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Incident Atrial Fibrillation and Disability-Free Survival in the Cardiovascular Health Study

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Abstract

OBJECTIVES—To assess the associations of incident atrial fibrillation (AF) in relation to disability-free survival and the risk of disability.

DESIGN—Prospective cohort study

SETTING—The Cardiovascular Health Study

PARTICIPANTS—4046 participants aged 65 years and older and enrolled in fee-for-service Medicare followed between 1991 and 2009. Individuals with prevalent AF, Activities of Daily Living (ADL) disability, or a history of stroke or heart failure at baseline were excluded.

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Author Contributions: All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Erin Wallace was responsible for developing the research question of interest, data collection, and data analysis for the project, and writing the manuscript. Susan Heckbert was the senior investigator on the project. She supervised all activities and aided in all aspects of the project, including development of the research question, analysis, and writing the manuscript. David Siscovick, Colleen Sitlani, Sascha Dublin, Pamela Mitchell, Michelle Odden, Calvin Hirsch, and Stephen Thielke assisted in the collection of data, development of the analytic methods, interpretation of data, and critically reviewed all drafts of the manuscript.

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MEASUREMENTS—Incident AF was identified by annual study ECG or using hospital discharge diagnosis or Medicare claims. Disability-free survival was defined as survival free of ADL disability (any difficulty or inability in bathing, dressing, eating, using the toilet, walking around the home, or getting out of a bed or chair). ADLs were assessed at annual study visits or by telephone interview. The association between incident AF and disability-free survival or the risk of disability was estimated using Cox proportional hazards models.

RESULTS—Over an average of 7.0 years of follow-up, 660 individuals (16.3%) developed incident AF and 3112 (77%) became disabled or died. Incident AF was associated with decreased disability-free survival (HR for death or ADL disability=1.71, 95% CI 1.55, 1.90) and a higher risk of ADL disability (HR=1.36, 95% CI 1.18, 1.58) compared to individuals with no history of AF. This association persisted after adjustment for interim stroke and heart failure.

CONCLUSION—These results suggest that AF is a risk factor for decreased functional longevity and disability in older adults, independent of other risk factors and comorbid conditions.

Keywords

Atrial fibrillation; disability; disability-free survival

INTRODUCTION

In older adults the onset of disability, whether from a gradual loss of physical function or after a catastrophic event such as a hip fracture, marks a critical turning point in life. It is often followed by a precipitous decline in health, soaring medical costs, and an increased risk of nursing home placement and death.[1, 2] On an individual level, it means a loss of personal autonomy and diminished quality of life in one's final years. Improvements in life expectancy and the burgeoning population of older adults have heightened interest in "successful aging", a concept which includes, amongst other factors, aging with intact physical function and free of disability.[3]

Atrial fibrillation is one potential risk factor for disability in older adults. AF is the most common cardiac arrhythmia in the U.S., affecting more than 10% of U.S. adults over the age of 80.[4] Symptoms and complications of AF include decreased cardiac and cerebral perfusion, reduced exercise tolerance, weakness, dizziness, and a rapid or irregular heart rate.[5, 6] These in turn may increase the likelihood of disabling falls or promote a sedentary lifestyle, hastening the onset of disability.

AF is associated with an increased risk of stroke,[7] heart failure,[8] dementia,[9, 10] and death,[11] but whether AF is associated with disability independent of these outcomes is largely unknown. The relationship between AF and incident disability or disability-free survival has yet to be studied prospectively in a population generalizable to older U.S. adults. We hypothesized that individuals with AF would be at higher risk of disability or death than those without AF.

METHODS

The Cardiovascular Health Study (CHS) is a population-based, longitudinal cohort study of risk factors for coronary heart disease and stroke in 5,888 individuals 65 years of age and older. The recruitment experience for CHS has been described elsewhere.[12]. For the first ten years of the study, participants underwent annual exams that included standardized questionnaires, laboratory tests, electrocardiograms (ECGs) and functional assessments. Individuals have been contacted by telephone every six months from the date of enrollment through the present day to ascertain changes in health status, hospitalizations, and medication use. CHS obtained medical records for all hospitalizations. Surveillance for AF and other clinical events was also conducted via a linkage to administrative claims data, which captured claims to Medicare for inpatient stays, outpatient visits, and physician claims. The institutional review boards for each community site approved the study, and all participants provided informed, written consent.

Administrative claims data used to identify AF were available approximately two years after CHS baseline and only in participants enrolled in fee-for-service Medicare (FFS). Because we used claims data to identify incident AF, this analysis was restricted to participants enrolled in FFS. In addition to excluding participants not enrolled in FFS, we excluded individuals with ADL disability, prevalent AF, a history of stroke or heart failure, or missing covariate data at the time of FFS enrollment. The final analytic cohort included 4046 individuals (Supplemental Figure S1). Follow-up extended from January 1, 1991 through June 30, 2009.

Incident atrial fibrillation

Incident AF (defined as either atrial fibrillation or atrial flutter), was ascertained from three sources: (1) ECGs from annual study examinations through 1999, (2) hospital discharge diagnoses (from CHS hospitalization or Medicare data), and (3) diagnoses of AF from outpatient or physician service claims (from Medicare data). For AF identified using hospital discharge or Medicare data, a diagnosis of AF was based on a single inpatient claim or hospital discharge diagnosis or 2 outpatient or physician claims within 365 days (ICD-9-CM code 427.31 or 427.32).[13] AF diagnosed as part of a hospitalization for valve surgery or coronary artery bypass grafting was excluded. The date of AF diagnosis was based on the earlier of: (1) the date of ECG indicating AF, (2) the admission date of the qualifying inpatient claim or hospital discharge diagnosis, or (3) the service date of the second qualifying outpatient or physician claim. Once an AF diagnosis was made, participants were classified thereafter as having AF.

Outcomes

The primary outcome was disability-free survival, defined as survival free of ADL disability. For the purposes of risk estimates, a failure was death or ADL disability. We defined ADL disability as reporting any difficulty or inability to perform one or more of the following tasks crucial for independent living: bathing, dressing, eating, using the toilet, walking around the home, and getting out of a bed or chair.[14, 15] ADLs were assessed annually at clinic visits the first ten years of the study or by telephone calls from enrollment through the

present day. Because disability can be transient, we also considered whether incident AF was associated with persistent ADL disability, defined as difficulty in at least one ADL for two consecutive occasions.[3]

Covariates

Participant age, year of birth, sex, race, education, clinic, physical activity (in kilocalories per week), alcohol use, and smoking history were self-reported at CHS study baseline. Alcohol use and smoking status were updated at clinic visits and the measurements closest to entry into FFS were used for the analysis. Body mass index (in kilograms per meters squared) and pulmonary function (forced expiratory volume in one second, FEV1) were measured at CHS study baseline. Diabetes was defined as use of insulin or oral hypoglycemic drugs, fasting serum glucose ≥ 126 mg/dL, or non-fasting serum glucose ≥ 200 mg/dL. Hypertension was defined as use of antihypertensive medications plus self-reported history of hypertension, or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Chronic kidney disease was defined as having a creatinine-based estimated glomerular filtration rate < 60 ml/min. Gait speed (time to walk 15 feet, converted to meters per second) was assessed at clinic visits. Subclinical brain abnormalities (subclinical infarcts and white matter grade) were detected using magnetic resonance imaging (MRI) at two visits, five years apart. Baseline and incident coronary heart disease, stroke, and heart failure were identified through semi-annual contacts or through linkage with hospitalization records and were confirmed by physician adjudication.[16, 17] Hip fractures were identified using discharge diagnosis codes (ICD-9 CM 820.0–820.9) from inpatient claims or hospitalization records.

Statistical Analysis

Kaplan-Meier curves for disability-free survival and ADL disability were plotted in individuals with and without incident AF and a difference in curves was evaluated using a log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between incident AF, modeled as a time-varying exposure, and the risk of death or ADL disability. The association between incident AF and the risk of incident ADL disability alone was also estimated. Analyses were repeated for the outcomes of persistent ADL disability or death, and persistent ADL disability alone. All estimates were adjusted for age, sex, race, clinic, education, BMI, FEV1, smoking status, alcohol use, physical activity, and the following time-varying covariates: hypertension, anti-hypertensive drug use, coronary heart disease, and diabetes. We examined whether the outcome risk varied over time by repeating the primary analyses and including a linear interaction term between time and AF status, and including AF-time interaction terms using cut-points of 2 and 5 years.

We conducted several secondary analyses. We repeated our analyses adjusting for incident stroke and heart failure during follow-up. Analyses were also repeated adjusted for interim hip fracture, time-varying gait speed, and time-varying chronic kidney disease. To assess the role of subclinical changes in the brain, analyses were repeated in the subsample of participants with both MRI assessments. Analyses were restricted to individuals without documented brain infarctions on the first MRI and adjusted for interim stroke, incident

subclinical infarction, and white matter grade from the second MRI. We also examined the outcome of worsening disability, defined as an increase in total ADL score, where scores were calculated as one point per ADL difficulty. Finally, we repeated our analyses of AF and the risk of ADL disability using competing risks regression to account for death as a competing risk.[18]

We assessed the robustness of our results to selection bias by performing sensitivity analyses including participants not enrolled in FFS and ignoring entry and exit from FFS. To examine bias due to participants dropping out of the study prior to death or the onset of disability, sensitivity analyses were performed using inverse probability weighting methods (IPW).[19] Statistical analyses were conducted using STATA version 13.0 (Stata Corp, College Station, Texas).

RESULTS

Over a mean follow-up of 7.0 years, 660 individuals (16.3%) developed incident AF. Of the individuals diagnosed with AF, 10% were identified from study ECG, 65% from an inpatient claim or hospital discharge diagnosis, and 25% from an outpatient or physician claim. Individuals who developed incident AF during follow-up were more likely to be male and white, and had a higher burden of comorbidity than individuals who did not develop AF (Table 1). Both individuals with and without incident AF had on average 7 measures of ADL over follow-up.

The crude incidence rate of death or disability was 100.5 per 1,000 person-years in individuals without incident AF and 207.8 per 1,000 person years in individuals with incident AF. Crude incidence rates for ADL disability alone were 62.5 per 1,000 person-years (41.7 for persistent ADL disability) and 97.8 per 1,000 person-years (86.2 for persistent ADL disability) in individuals without and with incident AF, respectively. Figures 1A and 1B display Kaplan-Meier curves for survival free of death or ADL disability and survival free of ADL disability for individuals with and without incident AF. There was evidence of a difference in the survival curves (log-rank $p<0.001$). There was no evidence that the hazards changed over time ($p>0.05$ for all time-AF interaction terms). At the time of their first occurrence of ADL difficulty, most participants (65%) indicated difficulty in only one ADL (mean of 1.6 ADLs). Most common was difficulty getting out of bed or chair, experienced by 68% of those with ADL difficulties.

After adjustment for participant characteristics, incident AF was associated with a higher risk of death or disability (adjusted HR=1.71, 95% CI 1.55, 1.90) (Table 2). Incident AF was also associated with a higher risk of disability (adjusted HR = 1.36, 95% CI 1.18, 1.58). Estimates were similar for the associations of incident AF and persistent ADL disability and persistent disability-free survival.

Adjustment for interim stroke and heart failure attenuated, but did not completely remove, the associations between incident AF and death or disability (Table 2). Additional adjustment for chronic kidney disease, interim hip fracture and gait speed measures had little effect on risk estimates (Supplemental Table S1). Adjustment for brain abnormalities also

attenuated risk estimates, although the association between incident AF and death or disability persisted (adjusted HR for ADL disability=1.18, 95% CI 0.90, 1.55; adjusted HR for death or disability=1.34, 95% CI 1.11, 1.62; Supplemental Table S2). We also observed that incident AF was associated a greater than two-fold risk of worsening ADL disability or death, and with worsening ADL disability alone (Supplemental Table S1). Estimates of the subhazard ratio for the association of incident AF with ADL disability using competing-risks regression were smaller in magnitude than hazard ratio estimates, although individuals with incident AF were still at higher risk for ADL disability than those without AF (adjusted SHR=1.21, 95% CI 1.04, 1.41). Sensitivity analyses using IPW to account for attrition and analyses including participants not enrolled in FFS Medicare yielded similar estimates as in the primary analysis (Supplemental Table S1).

DISCUSSION

This was the first study to examine the association between incident AF and the risk of disability in a population representative of older U.S. adults. The results of this study suggest that incident AF is a risk factor for disability and is associated with decreased survival free of disability. Importantly, we observed that even after adjustment for interim stroke or heart failure, individuals with incident AF experienced a 50% higher risk of death or disability and 24% higher risk of becoming disabled.

One prior study evaluated the association between AF and the risk of ADL disability using a post-hoc analysis of randomized controlled trial data in patients at high cardiovascular risk.[20] In that study, participants with prevalent or newly diagnosed AF were at higher risk of ADL disability than participants without AF, and the magnitude of association was similar to this study (adjusted HR=1.35, 95% 1.19, 1.54).

The onset of disability can occur as a result of a catastrophic event or may develop slowly over time.[21] In our study the relationship between incident AF and the risk of death or disability appeared to be partially, but not fully, mediated by the effects of interim stroke, heart failure, hip fracture, or changes in physical function, suggesting that other mechanisms may be at work.

Beyond stroke, AF may exert degenerative effects on the brain via hypoperfusion and or covert infarction.[6] Covert brain infarctions and white matter disease are associated with abnormalities in gait and balance,[22–24] disability,[24] and a higher risk of falls.[25] Cross-sectional studies have observed associations of prevalent AF with the presence of white matter abnormalities or covert infarction.[26, 27] However, other studies have found no association between prevalent AF and white matter findings.[28] In our analysis, adjustment for newly detected brain abnormalities resulted in attenuated risk estimates although individuals with AF were still at higher risk of disability and death. More research is needed to understand other pathophysiological mechanisms through which AF may lead to disability.

There were several limitations to this study. AF can be transient and asymptomatic, leading to misclassification in AF ascertainment. Assuming that errors in ascertaining AF were non-

differential, this would have attenuated the associations between incident AF and the risk of disability or death. Second, we were not able to differentiate between categories of AF such as paroxysmal, persistent, and permanent on the basis of the diagnosis codes. The risk of subsequent disability may differ by type of AF. Third, while our definition of AF excludes AF that occurred as part of a hospital stay for valve surgery or coronary artery bypass, we would have still missed other surgeries or acute illnesses that may have precipitated AF temporarily. These events, rather than the transient AF, may have led to ADL difficulty or death.

Our study has a number of strengths. We utilized a large prospective cohort study generalizable to older U.S. adults. We had rich and detailed information about potential confounders and important clinical factors which may mediate the relationship between AF and disability, such as stroke and heart failure. Multiple sources were used to identify incident AF, including AF detected on study ECG as well as AF diagnosed outside of the hospital, which lowered the likelihood of misclassification of AF status. Finally, we attempted to reduce the potential bias from missing data that is common in studies of aging by using IPW.

In conclusion, the results of this study suggest that incident AF is a risk factor for disability in older adults. Additional research is needed to understand the potential mechanisms through which AF influences disability and to examine whether prevention or treatment of AF can reduce the burden of disability in the elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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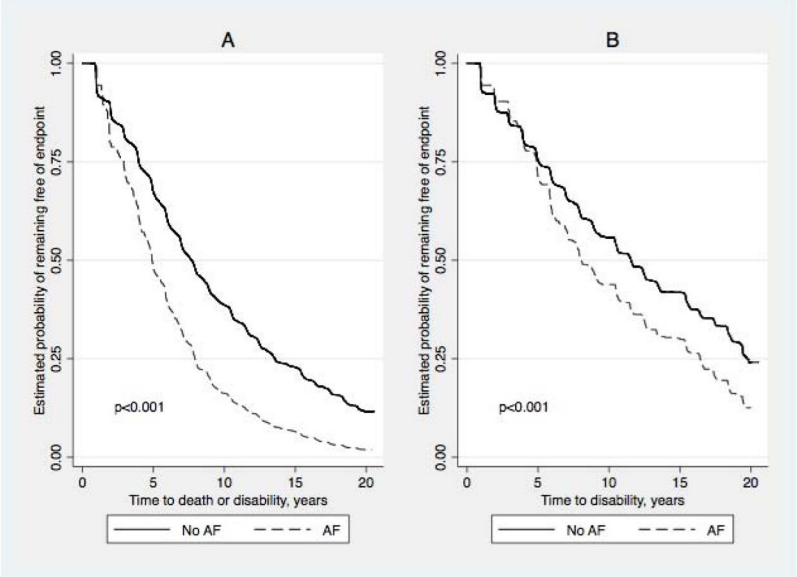

Figure 1.

Kaplan-Meier plots of disability-free survival (A) and ADL disability (B) in individuals with and without incident AF

P-value represents log-rank test of difference in curves.

Table 1

Baseline Characteristics of Participants

Characteristic	All N=4046	No AF during follow-up N=3386	Incident AF during follow-up N=660
Age, mean (±SD)	73 (5)	73 (5)	74 (5)
Male, %	41.8	39.6	53.0
White, %	86.5	85.6	91.2
Education beyond 12th grade, %	44.5	44.3	45.6
Smoking, %			
Current	12.2	12.3	12.0
Former	41.6	41	44.9
Alcohol use, %	51.7	51.5	52.9
Mean number of drinks per week (±SD)	5.0 (9.8)	5.1 (10)	5.0 (8.5)
Physical activity (kcal) per week, mean (±SD)	1838 (2071)	1844 (2079)	1805 (2031)
Body mass index (kg/m^2), mean (±SD)	26.4 (4.5)	26.4 (4.6)	26.2 (4.0)
Forced expiratory volume (FEV1), mean (±SD)	2.1 (0.7)	2.1 (0.6)	2.1 (0.7)
Diabetes, %	13.6	13.4	15
Coronary heart disease, %	17.4	15.7	26.1
Hypertension, %	55.2	54.5	58.6
Antihypertensive medication use, %	43.7	42.5	49.7
Gait speed (m/s), mean (±SD)	0.92 (0.2)	0.92 (0.2)	0.94 (0.2)

Table 2

Incident AF and the Risk of Incident ADL Disability or Death

	Hazard Ratio (95% Confidence Interval)[a]		
Outcome	**Minimally adjusted[b]**	**Fully adjusted[c]**	**Further adjusted for incident stroke and heart failure[c]**
ADL disability or death	1.79 (1.62, 1.98)	1.71 (1.55, 1.90)	1.50 (1.34, 1.66)
ADL disability	1.48 (1.29, 1.71)	1.36 (1.18, 1.58)	1.24 (1.07, 1.44)
Persistent ADL disability or death	1.76 (1.60, 1.94)	1.71 (1.56, 1.89)	1.48 (1.34, 1.64)
Persistent ADL disability	1.53 (1.33, 1.75)	1.40 (1.22, 1.61)	1.26 (1.09, 1.46)

[a] Referent category is No AF

[b] Adjusted for age, sex, race and clinic

[c] Adjusted for age, sex, race, clinic, education, BMI, FEV1, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)