Title

Impact of genetic variants on the upstream efficacy of renin-angiotensin system inhibitors for the prevention of atrial fibrillation

Authors

Roberts, Jason D
Dewland, Thomas A
Glidden, David V
et al.

Publication Date

2016-05-01

DOI

10.1016/j.ahj.2016.02.002

Peer reviewed

HHS Public Access

Author manuscript

Am Heart J. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Am Heart J. 2016 May ; 175: 9–17. doi:10.1016/j.ahj.2016.02.002.

Impact of Genetic Variants on the Upstream Efficacy of Renin-Angiotensin System Inhibitors for the Prevention of Atrial Fibrillation

Jason D. Roberts, MD, **Thomas A. Dewland, MD**, **David V. Glidden, PhD**, **Thomas J. Hoffman, PhD**, **Dan E. Arking, PhD**, **Lin Y. Chen, MD MS**, **Bruce M. Psaty, MD PhD**, **Jeffrey E. Olgin, MD**, **Alvaro Alonso, MD PhD**, **Susan R. Heckbert, MD PhD**, and **Gregory M. Marcus, MD MAS**

Section of Cardiac Electrophysiology, Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, California, USA (J.D.R., T.A.D., J.E.O., G.M.M.), Departments of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA (D.V.G., T.J.H.), Institute for Human Genetics, University of California San Francisco, San Francisco, California, USA (T.J.H.), McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA (D.E.A.), Department of Medicine, Cardiovascular Division, University of Minnesota, Minneapolis, Minnesota, USA (L.Y.C.), Cardiovascular Health Research Unit, University of Washington, Seattle, Washington, USA, (B.M.P, S.R.H.), Departments of Medicine and Health Services, University of Washington, Seattle, Washington, USA (B.M.P.), Group Health Research Institute, Group Health, Seattle, Washington, USA (B.M.P., S.R.H.), Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA (A.A.), Department of Epidemiology, University of Washington, Seattle, Washington, USA (S.R.H.)

Abstract

Background—Renin angiotensin system (RAS) inhibition via ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) may reduce the risk of developing atrial fibrillation (AF) in certain populations, but the evidence is conflicting. Recent genome wide association studies have identified several single nucleotide polymorphisms (SNPs) associated with AF, potentially identifying clinically relevant subtypes of the disease. We sought to investigate the impact of carrier status of 9 AF-associated SNPs on the efficacy of RAS inhibition for the primary prevention of AF.

Methods—We performed SNP-RAS inhibitor interaction testing with unadjusted and adjusted Cox proportional hazards models using a discovery (Cardiovascular Health Study [CHS]) and a

Address for correspondence: Gregory M Marcus, 500 Parnassus Ave, MUE 434, San Francisco, CA, 94143-1354, Phone: (415) 476-5706, Fax: (415) 476-3505.

Disclosures: None to report and no relevant relationships with industry.

replication (Atherosclerosis Risk in Communities [ARIC]) cohort. Additive genetic models were employed for the SNP analyses and two-tailed p-values < 0.05 were considered statistically significant

Results—Among 2796 CHS participants. none of the 9 *a priori* identified candidate SNPs exhibited a significant SNP-drug interaction. Two of the 9 SNPs, rs2106261 (16q22) and rs6666258 (1q21), revealed interaction relationships that neared statistical significance (with point estimates in the same direction for ACEi only and ARB only analyses), but neither association could be replicated among 8604 participants in ARIC.

Conclusions—Our study failed to identify AF-associated SNP genetic sub-types of AF that derive increased benefit from upstream RAS inhibition for AF prevention. Future studies should continue to investigate the impact of genotype on the response to AF treatment strategies in an effort to develop personalized approaches to therapy and prevention.

Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is a growing health epidemic associated with substantial clinical and economic burdens.[1–3] Previously shown to be an independent risk factor for death, patients with AF also suffer from a higher incidence of heart failure and a nearly 5-fold increased risk of stroke.[4–6] The devastating clinical and economic impacts of AF are further exacerbated by a lack of highly effective treatment strategies. Anti-arrhythmic drugs have failed to show clinical benefit relative to rate control strategies, while the long term efficacy of catheter ablation is modest.[7–10] The development of more efficacious treatment strategies will likely require improved insight into the pathophysiology underlying the arrhythmia.[11]

Population-based studies have revealed that a positive family history of AF is associated with an increased risk of developing the arrhythmia, particularly among individuals with no overt cardiovascular disease.[12–15] These findings provided rationale for large scale genome wide association studies (GWAS), which subsequently identified nine common single nucleotide polymorphisms (SNPs) that impart a heightened risk of arrhythmia development.[16–20] While these AF associated SNPs are non-coding and their precise function remains unknown, they have been hypothesized to influence the expression of nearby genes within the same genetic locus. The genes located within these 9 different loci are likely to participate in different biological pathways, which may result in each SNP predisposing to a different pathophysiologic sub-phenotype of AF. The notion of different pathophysiologic sub-phenotypes of AF is supported by its clinical heterogeneity, and if confirmed, highlights a potential role for a personalized approach to its management.[21–24]

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-II receptor blockers (ARBs) have been suggested to reduce the risk of developing AF based on retrospective findings from large randomized controlled trials, however two large randomized controlled trials among AF patients showed no benefit with respect to arrhythmia recurrence and major adverse cardiovascular outcomes.[25–29] The importance of the renin-angiotensin system (RAS) in AF pathogenesis has been supported by previous work in cell and animal models.[30,31] Among the 9 genetic loci implicated in AF, 2 contain genes involved in the

RAS. It is conceivable that upstream prevention of AF by ACEi and ARBs may be more effective among select sub-phenotypes of AF whose pathophysiology is driven by abnormalities in the RAS. To investigate this possibility, we examined the impact of these 9 AF-associated SNPs on the efficacy of ACEi and ARBs for AF primary prevention in two large population-based cohorts.

Methods

As a genetic association study, our investigation was conducted and reported in a manner consistent with STREGA guidelines.[32] The Cardiovascular Health Study (CHS) was used as a discovery cohort to determine the impact of genotype on the efficacy of RAS inhibitors (ACEi and ARBs) for the primary prevention of AF. Given predominately negative results in the primary analysis and in order to exclude a type II error, replication of two promising associations were investigated in the Atherosclerosis Risk in Communities (ARIC) study.

Cardiovascular Health Study (CHS)

CHS is a population-based cohort study designed to investigate risk factors for cardiovascular disease in the elderly. The design, recruitment, baseline characterization, and outcome ascertainment procedures for CHS have been previously described in detail.[33,34] Briefly, a total of 5,201 participants aged 65 years and older were recruited in 1989–1990 from Medicare eligibility lists in four US communities: Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pennsylvania. Written informed consent was obtained and all procedures were conducted under institutionally approved protocols for study of human participants.

Examinations in CHS

Participants underwent comprehensive examinations at study entry to document baseline demographics and prevalent medical co-morbidities.[33] Self-identified race was reported and dichotomized as white and non-white for analysis. Hypertension was defined as a reported history of physician-diagnosed hypertension and use of antihypertensive medications, a systolic blood pressure greater than or equal to 140 mm Hg, or a diastolic blood pressure greater than or equal to 90 mm Hg. Participants were classified as diabetic if they used an anti-hyperglycemic medication or had a fasting glucose concentration greater than or equal to 126 mg/dL. Prevalent heart failure was diagnosed by participant self-report and confirmed by medical record verification, while prevalent coronary artery disease was defined as angina, previous myocardial infarction, previous coronary artery bypass grafting, or previous angioplasty, all by participant self-report and confirmed by medical record verification.

Event Ascertainment in CHS

Follow-up was performed with alternating clinic visits and phone calls every six months until 1999 and semi-annual phone calls thereafter. Resting 12-lead ECGs were performed at each clinic visit through 1999. Prevalent AF at baseline was defined as a prior self-report of a physician diagnosis of the arrhythmia or its documentation on baseline ECG or Holter monitoring, while incident AF was ascertained on the basis of clinic visit ECGs and hospital discharge diagnosis codes that were supplemented with Medicare inpatient and outpatient

claims data.[35,36] Previous work on selected subgroups of CHS participants demonstrated that a similar approach to incident AF ascertainment using inpatient hospitalization codes had positive and negative predictive values of 98.6% and 99.9%, respectively.[37,38]

Medication Ascertainment in CHS

Medication use was assessed annually at clinic visits for the first 10 years and was documented during annual telephone interviews.[39] For clinic visits, study participants were instructed to bring all medications used within the prior two weeks. The name of each medication was recorded from the pill bottle and current usage was confirmed with the participant. During annual telephone interviews, participants were asked to read the names of the medications they had been taking for the prior two weeks from the pill bottles. Individual medications were coded as different classes of medications, including ACEi and ARBs.

Atherosclerosis Risk in Communities (ARIC)

ARIC is a population-based cohort study that enrolled 15,972 adults aged 45–64 years between 1987 and 1989 from 4 US communities: the northwest suburbs of Minneapolis, MN; Washington County, MD; Jackson, MS; and Forsyth County, NC. Participants underwent a comprehensive baseline assessment followed by annual phone interviews and 3 repeat examinations spaced approximately 3 years apart. Methods for ascertaining baseline hypertension, diabetes, heart failure, and coronary artery disease have been previously described.[40] Standard resting 12-lead ECGs were performed at each visit. Prevalent AF was identified from the baseline ECG, and incident AF was identified from study visit ECGs, hospital discharge diagnoses, and death certificates.[41] Medication ascertainment was only performed at the 4 clinical visits in a manner consistent with the protocol described for the CHS clinical visits.

Genotyping and Imputation

The genotyping and imputation methodology within CHS and ARIC have been previously described.[20] SNP genotyping in the original cohort of CHS (enrolled 1989–1990) was performed using the Illumina 370 CNV DNA microarray and analyzed using the BeadStudio variant calling algorithm (Illumina, San Diego, CA). All SNPs that were directly genotyped passed quality control filtering including a Hardy-Weinberg Equilibrium threshold of $< 10^{-5}$ and a SNP call rate of > 97%. The remaining SNPs were imputed using BIMBAM v0.99 with reference to HapMap CEU using release 22, build 36. Within the ARIC cohort, participants were genotyped using the Affymetrix 6.0 DNA microarray and results were analyzed using the Birdseed calling algorithm (Affymetrix, Santa Clara, CA). The two SNPs subjected to a replication analysis within ARIC (rs2106261 [16q22] and rs13376333 [1q21] [a surrogate for rs6666258; $r^2 = 1$]) were directly genotyped on the microarray and both met the aforementioned quality control criteria.

Statistical Analysis

Normally distributed continuous variables are presented as means ± standard deviation and were compared using the Student's t-test. Comparison of categorical values was performed

using the Chi-squared test. Time-to-event analyses using Cox proportional hazards models were employed to evaluate for associations between SNPs, medication use, and incident AF. Analyses were restricted to individuals of European ancestry without prevalent AF with documented ACEi or ARB status. An additive genetic model was employed for the SNP analyses. ACEi and ARB medication usage were each treated as time dependent covariates as the majority of study participants were initiated on these medications after their initial enrollment into the study. Individuals in CHS reported to have been treated with an ACEi or ARB in a given year were assumed to have received the medication for the entire year from the date of the visit and were assumed to have remained on the medication for the remainder of the study. In ARIC, a similar approach was utilized, however medication ascertainment was only performed at clinic visits that occurred approximately every 3 years.

Multivariable Cox proportional hazards models were performed to adjust for potential confounding. Covariates added to these models included baseline age, sex, hypertension, diabetes, and body mass index. The proportional hazards assumption was tested and observed to be satisfied for both genetic carrier status and the ACEi and ARB time-dependent covariates using log-minus-log plots and the Schoenfeld test. Study participants with prevalent coronary artery disease and congestive heart failure did not undergo GWAS analysis in CHS and therefore these participants were excluded from the analysis. Prevalent coronary artery disease and congestive heart failure were included as covariates in the models for the replication portion of the study using the ARIC cohort. Effect modification of the association between incident AF and ACEi and/or ARB use by genotype was evaluated through use of an interaction term in the Cox models. The SNP-drug interaction analyses were performed using both dominant and additive genetic models. An additive genetic model categorizes individuals as homozygous for the major allele, heterozygous, and homozygous for the minor allele, while a dominant genetic model classifies individuals as carriers and non-carriers of the minor allele. The reported p-values for interaction were determined from the additive genetic models.

Two-tailed p-values < 0.05 were considered statistically significant. SNP-drug interaction analyses were not adjusted for multiple hypothesis testing in an effort to minimize the possibility of a Type II error, coupled with each SNP having been identified *a priori* for this analysis based on strong evidence for their involvement in AF pathogenesis.[20] After completing the CHS analysis and encountering no clear statistically significant results, replication of 2 SNPs with nearly significant interaction results was performed in ARIC to exclude a type II error as an explanation for the negative results. Statistical analyses were performed using Stata version 12 (College Station, Tx, USA).

The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper. This work was made possible by an American Heart Association National Innovative Research Grant (G.M.M) and the Joseph Drown Foundation (G.M.M.).

Results

CHS Participant Characteristics

A total of 2796 individuals of European ancestry from the CHS cohort underwent genotyping, had serial documentation of ACEi and/or ARB medication usage, and had no prevalent AF. The mean age of the cohort was 72.3 (±5.2) years and 41.0% of participants were male. The remaining baseline clinical characteristics of the cohort are summarized in Table 1. During a median follow-up period of 10.5 years, a total of 518 and 136 study participants were initiated on an ACEi and an ARB, respectively. Of these, 9 were treated with both an ACEi and ARB during the study. Participants treated with RAS inhibition were more likely to be younger, female, hypertensive, and diabetic (Table 1). A total of 952 of the 2796 individuals were diagnosed with incident AF during the study period.

Association of SNPs with AF in CHS

The minor allele frequencies (MAFs) of the AF associated SNPs examined in CHS are reported in Table 2. Three of the AF-associated SNPs (rs2200733 [4q25], rs10824026 [10q22], and rs3807989 [7q31]) were directly genotyped, while the remaining SNPs were imputed. Among the 9 SNPs evaluated, the rs2200733 [4q25] genetic variant from the 4q25 locus had the strongest association with AF in unadjusted and adjusted analyses (Table 2). Two additional SNPs (rs6666258 [1q21] and rs10824026 [10q22]) were significantly associated with AF in unadjusted analyses. Following adjustment for the pre-specified covariates, the rs6666258 [1q21] association was no longer significant (p=0.063) whereas the association with rs10824026 [10q22] persisted (p=0.010). The association of a fourth SNP, rs3807989 [7q31], became significant on adjusted analysis (unadjusted p-value: 0.088, adjusted p-value: 0.032).

Association of ACEi and ARBs with AF in CHS

In analyses examining ACEi use alone, ARB use alone, or any RAS inhibition, pharmacologic treatment was associated with a reduced hazard of incident AF in both unadjusted and adjusted analyses (Figure 1). Among those prescribed an ACEi or ARB that developed incident AF, AF was observed a median 3.5 (interquartile range (IQR) 2.4 – 4.7) years after prescription.

Impact of Genotype on Efficacy of ACEi and ARBs for AF Prevention in CHS

Analysis for evidence of an impact of SNP genotype on the efficacy of medical therapy with ACEi for the prevention of incident AF revealed no significant interactions ($p<0.05$) on unadjusted and adjusted analyses in both the additive and dominant genetic models (Figure 2). Examination for an interaction between ARBs and the AF associated SNPs revealed a single significant SNP-drug interaction involving the rs10821415 SNP in unadjusted (p value for interaction = 0.020) and adjusted (p value for interaction = 0.037) analyses. The interaction between this SNP and ACEi was in the opposite direction and a non-significant p value for interaction (0.865) was observed in the combined ACEi/ARB-SNP interaction analysis (Figure 2).

Two SNPs, rs2106261 [16q22] and rs6666258 [1q21], exhibited SNP-drug interactions that were in consistent directions in both the ACEi and ARB analyses. Carriers of the rs2106261 [16q22] SNP, intronic in the *ZFHX3* gene, experienced a trend towards improved protection against incident AF with both ACEi (p value for interaction = 0.190) and ARBs (p value for interaction = 0.244) relative to non-carriers. Combined analysis examining for an interaction between the SNP and treatment with either an ACEi and/or an ARB did not reach statistical significance (p value for interaction = 0.101) (Figure 2). In contrast, genetic carriers of the disease-associated allele at rs6666258 [1q21], a SNP that is intronic in the *KCNN3*, appeared to derive less benefit from upstream RAS inhibition for AF prevention relative to non-carriers. This relatively reduced efficacy of RAS inhibition among rs6666258 [1q21] carriers was observed in both the ACEi and ARB analyses (Figure 2). In the combined ACEi/ARB analysis, the adjusted p value for interaction was 0.077. Because both of these SNPs exhibited similar point estimates for the ACEi-only and ARB-only analyses with relatively low p values, the interactions were tested in the ARIC cohort.

ARIC Participant Characteristics

Within the ARIC cohort, 8604 individuals of European ancestry underwent genotyping, had serial documentation of ACEi and/or ARB medication usage, and had no prevalent AF. The mean age among participants was 54.1 (±5.6) years and 46.3% were male. The remaining baseline clinical characteristics of the cohort are summarized in Supplemental Table 1. During a median follow-up period of 20.0 years, a total of 787 and 67 study participants were initiated on an ACEi and an ARB, respectively. Of these, 3 were treated with both an ACEi and ARB during the study. A total of 466 of the 8604 individuals were diagnosed with incident AF during the study period.

Association of ACEi and ARBs with AF in ARIC

In contrast to the results observed in CHS, ACEi use alone, ARB use alone, and any RAS inhibition each exhibited either no significant association or an *increased* hazard of incident AF in both unadjusted and adjusted analyses (Figure 1). Among those prescribed an ACEi or ARB that developed incident AF, AF was observed a median 9.9 (IQR 6.8 – 12.4) years after prescription.

Impact of Genotype on Efficacy of ACEi and ARBs for AF Prevention in ARIC

The observed impact of each of the two promising SNPs on RAS efficacy within CHS was not replicated within the ARIC cohort. In relation to their impact on incident AF risk, additive genetic analysis of rs1337633 [1q21] was associated with a statistically significant 1.23-fold increased hazard of incident AF (HR: 1.23, 95% CI: 1.08–1.41, p=0.003), whereas the association for rs2106261 [16q22] was not statistically significant (HR: 1.12, 95% CI: 0.94–1.32, p=0.204). On SNP-drug interaction analysis, genetic carrier status of the rs2106261 [16q22] SNP trended in the opposite direction (compared to observations in CHS) towards reduced efficacy of RAS inhibition among carriers of the minor allele for upstream prevention of AF (p value for interaction = 0.529). Similarly discordant findings were also observed for rs13376333 [1q21]. Carriers of rs1337633 [1q21] exhibited a non-significant reduced risk of AF in association with ACEi and/or ARB therapy relative to non-

carriers (p value for interaction = 0.768). In addition to being non-significant, the direction of association was also opposite that observed within CHS.

Discussion

Our investigation, which utilized two large, well-characterized prospective cardiovascular cohorts, found no evidence to support an interaction between AF risk SNPs and the efficacy of ACEi and/or ARBs for the primary prevention of incident AF. Within the CHS cohort, there were two SNPs that appeared to potentially modify the efficacy of RAS inhibition for the prevention of AF, however this finding was not replicated in the ARIC cohort and the initially promising findings were likely secondary to chance. The efficacy of RAS inhibition as upstream therapy for the prevention of AF does not appear to be modified by the current list of common genetic variants associated with the arrhythmia.

Insight into the genetics underlying AF risk among families with Mendelian inheritance patterns of the arrhythmia have increasingly highlighted that the pathophysiology of the arrhythmia is heterogeneous.[42] The arrhythmia has been associated with both gain- and loss-of-function mutations in a wide array of ion channels, among other genetic culprits, alluding to the presence of multiple sub-phenotypes of AF.[22] This notion is supported clinically by the variable response among AF patients with similar clinical profiles to both anti-arrhythmic drugs and catheter ablation.[23,43] Genetic characterization of the arrhythmia opens the possibility of delivering personalized forms of therapy that directly target the specific pathophysiology underlying the arrhythmia in a given individual. This gene-guided strategy may improve treatment efficacy while simultaneously reducing adverse events.

Among the 9 SNPs associated with AF from GWAS, two may potentially involve genes associated with RAS, namely rs2200733 [4q25] (residing in the vicinity of *ENPEP*, which encodes aminopeptidase A, an enzyme responsible for degrading angiotensin II to angiotensin III) and rs10821415 [9q22] (intronic within *C9orf3*, which encodes aminopeptidase O, an enzyme responsible for degrading angiotensin III to angiotensin IV). Despite the potential presence of sub-phenotypes of AF driven by altered RAS activity, we found no evidence to support a differential treatment effect of RAS inhibition for upstream AF prevention based on genetic carrier status of the 9 AF risk SNPs.

The results of our study do not support a current role for a pharmacogenomic approach to RAS inhibition among patients at risk of AF and provide conflicting results with respect to the efficacy of RAS inhibitors as upstream therapy for the prevention of incident AF. While CHS suggested that RAS inhibition was associated with a protective effective, either a lack of effect or an increased rate of incident AF was observed among participants treated with RAS inhibitors in ARIC. The explanation for this discrepancy is not immediately clear, however was not critical to our primary analysis, which focused on attempting to identify heterogeneity in the treatment effect of RAS inhibitors on the likelihood of developing incident AF within pre-specified genetic subgroups.

Confounding by indication is frequently an issue when examining the impact of medical therapy in an observational cohort. Indications for initiation of RAS inhibitors include

hypertension, ischemic heart disease, and congestive heart failure, which are also potent risk factors for AF.[37,44] As a result, study participants prescribed RAS inhibitors also presumably have an increased risk of developing AF relative to individuals not receiving these mediations. This phenomenon may account for the apparent increased risk of AF in association with RAS inhibitor use in ARIC, rather than a true causal effect. While we cannot exclude the possibility that confounding by indication influenced our results (ie, that particular types of patients were prescribed a drug based on characteristics relevant to our outcomes), we believe this is unlikely to be operative here as we are testing the effects of the SNPs on the outcomes within groups that were prescribed versus not prescribed a particular drug. Although randomized controlled trials evaluating the efficacy of RAS inhibition would perhaps be more ideal for this type of analysis owing to their ability to eliminate confounding, the longer follow-up of prospective cohorts such as CHS and ARIC is ideal given that the development of AF secondary to RAS likely occur over years and potentially decades. Notably, the median time between initiation of an ACEi/ARB and development of incident AF in CHS and ARIC was 3.5 and 9.9 years, respectively.

Our investigation has several limitations. Although our study involves a large number of participants, it is possible that our inability to detect an interaction between RAS inhibition and genetic carrier status may be secondary to inadequate power. While this is possible, the goal of this research was to identify clinically relevant predictors to guide selection of optimal candidates for RAS inhibition and, with these thousands of participants, we are confident that we have excluded an effect that might be worthy of translation into clinical practice. Another potential limitation of our study is that our results may not be generalizable to younger populations. As shown in Table 2, the impact of SNPs on the risk of incident AF within the CHS cohort was relatively small. These findings are likely secondary to a more modest role of genetics in the development of AF among the elderly relative to younger individuals who are more likely to develop the arrhythmia in the absence of conventional clinical risk factors. It is conceivable that the more modest role of genetics on the risk of AF in this population may have masked potential SNP-drug interactions. Although standardized and validated methods were utilized to ascertain AF, given that the arrhythmia may be asymptomatic, it is possible that incident AF cases may have been missed. Under ascertainment would presumably have been similar among the different analyzed subgroups, and it is possible that non-differential misclassification of the outcome may have contributed to our inability to identify a positive association owing to bias towards the null.

Conclusions

Our study failed to identify genetic sub-types of AF that preferentially benefit from RAS inhibition for primary prevention of the arrhythmia. Future studies should continue to investigate the impact of genotype on the response to AF treatment strategies in an effort to develop personalized approaches to therapy that improve care of both susceptible individuals and affected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: This work was made possible by an American Heart Association National Innovative Research Grant (G.M.M) and the Joseph Drown Foundation (G.M.M.). J.D.R. is supported by research fellowship grants from the Heart & Stroke Foundation of Canada and the Canadian Heart Rhythm Society. Grants for the Cardiovascular Health Study include: R01 HL80698-01, NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants HL080295 and HL102214, with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med. 1997; 337:1360–1369. [PubMed: 9358131]
2. Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of Total Incremental Health Care Costs in Patients With Atrial Fibrillation in the United States. Circ Cardiovasc Qual Outcomes. 2011; 4:313–320. [PubMed: 21540439]
3. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TSM. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006; 114:119–125. [PubMed: 16818816]
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998; 98:946–952. [PubMed: 9737513]
5. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003; 107:2920–2925. [PubMed: 12771006]
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke J Cereb Circ. 1991; 22:983–988.
7. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002; 347:1825–1833. [PubMed: 12466506]
8. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJM, Tijssen JGP, Crijns HJGM. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002; 347:1834–1840. [PubMed: 12466507]
9. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JMO, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey J-Y, O'Hara G, Pedersen OD, Rouleau J-L, Singh BN, Stevenson LW, Stevenson WG, Thibault B,

Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008; 358:2667–2677. [PubMed: 18565859]

10. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol. 2011; 57:160–166. [PubMed: 21211687]
11. Nattel S. New ideas about atrial fibrillation 50 years on. Nature. 2002; 415:219–226. [PubMed: 11805846]
12. Lubitz SA, Yin X, Fontes JD, Magnani JW, Rienstra M, Pai M, Villalon ML, Vasan RS, Pencina MJ, Levy D, Larson MG, Ellinor PT, Benjamin EJ. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. JAMA. 2010; 304:2263–2269. [PubMed: 21076174]
13. Fox CS, Parise H, D'Agostino RBS, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA. 2004; 291:2851–2855. [PubMed: 15199036]
14. Arnar DO, Thorvaldsson S, Manolio TA, Thorgeirsson G, Kristjansson K, Hakonarson H, Stefansson K. Familial aggregation of atrial fibrillation in Iceland. Eur Heart J. 2006; 27:708–712. [PubMed: 16428254]
15. Marcus GM, Smith LM, Vittinghoff E, Tseng ZH, Badhwar N, Lee BK, Lee RJ, Scheinman MM, Olgin JE. A first-degree family history in lone atrial fibrillation patients. Heart Rhythm. 2008; 5:826–830. [PubMed: 18468961]
16. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, Jonasdottir A, Baker A, Thorleifsson G, Kristjansson K, Palsson A, Blondal T, Sulem P, Backman VM, Hardarson GA, Palsdottir E, Helgason A, Sigurjonsdottir R, Sverrisson JT, Kostulas K, Ng MCY, Baum L, So WY, Wong KS, Chan JCN, Furie KL, Greenberg SM, Sale M, Kelly P, MacRae CA, Smith EE, Rosand J, Hillert J, Ma RCW, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature. 2007; 448:353–357. [PubMed: 17603472]
17. Benjamin EJ, Rice KM, Arking DE, Pfeufer A, van Noord C, Smith AV, Schnabel RB, Bis JC, Boerwinkle E, Sinner MF, Dehghan A, Lubitz SA, D'Agostino RBS, Lumley T, Ehret GB, Heeringa J, Aspelund T, Newton-Cheh C, Larson MG, Marciante KD, Soliman EZ, Rivadeneira F, Wang TJ, Eiríksdottir G, Levy D, Psaty BM, Li M, Chamberlain AM, Hofman A, Vasan RS, Harris TB, Rotter JI, Kao WHL, Agarwal SK, Stricker BHC, Wang K, Launer LJ, Smith NL, Chakravarti A, Uitterlinden AG, Wolf PA, Sotoodehnia N, Köttgen A, van Duijn CM, Meitinger T, Mueller M, Perz S, Steinbeck G, Wichmann H-E, Lunetta KL, Heckbert SR, Gudnason V, Alonso A, Kääb S, Ellinor PT, Witteman JCM. Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry. Nat Genet. 2009; 41:879–881. [PubMed: 19597492]
18. Gudbjartsson DF, Holm H, Gretarsdottir S, Thorleifsson G, Walters GB, Thorgeirsson G, Gulcher J, Mathiesen EB, Njølstad I, Nyrnes A, Wilsgaard T, Hald EM, Hveem K, Stoltenberg C, Kucera G, Stubblefield T, Carter S, Roden D, Ng MCY, Baum L, So WY, Wong KS, Chan JCN, Gieger C, Wichmann H-E, Gschwendtner A, Dichgans M, Kuhlenbäumer G, Berger K, Ringelstein EB, Bevan S, Markus HS, Kostulas K, Hillert J, Sveinbjörnsdóttir S, Valdimarsson EM, Løchen M-L, Ma RCW, Darbar D, Kong A, Arnar DO, Thorsteinsdottir U, Stefansson K. A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. Nat Genet. 2009; 41:876–878. [PubMed: 19597491]
19. Ellinor PT, Lunetta KL, Glazer NL, Pfeufer A, Alonso A, Chung MK, Sinner MF, de Bakker PIW, Mueller M, Lubitz SA, Fox E, Darbar D, Smith NL, Smith JD, Schnabel RB, Soliman EZ, Rice KM, Van Wagoner DR, Beckmann B-M, van Noord C, Wang K, Ehret GB, Rotter JI, Hazen SL, Steinbeck G, Smith AV, Launer LJ, Harris TB, Makino S, Nelis M, Milan DJ, Perz S, Esko T, Köttgen A, Moebus S, Newton-Cheh C, Li M, Möhlenkamp S, Wang TJ, Kao WHL, Vasan RS, Nöthen MM, MacRae CA, Stricker BHC, Hofman A, Uitterlinden AG, Levy D, Boerwinkle E, Metspalu A, Topol EJ, Chakravarti A, Gudnason V, Psaty BM, Roden DM, Meitinger T, Wichmann H-E, Witteman JCM, Barnard J, Arking DE, Benjamin EJ, Heckbert SR, Kääb S. Common variants in KCNN3 are associated with lone atrial fibrillation. Nat Genet. 2010; 42:240–244. [PubMed: 20173747]

20. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Müller-Nurasyid M, Krijthe BP, Lubitz SA, Bis JC, Chung MK, Dörr M, Ozaki K, Roberts JD, Smith JG, Pfeufer A, Sinner MF, Lohman K, Ding J, Smith NL, Smith JD, Rienstra M, Rice KM, Van Wagoner DR, Magnani JW, Wakili R, Clauss S, Rotter JI, Steinbeck G, Launer LJ, Davies RW, Borkovich M, Harris TB, Lin H, Völker U, Völzke H, Milan DJ, Hofman A, Boerwinkle E, Chen LY, Soliman EZ, Voight BF, Li G, Chakravarti A, Kubo M, Tedrow UB, Rose LM, Ridker PM, Conen D, Tsunoda T, Furukawa T, Sotoodehnia N, Xu S, Kamatani N, Levy D, Nakamura Y, Parvez B, Mahida S, Furie KL, Rosand J, Muhammad R, Psaty BM, Meitinger T, Perz S, Wichmann H-E, Witteman JCM, Kao WHL, Kathiresan S, Roden DM, Uitterlinden AG, Rivadeneira F, McKnight B, Sjögren M, Newman AB, Liu Y, Gollob MH, Melander O, Tanaka T, Stricker BHC, Felix SB, Alonso A, Darbar D, Barnard J, Chasman DI, Heckbert SR, Benjamin EJ, Gudnason V, Kääb S. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nat Genet. 2012; 44:670–675. [PubMed: 22544366]
21. Patton KK, Zacks ES, Chang JY, Shea MA, Ruskin JN, Macrae CA, Ellinor PT. Clinical subtypes of lone atrial fibrillation. Pacing Clin Electrophysiol. 2005; 28:630–638. [PubMed: 16008797]
22. Roberts JD, Gollob MH. Impact of genetic discoveries on the classification of lone atrial fibrillation. J Am Coll Cardiol. 2010; 55:705–712. [PubMed: 20170805]
23. Husser D, Adams V, Piorkowski C, Hindricks G, Bollmann A. Chromosome 4q25 variants and atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol. 2010; 55:747–753. [PubMed: 20170812]
24. Benjamin Shoemaker M, Muhammad R, Parvez B, White BW, Streur M, Song Y, Stubblefield T, Kucera G, Blair M, Rytlewski J, Parvathaneni S, Nagarakanti R, Saavedra P, Ellis CR, Patrick Whalen S, Roden DM, Darbar RD. Common atrial fibrillation risk alleles at 4q25 predict recurrence after catheter-based atrial fibrillation ablation. Heart Rhythm. 2013; 10:394–400. [PubMed: 23178686]
25. Vermes E, Tardif J-C, Bourassa MG, Racine N, Levesque S, White M, Guerra PG, Ducharme A. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. Circulation. 2003; 107:2926–2931. [PubMed: 12771010]
26. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation. 1999; 100:376–380. [PubMed: 10421597]
27. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol. 2005; 45:1832–1839. [PubMed: 15936615]
28. GISSI-AF Investigators. Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, Maggioni AP, Lucci D, Di Pasquale G, Tognoni G. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med. 2009; 360:1606–1617. [PubMed: 19369667]
29. Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG, Hohnloser SH, Joyner CD, Pfeffer MA, Connolly SJ. ACTIVE I Investigators. Irbesartan in patients with atrial fibrillation. N Engl J Med. 2011; 364:928–938. [PubMed: 21388310]
30. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation. 2001; 104:2608–2614. [PubMed: 11714658]
31. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. Circulation. 2000; 101:2612–2617. [PubMed: 10840013]
32. Little J, Higgins JPT, Ioannidis JPA, Moher D, Gagnon F, Von Elm E, Khoury MJ, Cohen B, Davey-Smith G, Grimshaw J, Scheet P, Gwinn M, Williamson RE, Zou GY, Hutchings K, Johnson CY, Tait V, Wiens M, Golding J, Van Duijn C, McLaughlin J, Paterson A, Wells G, Fortier I, Freedman M, Zecevic M, King R, Infante-Rivard C, Stewart A, Birkett N. STrengthening the REporting of Genetic Association studies (STREGA) - an extension of the STROBE statement. Eur J Clin Invest. 2009; 39:247–266. [PubMed: 19297801]

33. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. 1991; 1:263–276. [PubMed: 1669507]
34. Tell GS, Fried LP, Hermanson B, Manolio TA, Newman AB, Borhani NO. Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. Ann Epidemiol. 1993; 3:358–366. [PubMed: 8275211]
35. Ives DG, Fitzpatrick AL, Bild DE, Psaty BM, Kuller LH, Crowley PM, Cruise RG, Theroux S. Surveillance ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol. 1995; 5:278–285. [PubMed: 8520709]
36. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Benjamin EJ, Curtis LH. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. Circ Cardiovasc Qual Outcomes. 2012; 5:85–93. [PubMed: 22235070]
37. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997; 96:2455–2461. [PubMed: 9337224]
38. Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. Circulation. 2004; 110:368–373. [PubMed: 15262826]
39. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods, initial xperience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. J Clin Epidemiol. 1992; 45:683–692. [PubMed: 1607909]
40. Investigators TA. The Atherosclerosis Risk in Communit (aric) Stui)y: Design and Objectwes. Am J Epidemiol. 1989; 129:687–702. [PubMed: 2646917]
41. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009; 158:111–117. [PubMed: 19540400]
42. Lubitz SA, Ozcan C, Magnani JW, Kääb S, Benjamin EJ, Ellinor PT. Genetics of atrial fibrillation: implications for future research directions and personalized medicine. Circ Arrhythm Electrophysiol. 2010; 3:291–299. [PubMed: 20551423]
43. Parvez B, Vaglio J, Rowan S, Muhammad R, Kucera G, Stubblefield T, Carter S, Roden D, Darbar D. Symptomatic response to antiarrhythmic drug therapy is modulated by a common single nucleotide polymorphism in atrial fibrillation. J Am Coll Cardiol. 2012; 60:539–545. [PubMed: 22726630]
44. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994; 271:840–844. [PubMed: 8114238]

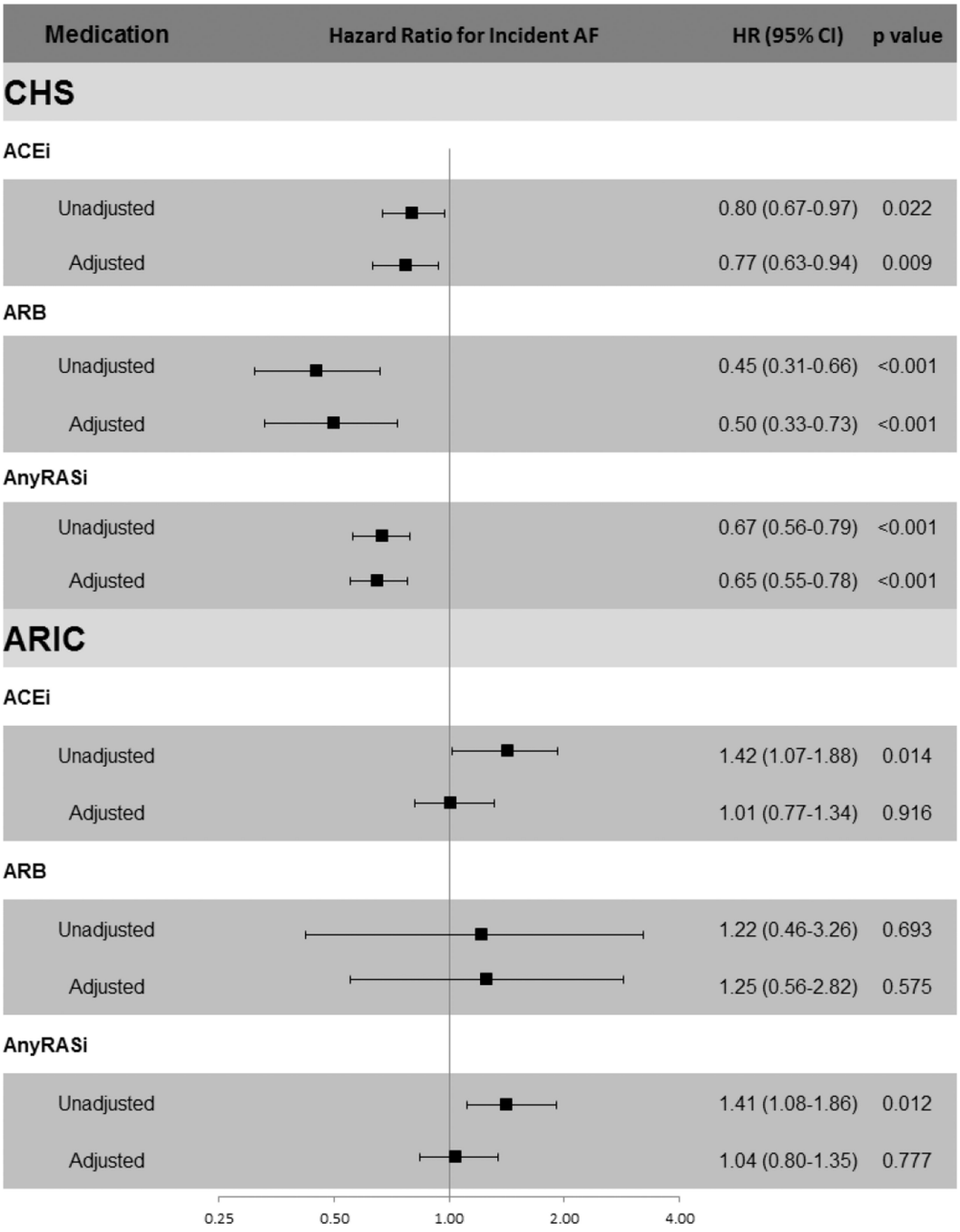

Figure 1.

Association of Treatment with an ACEi and/or ARB with the Risk of Incident Atrial Fibrillation in the CHS and ARIC cohorts

*Adjusted for baseline age, gender, body mass index, diabetes, and hypertension. CHS = Cardiovascular Health Study, ARIC = Atherosclerosis Risk in Communities, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker, AnyRASi = any renin-angiotensin system inhibitor (ACEi and/or ARB), AF = atrial fibrillation, HR = hazard ratio, CI = confidence intervals

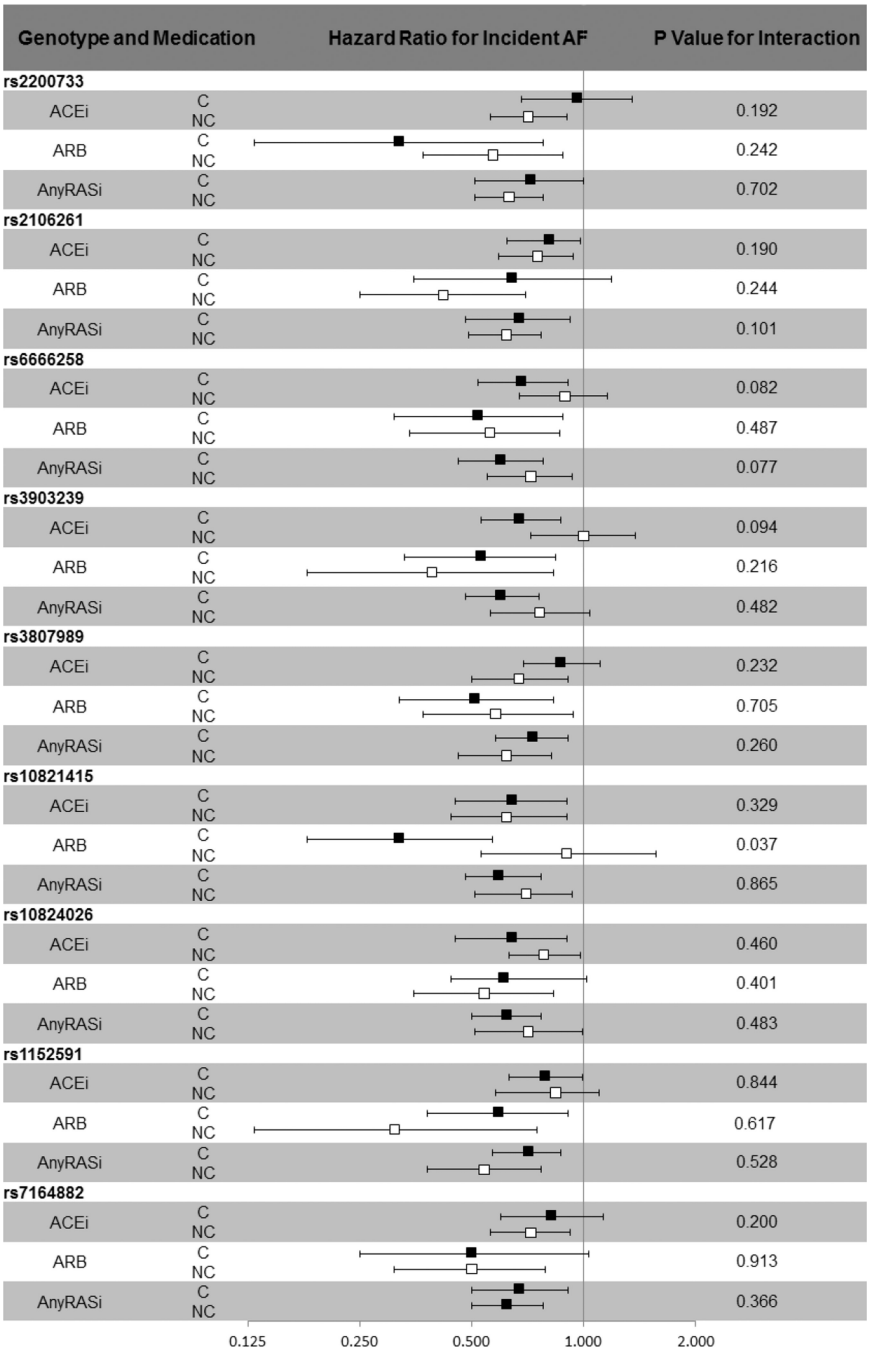

Figure 2.

Association of ACEi and ARBs with the Risk of Incident Atrial Fibrillation by Genetic Carrier Status in CHS.

*Adjusted for baseline age, gender, body mass index, diabetes, and hypertension. Point-estimates and p-values for interaction are provided from the dominant and additive genetic models, respectively.

ACEi = Angiotensin converting enzyme inhibitor, ARB = Angiotensin II receptor blocker, AnyRASi = Any renin-angiotensin system inhibitor (ACEi and/or ARB), AF = atrial fibrillation, C = carrier of minor genetic allele, NC = non-carrier of minor genetic allele

Table 1

Baseline Characteristics of CHS Study Participants

	RASi* n = 645	No RASi† n = 2151	p value
Age (years)	71.0 ± 4.5	72.7 ± 5.6	<0.001
Male (%)	231 (35.8)	915 (42.5)	0.002
Hypertension (%)	298 (46.2)	575 (26.7)	<0.001
Diabetes Mellitus (%)	59 (9.2)	94 (4.4)	<0.001
Body Mass Index (kg/m^2)	26.9 ± 4.5	26.1 ± 4.4	<0.001
Coronary Artery Disease (%)	0 (0)	0 (0)	1.0
Congestive Heart Failure (%)	0 (0)	0 (0)	1.0

*Treatment

†No Treatment with RASi at baseline or during follow-up, CHS = Cardiovascular Healthy Study, RAS = renin-angiotensin system inhibitor (ACEi or ARB), ACEi = ACE inhibitor, ARB = Angiotensin II receptor blocker

Table 2

Minor Allele Frequencies of SNPs and Hazard Ratios for Incident AF using an Additive Genetic Model

SNP	Genetic Locus	MAF (%)	HR (95% CI)	p value	Adjusted HR (95% CI)†	Adjusted p value
rs2200733	4q25	14.2	1.20 (1.05–1.37)	0.007	1.27 (1.11–1.45)	0.001
rs2106261	16q22	15.8	1.09 (0.95–1.25)	0.235	1.08 (0.94–1.25)	0.274
rs6666258	1q21	28.7	1.13 (1.01–1.26)	0.038	1.11 (0.99–1.25)	0.063
rs3903239	1q24	42.7	0.93 (0.84–1.04)	0.190	0.95 (0.85–1.06)	0.340
rs3807989	7q31	40.0	0.92 (0.84–1.01)	0.088	0.90 (0.82–0.99)	0.032
rs10821415	9q22	42.2	1.02 (0.92–1.13)	0.742	1.00 (0.90–1.11)	0.928
rs10824026	10q22	16.2	0.85 (0.73–0.98)	0.026	0.82 (0.71–0.95)	0.01
rs1152591	14q23	46.3	1.07 (0.96–1.18)	0.237	1.08 (0.98–1.20)	0.127
rs7164883	15q24	16.9	1.10 (0.95–1.26)	0.192	1.09 (0.95–1.26)	0.223

†Adjusted for baseline age, gender, body mass index, diabetes, and hypertension. SNP = single nucleotide polymorphism, MAF = minor allele frequency, HR = hazard ratio, CI = confidence interval.