Received: 9 August 2022 | Revised: 4 October 2022 | Accepted: 10 October 2022

DOI: 10.1111/jgs.18108

BRIEF REPORT

Journal of the American Geriatrics Society

Benefits and harms of oral anticoagulants for atrial fibrillation in nursing home residents with advanced dementia

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Funding information
National Institute on Aging; Paul B. Beeson Emerging Leaders Career Development Award in Aging, Grant/Award Number: K76AG059987; Robert E. Leet and Clara Guthrie Patterson Trust; Yale Claude D. Pepper Older Americans Independence Center, Grant/Award Number: P30AG021342

Abstract

Background: Approximately 20% of older persons with dementia have atrial fibrillation (AF). Nearly all have stroke risks that exceed the guideline-recommended threshold for anticoagulation. Although individuals with dementia develop profound impairments and die from the disease, little evidence exists to guide anticoagulant discontinuation, and almost one-third of nursing home residents with advanced dementia and AF remain anticoagulated in the last 6 months of life. We aimed to quantify the benefits and harms of anticoagulation in this population.

Methods: Using Minimum Data Set and Medicare claims, we conducted a retrospective cohort study with 14,877 long-stay nursing home residents aged ≥66 between 2013 and 2018 who had advanced dementia and AF. We excluded individuals with venous thromboembolism and valvular heart disease. We measured anticoagulant exposure quarterly, using Medicare Part D claims. The primary outcome was all-cause mortality; secondary outcomes were ischemic stroke and serious bleeding. We performed survival analyses with multivariable adjustment and inverse probability of treatment (IPT) weighting.

Results: In the study sample, 72.0% were female, 82.7% were aged ≥80 years, and 13.5% were nonwhite. Mean CHA_2DS_2VASC score was 6.19 ± 1.58. In multivariable survival analysis, anticoagulation was associated with decreased risk of death (HR 0.71, 95% CI 0.67–0.75) and increased bleeding risk (HR 1.15, 95% CI 1.02–1.29); the association with stroke risk was not significant (HR 1.08, 95% CI 0.80–1.46). Results were similar in models with IPT weighting. While >50% of patients in both groups died

Dr. Ouellet was supported by a Mentored Research Award from the Robert E. Leet and Clara Guthrie Patterson Trust and Pepper Scholars Award from the Yale Claude D. Pepper Older American Independence Center (P30AG021342). Dr. Cohen was supported by a Paul B. Beeson Emerging Leaders Career Development Award in Aging (K76AG059987). Dr. Skinner receives outside income from Sutter Health and the National Bureau of Economic Research, and holds equity in Dorsata, Inc. All other authors have no personal or financial conflicts of interest to disclose. The Investigators retained full independence in the conduct of this research.

within a year, median weighted survival was 76 days longer for anticoagulated individuals.

Conclusion: Persons with advanced dementia and AF derive clinically modest life prolongation from anticoagulation, at the cost of elevated risk of bleeding. The relevance of this benefit is unclear in a group with high dementia-related mortality and for whom the primary goal is often comfort.

KEYWORDS

advanced dementia, anticoagulation, atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) affects nearly one in five individuals with dementia.[1] As AF confers increased risk of ischemic stroke, clinicians must decide whether to prescribe anticoagulation to reduce this risk.[2] The mainstay of decision-making is the CHA_2DS_2-VASc score, which estimates stroke risk without treatment.[3] By virtue of their age and comorbidities, nearly all with both conditions meet the guideline-supported threshold for anticoagulation.[4]

Decision-making about anticoagulation for patients with AF and dementia is challenging. One motivation to reduce stroke risk is preventing deterioration in function and cognition, but persons with dementia already experience declines in these domains. Given the lag time to achieve stroke prevention with anticoagulation, dementia-related declines in life expectancy attenuate potential mortality benefits. Finally, anticoagulation-related harms may be greater in this population, as dementia increases the risk of anticoagulant-associated intracranial hemorrhage.[5]

While prior work has suggested that anticoagulation reduces risks of stroke and death in early dementia,[1,6] we know little about outcomes as the disease progresses. To address this gap, we focused on persons with the final, advanced stage of dementia, who have the least ability to derive benefit from stroke prevention. They already require help with self-care activities, are unable to communicate with familiar persons, and 40% die within 1 year.[7,8] However, the fact that approximately one-third of patients with advanced dementia and AF remain anticoagulated in their final six months[9] suggests clinical equipoise exists surrounding anticoagulation in this population. To examine its benefits and harms, we conducted a retrospective cohort study of US nursing home residents with advanced dementia and AF and estimated the associations between anticoagulation and mortality, stroke, and serious bleeding.

Key points

- For older adults with atrial fibrillation (AF) and advanced dementia, anticoagulation modestly reduced the risk of death at the expense of an increased risk of serious bleeding.
- The median mortality benefit of anticoagulation was small (approximately 2.5 additional months of life), which may not be clinically significant in a group with very high background mortality due to dementia.
- Clinicians should discuss the uncertainty and small magnitude of the benefit with surrogate decision-makers in the context of the most valued goals of care.

Why does this paper matter?

Although the potential benefits of anticoagulation for AF diminish as individuals with dementia develop more profound cognitive and functional loss, guidelines currently provide little guidance about when to consider discontinuation. This study provides valuable information to clinicians and surrogate decision-makers as they discuss whether to continue anticoagulation in patients with advanced dementia, who have high dementia-related mortality and for whom the primary goal is most frequently comfort.

METHODS

Cohort

Our cohort included persons aged ≥66 years living in US nursing homes at any time from 2013 to 2018 with incident advanced dementia and pre-existing AF. We identified advanced dementia using the Minimum Data Set

(MDS), a federally-mandated assessment of health conditions, function, and cognition, administered at nursing home admission and quarterly.[10] We defined advanced dementia by a diagnosis of Alzheimer's disease or another dementia, extensive or complete dependence in all activities of daily living (locomotion, transfers, bed mobility, dressing, toileting, personal hygiene, and eating), and a Cognitive Performance Scale (CPS) score of 5 or 6.[11,12] The CPS uses staff-reported information to assess cognition; residents with scores ≥5 are the most severely impaired.[13] To ensure that subjects had incident advanced dementia, we required an MDS assessment without advanced dementia in the prior 120 days.

We identified pre-existing AF using International Classification of Diseases (ICD)-9 and ICD-10 codes in Medicare claims, based on the Chronic Condition Warehouse (CCW) algorithm (Table S1).[14] AF was present if it appeared on one inpatient or two outpatient claims in the year before advanced dementia diagnosis.

Subjects had to be present in the available random 40% Part D beneficiary sample and to have continuous fee-for-service Medicare Parts A, B, and D in the 12 months prior to and after incident advanced dementia diagnosis (or until death, if patient died within 12 months of diagnosis). We excluded individuals who died within 14 days of meeting criteria for advanced dementia and those with other guideline-driven indications for anticoagulation, such as valvular heart disease and venous thromboembolism (Table S1).

Exposure

We used Part D claims to determine anticoagulant use on a quarterly basis from study entry to death or end of follow up (12 months), whichever occurred first. For each Part D claim for warfarin and the direct oral anticoagulants (dabigatran, apixaban, edoxaban, and rivaroxaban), we determined the intended treatment period based on the date of the claim and the number of days supplied. Following methods established in previous work,[15] if this period overlapped with ≥1 day of a particular quarter, we considered the individual exposed during that quarter. We chose this strategy to accommodate the possibility of intervening hospitalizations and episodes of nursing home care under the Medicare Skilled Nursing Facility benefit, when Part D does not cover medications.

Outcomes

The primary outcome was all-cause mortality within 12 months of follow-up, similar to prior outcomes studies in persons with advanced dementia.[8,16] Secondary outcomes were ischemic stroke and serious bleeding, ascertained by at least one inpatient claim during follow-up.[17–20]

Covariates

We selected covariates with the potential to confound the association between anticoagulant use and the study outcomes, including demographics, comorbid conditions (those in the CHA_2DS_2VASc stroke risk score, the ATRIA bleeding risk score,[19] and other serious conditions), use of other prescription medications associated with elevated risk of bleeding, total medication use, and markers of clinical decline (covariates listed in Table 1). Covariates were used for multivariable model adjustment and for creation of inverse probability of treatment (IPT) weights, a propensity score methodology to address indication/contraindication bias, that is, that the healthiest individuals may have been more likely to receive anticoagulation.[21]

We determined demographic characteristics using the Master Beneficiary Summary File. Comorbid chronic conditions were defined by claims in the associated CCW algorithm, with a standard 1-year lookback prior to cohort entry.[14] Prior myocardial infarction and stroke were ascertained via the CCW "ever" indicator to capture occurrences at any time while covered by Medicare. Bleeding history was defined by any inpatient or outpatient claim in the year before cohort entry.[19,20] Prescription medications associated with increased bleeding risk (antiplatelet agents and prescription nonsteroidal anti-inflammatory drugs) and total count of prescribed medications were measured in the 90 days prior to cohort entry using Part D claims. Feeding tube placement and dysphagia were determined using claims definitions with 1-year lookback.[22,23] Other markers of decline were ascertained using MDS data. Data missingness was minimal.

Statistical analyses

Associations between time-varying anticoagulation and each outcome were determined using extended Cox regression. We adjusted for confounding with two methods, multivariable adjustment, and IPT weighting.[24] IPT weights were calculated from multivariable logistic regression, modeling the associations between demographic and clinical characteristics and anticoagulant use at baseline. We used the constituent chronic conditions in the CHA_2DS_2VASc and ATRIA scores in developing

TABLE 1 Unweighted study cohort characteristics by baseline anticoagulant use

	Anticoagulant use at baseline ($n = 3678$)	No anticoagulant use at baseline ($n = 11,199$)
Demographics, *n* (%)		
Age (years)		
66 to 74	311 (8.5)	719 (6.4)
75 to 79	439 (11.9)	1104 (10.0)
80 to 84	808 (22.0)	2101 (18.8)
85 to 89	1073 (29.2)	3056 (27.3)
≥90	1047 (28.5)	4219 (37.7)
Female sex	2705 (73.5)	8010 (71.5)
Non-white race	519 (14.1)	1797 (16.0)
Medicaid eligible	2783 (75.7)	8365 (74.7)
Time in long-term care ≥1 year	2067 (56.2)	5579 (49.8)
Comorbid conditions, *n* (%)		
Heart failure	1638 (44.5)	4685 (41.8)
Hypertension	3269 (88.9)	10,082 (90.0)
Diabetes mellitus	1483 (40.3)	4172 (37.3)
Peripheral vascular disease	1612 (43.8)	4836 (43.2)
Stroke/transient ischemic attack	2186 (59.4)	6029 (53.8)
Myocardial infarction	367 (10.0)	1370 (12.2)
Anemia	1694 (46.1)	6007 (53.6)
Chronic kidney disease	1334 (36.3)	4728 (42.2)
Bleeding history	597 (16.2)	2091 (18.7)
Lymphoma	77 (0.7)	11 (0.3)
Solid tumor	172 (4.7)	589 (5.3)
Metastatic cancer	18 (0.5)	91 (0.8)
COPD	798 (21.7)	2725 (24.3)
Liver disease	56 (1.5)	293 (2.6)
Ischemic heart disease	1461 (39.7)	4899 (43.7)
Risk scores, mean ± SD		
CHA_2DS_2VASc (stroke)[a]	6.1 ± 1.53	5.9 ± 1.57
ATRIA (bleeding)[b]	5.4 ± 2.50	5.8 ± 2.57
Other medication use, *n* (%)		
Antiplatelet use	116 (3.2)	1165 (10.4)
Prescription NSAID use	125 (3.4)	439 (3.9)
Number of total medications		
0 to 5	413 (11.2)	2976 (26.6)
6 to 10	957 (26.0)	3749 (33.5)
>10	2308 (62.8)	4474 (39.9)
Markers of decline, *n* (%)		
Rejection of care	164 (4.5)	583 (5.2)
Falls	705 (19.2)	2215 (19.8)
Weight loss	411 (11.2)	1496 (13.4)
Pressure ulcer	580 (15.8)	2222 (19.8)

TABLE 1 (Continued)

	Anticoagulant use at baseline ($n = 3678$)	No anticoagulant use at baseline ($n = 11,199$)
Difficulty swallowing	1907 (51.8)	6056 (54.1)
Hospice use	374 (10.2)	1929 (17.2)
Feeding tube	300 (8.2)	1280 (11.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; NSAID, non-steroidal anti-inflammatory drug.

[a]The CHA_2DS_2VASc score is calculated as follows: age (65–74: 1 point, ≥75: 2 points), female sex (1 point), heart failure (1 point), diabetes mellitus (1 point), hypertension (1 point), stroke (2 points), vascular disease (1 point). Higher scores are associated with higher stroke risk.

[b]The ATRIA score is calculated as follows: age ≥75 (2 points), anemia (3 points), renal disease (3 points), prior bleeding (1 point), hypertension (1 point). Higher scores are associated with higher bleeding risk.

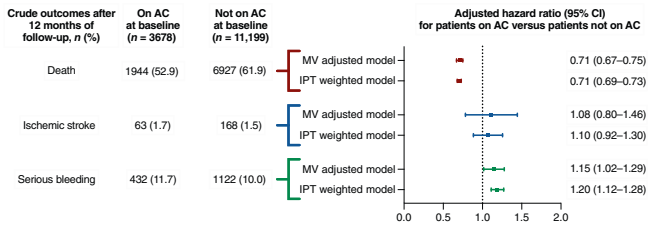

FIGURE 1 Crude outcome rates by baseline anticoagulant (table at left); adjusted hazard ratios for the associations between anticoagulant use and outcomes in multivariable adjusted models and IPT weighted models (forest plot). AC, anticoagulant; IPT, inverse probability of treatment; MV, multivariable. Covariates used in multivariable adjustment and in development of IPT weights included demographics, comorbid conditions, and nursing home assessment data, as detailed in Table 1.

the IPT weights and multivariable models, rather than the scores themselves, to avoid collinearity. We quantified mortality risk reduction by comparing IPT-weighted median days of survival between those on anticoagulation at any point from baseline to death and those who were not. We addressed the competing risk of death with two methods, the cause-specific and the subdistribution hazard functions.[25,26] Analyses used SAS v9.4 (Cary, NC). A two-sided p value <0.05 denoted statistical significance.

The Yale University and Dartmouth College institutional review boards approved this study. We followed the STROBE reporting guidelines.[27]

RESULTS

Baseline characteristics are presented in Table 1. Among 14,877 nursing home residents with AF and advanced dementia, 3678 (24.7%) were anticoagulated at baseline. Similar proportions of anticoagulated and not anticoagulated individuals were ≥80 years (79.7% vs 83.8%), female (73.5% vs 71.5%), and nonwhite (14.1% vs 16.0%). Chronic conditions were highly prevalent. There was minimal difference in mean CHA_2DS_2VASc score between those anticoagulated at baseline (6.1) and those who were not (5.9). Anticoagulated persons were more likely to receive >5 medications (88.8% vs 73.4%) and less likely to receive hospice care (10.2% vs 17.2%).

Crude outcome rates stratified by baseline anticoagulant use, as well as the results of survival modeling, are shown in Figure 1. Among individuals anticoagulated at baseline, 52.9% died versus 61.9% of those who were not. In multivariable survival analyses, anticoagulation was associated with reduced mortality (HR 0.71, 95% CI 0.67–0.75) and increased risk of serious bleeding (HR 1.15, 95% CI 1.02–1.29); there was no association with the risk of ischemic stroke (HR 1.08, 95% CI 0.80–1.46). Results were similar using IPT weighting (Figure 1). Results were similar when adjusted for the competing risk of death using subdistribution hazard and cause-specific hazard modeling (results not presented).

Median weighted survival was 76 days longer for those on anticoagulation at any time during follow-up than for those who were not (296 days [95% CI, 270–326] vs 220 days [95% CI, 212–232]).

DISCUSSION

In this retrospective cohort study, we examined the benefits and risks of anticoagulation among nursing home residents with advanced dementia and AF. Anticoagulation was associated with a small reduction in mortality; while the majority of both groups died within 1 year, survival was approximately 2.5 months longer in those who were anticoagulated. Over 1 year of follow-up, anticoagulation was associated with increased risk of serious bleeding. There was no relationship between anticoagulation and ischemic stroke.

Anticoagulation studies for patients with AF and early dementia have demonstrated a mortality benefit

with anticoagulation, at the expense of increased bleeding.[1,6] Our work builds on this by examining persons with advanced disease. Among anticoagulated persons, there was a modest mortality benefit and modest increase in bleeding. The size of the mortality benefit is not surprising, given the limited life expectancy that advanced dementia confers,[8] but it is notable that it was not accompanied by a reduction in stroke risk, which is the primary reason to prescribe anticoagulants for AF. Strokes may have been underdetected because either severe impairments limited neurologic exams or comfort-oriented goals of care limited further evaluation. Alternatively, the mortality benefit may be due to residual confounding, that is, that anticoagulated persons were healthier than persons who were not anticoagulated. Persons who were not anticoagulated were on fewer medications and were more likely to receive hospice, suggesting that clinicians responded to poor prognosis.

Our findings should be interpreted in the context of work showing that the primary goal of treatment for patients with advanced dementia is almost always comfort. In a seminal study, 96% of surrogate decision-makers selected comfort as the primary focus of care.[28] Patients with advanced dementia have such severe disability that there is little functional or cognitive impairment left to prevent, and the primary rationale for anticoagulation is life prolongation. The fact that more than 25% of our cohort nevertheless received anticoagulation suggests a need for clinicians to speak with surrogates when patients reach this stage about whether this treatment is aligned with their goals. The results of this study may aid such conversations. Surrogates who do primarily value life prolongation should consider the median mortality benefit associated with anticoagulation in the context of the very high 1-year mortality in the cohort overall. For those who prioritize comfort, continuing anticoagulation may not be goal-concordant, particularly given the increased bleeding risk.

Work is needed to examine the risks and benefits of anticoagulation for patients with AF who are in the middle stages of dementia, where evidence to guide decision-making is sparse. Goals of care are likely to be more variable for patients with moderate disease, and such persons have more function left to lose. Understanding the magnitude of mortality, cognitive, and functional benefits associated with anticoagulation in this population, along with bleeding risks, should be the focus of future investigation.

This study has several limitations. Residual confounding remains possible, given its observational nature. In addition, we lacked precision in our ability to determine the timing of the transition to advanced dementia due to our reliance on quarterly MDS assessments. To address this, we only included individuals with incident advanced dementia in the study cohort.

Furthermore, our exposure was assessed quarterly and relied on Part D claims, rather than daily administration records, which may have resulted in misclassification. As this study focused on nursing home patients, 81% of whom received prescription coverage from Part D,[29] our results may not generalize to community-dwellers or those with alternate prescription coverage. However, it is notable that approximately two-thirds of persons with advanced dementia die in nursing homes.[30] Despite these limitations, our study design allowed for the identification of a large, well-characterized, national cohort in a setting where a randomized trial would have numerous feasibility challenges (e.g., multiple sites and need for surrogate informed consent).

In summary, there was a modest increase in life expectancy and a modest increased bleeding risk among persons with advanced dementia and AF who received anticoagulation, with no difference in stroke risk. These findings may inform discussions between clinicians and surrogates about whether or not to continue anticoagulation when patients reach this stage of disease.

AUTHOR CONTRIBUTIONS

Overall study concept and design, interpretation of data, and preparation of manuscript: Gregory M. Ouellet. *Analysis and interpretation of data and critical revision of manuscript*: John R. O'Leary and Christopher G. Leggett. *Study design, interpretation of data and critical revision of manuscript*: Jonathan Skinner and Mary E. Tinetti. *Overall study concept and design, interpretation of data, and critical revision of manuscript*: Andrew B. Cohen.

ACKNOWLEDGMENTS

The authors thank Andrea Austin, PhD, senior biostatistician at CorEvitas, for her methodologic consultation in the pre-analytic phases of this work.

CONFLICT OF INTEREST

Dr. Skinner receives outside income from Sutter Health and the National Bureau of Economic Research, and holds equity in Dorsata, Inc. All other authors have no personal or financial conflicts of interest to disclose.

SPONSOR'S ROLE

The sponsors had no role in the study design, recruitment, data collection, qualitative analysis, or preparation of this manuscript. This study was supported by a Mentored Research Award from the Robert E. Leet and Clara Guthrie Patterson Trust. During this work, Dr. Ouellet received a support from a Pepper Scholar award from the Yale Claude D. Pepper Older Americans Independence

Center (P30AG021342). Dr. Cohen was supported by a Paul B. Beeson Emerging Leaders Career Development Award in Aging (K76AG059987).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1. ICD-9 and ICD-10 codes used for inclusion and exclusion criteria.

How to cite this article: Ouellet GM, O'Leary JR, Leggett CG, Skinner J, Tinetti ME, Cohen AB. Benefits and harms of oral anticoagulants for atrial fibrillation in nursing home residents with advanced dementia. *J Am Geriatr Soc*. 2022;1-8. doi:10.1111/jgs.18108