

Atrial Fibrillation Patients Treated With Long-Term Warfarin Anticoagulation Have Higher Rates of All Dementia Types Compared With Patients Receiving Long-Term Warfarin for Other Indications

T. Jared Bunch, MD; Heidi T. May, PhD; Tami L. Bair, RN; Brian G. Crandall, MD; Michael J. Cutler, DO, PhD; John D. Day, MD; Victoria Jacobs, NP; Charles Mallender, MD; Jeffrey S. Osborn, MD; Scott M. Stevens, MD; J. Peter Weiss, MD; Scott C. Woller, MD

Background—The mechanisms behind the association of atrial fibrillation (AF) and dementia are unknown. We previously found a significantly increased risk of dementia in AF patients taking warfarin with a low percentage of time in therapeutic range. The purpose of this study was to determine the extent to which AF itself increases dementia risk, in addition to long-term anticoagulation exposure.

Methods and Results—A total of 10 537 patients anticoagulated with warfarin (target INR 2–3), managed by the Clinical Pharmacist Anticoagulation Service with no history of dementia were included. Warfarin indication was for AF (n=4460), thromboembolism (n=5868), and mechanical heart valve(s) (n=209). Patients in the latter 2 categories were included only if they had no prior history of AF. The primary outcome was dementia. Patients with AF were older and had higher rates of hypertension, diabetes, heart failure, and stroke. AF patients experienced higher rates of total dementia (5.8% versus 1.6%, $P<0.0001$), Alzheimer disease (2.8% versus 0.9%, $P<0.0001$), and vascular dementia (1.0% versus 0.2%, $P<0.0001$). A propensity analysis of 6030 patients was performed to account for baseline demographics differences. Long-term risk of dementia remained significant in AF patients compared with matched non-AF patients (total dementia: hazard ratio [HR]=2.42 [1.85–3.18], $P<0.0001$; Alzheimer: HR=2.04 [1.40–2.98], $P<0.0001$; senile: HR=2.46 [1.58–3.86], $P<0.0001$). Low percent therapeutic range compared with a higher percent therapeutic range was associated with dementia risk in both AF (26–50% versus >75%: HR=2.51, $P=0.005$) and non-AF groups ($\leq 25\%$ versus >75%: HR=3.92, $P<0.0001$).

Conclusions—The presence of AF significantly increases risk of dementia, including Alzheimer's disease, compared with matched patients receiving warfarin anticoagulation for other reasons. Quality of anticoagulation management remains an important risk factor for dementia in all patients. (*J Am Heart Assoc.* 2016;5:e003932 doi: 10.1161/JAHA.116.003932)

Key Words: Alzheimer disease • anticoagulant drugs • atrial fibrillation • cognition • dementia

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with incidence rates that are growing dramatically with population aging.^{1,2} Many other chronic disorders of aging are also increasing, such as dementia. Dementia is a neurological disorder that impairs memory and

other cognitive abilities.^{3,4} Alzheimer disease (AD) is the most common type of dementia and represents 70% of all cases. Dementia is now listed among the leading causes of morbidity and mortality in developed countries.⁵

We previously reported that AF is independently associated with all types of dementia, including AD. Contrary to our initial expectations in studying 2 diseases that increase with aging, the disease association was most prominent in the younger AF patients (<70 years old, hazard ratio [HR] 2.30; 70–79 years, HR 1.07; 80–89 years, HR 0.81).³ In subsequent analysis by de Brujin and colleagues,⁶ the question of whether AF raises risk of dementia was studied. In this analysis of 6514 patients, the authors found a significantly increased risk of dementia in those patients with AF (HR 1.23) that persisted even when censoring for incident stroke. Similar to our study, the authors found the highest risk in the younger group with an HR of 1.81 for those <67 years old compared with 1.12 for those >65 years old.

From the Intermountain Medical Center Heart Institute, Intermountain Medical Center, Murray, UT (T.J.B., H.T.M., T.L.B., B.G.C., M.J.C., J.D.D., V.J., C.M., J.S.O., S.M.S., J.P.W., S.C.W.); Department of Internal Medicine, Stanford University, Palo Alto, CA (T.J.B.).

Correspondence to: T. Jared Bunch, MD, Intermountain Medical Center, Eccles Outpatient Care Center, 5169 Cottonwood St, Suite 510, Murray, UT 84107. E-mail: Thomas.bunch@gmail.org

Received May 19, 2016; accepted June 9, 2016.

© 2016 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley Blackwell. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

We hypothesized that if dementia was in the spectrum of cerebral injuries of stroke and hemorrhage, its etiology may arise from micro rather than macro events. An association between quality of management of warfarin therapy, as assessed by time in therapeutic range (TTR), and dementia has been reported by our team and others.^{7,8} We also found that the risk of dementia in AF patients who also require antiplatelet therapy is increased incrementally by time spent with a supratherapeutic INR.⁹ These studies suggest that anticoagulation treatment strategy and efficacy affect dementia risk. What is unclear is whether the presence of AF increases dementia beyond the treatment strategy. As such, we undertook a study to look at the risk of dementia in patients managed on a long-term basis with warfarin for both AF and non-AF indications. The study objectives were 2-fold. First, we sought to examine dementia risk based on warfarin efficacy in patients treated with long-term therapy for both AF and non-AF indications. Second, we sought to determine if AF increased dementia risk beyond that observed based on anticoagulation efficacy.

Methods

The study was a retrospective design involving chronically anticoagulated patients receiving warfarin (target INR 2–3) and managed by the Intermountain Healthcare (Salt Lake City, UT) Clinical Pharmacist Anticoagulation Service (CPAS). The institutional review board reviewed and approved the study as a minimal risk observational study, and individual patient consent requirement was waived. Patients with no history of dementia at time of CPAS enrollment were studied. Chronically anticoagulated patients for both AF and non-AF indications were included. CPAS is a dedicated anticoagulation management service that uses a standardized algorithmic approach to warfarin dose adjustment as we have previously described.^{10,11} Patients were included if they ≥ 18 years of age and received >1 INR measurement under CPAS supervision. The referring physician determined the indication of warfarin and long-term needs. The Intermountain Healthcare Urban Central Institutional Review Board approved this study.

Baseline demographics and characteristics were abstracted from the medical record by using *International Classification of Diseases Revisions 9 and 10* (ICD-9 and -10) codes at the time of CPAS enrollment. Patients with a history of dementia before CPAS referral were excluded. A history of dementia was determined by ICD-9 and -10 codes as well as the screening visit with the CPAS clinic that is used to evaluate patients for warfarin candidacy and to provide targeted drug education. In this visit, broad cognitive capacity is considered as a factor for candidacy. The extracted clinical variables were based on inpatient and

outpatient clinical visits and included age, hypertension, diabetes, hyperlipidemia, renal failure, smoking history, prior myocardial infarction or cerebrovascular accident, and heart failure. These data were extracted from a comprehensive electronic medical record that serves as a repository of clinical notes, laboratory results, and radiology studies and allows for clinical charting and real-time messaging. Included in the extracted data was use of medications (HMG-CoA reductase inhibitors [statins], angiotensin-converting enzyme inhibitors or angiotensin type II receptor blockers, β -blockers, and diuretics). Medication use prior to (“pre”) and any time after initiation of anticoagulation management by CPAS (“post”) were documented. Patients were determined to have AF based on ICD-9 code 427.31 and ICD-10 codes I48.0, I48.1, I48.2, and I48.91 and through review of the systemwide electrocardiogram database that includes ambulatory monitors. INR measurements were obtained as per clinical algorithm and at the discretion of the attending clinician. TTR was defined as the number of days with an INR between 2 and 3 divided by the total number of days. This number was then multiplied by 100 to determine the percent TTR and was stratified into the following categories: $>75\%$, 51% to 75%, 26% to 50%, and $\leq 25\%$.

The primary outcome was a composite of dementia subtypes defined by neurologist-entered ICD-9 codes (290–294, 331) and ICD-10 codes (F01–F03, G30). The secondary end points were specific dementia subtype classification (vascular, senile, or AD). By limiting dementia diagnosis to only ICD codes entered by neurologists, we hoped to minimize misclassification. In an earlier study of >1000 patients with cranial or magnetic resonance imaging classified with dementia by this method, diagnostic accuracy was 87%.³ Death was determined by medical records, state of Utah death certificates, and the Social Security death master file. Patients were censored at dementia diagnosis, death, or last known contact date. Patients not listed as deceased in any registry were considered to be alive.

The Student *t* test, the χ^2 statistic, and Fisher’s exact test were used to characterize the population. Continuous variables were described as mean \pm SD, and discrete variables were described as frequencies. A propensity analysis was performed to minimize variance in confounding baseline characteristics. To estimate the propensity score, a logistic regression model was used in which anticoagulation use was regressed on the baseline characteristics. Patients were then matched 1:1 on propensity score (± 0.01) and index date (± 6 months). Multivariable Cox hazard regression (SPSS, version 21.0) was used to determine dementia incidence by percentage categories of TTR. Covariables included baseline risk factors that were documented either at or before the index (baseline) date. All of the baseline risk factors listed in Table 1 were included in the multivariable model and

Table 1. Baseline Characteristics of Patients Managed With Long-Term Warfarin Anticoagulation Compared by Indication

	AF (n=4460)	Valve (n=209)	Thromboembolism (n=5686)	P Value
Age, y	72.5±11.2	56.4±13.5	58.7±16.3	<0.0001
Sex (male)	53.5%	55.5%	49.0%	<0.0001
Hypertension	77.1%	62.2%	50.3%	<0.0001
Hyperlipidemia	63.8%	57.4%	39.9%	<0.0001
Diabetes	30.5%	24.4%	19.1%	<0.0001
Smoking	23.3%	24.9%	19.0%	<0.0001
Heart failure	38.9%	40.2%	12.7%	<0.0001
Prior stroke	8.3%	2.9%	3.1%	<0.0001
Prior TIA	7.3%	4.8%	3.6%	<0.0001
Coronary artery disease	44.0%	44.0%	18.6%	<0.0001
Prior myocardial infarction	8.0%	5.7%	4.6%	<0.0001
Renal failure	9.8%	10.0%	7.5%	<0.0001
Prior CABG	7.6%	22.5%	2.1%	<0.0001
Prior PCI	8.5%	7.2%	4.1%	<0.0001
Prior malignancy	17.9%	8.6%	12.0%	<0.0001
Prior fall	22.7%	12.0%	19.8%	<0.0001
Prior major bleed	9.4%	5.7%	8.5%	0.08
Sleep apnea	23.6%	15.3%	18.7%	<0.0001
CHADS ₂				<0.0001
0–1	31.5%	53.6%	67.8%	
2–4	63.4%	45.5%	31.2%	
≥5	5.1%	1.0%	1.0%	
CHADS ₂ -VASc				<0.0001
0–1	10.6%	26.3%	5.4%	
2–4	57.3%	58.4%	49.4%	
≥5	32.1%	15.3%	45.2%	
EF (%), n=7410	55.5±13.3	57.0±12.1	59.3±11.7	<0.0001
ACE inhibitor	53.7%	74.2%	39.4%	<0.0001
β-Blocker	74.9%	91.9%	44.8%	<0.0001
Diuretic	78.3%	97.6%	56.8%	<0.0001
ARB	28.8%	30.1%	19.7%	<0.0001
CCB	51.8%	53.1%	29.5%	<0.0001
Statin	64.8%	73.2%	51.3%	<0.0001
Antiplatelet	62.5%	90.4%	41.2%	<0.0001
Mean INR draws	37.2±35.7 (median 28)	50.1±38.1 (median 42)	30.7±33.9 (median 19)	<0.0001

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin type II receptor blocker; CABG, coronary artery bypass graft surgery; CCB, calcium channel blocker; CHADS₂-VASc, (congestive heart failure, blood pressure consistently above 140/90 mm Hg or treated hypertension on medication, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism)–(vascular disease [eg, peripheral artery disease, myocardial infarction, aortic plaque], age 65–74 years, female sex); EF, ejection fraction; INR, international normalized ratio; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

predated the end points. Final models retained only significant ($P<0.05$) and confounding (10% change in HR) covariables. Kaplan–Meier survival curves and the log rank

test were used to estimate survival rates free of dementia. Two-tailed P -values of <0.05 were designated to be nominally significant.

Results

The general population referred for warfarin management by CPAS, without a prior history of dementia, included 10 537 patients (Table 1). Of these patients, 4460 patients received warfarin for AF, 209 patients received warfarin for mechanical valvular heart disease, and 5868 patients received warfarin for thromboembolism. Patients treated with anticoagulation because of AF were older and higher rates of hypertension, diabetes, and stroke. Patients who received anticoagulation for AF or prosthetic valvular heart disease were more likely to have heart failure and ischemic heart disease compared with those treated for thromboembolism.

Follow-up duration for the AF group was 2293.6±1536.1 (median 2021.5) days, compared with 3079.7±1171.8 (median 3010.0) days for the valve group and 2936.4±1663.4 (median 2653.0) days for the thromboembolism group ($P<0.0001$). Incident dementia rates at last follow-up are shown in Table 2 for AF versus non-AF indication. All types of dementia were increased in the AF indication group compared with the non-AF indication group with a multivariate adjusted HR of 1.59 ($P<0.0001$). Specifically, total dementia (5.8% versus 1.6%, $P<0.0001$) and senile (2.0% versus 0.6%, $P<0.0001$), vascular (1.0% versus 0.2%, $P<0.0001$), and Alzheimer dementia (2.8% versus 0.9%, $P<0.0001$) were all higher in the AF indication group versus the non-AF indication group.

The TTR in the AF (≤ 25 , $n=419$; 26–50, $n=767$; 51–75, $n=1989$; >75 , $n=1285$) and the non-AF indication (≤ 25 , $n=708$; 26–50, $n=1076$; 51–75, $n=2461$; >75 , $n=1880$) groups were compared to determine impact on dementia risk. In the AF indication group, the multivariate adjusted risk for dementia was incrementally higher as TTR worsened (51–75% versus >75 %: HR=1.30, $P=0.10$; 26–50% versus >75 %: HR=1.57, $P=0.02$; ≤ 25 % versus >75 %: HR=1.92, $P=0.005$). A similar pattern was seen in the non-AF indication group (51–75% versus >75 %: HR=1.57, $P=0.13$; 26–50% versus >75 %: HR=2.69, $P=0.002$; ≤ 25 % versus >75 %: HR=3.87, $P<0.0001$) (Figure 1A and 1B). No significant interaction (P -interaction=0.58) was found between TTR and the presence of AF. Within the TTR categories, we further explored INR variability. Overall median INR variability decreased with percent time TTR increase (≤ 25 : 2.35; 26–50%: 1.79; 51–75%: 1.17; ≥ 75 %: 0.92; $P\leq 0.0001$). This variability trend was seen in the both the AF and non-AF groups, with more variability in all TTR categories in the non-AF group (≤ 25 : 2.61; 26–50%: 1.92; 51–75%: 1.30; ≥ 75 %: 1.07; $P\leq 0.0001$) versus the AF group (≤ 25 : 1.90; 26–50%: 1.58; 51–75%: 1.02; ≥ 75 %: 0.73; $P\leq 0.0001$).

Given the broad variances in baseline demographics between anticoagulation indication groups, a secondary propensity analysis of 6030 patients was performed. The baseline demographics of this population are shown in

Table 2. Baseline Characteristics of Patients Managed With Long-Term Warfarin Anticoagulation Compared by Indication With Variables Used to Create the Propensity Analysis With Exception of CHADS₂ and TTR Category

	Non-AF Indication	AF Indication	<i>P</i> Value
Age, y	69.3±10.9	69.3±11.2	0.89
Sex (male)	51.5%	52.7%	0.37
Hypertension	69.8%	71.3%	0.21
Hyperlipidemia	55.8%	58.1%	0.07
Diabetes	26.6%	27.1%	0.64
Smoking	19.9%	21.7%	0.09
Heart failure	25.5%	26.2%	0.54
Prior stroke	4.9%	5.2%	0.60
Prior TIA	5.9%	5.9%	0.96
Coronary artery disease	34.1%	35.6%	0.29
Renal failure	9.6%	9.6%	0.93
Prior CABG	5.5%	6.0%	0.38
Prior PCI	7.3%	7.1%	0.80
Prior bleed	21.8%	22.8%	0.42
Prior malignancy	15.7%	16.0%	0.75
Prior fall	19.3%	20.8%	0.13
Prior major bleed	9.3%	9.1%	0.79
Sleep apnea	20.6%	22.5%	0.08
CHADS ₂			0.30
0–1	45.6%	43.6%	
2–4	52.2%	54.2%	
≥ 5	2.2%	2.2%	
TTR category			0.09
>75 %	27.9%	30.1%	
51–75%	44.9%	44.6%	
26–50%	18.3%	16.2%	
≤ 25 %	8.9%	9.0%	

AF indicates atrial fibrillation; CABG, coronary artery bypass graft surgery; CHADS₂, congestive heart failure, blood pressure consistently above 140/90 mm Hg or treated hypertension on medication, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TTR, time in therapeutic range.

Table 2, displayed to highlight the frequencies of known cardiovascular disease states associated with dementia. The propensity analysis produced similarly matched populations, which is reflected by having no significant differences in baseline characteristics between the groups. Incident dementia rates remained significantly elevated in the AF indication group (Table 3). There was 3-fold increase in dementia in the AF group compared with the non-AF indication group.

After multivariate adjustment, all forms of dementia remained significantly increased in the AF group compared

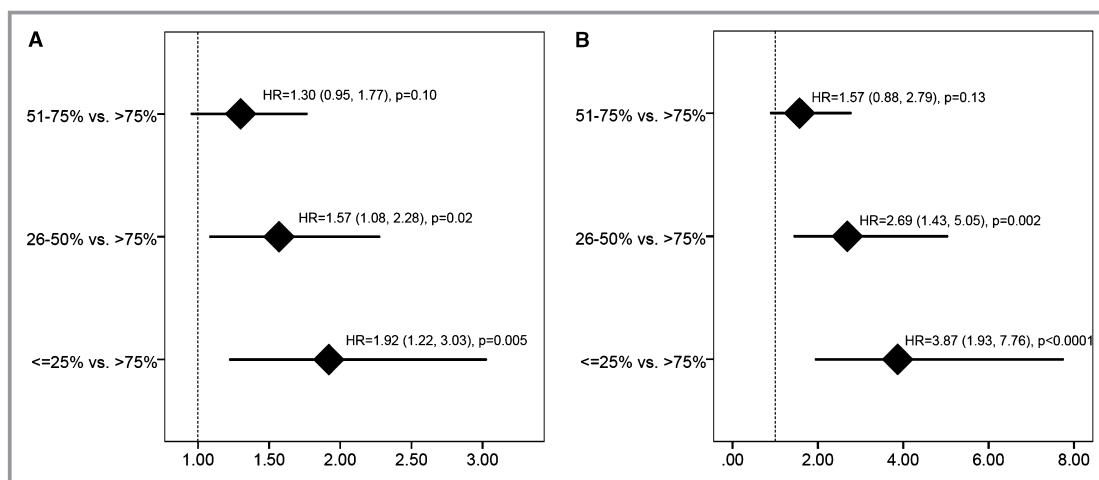


Figure 1. A and B, Multivariate adjusted hazard ratio for risk of dementia in patients without baseline dementia based on time in therapeutic range (TTR). Patients with atrial fibrillation (A) and patients with a reason for chronic anticoagulation that was not atrial fibrillation (B).

with the non-AF group (Figure 2). The survival free curve for total dementia (Figure 3A) and for AD (Figure 3B) showed an increased risk of dementia in the AF group that continued to increase with time.

Discussion

There are several important clinical findings in this study. First, among patients receiving long-term warfarin, AF patients have more baseline risk factors for dementia (eg, hypertension, diabetes, prior stroke) than do non-AF patients. Regardless of warfarin indication (AF versus non-AF), the efficacy of therapy is strongly associated with dementia, with lower percent TTR patients having the highest dementia risk. AF patients experience much higher rates of all forms of dementia, including AD, compared with patients managed with long-term warfarin without AF. Dementia risk in AF patients persisted even when differences in baseline variables were accounted for through a propensity analysis.

One of the most feared complications of AF is disabling stroke. The majority of strokes in patients with AF are

macroembolic and are thought to originate from the left atrial appendage. Patients with AF tend to have larger strokes at older ages and as a consequence are at particular risk for cognitive decline that is associated with significant functional deficit and dependency.¹² Anticoagulation is the frontline therapy for stroke prevention with vitamin K antagonists such as warfarin, which is the most common agent used worldwide. However, long-term anticoagulation exposure raises the risk of intracranial bleeding. Unfortunately, risk of stroke and

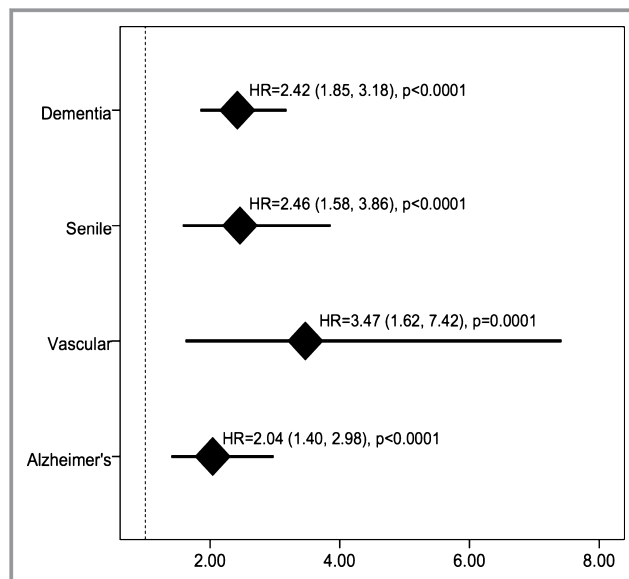


Figure 2. Multivariate adjusted hazard ratio for all types of dementia coded by neurologists in patients chronically anticoagulated with atrial fibrillation vs a non-atrial fibrillation indication. With all forms of dementia, there was an increased risk of dementia.

Table 3. Incident Dementia Rates at Last Follow-up Compared by Anticoagulation Indication Derived From the Propensity Analysis

	AF Indication	Non-AF Indication	P Value
Dementia	5.2% (156)	2.6% (79)	<0.0001
Senile	1.9% (58)	1.0% (29)	0.02
Vascular	0.9% (26)	0.3% (9)	0.004
Alzheimer	2.4% (72)	1.4% (43)	0.006

AF indicates atrial fibrillation.

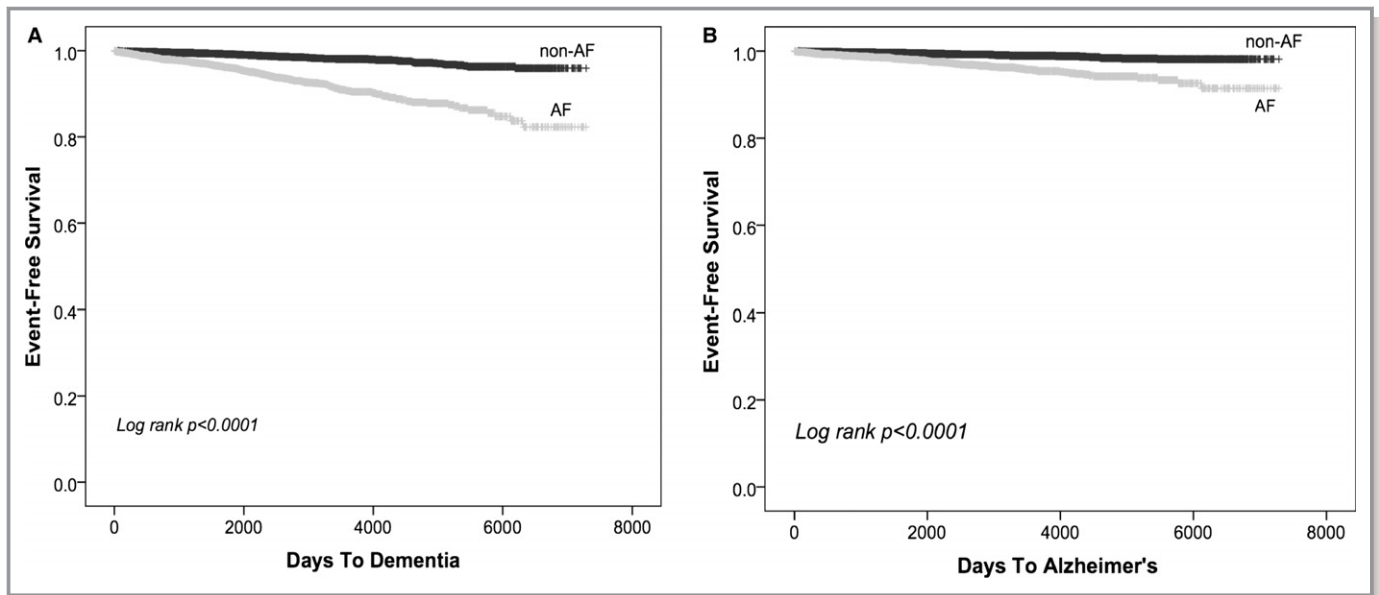


Figure 3. Kaplan–Meier estimated for survival free of total dementia (A) and Alzheimer dementia (B) in patients chronically anticoagulated for atrial fibrillation compared with patients chronically anticoagulated for a non-atrial fibrillation indication.

bleed increases in AF patients with aging and acquisition of coexistent cardiovascular risk factors such as high blood pressure, diabetes, and prior stroke.¹³ These evolving risks present a challenging situation with a therapy used to reduce embolic cerebral ischemic events that increases risk of hemorrhagic cerebral ischemic events.

This study highlights a significant potential cognitive risk with long-term anticoagulation exposure, regardless of underlying disease that prompted initiation of the therapy, in those patients who have consistently poor precision in achieving target serum drug levels. Dementia risk should be considered as a potential long-term complication with warfarin anticoagulation exposure. This risk consideration is particularly important in light of recently updated consensus guidelines that have recommended anticoagulation in AF patients with a CHADS₂/CHADS₂-VASc ([congestive heart failure, blood pressure consistently above 140/90 mm Hg or treated hypertension on medication, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism]–[vascular disease (eg, peripheral artery disease, myocardial infarction, aortic plaque), age 65–74 years, female sex]) score of ≥1 rather than ≥2.¹⁴ These recommendations were made based on risk of stroke versus risk of major bleed. However, as noted in this study, macro organ injury is just one part of the spectrum of risk. Inclusion of patients with lower CHADS₂ scores often leads to both earlier and broader exposure to anticoagulation and thereby may increase dementia risk unintentionally.

This study is supportive of our hypothesis that AF is independently associated with an increase dementia risk beyond that attributed to anticoagulation. There are several

potential explanations why AF may further increase risk. First, long-term anticoagulation in patients for thromboembolism would likely expose these patients to cerebral ischemic events primarily as a result of micro and macro bleeds. AF stems from unique risk factors and is associated with a risk of both macro and micro emboli from the left atrium/appendage, as well as from other vascular sources that raise the risk of AF genesis. In addition, long-term anticoagulation is recommended in most AF patients and, when initiated, it is with lifetime duration intent unless it becomes contraindicated. As such, AF patients share the risks of all chronically anticoagulated patients but also have additive risk from embolic events.

There are also many other potential mechanisms in addition to anticoagulation efficacy that may explain the augmented risk of dementia in AF patients. AF patients can have marked irregularity of the RR intervals that can result in relative periods of low perfusion coupled with a decrease in cardiac efficacy from loss of atrioventricular synchrony. Hypoperfusion of the brain in AF patients has been shown to result in leukoaraiosis or white matter changes and impaired resolution of micro emboli from the vessels resulting in embolic infarctions.¹⁵ Other potential mechanisms include augmentation of systemic inflammation in patients with AF,¹⁶ genetic factors that increase AF and early thromboembolism,¹⁷ and risk factors that drive AF that also increase risk of cognitive decline such as sleep apnea.

Limitations

This is an observational study that used a large healthcare database for the purpose of identifying relations and not

causality. Additional prospective trials with the specific aim to examine cognitive decline as a function of warfarin therapy variability are required to solidify the association observed here and determine potential causality. This study relies on physicians to diagnose and document patient diseases with appropriate ICD-9 and -10 codes. We attempted to minimize mischaracterization of dementia by using only codes entered by neurology specialists. Despite this approach, there is risk of disease misclassification. In addition, patients with moderate cognitive decline or dementia are often not referred to neurology specialists. Regarding risk of cognitive dysfunction at warfarin initiation, an additional screen was provided by the CPAS clinic to determine if the patient was capable of reliably using the medication and attending serial follow-up testing; a limitation to consider in interpreting our results is the potential to miss subclinical dementia at the time of warfarin initiation. Also, patients who consent to receive careful management by our CPAS clinic and attend serial follow-up visits are a distinct group, which introduces a potential selection bias in the study population. The diagnosis of AF was made by using ICD-9 and -10 codes, a broad ECG database, and medical records, and we recognize that occurrences of AF in this study may be underreported because of the presence of subclinical events. However, with underestimation of AF rates in the non-AF group, we would anticipate that dementia rates, if anything, would have been overestimated. With our propensity analysis, we sought to control for the multiple risk factors that drive AF and its morbidities. However, since this was an observational trial without predefined collected variables known to convey risk of dementia, there is the possibility that unmeasured factors that were not accounted for in the propensity analysis can introduce bias into the measured outcomes. Finally, the associations were found in a retrospective design and as such causality cannot be established. Regardless, these findings should serve as background data for prospective trials that examine this topic.

Conclusion

The presence of AF significantly increases risk of dementia, including Alzheimer, compared with matched patients receiving warfarin anticoagulation for other reasons. However, quality and efficacy of anticoagulation management represented as percent TTR remain important risk factors for dementia in both AF and non-AF patients.

Disclosures

Dr Osborn reports conflicts of interest as minor for speakers honorarium/consulting with Medtronic, Cook, Boston

Scientific, and St. Jude Medical. Dr Weiss reports conflicts of interest as minor for speaker honorarium/consulting with Stereotaxis and Biosense Webster. The remaining authors have no disclosures to report.

References

- Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112:1142–1147.
- Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
- Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, Day JD. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm*. 2010;7:433–437.
- Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. *Vasc Health Risk Manag*. 2008;4:363–381.
- Newton JN, Briggs AD, Murray CJ, Dicker D, Foreman KJ, Wang H, Naghavi M, Forouzanfar MH, Ohno SL, Barber RM, Vos T, Stanaway JD, Schmidt JC, Hughes AJ, Fay DF, Ecob R, Gresser C, McKee M, Rutter H, Abubakar I, Ali R, Anderson HR, Banerjee A, Bennett DA, Bernabe E, Bhui KS, Biryukov SM, Bourne RR, Brayne CE, Bruce NG, Brugha TS, Burch M, Capewell S, Casey D, Chowdhury R, Coates MM, Cooper C, Critchley JA, Dargan P, Dherani MK, Elliott P, Ezzati M, Fenton KA, Fraser MS, Furst T, Greaves F, Green MA, Gunnell DJ, Hannigan BM, Hay RJ, Hay SI, Hemingway H, Larson HJ, Looker KJ, Lunevicius R, Lyons RA, Marcesnes W, Mason-Jones AJ, Matthews FE, Moller H, Murdoch ME, Newton CR, Pearce N, Piel FB, Pope D, Rahimi K, Rodriguez A, Scarborough P, Schumacher AE, Shiu I, Smeeth L, Tedstone A, Valabhji J, Williams HC, Wolfe CD, Woolf AD, Davis AC. Changes in health in England, with analysis by English regions and areas of deprivation, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:2257–2274.
- de Bruijn RF, Heeringa J, Wolters FJ, Franco OH, Stricker BH, Hofman A, Koudstaal PJ, Ikram MA. Association between atrial fibrillation and dementia in the general population. *JAMA Neurol*. 2015;72:1288–1294.
- Jacobs V, Woller SC, Stevens S, May HT, Bair TL, Anderson JL, Crandall BG, Day JD, Johannig K, Long Y, Mallender C, Olson JL, Osborn JS, Weiss JP, Bunch TJ. Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. *Heart Rhythm*. 2014;11:2206–2213.
- Kwok CS, Loke YK, Hale R, Potter JF, Myint PK. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. *Neurology*. 2011;76:914–922.
- Jacobs V, Woller SC, Stevens SM, May HT, Bair TL, Crandall BG, Cutler M, Day JD, Weiss JP, Osborn JS, Mallender C, Anderson JL, Bunch TJ. Percent time with a supratherapeutic INR in atrial fibrillation patients also using an antiplatelet agent is associated with long-term risk of dementia. *J Cardiovasc Electrophysiol*. 2015;26:1180–1186.
- Anderson JL, Horne BD, Stevens SM, Woller SC, Samuelson KM, Mansfield JW, Robinson M, Barton S, Brunisholz K, Mower CP, Huntinghouse JA, Rollo JS, Siler D, Bair TL, Knight S, Muhlestein JB, Carlquist JF. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). *Circulation*. 2012;125:1997–2005.
- Rocha BH, Langford LH, Towner S. Computerized management of chronic anticoagulation: three years of experience. *Stud Health Technol Inform*. 2007;129:1032–1036.
- Ankolekar S, Renton C, Sare G, Ellender S, Sprigg N, Wardlaw JM, Bath PM. Relationship between poststroke cognition, baseline factors, and functional outcome: data from “Efficacy of Nitric Oxide in Stroke” Trial. *J Stroke Cerebrovasc Dis*. 2014;23:1821–1829.
- Whisenant B, Kar S, Bunch TJ. Left atrial appendage occlusion addresses the tremendous unmet needs of stroke prevention in atrial fibrillation that persist despite recent advances in anticoagulation therapy. *Circulation*. 2014;130:1516–1523.
- Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719–2747.

15. Thacker EL, McKnight B, Psaty BM, Longstreth WT Jr, Sitlani CM, Dublin S, Arnold AM, Fitzpatrick AL, Gottesman RF, Heckbert SR. Atrial fibrillation and cognitive decline: a longitudinal cohort study. *Neurology*. 2013;81:119–125.
16. Crandall MA, Horne BD, Day JD, Anderson JL, Muhlestein JB, Crandall BG, Weiss JP, Lappe DL, Bunch TJ. Atrial fibrillation and CHADS2 risk factors are associated with highly sensitive C-reactive protein incrementally and independently. *Pacing Clin Electrophysiol*. 2009;32:648–652.
17. Rollo J, Knight S, May HT, Anderson JL, Muhlestein BJ, Bunch TJ, Carlquist J. Incidence of dementia in relation to genetic variants at 4Q25 and APOE ε4 in atrial fibrillation patients. *Pacing Clin Electrophysiol*. 2015;38:171–177.