Association of frailty and cognitive impairment with benefits of oral anticoagulation in patients with atrial fibrillation

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Background The incidence of cognitive impairment and frailty increase with age and may impact both therapy and outcomes in atrial fibrillation (AF).

Methods We examined the prevalence of clinically recognized cognitive impairment and frailty (as defined by the American Geriatric Society Criteria) in the Outcomes Registry for Better Informed Care in AF (ORBIT AF) and associated adjusted outcomes via multivariable Cox regression. The interaction between cognitive impairment and frailty and oral anticoagulation (OAC) in determining outcomes was examined.

Results Among 9749 patients with AF [median (IQR) age 75 (67–82) y, 57% male], cognitive impairment and frailty was identified in 293 (3.0%) and 575 (5.9%) patients respectively. Frail patients (68 vs 77%, $P < .001$) and those with cognitive impairment (70 vs 77%, $P = .006$) were both less likely to receive an OAC. Both cognitive impairment [HR (95% CI) 1.34 (1.05–1.72), $P = .0198$] and frailty [HR 1.29 (1.08–1.55), $P = .0060$] were associated with increased risk of death. Cognitive impairment and frailty were not associated with stroke/transient ischemic attack (TIA) or major bleeding. In multivariable analysis, there was no interaction between OAC use and cognitive impairment or frailty in their associations with mortality, major bleeding and a composite end point of stroke, non-central nervous system systemic embolism, TIA, myocardial infarction or cardiovascular death.

Conclusion Those with cognitive impairment or frailty in AF had higher predicted risk for stroke and higher observed mortality, yet were less likely to be treated with OAC. Despite this, the benefits of OAC were similar in patients with and without cognitive impairment or frailty. (Am Heart J 2019;211:77-89.)

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults and is projected to affect 12 to 15 million people in the USA by 2050.[1] The prevalence of AF increases with age, such that 10% of individuals over the age of 85 years have AF.[2] The prevalence of cognitive impairment and frailty also increase with aging. Frailty is a syndrome characterized by reduced physiologic reserve and increased susceptibility to disability.[3] A complex interplay between AF, cognitive impairment and frailty may increase morbidity and mortality in the elderly. AF is associated with a 40% increase in risk of cognitive impairment independent of the occurrence of stroke.[4] The frail state is also more common in individuals with AF.[5,6] Cognitive impairment and frailty may in turn affect management of AF. For instance, frailty and cognitive impairment may adversely affect the effectiveness of oral anticoagulation (OAC) due to poor compliance and inability to adhere to monitoring requirements or deter a physician from prescribing an oral anticoagulant.[7]

Stroke due to systemic embolism is the most serious consequence of AF. AF increases the risk of stroke by 5 fold and the risk increases with advancing age.[8] OAC is

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however significantly underutilized in the elderly.[9] Perceived safety concerns and frailty are frequently cited as reasons for non-initiation and discontinuation of OAC in the elderly, despite elevated stroke risk.[9-13] While cognitive impairment and the frail state may influence the perception of bleeding risk and the decision to anticoagulate, the impact of these co-morbid conditions on outcomes in AF are not known.

Understanding the incidence, factors associated with and outcomes of AF patients with cognitive impairment and frailty is essential to the optimal management of this growing population of patients. The primary objectives of this study were to (1) examine how OAC treatment patterns varied as a function of cognitive impairment and frailty vs not; (2) examine outcomes as a function of cognitive impairment and frailty and (3) determine whether the benefits of OAC for stroke prevention varied as a function of cognitive impairment and frailty vs not in a large cohort of AF patients enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF).

Methods

The ORBIT-AF registry enrolled 10,137 individuals over the age of 18 years with electrocardiographic evidence of AF at 176 sites in the USA from June 2010 to August 2011. Enrolling sites were selected to be geographically representative and included a variety of providers including primary care physicians, cardiologists and electrophysiologists. The study design and cohort are described elsewhere.[14] Patients with electrocardiographic documentation of atrial fibrillation ≥18 years of age with an anticipated life expectancy of >6 months who are able to provide informed consent and adhere to scheduled follow-up visits were eligible for enrollment. Exclusion criteria included transient AF due to a reversible cause, enrollment is a clinical trial of antithrombotic therapy and employee or immediate family member of the investigator/study center. Data on demographics, clinical characteristics, AF treatment strategies and outcomes was collected by each site at enrollment and longitudinally every 6 months for up to 36 months. The Duke Clinical Research Institute was responsible for design and conduct of the study. All study participants provided written informed consent. The study was approved by the Duke Institutional Review Board and local institutional review boards at participating sites. This work was funded by the ORBIT AF Registry which is sponsored by Janssen Scientific Affairs, LLC, Titusville, NJ. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

The diagnosis of cognitive impairment including dementia at enrollment was documented by the treating physician. Systematic neurocognitive testing of all participants was not performed. All enrollees were tested for frailty using the American Geriatric Society's Geriatric Evaluation and Management Tool at enrollment.[15,16] This tool uses a combination of indicators of functional decline including weight loss, self-reported exhaustion, low activity level, motor slowing and weakness in grip strength to define frailty.

The outcomes of interest were (1) all-cause mortality, (2) cardiovascular mortality, (3) stroke/TIA/non-central nervous system (CNS) systemic embolism, (4) composite of major adverse cardiovascular and neurologic events (MACNE: cardiovascular death, myocardial infarction or stroke/TIA/non-CNS systemic embolism), (5) major bleeding and (6) clinically significant bleeding. Major bleeding was defined per the International Society on Thrombosis and Hemostasis criteria as the presence of one or more of the following (1) fatal bleeding (2) symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) and (3) bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of ≥2 U of whole blood or red cells.[17] Clinically significant bleeding was defined as a bleeding event that led to a clinical intervention without meeting the major bleeding ISTH criteria. Cardiovascular death included heart failure, sudden cardiac death, stroke related, MI related or other type of CV death.

Statistical methods

Baseline characteristics are presented overall, by cognitive impairment and by frailty. Categorical variables are presented as frequencies and percentages and differences between the groups were assessed by the Chi-Square test. Continuous variables are presented as median (Q1-Q3) and differences between the groups were assessed by the Wilcoxon rank sum test.

To identify factors associated with cognitive impairment at baseline, a multivariable generalized estimating equation (GEE) logistic regression model with constant correlation between patients within sites (exchangeable working correlation structure) was fit using all the clinical and demographic characteristics listed in the candidate variable list (see Appendix Table A). Backward selection with an inclusion criterion of $P < .05$ was used to build the model. All continuous variables were evaluated for non-linearity with the outcome and non-linear relationships were accounted for using linear splines. The same analysis strategy was used to identify factors associated with frailty. Odds ratio (OR) with corresponding 95% confidence interval (CI) and P are presented.

To evaluate the association between cognitive impairment and outcomes (except for clinically significant bleeding), Cox regression modeling was used. For clinically significant bleeding, a discrete time Cox model was used since actual event dates were not collected, but events were ascertained at each 6-month visit. Robust standard errors were used to account for within site clustering for both models. Each

model was adjusted for clinically relevant variables plus any additional variables that were previously found to be statistically significant covariates for any of the outcomes under evaluation (see Appendix Table B). All continuous variables were fit with restricted cubic splines. The same process was used to evaluate the association between frailty and outcomes. Hazard ratios (HR) with corresponding 95% CI and *P* are presented along with the event rates per 100 patient years.

To evaluate the association between OAC use at baseline with outcomes according to cognitive impairment status, Cox proportional hazards modeling with robust standard errors to account for within site clustering was used. The association of OAC use with outcomes was adjusted with overlap weighting of the propensity to receive OAC. Overlap weighting places the greatest weight on patients that are most comparable between the two treatment groups of interest (here OAC vs no OAC). The propensity score was calculated using imputed data, adjusted for all covariates identified as factors associated with OAC treatment and outcomes of interest based on clinical knowledge (see Appendix Table C). All continuous variables were evaluated for non-linearity with OAC use at baseline and non-linear variables were fit with restricted cubic splines. An interaction term between OAC use and cognitive impairment was added to each outcome model and $P < .05$ was considered statistically significant. Adjusted survival curves for each outcome, each figure illustrating the 4 combinations OAC (yes/no) and cognitive impairment (yes/no) are presented. The same analysis strategy was repeated for frailty. The proportional hazard assumption was tested in all the models and it was not met for frailty in the stroke/TIA and the composite endpoint models. Similarly, the assumption was violated for cognitive impairment in the major bleeding model. The assumption was met in all other models by covariate combinations. Time varying Cox regression models were fit in the necessary cases and the results consistently remained non-significant. Since the results were similar, findings from the Cox regression models are reported.

All candidate variables had <2% missing, except for level of education (4%), estimated glomerular filtration rate (7%), hemoglobin (10%), left ventricular hypertrophy (9%), hematocrit (10%), left ventricular ejection fraction type (10%), and left atrial diameter type (14%). Missing data was handled with multiple and single imputation and imputed values were obtained by Markov Chain Monte Carlo (MCMC) or regression methods.[18] Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC), and two-tailed $P < .05$ was considered significant for all statistical tests.

Results

This analysis included 9749 subjects enrolled in the ORBIT-AF registry at 174 sites after excluding 388 subjects without follow-up. Cognitive impairment, frailty, or both were identified in 293/9749 (3.0%), 575/9722 (5.9%), and 67/9722 (0.7%) patients, respectively. Data on frailty was not available in 27 subjects and these were excluded from the analysis on frailty. The baseline characteristics of the entire cohort and stratified by the presence of frailty and cognitive impairment are presented in Table I. Median age was 75.0 (67.0-82.0) years and 57.4% were male. OAC was prescribed to 7445 (76.4%) at baseline of whom 6965 (71.4%) were on Warfarin and the rest on Dabigatran. Patients with frailty were more likely to have persistent or permanent AF than those without frailty (54.1% vs 44.2%).

In univariate analysis, those with cognitive impairment had higher CHA_2DS_2-VASc risk score [5.0 (4.0-6.0) vs 4.0 (3.0-5.0), $P < .0001$]. Bleeding risk scores, including HAS-BLED and ORBIT, were also higher in patients with cognitive impairment. Subjects with cognitive impairment were less likely to be prescribed an OAC (69.6% vs 76.6%, $P = .0058$). There was no difference in the reported European Heart Rhythm Association (EHRA) score of AF symptoms between those with and without cognitive impairment. In univariate analysis, frail subjects had higher CHA_2DS_2-VASc risk score [5.0 (4.0-6.0) vs 4.0 (3.0-5.0), $P < .0001$] and also higher HAS-BLED and ORBIT bleeding risk score. Frail subjects were less likely to receive an OAC (67.5 vs 76.9%, $P < .0001$). Factors independently associated with cognitive impairment and frailty are presented in Tables II and III respectively.

Outcomes in AF patients with cognitive impairment and frailty

During a median follow-up of 931 (inter-quartile range 668–1088) days, stroke/TIA/non-CNS systemic embolism occurred in 350 (1.6 events per 100 patient years) in the whole cohort. Major bleeding and clinically significant bleeding were seen in 821 (3.8 events per 100 patient years) and 1095 (5.2 events per 100 patient years) respectively. Death from any cause occurred in 1244 (5.6 events per 100 patient years) and CV deaths in 500 (2.3 events per 100 patient years). The association between cognitive impairment or frailty and the outcomes of interest are presented in Tables IV and V respectively. Cognitive impairment and frailty were independently associated with death from any cause, but not stroke/TIA/non-CNS systemic embolism, major bleeding and clinically significant bleeding.

Oral anticoagulation and outcomes in AF patients with cognitive impairment and frailty

The modification by each one of the exposures (cognitive impairment and frailty) on the observed association between outcomes and OAC use was examined. No interaction was noted between cognitive impairment and OAC use in determining all-cause death

Table I. Baseline characteristics of the overall cohort and stratified by cognitive impairment/dementia and frailty

	Overall N = 9749	Cognitive impairment or dementia N = 293	No cognitive impairment or dementia N = 9456	*P*	Frailty N = 575	No frailty N = 9147	*P*
Age (year)	75.0 (67.0–82.0)	82.0 (76.0–87.0)	75.0 (67.0–81.0)	<.0001	83.0 (77.0–88.0)	74.0 (66.0–81.0)	<.0001
< 60 y	1042 (10.7%)	6 (2.1%)	1036 (11.0%)		16 (2.8%)	1025 (11.2%)	
60–69 y	2174 (22.3%)	25 (8.5%)	2149 (22.7%)		45 (7.8%)	2123 (23.2%)	
70–79 y	3281 (33.7%)	88 (30.0%)	3193 (33.8%)		120 (20.9%)	3151 (34.5%)	
≥ 80 y	3252 (33.3%)	174 (59.4%)	3078 (32.6%)		394 (68.5%)	2848 (31.1%)	
Male	5599 (57.4%)	137 (46.8%)	5462 (57.8%)	.0002	234 (40.7%)	5347 (58.5%)	<.0001
Race							
White	8719 (89.4%)	245 (83.6%)	8474 (89.6%)	.0038	520 (90.4%)	8172 (89.3%)	.0601
Black or African American	477 (4.9%)	24 (8.2%)	453 (4.8%)	.	35 (6.1%)	442 (4.8%)	
Hispanic	398 (4.1%)	20 (6.8%)	378 (4.0%)	.	15 (2.6%)	383 (4.2%)	
Other	139 (1.4%)	4 (1.4%)	135 (1.4%)	.	4 (0.7%)	135 (1.5%)	
Level of Education							
Some school	1364 (14.0%)	76 (25.9%)	1288 (13.6%)	<.0001	134 (23.3%)	1230 (13.4%)	<.0001
High School Graduate	4963 (50.9%)	126 (43.0%)	4837 (51.2%)	.	297 (51.7%)	4665 (51.0%)	
College Graduate	2214 (22.7%)	63 (21.5%)	2151 (22.7%)	.	88 (15.3%)	2125 (23.2%)	
Post Graduate	811 (8.3%)	15 (5.1%)	796 (8.4%)	.	33 (5.7%)	778 (8.5%)	
BMI (kg/m^2)	29.1 (25.4–34.0)	26.5 (23.3–30.6)	29.2 (25.4–34.1)	<.0001	26.0 (22.1–30.5)	29.3 (25.6–34.2)	<.0001
Medical history							
Hypertension	8103 (83.1%)	248 (84.6%)	7855 (83.1%)	.4791	486 (84.5%)	7591 (83.0%)	.3417
Diabetes	2874 (29.5%)	107 (36.5%)	2767 (29.3%)	.0073	175 (30.4%)	2686 (29.4%)	.5850
Hyperlipidemia	7042 (72.2%)	225 (76.8%)	6817 (72.1%)	.0769	408 (71.0%)	6610 (72.3%)	.4973
COPD	1605 (16.5%)	68 (23.2%)	1537 (16.3%)	.0016	158 (27.5%)	1437 (15.7%)	<.0001
Chronic Kidney Disease	3361 (34.5%)	128 (43.7%)	3233 (34.2%)	.0023	265 (46.1%)	3076 (33.6%)	<.0001
Peripheral Vascular Disease	1309 (13.4%)	61 (20.8%)	1248 (13.2%)	.0002	126 (21.9%)	1177 (12.9%)	<.0001
Stroke/TIA	1479 (15.2%)	83 (28.3%)	1396 (14.8%)	<.0001	152 (26.4%)	1323 (14.5%)	<.0001
Congestive Heart Failure	3204 (32.9%)	128 (43.7%)	3076 (32.5%)	<.0001	297 (51.7%)	2890 (31.6%)	<.0001
Prior Myocardial Infarction	1562 (16.0%)	60 (20.5%)	1502 (15.9%)	.0348	104 (18.1%)	1447 (15.8%)	.1498
Laboratory data							
Estimated Glomerular Filtration Rate (mg/dL)	66.8 (52.7–82.1)	62.2 (47.6–74.0)	67.1 (52.9–82.4)	<.0001	60.3 (44.9–73.2)	67.5 (53.4–82.6)	<.0001
Hematocrit (%)	40.2 (36.9–43.3)	39.4 (35.6–42.6)	40.2 (36.9–43.3)	.0011	38.0 (34.5–41.2)	40.3 (37.0–43.4)	<.0001
Type of AF							
First Detected/New Onset	438 (4.5%)	7 (2.4%)	431 (4.6%)	.2098	26 (4.5%)	409 (4.5%)	<.0001
Paroxysmal AF	4940 (50.7%)	151 (51.5%)	4789 (50.6%)	.	238 (41.4%)	4695 (51.3%)	
Persistent/Permanent AF	4371 (44.8%)	135 (46.1%)	4236 (44.8%)		311 (54.1%)	4043 (44.2%)	
AF Management Strategy							
Rate Control	6641 (68.1%)	226 (77.1%)	6415 (67.8%)	.0007	456 (79.3%)	6168 (67.4%)	<.0001
Rhythm Control	3083 (31.6%)	66 (22.5%)	3017 (31.9%)	.	113 (19.7%)	2960 (32.4%)	
Medications							
Beta Blockers	6268 (64.3%)	170 (58.0%)	6098 (64.5%)	.0227	358 (62.3%)	5889 (64.4%)	.3017
Calcium Channel Blockers	2965 (30.4%)	86 (29.4%)	2879 (30.4%)	.6875	177 (30.8%)	2781 (30.4%)	.8493
Digoxin	2296 (23.6%)	96 (32.8%)	2200 (23.3%)	.0002	190 (33.0%)	2100 (23.0%)	<.0001
Antiplatelet Therapy	4618 (47.4%)	128 (43.7%)	4490 (47.5%)	.1999	289 (50.3%)	4314 (47.2%)	.1490
Oral anticoagulant therapy	7445 (76.4%)	204 (69.6%)	7241 (76.6%)	.0058	388 (67.5%)	7037 (76.9%)	<.0001
CHA_2DS_2VASc Risk Score	4.0 (3.0–5.0)	5.0 (4.0–6.0)	4.0 (3.0–5.0)	<.0001	5.0 (4.0–6.0)	4.0 (3.0–5.0)	<.0001
ORBIT Score	2.0 (1.0, 4.0)	3.0 (2.0–4.0)	2.0 (1.0–4.0)	<.0001	3.0 (2.0–4.0)	2.0 (1.0–3.0)	<.0001
HAS-BLED Score (without labile INR)	2.0 (1.0–2.0)	2.0 (2.0–3.0)	2.0 (1.0–2.0)	<.0001	2.0 (2.0–3.0)	2.0 (1.0–2.0)	<.0001
EHRA Score							
No Symptoms	3726 (38.2%)	116 (39.6%)	3610 (38.2%)	.4962	151 (26.3%)	3575 (39.1%)	<.0001
Mild (normal daily activity not affected)	4390 (45.0%)	125 (42.7%)	4265 (45.1%)	.	262 (45.6%)	4125 (45.1%)	
Severe (normal daily activity affected)	1430 (14.7%)	49 (16.7%)	1381 (14.6%)	.	145 (25.2%)	1285 (14.0%)	
Disabling (normal daily activity discontinued)	175 (1.8%)	3 (1.0%)	172 (1.8%)	.	16 (2.8%)	159 (1.7%)	

Table I (*continued*)

	Overall N = 9749	Cognitive impairment or dementia N = 293	No cognitive impairment or dementia N = 9456	*P*	Frailty N = 575	No frailty N = 9147	*P*
Functional Status							
Living independently	8882 (91.1%)	162 (55.3%)	8720 (92.2%)	<.0001	373 (64.9%)	8483 (92.7%)	<.0001
Living with assistance or Resides in assisted living facility/skilled nursing home/bedbound	864 (8.9%)	131 (44.7%)	733 (7.8%)	.	202 (35.1%)	662 (7.2%)	

Table II. Independent associations of cognitive impairment in patients with atrial fibrillation

Variable	*OR (95% CI)*	*P*	*Global P*
Age (per 5 year increase and >70 years)	1.38 (1.26–1.51)	<.0001	.
History of frailty	2.80 (2.06–3.81)	<.0001	.
Prior stroke/TIA	1.69 (1.29–2.21)	0.0001	.
History of diabetes	1.53 (1.18–1.97)	0.0011	.
BMI (per 1 kg/m^2 increase)	0.97 (0.95–0.99)	0.0110	.
Level of education			0.0010
High school graduate (vs Some school)	0.57 (0.42–0.77)	0.0002	
College graduate (vs Some school)	0.71 (0.50–1.00)	0.0481	.
Post graduate (vs Some school)	0.46 (0.26–0.81)	0.0071	.

Table III. Independent associations of frailty in patients with atrial fibrillation

Variable	*OR (95% CI)*	*P*	*Global P*
BMI (per 1 kg/m^2 increase truncated at 30)	0.92 (0.90–0.95)	<.0001	.
Cognitive impairment/dementia	2.41 (1.75–3.32)	<.0001	.
Anemia	1.70 (1.40–2.08)	<.0001	.
Female sex	1.55 (1.29–1.87)	<.0001	.
Prior stroke/TIA	1.57 (1.28–1.94)	<.0001	.
COPD	1.57 (1.27–1.94)	<.0001	.
Congestive heart failure			<.0001
NYHA Class I (vs no CHF)	1.06 (0.78–1.45)	0.6959	
NYHA Class II (vs no CHF)	1.47 (1.15–1.86)	0.0017	.
NYHA Class III or IV (vs no CHF)	2.70 (2.07–3.52)	<.0001	.
Current OAC use (vs none)	0.69 (0.56–0.84)	0.0003	.
Current AAD use (vs none)	0.68 (0.54–0.86)	0.0012	.
Age			0.0039
Age (per 5 year increase and ≤85 years)	1.32 (1.23–1.43)	<.0001	
Age (per 5 year increase and >85 years)	1.84 (1.53–2.23)	<.0001	.
eGFR			0.0107
eGFR (per 5 mg/dL increase and ≤75 mg/dL)	0.97 (0.93–1.00)	0.0690	
eGFR (per 5 mg/dL increase and >75 mg/dL)	1.06 (1.01–1.11)	0.0152	.

(*P* = .5), major bleeding (*P* = .9), and composite end point of CV death, MI, stroke, TIA or non-CNS systemic embolism (*P* = .9). Likewise, there was no statistically significant interaction between frailty and OAC use in determining all-cause death (*P* = .8), major bleeding (*P* = .3) and composite end point of CV death, MI, stroke, TIA or non-CNS systemic embolism (*P* = .4). Adjusted event free survival curves of freedom from all-cause death, major bleeding and the composite end point stratified by cognitive impairment and OAC use are presented in Figure 1. Figure 2 shows adjusted event free survival curves of outcomes stratified by frailty and OAC use.

Discussion

In a large multicenter cohort of patients with AF, cognitive impairment and frailty was diagnosed in 3% and 6% of patients, respectively. Frail individuals and those

Table IV. Association between cognitive impairment and outcomes.

	Number of events (Incidence rate)		*Unadjusted analysis*		*Adjusted analysis*	
Outcome	*Cognitive impairment/dementia (N = 293)*	*No Cognitive impairment/dementia (N = 9456)*	*Unadjusted HR (95% CI)*	*Unadjusted P*	*Adjusted HR (95% CI)*	*Adjusted P*
Death	75 (13.53)	1169 (5.38)	2.57 (1.99–3.31)	<.0001	1.34 (1.05–1.72)	.0198
Stroke/TIA/non-CNS embolism	13 (2.39)	337 (1.58)	1.53 (0.85–2.74)	.1547	0.86 (0.46–1.60)	.6322
Major bleeding	28 (5.37)	793 (3.80)	1.40 (0.91–2.15)	.1269	0.97 (0.60–1.56)	.8907
Clinically significant bleed	33 (6.07)	1062 (5.13)	1.19 (0.79–1.78)	.4022	0.93 (0.63–1.39)	.7237
CV death, MI, Stroke/TIA/non-CNS embolism	35 (6.43)	839 (3.94)	1.65 (1.16–2.34)	.0051	0.90 (0.60–1.33)	.5856

Incidence rate represents event rate per 100 patient-years.

Table V. Association between frailty and outcomes

	Number of events (Incidence rate)		*Unadjusted analysis*		*Adjusted analysis*	
Outcome	*Frail (N = 575)*	*Not Frailty (N = 9147)*	*Unadjusted HR (95% CI)*	*Unadjusted P*	*Adjusted HR (95% CI)*	*Adjusted P*
Death	182 (16.46)	1054 (4.99)	3.37 (2.79–4.07)	<.0001	1.29 (1.08–1.55)	.0060
Stroke/TIA/non-CNS embolism	30 (2.80)	319 (1.53)	1.84 (1.24–2.71)	.0023	0.96 (0.63–1.46)	.8541
Major bleeding	74 (7.13)	745 (3.67)	1.93 (1.36–2.72)	.0002	1.13 (0.80–1.60)	.4708
Clinically significant bleed	78 (7.40)	1015 (5.04)	1.49 (1.06–2.08)	.0201	1.05 (0.76–1.43)	.7751
CV death, MI, Stroke/TIA/non-CNS embolism	90 (8.44)	780 (3.77)	2.27 (1.79–2.87)	<.0001	0.97 (0.77–1.23)	.8035

Incidence rate represents event rate per 100 patient-years.

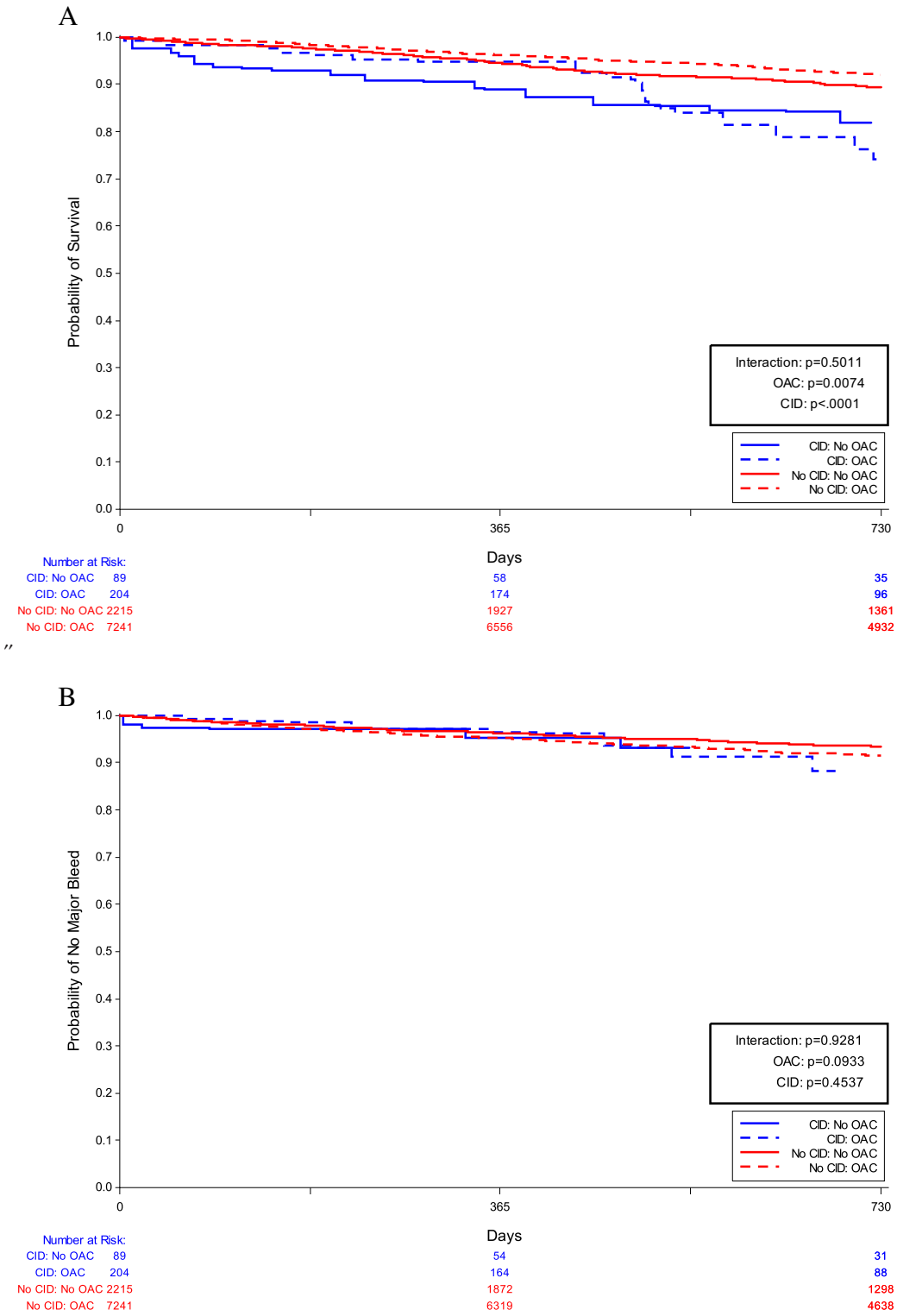
with cognitive impairment had higher risk of stroke as assessed by the CHA_2DS_2-VASc risk score but were less likely to receive OAC. Both cognitive impairment and frailty were independently associated with increased mortality, but not stroke/TIA and major bleeding. The treatment effect of OAC on clinical outcomes is similar between frail and non-frail patients and similarly between cognitively impaired and non-cognitively impaired patients.

Our findings are consistent with prior cross-sectional studies that have reported lower rate of OAC use in patients with dementia.[19,20] Cognitive impairment has previously been associated with lower time in therapeutic range in patients on vitamin K antagonist, raising concern for both lack of efficacy and higher bleeding risk with anticoagulation.[21] Cognitive impairment was associated with increased the risk of death, but not of stroke/TIA and major hemorrhage in the ORBIT-AF cohort. Moreover, there was no interaction between OAC use and cognitive impairment in determining the outcomes of interest. Thus, while cognitively impaired AF patients had higher risk of stroke as evidenced by higher CHA_2DS_2-VASc score, they are likely to experience a similar benefit compared with those patients without cognitive impairment. The diagnosis of cognitive impairment did not increase the outcome of major hemorrhage in the setting of anticoagulation. Hence AF patients with cognitive impairment should be considered for OAC based on their clinical factors (ie, risk stratification scores). Therapeutic anticoagulation with a vitamin K antagonist has been shown to reduce the incidence of cognitive impairment in AF.[22] The role of OAC in slowing the progression of milder forms of cognitive impairment to more severe forms is not known. By preventing both clinically overt and silent cerebral thromboembolism, OAC may stall this progression in AF patients with mild cognitive impairment. While the current study supports the safety of this approach, future prospective studies will be required to investigate effectiveness.

Our findings are consistent with previous reports of association of frailty with AF symptoms and age.[23] This may suggest either worsening of the frail state due to AF or greater perception of symptoms in patients with pre-existing frailty. The presence of frailty was also associated with a greater than 2-fold increase in cognitive impairment. While the association between frailty and cognitive impairment in the general population has been previously reported, our findings extend this association to patients with AF.[24]

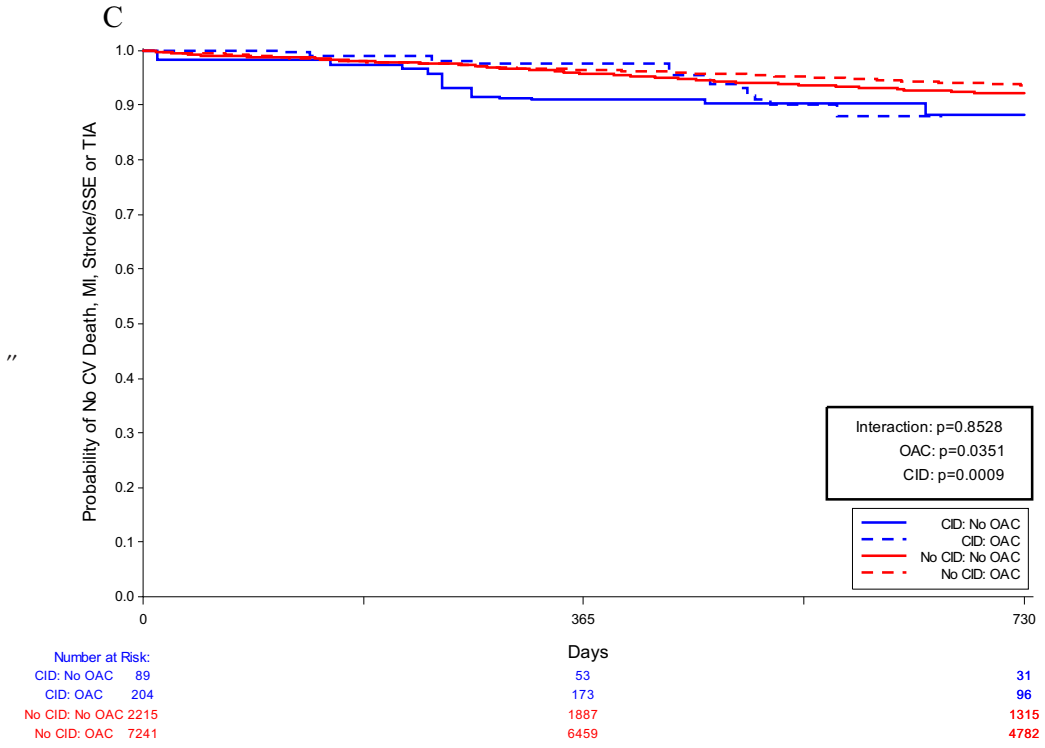
Frailty was associated with an increased risk of mortality in AF, but not that of stroke/TIA and major bleeding. Frailty has previously been associated with

Figure 1



Survival free of outcome event in AF patients stratified by cognitive impairment/dementia (CID) and oral anticoagulation use after adjustment for confounders.A, Survival in AF patients stratified by cognitive impairment/dementia (CID) and oral anticoagulation use.B, Survival free of major bleeding in AF patients stratified by cognitive impairment and oral anticoagulation use.C, Survival free of composite end point of stroke/TIA/non-CNS systemic embolism, myocardial infarction, and cardiovascular death stratified by cognitive impairment and oral anticoagulation use.

Figure 1



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increased mortality in the general population and in hospitalized patients with heart failure.[21,25-27] As a result of its influence on survival, it is conceivable that the frail state may have significant impact on the effectiveness of AF treatment modalities. Routine assessment of frailty indices has not been a part of trials of AF treatment, thus limiting their applicability to the very elderly and frail AF patients. The role of such assessment in guiding AF therapy should be the explored in future prospective studies.

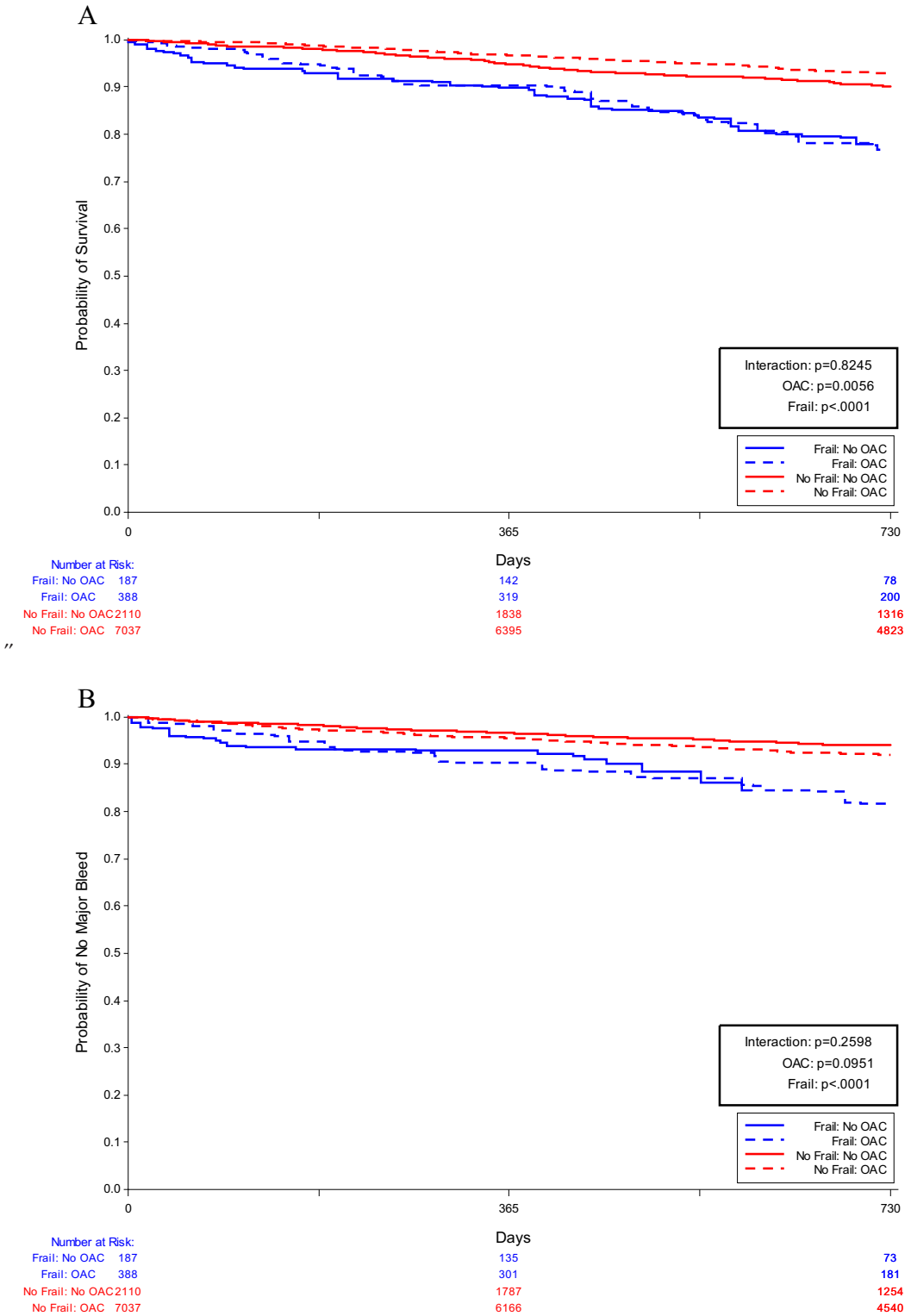
Despite a high risk of stroke as reflected by the higher CHA_2DS_2-VASc risk score, frail patients were less likely to be on OAC. We have previously reported that frailty and risk of falls are important determinants of failure to start OAC or discontinuation of OAC in the ORBIT-AF registry.[11,12] Time in therapeutic range on warfarin at baseline was also lower in frail AF patients in the ORBIT-AF registry, indicating poor efficacy of anticoagulation.[7] Prior smaller studies of the relationship between frailty and lower OAC use are largely consistent with our findings,[10,28,29] with the exception of Nyugen et al who reported no such relationship.[30] It is notable that the rate of anticoagulation in the overall cohort (76%) and in frail individuals (68%) in ORBIT-AF were higher than previously reported in other cohorts.[29,31]

Bertozzo et al reported that physician-perceived frailty or low life expectancy accounted for 46% of warfarin discontinuation in AF patients over the age of 80 years. They also noted a high rate of death, bleeding and stroke after stopping warfarin in frail patients.[32] Whether frailty influences outcomes of anticoagulation in AF enough to warrant withholding of this therapy was previously not known. We present contemporary, nationwide data from community practice on the impact of frailty on the safety and efficacy of OAC in AF. The observed associations between OAC therapy and outcomes were similar between frail and non-frail patients. It is also notable that frailty was not associated with an increased risk of major hemorrhage. These data suggest that frailty should not be a contraindication to OAC prescription in this population. Similarly, Pilotto et al reported lower mortality in anticoagulated AF patients regardless of functional condition and frailty.[29]

Limitations

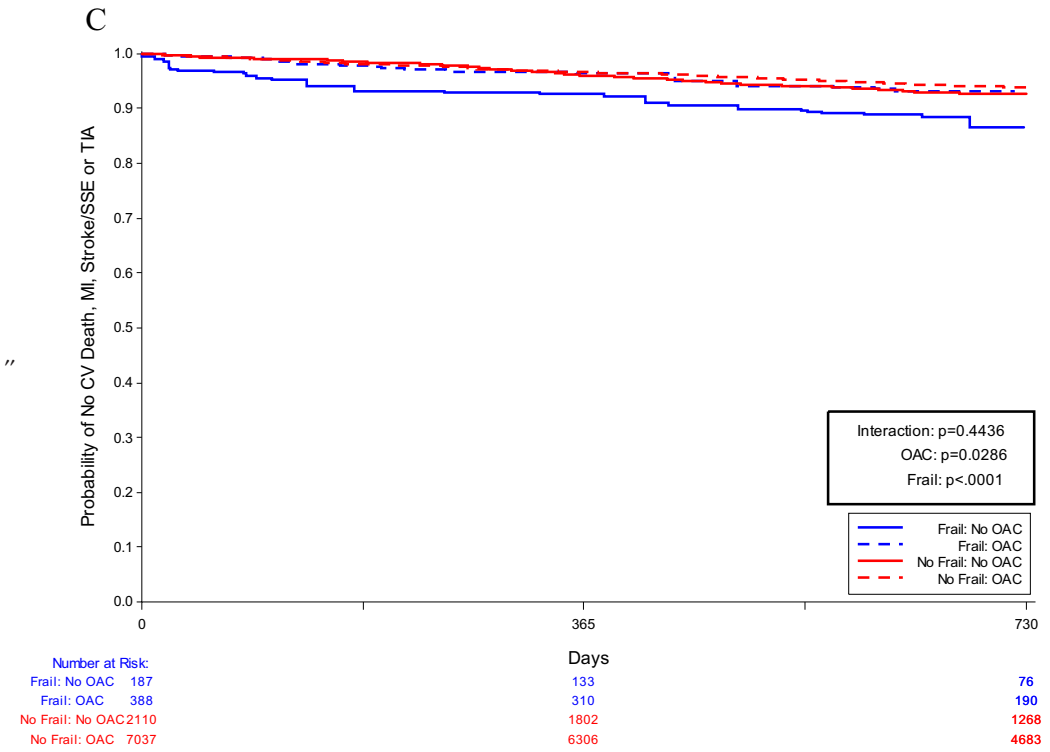
This study has several strengths. It presents real world experience in a large AF cohort and included a significant proportion of patients over the age of 75 years, a population that is underrepresented in randomized clinical trials. However, these data are from an observational study subject to confounding by indication, i.e. individuals prescribed OAC may be inherently different from those not prescribed OAC. Several potential confounders were adjusted for in the analysis, but the influence of unrecognized confounders

Figure 2



Survival free of outcome event in AF patients stratified by frailty status and oral anticoagulation use after adjustment for confounders.A, Survival in patients with atrial fibrillation stratified by frailty status and oral anticoagulation. B, Survival free of major hemorrhage stratified by frailty status and oral anticoagulation. C, Survival free of composite end point of stroke/TIA/non-CNS systemic embolism, myocardial infarction, and cardiovascular death stratified by frailty status and oral anticoagulation.

Figure 2



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cannot be ruled out. Hence these findings should be confirmed in future prospective studies.

The numbers of patients who are frail or with cognitive impairment are small so interpretation should be made in light of this limitation. The prevalence of cognitive impairment in this study is comparable to that of some studies,[33] but lower than that reported in others.[34] The prevalence is influenced by the diagnostic tests used as well as the characteristics of the cohort. The observed lower prevalence in this study may be related to the fact that systematic neurocognitive testing of all patients was not performed and cognitive impairment is frequently under-diagnosed in the community setting.[35,36] Moreover, the diagnosis of cognitive impairment by the treating physician could not be validated in the registry. The reported incidence of frailty in AF is also highly variable and is heavily influenced by the diagnostic test used, thus limiting direct comparisons between studies.[10,28,30] We used the criteria recommended by the American Geriatric Society, which include validated low cost tools, thus improving the reproducibility of these results and applicability to clinical practice. AF patients with severe cognitive impairment or severe frailty or other co-morbidities who were unable to report for follow-up visits may have been excluded from the study, thus underestimating the prevalence. Hence, these results may not be generalizable to groups of patients with greater severity of frailty or cognitive impairment, more co-morbidities or higher bleeding risk than noted in the registry. Moreover, the median HAS-BLED score was 2 and the findings may not be generalizable to subsets of AF patients with higher risk of bleeding. Longitudinal assessment for development of new diagnosis of cognitive impairment and frailty during follow-up was not performed. The median follow-up was 931 days and longer term trends in outcomes need further assessment.

At study enrollment, dabigatran was used by 5% of patients in the analysis population and was the only direct oral anticoagulant (DOAC) available. During the course of the ORBIT AF registry, additional DOACs became available, but use was still limited (9%-16%) across follow-up visits. Thus, the data presented are applicable only to warfarin treated patients, limiting its applicability to AF patients treated with DOAC.

Conclusions

In a multicenter cohort of AF patients, cognitive impairment and frailty patients were less likely to receive anticoagulation. Both conditions were associated with increased risk of mortality, but not stroke/TIA or major hemorrhage. Both conditions also did not appear to modify the association between oral anticoagulation and outcomes such as mortality, major bleeding and MACNE. Hence the

presence of cognitive impairment or frailty does not appear to be a contraindication to anticoagulation in AF patients.

Disclosures

M Madhavan: Consultant to Convatec. D Holmes: None. JP Piccini: ARCA biopharma, Boston Scientific, GE Healthcare, and Johnson & Johnson/Janssen Scientific Affairs and consultancies to Forest Laboratories, Janssen Scientific Affairs, Pfizer/ Bristol Myers Squibb, Spectranetics, and Medtronic. JE Ansell: Consultant activities and honoraria from: Bristol Myers Squibb, Pfizer, Daiichi Sankyo, Berhenger Ingelheim, Janssen, Instrumentation Laboratories, Perosphere Inc, Equity interest: Perosphere, Inc. GC Fonarow: consultant to Janssen. EM Hylek: honoraria, modest: Boehringer-Ingelheim, Bayer, and consultant/advisory board, modest: Daiichi Sankyo, Ortho-McNeil-Janssen, Johnson & Johnson, Boehringer-Ingelheim, Bristol-Myers Squibb. PR Kowey: Consultant J&J, Daiich-Sankyo, Bristol Myers Squibb, BI. KW Mahaffey: financial disclosures can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. L Thomas: Participation in research with Novartis, Boston Scientific, Gilead Sciences, Inc, Janssen Scientific. ED Peterson: Research support from Eli Lilly & Company and Janssen. BJ Gersh: modest DSMB/Advisory Board support from Medtronic, Baxter Healthcare Corporation, InspireMD, Cardiovascular Research Foundation, PPD Development, LP, Boston Scientific, and St. Jude.

Appendix A

Appendix Table A. Candidate variable list for factors associated with cognitive impairment/dementia at baseline and frailty at baseline.

Demographics
1. Age, years
2. Race – African American/Hispanic/White/Others
3. Gender – Male/Female
4. Level of Education – Some School/High School Graduate/College Graduate/Post Graduate

Medical History
1. Diabetes – Yes/No
2. Anemia – Yes/No
3. Frailty – Yes/No (in CI model only)
4. Cognitive Impairment/Dementia (in Frailty model only)
5. COPD – Yes/No

Cardiovascular History
1. Peripheral Vascular Disease – Yes/No
2. Sinus Node Dysfunction/Sick Sinus Syndrome – Yes/No
3. Stroke or TIA – Yes/No
4. Hemorrhagic stroke – Yes/No
5. Congestive Heart Failure (CHF) – No CHF/NYHA Class I/NYHA Class II/NYHA Class III or NYHA Class IV
6. Significant Valvular Disease – Yes/No

Coronary Artery Disease History
1. Prior MI – Yes/No

Vital Signs and AF status
1. Body Mass Index, kg/m^2
2. Electrocardiographic evidence of LVH – Yes/No/Unknown-ventricularly paced

(continued on next page)

Laboratory Data
1. eGFR (MDRD), mg/dL
2. Hemoglobin, g/dL

Atrial Fibrillation Diagnosis
1. Time from AF diagnosis >12 months – Yes/No

Current Medications
1. Oral anticoagulation (OAC) – Yes/No
2. Beta blocker – Yes/No
3. Digoxin – Yes/No
4. Any antiarrhythmic use – Yes/No

Appendix Table B. Adjustment list for outcome models

Demographics
1. Age, years
2. Race – African American/Hispanic/White/Others
3. Gender – Male/Female
4. Level of Education – Some School/High School Graduate/College Graduate/Post Graduate
5. Payor/Insurance – Medicare or Medicaid/private/Others

Medical History
1. Smoking – Current/Recent or Former/Non-smoker
2. Cancer – Yes/No
3. Hypertension – Yes/No
4. Osteoporosis – Yes/No
5. Diabetes – Yes/No
6. Hypothyroidism – Yes/No
7. GI Bleed – Yes/No
8. Obstructive Sleep Apnea – Yes/No
9. Hyperlipidemia – Yes/No
10. Anemia – Yes/No
11. Cognitive Impairment/Dementia – Yes/No
12. Frailty – Yes/No
13. COPD – Yes/No

Cardiovascular History
1. Peripheral Vascular Disease – Yes/No
2. Stroke or TIA – Yes/No
3. Congestive Heart Failure (CHF) – No CHF/NYHA Class I/NYHA Class II/NYHA Class III or NYHA Class IV
4. Significant Valvular Disease – Yes/No

Coronary Artery Disease History
1. History of Coronary Artery Disease – Yes/No

Vital Signs and AF status
1. Height, cm
2. Heart Rate, bpm
3. Diastolic Blood Pressure, mmHg
4. Systolic Blood Pressure, mmHg
5. Body Mass Index, kg/m^2
6. Intraventricular Conduction – RBBB/LBBB/Non-specific IVCD or Unknown-Ventricularly Paced/none

Echocardiographic Assessment (TTE or TEE)
1. LAD Type – Normal/Mild enlargement/Moderate enlargement/Severe enlargement

Laboratory Data
1. eGFR (MDRD), mg/dL
2. Hematocrit, %

Atrial Fibrillation Diagnosis
1. Type of AF – First Detected or New Onset/Paroxysmal AF/Persistent AF /Permanent AF
2. AF management strategy – Rate Control/Rhythm Control
3. Prior Cardioversions – Yes/No
4. Catheter Ablation of AF – Yes/No
5. AV Node or HIS Bundle Ablation – Yes/No

Functional Status
1. Functional Status – Living independently/Living with assistance or Resides in assisted living facility or Resides in skilled nursing home or Bedbound

Appendix Table C. Adjustment list for OAC propensity model

Demographics
1. Age, years
2. Race – African American/Hispanic/White/Others
3. Gender – Male/Female
4. Level of Education – Some School/High School Graduate/College Graduate/Post Graduate
5. Payor/Insurance – Medicare or Medicaid/private/Others

Medical History
1. Smoking – Current/Recent or Former/Non-smoker
2. Cancer – Yes/No
3. Hypertension – Yes/No
4. Osteoporosis – Yes/No
5. Diabetes – Yes/No
6. Hyperthyroidism – Yes/No
7. Hypothyroidism – Yes/No
8. GI Bleed – Yes/No
9. Obstructive Sleep Apnea – Yes/No
10. Dialysis – Yes/No
11. Hyperlipidemia – Yes/No
12. Anemia – Yes/No
13. Cognitive Impairment/Dementia – Yes/No
14. Frailty – Yes/No
15. COPD – Yes/No
16. Alcohol Abuse – Yes/No

Cardiovascular History
1. Peripheral Vascular Disease – Yes/No
2. Sinus Node Dysfunction/Sick Sinus Syndrome – Yes/No
3. Stroke or TIA – Yes/No
4. Congestive Heart Failure (CHF) – No CHF/NYHA Class I/NYHA Class II/NYHA Class III or NYHA Class IV
5. Significant Valvular Disease – Yes/No

Coronary Artery Disease History
1. History of Coronary Artery Disease – Yes/No

Vital Signs and AF status
1. Height, cm
2. Heart Rate, bpm
3. Diastolic Blood Pressure, mmHg
4. Systolic Blood Pressure, mmHg
5. Body Mass Index, kg/m^2
6. Intraventricular Conduction – RBBB/LBBB/Non-specific IVCD or Unknown-Ventricularly Paced/none

Echocardiographic Assessment (TTE or TEE)
1. LVEF – Normal (≥50%)/Mild dysfunction (>40%, <50%)/Moderate dysfunction (≥30%, ≤40%)/Severe dysfunction (<30%)
2. LAD Type – Normal/Mild enlargement/Moderate enlargement/Severe enlargement

Laboratory Data
1. eGFR (MDRD), mg/dL
2. Hematocrit, %

Atrial Fibrillation Diagnosis
1. Type of AF – First Detected or New Onset/Paroxysmal AF/Persistent AF /Permanent AF
2. AF management strategy – Rate Control/Rhythm Control
3. Prior Cardioversions – Yes/No
4. Prior antiarrhythmic drug – Yes/No
5. Catheter Ablation of AF – Yes/No
6. AV Node or HIS Bundle Ablation – Yes/No
7. Surgical/hybrid maze – Yes/No

Functional Status
1. Functional Status – Living independently/Living with assistance or Resides in assisted living facility or Resides in skilled nursing home or Bedbound

Current Medications
1. Contraindication to oral anticoagulation – Yes/No
2. Antiplatelet therapy (aspirin, clopidogrel, prasugrel, ticagrelor or aggrenox – Yes/No

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