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Authors
Rouch, Laure
Xia, Feng
Bahorik, Amber
et al.

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Atrial fibrillation is associated with greater risk of dementia in older veterans

Laure Rouch[a], **Feng Xia**[b], **Amber Bahorik**[a], **Jeffrey Olgin**[c], **Kristine Yaffe**[d]

[a]Department of Psychiatry, University of California, San Francisco, USA

[b]Northern California Institute for Research and Education, San Francisco, USA

[c]Division of Cardiology, Department of Medicine, University of California, San Francisco, USA

[d]Departments of Psychiatry, Neurology, and Epidemiology, University of California, San Francisco, San Francisco VA Medical Center, San Francisco, CA, USA

Abstract

Objectives: To examine the association of atrial fibrillation (AF) with incident dementia in older veterans and the effect of anticoagulation on that association.

Methods: 407,871 veterans aged ≥ 55 years receiving care from US Veterans Health Administration between August 2003 and September 2015 were included in our retrospective study. AF and incident dementia were determined according to ICD-9-CM codes. Logistic regressions with veterans grouped into high-dimensional propensity scores deciles were used, and a mediation analysis was employed to examine the extent of cardio/cerebrovascular diseases that may also account for that association.

Results: AF was associated with greater dementia risk (OR = 1.14; 95% CI 1.07–1.22), partially mediated by cardio/cerebrovascular disease. Among veterans with AF taking anticoagulants, the risk of dementia was 44% higher (OR =1.44; 95% CI 1.27–1.63) compared to those without anticoagulants, likely related to AF severity.

Conclusions: Our findings underscore the importance of considering cognitive function in the management of AF patients.

Keywords

atrial fibrillation; dementia; anticoagulation; epidemiology

Corresponding Author Dr Laure ROUCH, PharmD, PhD, Department of Psychiatry, University of California, San Francisco, 4150 Clement St, San, Francisco, CA 94121. Tel: (+1) 628 867 9317, rouch.l@chu-toulouse.fr.

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Study concept and design: all authors
Acquisition of data: Xia, Yaffe
Analysis and interpretation of data: all authors
Preparation of manuscript: Rouch, Bahorik, Xia, Yaffe

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Objective

Both atrial fibrillation (AF) and dementia predominantly affect the elderly and exert a heavy burden on health care systems. Several lines of data suggest that AF is associated with cognitive impairment and dementia [1,2]; however the evidence, especially among older adults, is conflicting [1,3–6]. Small sample size and cross-sectional designs are methodological limitations that may explain the inconsistent findings. Furthermore, the mechanisms underlying the association between AF and dementia still need further investigation. AF-related ischemic stroke has been suggested as one of the primary mechanisms.[7] Given the preventive effect of anticoagulation on stroke, it is plausible that use of anticoagulants in patients with AF may delay dementia onset [7] but the evidence is still limited [8,9]. Finally, no study has focused on risk of dementia among veterans with AF, a population who may be at greater risk for developing dementia due to their high prevalence of military-related risk factors and cardiovascular diseases.

Thus, we aimed to examine the association between AF and risk of dementia in older veterans and the extent to which other cardio/cerebrovascular diseases may explain this relationship. We also investigated whether the risk of dementia in veterans with AF differed according to anticoagulation therapy.

Methods

We performed a retrospective cohort study based on a 2% random sample of the United States' Veterans Health Administration (VHA) healthcare system patients aged ≥ 55 years who received VHA care (inpatient or outpatient visits) between August 2003 and September 2015 (N = 855,117). Veterans with prevalent dementia over the baseline period were excluded (n = 46,574) as well as those without at least 1 follow-up visit (n = 400,672), leading to a final sample size of 407,871 veterans. We identified newly diagnosed AF cases as the first diagnosis plus one subsequent diagnosis documented as part of routine clinical care during a 4-year baseline period by using the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM). We then estimated a high-dimensional propensity score (hd-PS) for all veterans in the cohort (n = 407,871); a detailed description of the hd-PS method can be found elsewhere [10]. The use of hd-PS is meant to minimize residual confounding in administrative healthcare databases and to approximate risk estimates observed in a randomized clinical trial. The hd-PS is a computerized algorithm that empirically identifies candidate covariates, prioritizes, and integrates them into a propensity-score-based confounder adjustment model. Empirically derived covariates may serve as proxies for unmeasured confounding variables. The hd-PS approach has been found to ensure optimal balance of patient backgrounds [11]. A statistical procedure (SAS PharmacoEpi Toolkit at http://www.drugepi.org) was used to estimate a hd-PS for each veteran within the cohort, which represents the predicted probability of having newly diagnosed AF (n=16,382) during the 4-year baseline vs. no AF (n=391,489), conditional on all baseline covariates. We included the following covariates within the hd-PS model: age, race, sex, education, hypertension, diabetes, obesity, hypothyroidism, chronic obstructive pulmonary disease (COPD), depression, anxiety, alcohol abuse, and smoking.

Demographic data, including age and race/ethnicity were based on self-report. We used ZIP code and 2016 American Community Survey data to classify veterans as living in broad educational strata. Medical comorbidities were coded as present at baseline if they were identified during the 4-year baseline period using ICD-9-CM codes, and included depression, anxiety, hypothyroidism, COPD, alcohol abuse, smoking, diabetes, obesity, hypertension, myocardial infarction (MI), congestive heart failure (CHF), transient ischemic attack (TIA)/stroke, valvular heart disease. Anticoagulation therapy was collected from centralized pharmacy records and included warfarin and direct oral anticoagulants (DOAC): apixaban, dabigatran, edoxaban. Incident dementia was identified using the VA Dementia Steering Committee (2016 version) list of ICD-9-CM codes.

Baseline characteristics of patients according to AF status and anticoagulation were compared using t-tests for continuous variables and Chi-square (χ^2) tests for categorical variables. We grouped veterans into hd-PS based deciles and used logistic regression models to estimate the odds of developing dementia as a function of AF status. Models were unadjusted and adjusted in steps for (1) demographics and (2) demographics and comorbidities (depression, anxiety, hypothyroidism, COPD, alcohol abuse, smoking, diabetes, hypertension, and obesity). We then examined the extent to which MI, CHF, TIA/stroke, and valvular heart disease may mediate the association between AF and risk of dementia. We fit logistic regression models (1) for dementia on AF, adjusting for each mediator and other potential confounders and (2) for each mediator on AF, adjusting for other potential confounders. We employed a SAS Macro developed for causal mediation analysis for binary outcomes, and binary mediators[12] to derive the direct, indirect, and total effects, and proportion mediated for each mediation model. Lastly, the Sobel test [13,14] was used to assess whether the indirect effect of AF on dementia through each mediator was statistically different from zero (reported as z-statistic, p-value with statistical significance set at $p < 0.05$).

Analyses were done using SAS version 9.4; all statistical tests were two-sided, and significance was set at $p<0.05$. All study procedures were approved by institutional review boards at the University of California, San Francisco; San Francisco Veterans Affairs Medical Center; and US Army Medical Research and Materiel Command, Office of Research Protections, Human Research Protection Office. Informed consent was waived because the data were deidentified administrative data.

Results

Compared to those without AF, veterans with AF were more likely to have other medical conditions such as hypertension, diabetes, obesity, MI, CHF, TIA/stroke, and valvular heart disease. Veterans with AF were also more likely to be prescribed anticoagulants (44.1 vs. 1.7%, χ^2=85,644.8, df=1, $p<0.001$) compared to those without AF (Table 1). Among veterans with AF, those with anticoagulants were significantly younger (74.0 vs. 76.7 years, t=19.5, df=15,685, $p\leq0.001$), more likely to be black and less educated. They had significantly more hypertension (20.7 vs. 17.8%, χ^2 = 21.7, df=1), diabetes (14.2 vs. 10.8%, χ^2 = 44.1, df=1), obesity (13.1 vs. 9.5%, χ^2 = 53.2, df=1), cardio/cerebrovascular disease such as MI (9.8 vs. 6.8%, χ^2 = 46.6, df=1), CHF (27.7 vs. 14.5%, χ^2 = 429.6, df=1),

valvular heart disease (14.8 vs. 8.2%, χ^2 = 176.9, df=1) and TIA/stroke (13.8 vs. 9.0%, χ^2 = 97.0, df=1) (all p≤0.001). Study participants were followed up for a median (interquartile range) of 3.4 (1.7–5.6) years until dementia, death, or their most recent clinical visit (whichever occurred first). A total of 1,133 (6.9%) veterans with AF developed dementia over the follow-up compared to 18,731 (4.8%) veterans without AF (χ^2 = 154.2, df=1, p<0.001).

After adjusting for demographics, those with AF were slightly more likely to develop dementia compared to those without AF (OR = 1.16; 95% CI 1.08–1.23, p<0.001, Wald χ^2 = 18.6, df = 1). After further adjustment for depression, anxiety, hypothyroidism, COPD, alcohol abuse, smoking, diabetes, hypertension, and obesity, the adjusted OR (95% CI) for developing dementia was similar (OR = 1.14; 95% CI 1.07–1.22, p<0.001, Wald χ^2 = 15.0, df = 1) (Table 2). CHF was estimated to mediate 21% of the effect of AF on developing dementia. The association between AF and CHF (Wald χ^2 = 6036.01, df=1, p<0.001; OR = 5.56, 95% CI 5.33, 5.81) was significant as was the relationship between CHF and dementia (Wald χ^2 = 27.04, df=1, p<0.001; OR = 1.18, 95% CI 1.10, 1.25). The direct effect was 1.09 (95% CI 1.02, 1.17) and the indirect effect was 1.02 (95% CI 1.01, 1.03). We tested the significance of the indirect effect using the Sobel test. We found that the indirect effect was statistically different from zero suggesting that CHF significantly mediates the effect of AF on dementia (z=5.32, p<0.001). Similar findings were observed with valvular heart disease, TIA/stroke, and MI, with each estimated to significantly mediate 13%, 12% and 10% respectively, of the effect of AF on developing dementia. Among veterans with AF taking anticoagulants, after multivariable adjustment for demographics and comorbidities, the risk of dementia was 44% higher (OR =1.44; 95% CI 1.27–1.63, p<0.001, Wald χ^2 = 47.5, df = 1) compared to those without anticoagulants (Table 2).

Conclusions

Our study of over 400,000 is the first to investigate the relationship between AF and dementia risk in older veterans. We found that AF was associated with a modest increase in risk of dementia and that this association was partially mediated by TIA/stroke, MI, CHF, and valvular heart disease. Furthermore, dementia risk was higher among patients taking anticoagulants, likely due to indication bias of greater AF severity.

The association between AF and incident dementia has been investigated in prospective observational studies and meta-analyses [15]. The association seems to be more evident in middle-aged and young-old populations [1,2]. However, in older adults, studies have produced conflicting results [4–6,16]. Our study is one of the largest to report in the elderly an increased risk of dementia associated with AF of approximately 15%. The magnitude of the effect is consistent with previous findings [17,18], including the Rotterdam Study [1] in which older participants with AF had a 12% greater dementia risk. This association was partially mediated by cardiovascular disease and TIA/stroke, underscoring the need for their adequate management in patients with AF. Moreover, patients with AF should be periodically screened for dementia, and ongoing and future treatment trials should also consider including dementia among the outcomes assessed.

Several mechanisms may explain how AF may increase risk for dementia. Stroke is recognized as the most feared complication in AF, and usually results from circulatory stasis leading to thrombus formation and embolism to the brain [1]. Persistent AF may also lead to chronic cerebral hypoperfusion and hypoxia, which may in turn cause damage to the brain [1]. Furthermore, AF is associated with the expression of cardiac and systemic inflammatory markers [7] that in turn may increase risk of dementia.

We observed greater dementia risk among patients taking anticoagulants. Some studies showed a trend toward a protective effect of warfarin therapy on cognitive outcomes in patients with AF [8,9] whereas others did not [19,20]. A recent meta-analysis failed to find a protective effect of anticoagulants on dementia among AF patients [20]. Similarly, the Birmingham Atrial Fibrillation Treatment of the Aged Study did not report any important advantage of warfarin instead of aspirin in preventing cognitive decline in patients with AF [19]. Although effective in stroke prevention, anticoagulation may lead to cerebral microbleeds thereby contributing to a higher risk of dementia.

Several limitations need to be considered in interpretation of the data. Participants were predominantly male and white, limiting the generalizability of our findings. AF and dementia were diagnosed as part of routine clinical care using ICD-9-CM administrative codes; however, this is supported in relevant validation studies [21]. Although misclassification cannot be fully ruled out, AF and dementia rates were consistent with previous findings in similar populations [22,23]. Newly diagnosed AF cases were identified according to 2 diagnoses over the baseline period, reducing the risk of misclassification. Yet, AF was coded without distinction between its paroxysmal, persistent, and permanent forms, the latter being associated with a higher risk of cognitive impairment. ICD-9-CM dementia diagnosis was less sensitive than structured diagnostic interviews and brain imaging was not available in our study. However, these methodological considerations may have led to an underestimation of the association between AF and dementia. Although we used a hd-PS approach, residual confounding may still exist. Inclusion of surrogates and mediators in hd-PS analyses may also increase bias [24]; therefore, we excluded variables such as dyslipidemia, significantly associated with AF but not with dementia as well as MI, CHF, TIA/stroke, and valvular heart disease, considered as potential mediators. Bias can also occur in hd-PS through the inclusion of collider variables; however, this is usually negligible [25]. Lack of data on the duration of antithrombotic treatment, quality of anticoagulation control and treatment adherence represent other limitations of our study. Finally, we did not investigate the specific effect of direct oral anticoagulants because their use has only recently increased, and the number of subjects was insignificant. Importantly, our study has several strengths, including its longitudinal design to determine the effects of AF on dementia risk in a very large sample of older veterans and a relatively long follow-up period. We considered newly diagnosed AF, rarely accounted for in studies involving older populations, which may in turn have slightly underestimated the association with dementia. We also used high-dimensional propensity scores resulting in a substantial improvement of control for confounding. Finally, we examined the extent to which the association between AF and dementia was mediated by stroke/TIA, CHF, MI, and valvular heart disease.

Overall, we found, in a very large cohort of older veterans, that AF increased dementia risk by approximately 15%. Although this association may have been slightly underestimated, it was consistent with previous findings and represents a clinically meaningful increase in dementia risk. This association was partially mediated by TIA/stroke and cardiovascular disease. Our findings underscore the importance of considering cognitive function and effectively treating cardiovascular disease in the management of AF patients. It remains unproven if antithrombotic therapy, which is effective for reducing ischemic stroke, is also beneficial for cognitive function. This is currently being investigated in on-going randomized clinical trials [26].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest

Laure Rouch, Feng Xia, Amber Bahorik and Jeffrey Olgin report no conflicts with any product mentioned or concept discussed in this article. Kristine Yaffe reports grants from Department of Defense/Veterans Administration and NIA, during the conduct of the study; she serves on DSMBs for Eli Lilly and NIH-sponsored studies and is a board member of Alector. Dr. Yaffe is also a member of the Beeson Scientific Advisory Board and the Global Council on Brain Health.

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Highlights

What is the primary question addressed by this study?

This is the first study to investigate the association between atrial fibrillation and dementia in veterans, a specific population at greater risk for dementia due to elevated general and military risk factors, but also at higher risk of developing cardiovascular disease.

What is the main finding of this study?

Our findings add to the literature that veterans with atrial fibrillation are more likely to develop dementia compared to those without atrial fibrillation, and that this association is partially mediated by TIA/stroke and cardiovascular disease.

What is the meaning of the finding?

These results underscore the importance of considering cognitive function in the management of atrial fibrillation patients and the need for further research on the effects of antithrombotic therapy on cognitive function.

Table 1.

Baseline characteristics of 407,871 veterans with or without Atrial Fibrillation

	Atrial Fibrillation		
	No (N=391,489)	**Yes (N=16,382)**	**Statistical test***
Demographics			
Age, y, mean (SD)	71.7 (8.9)	75.5 (8.8)	t=−54.0, df=17,819, p<0.001
Female	13,091 (3.3)	245 (1.5)	χ^2=169.9, df=1, p<0.001
Race			χ^2=718.1, df=4, p<0.001
Non-Hispanic White	327,622 (83.7)	14,984 (91.5)	
Non-Hispanic Black	42,495 (10.9)	885 (5.4)	
Hispanic	4.046 (1.0)	120 (0.7)	
Asian	2,023 (0.5)	60 (0.4)	
Others/unknown	15,303 (3.9)	333 (2.0)	
>25% college-educated in zip code [a]	159,536 (42.0)	6,876 (43.1)	χ^2=8.1, df=1, p=0.004
Comorbidities			
Diabetes	36,151 (9.2)	2,017 (12.3)	χ^2=175.6, df=1, p<0.001
Hypertension	58,144 (14.9)	3,119 (19.0)	χ^2=216.0, df=1, p<0.001
Obesity	37,656 (9.6)	1,820 (11.1)	χ^2=40.0, df=1, p<0.001
Hypothyroidism	14,596 (3.7)	1,185 (7.2)	χ^2=519.4, df=1, p<0.001
Chronic obstructive pulmonary disease	37,433 (9.6)	2,524 (15.4)	χ^2=608.0, df=1, p<0.001
Depression	30,890 (7.9)	1,495 (9.1)	χ^2=32.8, df=1, p<0.001
Anxiety	20,763 (5.3)	970 (5.9)	χ^2=11.9, df=1, p<0.001
Alcohol abuse	14,243 (3.6)	628 (3.8)	χ^2=1.7, df=1, p=0.19
Smoking	31,961 (8.2)	1,534 (9.4)	χ^2=30.0, df=1, p<0.001
Myocardial infarction	11,859 (3.0)	1,331 (8.1)	χ^2=1,304.7, df=1, p<0.001
Transient ischemic attack/Stroke	23,253 (5.9)	1,822 (11.1)	χ^2=731.9, df=1, p<0.001
Congestive heart failure	14,638 (3.7)	3,330 (20.3)	χ^2=10,274.2, df=1, p<0.001
Valvular heart disease	11,885 (3.0)	1,824 (11.1)	χ^2=3,174.8, df=1, p<0.001
Anticoagulation therapy	6,723 (1.7)	7,231 (44.1)	χ^2=85,644.8, df=1, p<0.001
Warfarin	6,683 (1.7)	7,039 (43.0)	χ^2=82,339.3, df=1, p<0.001

Values are N (%) unless otherwise specified.

*t-test (t) for continuous variables and Chi-square (χ^2) test for categories variables were performed; df = degrees of freedom, p = p-value.

[a]Education has 11,746 (2.9%) missing values.

Table 2.

Unadjusted and adjusted risk of dementia by Atrial Fibrillation and anticoagulation therapy among 407,871 veterans

	Number of subjects	Incident dementia cases	Unadjusted model				Model 1				Model 2			
			Odds Ratio (95% CI)	p-value	Wald χ^2	df	Odds Ratio (95% CI)	p-value	Wald χ^2	df	Odds Ratio (95% CI)	p-value	Wald χ^2	df
No AF	391,489	18,731	ref.				ref.				ref.			
AF, with or without anticoagulant	16,382	1,133	1.48 (1.39, 1.57)	<0.001	152.3	1	1.16 (1.08, 1.23)	<0.001	18.6	1	1.14 (1.07–1.22)	<0.001	15.0	1
AF, no anticoagulant	9,151	582	ref.				ref.				ref.			
AF, with anticoagulant	7,231	551	1.21 (1.08, 1.37)	0.002	9.9	1	1.47 (1.30, 1.66)	<0.001	56.8	1	1.44 (1.27, 1.63)	<0.001	47.5	1

AF = atrial fibrillation; df = degrees of freedom

Model 1: adjusted for demographics (age, race, sex, education)

Model 2: adjusted for demographics + comorbidities (depression, anxiety, hypothyroidism, COPD, alcohol abuse, smoking, diabetes, hypertension, and obesity).