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Risk Factors Influencing Outcomes of Atrial Fibrillation in ALLHAT

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Abstract

Background and Aims—ALLHAT, a randomized, double-blind, active-controlled, multicenter clinical trial of high risk hypertensive participants, compared treatment with an ACE-inhibitor (lisinopril) or calcium channel blocker (amlodipine) with a diuretic (chlorthalidone). Primary outcome was the occurrence of fatal coronary heart disease or nonfatal myocardial infarction. For this report, post-hoc analyses were conducted to determine the contribution of baseline characteristics of participants with or without baseline or incident atrial fibrillation (AF) and atrial flutter (AFL) to stroke, heart failure (HF), coronary heart disease (CHD), and mortality outcomes.

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Methods and Results—Minnesota Coding of baseline and biennial in-trial ECGs was used to determine the 334 baseline and 537 incident AF/AFL cases, respectively participants with AF/AFL: Cox regression was used to estimate hazard ratios of presence versus absence of either baseline or incident AF/AFL (as time-dependent covariate) for occurrence of stroke, CHD, HF, or mortality, while adjusting for selected baseline characteristics. Adjusted Cox regression was used to obtain hazard ratios (HRs) for presence versus absence of selected baseline characteristics among those with and without either baseline or incident AF/AFL. After adjusting for baseline characteristics, baseline AF/AFL was associated with stroke, HF, and mortality (HRs [95% CIs] 3.18, [2.34-4.33]; 2.65 [2.02-3.49]; and 2.10 [CI, 1.73-2.55], respectively, $P<0.05$). Incident AF/AFL was a significant risk factor for HF and mortality (HRs 2.80 and 2.06, respectively, $P<0.05$). Risk factor profiles for clinical outcomes for those with and without baseline or incident AF/AFL were largely similar.

Conclusions—AF/AFL is a significant risk factor for stroke, HF, and mortality. Additional risk factors for these outcomes were generally similar for participants with and without baseline or incident AF/AFL.

Keywords

Atrial fibrillation; heart failure; stroke; fatal CHD; hypertension

Introduction

Atrial fibrillation and atrial flutter (AF/AFL) are associated with substantially increased risk of major clinical events and death. [1] Hypertension is a major risk factor for AF with the highest population attributable risk (>20%) vs. diabetes <5%). [1-2] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) provides a unique opportunity to study the aftermath of prevalent and incident AF/AFL in a clinically and demographically diverse all-hypertensive cohort (N=42,418; age 55+) treated to a goal of <140 mmHg. We have previously reported, similar to others, that over a 4-8 years (mean 4.9) of follow-up, AF/AFL prevalent at baseline was associated with substantially increased risks of stroke (hazard ratio [HR] 3.63), heart failure (HF) (HR 3.17), fatal coronary heart disease (CHD) or non-fatal myocardial infarction (MI) (HR 1.64), and mortality (HR 2.82). [1,3-11] There was a 2-fold increased risk of mortality when AF/AFL was present at baseline or developed during follow-up.[4]

In this report we extend our study to examine which risk factors were independently associated with stroke, HF, non-fatal myocardial infarction (MI), and mortality in people with AF/AFL compared to people without. We do so to better define the risk factors that deserve special attention in people with AF/AFL and to determine the extent to which outcomes are associated with AF/AFL alone. Consistent with previous reports,[3,12] the analyses for this study will represent combined AF and AFL events (AF/AFL).

Methods

The rationale and design of the ALLHAT study have been reported.[13] Briefly, ALLHAT was a randomized, double-blind, practice-based, multicenter clinical trial sponsored by the

National Heart, Lung, and Blood Institute. It was designed to determine whether the calcium-channel blocker amlodipine, the ACE-inhibitor lisinopril, or the alpha-blocker doxazosin, was superior to the thiazide-like diuretic chlorthalidone in preventing CHD (primary outcome) or other CVD events. A lipid-lowering trial (LLT) component involved a subset of participants randomly assigned to open-label pravastatin or usual care.[9] Participants were hypertensive men and women 55 years old with at least 1 additional CHD risk factor. Individuals with a history of hospitalized or treated symptomatic HF and/or known left ventricular dysfunction (ejection fraction <35%) were excluded. Individuals with a history or ECG evidence of AF/AFL were not excluded.[13] Data regarding use of non-study medications, including warfarin, were not collected. All participants gave written informed consent, and all centers obtained institutional review board approval. Active follow-up ended March, 2002.[14-15] The doxazosin comparison with chlorthalidone was terminated early [16] and is not considered here due to differential follow-up.

ECG analysis

ECGs were recorded at clinical sites using standardized procedures at baseline and biannually, and forwarded to the ECG Reading Center (University of Minnesota, Minneapolis). Baseline and follow-up ECGs were centrally coded for rhythm, with AF and AFL coded separately using Minnesota Code definitions.[17] As noted previously, AF and AFL are considered together (AF/AFL).

Statistical methods

Statistical analyses were undertaken with STATA Software (version 13) (2013; Stata Corporation, College Station, TX). Outcomes of interest assessed were stroke, CHD, HF, and all-cause mortality after adjustment for baseline AF/AFL (fixed covariate) or incident AF/AFL (time-dependent covariate) in a time-dependent Cox PH model, including other baseline indicator covariates used in the previous ALLHAT AF/AFL paper: randomized antihypertensive treatment, age, sex, history of diabetes, current smoking status, history of CHD, presence of LVH, history of atherosclerotic CVD, history of aspirin use, prior antihypertensive treatment, body mass index (BMI), and estimated glomerular filtration rate (eGFR) [2]. HRs and 95% confidence intervals (CIs) were obtained from the Cox models, with testing for significant interactions ($P<0.05$) between either baseline or incident AF/AFL and the selected baseline covariates of interest. Given the many multivariate, subgroup, and interaction analyses performed, statistical significance at the 0.05 level should be interpreted cautiously.

Results

Baseline ECGs with AF/AFL status were available for 92.0% ($n=30,704$) of the 33,357 ALLHAT participants randomized to chlorthalidone, amlodipine, or lisinopril. The proportion of participants missing AF/AFL status (7.8% chlorthalidone, 8.0% amlodipine, 8.2% lisinopril) did not differ by treatment group ($P=0.617$). Pre-existing AF/AFL was present in 334 (1.1%) of the 30,704 participants evaluated. Of these, only 16 had AFL. The prevalence of AF/AFL was 10.5, 11.9, and 10.6 per 1,000 participants in the chlorthalidone, amlodipine, and lisinopril groups, respectively. There were follow-up ECGs on participants

who did not have baseline ECGs. One could have a missing baseline ECG, a normal 2-year ECG, and a 4-year ECG with AF or AFL. Therefore, the denominator for calculating incident AF/AFL rose from 30,370 (30,704 - 334) to 31,692, which included 502 cases of AF and 35 cases of AFL. The incidence of AF/AFL during the trial was 15.7, 17.1, and 15.0 per 1000 participants in chlorthalidone, amlodipine, and lisinopril groups, respectively.

Table 1 shows adjusted Cox regression models for risk of AF/AFL and demographic and clinical characteristics at baseline on development of four major clinical outcomes. Prevalent baseline AF/AFL remained a significant risk factor ($P<0.05$) for stroke ($n=1254$; $HR=3.18$), HF ($n=1800$; $HR=2.65$), and mortality ($n=4063$; $HR=2.10$), but not for CHD ($n=2546$; $HR=1.23$, $P=NS$). Several established cardiovascular risk factors were independently associated with an increased risk of each of the four outcomes reported here: age >70 -79 or >80 years, diabetes, smoking, LVH, ASCVD, and $eGFR<60$. Male sex was associated with an increased risk of stroke, CHD and death, but not HF. Black race was associated with an increased risk of stroke and all-cause mortality and similar risk of CHD and HF.

New-onset AF/AFL manifested by appearance on biennial ECGs is an independent significant risk factor for HF and death (HRs 2.80 and 2.08, respectively, $P<0.05$) even when adjusting for other important baseline characteristics, including randomized treatment assignment, but not for stroke or CHD (HRs 1.63 and 1.20, respectively, $P=NS$) (Table 2). Advanced age (>80) is the strongest independent predictor of all outcomes. Age >70 , diabetes, smoking, LVH, ASCVD, and $eGFR$ were independent increased risk predictors for each of the four outcomes. Male sex was an independent risk predictor for stroke, CHD and death, but not for HF. $HDL<35$ was an independent risk predictor for CHD and HF. Blacks had higher adjusted risks of stroke and total mortality.

Table 3 presents, stratified by those with and without prevalent AF/AFL at baseline, the HRs of selected baseline demographic and clinical characteristics for the occurrence of stroke, CHD, HF, and all-cause mortality. There was no differential effect on stroke by race, diabetes status, smoking status, CHD history, presence of LVH, ASCVD history, prior antihypertensive treatment, aspirin use, BMI subgroup, $eGFR$ subgroup, or HDL subgroup among those with and without AF/AFL. There were significant interactions for sex and age ($P<0.05$) with the increase in stroke risk associated with AF/AFL. For those with and without baseline AF/AFL, the HRs for stroke in men were 0.68 ($P=0.249$) and 1.31 ($P<0.001$), respectively (interaction $P=0.039$), and for those aged 70–79 years HRs were 0.63 ($P=0.222$) and 1.77 ($P<0.001$), respectively (interaction $P=0.012$). Specifically, men and older individuals without AF/AFL were at significantly higher risk of stroke compared to women and those aged 55–69 years of age. However, when AF/AFL was present on baseline ECGs, the risk of stroke in women was similar to that of men, and the risk of stroke in those aged 55–69 years did not differ from those aged 70–79 years.

There was no differential effect on CHD by any of the listed characteristics except age among those with and without AF/AFL. For those with and without baseline AF/AFL, HRs for participants aged 70–79 years were 0.80 ($P=0.566$) and 1.44 ($P<0.001$), respectively. There was no differential effect on HF by any of the listed characteristics except aspirin use. For those with and without baseline AF/AFL, the HRs for those on aspirin at baseline were

0.58 ($P=0.107$) and 1.16 ($P=0.003$), respectively. Finally, there was no differential effect on all-cause mortality for any of the baseline characteristics except eGFR among those with and without AF/AFL. For those with and without baseline AF/AFL, HRs for those with an eGFR<60 were 0.95 ($P=0.842$) and 1.63 ($P<0.001$), respectively.

Table 4 presents HRs of selected baseline demographic and clinical characteristics for those with incident AF/AFL and those who do not develop new-onset AF/AFL prior to the occurrence of stroke, CHD, HF, and all-cause mortality. There was no differential effect on stroke by any of the characteristics except race among those with and without AF/AFL. For those with and without incident AF/AFL, the HRs for Blacks were 4.93 ($P=0.002$) and 1.35 ($P<0.001$), respectively.

There was no differential effect on CHD by any of the characteristics except diabetes and HDL status among those with and without AF/AFL. For those with and without incident AF/AFL, HRs for those with diabetes at baseline were 0.67 ($P=0.362$) and 1.79 ($P<0.001$), respectively; and for those with HDL<35 mg/dL, 0.31 ($P=0.032$) and 1.21 ($P<0.001$), respectively.

There was no differential effect on HF by any of the characteristics except diabetes, HDL status, and race among those with and without AF/AFL. For those with and without incident AF/AFL, HRs for those with diabetes at baseline were 1.02 ($P=0.957$) and 2.10 ($P<0.001$), respectively; for those with HDL<35 mg/dL, were 0.35 ($P=0.017$) and 1.22 ($P=0.001$), respectively; and for Blacks were 2.46 ($P=0.012$) and 1.07 ($P=0.203$), respectively.

There was no differential effect on mortality by any of the characteristics except diabetes, HDL status, and race among those with and without AF/AFL. For those with and without incident AF/AFL, HRs for those with diabetes at baseline were 0.85 ($P=0.488$) and 1.74 ($P<0.001$), respectively; for those with HDL<35 mg/dL, 0.62 ($P=0.049$) and 1.09 ($P=0.031$), respectively; and for Blacks, 2.27 ($P<0.001$) and 1.17 ($P<0.001$), respectively.

Discussion

Previously we examined the contributions of prevalent and incident AF/AFL to the ALLHAT outcomes. [3] Certain risk factors present at baseline were associated with both prevalent and incident AF/AFL. Because both were associated with high rates of stroke, HF, CHD and MI, and mortality, we undertook the current investigation in an attempt to determine whether AF/AFL alone accounted for differences in outcomes previously found or whether specific risk factors contributed differentially to specific outcomes whether or not AF/AFL was present. Accordingly, we used the same risk factors as in the previous analyses for the current investigation.

This analysis of the ALLHAT data shows that in high CVD risk patients with treated and controlled hypertension,[15] AF/AFL present on a baseline ECG, i.e., prevalent AF/AFL, was independently associated with increased risks of stroke, HF, and mortality, but not CHD, over a mean follow-up of 5.1 years (up to 8 years) (Table 1). Similarly, incident AF/AFL is a strong predictor of HF and mortality, but not of stroke or CHD, after accounting for the same common risk factors for AF/AFL among those with these outcomes (Table 2).

We now show that risk profiles were generally similar for each of the major outcomes previously reported in ALLHAT [3] for both baseline and incident AF/AFL compared to non-AF/AFL patients. When these observations were extended for the same outcomes for incident AF/AFL separately, compared to non-AF/AFL patients, there were also similar risk profiles. The likelihood of success by focusing on risk factors to reduce the major outcomes associated with AF/AFL in high risk populations does not seem high, given the significant interactions noted in Table 3 and 4. Most of the interactive factors are unalterable, such as age, gender and preexisting conditions.

The absence of a constellation of modifiable risk factors specific to patients with AF/AFL lends itself to a recommendation for aggressive treatment of modifiable risk factors to prevent AF/AFL and the associated increased risk of stroke, HF and mortality. Nevertheless, better management of diabetes, raising of HDL levels and controlling blood pressure (BP) to stabilize or reduce LVH may be favorable influences on the outcome of HF in hypertensive populations with and without AF/AFL.

Risk factors for stroke, CHD, HF, and mortality in those with and without incident AF/AFL are comparable, with several notable exceptions. For stroke and death, the risk seems to be higher in Blacks with versus without AF/AFL. However, for HF the opposite is seen: the risk appears higher in Blacks without versus with AF/AFL. For CHD, HF, and death, the risk appears higher in those with diabetes for those without versus those with AF/AFL, and, for CHD, HF and mortality, the higher in those with HDL<35 mg/dl for those without versus those with AF/AFL.

While much attention in the literature has been directed at risk factors associated with the risk of AF/AFL, its prevalence in the population, and prevention of complications of stroke and thromboembolism, our data demonstrate that the cluster of risk factors that increase the likelihood of major outcomes in those with AF/AFL presage similar dire outcomes for those without AF/AFL. Efforts to reduce the influence of clusters of risk factors in high risk population are likely to benefit those with AF/AFL or those who develop AF/AFL, as well as those who avoid this important complication. [18-22]

A risk score for the development of AF has been developed from the Framingham database which includes age, sex, body mass index, systolic BP, treatment for hypertension, PR interval, cardiac murmur and HF, with body mass index performing less well than the other factors. [23] Applied separately to three large databases, the risk score performed well in predicting the occurrence of AF in both white and African-American participants. [24] It is noteworthy that the prediction model includes systolic BP, hypertension treatment, and HF.

The current report from ALLHAT suggests that the risk factors that were associated with prevalent and incident AF/AFL and with the outcomes of stroke, HF, CHD and mortality are interactive, and that some combinations of risk factors may effectively neutralize the added presence of AF/AFL. Additional studies utilizing this database to determine the potential influence of concurrent factors, such as in-trial HF on stroke, CHD, and mortality following incident AF/AFL, are warranted. [25,26]

Although, as previously reported, ALLHAT did not support a preferential treatment effect of lisinopril versus chlorthalidone or amlodipine on incident of AF/AFL as found in other studies, a recent report suggesting that in-trial BP lowering may decrease the occurrence of incident AF/AFL, possibly operative in ALLHAT (unrelated to specific therapies), affecting both the arrhythmia and associated outcomes. [27] The prior report from the same study showing the added benefit of Losartan over the beta-blocker atenolol (in patients not requiring the beta-blocker for rate control) included only AF/AFL patients who also met multiple classical criteria for LVH, a restriction not applied in ALLHAT, making direct comparisons difficult. AF/AFL patients in this study were older, more likely male, with higher rates of CHD, cerebrovascular disease, peripheral vascular disease, and diabetes. The authors suggested the possibility that outcome results were associated with reduction in parameters associated with LVH.[28]

Most hypertension outcomes trials include patients with few other clinical risks or do not provide sufficient detail regarding other outcomes for comparison to our study. In a major mega-analysis of antihypertension treatment and the development of HF (which included 223,313 participants), only one of the major trials summarized in the study (ALLHAT) included diabetic participants; other risk factors are not summarized and outcomes other than HF are not tabulated.[29] This approach is common in trials focused on stroke as the outcome of interest.

The strengths of this study include the uniquely large and well-defined ALLHAT database, composed of individuals known to be at high risk for the complication of AF/AFL and thus well-suited to assess the risks associated with the development and outcomes of this complication. Manifest HF was an enrollment exclusion; thus, AF/AFL present at baseline or occurring during the trial was not a complication of pre-existing HF.

Weaknesses include the absence of hypotheses related to AF/AFL as a primary outcome in the study protocol; the results obtained here are observational. In addition, none of the main or interaction hypotheses was pre-specified. The lack of data regarding Warfarin use and the inability to distinguish paroxysmal vs. sustained AF also limit this study. Given the many analyses that were performed, the findings, especially tests of interaction, should be interpreted with caution.

ALLHAT has provided the opportunity to annotate the contributions of this major arrhythmia to clinical outcomes of this trial. The high risk hypertensive cohort was not assembled to address issues related to AF/AFL, nor was study therapy specifically directed toward the prevention or management of AF/AFL or its complications. Nonetheless, investigation of the constellation of risk factors for AF/AFL and for its consequent cardiovascular outcomes in the ALLHAT and other large patient populations moves us closer to identifying those risks that might serve as targets of prevention and early intervention in such high-risk patients.

Implications

Not only is atrial fibrillation associated with substantially increased risk of acute ischemic stroke and transient ischemic attacks (TIAs), but its prevalence in both continues to rise. [8]

Further, anticoagulation, the major treatment of AF patients, in particular is fraught with the potential for hemorrhagic stroke complications, thus highlighting the importance of the influence of risk factors contributing to AF/AFL in high-risk populations. Understanding and controlling risk factors associated with AF/AFL is of paramount importance if we are to stem its devastating sequelae, made all the more complicated by decreasing economic and social resources to care for the mostly older-age victims of stroke.

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Declaration of Helsinki: The study complies with the Declaration of Helsinki. All clinical sites had local ethics board approvals; post-trial follow-up was approved by the ethics board at the University of Texas Health Science Center at Houston. Written informed consent was obtained from all subjects or their legally authorized representatives.

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Table 1
Adjusted Cox regression for risk of atrial fibrillation and other characteristics at baseline on development of major outcomes

Baseline Characteristics	Stroke(n=1254) HR(95% CI)	CHD(n=2546) HR(95% CI)	HF(n=1800) HR(95% CI)	All-cause Mortality(n=4063) HR(95% CI)
Amlodipine vs Chlorthalidone	0.95(0.83–1.09)	1.02(0.93–1.12)	1.40(1.25–1.56)	0.98(0.91–1.06)
Lisinopril vs Chlorthalidone	1.17(1.03–1.33)	1.00(0.91–1.10)	1.21(1.08–1.35)	1.00(0.92–1.07)
Atrial fibrillation	3.18(2.34–4.33)	1.23(0.89–1.70)	2.65(2.02–3.49)	2.10(1.73–2.55)
Aged 70–79 years	1.73(1.53–1.95)	1.43(1.31–1.56)	1.79(1.61–1.98)	1.97(1.83–2.11)
Aged 80 years	2.57(2.11–3.13)	2.28(1.98–2.63)	3.46(2.97–4.03)	4.25(3.85–4.69)
Men	1.29(1.14–1.45)	1.45(1.33–1.59)	1.05(0.95–1.16)	1.49(1.39–1.59)
Diabetic	1.80(1.60–2.03)	1.78(1.64–1.94)	2.06(1.87–2.28)	1.72(1.61–1.84)
Smoker	1.48(1.29–1.71)	1.49(1.35–1.65)	1.32(1.16–1.49)	1.90(1.77–2.05)
CHD present	1.03(0.90–1.19)	1.31(1.19–1.45)	1.43(1.28–1.61)	1.10(1.01–1.19)
LVH present	1.92(1.59–2.31)	1.79(1.56–2.07)	2.24(1.92–2.61)	1.53(1.37–1.71)
ASCVD present	1.44(1.25–1.65)	1.50(1.36–1.67)	1.55(1.37–1.75)	1.39(1.29–1.51)
Aspirin use	1.09(0.96–1.23)	1.12(1.03–1.22)	1.14(1.03–1.26)	0.94(0.88–1.01)
Treated for hypertension	1.06(0.87–1.30)	1.07(0.93–1.23)	1.23(1.02–1.47)	1.01(0.90–1.12)
BMI 30 kg/m ²	0.94(0.84–1.06)	0.93(0.85–1.01)	1.25(1.14–1.38)	0.88(0.82–0.94)
eGFR < 60 mL/min	1.41(1.23–1.61)	1.33(1.21–1.46)	1.64(1.48–1.82)	1.61(1.50–1.72)
HDL < 35 mg/dL	1.10(0.95–1.26)	1.19(1.08–1.31)	1.20(1.07–1.35)	1.08(1.00–1.16)
Black	1.36(1.20–1.54)	0.91(0.83–0.99)	1.06(0.95–1.18)	1.17(1.10–1.26)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body-mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HF, heart failure; LVH, left ventricular hypertrophy. Treatment for hypertension refers to use of any prescribed antihypertensive medication at the time of randomization to ALLHAT.

Adjusted Cox regression for risk of incident atrial fibrillation and other baseline characteristics on development of major outcomes**Table 2**

Baseline Characteristics	Stroke(n=1211)	CHD(n=2508)	HF(n=1746)	All-cause Mortality(n=3955)
	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
Amlodipine vs Chlorthalidone	0.93(0.81–1.07)	1.03(0.94–1.13)	1.39(1.24–1.55)	0.99(0.92–1.07)
Lisinopril vs Chlorthalidone	1.17(1.02–1.34)	1.00(0.91–1.10)	1.20(1.07–1.35)	1.01(0.93–1.09)
Incident atrial fibrillation	1.63(0.97–2.72)	1.20(0.82–1.75)	2.80(2.03–3.86)	2.08(1.68–2.57)
Aged 70-79 years	1.77(1.56–2.00)	1.44(1.32–1.57)	1.77(1.59–1.97)	1.96(1.82–2.10)
Aged 80 years	2.60(2.13–3.19)	2.31(2.00–2.66)	3.46(2.96–4.04)	4.25(3.85–4.69)
Men	1.31(1.16–1.48)	1.46(1.33–1.59)	1.05(0.95–1.17)	1.47(1.37–1.58)
Diabetic	1.81(1.61–2.05)	1.78(1.63–1.93)	2.08(1.88–2.30)	1.72(1.60–1.84)
Smoker	1.51(1.31–1.74)	1.50(1.35–1.65)	1.33(1.17–1.51)	1.92(1.78–2.07)
CHD present	1.00(0.86–1.16)	1.31(1.19–1.45)	1.43(1.27–1.61)	1.07(0.99–1.16)
LVH present	1.93(1.60–2.33)	1.79(1.55–2.06)	2.22(1.90–2.59)	1.50(1.34–1.68)
ASCVD present	1.44(1.25–1.66)	1.50(1.35–1.66)	1.56(1.38–1.76)	1.40(1.30–1.52)
Aspirin use	1.12(0.99–1.26)	1.12(1.03–1.22)	1.17(1.05–1.29)	0.95(0.89–1.02)
Treated for hypertension	1.04(0.85–1.27)	1.07(0.93–1.23)	1.20(0.99–1.44)	1.00(0.89–1.11)
BMI 30 kg/m ²	0.93(0.83–1.05)	0.92(0.85–1.00)	1.25(1.13–1.38)	0.87(0.81–0.93)
eGFR < 60 mL/min	1.42(1.24–1.63)	1.34(1.22–1.47)	1.66(1.49–1.85)	1.62(1.51–1.75)
HDL < 35 mg/dL	1.12(0.97–1.29)	1.19(1.08–1.31)	1.19(1.06–1.34)	1.07(0.99–1.16)
Black	1.37(1.21–1.55)	0.92(0.84–1.00)	1.09(0.98–1.21)	1.19(1.11–1.27)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body-mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HF, heart failure; LVH, left ventricular hypertrophy

Table 3
Adjusted Cox regressions for risk of selected baseline characteristic on development of major outcomes among those with and without atrial fibrillation at baseline

Baseline Characteristic	Stroke(n=43, 1211)		CHD(n= 38, 2508)		HF(n= 54, 1746)		All-cause Mortality(n=108, 3955)	
	Atrial fibrillation	No atrial fibrillation	Atrial fibrillation	No atrial fibrillation	Atrial fibrillation	No atrial fibrillation	Atrial fibrillation	No atrial fibrillation
Amlodipine	1.40(0.68–2.88)	0.93(0.81–1.07)	0.53(0.22–1.28)	1.03(0.94–1.13)	1.67(0.88–3.19)	1.39(1.24–1.55)	0.69(0.43–1.09)	0.99(0.92–1.07)
Lisinopril	1.07(0.48–2.42)	1.17(1.02–1.34)	0.74(0.32–1.69)	1.00(0.91–1.10)	1.36(0.67–2.76)	1.20(1.07–1.35)	0.55(0.33–0.93)	1.01(0.93–1.09)
Aged 70-79 years	0.63(0.30–1.33) *	1.77(1.57–2.01)	0.80(0.37–1.71) *	1.44(1.32–1.57)	1.56(0.78–3.13)	1.79(1.61–1.98)	1.68(1.04–2.74)	1.97(1.84–2.12)
Aged 80 years	1.44(0.60–3.46)	2.61(2.14–3.20)	1.39(0.48–3.99)	2.31(2.00–2.66)	3.07(1.30–7.24)	3.49(2.99–4.08)	3.40(1.87–6.17)	4.28(3.88–4.73)
Men	0.68(0.36–1.30) *	1.31(1.16–1.48)	1.21(0.56–2.59)	1.46(1.34–1.59)	0.78(0.44–1.37)	1.06(0.96–1.18)	1.57(1.00–2.45)	1.48(1.38–1.59)
Diabetic	1.58(0.78–3.19)	1.82(1.61–2.05)	1.84(0.90–3.78)	1.78(1.63–1.93)	1.36(0.74–2.51)	2.08(1.89–2.31)	1.90(1.23–2.92)	1.72(1.61–1.84)
Smoker	0.68(0.20–2.36)	1.51(1.31–1.74)	1.28(0.47–3.50)	1.50(1.36–1.65)	1.08(0.44–2.65)	1.33(1.17–1.51)	1.34(0.73–2.47)	1.92(1.78–2.07)
CHD present	1.96(0.97–3.96)	1.00(0.86–1.16)	1.09(0.51–2.34)	1.32(1.19–1.45)	1.12(0.59–2.11)	1.44(1.28–1.62)	1.64(1.05–2.57)	1.08(1.00–1.17)
LVH present	1.37(0.40–4.70)	1.94(1.60–2.34)	2.01(0.57–7.01)	1.79(1.55–2.06)	1.57(0.47–5.29)	2.25(1.93–2.63)	1.78(0.90–3.52)	1.52(1.35–1.70)
ASCVD present	1.19(0.48–2.95)	1.44(1.25–1.66)	1.53(0.61–3.82)	1.50(1.35–1.66)	1.14(0.56–2.32)	1.56(1.37–1.76)	1.01(0.59–1.71)	1.40(1.30–1.52)
Aspirin use	0.57(0.26–1.23)	1.11(0.99–1.26)	1.14(0.55–2.34)	1.12(1.03–1.22)	0.58(0.30–1.13) *	1.16(1.05–1.29)	0.81(0.52–1.26)	0.95(0.88–1.01)
Treated for hypertension	2.08(0.48–8.92)	1.04(0.85–1.27)	0.91(0.26–3.19)	1.07(0.93–1.23)	2.94(0.70–12.39)	1.20(1.00–1.44)	1.42(0.65–3.14)	1.00(0.89–1.11)
BMI 30 kg/m ²	1.02(0.53–1.99)	0.93(0.83–1.05)	1.31(0.65–2.64)	0.92(0.85–1.00)	1.07(0.60–1.91)	1.26(1.14–1.39)	1.00(0.66–1.54)	0.87(0.82–0.94)
eGFR < 60	1.00(0.47–2.10)	1.42(1.24–1.63)	0.71(0.30–1.67)	1.34(1.22–1.48)	1.05(0.55–1.99)	1.66(1.49–1.85)	0.95(0.60–1.52) *	1.63(1.52–1.75)
MI/min HDL < 35 mg/dL	0.51(0.23–1.15)	1.12(0.97–1.30)	1.03(0.50–2.12)	1.19(1.08–1.31)	1.16(0.62–2.16)	1.20(1.06–1.35)	0.88(0.56–1.37)	1.08(1.00–1.17)
Black	0.97(0.44–2.15)	1.37(1.21–1.55)	0.37(0.11–1.25)	0.91(0.83–1.00)	0.39(0.15–1.03)	1.08(0.97–1.20)	0.96(0.58–1.60)	1.18(1.10–1.26)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body-mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HF, heart failure; LVH, left ventricular hypertrophy.

* Statistically significant interactions of baseline atrial fibrillation and baseline variable: Stroke - age 70-79 years ($P=0.012$), men ($P=0.039$); CHD - age 70-79 years ($P=0.038$); HF - aspirin use ($P=0.034$); Mortality-eGFR < 60 ($P=0.017$).

Table 4
Adjusted Cox regression for risk of selected baseline characteristics on development of major outcomes among those with and without incident atrial fibrillation

Baseline Characteristic	Stroke(n=15, 1196)		CHD(n=27, 2481)		HF(n=39, 1707)		All-cause Mortality(n=88, 3867)	
	Atrial fibrillation	No atrial fibrillation	Atrial fibrillation	No atrial fibrillation	Atrial fibrillation	No atrial fibrillation	Atrial fibrillation	No atrial fibrillation
Amlodipine	0.57(0.12–2.84)	0.94(0.81–1.08)	0.95(0.39–2.32)	1.03(0.94–1.13)	1.13(0.56–2.31)	1.39(1.25–1.56)	0.71(0.42–1.22)	1.00(0.93–1.08)
Lisinopril	2.04(0.68–6.07)	1.16(1.02–1.33)	0.61(0.22–1.67)	1.01(0.92–1.11)	0.57(0.23–1.42)	1.22(1.08–1.37)	0.72(0.43–1.22)	1.02(0.94–1.10)
Aged 70–79 years	1.30(0.45–3.74)	1.79(1.58–2.03)	0.89(0.39–2.01)	1.46(1.34–1.59)	0.90(0.45–1.81)	1.82(1.63–2.02)	1.28(0.80–2.05)	1.99(1.86–2.14)
Aged 80 years	0.98(0.12–8.15)	2.65(2.17–3.25)	2.11(0.68–6.54)	2.33(2.02–2.69)	2.93(1.21–7.09)	3.51(3.00–4.11)	3.46(1.91–6.27)	4.29(3.88–4.74)
Men	1.09(0.35–3.41)	1.32(1.16–1.49)	0.96(0.42–2.20)	1.46(1.34–1.60)	0.71(0.37–1.37)	1.06(0.96–1.18)	1.29(0.79–2.09)	1.48(1.38–1.59)
Diabetic	1.00(0.34–2.93)	1.83(1.62–2.07)	0.67(0.28–1.58)*	1.79(1.65–1.95)	1.02(0.52–1.98)*	2.10(1.90–2.33)	0.85(0.53–1.35)*	1.74(1.62–1.86)
Smoker	2.12(0.60–7.52)	1.51(1.31–1.74)	3.45(1.46–8.17)	1.48(1.34–1.64)	1.63(0.68–3.90)	1.33(1.17–1.51)	2.78(1.70–4.55)	1.91(1.77–2.06)
CHD present	0.40(0.13–1.27)	1.02(0.88–1.18)	0.86(0.40–1.85)	1.32(1.20–1.46)	1.28(0.68–2.41)	1.44(1.28–1.62)	1.17(0.77–1.79)	1.07(0.99–1.16)
LVH present	3.28(1.04–10.31)	1.94(1.60–2.34)	1.29(0.39–4.30)	1.82(1.58–2.10)	1.68(0.70–4.00)	2.27(1.94–2.66)	1.29(0.69–2.43)	1.54(1.37–1.72)
ASCVD present	1.16(0.39–3.40)	1.44(1.25–1.66)	1.13(0.49–2.60)	1.50(1.35–1.67)	2.49(1.09–5.68)	1.54(1.36–1.75)	1.41(0.88–2.26)	1.41(1.30–1.53)
Aspirin use	1.38(0.50–3.80)	1.11(0.98–1.25)	0.62(0.28–1.35)	1.12(1.03–1.22)	1.00(0.53–1.88)	1.17(1.05–1.29)	0.75(0.49–1.15)	0.95(0.89–1.02)
Treated for hypertension	1.11(0.15–8.45)	1.04(0.85–1.27)	†	1.06(0.92–1.22)	1.30(0.31–5.40)	1.19(0.99–1.44)	0.77(0.36–1.68)	1.00(0.90–1.12)
BMI 30 kg/m ²	0.80(0.28–2.24)	0.94(0.83–1.06)	0.72(0.33–1.56)	0.93(0.85–1.01)	0.67(0.35–1.31)	1.27(1.15–1.41)	0.73(0.48–1.14)	0.88(0.82–0.94)
eGFR < 60 ml/min	0.72(0.20–2.54)	1.44(1.25–1.65)	1.43(0.64–3.19)	1.34(1.22–1.47)	1.23(0.62–2.44)	1.67(1.50–1.86)	1.19(0.75–1.87)	1.64(1.52–1.76)
HDL < 35 mg/dL	0.42(0.12–1.50)	1.14(0.98–1.31)	0.31(0.11–0.91)*	1.21(1.10–1.33)	0.35(0.14–0.83)*	1.22(1.09–1.38)	0.62(0.38–1.00)*	1.09(1.01–1.18)
Black	4.93(1.78–13.65)*	1.35(1.19–1.53)	1.05(0.36–3.04)	0.91(0.83–1.00)	2.46(1.22–4.97)*	1.07(0.96–1.19)	2.27(1.44–3.58)*	1.17(1.09–1.25)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body-mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HF, heart failure; LVH, left ventricular hypertrophy.

* Statistically significant interactions of incident atrial fibrillation and baseline variable: Stroke – Black($P=0.013$); CHD – diabetes($P=0.025$), HDL < 35($P=0.013$); HF – diabetes($P=0.034$), HDL < 35($P=0.005$), Black($P=0.022$); Mortality – diabetes($P=0.003$), HDL < 35($P=0.022$), Black($P=0.005$).

† Failure to converge due to lack of new onset CHD events in those with incident atrial fibrillation, within the subset of participants that were not treated for hypertension at baseline(a small percentage of participants overall had not been treated for hypertension at baseline).