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Association and impact of hypertension defined using the 2017 AHA/ACC guidelines on the risk of atrial fibrillation in the ARIC cohort

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Association and impact of hypertension defined using the 2017 AHA/ACC guidelines on the risk of atrial fibrillation in the ARIC cohort

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Abstract

Association and impact of hypertension defined using the 2017 AHA/ACC guidelines on the risk of atrial fibrillation in the ARIC cohort

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Background

Atrial Fibrillation (AF) is a common chronic arrhythmia, occurring in 2.3 million adults in the United States (4). Amongst the risk factors for AF, hypertension has the largest population attributable fraction for AF incidence and plays a major role in the management and prognosis of AF (1, 2, 10). The most recent hypertension guideline, released in the Fall of 2017 by the American College of Cardiology/American Heart Association refined the guidelines released by JNC7 and JNC8 by lowering the threshold to define hypertension (5, 6, 18, 39). The goal of this study was to understand the association between hypertension and risk of AF using the diagnostic categories in the new guidelines, and evaluate the population attributable fraction of hypertension with the new definitions.

Methods

We conducted a prospective analysis of the Atherosclerosis Risk in Communities Study (ARIC) cohort data from 1987 to 2016. Cox proportional models were used to estimate hazard ratios of AF among individuals with hypertension based on the JNC7 and 2017 ACC/AHA guidelines. We performed stratified analyses by sex and race to explore effect modification. We also calculated population-attributable fractions (PAFs) to determine the possible impact of preventing hypertension on AF occurrence. Poisson models were used to obtain the risk ratios.

Results

We identified 1573 cases of incident AF during the study period. The prevalence of hypertension was 28.5% and 42.9% using the JNC7 and 2017 ACC/AHA definitions, respectively. In terms of the JNC7 guidelines, the hazard ratio was 1.6, 95% CI [1.49, 1.83] after adjusting for age, sex and race. The AF incidence rate per 1000 person-years was 6.6 and 10.8 for no hypertension and hypertension respectively. In terms of the 2017 AHA/ACC guidelines, the hazard ratio was 1.5, 95% CI [1.37, 1.68] after adjusting for age, sex and race. The AF incidence rate per 1000 person-years was 6.4 and 9.6 for no hypertension and hypertension respectively (Table 5). The PAF was 12% (95% CI [0.09, 0.14]) and 14% (95% CI [0.10, 0.18]) under the old and new guidelines, respectively.

Conclusions

In conclusion, our study showed a slight increase in PAF values. However, there was no difference in the risk of AF by hypertension status between the JNC7 and 2017 AHA/ACC guidelines. These results indicate that changes in the blood pressure cutoff to define hypertension will only have a limited impact regarding the incidence of AF. Additional studies are needed to confirm this finding. Moreover, further studies should incorporate other variables we had not considered such as: aspirin and statin medications, ECG p wave terminal force 1 in V1, HF history, MI history, and diabetes history that may influence the risk of AF.

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Chapter 1: Literature Review and Background

Atrial Fibrillation

Atrial Fibrillation (AF) is an arrhythmia characterized by irregular and rapid heart rate that can lead to other cardiovascular problems such as stroke or heart failure (19). In AF, the electrical signals in the atria (upper chambers of the heart) are disordered resulting in fewer electrical impulses getting through to the ventricles (19). This leads to a fast and irregular rhythm of the heart. Individuals who have AF usually have a heart rate between 100-175 beats/min whereas the average heart rate is 60-100 beats/min (19). Some of the common symptoms of AF are palpitations, fatigue, shortness of breath, and chest pain (19). There are three types of AF that an individual can develop: paroxysmal, persistent, and longstanding persistent AF (20). People with asymptomatic and paroxysmal AF may not require treatment and their heart rhythm may go back to normal (20). However, individuals with long-term symptoms may need treatment to control their heart rate and prevent further problems (20).

AF is usually treated with anticoagulants, anti-arrhythmic drugs, or rate controllers. For example, warfarin and direct oral anticoagulants are common anticoagulants for individuals with AF who are at risk for stroke (20). Metoprolol and atenolol (common beta blockers) and diltiazem and verapamil (common calcium blockers) are used to control heart rate. Medications such as amiodarone and sotalol are also used to control heart rhythm. Sometimes, when an individual develops AF for the first time, electrical procedures such as electrical cardioversion or catheter ablation is used to restore an individual's heart rhythm (20, 25). The presence and type of AF is usually determined by an electrocardiogram (EKG) with results confirmed by a cardiologist. An EKG shows the rate and rhythm of an individual's heart by recording the heart rate for a few seconds (19, 20, 21).

In the U.S., AF is a common chronic arrhythmia with around 2.3 million adults having the condition. By 2020, this number is expected to increase to 5.6 million and by 2050, it will increase to 5.6 million (4). The mean age of people with AF is 75 years old with 70% of the patient population being 65-85 years old. Though AF is uncommon before 60 years of age, the prevalence doubles with each decade. By age 80, 10% of the population has AF (4, 14). However, the magnitude of people with AF may be underestimated due to how often the condition goes undetected (4, 22). AF is more common among men than women and among whites than blacks (4, 37).

Several studies have consistently shown that African Americans have a lower prevalence and incidence of AF compared to whites. For example, in the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, the prevalence of AF was 32% lower among African Americans compared to whites (14, 23). Additionally, the Cardiovascular Health Study showed the incidence of AF was 53% lower among African-American compared to whites (23, 24). In another study, the 5-year AF incidence was significantly lower among blacks than non-blacks.; 6.1% of blacks developed AF whereas around 8.3% of non-blacks developed AF ($p=0.03$). Additionally, blacks had a 37% lower risk of developing AF compared to non-blacks (25). At last, looking at the cumulative risk of AF at age 80, white men had 21% cumulative risk and white women had 17% cumulative risk while African-American men and women had an 11% cumulative risk of AF (23). Thus, though risk factors for AF are more prevalent among African Americans, whites tended to have a higher incidence of AF regardless of sex and age.

Studies have also shown a higher prevalence of AF among men than women. For example in the ATRIA study, the prevalence of AF among men aged 85 or older was 11.0% whereas among women it was 9.0% ($p<0.001$) (14). In the Framingham Heart Study, men had a

1.5 times higher risk of developing AF than women during a 38 year follow up period after adjusting for other risk factors such as age (4, 26). Other studies, however, have found that after a certain age group (after age 75), the absolute number of women and men with AF is the same (27). This is because the incidence of AF greatly increases with age and because there are more women older than age 75, the absolute number remains the same (27).

Burden of Atrial Fibrillation

As previously mentioned, several studies have suggested that the prevalence and incidence of AF will continue to rise in the upcoming years. With this increase, the burden of AF will also rise. Currently, the U.S. spends between $2.1-$6 billion annually on AF related care and treatment (2, 4, 24). This will continue to increase with an aging population and increases in comorbidities such as hypertension, diabetes, heart failure, chronic kidney disease, and obesity (28, 36). AF has also contributed greatly to an increase in hospitalizations and treatment costs. For example, using the Nationwide Inpatient Sample, a study found that AF hospitalizations increased by 23% from 2000 to 2010. The average cost of AF hospitalization also increased from $6410 to $8439 by 2010 ($p<0.001$) (29). Thus, AF has a great negative impact on U.S. health care systems.

This increase in the number of individuals with AF will also impact the burden of stroke, heart failure, and other cardiovascular problems in the population. For example, the prevalence of stroke is 30% among AF patients between 80-89 years old (12). Additionally, in a different study, it was found that AF accounts for more than 15% of strokes in the U.S. This number increases to 36% among individuals greater than age 80 (30). Furthermore, AF accounts for 20% of cryptogenic (i.e. of unknown etiology) strokes and around 100,000-125,000 embolic strokes annually, with more than 20% of strokes being fatal (30). It was also found that patients who had

ischemic stroke and AF were more likely "to be chronically disabled, bedridden, and [required] constant nursing care" (30). Thus, AF has a substantial negative impact on the quality and quantity of life of individuals.

AF can also lead to congestive heart failure and vice versa. In one study, three cardiologists assessed cases of heart failure through clinical assessment, electrocardiography, chest radiography, and echocardiography and found that 5% of the cases were due to AF alone (31). In several other studies, AF and CHF often co-exist. For example, in a contemporary heart failure cohort, when looking at the severity of their disease, AF occurs in 10% of patients in functional heart failure class I or II or in 50% of patients with heart failure class IV (32). Additionally, 25-30% of patients who had developed heart failure also developed AF concurrently (32). In the Studies Of Ventricular Dysfunction (SOLVD) prevention and treatment trial, it was found that AF was an independent predictor of adverse outcomes, including increased mortality, in patients with heart failure (32). In the Framingham study, 21% of the patients developed Atrial Fibrillation (AF) and heart failure (HF) at the same time whereas 38% of the patients developed AF first. One possibility to how AF can lead to heart failure is the effect it has on an individual's cardiac output. Patients with AF have a loss of atrial systole which impairs LV filling and decreases cardiac output by 25% (33). Thus, AF plays a crucial role in the development and persistency of heart failure.

Overall, AF contributes to a variety of heart problems making it a big public health burden. Thus, understanding the risk of AF and its prevention will be very beneficial in preventing stroke, heart failure, and reducing the burden of the illness.

Hypertension and Atrial Fibrillation

Common risk factors for AF are obesity, diabetes, smoking status, heavy drinking, prior cardiac disease, and hypertension (4,10). Amongst the risk factors listed, hypertension has the largest population attributable fraction for AF incidence and plays a major role in the management and prognosis of AF (1, 2, 10). Hypertension is also very common among individuals with AF. Often times both AF and hypertension co-exist. For example, a study conducted in Germany found that hypertension was the most common co-existing condition among AF patients, with 69% percent of patients having hypertension (8). In other studies, up to 90% of patients with AF are hypertensive (2). Additionally, there is some evidence that even prehypertension can increase the risk of AF. For example, in one study systolic blood pressure (SBP) greater than 140 mmHg and between 128-138 mmHg, both led to incident AF (1). However, in other studies there was a lower risk of AF among patients with SBP less than 130 mmHg and SBP between 131-141 mmHg compared to SBP greater than 141 mmHg (1). Thus, the dose-response relationship of blood pressure and AF risk is relatively uncertain (1).

Individuals with hypertension also have a 1.8-fold higher risk of developing AF and have 1.5-fold increased risk of AF becoming permanent. Hypertension is also related to other co-morbidities such as coronary artery disease, heart failure, metabolic syndrome, chronic kidney disease, and sleep apnea which also increase the risk of AF (2). Additionally, one in six cases of AF is due to hypertension (1). Hypertension also tends to increase the likelihood of stroke or ischemic events among AF patients. For example, in one study of 364 AF patients, hypertension was a major risk factor for ischemic events, with an OR of 7.1 (2).

Consequences of hypertension such as left ventricular hypertrophy (LVH), kidney dysfunction, and cardiovascular disorders are also risk factors for the onset of AF (1). For example, there is substantial evidence that hypertension leads to LV hypertrophy and arterial

stiffening (1, 34). In hypertensive patients, LV hypertrophy and arterial stiffness are associated with a higher incidence of AF (1, 34). The Cardiovascular Health Study has found that individuals with LV hypertrophy confirmed by electrocardiography had a 50% increase risk of developing AF and individuals with LV hypertrophy confirmed by echocardiography had a 39% increase risk of developing AF (1, 34). In the Framingham Heart study, arterial stiffness and endothelial function were associated with an increased risk of AF independently of other risk factors (1, 35). Though LV hypertrophy is associated with a higher incidence of AF, rapid ventricular conduction in AF can lead to LV dysfunction, or in some instances, cardiomyopathy. Hypertension also results in cardiac structural changes such as atrial remodeling that increases the development of AF (2). Through various studies, it has been established that hypertension is a causal factor between increased left atrial size and AF (2). For example, in a longitudinal Framingham study, patients with higher systolic blood pressure and antihypertensive treatment had larger atrial size and greater left atrial enlargement during adulthood. This leads to a higher pulsatile load and promotes dilatation and eventually leads to AF due to a greater tissue area being susceptible to reentry (2). The renin angiotensin aldosterone system (RAAS) also plays a role in hypertension and AF. The RAAS is key in the regulation of blood pressure. Many hypertensive patients have high levels of angiotensin II (part of RAAS). Angiotensin II promotes AF through effecting cardiac ion channel and proinflammatory mechanisms (2). Aldosterone (also part of RAAS) also plays an important role in developing AF through changing the myocardium and cardiac interstitial milieu (2). Thus, hypertension has a big impact on the pathogenesis, management, and prognosis of atrial fibrillation. Early detection and management of hypertension is thus very important to prevent and manage AF (2).

JNC7 and JNC8 Guidelines

Over the years, several guidelines have been released related to the diagnosis and control of hypertension in the population. The guideline prior to the recent 2017 guideline released by the American College of Cardiology (ACC) and American Heart Association (AHA) was the 2014 Joint National Committee's eight (JNC8) report (3, 18, 40). This report came after the 2003 Joint National Committee's seventh (JNC7) report and focused on developing recommendations based on systematic reviews of clinical trials. The diagnostic criteria for hypertension remained the same as JNC7, however, JNC8 updated recommendations and changed targets for treatment (3, 18, 40). Initially, the JNC8 aimed to create an updated guideline for hypertension in conjunction with the National Institute of Health (NIH). However, the NIH eventually withdrew from the guideline development process and the JNC8 panel published the recommendations on their own (3, 18).

There were 9 recommendations as part of the JNC8 report for hypertension. Recommendations one through four were based on various randomized controlled trails (RCTs) whereas recommendations five through nine were based on expert opinions (3). The first JNC8 recommendation was to lower the systolic blood pressure (SBP) and diastolic blood pressure (DBP) goals to a SBP<150 mmHg and DBP<90 mmHg among individuals older than 60 years old (3). The second to fifth recommendations focused on treatment of hypertension in younger individuals. For all individuals less than 60 years old and greater 18 years old or individuals with diabetes or CKD, the blood pressure goal recommended was SBP<140 mmHg and DBP<90 mmHg (3). This recommendation was based on several studies such as the Hypertension Optimal Treatment (HOT) trial. The trial randomized 18790 patients with hypertension (between 50 to 80 years) into three target groups: DBP ≤90, ≤85, or ≤80 mm Hg and found that the rate of myocardial infarction (MI), cardiovascular events especially among diabetic patients, and

cardiovascular mortality was reduced among individuals in the lowest blood pressure target group (3). The sixth to ninth recommendations focused on race and treatment. In the general population, first-line treatments used to control hypertension should be either a thiazide-type diuretic, CCB, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blockers (ARB) (3). In the black population, treatment for hypertension should include thiazide-type diuretic or CCB. Individuals older than age 18 and with CKD, treatment for hypertension should include ACEI or ARB (3). Again, these recommendations were based on several RCTs examining blood pressure effects of various treatments (3).

Overall, the JNC8 was a major improvement in providing evidence-based recommendations for hypertension treatment and management compared to previous guidelines such as JNC7. However, improvements can still be made (3). The JNC8 guidelines focused on only RCTs. Having various other studies such as high-quality observational studies may be useful in creating more effective recommendations (3). Additionally, having a more lenient blood pressure target for individuals greater than 60 years old may lead to reappearance of strokes. Thus, more research is needed to understand the interplay between hypertensive risk and treatments, and would be useful to use atherosclerotic cardiovascular disease (ASCVD) risk-cut offs to understand the risk (3).

The 2017 ACC/AHA Guideline

The new guideline published by ACC/AHA at the end of 2017 attempted to be more comprehensive. These new guidelines were developed and written by nine health professional organizations and 21 experts, respectively (39). Four systematic reviews were conducted to address 4 themes (39):

1. "self-directed and/or ambulatory blood pressure monitoring compared with office-based blood pressure measurement to prevent adverse outcomes and achieve better blood pressure control" (39)
2. "the optimal target for blood pressure lowering during antihypertensive therapy" (39)
3. "whether various antihypertensive drug classes differ in their comparative benefits" (39)
4. "whether initiating treatment with 1 antihypertensive drug is more or less beneficial than starting with 2 drugs" (39)

The ACC/AHA writing committee used the Task Force on Clinical Practice Guidelines to make 106 recommendations. Each recommendation was described with the strength (class) of the recommendation and quality (level) of evidence (39). The main recommendation that has been changed are the classifications for hypertension. Normal blood pressure remains the same as JNC7, however, the new guidelines replaced "prehypertension" with "elevated blood pressure" and "stage 1 hypertension". Elevated blood pressure is defined as a SBP of 120-129 mmHg and a DBP of less than 80 mmHg. Stage 1 hypertension is considered a SBP of 130-139 mm Hg or a DBP of 80-89 mm Hg. Stage 2 remains the same as hypertension with a SBP of 140 mmHg or higher or a DBP of 90 mmHg or higher (39). Prehypertension was reclassified to stage 1 because of studies showing double the risk of CVD compared to individuals with normal hypertension (39).

Currently, optimal thresholds for blood pressure in relation to incident AF remains uncertain. Additionally, it is unclear whether individuals labeled as hypertensive with the 2017 AHA/ACC guidelines are at a similarly increased risk of AF and whether the new guidelines will be beneficial in preventing the onset of AF. Thus, the goal of this study is to understand the association between hypertension and risk of AF using the diagnostic categories from the 2017

ACC/AHA guidelines, and to evaluate the population attributable fraction under these guidelines. We used the JNC7 guidelines to make the comparison, because the diagnostic criteria for hypertension remained the same in JNC8 (only recommendations and targets treatments changed). Results from the study will help inform the ideal blood pressure range for people with hypertension and risk of AF. Additionally, the study will help to estimate the potential impact of hypertension prevention under the new guidelines.

Chapter 2: Thesis Manuscript
Introduction

Atrial Fibrillation (AF) is a common chronic arrhythmia, occurring in 2.3 million adults in the United States. Most of the population that develop AF are over the age of 65 with higher rates among men than women and among whites than blacks (4). It is projected that by the year 2050, the prevalence of AF will increase by 2.5-fold because of a growing elderly population (13, 14). This increase in the number of individuals with AF will also impact the burden of stroke, heart failure, and other cardiovascular problems in the population. Common risk factors for AF are obesity, diabetes, smoking, heavy drinking and hypertension. Amongst the risk factors listed, hypertension has the largest population attributable fraction for AF incidence and plays a major role in the management and prognosis of AF (1, 2, 10). Hypertension is very common among individuals with AF, with studies showing prevalence of 69 to 90% of hypertension among AF patients (2, 8, 9). Individuals with hypertension have a 1.7-fold higher risk of developing AF. One in six cases of AF is possibly due to hypertension (1). Thus, early detection and management of hypertension is very important to prevent and manage AF.

Previous guidelines released by the 7th Joint National Committee (JNC7) defined hypertension as a systolic blood pressure (SBP) ≥140 or diastolic blood pressure (DBP) ≥90 mmHg regardless of age. Blood pressure was divided into the following ranges: Normal= <120/80, Prehypertension=120-139/80-89, Stage 1 hypertension= 140-159/90-99, Stage 2 hypertension= ≥160/100 (18, 40). However, the American Heart Association/American College of Cardiology released new guidelines at the end of 2017 lowering the threshold to define elevated blood pressure and thus impacting the number of individuals diagnosed with hypertension. The new recommended blood pressure range is divided into the following categories: Normal <120 and <80, Prehypertension 120-129 and <80, Stage 1 hypertension 130-

139 or 80-89, Stage 2 hypertension ≥140 or ≥90 (6, 39). This change means more individuals will be diagnosed with hypertension. However, it is uncertain whether individuals labeled as being hypertensive with the new guidelines are at similarly increased risk of AF.

The goal of this study is to understand the association between hypertension and risk of AF using the diagnostic categories in the new guidelines, and evaluate the population attributable fraction of hypertension with the new definitions. Results from these analyses will contribute to inform the ideal blood pressure range for people with hypertension and risk of AF. Additionally, the study will help us estimate the potential population impact of preventing hypertension under the new guidelines.

Methods

Study Population

Our data came from Atherosclerosis Risk in Communities (ARIC) dataset. The Atherosclerosis Risk in Communities (ARIC) cohort aims to investigate the epidemiology of atherosclerosis, clinical atherosclerotic diseases, and variation in cardiovascular risk factors, treatment and disease. The cohort study began in 1987, recruiting participants from four U.S. communities: Washington County in Maryland, Forsyth County in North Carolina, Jackson in Mississippi, and the northwest suburbs of Minneapolis in Minnesota. There were approximately 4,000 participants selected from each community through probability sampling. A total of 15,792 participants aged 45-64 (7,082 were men and 11,526 were white) were enrolled. Each participant was examined extensively in terms of clinical, social, and demographic data with the baseline data gathered in 1987-89. Participants have had periodic reevaluations since (1990-92, 1993-95, 1996-98, 2011-2013, and 2016-2017). The participants were also followed-up annually (biannually since 2012) by telephone to stay in contact, ascertain cardiovascular events, and to measure the health status of the cohort. During the follow-up, a questionnaire collected information on general health, hospitalization and the occurrence of cardiovascular diseases was administered. More information about the design and objectives of the study can be found on the ARIC website as well as in published articles (11).

For the present analysis, we included ARIC participants who had baseline blood pressure readings at visit 1 (1987-89). We excluded participants who had AF at baseline or missing ECG (N=346), individuals of a race other than white or black, as well as non-whites from the Minneapolis and Washington County Centers (N=103), an eGFR value of less than 60 ml/min/1.73 m^2 (N=73), and participants who had prevalent diabetes, coronary heart disease, stroke or heart failure (N=6028). We also excluded participants who had missing values for the

outcome, exposure, or covariates (N=35). After excluding participants who did not meet our study criteria, our final sample size was 9207 participants (flow chart for final sample size is indicated in figure 1).

Assessment of blood pressure

Sitting systolic and diastolic blood pressure was taken 3 times at baseline after a 5-minute rest. A random zero sphygmomanometer was used to take these measurements. The second and third measurements were averaged and used in the analysis. Those that used blood pressure lowering medications were categorized as hypertensive under the JNC7 guidelines and stage 2 hypertensive under the 2017 AHA/ACC guidelines. (1, 11, 15, 41)

Assessment of Incident AF

We used three methods to identify cases of AF in the ARIC cohort: ECG performed at study visits, hospital discharge codes, and death certificates. The ECG studies were performed with a 12-lead ECG during study exams. The data obtained was transmitted electronically to the ECG reading center at EPICARE in North Carolina (Wake Forest School of Medicine, Winston-Salem). The data was processed using the GE Marquette 12-SL program. The incidence of AF by using an ECG was identified by a computer algorithm and then confirmed by a cardiologist. A cardiologist also read over ECGs with any other rhythm abnormalities to reduce the possibility of any missed AF incidents. Hospitalizations during the study period were identified with follow-up phone calls and monitoring local hospitals. Information such as discharge codes were collected from these hospitals by abstractors. If a patient had discharge codes ICD-9-CM codes 427.31 or 427.32 (ICD-10-CM code I48.x after October 1, 2015), then they were considered to have AF. Cases where a patient had open heart surgery in association with AF were excluded.

Finally, if a patient had codes such as ICD-9 427.3 or ICD-10 I48 in their death certificates, then the patient was considered to have AF (16).

Assessment of covariates

The covariates used in our study were: sex, race, education, study center, height, body mass index (BMI), smoking status, and alcohol usage. Most of data for these covariates were obtained by a questionnaire administered to the participants. For our study, sex was categorized as male or female, race was categorized as White, Black, Asian, or American Indian, and education level was categorized as grade school, high school but no degree, high school graduate, vocational school, college or graduate/professional school. Smoking status was self-reported with categories defined as never, current, and former smoker. Alcohol usage was also self-reported with categories defined as never, current and former drinker. BMI was defined as measured weight (kg)/height $(m)^2$ (1, 11, 17).

Statistical Analysis

Analysis was conducted using SAS 9.4 statistical software. Cox proportional models were used to estimate the hazard ratios and 95% confidence interval of AF incidence among individuals with hypertension based on the JNC7 and 2017 AHA/ACC guidelines. For our independent variable, both the new and old hypertensive guidelines were divided into categories established by JNC7 and 2017 AHA/ACC, as indicated in Table 1. Participants using antihypertensive medication were labeled as stage 2 regardless of their visit blood pressure. Two separate analysis were conducted to fully understand the impact of changing the hypertension guidelines. The first analysis looked at hypertension classified into more specific categories in both the JNC7 and 2017 AHA/ACC guidelines. The reference was a normal hypertension value in both guidelines. The hazard ratios from this analysis compared the risk of AF among

individuals with prehypertension, hypertension, stage 1, or stage 2 each to normal. The second analysis looked at hypertension as a binary variable. For the JNC7 guideline, prehypertension and normal were combined in the reference group. For the 2017 AHA/ACC guideline, elevated and normal blood pressure were combined as the reference group whereas stage 1 and stage 2 were combined to define hypertension. The hazard ratios from this analysis compared the risk of AF among individuals with hypertension to those without hypertension. A stratified analyses by sex and race was also performed to explore effect modification. Covariate adjustment was done through two separate models. Model 1 adjusted for age, sex and race, while model 2 additionally adjusted for education, study center, height, BMI, smoking status, and alcohol use.

We also calculated the population-attributable fractions (PAFs) to determine the possible impact of preventing hypertension on AF occurrence. PAFs were computed according to the following formula (10): $PAF=pd_i[(RR_i-1)/RR_i]$, where pd_i is the proportion of cases falling into *i*th exposure level and RR_i is the relative risk (RR) comparing *i*th exposure level with unexposed group (i=0). Poisson models were used to obtain RRs. The offset in the Poisson model was calculated at the time from visit 1 to AF incidence, death or lost to follow up until December 31, 2015 whichever event came first (10).

Results

Basic Demographic Characteristics of participants in ARIC study

After applying exclusion criteria, there were 9207 adults in our final sample. The mean age at baseline was 53.7 years old (SD=5.1). The percentage of whites was 76% (n=6999). The percentage of women were 56% (n=5183). Most individuals in the sample had an intermediate or advanced education with 42% of individuals having an intermediate education (n=3862) and 38.3% of individuals having an advanced education (n=3524). Based on the JNC7 guidelines, 46.4% individuals had normal BP (n=4273), 25.1% of individuals were prehypertensive (n=2315) and 28.5% of individuals were hypertensive (n=2619). The overall mean (SD) systolic blood pressure (SBP) was 119.8 (18.3) with the SBP being 106.2 (8.3), 126.1 (6.4), and 136.6 (20.1) in the normal, prehypertensive, and hypertension groups respectively. The overall mean (SD) diastolic blood pressure (DBP) was 73.2 (18.3) with the DBP being 66.4 (7.1), 76.2 (7.5), and 81.6 (11.8) and in the normal, prehypertensive and hypertension groups respectively.

Based on the 2017 ACC/AHA guidelines, 46.4% individuals had normal BP (n=4273), 10.7% of individuals had elevated BP (n=986), 14.4% of individuals were stage 1 hypertensive (n=1329), and 28.5% of individuals were stage 2 hypertensive (n=2619). Mean SBP (SD) was 106.2 (8.3), 123.9 (2.8), 127.8 (7.8) and 136.6 (20.1) in the normal, elevated, stage 1 and stage 2 hypertension groups respectively. Mean (SD) DBP was 66.4 (7.1), 71.5 (6.2), 80.0 (6.2), and 81.6 (11.8) in the normal, elevated, stage 1, stage 2 hypertension groups respectively. The percentage of individuals taking hypertension medication in the cohort was 18.8% (n=1732) (Table 2 and 3).

Association of hypertension (dichotomous) with AF using JNC 7 and 2017 ACC/AHA definitions

During follow-up, we identified 1573 cases of incident AF overall. The hazard ratio of AF comparing hypertension vs no hypertension using the JNC7 definition was 1.6, 95% CI [1.49, 1.83] after adjusting for age, sex and race. The incidence rate of AF per 1000 person-years were 6.6 and 10.8 for no hypertension and hypertension respectively. In terms of the 2017 AHA/ACC guidelines, the corresponding hazard ratio was 1.5, 95% CI [1.37, 1.68] after adjusting for age, sex and race. The incidence rates for AF per 1000 person-years were 6.4 and 9.6 for no hypertension and hypertension respectively (Table 5).

Hazard ratios were also stratified by sex and race. For both sex and race, the hazard ratios were quite similar in both JNC7 and 2017 AHA/ACC guidelines. Interaction was only significant for sex in the 2017 AHA/ACC guidelines (p=0.02) (Table 6).

Association of BP with AF using JNC 7 and 2017 ACC/AHA guideline categories

In terms of the JNC7 guidelines, the hazard ratio of AF for prehypertension and hypertension, compared to normal blood pressure, was 1.3, 95% CI [1.11 1.43] and 1.8, 95% CI [1.61, 2.05] respectively after adjusting for age, sex and race. The AF incidence rates per 1000 person-years was 5.9, 8.0, and 10.8 for normal blood pressure, prehypertension, and hypertension respectively. In terms of the 2017 AHA/ACC guidelines, the hazard ratios for elevated, stage 1 and stage 2, compared to normal blood pressure, were: 1.3, 95% [2.08, 1.51], 1.2, 95% [1.07, 1.46], 1.8, 95% [1.61, 2.05] respectively after adjusting for age, sex, and race. The incidence rates for AF per 1000 person-years were 5.9, 9.2, 7.6, and 10.8 for normal, elevated, stage 1, and stage 2, respectively (Table 4).

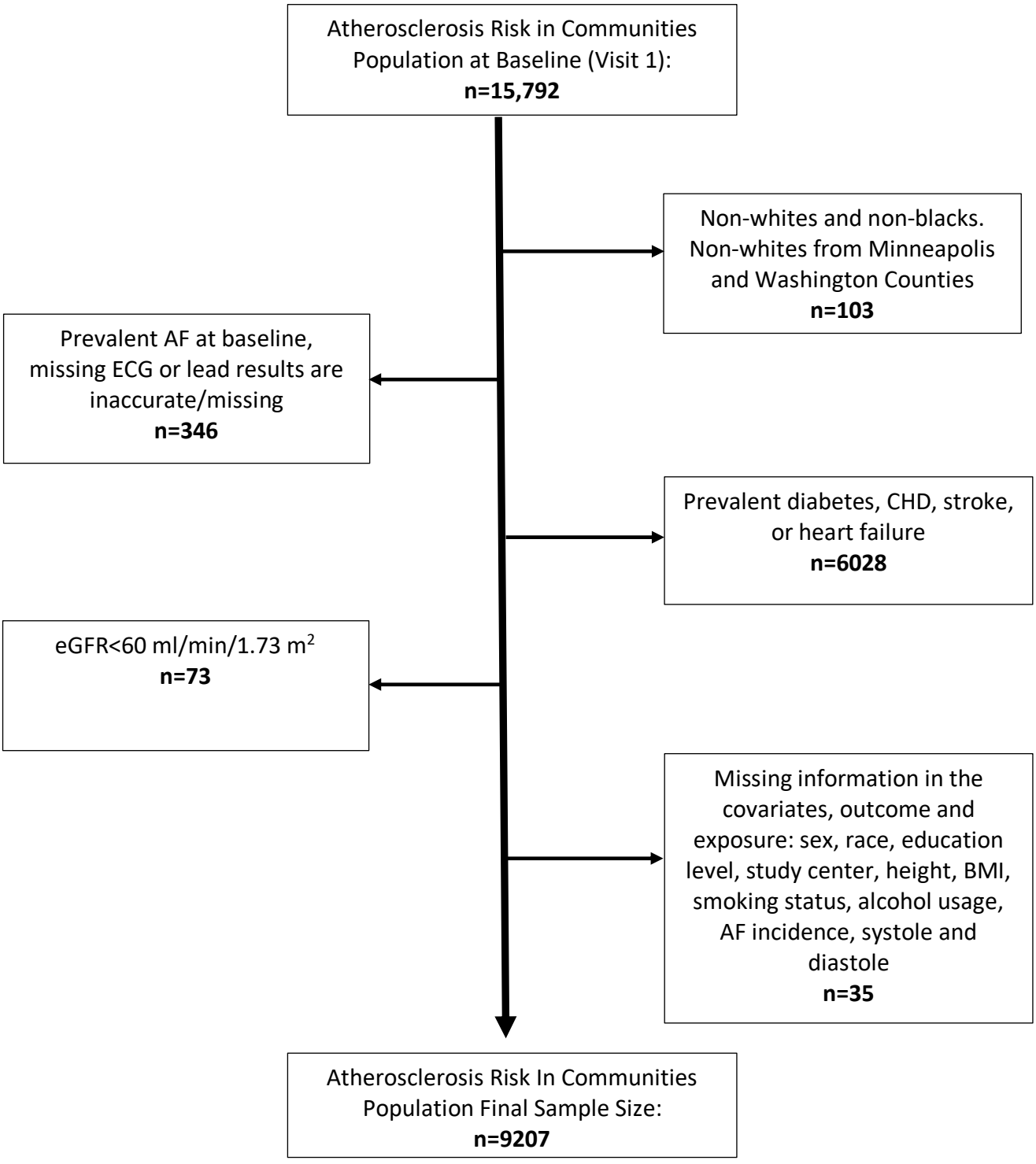
Population Attributable Factor (PAF) of the JNC7 and 2017 AHA/ACC guidelines

Using the JNC 7 guidelines, the prevalence of normal BP, prehypertension, and hypertension were 46.4%, 25.1%, and 28.5% respectively. The PAF was 3% (95% CI [0.00,

0.06]) and 11% (95% CI [0.07, 0.14]) for prehypertension and hypertension, respectively. In contrast, using categories defined in the 2017 ACC/AHA guidelines, the prevalence of normal, elevated, stage 1 and stage 2 hypertension was 46.4%, 10.7%, 14.4% and 28.5% respectively. The PAF was 2% (95% CI [0.00, 0.03]), 1% (95% CI [-0.01, 0.03]), and 11% (95% CI [0.07, 0.14]) respectively. When the data was recategorized into binary variables, the prevalence of hypertension was 28.5% using the JNC 7 definition and 42.9% with the 2017 ACC/AHA definition. The PAF was 12% (95% CI [0.09, 0.14]) and 14% (95% CI [0.10, 0.18]) under the old and new guidelines respectively (Table 7 and 8).

Figures and Tables

Figure 1: Flow Chart for the Final Sample Size in ARIC population visit 1



*adapted from various ARIC studies

Table 1: Categories established by JNC8 and AHCC

JNC 7		2017 ACC/AHA	
Normal	<120 and <80	Normal	<120 and <80
Prehypertensive	120-139 or 80-90	Elevated	120-129 and <80
Hypertensive	≥140 or ≥90	Stage 1	130-139 or 80-89
		Stage 2	≥140 or ≥90

Table 2: Demographic Characteristics of participants in the ARIC study based on the JNC 7 categories

	Normal	Prehypertension	Hypertension	Total
N (%)	4273 (46.4)	2315 (25.1)	2619 (28.5)	9207 (100)
Age, mean in yrs (SD)	52.5 (5.5)	54.3 (5.7)	55.0 (5.6)	53.7 (5.1)
White, n (%)	3709 (86.8)	1731 (74.8)	1559 (59.5)	6999 (76.0)
Women, n (%)	2532 (59.3)	1180 (51.0)	1471 (56.2)	5183 (56.3)
Education Level, n (%)				
No education or Basic education	608 (14.2)	471 (20.4)	742 (28.3)	1821 (19.8)
Intermediate Education	1815 (42.5)	977 (42.2)	1070 (40.9)	3862 (42.0)
Advanced Education	1850 (43.3)	867 (37.5)	807 (30.8)	3524 (38.3)
Smokers, n (%)				
Current	1204 (28.2)	536 (23.2)	682 (26.0)	2422 (26.3)
Former	1315 (30.8)	789 (34.1)	799 (30.5)	2903 (31.5)
Never	1754 (41.1)	990 (42.8)	1138 (43.5)	3882 (42.2)
Drinkers, n (%)				
Current	2728 (63.8)	1356 (58.6)	1392 (53.3)	5476 (59.5)
Former	705 (16.5)	377 (16.3)	484 (18.5)	1566 (17.0)
Never	840 (19.7)	582 (25.1)	743 (28.4)	2165 (23.5)
BMI (kg/m2), mean (SD)	25.8 (4.2)	27.6 (5.2)	28.7 (5.8)	27.1 (5.1)
Height (cm), mean (SD)	168.5 (9.3)	169.1 (9.5)	168.2 (9.3)	168.6 (9.3)
SBP, mean (SD)	106.2 (8.3)	126.1 (6.4)	136.6 (20.1)	119.8 (18.3)
DBP, mean (SD)	66.4 (7.1)	76.4 (7.5)	81.6 (11.8)	73.2 (11.0)
Hypertension medication, n (%)	0	0	1732 (66.2)	1732 (18.8)

Table 3: Demographic Characteristics of participants in the ARIC study based on the 2017 ACC/AHA Guideline Categories

	Normal	Elevated	Stage 1	Stage 2	Total
N (%)	4273 (46.4)	986 (10.7)	1329 (14.4)	2619 (28.5)	9207 (100)
Age, mean in yrs (SD)	52.5 (5.5)	55.2 (5.7)	53.6 (5.7)	55.0 (5.6)	53.7 (5.7)
Whites, n (%)	3709 (86.8)	797 (80.8)	934 (70.3)	1559 (59.5)	6999 (76.0)
Women, n (%)	2532 (59.3)	529 (53.7)	651 (49.0)	1417 (56.2)	5183 (56.3)
Education Level, n (%)					
No education or Basic education	608 (14.2)	202 (20.5)	269 (20.2)	742 (28.3)	1821 (19.8)
Intermediate Education	1815 (42.5)	416 (42.2)	561 (42.2)	1070 (40.9)	3862 (42.0)
Advanced Education	1850 (43.3)	368 (37.3)	499 (37.6)	807 (30.8)	3524 (38.3)
Smokers, n (%)					
Current	1204 (28.2)	250 (25.4)	286 (21.5)	682 (26.0)	2422 (26.3)
Former	1315 (30.8)	330 (33.5)	459 (34.5)	799 (30.5)	2903 (31.5)
Never	1754 (41.2)	406 (41.2)	584 (43.9)	1138 (43.5)	3882 (42.2)
Drinkers, n (%)					
Current	2728 (63.8)	584 (59.2)	772 (58.1)	1392 (53.2)	5476 (59.5)
Former	705 (16.5)	161 (16.3)	216 (16.3)	484 (18.5)	1566 (17.0)
Never	840 (19.7)	241 (24.4)	341 (25.7)	743 (28.4)	2165 (23.5)
BMI (kg/m2), mean (SD)	25.8 (4.2)	27.2 (4.8)	27.9 (5.3)	28.7 (5.8)	27.1 (5.1)
Height (cm), mean (SD)	168.5 (9.3)	168.5 (9.5)	169.6 (9.4)	168.2 (9.3)	168.6 (9.3)
SBP	106.2 (8.3)	123.9 (2.8)	127.8 (7.8)	136.6 (20.1)	119.8 (18.3)
DBP	66.4 (7.1)	71.5 (6.2)	80.0 (6.2)	81.6 (11.8)	73.2 (11.0)
Hypertension medication	0	0	0	1732 (66.2)	1732 (18.8)

Table 4: Hazard Radios (95% confidence intervals) of atrial fibrillation by categories of blood pressure according to JNC 7 and 2017 ACC/AHA definitions, ARIC 1987-2016

JNC 7	**Normal**	**Prehypertension**		**Hypertension**
N. of AF cases	584	408		581
Person-years	98994	50748		53910
Incidence rate (per 1000 py)	5.9	8.0		10.8
HR (95%CI)1	1 (ref.)	1.26 (1.11, 1.43)		1.82 (1.61, 2.05)
HR (95%CI)2	1 (ref.)	1.23 (1.08, 1.40)		1.69 (1.50, 1.92)
2017 ACC/AHA	**Normal**	**Elevated**	**Stage 1**	**Stage 2**
N. of AF cases	584	186	222	581
Person-years	98994	20280	29372	53910
Incidence rate (per 1000 py)	5.9	9.2	7.6	10.8
HR (95%CI)1	1 (ref.)	1.3 (2.08, 1.51)	1.2 (1.07, 1.46)	1.8 (1.61, 2.05)
HR (95%CI)2	1 (ref.)	1.2 (1.04, 1.45)	1.3 (1.06, 1.45)	1.7 (1.50, 1.92)

1. Age, sex, race adjusted.

2. Age, sex, race, height, education, field center, BMI, smoking, drinking adjusted

Table 5: Hazard Radios (95% Confidence intervals) of atrial fibrillation according to hypertension defined according to JNC 7 and 2017 ACC/AHA guidelines, ARIC 1987-2016

JNC 7	**No HTN**	**HTN**
N. of AF cases	992	581
Person-years	149742	53910
Incidence rate (per 1000 py)	6.6	10.8
HR (95%CI)1	1 (ref.)	1.651 (1.49, 1.83)
HR (95%CI)2	1 (ref.)	1.544 (1.39, 1.72)
2017 ACC/AHA	**No HTN**	**HTN**
N. of AF cases	770	803
Person-years	120370	83283
Incidence rate (per 1000 py)	6.4	9.6
HR (95%CI)1	1 (ref.)	1.5 (1.37, 1.68)
HR (95%CI)2	1 (ref.)	1.5 (1.31, 1.61)

1. Age, sex, race adjusted.

2. Age, sex, race, height, education, field center BMI, smoking, drinking adjusted

Table 6: Hazard ratios (95% confidence intervals) of atrial fibrillation by hypertension definitions stratified by race and sex, ARIC 1987-2016

JNC 7	**HTN**
Women	1.6 (1.40, 1.91)
Men	1.5 (1.26, 1.72)
p-value for interaction	0.48
Whites	1.5 (1.32, 1.69)
Blacks	1.8 (1.40, 2.34)
p-value for interaction	0.20
2017 ACC/AHA	**HTN**
Women	1.7 (1.44, 1.96)
Men	1.3 (1.10, 1.47)
p-value for interaction	0.02
Whites	1.5 (1.30, 1.63)
Blacks	1.5 (1.11, 1.99)
Interaction	0.96

1.Age, sex, race, height, education, field center BMI, smoking, drinking adjusted

Table 7: Rate Ratios and Population Attributable Factor of atrial fibrillation by BP categories according to JNC 7 and 2017 ACC/AHA guidelines, ARIC 1987-2016

JNC 7	**Normal**	**Prehypertension**		**Hypertension**
Prevalence, n (%)	46.4	25.1		28.5
RR (95%CI)	1 (ref.)	1.13 (0.99,1.28)		1.40 (1.24, 1.59)
PAF % (95%CI)		3 (0.00, 0.06)		11 (0.07, 0.14)
2017 ACC/AHA	**Normal**	**Elevated**	**Stage 1**	**Stage 2**
Prevalence, %	46.4	10.7	14.4	28.5
RR (95%CI)	1 (ref.)	1.16 (0.98, 1.37)	1.10 (0.94,1.29)	1.40 (1.06, 1.24)
PAF % (95%CI)		2 (0.00, 0.03)	1 (-0.01, 0.03)	11 (0.07, 0.14)

1.Age, sex, race, height, education, field center BMI, smoking, drinking adjusted

Table 8: Rate Ratios and Population Attributable Factor of atrial fibrillation by hypertension definition according to JNC 7 and 2017 ACC/AHA guidelines, ARIC 1986-2016

JNC 7	**No HTN**	**HTN**
Prevalence, n (%)	71.6	28.5
RR (95%CI)	1 (ref.)	1.19 (1.12, 1.26)
PAF % (95% CI)		12 (0.09, 0.14)
2017 ACC/AHA	**No HTN**	**HTN**
Prevalence, %	57.1	42.9
RR (95%CI)	1 (ref.)	1.39 (1.02, 1.94)
PAF % (95% CI)		14 (0.10, 0.18)

1. Age, sex, race, height, education, field center BMI, smoking, drinking adjusted

Chapter 3: Discussion/Conclusions

Hypertension is very common among individuals with AF. Often times both AF and hypertension co-exist. For example, various studies have shown that more than 90% of patients with AF also have hypertension (2, 8, 9). Additionally, hypertension has the largest population attributable fraction for AF incidence and plays a major role in the management and prognosis of AF (1, 2, 10). Studies have also shown that once hypertension occurs, an individual is predisposed to developing AF even if the blood pressure improves in later years (1). Thus, understanding the risk of AF in association with hypertension will be crucial in preventing AF, reducing AF incidence rates, and subsequently preventing strokes. Several guidelines have been released over the years to identify individuals with hypertension based on an increased risk of adverse outcomes, and prevent its consequences at optimal levels. The most recent hypertension, guideline, released in the fall of 2017 by the ACC/AHA refined the guidelines released by JNC7 and JNC8 by lowering the threshold to define hypertension. This means more individuals will be diagnosed with hypertension under the new guidelines. The rationale for this change is based on the observed increased risk of cardiovascular disease even among individuals in the old prehypertensive category and the results from the SPRINT trial, showing benefit in the treatment of BP targeting a SBP of <120 mmHg (42). However, the risk of AF among individuals newly diagnosed with hypertension is uncertain. The goal of our study was to understand the association between hypertension and risk of AF using the diagnostic categories in the new guidelines, and evaluate the population attributable fraction of newly defined hypertension. This would help inform the ideal blood pressure range for people with hypertension and risk of AF and help estimate the potential population impact of preventing hypertension under the new guidelines.

Results from the study show a general increase in the number of individuals with hypertension which coincides with other studies that also estimated an increase. However, whereas other studies predicted a 14% increase in the prevalence of hypertension, our study also showed a 14% increase (39). The number of cases of AF with hypertension increased from 28.5 (JNC7 guidelines) to 42.9 (2017 AHA/ACC guidelines), which was estimated in studies. When looking at the table 1 and 2 for demographic characteristics, we see all of the individuals under prehypertension were recategorized into "elevated" and "stage 1" hypertension with "normal" and "hypertension" under the JNC7 guidelines remaining the same as "normal" and "stage 2" hypertension under the 2017 ACC/AHA guidelines. I expected to see an increase in the risk of AF under the 2017 ACC/AHA guidelines, however, this was not the case. In both the new and old guidelines (dichotomous hypertension and BP categories), the hazard ratios and confidence intervals were very similar. The JNC7 and 2017 ACC/AHA guidelines both had significant hazard ratios indicating that both hypertensive guidelines lead to an equal risk of developing AF. Thus, the optimal range for blood pressure in predicting (and potentially preventing) AF remains unclear. An explanation for these results could be that we evaluated the systolic and diastolic blood pressure for both guidelines instead of the pulse pressure. The guidelines do not address pulse pressure; however, studies such as the Framingham Heart Study and Multi-Ethnic Study of Atherosclerosis have shown that pulse pressure plays an important role in determining incident AF (2, 38). The Framingham Heart Study found that for each 20mmHg increase in pulse pressure there was a 24% increase in the risk of AF (2). Thus for this population, analyzing pulse pressure may be more relevant.

In terms of the population attributable fraction (PAF), we see a slightly higher PAF for individuals under the new guidelines. Though the JNC7 and 2017 AHA/ACC guidelines had

similar PAFs in the non-binary data, the PAFs for the binary data was 12% and 14% for the old and new guidelines respectively (10). Based on various studies, I had expected about the same or bigger difference in PAFs. For example, a study conducted with the ARIC population showed that borderline levels (SBP 120 - 139 mmHg or DBP 80 – 89) of risk factors explained an additional 6.5% of AF cases. Additionally, while looking at the PAFs, elevated blood pressure contributed for 21.6% of incident AF and this number increased to 24.5% with borderline levels of blood pressure (10). Having only slightly higher PAF using the 2017 AHA/ACC guidelines means that there is a limited potential impact in preventing hypertension with these new guidelines, however, further research is needed to understand the degree to which these new hypertension guidelines will be beneficial.

There were several results in the study that I found interesting. First, when comparing the incident rates between the JNC7 and 2017 AHA/ACC guidelines, the rates actually decreased from 10.8 (JNC 7) to 9.6 per 1000 person-years (2017 ACC/AHA). Since the study was conducted over 25 years (1987-2015), the total person-years may have out-numbered the new cases of AF resulting to an ultimate decrease in incidence rate. Additionally, incident rates may be underestimated depending on if the cases of AF were truly captured in the study. The results for interaction with sex was also noteworthy. When the JNC7 and 2017 AHA/ACC guidelines were stratified by race and sex, the interaction between sex was statistically significant under the new guidelines, but statistically insignificant under the JNC7 guidelines (0.02 and 0.48 respectively). One explanation for this result could be the increase in the number of young individuals with hypertension. After age 75, the absolute number of women and men with AF is the same (27). However since the new guidelines lower the threshold for hypertension, more

young women and men are included in the hypertensive group thus highlighting this difference. However, this is speculative and requires confirmation.

Strengths and Limitations

There were several strengths in our study. First, we had a large sample size. The study participants were from four geographically diverse communities and the final sample size was 9207 individuals, with a total of 1573 AF events, providing enough events in each category. Additionally, our study had extensive information on other risk factors for AF, allowing us to adjust for potential confounders. However, there were several limitations in our study. First, though we adjusted for some variables we did not account for the other variables in the study such as aspirin and statin medications and ECG p wave terminal force 1 in V1 which may have played an important role in the incident of AF. Secondly, the study did not include different subsets of AF such as paroxysmal, persistent, or permanent AF. Thus, we were unable to see how the new guidelines affected this risk of AF among the subsets; whether certain subsets had a higher incidence than others. At last, some cases of AF may not have been discovered due to how we obtained our AF cases. Our AF cases were ascertained through hospital discharge codes, ECG results, and death certificates. Some cases, however, may not have been classified as AF due to misclassification or AF not being severe enough which would result in an underestimation of the risk of AF. Additionally, we excluded individuals who had missing ECGs which may have also underestimated the risk of AF due to not capturing all individuals with AF.

In conclusion, our study showed a slight increase in PAF values, however, the overall difference in the risk of AF among the JNC7 and the 2017 AHA/ACC were the same. These results indicate that the blood pressure range for the risk of AF may be higher thus, redefining the guidelines would not have much of an impact. Additional studies is needed to see if this is

true. Moreover, further studies should incorporate other variables we had not considered that may influence the risk of AF.

Chapter 4: Implications and Recommendations

Our data provides us with a better understanding of the risk of AF in relationship to hypertension. Understanding this association can inform public health policies and interventions, and would eventually help prevent cardiovascular complications such as heart failure and stroke. Our data shows that when comparing the 2017 ACC/AHA and JNC 7 guidelines, the association of hypertension with AF remains essentially the same. Thus, the blood pressure cutoff to predict the incidence of AF may be higher. Additional research is needed to understand the optimal range of blood pressure in relation to AF. In terms of our PAF results, our analysis shows that the impact of the new definition is limited in terms of population impact. Even though lowering the blood pressure threshold may be beneficial for other endpoints, our results do not support the lower threshold regarding prevention of AF. Furthermore, I would recommend further studies on the risk of AF under the new hypertension guidelines by incorporating other variables such as aspirin and statin medications, ECG p wave terminal force 1 in V1, HF history, MI history, and diabetes history which may have influenced the incidence of AF. I would also look at the subsets of AF to see how the new guidelines affected this risk of AF among the subsets. At last, though no change was found between hypertension and AF, it would be beneficial to see how the new hypertension guidelines affect other health outcomes such as coronary heart disease, heart failure, stroke, and transient ischemic attacks independently and whether these new guidelines are better predictors for other health conditions.

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