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Association of Antihypertensive Combinations with Cardiovascular Outcomes in
Patients with Atrial Fibrillation

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Master of Public Health

Epidemiology

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Patients with Atrial Fibrillation
By

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Abstract

Association of Antihypertensive Combinations with Cardiovascular Outcomes in Patients with Atrial Fibrillation

By Nimisha Ganesh

Objective: Hypertension remains the most important manageable predisposing risk factor for atrial fibrillation (AF) [1]. The study focuses on the comparative outcomes of different antihypertensive therapy combinations in AF patients. The specific aims of the analysis were: 1) to evaluate the risk of myocardial infarction, heart failure and stroke outcomes in AF patients by type of antihypertensive therapy; 2) to determine if sex influences the association of antihypertensive treatments with outcomes in patients with AF.

Methods: This analysis used the MarketScan Commercial and the MarketScan Medicare Supplemental Databases (Truven Health Analytics) to identify patients with nonvalvular AF who were prescribed with antihypertensives. We selected 970,428 patients who had at least one antihypertensive medication prescription after their date of diagnosis of non-valvular AF. Cox proportional hazards models were used to determine the association between antihypertensive treatments and the time until outcome. Follow-up started at the date of the first prescription of antihypertensive medication after the diagnosis of AF and continued until a hospitalization for the outcome of interest (myocardial infarction, heart failure, stroke), September 30, 2015, or patient health plan disenrollment, whichever occurred first.

Results: Among 970,428 eligible AF patients, there were 12,441 myocardial infarctions, 49,308 heart failures, and 17,250 strokes. The incidence of heart failure was generally higher when compared to myocardial infarction and stroke in the study population. Compared to patients prescribed with beta blockers the incidence rates and hazard ratios (HR) for myocardial infarction, heart failure and stroke were the highest in patients prescribed with 4 or more antihypertensives (HR 3.66, 95%CI 3.30-4.05 for myocardial infarction, HR 12.81, 95%CI 11.63-14.11 for heart failure and HR 1.52, 95% CI 1.42-1.63 for stroke). Men presented increased risk for stroke compared to women, for all categories of hypertension management. Risk for heart failure was higher in men when compared to women for all categories except triple therapy combinations (other than angiotensin converting enzyme inhibitors/beta blockers/diuretic or angiotensin receptor blockers/beta blockers/diuretic).

Conclusions: The analysis identified higher risk of most outcomes among patients taking multiple antihypertensive medications, which could be explained by higher severity of underlying hypertension in that group. We could not identify the most effective hypertension management strategy; however, our findings corroborate the relevance of hypertension as a risk factor for adverse outcomes in AF patients and the importance of optimizing strategies for hypertension management in these patients.

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Table of Contents

1. Introduction

1.1. Hypertension and Atrial Fibrillation

Hypertension continues to increase in prevalence and is a significant risk for a wide variety of cardiovascular events [2]. Various factors such as dietary indiscretions, obstructive sleep apnea, obesity, and aging are partly responsible for the high prevalence of hypertension [3]. Hypertension leads to increased risk of various cardiovascular diseases, including coronary artery disease, heart failure and various arrhythmias such as atrial fibrillation (AF), ventricular arrhythmias, and sudden cardiac arrest [4]. Hypertension remains the most common risk factor for the development and prognosis of AF. AF and arterial hypertension often coexist, not only because arterial hypertension increases the incidence of new onset of AF, but also because those two conditions share common risk factors that increase the incidence of both [5]. There are several inferences entangled with the development of AF in patients with hypertension, the most important of which is the increased risk of thromboembolism and stroke. Heart failure can be a precipitant of AF, depending on the degree of left ventricular hypertrophy (LVH). The risk of ventricular arrhythmias as well as sudden cardiac death is increased by the development of hypertension adversely affecting the conduction system.[6]

1.2 Epidemiology

Hypertension, with a prevalence of 29% (estimated in 2014), is the most common risk factor for cardiovascular diseases. Prevalence of hypertension increases with age with 64.9% of the hypertensive cases around 60 years or older. The pattern is consistent among both men (8.4% for those aged 18–39, 34.6% for 40–59, and 63.1% for 60) and women (6.1% for those aged 18–39, 29.9% for 40–59, and 66.5% for 60). The prevalence is projected to increase to 41.4% in 2030 [7]. The most common sustained arrhythmias in adults, AF, is particularly associated with

hypertension. The estimated AF prevalence in the United States is approximately 5.2 million and is expected to rise to 12.1 million by 2030. There is a 1.8-fold increased risk of developing new-onset AF and a 1.5-fold increased risk of progression to permanent AF associated with hypertension. The lifetime risk for the development of AF in this population is as high as 25% at 40 years of age. Almost 60% of patients with AF have hypertension. Owing to the aging population, a 2 to 3 times increase in the total number of patients with AF is expected over the next 20 to 30 years. In addition, ventricular arrhythmias and sudden cardiac deaths can be a direct consequence of hypertension and AF. A secondary analysis of the LIFE study showed that the presence of LVH and AF increased the risk of sudden cardiac death by three to four-fold. Also, in-hospital ventricular fibrillation can be independently predicted by hypertension. [7]

1.3 Pathogenesis

The pathogenesis underlying the association of arrythmias and hypertension is complex. In hypertensive patients when no other cardiac risk factors present, the incidence and prevalence of cardiac arrhythmias is directly related to the status of hypertension or hypertension-related heart disease. Cardiac remodeling manifestations shows that the incidence of AF, ventricular arrhythmias, and heart failure increases with the progression of hypertensive heart disease [8]. An increase in left atrial size, sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) activation, nerve abnormalities, and microvascular ischemia are some of the factors attributed to the development of AF in hypertensive individuals [9]. Left ventricular hypertrophy (LVH) is strongly related to chronic hypertension and promotes the development of cardiac arrhythmias significantly. Intracardiac pressure and chronic increase in afterload causes the hypertrophy of cardiac muscle and in-turn stimulates collagen deposition in the heart which leads to an increased myocardial mass [7]. The series of functional

maladaptation from LVH is initiated by diastolic dysfunction that progresses to decreased systolic function by remodeling. The chronicity of AF can be assessed by increased left atrial size. Increased left atrial pressure results from chronic elevation in the left ventricular end-diastolic pressure. In turn, enlargement of the atrium is caused by chronic elevation of the left atrial pressure [7,9]. Electrical dissociation among muscle bundles occurs due to the stretching of atrium, which facilitates the onset and maintenance of AF. Hence, AF is induced and prolonged by tissue remodeling caused by the alterations in atrial characteristics [7].

Activation of the SNS and the RAAS plays a major role in the onset and development of hypertension and various arrhythmias. Peripheral vasoconstriction caused by the activation of the SNS results in an elevated systemic blood pressure. An increased SNS activation causes a reduction in the refractory period of cardiac muscles and leads to both atrial and ventricular arrhythmias. Angiotensin II, a mediator of RAAS, is involved in the development of cardiac fibrosis [7,9].

Electrical abnormalities promoting arrhythmogenesis in patients with hypertension occur early in hypertensive heart disease. Decreased refractoriness and prolonged conduction velocity of the atria are two specific abnormalities. In addition to this, a precipitated activity characterized by an early and delayed after depolarizations are assumed to have a role in the initiation of AF related to hypertensive heart disease. QRS and QT prolongation due to LVH as a result of prolonged action potential duration and QT dispersion, which can in-turn lead to an increased propensity for an early after depolarization, which is associated polymorphic ventricular tachycardia [7,9].

Ventricular arrhythmia associated with microvascular ischemia is another relevant mechanism. Changes in the microvasculature precipitates subendocardial ischemia which

precipitates LVH resulting in myocardial scar tissue formation and fibrosis. These are established substrates for ventricular arrhythmias and sudden cardiac death. Hypertension remains a strong risk factor for coronary obstruction which leads to the development of ischemia of the microvasculature. Formation of infarction scar tissues serves as a substrate for macro reentrant arrhythmias like ventricular tachycardia. Besides, LVH causes a diminished coronary flow reserve. In turn, decreased coronary flow reserve results in an increased risk of further ischemia and thus ventricular arrhythmias [7,9].

1.4 Management of Arrhythmias in Patients with Hypertension

Adequate management of hypertension is associated with a decreased incidence and better prognosis of AF in many studies [10]. There is sufficient evidence attributing the reduction in the AF incidence to antihypertensives that target the RAAS [11,12,13,14]. These mechanisms are found be very relevant in the management of AF. An elevated angiotensin II and angiotensin-converting enzymes levels are found in patients with AF. In addition to the blood pressure control, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) render cardioprotective actions due to their antiapoptotic and fibro lytic properties. The LIFE study observed the new-onset AF occurred only in 150 losartan-treated patients (an ARB) compared with 221 atenolol-treated patients (a beta blocker), thus establishing the antiarrhythmic property of ARBs [15, 16]. The result of this study suggests a mechanism of action relating to RAAS. Managing hypertension to prevent left atrio-ventricular hypertrophy with antihypertensive drugs such as ACE-Is and ARBs seems to be essential to improve the prognosis of AF. Though beta blockers are commonly used for acute and chronic heart rate control in AF, they are not considered first-line therapies for hypertension [17]. In a study of 85 hypertensive patients with or without left ventricular hypertrophy higher proportion of atrial premature beats

were observed than in an age-matched control group. Treatment with beta-blockers and calcium channel blockers resulted in a decreased premature atrial contractions frequency [18]. A meta-analysis of 12,000 patients with heart failure, the incidence of new onset AF was found to be significantly reduced in patients who on beta-blockers, with a reduction in the risk by 27% [19]. However, LIFE study findings are suggestive of the superiority of RAAS blockade to beta-blockade in the management of hypertension [15].

There is a high prevalence of ventricular arrhythmias in hypertensive patients, and this association presents significant implications clinically. Findings of the Atherosclerosis Risk in Communities (ARIC) study, including more than 15,000 African American and white men and women, points that the frequent and complex ectopic beats are related to high blood pressure [20]. The LVH induced by hypertension is associated with sustained ventricular arrhythmias. Elevated systemic blood pressure does not directly cause arrhythmias; however, the acute or chronic ventricular overload can overtime accumulate both electrical and physiologic properties that may aggravate under pathologic conditions such as ischemic scars.

Elevated systemic blood pressure is also associated with sudden cardiac death or heart failure, particularly in patients with left ventricular hypertrophy. LVH perpetuates long-term risk of sudden cardiac arrest and death irrespective of hypertension status. The risk for sudden cardiac death is directly related to the degree of LVH. The association between the increased left ventricular mass and sudden cardiac death is characterized by prolonged repolarization, oxygen supply-demand imbalance, compromised coronary flow reserve and resulting myocardial ischemia. Significant evidence suggests that optimum management of hypertension together with reductions in LVH can alleviate the risk of sudden cardiac death to a greater extend. Therefore, it is important to study the role of antihypertensive drugs on the risk of sudden cardiac death.

Thiazide diuretics has been found to influence a dose-dependent increase in sudden cardiac death. This could be due to the increased risk of hypokalemia, QT prolongation, QT dispersion, and the propensity for arrhythmogenic early and delayed after-depolarizations by thiazides [21], while antihypertensives such as ARBs and ACE-Is were found to be associated with a decreased risk of cardiac death.

Almost one-half of the patients with heart failure presents a preserved ejection fraction (HFpEF). Heart failure with preserved ejection factor is frequently associated with uncontrolled AF and hypertension [21]. These two conditions—AF and hypertension—demand an aggressive management during the decompensated heart failure episodes. The risk of HFpEF increases with old age, elevated blood pressure, elevated blood glucose, obesity, and chronic kidney diseases. These are some of same factors that predispose for the onset and adverse prognosis of AF. An aggressive cardiac rhythm and rate management for AF is essential for the management of HFpEF. Likewise, an effective blood pressure management is important in the case of an acute exacerbation of HFpEF [21].

1.5 Public Health Implications

AF is the most common type of sustained arrhythmia and almost one in four individuals develops this condition within their lifetime [7]. According to the Centers for Disease Control and Prevention, almost 2% of individuals below 65 years of age and about 9% of people above 65 presents AF [22]. AF is associated with significant burden in term of both morbidity and mortality. Hospitalizations and the cost attributable to AF have increased drastically over the past decade and the estimated healthcare cost is more than 1 percent of all the healthcare costs in the developed countries, and this burden is assumed to increase with a high trajectory in the future owing to the aging population in the western countries. Therefore, it is very essential that

the healthcare authorities consider any novel strategy that aims at improving the AF outcomes with care. The rising prevalence of both AF and hypertension and their attributable treatment costs constitute a heavy financial burden; therefore, many economic analyses focusing on the assessment of the cost effectiveness and pharmacoeconomic considerations of AF and hypertension are being conducted.

As explained by various epidemiological and clinical studies, there exist a close link between elevated systemic blood pressure, LVH, and AF. The cardiac hemodynamics and its structural properties and electrophysiological activities are altered by chronic and uncontrolled hypertension which leads to the development of AF, various other arrhythmias, and sudden cardiac death. This indicates that the optimal management of blood pressure with different antihypertensive agents, more essentially, to regress LVH can prevent AF and associated sudden cardiac death. Although antihypertensive drugs are known to reduce mortality in individuals with hypertension, the effects of different cardiovascular pharmacotherapies on mortality among patients with hypertension and AF have been less thoroughly explored [23]. Treatment with ACE-Is and ARBs has been shown to decrease ventricular ectopy and sudden cardiac death [11, 12, 13, 14]. In patients who require additional hypertension management, beta blockers are proven effective. There is sufficient evidence to suggest that mineralocorticoid receptor antagonists are a promising therapeutic approach to reduce myocardial fibrosis, though further studies are needed to validate its use in prevention of ventricular arrhythmia and sudden cardiac death in hypertensive heart disease [24].

2. Methods

2.1 Study Population

We used the MarketScan Commercial and the MarketScan Medicare Supplemental

Databases (Truven Health Analytics) to identify patients with nonvalvular AF who were prescribed antihypertensives. These MarketScan databases consist of paid claims and health encounter data with over twenty billion service records for the medical experience of insured employees and their dependents and for retirees with Medicare supplemental insurance paid by employers in the United States. The claims and encounter data were linked to detailed patient information of the enrollees. Claims and enrollment data are linked via a common synthetic patient identifier created by Truven Health Analytics as part of the data preparation to facilitate analysis while ensuring patient confidentiality [25].

We selected 970,428 patients who had a prescription for an antihypertensive medication after their date of diagnosis of non-valvular AF. The earliest prescription date (index date) of major antihypertensive classes (ACE-Is, ARBs, alpha-beta blockers, beta blockers, calcium channel blockers, diuretics, and alpha blockers) after the AF diagnosis was examined for the selected subjects.

2.2 Specific Aims

The primary research question focuses on the comparative outcomes of different antihypertensive therapy combinations in AF patients.

The specific aims of the analysis were:

- To evaluate the risk of myocardial Infarction, heart failure and stroke outcomes in AF patients by type of antihypertensive therapy.

- To determine if the association of type of antihypertensive therapy with outcomes was influenced by sex.

2.3 Definition of the Exposure

The defined exposure was the antihypertensive medication prescribed after the date of

diagnosis of non-valvular AF. We classified the study sample into seven groups based on their antihypertensive prescription. The seven antihypertensive groups are: beta blocker only, other single therapy, beta blocker + other, other dual therapy combinations, ACE-I/ beta blocker/diuretic or ARB/beta blocker/diuretic, other triple therapy combinations, and four or more drugs. These were the most frequently prescribed antihypertensive combinations in the study sample.

2.4   Identification of Prespecified Covariates

Prespecified covariates were derived using information before the date of initiation of the antihypertensive therapy obtained from all MarketScan data sources (i.e., demographic data, inpatient, outpatient, and pharmacy claims).

Validated published algorithms were used to define numerous prespecified comorbidities, Table 1 in the supplement provides details of the details of the covariates considered. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes used to identify the numerous prespecified comorbidities are given in the supplement (Table 2).

AF was defined by an ICD-9-CM code 427.31 or 427.32 in any position based on at least 1 inpatient claim or 2 outpatient claims separated by at least 7 days but <1 year for enrollees without history of mitral stenosis (*ICD-9-CM* 394.0) or mitral valve disorder (*ICD-9-CM* 424.0) [25].

2.5 Endpoints

Myocardial infarction, heart failure and stroke were the outcomes of interest as relevant complications in patients with AF. The study population was followed from the earliest date of prescription claims for antihypertensive medication (index date) until the patient incurred a claim for myocardial infarction, heart failure or stroke. If none of these outcomes are observed the patient is followed up until censored at death, or patient health plan disenrollment or the last date of claims data that is available (September 30, 2015), whichever occurs first. The ICD-9-CM codes used to define the outcomes are presented in Table 2 of the supplement.

2.6 Statistical Analysis

Baseline characteristics are presented as percentages and mean (SD) for the entire cohort and across the different antihypertensive treatment categories (Table 1). Continuous variables are presented as mean values. Follow-up started at the date of first prescription of antihypertensive medication after the diagnosis of AF and continued until a hospitalization for the outcome of interest (myocardial infarction, heart failure, stroke), September 30, 2015, or patient health plan disenrollment, whichever occurred earlier. Cox proportional hazards models were used to determine the association between the antihypertensive treatment and the time until outcome in AF patients adjusting for potential confounders. Separate models were developed to assess the survival time for myocardial infarction, heart failure and stroke separately.

Age-adjusted models were developed to compare the AF outcomes between male and female patients.

The general equation for the Cox proportional hazards model used is as follows:

$h(t) = h0(t) \times exp\ (b_1 Antihypertensive category + b_2 Age\ at\ AF\ diagnosis + b_3 Sex + b_4 MI + b_5 PAD + b_6 GI\ Bleeding + b_7 SCerebral\ Bleeding + b_8 Other\ Bleeding + b_9 Anemia + b_{10} Coagulopathy + b_{11} Mood\ Disorders + b_{12} Cognitive\ Impairment + b_{13} Liver\ Disease + b_{14} Alcohol + b_{15} Hypertension + b_{16} CHF + b_{17} CAD + b_{18} Hyperlipidemia + b_{19} Stroke + b_{20} Arthritis + b_{21} Asthma + b_{22} Cancer + b_{23} CKD + b_{24} COPD + b_{25} Dementia + b_{26} Depression + b_{27} DM + b_{28} Hepatitis + b_{29} Osteoporosis + b_{30} Schizophrenia + b_{31} Substance\ Abuse)$

Where t represents the survival time, that is the time until hospitalization due to myocardial infarction, heart failure, or stroke, September 30, 2015, or patient health plan disenrollment. $h(t)$ is the hazard function determined by a set of covariates. The coefficients (b_{1-31}) measure the impact of covariates (i.e. log(hazard ratios)). The term $h0$ is called the baseline hazard. It corresponds to the value of the hazard if all the covariates are equal to zero. The t in $h(t)$ indicates that the hazard may vary over time. We included the covariates in the model to account for any confounding that may occur. The sufficiently large sample size eliminates the need for confounding tests, with the covariates selected by a-priori decision, based on evidence from literature as factors that can influence the type of antihypertensive medication received and the risk of developing any of the outcomes of interest.

We tested for interactions using Wald chi-square test between the antihypertensive category and sex to determine the effect of treatment on outcomes differs by sex in AF. The interactions were assessed separately for each of the 3 outcomes. Specifically, a multiplicative interaction was assessed by including an antihypertensive category by sex product term in the models. All the antihypertensive treatment categories were compared with the beta blocker-only group, which was set as the reference category. The Proportional Hazard's function assumes that

each covariate has a multiplicative effect in the hazards function that is constant over time. The proportional hazards assumption was not tested in this study because the follow-up time was very short.

All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1 Patient Characteristics

Table 1 presents the baseline characteristics of the study population. In the 970,428 AF patients, mean age (SD) was 70 ± 13 years, and 41% were females. The most prevalent antihypertensive prescribed in the study sample was beta-blocker (77%) followed by diuretics (53%). Alpha-beta blockers and alpha blockers remains the least prescribed (0.8% and 4.6% respectively). Of the 28 covariates identified, hypertension (67%), hyperlipidemia (47%) and coronary artery disease (37%) and diabetes mellitus (30%) were the most prevalent.

3.2 Incidence Rates

The incident rates per 100 person years for all categories of antihypertensives were estimated for myocardial infarction, heart failure and stroke outcomes (Table 3). The incidence rates for all the 3 outcomes were particularly high in patients prescribed with 4 or more anti-hypertensives. The incidence of heart failure was generally higher when compared to myocardial infarction and stroke in the study population. The heart failure incidence was notably high in AF patients prescribed with a triple combination of ACE-I/beta blocker/diuretic or ARB/beta blocker/diuretic (5.35 cases per 100 Person years) and in patients prescribed with 4 or more antihypertensive combinations (4.43 cases per 100 Person years).

3.3 Myocardial Infarction

Over the mean follow-up of 2 years, 12,441 AF patients were hospitalized due to myocardial infarction. Adjusted hazard ratios (HR) by antihypertensive category and outcome are presented in Table 4, Figure 1. Atrial fibrillation patients prescribed with 4 or more antihypertensive drugs and ACE-I/beta blocker/diuretic or ARB/beta blocker/diuretic triple combination therapy were associated with a stronger increased risk [HR 3.66, 95% CI (3.30, 4.45) and HR: 3.05, 95% CI (2.74, 3.40) respectively] of myocardial infarction compared to other antihypertensive therapies. Results were consistent when stratified by sex (Table 5, Figure 2). The HR implies that after adjustment for predefined covariates, there was 3.7 times increased risk for myocardial infarction outcome in AF patients prescribed with 4 or more antihypertensives with reference to AF patients prescribed with only beta blocker. Similarly, AF patients prescribed with a triple combination therapy (specifically, ACE-I/beta blocker/diuretic or ARB/beta blocker/diuretic) presents 3 times increased risk for myocardial infarction outcome when compared to beta blocker-only hypertension management.

A dual therapy combination of beta blocker and other antihypertensive was associated with the least risk for myocardial infarction in AF patients [HR: 1.99, 95% CI (1.78, 2.21)]. There is a 10% increased risk of myocardial infarction outcome with this therapy in reference to beta blocker only therapy for hypertension management in AF patients.

When stratified by sex, the dual therapy combination of beta blocker + other antihypertensive was associated with the lowest increase in risk of myocardial infarction outcome in AF patients. Both men and women presented a HR of 2.0, implying twice the risk for MI outcome when compared to the beta blocker only therapy.

3.4   Heart Failure

Mean follow-up time for heart failure outcome was 2 years, during which 49,308 AF patients were estimated to be hospitalized due to heart failure. Adjusted HR by antihypertensive category and outcome are presented in Table 4, Figure 1. The estimated risk for heart failure was much higher across all categories of antihypertensive combinations when compared to the other outcomes studied, i.e., myocardial infarction and stroke.

AF patients prescribed with 4 or more Antihypertensive drugs and ACE-I/beta blocker/diuretic or ARB/beta blocker/diuretic triple combination therapy were associated with a stronger increased risk [HR 12.81, 95% CI (11.63, 14.11) and HR: 12.57, 95% CI (11.41, 13.86) respectively] of heart failure when compared to other antihypertensive therapies. Similar results were obtained when sex-stratified models were used (Table 5, Figure 2). The HR can be interpreted as the following: after adjusting for predefined covariates, there was 12.8 times increased risk for heart failure outcome in AF patients prescribed with 4 or more antihypertensives with reference to AF patients prescribed with only beta blocker. Similarly, AF patients prescribed with a triple combination therapy (specifically, ACE-I/beta blocker/diuretic or ARB/beta blocker/diuretic presented 3 times increased risk for heart failure outcome when compared to beta blocker-only hypertension management.

Single therapy hypertension management was associated with the lowest increase in heart failure [HR: 3.12, 95% CI (2.79, 3.48)], which is a 3 times increased risk for heart failure outcome when compared to beta blocker only therapy for hypertension management in AF patients.

When stratified by sex, single therapy hypertension management presented the lowest increase in risk for heart failure outcome in AF patients. These results are fairly consistent in

male and female patients. Male and female AF patients presented a HR of 3.3 (95% CI 2.8, 3.7) and 2.9 (95% CI 2.4, 3.5) respectively, implying almost thrice the risk for heart failure outcome when compared to the beta blocker only therapy.

There was a marked difference in the estimated risk for heart failure outcome between male and female AF patients. In general, males showed a higher HR across all antihypertensive categories when compared to that of females, except for triple therapy antihypertensive combinations excluding ACE-I/beta blocker/diuretic and ARB/beta blocker/diuretic combination groups.

3.5 Stroke

The study population was followed-up for approximately 2 years to estimate the hospitalizations due to stroke. 17,250 AF patients on antihypertensive therapy were found to be hospitalized for stroke during the follow-up period. Adjusted HR by antihypertensive category and outcome are presented in Table 4, Figure 1 of the supplement.

AF patients prescribed with 4 or more antihypertensive drugs had a slightly increased risk [HR 1.52, 95% CI (1.42, 1.63)] for stroke compared to other antihypertensive therapies. Results were consistent when stratified by sex (Table 5, Figure 2). The HR implies that after adjustment for predefined covariates, there was a 50% increased risk for stroke outcome in AF patients prescribed with 4 or more antihypertensives with reference to AF patients on beta blocker-only hypertension management. Similarly, AF patients on other antihypertensive combinations estimated comparable HR.

When sex-stratified survival models were used, male AF patients presented slightly elevated risk for Stroke outcome when compared with female patients.

3.6   Interaction with Sex

The Wald chi-square test of the product term i.e., antihypertensive category by sex, gave p-values less than 0.05, indicating statistically significant interaction between the antihypertensive treatment group and sex across all the three models. This implies that the efficacy of the antihypertensive combinations for the management of hypertension in AF patients are significantly affected by sex when the effect due to the predefined covariates are accounted for. From the stratified Cox proportional hazards model, it is observed that, male patients presented an increased risk for stroke outcome when compared to female patients for all categories of antihypertensives studied, with reference to beta blocker-only therapy (Table 5). The HR and 95% CI in men and women undergoing a combination of four or more antihypertensives were HR 1.7, 95% CI 1.5-1.8 and HR 1.4, 95% CI 1.3-1.5 respectively.

The outcome of heart failure estimated the highest hazard ratios for both male and female patients. In male AF patients on a combination of ACEI/BB/Diuretic or ARB/BB/Diuretic antihypertensive triple therapy, a Hazards ratio of 13.1, 95% CI 11.6-14.9 was measured whereas, in corresponding female AF patients a Hazard ratio of 11.6, 95% CI 9.9-13.6 was measured, when beta blocker-only therapy was set as the reference. For all the combinations of antihypertensives studied, except for the triple therapy combinations excluding ACEI/BB/diuretic or ARB/BB/diuretic, male patients showed an increased HR. However, for the "Other" triple therapy combinations, female patients estimated a higher Hazard ratio of 6.3, 95% CI 5.4-7.4, while corresponding male patients recorded HR 5.4, 95% CI 4.8-6.1. when beta blocker-only therapy was set as the reference.

The risk for Myocardial infarction outcome in both male and female AF patients were largely comparable. However, a slightly elevated risk was observed in male patients on four or

more antihypertensives combination (HR 3.7, 95% CI 3.3-4.2) when compared with corresponding female AF patients (HR 3.6, 95% 3.0-4.3) when the reference was set as beta blocker-only therapy. Risk associated with MI in male patients on "other" triple combination therapy was 2.4 (95% CI 2.1-2.7), while corresponding female patients on the same therapy presented an HR of 2.1 (95% CI 1.7, 2.5). The detailed comparison of gender stratified Hazard ratios are represented in Table 5 and Figure 2.

4. Discussion

The results indicates that the incidence of heart failure was generally higher when compared to myocardial infarction and stroke in this study population of patients with AF. Compared to patients prescribed with beta blockers the incidence rates and HR for myocardial infarction, heart failure and stroke were the highest in patients prescribed with 4 or more antihypertensives. Men presented an increased risk for stroke compared to women, for all categories of antihypertensives prescribed. Risk for heart failure was higher in men when compared to women for all categories except triple therapy combinations (other than ACE-I/Beta blocker/Diuretic or ARB/Beta blocker/Diuretic).

Our results are concordant with the evidence from previously published studies. The effectiveness of ACE-I and ARBs on the management of hypertension in AF patients have been documented by 4 meta-analysis [11, 12, 13, 14]. The studies explain the comparative efficacy of the treatment groups (Table 1) with reference to Beta blocker-only therapy in managing the prognosis of AF outcomes. A dual therapy combination of beta blocker and other antihypertensive showed a higher efficacy in controlling the prognosis to myocardial infarction outcome with reference to beta blocker-only therapy when compared to the other antihypertensive combinations considered for the study. A study conducted by Marott *et al*, in

Denmark estimated a lower HR for the onset of AF when ACE-I and ARB monotherapy used for hypertension management compared with beta blocker only therapy. The lowest HRs were associated with ACE-I and ARB monotherapy [26].

In the management of heart failure outcome, antihypertensive monotherapy (other than beta blocker) showed higher efficacy (with reference to beta blocker only therapy), when compared to the other antihypertensive combinations considered in the model. For the management of stroke outcome, most of the antihypertensive combinations showed comparable efficacy. Dual therapy combinations (other than beta blocker dual therapy) showed slightly higher efficacy in reference to beta blocker-only therapy, when compared to the other Antihypertensive combinations considered in the study.

Resistant hypertension is a prevalent clinical problem and may be defined as uncontrolled hypertension in spite of the use of over three antihypertensive agents belonging to different classes, which usually includes a Diuretic, commonly a thiazide-like, a long-acting calcium channel blocker, and a renin- angiotensin system blocker, either an ACE-I or an ARB, at maximal or maximally tolerated doses [27]. Resistant hypertension may be a high-risk phenotype, which leads to cardiovascular disease outcomes and elevated all-cause mortality. It is observed that, excess of aldosterone is prevalent in patients with resistant hypertension, and therefore, addition of amiloride or spironolactone to the standard 3-drug antihypertensive regimen could be effective at getting the blood pressure to goal in most of these patients [28]. Refractory type hypertension may be defined as the uncontrolled blood pressure despite use of over five antihypertensive agents of different classes, including a long-acting thiazide-like diuretic and a mineralocorticoid receptor antagonist, at maximal or maximally tolerated doses [27]. Both resistant hypertension and refractory hypertension are characterized by 3 or more

prescribed medication for their management and requires over 3 drugs for their management. Observational studies and clinical trials focusing on the antihypertensive treatment have shown that patients with resistant hypertension are at increased risk of cardiovascular disease such as Myocardial infarction, Heart failure and Stroke when compared with patients with more easily controlled hypertension, as well as higher risk of incident cardiovascular events, even after effective BP control is achieved [27,28].

Our study indicated that antihypertensive combination therapy with 3 or more drugs is associated with increased risk for cardiovascular outcomes, such as myocardial infarction, heart failure and stroke in AF patients. Patients with more severe hypertension that warrants more aggressive therapy with combination drugs could experience higher risk of cardiovascular outcomes as observed in our study. Therefore, confounding effects of these comorbidities should be considered before any inferences about the comparative efficacy of antihypertensive combinations are made based on our results.

5. Strengths and Limitations

This study has several strengths, including being a real-world analysis that focuses on a less explored domain: antihypertensive treatment efficacy and cardiovascular outcomes in patients with AF. The sufficiently large sample size, complete with prescription, hospitalization records and date and time information make it suitable for building strong survival models.

We acknowledge the following limitations: First, the Marketscan database is primarily a billing database and not a clinical research database. Therefore, our study lacks generalizability since the data does not cover all sections of the population: the uninsured population, for instance are left out. Second, important clinical parameters such as BP measurement, are not available from the claims database. This is likely to result in uncontrolled confounding. Third, study findings

rely on our ability to accurately ascertain outcomes, chronic conditions, and covariates using diagnostic codes in administrative data. Validated algorithms were used to ascertain events of interest and it is likely that any misclassification is nondifferential. To identify chronic conditions, we required 2 occurrences of a diagnostic code separated by more than 30 days to reduce false-positive diagnoses. Fourth, residual confounding may exist. Baseline confounding factors that contribute to treatment decisions may be accounted for only partially due to missing information and mismeasurement of those confounders. Fifth, the geriatric conditions that contribute to the complexity of comorbidities with outcomes are not well defined in the claims data base. Finally, lack of mortality data could affect the definition of our endpoints in the survival analysis.

6. Conclusions

Over the recent decade, AF has emerged as a major clinical and public health concern in the United States and worldwide. Since uncontrolled elevated systemic blood pressure affects the structure and functionality of the left atrium, hypertension can be considered the most important controllable predisposing factor for AF. The analysis supports the role of antihypertensives in the management of the cardiovascular outcomes in AF patients. Though a definite and most effective hypertension management is not identified, the findings of the study corroborate the need for multifactorial cohort studies to elucidate the complex factors that precipitates the cardiovascular outcomes and modify the treatment plans to improve the quality of life in AF.

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SUPPLEMENTARY MATERIALS

Table 1: Percentage of characteristics stratified by prescribed antihypertensive class at baseline.

		Alpha-Beta Blockers	Alpha Blockers	Beta Blockers	ACE Inhibitors	Calcium Channel Blockers	ARB	Diuretics
N (%)	970,428	9,704 (0.8)	44,639 (4.60)	747,229 (77)	388,171 (40)	417,284(43)	232,902 (24)	514,326 (53)
Females	41	48	14	40	36	45	45	46
Age at AF diagnosis	70 ± 13	69 ± 13	74 ± 11	69 ± 13	70 ± 13	71 ± 13	71 ± 12	73 ± 12
MI	8.3	8	7.5	9.2	10	6.6	7.8	9.2
PAD	11	14	13	11	11	11	11	13
GI Bleeding	6.9	8.3	7.5	6.7	6.5	6.9	6.6	7.5
Prior Cerebral Bleeding	1.1	2.5	1	1	1.1	1.1	0.9	1.1
Other Bleeding	8.5	10	10.3	8.3	8.1	8.3	8.1	8.9
Anemia	19	28	22	18	17	18	18	21
Coagulopathy	5.9	6.7	6.3	5.8	5.7	5.3	5.3	6.5
Mood Disorders	7.7	7.7	6.3	7.3	7	7.5	6.5	7.6
Cognitive Impairment	2.5	2.9	2	2.2	2.3	2.4	1.7	2.6
Liver Disease	4.1	5	3.5	4	3.6	3.9	3.7	4.3
Alcohol Abuse	1.7	1.5	1.3	1.7	1.8	1.6	1.2	1.6
HTN	67	82	73	67	72	72	76	70
CHF	23	25	23	24	26	20	23	34
CAD	37	38	40	39	41	34	39	41
Hyperlipidemia	47	47	48	47	48	46	49	44
Stroke	17	24	18	17	17	17	17	18
Arthritis	24	26	25	23	23	24	25	26
Asthma	7.1	6.6	6.7	6.2	6.2	8.1	7.9	8
Cancer	20	21	24	20	19	20	20	21
CKD	16	32	23	16	16	17	17	20
COPD	18	16	19	17	17	19	17	22
Dementia	5.7	5.6	4.6	5.1	5.2	5.4	3.9	6.2
Depression	8	8	6.5	7.6	7.3	7.7	6.8	7.8
DM	30	40	36	31	36	32	36	35
Hepatitis	0.92	1.42	0.81	0.92	0.83	0.90	0.79	0.90
Osteoporosis	5.3	5.6	3.1	5	4.4	5.6	5.2	5.7

Schizophrenia	2	2.4	1.7	1.9	1.9	1.9	1.4	2.2
Substance Abuse	2.5	2.6	2.1	2.4	2.5	2.3	1.7	2.3

ACE: Angiotensin converting enzyme. ARB: angiotensin receptor blocker

Table 2: International Classification of Diseases, Ninth Revision Clinical Modifications (ICD-9-CM) code set used to define the covariates.

Outcome	ICD-9-CM Codes
Endpoints	
Stroke	346.6, 414.12, V45.81, V45.82, 430-437, 444
Myocardial infarction	410, 412
Heart Failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.9, 428
Comorbidities	
Hypertension	362.11, 401, 402, 403, 404, 405, 437.2
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Coronary artery disease	410, 411, 412, 413, 414.0, 414.12, 414.2, 414.3, 414.8, 414.9, V45.81, V45.82
Hyperlipidemia	272.0, 272.1, 272.2, 272.3, 272.4
Arthritis	714, 715, 720.0, 721.0, 721.1, 721.2, 721.3, V13.4, 721.90, 721.91
Peripheral artery disease	440.0, 440.2, 440.9, 443.9
Gastrointestinal bleeding	456.20, 530.82, 535.x1, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.85, 455.2, 455.5, 455.8, 456.0, 530.7, 531.0 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 569.3, 578.0, 578.1, 578.9
Cerebral bleeding	430, 431, 432, 852
Other bleeding	423.0, 459.0, 568.81, 593.81, 599.7, 623.8, 626.6, 719.1, 784.7, 784.8, 786.3
Anemia	280-285
Coagulopathy	286, 287.1, 287.3, 287.4, 287.5
Mood disorder	293.83, 296, 311
Cognitive impairment and dementia	290, 293.0, 293.1, 294, 310.0, 310.2. 310.81, 310.89, 310.9, 331, 797
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0, 456.1, 456.2, 572.x, 573.3, 573.4, 573.8, 573.9, V42.7
Alcohol abuse	265.2, 291.1, 291.2, 291.3, 291.5, 291.6, 291.7, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3, V11.3, 980
Asthma	493
Cancer	140.0, 140.1, 140.3-140.9, 141.0-141.6, 141.8, 141.9, 142.0, 142.1, 142.2, 142.8, 142.9, 143.0, 143.1, 143.8, 143.9, 144.0, 144.1, 144.8, 144.9, 145.0-145.6, 145.8, 145.9, 146.x, 147.0-147.3, 147.8, 147.9, 148.0-148.3, 148.8, 148.9, 149.0, 149.1, 149.8, 149.9, 150.0-150.5, 150.8, 150.9, 151.0-151.6, 151.8, 151.9, 152.0-152.3, 152.8, 152.9, 153.x, 154.0-154.3, 154.8, 155.0-155.2, 156.0-156.2, 156.8, 156.9, 157.0-157.4, 157.8, 157.9, 158.0, 158.8, 158.9, 159.0, 159.1, 159.8, 159.9, 160.0-160.5, 160.8, 160.9, 161.0-161.3, 161.8, 161.9, 162.0, 162.2-162.5, 162.8, 162.9, 163.0, 163.1, 163.8., 163.9, 164.0-164.3, 164.8, 164.9, 165.0, 165.8, 165.9, 170.x,
	171.0, 171.2-171.9, 172.x, 173.x, 174.0-174.6, 174.8, 174.9, 175.0, 175.9, 176.0-176.5, 176.8, 176.9, 179, 180.0, 180.1, 180.8, 180.9, 181, 182.0, 182.1, 182.8, 183.0, 183.2-183.5, 183.8, 183.9, 184.0-184.4, 184.8, 184.9, 185, 186.0, 186.9, 187.x, 188.x, 184.0-184.4, 186.0, 186.9, 187.x, 188.x, 189.0-189.4, 189.8, 198.9, 192.0-192.3, 192.8, 192.9, 193, 194.0, 194.1, 194.3-194.6, 194.8, 194.9, 195.0-195.5, 195.8, 196.0-196.3, 196.5, 196.6, 196.8, 196.9, 197.x, 198.x, 199.0-199.2, 203.0, 203.1, 203.8, 204.0-204.2, 204.8, 204.9, 205.0-205.3, 205.8, 205.9, 206.0-206.2, 206.8, 206.9, 207.0-207.2, 207.8, 208.0-208.2, 208.8, 208.9, 230.x, 231.0-231.2, 231.8, 231.9, 232.x, 233.x, 234.0, 234.8, 234.9, 795.0, V10.3, V10.9, V71.1, 173.00-173.02, 173.09, 173.10-173.12, 173.19, 173.20-173.22, 173.29, 173.30-173.32, 173.39, 173.40-173.42, 173.49, 173.50-173.52, 173.59, 173.60-173.62, 173.69, 173.70-173.72, 173.79, 173.80-173.82, 173.89, 173.90-173.92, 173.99, 198.81, 198.82, 198.89, 200.x, 201.x, 202.x, 203.x, 204.x, 205.x, 206.x, 207.x, 208.x, 209.x, 233.3x, 258.02, 258.03, 511.81, 789.51, 795.00-795.04, 795.06, 795.10-795.14, 795.16, 796.70-796.74, 796.76, V10.x

Chronic kidney disease	236.91, 249.40, 249.41, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 753.1x, V45.11, V45.12, V56.31, V56.32, 189.0, 198.9, 223.0, 250.4, 271.4, 440.1, 442.1, 572.4, 753.2, 792.5, 794.4, 016.0, 095.4, V42.0, V45.1, V56.0, V56.1, V56.2, V56.8, 580-588, 591
Chronic pulmonary disease	490, 491, 492, 494, 496
Depression	296.2, 296.3, 296.5x, 296.6, 296.89, 298.0, 300.4, 309.1, 311
Diabetes	249, 250, 357.2, 362.01, 362.02, 366.41, 790.2, 791.5, 791.6, V45.85, V53.91, V65.46
Hepatitis	070, 072.71, 571.4, 573.1, 573.2, 573.3
Osteoporosis	733.0
Schizophrenia	293.81, 293.82, 295, 297, 298
Substance abuse	291, 292, 303, 304, 305.x, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3, 648.3, 655.5, 760.71, 760.72, 760.73, 760.75, 779.5, 965.0, 980.0, V65.42

Table 3: Incidence Rates of Outcomes by Antihypertensive Category

INCIDENCE RATE OF MI BY ANTIHYPERTENSIVE CATEGORY			
Antihypertensive Category	*N*	*Person years*	*no. of cases per 100 PY*
BB only	406	214923.4	0.19
Other single therapy	330	144708.2	0.23
BB + Other	1981	402510.5	0.49
Other dual therapy combination	391	142130.6	0.28
ACEI/BB/Diuretic or ARB/BB/Diuretic	2543	272481.0	0.93
Other triple therapy combination	1906	328735.8	0.58
Four or more drugs	4884	477746.7	1.02
INCIDENCE RATE OF HF BY ANTIHYPERTENSIVE CATEGORY			
Antihypertensive Category	*N*	*Person years*	*no. of cases per 100 PY*
BB only	423	215057.0	0.20
Other single therapy	1269	144119.0	0.88
BB + Other	5544	399700.0	1.39
Other dual therapy combination	2128	140724.6	1.51
ACEI/BB/Diuretic or ARB/BB/Diuretic	13881	259461.1	5.35
Other triple therapy combination	5884	324753.7	1.81
Four or more drugs	20179	455739.5	4.43
INCIDENCE RATE OF STROKE BY ANTIHYPERTENSIVE CATEGORY			
Antihypertensive Category	*N*	*Person years*	*no. of cases per 100 PY*
BB only	1020	214375.7	0.48
Other single therapy	855	144239.5	0.59
BB + Other	3008	401497.2	0.75

Other dual therapy combination	1100	141389.9	0.78
ACEI/BB/Diuretic or ARB/BB/Diuretic	2568	272804.5	0.94
Other triple therapy combination	3139	327154.8	0.96
Four or more drugs	5560	476980.5	1.17

ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. BB: beta blocker.

Table 4: Hazard Ratios for Outcomes per Antihypertensive Category

ANTIHYPERTENSIVE CATEGORY	HR	P-VALUE	95% HAZARD RATIO CONFIDENCE LIMITS	
Myocardial Infarction				
BB only	1.00			
Other single therapy	1.02	0.8333	0.88	1.18
BB + Other	1.99	<.0001	1.78	2.21
Other dual therapy combination	1.11	0.1384	0.97	1.28
ACEI/BB/Diuretic or ARB/BB/Diuretic	3.05	<.0001	2.74	3.40
Other triple therapy combination	2.28	<.0001	2.05	2.54
Four or more drugs	3.66	<.0001	3.30	4.05
Heart Failure				
BB only	1.00			
Other single therapy	3.12	<.0001	2.79	3.48
BB + Other	4.76	<.0001	4.31	5.26
Other dual therapy combination	4.62	<.0001	4.16	5.13
ACEI/BB/Diuretic or ARB/BB/Diuretic	12.57	<.0001	11.41	13.86
Other triple therapy combination	5.87	<.0001	5.31	6.48
Four or more drugs	12.81	<.0001	11.63	14.11
Stroke				
BB only	1.00			
Other single therapy	0.91	0.0552	0.84	1.00
BB + Other	1.17	<.0001	1.09	1.26
Other dual therapy combination	1.02	0.6670	0.94	1.11
ACEI/BB/Diuretic or ARB/BB/Diuretic	1.23	<.0001	1.14	1.33
Other triple therapy combination	1.32	<.0001	1.23	1.42
Four or more drugs	1.52	<.0001	1.42	1.63

Results from Cox proportional hazards model adjusted for Sex, MI, PAD, GI Bleeding, Prior Cerebral Bleeding, Other Bleeding, Anemia, Coagulopathy, Mood disorders, Cognitive impairment, Liver Disease, Alcohol abuse, HTN, CHF, CAD, Hyperlipidemia, Stroke, Arthritis,

Asthma, Cancer, CKD, COPD, Dementia, Depression, DM, Hepatitis, Osteoporosis, Schizophrenia, Substance abuse.
ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. BB: beta blocker.

Table 5: Hazard Ratio for Outcomes Stratified by Sex

ANTIHYPERTENSIVE	MALE	FEMALE
Myocardial Infarction		
BB only	1.0	1.0
Other single therapy	0.9 [0.7, 1.1]	1.2 [1.0, 1.6]
BB + Other	2.0 [1.7, 2.3]	2.0 [1.6, 2.4]
Other dual therapy combination	1.1 [0.9, 1.3]	1.1 [0.9, 1.4]
ACEI/BB/Diuretic or ARB/BB/Diuretic	3.0 [2.6, 3.4]	3.2 [2.6, 3.8]
Other triple therapy combination	2.4 [2.1, 2.7]	2.1 [1.7, 2.5]
Four or more drugs	3.7 [3.3, 4.2]	3.6 [3.0, 4.3]
Heart Failure		
BB only	1.0	1.0
Other single therapy	3.3 [2.8, 3.7]	2.9 [2.4, 3.5]
BB + Other	4.9 [4.3, 5.5]	4.6 [3.9, 5.4]
Other dual therapy combination	4.9 [4.3, 5.6]	4.3 [3.6, 5.1]
ACEI/BB/Diuretic or ARB/BB/Diuretic	13.1 [11.6, 14.9]	11.6 [9.9, 13.6]
Other triple therapy combination	5.4 [4.8, 6.1]	6.3 [5.4, 7.4]
Four or more drugs	13.0 [11.5, 14.7]	12.5 [10.7, 14.6]
Stroke		
BB only	1.0	1.0
Other single therapy	1.0 [0.9, 1.2]	0.8 [0.7, 0.9]
BB + Other	1.2 [1.1, 1.4]	1.1 [1.0, 1.2]
Other dual therapy combination	1.1 [0.9, 1.3]	0.9 [0.8, 1.0]
ACEI/BB/Diuretic or ARB/BB/Diuretic	1.4 [1.2, 1.5]	1.1 [1.0, 1.2]
Other triple therapy combination	1.4 [1.2, 1.5]	1.2 [1.1, 1.4]
Four or more drugs	1.7 [1.5, 1.8]	1.4 [1.3, 1.5]

Results from Cox proportional hazards model adjusted for Sex, MI, PAD, GI Bleeding, Prior Cerebral Bleeding, Other Bleeding, Anemia, Coagulopathy, Mood disorders, Cognitive

impairment, Liver Disease, Alcohol abuse, HTN, CHF, CAD, Hyperlipidemia, Stroke, Arthritis, Asthma, Cancer, CKD, COPD, Dementia, Depression, DM, Hepatitis, Osteoporosis, Schizophrenia, Substance abuse.

ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. BB: beta blocker.

Figure 1: Forest Plot representing Hazard Ratios for Antihypertensive Categories (Reference = Beta Blocker-only Therapy). Results from Cox proportional hazards model adjusted for Sex, MI, PAD, GI Bleeding, Prior Cerebral Bleeding, Other Bleeding, Anemia, Coagulopathy, Mood disorders, Cognitive impairment, Liver Disease, Alcohol abuse, HTN, CHF, CAD, Hyperlipidemia, Stroke, Arthritis, Asthma, Cancer, CKD, COPD, Dementia, Depression, DM, Hepatitis, Osteoporosis, Schizophrenia, Substance abuse.
ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. BB: beta blocker.

Myocardial Infarction	
Four or more drugs	3.7 [3.30, 4.05]
Other dual therapy combination	2.3 [2.05, 2.54]
BB + other	3 [2.74, 3.40]
Other triple therapy combination	1.1 [0.97, 1.28]
ACEI/BB/Diuretic or ARB/BB/Diuretic	2 [1.78, 2.21]
Other single therapy	1 [0.88, 1.18]

Heart failure	
Four or more drugs	4.6 [4.16, 5.13]
Other dual therapy combination	12.6 [11.41, 13.86]
BB + other	4.8 [4.31, 5.26]
Other triple therapy combination	12.8 [11.63, 14.11]
ACEI/BB/Diuretic or ARB/BB/Diuretic	3.1 [2.79, 3.48]
Other single therapy	5.9 [5.31, 6.48]

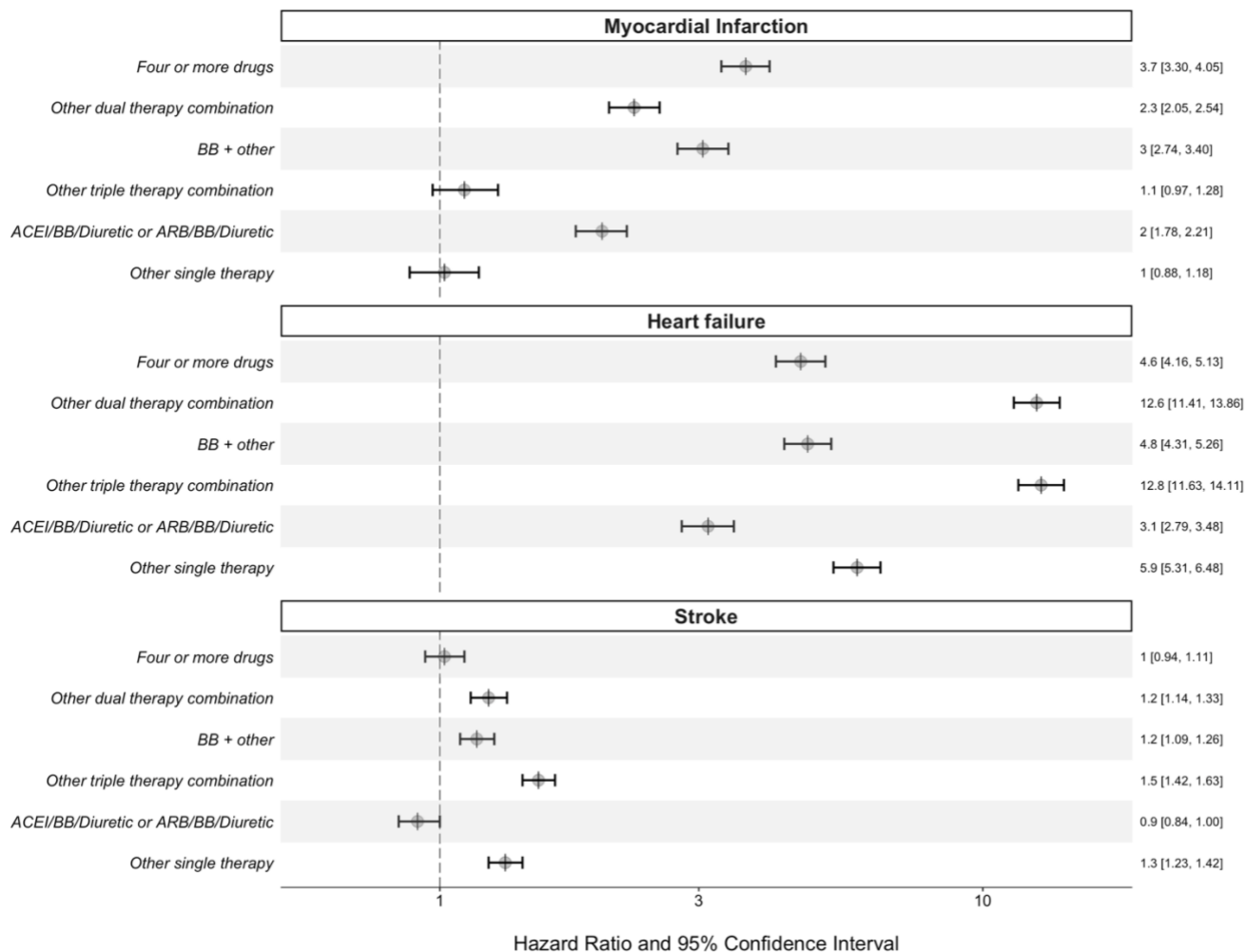| Stroke	
Four or more drugs	1 [0.94, 1.11]
Other dual therapy combination	1.2 [1.14, 1.33]
BB + other	1.2 [1.09, 1.26]
Other triple therapy combination	1.5 [1.42, 1.63]
ACEI/BB/Diuretic or ARB/BB/Diuretic	0.9 [0.84, 1.00]
Other single therapy	1.3 [1.23, 1.42]

Hazard Ratio and 95% Confidence Interval

Figure 2: Forest Plot representing Hazard Ratios for Antihypertensive Categories Stratified by Sex (Reference = Beta Blocker-only Therapy). Results from Cox proportional hazards model adjusted for Sex, MI, PAD, GI Bleeding, Prior Cerebral Bleeding, Other Bleeding, Anemia, Coagulopathy, Mood disorders, Cognitive impairment, Liver Disease, Alcohol abuse, HTN, CHF, CAD, Hyperlipidemia, Stroke, Arthritis, Asthma, Cancer, CKD, COPD, Dementia, Depression, DM, Hepatitis, Osteoporosis, Schizophrenia, Substance abuse.
ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. BB: Beta blocker.