, stroke, heart failure (HF), or peripheral artery disease (PAD). Cox proportional hazards regression was used to examine the effect of aTRH on CVD risk. Potential modifications of sex and age on this association were examined on the multiplicative scale by interaction term and additive scale by joint effects and relative excess risk for interaction (RERI).

Research results

Of the total study participants, 5,030 experienced a CVD event during a mean of 4.7 years follow-up. aTRH was associated with a 30% increase in risk of CVD compared to non-aTRH (Hazards ratio, HR=1.3). Sex and age modified this relationship on both multiplicative and additive scales independently. Stratified by sex, aTRH was associated with a 64% increase in risk of CVD in women, and a 13% increase in risk of CVD in men. Stratified by age, aTRH had a stronger impact on the risk of CVD in participants aged <65 than it did in those aged ≥65. Significant two-way interactions of sex and aTRH, and age and aTRH on risk of CVD were observed ($p<0.05$). The observed joint effect of aTRH and ages ≥ 65 years in males was less than what was expected for both additive and multiplicative models, although three-way interaction of sex, age, and aTRH on the risk of CVD and CHD did not reach a statistical significance ($P>0.05$).

Research conclusions

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age.

Research perspectives

Further studies are warranted to test these mechanisms.

ACKNOWLEDGEMENTS

The manuscript was prepared using ALLHAT Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI). However, the opinions expressed in the report are those of the authors and do not necessarily represent the review of the NHLBI.

82424_Auto_Edited.docx

ORIGINALITY REPORT

4%
SIMILARITY INDEX

PRIMARY SOURCES

1	dmsjournal.biomedcentral.com Internet	23 words — 1%
2	Fred Stephen Sarfo, Bruce Ovbiagele. "Apparent Treatment Resistant Hypertension Among Stroke Survivors in Ghana", Journal of Stroke and Cerebrovascular Diseases, 2020 Crossref	18 words — < 1%
3	www.medrxiv.org Internet	15 words — < 1%
4	cmbi.bjmu.edu.cn Internet	14 words — < 1%
5	core.ac.uk Internet	14 words — < 1%
6	nottingham-repository.worktribe.com Internet	14 words — < 1%
7	www.timewarner.com Internet	14 words — < 1%
8	www.science.gov Internet	13 words — < 1%

9	Eduardo Pimenta. "Mechanisms and Treatment of Resistant Hypertension", The Journal of Clinical Hypertension, 3/2008 Crossref	12 words — < 1%
10	www.cdc.gov Internet	12 words — < 1%
11	www.frontiersin.org Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS