HHS Public Access

Author manuscript

Ann Pharmacother. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Ann Pharmacother. 2015 April ; 49(4): 378–386. doi:10.1177/1060028014568447.

Use of statins and antihypertensive medications in relation to risk of longstanding persistent atrial fibrillation

Evan L Thacker, PhD,
Cardiovascular Health Research Unit and Department of Epidemiology, University of Washington, Seattle, WA; and Department of Health Science, Brigham Young University, Provo, UT

Paul N Jensen, PhD, MPH,
Cardiovascular Health Research Unit and Department of Epidemiology, University of Washington, Seattle, WA

Bruce M Psaty, MD, PhD,
Cardiovascular Health Research Unit and Departments of Epidemiology, Medicine, and Health Services, University of Washington, Seattle, WA; and Group Health Research Institute, Seattle, WA

Barbara McKnight, PhD,
Cardiovascular Health Research Unit and Department of Biostatistics, University of Washington, Seattle, WA

WT Longstreth Jr, MD, MPH,
Departments of Epidemiology, Medicine, and Neurology, University of Washington, Seattle, WA

Sascha Dublin, MD, PhD,
Department of Epidemiology, University of Washington, Seattle, WA; and Group Health Research Institute, Seattle, WA

Katherine M Newton, PhD,
Department of Epidemiology, University of Washington, Seattle, WA; and Group Health Research Institute, Seattle, WA

Nicholas L Smith, PhD,
Cardiovascular Health Research Unit and Department of Epidemiology, University of Washington, Seattle, WA; and Group Health Research Institute, Seattle, WA; and Epidemiologic Research and Information Center, Veterans Affairs Office of Research and Development, Seattle, WA

David S Siscovick, MD, and

Corresponding author: Dr. Thacker; Mail: Brigham Young University, LSB 2051, Provo, UT 84602; elt@byu.edu; Phone: 801-422-2294; Fax: 801-422-0004.

This research was presented at the American Heart Association 52nd Cardiovascular Disease Epidemiology and Prevention Conference, San Diego, CA, March 2012.

Conflicts of interest: Dr. Thacker has received research support from Amgen, Inc. (PI: Paul Muntner, University of Alabama at Birmingham) and a Clinical Research Loan Repayment Program award from the National Heart, Lung and Blood Institute, National Institutes of Health. Dr. Dublin has received a Merck/American Geriatrics Society New Investigator Award. Dr. Psaty is a member of the DSMB for a trial of a device funded by the manufacturer and a member of the steering committee for the Yale Open Data Access Project funded by Medtronic. The other authors have no disclosures.

Cardiovascular Health Research Unit and Departments of Medicine and Epidemiology, University of Washington, Seattle, WA; and New York Academy of Medicine, New York, NY

Susan R Heckbert, MD, PhD
Cardiovascular Health Research Unit and Department of Epidemiology, University of Washington, Seattle, WA; and Group Health Research Institute, Seattle, WA

Abstract

Background—After an initial episode of atrial fibrillation (AF), patients may develop longstanding persistent or permanent AF.

Objective—We evaluated whether use of statins, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers is associated with lower risk of longstanding persistent AF after an initial AF episode.

Methods—We conducted a population-based inception cohort study of participants enrolled in Group Health, aged 30–84 with newly-diagnosed AF in 2001–2004. We included only participants whose initial AF episode terminated within six months of onset. We ascertained the primary outcome of longstanding persistent AF from medical records, electrocardiograms, and administrative data. We determined time-varying medication use from Group Health pharmacy data.

Results—Among 1,317 participants with incident AF, 304 developed longstanding persistent AF. Our study suggests that current statin use vs. never use may be associated with lower risk for longstanding persistent AF. However, the association was not statistically significant when adjusted for age, sex, cardiovascular risk factors, and current use of antiarrhythmic medication (hazard ratio [HR] = 0.77; 95% confidence interval [CI]: 0.57, 1.03). In lagged analyses intended to reduce healthy user bias, current statin use one year prior vs. never use one year prior was not associated with risk for longstanding persistent AF (HR = 0.91; 95% CI: 0.67, 1.24). ACE inhibitor, ARB, and beta-blocker use were not associated with risk for longstanding persistent AF.

Conclusions—Current statin use may confer protection that wanes after discontinuing use. Alternatively, healthy user bias or chance may explain the association. The association of statin use with longstanding persistent AF warrants further investigation.

Keywords

antihypertensive agents; longstanding persistent atrial fibrillation; cohort studies; electrocardiography; hydroxymethylglutaryl-CoA reductase inhibitors; statins

INTRODUCTION

Patients who have a first-diagnosed episode of atrial fibrillation (AF) that terminates usually experience recurrent AF episodes, and some later progress to persistent or permanent AF.[1] Concepts of AF subtypes have evolved over time. Current guidelines define paroxysmal AF as terminating within 7 days of onset, persistent AF as being sustained longer than 7 days, longstanding persistent AF as being sustained longer than 12 months, and permanent AF as a decision to stop attempting to restore or maintain sinus rhythm.[1]

Some recent studies suggest that persistent, longstanding persistent, or permanent AF are associated with worse prognosis than paroxysmal AF, including higher rates of thromboembolism,[2–5] heart failure,[4,6,7] myocardial infarction,[3] mortality,[5,6] and hospitalization.[2,3] Moreover, restoration and maintenance of sinus rhythm is more difficult to achieve in persistent AF than in paroxysmal AF.[1,8] Patients with ongoing persistent AF report lower quality of life[9,10] and have lower exercise capacity[10] on average compared with patients diagnosed with persistent AF who achieved and maintained sinus rhythm through treatment. Given the potential for adverse outcomes associated with persistent, longstanding persistent, or permanent AF, identifying modifiable risk factors for AF progression is important.[11]

Patients with AF often receive lipid-lowering and antihypertensive medications due to comorbidities including hyperlipidemia, hypertension, coronary heart disease, valvular heart disease, and heart failure. Use of cardiovascular medications might affect prognosis of AF by modulating the heart's susceptibility to arrhythmia. Prior studies suggest that use of statins,[12–15] angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs),[16–18] and beta-blockers[19–20] may reduce AF incidence or progression. In this study we assessed whether use of these agents is associated with lower risk of longstanding persistent AF among study participants whose initial AF episode terminated.

METHODS

Study design, setting, and participants

Participants were enrollees of Group Health, an integrated health system in Washington state. They were enrolled in this observational population-based inception cohort study at the date of onset of their initial AF episode, defined as the first electrocardiogram (ECG)-confirmed occurrence of AF or atrial flutter followed by documented sinus rhythm within six months. We included participants with atrial flutter because it often coexists with AF in the same individual, and AF may be misdiagnosed as atrial flutter.[1] Study methods were detailed previously.[21,22] The Group Health Human Subjects Review Committee approved the study. Waiver of consent was granted for participants with language or cognitive difficulty and for participants who had died. All other participants provided written consent or verbal consent by telephone.

Group Health enrollees were eligible for this study if they were 30–84 years old, experienced their initial AF episode between October 2001 and December 2004, had not received a prior AF diagnosis code during their entire Group Health enrollment (mean of 22 years), and their initial AF episode terminated either spontaneously or by pharmacologic or electrical cardioversion within six months. We excluded participants who had perioperative AF that resolved before hospital discharge, participants who had AF as part of a hospitalized terminal illness, and participants who had a pacemaker implanted prior to their initial AF episode. We used inpatient and outpatient International Classification of Diseases, 9th Revision (ICD-9) codes 427.31 (atrial fibrillation) and 427.32 (atrial flutter) to identify AF, and confirmed eligibility by medical record review. We required that medical records show initial AF was confirmed by 12-lead ECG and recognized by a physician. Finally, we required participants to have had at least four Group Health visits before their initial AF

episode, to increase the likelihood that information would be available on pre-existing health conditions.

During the study period there were 1,953 participants with newly diagnosed AF. We excluded 391 whose initial AF episode did not terminate within six months, 122 who had less than six months of follow-up after their initial AF episode terminated, and 123 who had missing values for covariates used in multivariate models, leaving 1,317 participants eligible for analyses of longstanding persistent AF.

Assessment of medication use and covariates

Prescription medication use was assessed from the Group Health automated pharmacy database, which contains records of all prescriptions filled at Group Health pharmacies since 1977. Among Group Health members aged 65 years and older (not the present study participants specifically), 96% report filling all or almost all prescriptions through Group Health pharmacies.[23] Each pharmacy record includes medication type, daily dose, quantity dispensed, and intended days supply of the prescription. We used pharmacy records to create time-varying medication use variables, updated daily from before initial AF onset through the end of follow-up. For each medication, a participant's follow-up days were classified as current use when the most recent prescription filled included enough pills to last through the current date, assuming 80% adherence to prescribing instructions. Otherwise, follow-up days were classified as former use if the participant had ever filled a prescription for the medication in the past, or never use if the participant had never filled a prescription for the medication. This approach for creating time-varying medication use variables was applied to statins, antihypertensive medications, and antiarrhythmic medications. We identified modal daily dose of each medication from the distribution of daily dose values from all prescriptions for that medication. For periods of current use, daily dose was categorized as low (below modal dose), medium (modal dose), or high (above modal dose).[22]

Baseline clinical characteristics were determined by medical record review as follows, using information recorded up to the day prior to the initial AF episode. Body mass index was calculated as weight[kg]/height[m^2] using the most recent weight prior to the initial AF episode and height measured during adulthood. Diabetes was defined as physician diagnosis plus current use of insulin or other antidiabetic agents. Systolic and diastolic blood pressures were the most recent outpatient measurements prior to the initial AF episode. Hypertension was defined as physician diagnosis plus current use of antihypertensive medication. Total cholesterol to high density lipoprotein (HDL) cholesterol ratio was calculated as total cholesterol[mg/dL]/HDL cholesterol[mg/dL] using the most recent measurements prior to the initial AF episode. Coronary heart disease was defined as history of hospitalization for myocardial infarction, coronary artery bypass, or angioplasty, or physician diagnosis of probable or definite angina. Chronic heart failure was defined as physician diagnosis plus ongoing medical treatment with medications such as furosemide, ACE inhibitors, digitalis, vasodilators, hydralazine, nitrates, or beta-blockers, as documented in the medical record. Valvular heart disease was defined as physician diagnosis of moderate to severe valvular heart disease or a prosthetic valve. History of stroke was defined as physician diagnosis of definite or probable stroke. Chronic kidney disease was defined as estimated glomerular

filtration rate <60 mL/min/1.73 m^2 by the CKD-EPI equation[24] using the most recent serum creatinine measurement prior to the initial AF episode. Participants who were missing values for these characteristics were excluded from analyses (123 participants were missing body mass index, chronic kidney disease, or total cholesterol:HDL ratio).

Ascertainment of longstanding persistent AF

Rhythm status during follow-up was determined from three data sources as follows.

1. From medical records we obtained dates and results of ECGs, Holter monitors, rhythm strips, electrical cardioversions, other types of rhythm documentation, and results of AF ablation and maze procedures, from the initial AF episode through the date of medical record review, a mean of two years after the initial AF episode.
2. From the Group Health ECG database we obtained dates and results of all ECGs done at Group Health facilities, all of which were interpreted by Group Health cardiologists for presence or absence of AF, from the initial AF episode through December 31, 2009, a mean of seven years after the initial AF episode.
3. From Group Health administrative databases we obtained dates of ICD-9 and Current Procedural Terminology (CPT) procedure codes for electrical cardioversion (ICD-9: 99.61 and 99.62; CPT: 92960) and for ablation and maze procedures (ICD-9: 37.33 and 37.34; CPT: 93651). We used these codes to augment information available from medical records, from the initial AF episode through December 31, 2009, a mean of seven years after the initial AF episode. Specificity of each electrical cardioversion, ablation, and maze procedure code was ≥ 99% relative to procedures documented in medical records, suggesting that using these codes to detect the presence of AF was appropriate for follow-up beyond the time period covered by medical record review.

Using data from sources described above, we defined longstanding persistent AF as AF present after the initial AF episode terminated, on two separate occasions 6–36 months apart with no documented sinus rhythm in the interim. Although guidelines suggest defining longstanding persistent AF as AF present for 12 months,[1] we used six months as a lower bound to increase sensitivity for detecting longstanding persistent AF in participants who may have had incomplete or infrequent rhythm documentation. Recognizing our ability to detect longstanding persistent AF in Group Health data was imperfect, in sensitivity analyses we modified the definition of longstanding persistent AF to require AF present on four separate occasions 6–36 months apart, two occasions 12–36 months apart, or two occasions 6–18 months apart.

Upon recurrence of AF, we required a minimum of six months of follow-up to establish whether the outcome of longstanding persistent AF occurred. Therefore, participants who had less than six months of follow-up after the initial AF episode terminated were excluded from analyses. For the same reason, participants who had at least six months of follow-up who reached the end of the study without meeting the definition of longstanding persistent AF were censored six months prior to the end of their follow-up time. Thus, analysis of follow-up time for longstanding persistent AF ended on the first date of the qualifying

longstanding persistent AF interval or six months prior to whichever of the following occurred first: death; an AF ablation or maze procedure; disenrollment from Group Health; or end of the study on December 31, 2009.

Statistical analysis

We used Cox proportional hazards models with study time as the time scale to estimate cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs).[25] Time zero was date of onset of the initial AF episode. Follow-up time was left-truncated, with each participant entering follow-up when their initial AF episode terminated.[26] Termination of AF occurred within seven days of onset of the initial AF episode in 71% of participants, but was allowed to be up to six months after onset. We examined associations of time-varying use of statins, ACE inhibitors or ARBs, and beta-blockers with risk of longstanding persistent AF, adjusted for age, sex, baseline clinical characteristics including body mass index, diabetes, hypertension, coronary heart disease, valvular heart disease, heart failure, prior stroke, chronic kidney disease, and time-varying use of antiarrhythmic medication. Models for statins were also adjusted for baseline total cholesterol:HDL ratio. Models for ACE inhibitors or ARBs and for beta-blockers were also adjusted for baseline systolic and diastolic blood pressure.

Our primary interest was comparing the risk for longstanding persistent AF among participants currently using a medication as of the previous day of follow-up (current use) vs. participants never having used that medication as of the previous day of follow-up (never use). In our analyses we addressed two potential biases that may arise in epidemiologic studies of medication use: healthy user bias and confounding by indication. For analyses of statin use and ACE inhibitor or ARB use, healthy user bias may arise because participants who continue use of medications may tend to have better underlying health than participants who discontinue use of medications. To address the possibility of healthy user bias, we analyzed former use vs. never use, as well as current use one year prior to outcome occurrence and former use one year prior to outcome occurrence vs. never use one year prior to outcome occurrence (one-year lagged analyses). For analyses of beta-blocker use, confounding by indication may arise because beta-blockers are used for heart rate control in AF, and participants receiving vs. not receiving treatment for rate control might have different underlying risks of longstanding persistent AF. To address the possibility of confounding by indication, we analyzed current beta-blocker use vs. current nondihydropyridine calcium channel blocker (CCB) use, another rate-control treatment, rather than current beta-blocker use vs. never use.

RESULTS

Baseline characteristics of the cohort of 1,317 participants followed for longstanding persistent AF are shown in Table 1. During follow-up, participants used statins for 38% of follow-up time, ACE inhibitors or ARBs for 43% of follow-up time, and beta-blockers for 52% of follow-up time. Use of these medications during follow-up was more common among participants with baseline clinical cardiovascular disease, obesity, diabetes, hypertension, and chronic kidney disease than among participants without these

characteristics. Antiarrhythmic medication use was uncommon in this cohort after the initial diagnosis of atrial fibrillation; during follow-up, participants used amiodarone for 5% of follow-up time and other antiarrhythmic agents for 2% of follow-up time. There were 304 cases of longstanding persistent AF and 257 deaths during a mean of 3.8 years of follow-up.

Results of adjusted models for longstanding persistent AF are shown in Table 2. Hazard ratios were similar across age- and sex-adjusted and fully adjusted models. Current statin use vs. never use was associated with a 23% lower risk of longstanding persistent AF, though the estimate did not reach statistical significance (HR = 0.77; 95% CI: 0.57, 1.03). Analyses of current daily statin dose suggested that high dose statin use vs. never use may be associated with lower risk for longstanding persistent AF (HR = 0.61; 95% CI: 0.36, 1.03). Medium dose statin use vs. never use may also be associated with lower risk (HR = 0.70; 95% CI: 0.49, 1.00). Low dose statin use vs. never use was not associated with longstanding persistent AF (HR = 1.08; 95% CI: 0.70, 1.66). The trend in risk for the outcome across statin dose categories was statistically significant (for each higher dose category, HR = 0.84; 95% CI: 0.73, 0.97). In contrast, current statin use one year prior vs. never use one year prior was not associated with risk of longstanding persistent AF. Former statin use vs. never use was not associated with risk of longstanding persistent AF in either non-lagged or lagged analyses. ACE inhibitor or ARB use and beta-blocker use were not associated with risk of longstanding persistent AF. Modifying the definition of longstanding persistent AF resulted in lower numbers of longstanding persistent AF events. Longstanding persistent AF by these modified definitions occurred at a lower rate among current statin users compared with never users, just as in our primary analysis. However, these sensitivity analyses lacked sufficient precision, and did not support a statistically significant association of current statin use with lower risk of longstanding persistent AF (Table 3).

DISCUSSION

In this population-based inception cohort study of participants whose initial AF episode terminated, we observed that current statin users had a lower risk of longstanding persistent AF than participants who had never used statins. However, this association fell short of statistical significance. Use of ACE inhibitors, ARBs or beta-blockers was not associated with risk of longstanding persistent AF.

Our finding for current statin use may reflect an acute protective effect of statin use that does not persist after statin discontinuation. Alternatively, our finding may result from healthy user bias or chance. Although the risk of longstanding persistent AF was estimated as 23% lower among current statin users than among never users, the 95% confidence interval contained the null hypothesis of a hazard ratio of 1.0, reducing our ability to rule out chance as an explanation. Healthy user bias could occur if participants who initiate or persist with statin use tend to be healthier, perhaps carrying a lower underlying risk of longstanding persistent AF, while those who discontinue statin use tend to be less healthy, perhaps carrying a higher underlying risk of longstanding persistent AF. Healthy user bias was illustrated in a study of statin use and incident dementia, wherein current statin use was associated with lower dementia risk, but current statin use one year prior was not associated with dementia risk, and former statin use one year prior was associated with higher dementia

risk.[27] In our study, statin discontinuation was not associated with higher risk of longstanding persistent AF. Our analysis did not provide support for healthy user bias, but also did not rule it out as an explanation. Points in favor of a modest protective effect of current statin use include the dose-dependent relationship we observed in this study, biologic plausibility of an effect of statins on AF pathogenesis through reducing inflammation and oxidative stress,[28] and consistency with recent meta-analyses which showed lower risk of AF recurrence among statin users.[12,14,15] Our study provides new information by focusing on longstanding persistent AF, which may be a more severe outcome than recurrent AF.[2–10]

ACE inhibitor or ARB use vs. diuretic use was associated with lower risk of new-onset AF among Group Health enrollees with hypertension.[22] Meta-analyses of randomized trials have shown ACE inhibitors and ARBs to reduce risk for recurrent AF,[16–18] however the GISSI-AF trial of valsartan vs. placebo showed no relationship with AF recurrence or progression after cardioversion.[29] Consistent with the GISSI-AF trial, we did not observe an association of ACE inhibitor or ARB use with longstanding persistent AF in our study.

Beta-blockers have been shown to reduce incidence of new-onset AF in patients with heart failure[20] and to reduce recurrent AF after cardioversion.[19] Beta-blocker use vs. diuretic use was not associated with lower risk of new-onset AF among Group Health enrollees with hypertension,[22] but beta-blocker use vs. CCB use was associated with lower risk of new-onset AF among patients in the United Kingdom General Practice Research Database.[30] Beta-blockers are a common treatment for rate control in AF,[1] and therefore would tend to be prescribed preferentially to patients thought to be most likely to experience AF recurrence or progression. Therefore if comparing current beta-blocker use to never use or nonuse, we might expect to see higher rates of longstanding persistent AF among beta-blocker users, obscuring any potential inverse association. To reduce this possibility we compared beta-blockers to nondihydropyridine CCBs, which are also used for rate control.[1] Using this approach we found no association of beta-blocker use with risk of longstanding persistent AF.

Our study had strengths including a cohort representative of routine clinical practice, broad inclusion criteria to enhance generalizability, comprehensive assessment of prescription medication use based on the Group Health pharmacy database, and multiple data sources for documenting heart rhythm changes during follow-up.

Our study had limitations. Medication use was not randomly assigned. Our efforts to address healthy user bias and confounding by indication may have been inadequate. Prescription medication use may have been misclassified because participants do not necessarily use prescriptions they fill. We investigated a few classes of cardiovascular medication but left other classes such as diuretics and dihydropyridine calcium channel blockers unexplored. Longstanding persistent AF status may have been misclassified by of our definition. When we modified the definition to reduce false positives we were left with insufficient precision to assess the associations of interest. Finally, our cohort included only participants with incident AF who came to medical attention and were diagnosed with a 12-lead ECG; people with undiagnosed AF could not be identified for inclusion.

Our investigation of use of statins and antihypertensive medications among participants whose initial AF episode terminated suggested an association consistent with a protective effect of current statin use. However, non-causal explanations are plausible. The association of statin use with longstanding persistent AF warrants further investigation.

Acknowledgments

Funding: This research was supported by NHLBI grant R01 HL068986 (PI: Heckbert), NHLBI training grant T32 HL007902 (PI: Siscovick; Trainees: Thacker, Jensen), and NIA grant K23 AG028954 (PI: Dublin).

References

1. January CT, Wann S, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014 Apr 10. Epub ahead of print. 10.1161/CIR.0000000000000041
2. de Vos CB, Pisters R, Nieuwlaat R, et al. Progression from paroxysmal to persistent atrial fibrillation: clinical correlates and prognosis. J Am Coll Cardiol. 2010; 55:725–31.10.1016/j.jacc.2009.11.040 [PubMed: 20170808]
3. de Vos CB, Breithardt G, Camm AJ, et al. Progression of atrial fibrillation in the REgistry on Cardiac rhythm disORDers assessing the control of Atrial Fibrillation cohort: clinical correlates and the effect of rhythm-control therapy. Am Heart J. 2012; 163:887–93.10.1016/j.ahj.2012.02.015 [PubMed: 22607868]
4. Chiang C-E, Naditch-Brûlé L, Murin J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the Real-Life Global Survey Evaluating Patients with Atrial Fibrillation international registry. Circ Arrhythm Electrophysiol. 2012; 5:632–9.10.1161/circep.112.970749 [PubMed: 22787011]
5. Al-Khatib SM, Thomas L, Wallentin L, et al. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. Eur Heart J. 2013; 34:2464–71.10.1093/eurheartj/eht135 [PubMed: 23594592]
6. Conen D, Chae CU, Glynn RJ, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA. 2011; 305:2080–87.10.1001/jama.2011.659 [PubMed: 21610240]
7. Potpara TS, Stankovic GR, Beleslin BD, et al. A 12-year follow-up study of patients with newly diagnosed lone atrial fibrillation: implications of arrhythmia progression on prognosis: the Belgrade Atrial Fibrillation Study. Chest. 2012; 141:339–47.10.1378/chest.11-0340 [PubMed: 21622553]
8. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012; 14:528–606.10.1093/europace/eus027 [PubMed: 22389422]
9. Hagens VE, Ranchor AV, Van Sonderen E, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. results from the Rate Control Versus Electrical Cardioversion (RACE) Study. J Am Coll Cardiol. 2004; 43:241–7.10.1016/j.jacc.2003.08.037 [PubMed: 14736444]
10. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med. 2005; 352:1861–72.10.1056/NEJMoa041705 [PubMed: 15872201]
11. Sandhu RK, Conen D, Tedrow UB, et al. Predisposing factors associated with development of persistent compared with paroxysmal atrial fibrillation. J Am Heart Assoc. 2014; 3:e000916.10.1161/JAHA.114.000916 [PubMed: 24786144]
12. Liu T, Li L, Korantzopoulos P, Liu E, Li G. Statin use and development of atrial fibrillation: a systematic review and meta-analysis of randomized clinical trials and observational studies. Int J Cardiol. 2008; 126:160–70.10.1016/j.ijcard.2007.07.137 [PubMed: 18031847]
13. Lee YL, Blaha MJ, Jones SR. Statin therapy in the prevention and treatment of atrial fibrillation. J Clin Lipidol. 2011; 5:18–29.10.1016/j.jacl.2010.11.002 [PubMed: 21262503]

14. Bang CN, Greve AM, Abdulla J, Køber L, Gislason GH, Wachtell K. The preventive effect of statin therapy on new-onset and recurrent atrial fibrillation in patients not undergoing invasive cardiac interventions: a systematic review and meta-analysis. Int J Cardiol. 2013; 176:624–30.10.1016/j.ijcard.2012.08.056 [PubMed: 22999824]
15. Fauchier L, Clementy N, Babuty D. Statin therapy and atrial fibrillation: systematic review and updated meta-analysis of published randomized controlled trials. Curr Opin Cardiol. 2013; 28:7–18.10.1097/HCO.0b013e32835b0956 [PubMed: 23160338]
16. Bhuriya R, Singh M, Sethi A, et al. Prevention of recurrent atrial fibrillation with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: a systematic review and meta-analysis of randomized trials. J Cardiovasc Pharmacol Ther. 2011; 16:178–84.10.1177/1074248410389045 [PubMed: 21285399]
17. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol. 2005; 45:1832–39.10.1016/j.jacc.2004.11.070 [PubMed: 15936615]
18. Han M, Zhang Y, Sun SJ, et al. Renin-angiotensin system inhibitors prevent the recurrence of atrial fibrillation: a meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol. 2013; 62:405–15.10.1097/FJC.0b013e3182a094a1 [PubMed: 23921300]
19. Kuhlkamp V, Bosch R, Mewis C, Seipel L. Use of beta-blockers in atrial fibrillation. Am J Cardiovasc Drugs. 2002; 2:37–42.10.2165/00129784-200202010-00005 [PubMed: 14727997]
20. Abi Nasr I, Bouzamondo A, Hulot J-S, Duborg O, Le Heuzey J-Y, Lechat P. Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: a meta-analysis. Eur Heart J. 2007; 28:457–62.10.1093/eurheartj/ehl484 [PubMed: 17289748]
21. Thacker EL, McKnight B, Psaty BM, et al. Association of body mass index, diabetes, hypertension, and blood pressure levels with risk of permanent atrial fibrillation. J Gen Intern Med. 2013; 28:247–53.10.1007/s11606-012-2220-4 [PubMed: 22972153]
22. Heckbert SR, Wiggins KL, Glazer NL, et al. Antihypertensive treatment with ACE inhibitors or beta-blockers and risk of incident atrial fibrillation in a general hypertensive population. Am J Hypertens. 2009; 22:538–44.10.1038/ajh.2009.33 [PubMed: 19265792]
23. Saunders, KW.; Davis, RL.; Stergachis, A. Group Health Cooperative. In: Strom, BL., editor. Pharmacoepidemiology. Chichester, UK: Wiley & Sons; 2005. p. 223-39.
24. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–12.10.7326/0003-4819-150-9-200905050-00006 [PubMed: 19414839]
25. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics. 1978; 34:541–54.10.2307/2530374 [PubMed: 373811]
26. Klein JP, Rizzo JD, Zhang MJ, Keiding N. Statistical methods for the analysis and presentation of the results of bone marrow transplants. part 1: unadjusted analysis. Bone Marrow Transplant. 2001; 28:909–15.10.1038/sj.bmt.1703260 [PubMed: 11753543]
27. Rea TD, Breitner JC, Psaty BM, et al. Statin use and the risk of incident dementia: the Cardiovascular Health Study. Arch Neurol. 2005; 62:1047–51.10.1001/archneur.62.7.1047 [PubMed: 16009757]
28. Sánchez-Quiñones J, Marín F, Roldán V, Lip GYH. The impact of statin use on atrial fibrillation. Q J Med. 2008; 101:845–61.10.1093/qjmed/hcn101
29. Disertori M, Latini R, et al. GISSI-AF Investigators. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med. 2009; 360:1606–17.10.1056/NEJMoa0805710 [PubMed: 19369667]
30. Schaer BA, Schneider C, Jick SS, Conen D, Osswald S, Meier CR. Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: a nested case-control study. Ann Intern Med. 2010; 152:78–84.10.1059/0003-4819-152-2-201001190-00005 [PubMed: 20083826]

Table 1

Baseline characteristics of Group Health enrollees followed for longstanding persistent atrial fibrillation

Characteristic[a]	N = 1,317
Demographic characteristics	
Age, y, mean (SD)	69.6 (10.7)
Male, %	50.7
White race, %	92.9
Group Health enrollment, y, mean (SD)	22.4 (13.4)
Setting of initial AF diagnosis	
Outpatient, %	33.1
Urgent care, %	11.1
Emergency department, %	40.4
Inpatient, %	12.6
Other, %	1.4
Clinical characteristics	
Body mass index, kg/m^2, mean (SD)	29.7 (7.3)
Body mass index ≥25.0 (overweight or obese), %	74.5
Diabetes, %	16.4
Hypertension, %	54.8
Systolic blood pressure, mm Hg, mean (SD)	136.2 (20.4)
Diastolic blood pressure, mm Hg, mean (SD)	76.7 (11.7)
Total cholesterol, mg/dL,[b] mean (SD)	205.0 (42.6)
HDL cholesterol, mg/dL,[b] mean (SD)	55.7 (21.5)
Total cholesterol:HDL ratio, mean (SD)	4.0 (1.3)
Coronary heart disease, %	20.8
Valvular heart disease, %	5.5
Heart failure, %	6.9
Prior stroke, %	6.4
Chronic kidney disease, %	30.8
Medication use just prior to initial AF episode	
Statins, %	21.6
ACE inhibitors or ARBs, %	31.7
Beta-blockers, %	28.2
Nondihydropyridine CCBs, %	4.3
Antiarrhythmics, %	0.8
Digoxin, %	2.4

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HDL, high density lipoprotein

[a] Baseline characteristics were determined by medical record review using information recorded up to the day prior to the initial AF episode. 4 participants had missing values for race, 4 for years of Group Health enrollment, and 18 for location of initial AF diagnosis.

[b] mg/dL may be converted to mmol/L by multiplying by 0.0259.

Table 2

Hazard ratios of longstanding persistent atrial fibrillation[a]

			Age- and sex-adjusted		Fully adjusted[b]	
Medication use	**Events**	**Person-years**	**HR**	**95% CI**	**HR**	**95% CI**
Overall	304	5,001	---			---
Statins: Non-lagged[c]						
Never use	175	2,474	1.00	reference	1.00	reference
Current use	89	1,890	0.77	0.60, 1.00	0.77	0.57, 1.03
Former use	40	636	1.01	0.72, 1.43	1.03	0.71, 1.50
Statins: Lagged[d]						
Never use one year prior	195	2,812	1.00	reference	1.00	reference
Current use one year prior	83	1,641	0.91	0.69, 1.18	0.91	0.67, 1.24
Former use one year prior	25	539	0.79	0.52, 1.20	0.81	0.52, 1.27
ACE inhibitors or ARBs: Non-lagged[c]						
Never use	112	1,768	1.00	reference	1.00	reference
Current use	130	2,171	0.98	0.76, 1.26	0.93	0.69, 1.26
Former use	62	1,063	0.92	0.67, 1.27	0.87	0.62, 1.23
ACE inhibitors or ARBs: Lagged[d]						
Never use one year prior	131	2,046	1.00	reference	1.00	reference
Current use one year prior	113	1,980	1.00	0.78, 1.30	0.97	0.71, 1.32
Former use one year prior	59	967	1.01	0.74, 1.38	0.97	0.69, 1.37
Beta-blockers[c,e]						
Current nondihydropyridine CCB use	27	382	1.00	reference	1.00	reference
Current beta-blocker use	157	2,407	0.98	0.65, 1.47	1.01	0.67, 1.53

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio

[a] Longstanding persistent atrial fibrillation was defined as atrial fibrillation present on two separate occasions 6–36 months apart, without any documented sinus rhythm.

[b] Adjusted for age, sex, body mass index, diabetes, hypertension, coronary heart disease, valvular heart disease, heart failure, prior stroke, chronic kidney disease, and current use of antiarrhythmic medication. Models for statins were also adjusted for total cholesterol:HDL ratio. Models for ACE inhibitors or ARBs and for beta-blockers were also adjusted for systolic and diastolic blood pressure.

[c] Never, current, and former medication use as of the previous day of follow-up.

[d] To reduce healthy user bias, statin use and ACE inhibitor or ARB use were lagged by one year.

[e] To reduce confounding by indication, current beta-blocker use was compared with current nondihydropyridine CCB use. Person-time with concurrent use of both a beta-blocker and a nondihydropyridine CCB (214 person-years) and person-time with no current use of either a beta-blocker or a nondihydropyridine CCB (1,997 person-years) was excluded.

Table 3

Hazard ratios of longstanding persistent atrial fibrillation for alternative definitions of longstanding persistent atrial fibrillation[a]

			Fully adjusted[b]	
Medication use	**Events**	**Person-years**	**HR**	**95% CI**
Longstanding persistent AF definition: AF present on four separate occasions with the first and fourth occasions 6–36 months apart with no documented sinus rhythm in between				
Overall	183	5,413		
Statins: Non-lagged[c]				
Never use	101	2,711	1.00	reference
Current use	53	2,031	0.84	0.58, 1.23
Former use	29	671	1.45	0.92, 2.28
Statins: Lagged[d]				
Never use one year prior	117	3,065	1.00	reference
Current use one year prior	48	1,769	0.91	0.61, 1.35
Former use one year prior	17	571	0.98	0.57, 1.70
ACE inhibitors or ARBs: Non-lagged[c]				
Never use	68	1,919	1.00	reference
Current use	76	2,365	0.91	0.62, 1.35
Former use	39	1,129	0.92	0.60, 1.43
ACE inhibitors or ARBs: Lagged[d]				
Never use one year prior	79	2,209	1.00	reference
Current use one year prior	68	2,165	0.99	0.67, 1.47
Former use one year prior	35	1,031	0.98	0.63, 1.52
Beta-blockers[c,e]				
Current nondihydropyridine CCB use	16	436	1.00	reference
Current beta-blocker use	93	2,615	1.06	0.62, 1.80
Longstanding persistent AF definition: AF present on two separate occasions 12–36 months apart with no documented sinus rhythm in between				
Overall	239	4,626		
Statins: Non-lagged[c]				
Never use	136	2,334	1.00	reference
Current use	70	1,717	0.81	0.58, 1.13
Former use	33	575	1.15	0.76, 1.74
Statins: Lagged[d]				
Never use one year prior	150	2,652	1.00	reference
Current use one year prior	65	1,480	1.00	0.71, 1.41
Former use one year prior	23	487	1.06	0.66, 1.70
ACE inhibitors or ARBs: Non-lagged[c]				
Never use	89	1,666	1.00	reference
Current use	109	2,005	1.01	0.73, 1.41
Former use	41	955	0.75	0.50, 1.13

			Fully adjusted[b]	
Medication use	**Events**	**Person-years**	**HR**	**95% CI**
ACE inhibitors or ARBs: Lagged[d]				
Never use one year prior	104	1,931	1.00	reference
Current use one year prior	93	1,820	1.05	0.75, 1.48
Former use one year prior	41	876	0.89	0.60, 1.33
Beta-blockers[c,e]				
Current nondihydropyridine CCB use	26	358	1.00	reference
Current beta-blocker use	118	2,254	0.78	0.51, 1.20
Longstanding persistent AF definition: AF present on two separate occasions 6–18 months apart with no documented sinus rhythm in between				
Overall	258	5,224		
Statins: Non-lagged[c]				
Never use	144	2,594	1.00	reference
Current use	78	1,975	0.80	0.58, 1.10
Former use	36	655	1.12	0.75, 1.67
Statins: Lagged[d]				
Never use one year prior	164	2,940	1.00	reference
Current use one year prior	72	1,718	0.90	0.65, 1.25
Former use one year prior	21	558	0.79	0.49, 1.28
ACE inhibitors or ARBs: Non-lagged[c]				
Never use	89	1,863	1.00	reference
Current use	107	2,267	0.96	0.68, 1.33
Former use	62	1,094	1.11	0.77, 1.61
ACE inhibitors or ARBs: Lagged[d]				
Never use one year prior	104	2,149	1.00	reference
Current use one year prior	98	2,072	1.07	0.76, 1.50
Former use one year prior	55	995	1.17	0.81, 1.69
Beta-blockers[c,e]				
Current nondihydropyridine CCB use	23	407	1.00	reference
Current beta-blocker use	132	2,502	1.02	0.65, 1.59

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio

[a] The definition of longstanding persistent AF used in primary analyses (see Table 2) was AF present on two separate occasions 6–36 months apart without any documented sinus rhythm.

[b] Adjusted for age, sex, body mass index, diabetes, hypertension, coronary heart disease, valvular heart disease, heart failure, prior stroke, chronic kidney disease, and current use of antiarrhythmic medication. Models for statins were also adjusted for total cholesterol:HDL ratio. Models for ACE inhibitors or ARBs and for beta-blockers were also adjusted for systolic and diastolic blood pressure.

[c] Never, current, and former medication use as of the previous day of follow-up.

[d] To reduce healthy user bias, statin use and ACE inhibitor or ARB use were lagged by one year.

[e] To reduce confounding by indication, current beta-blocker use was compared with current nondihydropyridine CCB use. Person-time with concurrent use of both a beta-blocker and a nondihydropyridine CCB and person-time with no current use of either a beta-blocker or a nondihydropyridine CCB was excluded.