Atrial Fibrillation and Cardiovascular Outcomes in the Elderly

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Background: *Prior studies have not examined which cardiovascular outcomes most frequently develop in participants with atrial fibrillation (AF) from population-based cohorts of the elderly.*

Methods: *This analysis included 4,304 (85% white; 61% women) participants from the Cardiovascular Health Study who were free of baseline cardiovascular disease. AF cases were identified at baseline and as time-updated events during follow-up. Kaplan-Meier estimates were used to compute the 1-, 5-, 10-, and 15-year cumulative incidence rates of the following outcomes: coronary heart disease (CHD), myocardial infarction (MI), heart failure, and ischemic stroke. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between AF and each outcome.*

Results: *For all time periods, the cumulative incidence estimates of CHD, MI, heart failure, and ischemic stroke were higher for those with AF compared with those without AF. Heart failure was the most frequent outcome in those with AF, while CHD events were the most frequently detected outcome in participants without AF. Compared with persons who did not have AF, the risk of heart failure was higher in those with AF (HR = 3.18, 95% CI = 2.78–3.64), and the magnitude of this association was greater than the other outcomes of interest (CHD: HR = 1.76, 95% CI = 1.54–2.03; MI: 1.40, 95% CI = 1.14–1.71; ischemic stroke: HR = 1.98, 95% CI = 1.63–2.39).*

Conclusions: *AF is associated with several adverse cardiovascular outcomes and heart failure is the most frequently detected event. Potentially, risk factor modification strategies for the primary prevention of heart failure will reduce the morbidity and mortality associated with AF. (PACE 2016; 39:907–913)*

atrial fibrillation, outcomes, epidemiology

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice and its prevalence is expected to double by the year 2050.[1] This arrhythmia is a major public health problem associated with many comorbid conditions and it places a significant financial burden on the health care system.[2] Additionally, numerous reports have shown that AF is associated with an increased mortality risk.[3–9] Although mortality from AF classically has been associated with stroke,[10] recent reports have identified other conditions that likely contribute to the excess risk of death, including heart failure[11,12] and myocardial infarction (MI).[13–15] The underlying link between AF and cardiovascular events has been linked to common risk factors,[16] autonomic imbalances,[17,18] inflammation,[19] and abnormalities in hemostasis.[20]

AF has been associated with an increased risk of MI, heart failure, stroke, and mortality in populations of women and Medicare beneficiaries.[6,21] However, the event-specific risks of adverse cardiovascular outcomes associated with AF have not been reported in population-based cohorts of older adults. Due to the expected growth in persons 65 years and older,[22] knowledge of common conditions associated with AF is of paramount importance for physicians and public health officials with aims of reducing the current and future burden of AF. Therefore, this study aimed to examine the risk of adverse cardiovascular outcomes associated with AF in the Cardiovascular Health Study (CHS) to determine which events are most frequent and likely to negatively impact survival in older adults.

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Methods

Study Population

Details of CHS have been previously described.[23] Briefly, CHS is a prospective population-based cohort study of risk factors for coronary heart disease (CHD) and stroke in individuals 65 years and older. A total of 5,888 participants with Medicare eligibility were recruited from four field centers located in the following United States locations: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. Participants were followed with semiannual contacts, alternating between telephone calls and surveillance clinic visits. CHS clinic exams ended in June 1999 and since that time two yearly phone calls to participants have been used to identify events and collect data. The institutional review board at each site approved the study and written informed consent was obtained from participants at enrollment.

In this analysis, we examined the association between AF and several adverse cardiovascular outcomes (e.g., CHD, MI, heart failure, and ischemic stroke). Participants were excluded if any of the following criteria were met: baseline CHD, MI, heart failure, and ischemic stroke were present; baseline covariate data were missing; or follow-up data were missing.

Atrial Fibrillation

Baseline AF cases were identified during the initial study electrocardiogram tracing or through a self-reported history of a physician diagnosis. Incident AF cases were identified during the annual study electrocardiograms that were performed annually until 1999. Additionally, hospitalization discharge data were used to identify AF cases using International Classification of Diseases codes 427.31 and 427.32. AF cases that were identified after the baseline study visit were included as time-updated events if they occurred prior to each outcome of interest.

Outcomes

The outcomes of interest were the development of CHD, MI, heart failure, and ischemic stroke. The ascertainment and adjudication of baseline and incident cases of cardiovascular disease events in CHS have been previously described.[24–26] Adjudicated incident CHD was defined as one of the following: fatal or nonfatal MI, angina pectoris without MI, coronary revascularization procedures (angioplasty and coronary artery bypass graft surgery), or other fatal CHD events. Fatal and nonfatal heart failure events were determined from both the physician diagnosis and/or treatment defined by a current prescription for typical therapies (e.g., diuretics, digitalis, and vasodilators). Additionally, typical symptoms, signs, and chest x-ray findings of heart failure were reviewed by the CHS Events Committee. All suspected stroke events and stroke-related deaths were reviewed by the Cerebrovascular Adjudication Committee, and included fatal and nonfatal ischemic strokes. A detailed description of the ascertainment of each clinical event is described in the Supporting information.

Covariates

Participants' characteristics were collected during the initial CHS interview and questionnaire. Age, sex, race, income, education, and smoking status were self-reported. Annual income was dichotomized at $25,000 and education was dichotomized at "high school or less." Smoking was defined as current or ever smoker. Participants' blood samples were obtained after a 12-hour fast at a local field center. Measurements of total cholesterol, high-density lipoprotein cholesterol, and plasma glucose were used in this analysis. Diabetes was defined by a self-reported history of a physician diagnosis, a fasting glucose value $\geq$ 126 mg/dL, or by the current use of insulin or oral hypoglycemic medications. Blood pressure was measured for each participant in the seated position and systolic measurements were used in this analysis. The use of aspirin and antihypertensive medications were self-reported. Body mass index was computed as the weight in kilograms divided by the square of the height in meters.

Statistical Analysis

Categorical variables were reported as frequency and percentage while continuous variables were recorded as mean $\pm$ standard deviation. Statistical significance for categorical variables was tested using the χ^2 method and the Student's *t*-test for continuous variables. Comparisons were examined between participants with and without AF. We examined the association between AF and each outcome. Follow-up time was defined as the time from the initial study exam until one of the following: outcome of interest, death, loss to follow-up, or end of follow-up (December 31, 2010). For time-updated AF events, the time between the baseline visit and AF diagnosis was considered as non-AF follow-up. AF events that occurred within 30 days of the outcome of interest were not included, as these events were possibly related to the development of each outcome rather than AF influencing its development. Kaplan-Meier estimates were used to compute the

1-, 5-, 10-, and 15-year cumulative incidence estimates of each outcome among those with and without AF.[27] Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between AF and each outcome, separately. Multivariable models were constructed as follows: Model 1 adjusted for age, sex, race, education, and income; Model 2 adjusted for Model 1 covariates plus body mass index, high-density lipoprotein cholesterol, total cholesterol, smoking, systolic blood pressure, diabetes, aspirin, and antihypertensive medications. The proportional hazards assumption was not violated in our analyses. Statistical significance was defined as $P < 0.05$. SAS Version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

A total of 4,304 (85% white; 61% women) participants were included in the final analysis. There were 1,321 (31%) participants with evidence of AF during the study period. Of these, 172 (13%) AF cases were identified at baseline. The baseline characteristics stratified by the presence of AF are shown in Table I.

Over a median follow-up of 11 years, a total of 1,561 CHD events, 761 MIs, 1,293 cases of heart failure, and 633 ischemic strokes were detected. The 1-, 5-, 10-, and 15-year cumulative incidence estimates of each outcome are shown in Table II and depicted in Figure 1. Heart failure was the most frequent outcome in those with AF, while CHD events were the most frequently detected outcome in those without AF. For all time periods, the cumulative incidence estimates of each outcome were higher for those with AF compared with those without AF.

Table II.

1-, 5-, 10-, and 15-Year Cumulative Incidence Estimates Cardiovascular Outcomes

	1-Year	5-Year	10-Year	15-Year
Atrial fibrillation				
CHD	5.6%	25%	46%	57%
Myocardial infarction	2.3%	11%	20%	25%
Heart failure	6.6%	26%	50%	65%
Ischemic stroke	3.1%	11%	21%	28%
No atrial fibrillation				
CHD	2.1%	14%	27%	40%
Myocardial infarction	0.97%	6.0%	13%	21%
Heart failure	1.0%	7.1%	18%	29%
Ischemic stroke	0.91%	4.9%	11%	16%

CHD = coronary heart disease.

Table I.

Characteristics (N = 4,304)

Characteristic	AF (n = 1,321)	No AF (n = 2,983)	P Value*
Age (years)			
65–70 (%)	544 (41)	1,406 (47)	
71–74 (%)	329 (25)	709 (24)	
75–80 (%)	309 (23)	614 (21)	
>80 (%)	139 (11)	254 (8.0)	0.002
Male (%)	594 (45)	1,103 (37)	<0.001
Black (%)	141 (11)	486 (16)	<0.001
Education, high school or less (%)	737 (56)	1,679 (56)	0.76
Income, <$25,000 (%)	797 (60)	1,872 (63)	0.13
Current or former smoker (%)	692 (52)	1,571 (53)	0.87
Diabetes (%)	213 (16)	388 (13)	0.010
Systolic blood pressure, mean ± SD (mm Hg)	140 ± 21	139 ± 20	0.010
Body mass index, mean ± SD (kg/m^2)	27 ± 4.1	26 ± 4.0	0.037
HDL cholesterol, mean ± SD (mg/dL)	54 ± 15	56 ± 16	0.004
Total cholesterol, mean ± SD (mg/dL)	209 ± 39	214 ± 39	<0.001
Antihypertensive medication use (%)	578 (44)	1,111 (37)	<0.001
Aspirin use (%)	407 (31)	833 (28)	0.054

*Statistical significance for continuous data was tested using the Student's *t*-test and for categorical data was tested using the χ^2 test.
AF = atrial fibrillation; HDL = high-density lipoprotein; SD = standard deviation.

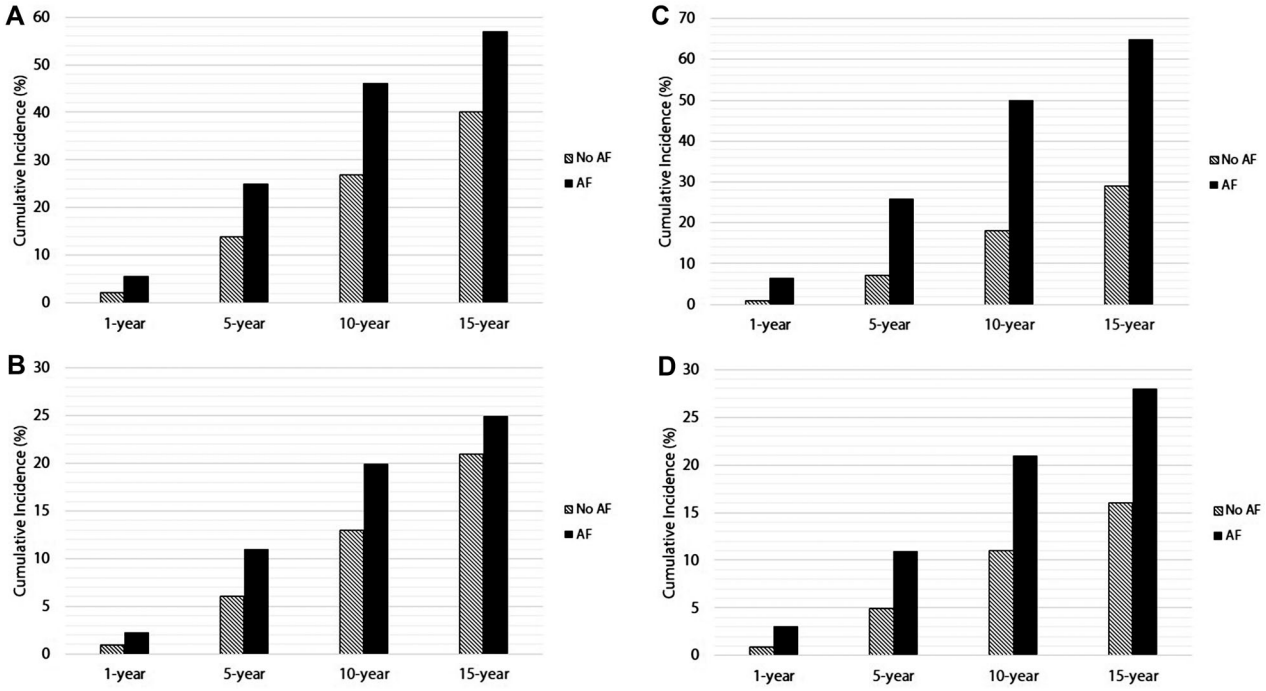

Figure 1. *Cumulative incidence of cardiovascular outcomes associated with atrial fibrillation. 1-, 5-, 10-, and 15-year cumulative incidence estimates of CHD (A), MI (B), heart failure (C), and (D) ischemic stroke for those with and without AF are shown.*
AF = atrial fibrillation; CHD = coronary heart disease; MI = myocardial infarction.

In a multivariable Cox regression model adjusted for potential confounders and cardiovascular disease risk factors, AF was associated with all outcomes examined (Table III). The magnitude of the risk for heart failure events was higher than that observed for other outcomes. The multivariable HRs for each outcome are shown in Table III.

Discussion

In this cohort of older adults, our findings confirm that an increased risk of CHD, MI, heart failure, and ischemic stroke exists in persons who have AF. Additionally, we have identified heart failure as the most frequently detected cardiovascular outcome in community-dwelling older adults with AF.

Although the mortality associated with AF has improved over the past 50 years,[8] AF remains an important public health problem due to the projected increases in its prevalence and the significant financial burden it places on the health care system.[1,2] Several reports have demonstrated that AF is associated with

Table III.

Risk of Cardiovascular Outcomes Associated with Atrial Fibrillation

Outcome	Events	Model 1* HR (95% CI)	P Value	Model 2† HR (95% CI)	P Value
Coronary heart disease	1,561	1.77 (1.54–2.03)	<0.001	1.76 (1.54–2.03)	<0.001
Myocardial infarction	761	1.41 (1.16–1.73)	<0.001	1.40 (1.14–1.71)	0.001
Heart failure	1,293	3.29 (2.87–3.76)	<0.001	3.18 (2.78–3.64)	<0.001
Ischemic stroke	633	2.05 (1.70–2.48)	<0.001	1.98 (1.63–2.39)	<0.001

*Adjusted for age, sex, race, education, and income.
†Adjusted for Model 1 covariates plus smoking, systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol, aspirin, and antihypertensive medications.
CI = confidence interval; HR = hazard ratio.

a significant mortality risk,[3–9] and identified CHD,[14] MI,[13–15] heart failure,[5,11,12] and stroke[4–6,28] as conditions that likely influence mortality in this population. Our findings confirm that the aforementioned outcomes are common in persons with AF from a community-based sample of older adults. Additionally, we identified heart failure as the most frequent cardiovascular outcome in older adults with AF, and this finding is in agreement with a retrospective analysis of a nationally representative sample of fee-for-service Medicare beneficiaries.[21]

Prior reports from population-based cohort studies have examined the association of AF with various cardiovascular outcomes in isolation. To our knowledge, none have attempted to determine which events are most commonly associated with AF in a population-based cohort of elderly participants, or compared the magnitude of the risk for each outcome. One report from the Renfrew/Paisley Study in Scotland showed that AF was an independent predictor of cardiovascular events (Relative Risk (RR) = 3.0, 95% CI = 2.1–4.2), fatal and nonfatal strokes (RR = 3.2, 95% CI = 1.0–5.0), and heart failure (RR = 3.4, 95% CI = 1.9–6.2) over 20 years of follow-up in men and women between 45 and 64 years of age.[5] However, the aforementioned study was limited as it included a younger population than the current report, and was limited to residents of Scotland. Another report examined the frequency of adverse cardiovascular events in patients with AF but that study was limited to persons with the arrhythmia and no comparison was made between those with and without AF.[21] In contrast, the data presented in this analysis demonstrate that the most frequent cardiovascular outcome differs by the presence of AF, as persons with AF were more likely to develop heart failure, and persons without AF were more likely to develop CHD. Our results also are generalizable to the black and white elderly persons of the United States, and are not limited to specific populations.

Overall, heart failure was the most frequent outcome among those with AF. Heart failure has been recognized as a vastly underreported cause of death in the general population.[29] This suggests that the development of heart failure in AF possibly plays a larger role in the excess risk of death observed in AF than previously thought. This is supported by data from the Framingham Heart Study that showed the mortality risk in AF increases considerably with the development of heart failure.[11] AF also was associated with several adverse cardiovascular outcomes that negatively influence survival. Overall, these findings suggest that AF is a marker for terminal illness rather than a disease that independently influences mortality. Data from Olmstead County, Minnesota, which showed that the excess risk of death with AF was limited to the first 90 days of diagnosis but not 1 year after AF diagnosis support this hypothesis.[7] Nonetheless, our findings suggest that patients with AF will benefit from intense risk factor modification strategies to prevent the development of adverse cardiovascular outcomes and implicate heart failure as a condition which merits closer attention if developed in persons with AF.

Although the underlying mechanism that links AF with ischemic stroke has been well-documented,[10] the underlying pathophysiology that explains the excess risk for other cardiovascular events has yet to be fully elucidated. Shared risk factors provide a possible explanation, as many AF risk factors also are associated with an increased risk for CHD and heart failure.[16] However, our results remained statistically significant after accounting for many of these comorbid conditions. Poorly controlled heart rate in persons with AF results in myocardial injury with increased oxygen demand (e.g., demand ischemia) that leads to non-ST elevation MI in persons with partially occluded coronary arteries.[15,20] The dysynchronous rhythm of AF combined with elevated heart rates among those who are poorly rate controlled also predisposes to heart failure.[30] AF is associated with higher levels of inflammation,[31] and both CHD and heart failure have been linked to the dysfunctional regulation of this cellular process.[32,33] Additionally, we cannot exclude that patients possibly have subclinical left ventricular dysfunction or myocardial ischemia that leads to AF, and after disease progression, cardiovascular outcomes likely develop. This suggests that AF represents an epiphenomena of silent cardiovascular disease that subsequently manifests clinically. We provide several explanations that link AF with CHD and heart failure events; however, further research is needed to better understand the increased risk of cardiovascular events observed with AF.

Our findings should be interpreted in the context of certain limitations. Several baseline characteristics were self-reported and possibly resulted in misclassification due to recall bias. We also included several covariates in our multivariable models that likely influenced the development of each condition but we acknowledge that residual confounding is possible. The population of CHS was limited to whites and blacks older than 65 years of age, and limits the generalizability of our findings to other populations. AF was ascertained by study-scheduled electrocardiograms and hospitalization data. Therefore, it is possible that asymptomatic cases or self-limited episodes (e.g., paroxysmal

AF) were missed. Additionally, it is possible that the risk of each cardiovascular outcome varies by AF type (e.g., paroxysmal, persistent, and permanent) and we were unable to examine this in our cohort. Furthermore, it is possible that the true risk associated with each cardiovascular outcome is greater for nonfatal events when accounting for death, but we did not explore this hypothesis.

In conclusion, we have shown that AF is associated with several adverse cardiovascular outcomes and identified heart failure as the most frequent condition developed in older persons with AF. Overall, AF was associated with several conditions that negatively influence mortality, suggesting that AF is a marker of a poor cardiovascular profile in which adverse events are likely to develop. Potentially, risk factor modification strategies (e.g., lifestyle and medication) for the primary prevention of heart failure will reduce the morbidity and mortality associated with AF.

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References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285:2370–2375.
2. Kim MH, Johnston SS, Chu BC, 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.
3. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995; 98:476–484.
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.
5. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-Year follow-up of the Renfrew/Paisley study. Am J Med 2002; 113:359–364.
6. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, Albert CM. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA 2011; 305:2080–2087.
7. Chamberlain AM, Gersh BJ, Alonso A, Chen LY, Berardi C, Manemann SM, Killian JM, et al. Decade-long trends in atrial fibrillation incidence and survival: A community study. Am J Med 2015; 128:260–267.
8. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, et al. 50 Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: A cohort study. Lancet 2015; 386:154–162.
9. O'Neal WT, Efird JT, Judd SE, McClure LA, Howard VJ, Howard G, Soliman EZ. Impact of awareness and patterns of nonhospitalized atrial fibrillation on the risk of mortality: The Reasons for Geographic And Racial Differences in Stroke (REGARDS) Study. Clin Cardiol 2016; 39:103–110.
10. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke 1991; 22:983–988.
11. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. Circulation 2003; 107:2920–2925.
12. O'Neal WT, Qureshi W, Zhang ZM, Soliman EZ. Bidirectional association between atrial fibrillation and congestive heart failure in the elderly. J Cardiovasc Med (Hagerstown) 2016; 17:181–186.
13. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, et al. Atrial fibrillation and the risk of myocardial infarction. JAMA Intern Med 2014; 174:107–114.
14. O'Neal WT, Sangal K, Zhang ZM, Soliman EZ. Atrial fibrillation and incident myocardial infarction in the elderly. Clin Cardiol 2014; 37:750–755.
15. Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, et al. Atrial Fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2015; 131:1843–1850.
16. 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.
17. O'Neal WT, Almahmoud MF, Soliman EZ. Resting heart rate and incident atrial fibrillation in the elderly. Pacing Clin Electrophysiol 2015; 38:591–597.
18. O'Neal WT, Qureshi WT, Blaha MJ, Keteyian SJ, Brawner CA, Al-Mallah MH. Systolic blood pressure response during exercise stress testing: The Henry Ford ExercIse Testing (FIT) Project. J Am Heart Assoc 2015; 4:e002050.
19. O'Neal WT, Efird JT, Yeboah J, Nazarian S, Alonso A, Heckbert SR, Soliman EZ. Brachial flow-mediated dilation and incident atrial fibrillation: The multi-ethnic study of atherosclerosis. Arterioscler Thromb Vasc Biol 2014; 34:2717–2720.
20. O'Neal WT, Soliman EZ, Howard G, Howard VJ, Safford MM, Cushman M, Zakai NA. Inflammation and hemostasis in atrial fibrillation and coronary heart disease: The REasons for Geographic And Racial Differences in Stroke study. Atherosclerosis 2015; 243:192–197.
21. Piccini JP, Hammill BG, Sinner MF, Hernandez AF, Walkey AJ, Benjamin EJ, Curtis LH, et al. Clinical course of atrial fibrillation in older adults: The importance of cardiovascular events beyond stroke. Eur Heart J 2014; 35:250–256.
22. Odden MC, Coxson PG, Moran A, Lightwood JM, Goldman L, Bibbins-Domingo K. The impact of the aging population on coronary heart disease in the United States. Am J Med 2011; 124:827–833.
23. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, et al. The Cardiovascular Health Study: Design and rationale. Ann Epidemiol 1991; 1:263–276.
24. Psaty BM, Kuller LH, Bild D, Burke GL, Kittner SJ, Mittelmark M, Price TR, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. Ann Epidemiol 1995; 5:270–277.
25. Ives DG, Fitzpatrick AL, Bild DE, Psaty BM, Kuller LH, Crowley PM, Cruise RG, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol 1995; 5:278–285.
26. Price TR, Psaty B, O'Leary D, Burke G, Gardin J. Assessment of cerebrovascular disease in the Cardiovascular Health Study. Ann Epidemiol 1993; 3:504–507.
27. Gray RJ, Tsiatis AA. A linear rank test for use when the main interest is in differences in cure rates. Biometrics 1989; 45:899–904.
28. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, Tsang TS. Mortality trends in patients diagnosed with first atrial fibrillation: A 21-year community-based study. J Am Coll Cardiol 2007; 49:986–992.
29. Murdoch DR, Love MP, Robb SD, McDonagh TA, Davie AP, Ford I, Capewell S, et al. Importance of heart failure as a cause of death. Changing contribution to overall mortality and coronary heart disease mortality in Scotland 1979-1992. Eur Heart J 1998; 19:1829–1835.

30. Gupta S, Figueredo VM. Tachycardia mediated cardiomyopathy: Pathophysiology, mechanisms, clinical features and management. Int J Cardiol 2014; 172:40–46.
31. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003; 108:3006–3010.
32. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004; 350:1387–1397.
33. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, Sawyer DB, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: The Framingham Heart Study. Circulation 2003; 107: 1486–1491.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Supplemental Methods