IJC Heart & Vasculature 33 (2021) 100739

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Prognostic value of geriatric conditions for death and bleeding in older patients with atrial fibrillation

Weijia Wang [a,*,1], Darleen Lessard [b], Jane S. Saczynski [c], Robert J. Goldberg [b], Jordy Mehawej [b], Ely Gracia [a], David D. McManus [a,b]

[a] Cardiology Division, Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA
[b] Department of Population and Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, USA
[c] Department of Pharmacy and Health System Sciences, Northeastern University, Boston, MA, USA

ARTICLE INFO

Article history:
Received 23 July 2020
Received in revised form 20 January 2021
Accepted 8 February 2021

Keywords:
Atrial fibrillation
Social isolation
Frailty
Depression
Bleeding

ABSTRACT

Background: Geriatric conditions, such as frailty and cognitive impairment, are prevalent in older patients with atrial fibrillation (AF). We examined the prognostic value of geriatric conditions for predicting 1-year mortality and bleeding events in these patients.

Methods: SAGE (Systematic Assessment of Geriatric Elements)-AF study is a multicenter cohort study which enrolled individuals (mean age 75 years, 48% women, 86% taking oral anticoagulation) 65 years and older with AF and CHA_2DS_2 -VASc score of 2 or higher from clinics in Massachusetts and Georgia, USA between 2016 and 2018. A six-component geriatric assessment included validated measures of frailty, cognitive function, social support, depressive symptoms, vision, and hearing was performed at baseline. Study endpoints included all-cause mortality and clinically relevant bleeding.

Results: At 1 year, 1,097 (96.5%) individuals attended the follow up visit, 44 (3.9%) had died, and 56 (5.1%) had clinically relevant bleeding. After adjustment for demographic and clinical factors, social isolation (odds ratio [OR] 1.69, 95% confidence interval [CI]: 1.01–2.84), depression (OR 1.94, 95% CI: 1.28–2.95) and frailty (OR 2.55, 95% CI: 1.55–4.19) were significantly associated with the composite endpoint of death or clinically relevant bleeding. After multivariable adjustment, depression (OR 1.79, 95% CI 1.09–2.93) and frailty (OR 2.83, 95% CI 1.55–5.17) were significantly associated with clinically relevant bleeding.

Conclusions: Social isolation, depression, and frailty were prognostic of dying or experiencing clinically relevant bleeding during the coming year in older men and women with AF. Assessing geriatric impairments merits consideration in the care of these patients.

Atrial fibrillation (AF) is prevalent among older men and women and increases their risk for stroke [1]. Oral anticoagulation is the cornerstone of stroke prevention in patients with AF who are at elevated stroke risk [2] although it also increases their risk for bleeding [3]. Physicians are commonly confronted with the dilemma that patients at high stroke risk are also more prone to bleeding.

Physical, sensory, cognitive, and psychosocial impairments are common in older men and women with AF [4]. These conditions include, but are not limited to, frailty, hearing and vision loss, cognitive impairment, depression, and social isolation. Depression has been previously associated with an increased risk for stroke and bleeding in patients with AF who were treated with warfarin [5]. However, there has been no systematic evaluation about the prognostic value of a comprehensive set of geriatric conditions to important clinical outcomes, including total mortality and bleeding, among older individuals with AF.

Using data from the SAGE-AF study of older men and women with AF [4], we examined the association between several systemically measured geriatric conditions and the risk of dying as well as experiencing episodes of bleeding during a one-year follow up.

* Corresponding author at: Cardiology Division, Department of Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA.
E-mail address: Weijia.Wang@umassmemorial.org (W. Wang).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcha.2021.100739
2352-9067/

1. Methods

1.1. Study sample

The details of the SAGE-AF study have been previously described [4,6]. In brief, the inclusion criteria consisted of the following: 1) have an ambulatory visit at one of 4 Central Massachusetts practices (University of Massachusetts Memorial Health Care internal medicine, cardiology, or electrophysiology, Heart Rhythm Associates of Central Massachusetts), 1 practice in Eastern Massachusetts (Boston University cardiology), or 2 practices in Central Georgia (Family Health Center and Georgia Arrhythmia Consultants), 2) AF is present on an electrocardiogram or Holter monitor or is noted in any clinic note or hospital record), 3) be 65 years or older, and 4) have a CHA2DS2VASC [7] risk score $\geq$ 2. Participants were not eligible if they had an absolute contraindication to the receipt of oral anticoagulation, if they had an indication for oral anticoagulation other than AF (i.e., mechanical heart valve), if they could not provide informed consent, if they did not speak English, if they had a planned invasive high bleeding risk procedure, if they were incarcerated, or if they were unwilling or unable to participate in planned follow-up visits. The study enrollment and the assessment of geriatric conditions were independent of the timing of initiating anticoagulation therapy.

The follow-up visit was performed at 1 year after study enrollment. All participants provided informed written consent. Study protocols were approved by the Institutional Review Boards at the University of Massachusetts Medical School, Boston University, and Mercer University.

1.2. Data abstraction

Trained study staff abstracted pertinent patient sociodemographic and clinical data from the medical record including participants' age, sex, race, insurance type, comorbidities relevant to stroke and bleeding risk (i.e.,., diabetes, hypertension, heart failure, anemia, chronic kidney disease), and cardiovascular treatments (i.e., use of anti-platelets). Relevant laboratory data, including serum creatinine, hemoglobin, and international normalized ratio values (over the past 4 weeks), were also abstracted.

1.3. Assessment of geriatric conditions

Validated measures were used to assess the presence of 6 geriatric conditions: frailty, cognitive dysfunction, social support, depressive symptoms, and vision and hearing impairment. Frailty was assessed by the Cardiovascular Health Survey frailty scale [8]. Its components include weight loss/shrinking, exhaustion, low physical activity, slow gait speed, and weakness. Each component receives a point and the scale ranges from 0 to 5 (0: not frail, 1–2: pre-frail, 3 or more: frail). Cognition was assessed by the Montreal Cognitive Assessment Battery (MoCA) [9], a 30-item screening tool validated to detect mild cognitive impairment. Higher scores indicate better cognitive function, with a score < 23 indicating cognitive impairment [10]. Instead of the traditional cutoff of < 26 in MoCA, we chose the cutoff at < 23. The lower cutoff was chosen because it was previously shown to correspond to the cutoff for mild cognitive impairment and dementia (<27) in the most widely used Mini-Mental State Examination (MMSE) score [10] with sensitivity ranging from 71% to 78% and specificity 88% to 96% [11]. The social support available to participants was assessed by a 5-item modified version of the Social Support Scale and the 6-item Social Network Scale [12]. Lower scores indicate less social support and a score of < 12 indicates social isolation. The Patient Health Questionnaire (PHQ-9) was used to assess patient's depressive symptoms [13] with a score $\geq$ 5 indicating high depressive symptoms. Visual and hearing impairment were self-reported and categorized as either impaired or otherwise.

1.4. Assessment of death and bleeding events

For participants who died during the 1-year follow-up, the date of death was collected from the medical record and review of death certificates by an adjudication committee comprised of physicians.

Self-reported episodes of bleeding were obtained from scripted interviews and were graded as either major, clinically relevant non-major, and minor according to the International Society on Thrombosis and Hemostasis scale [14]. Major bleeding included fatal bleeding, symptomatic bleeding in a critical area or organ (e.g., intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), or bleeding that resulted in a fall in hemoglobin of 2 g/dL, leading to transfusion of $\geq$ 2 units of whole blood. Clinically relevant, non-major bleeding included all cases of overt bleeding not meeting our criteria for the presence of major bleeding, but required medical intervention (e.g., macroscopic hematuria), an unscheduled contact (visit or telephone) with a physician, temporary interruption of anticoagulation, pain (e.g., hematoma), or impairment of daily activities (e.g., inability to walk due to a hematoma). Episodes of minor bleeding included all cases of bleeding (e.g., minor bruising, epistaxis) not classified as clinically relevant or major bleeding.

We defined three bleeding outcomes which are progressively more severe and less inclusive. They were: 1) any bleeding, which includes major, clinically relevant non-major, and minor bleeding events; 2) clinically relevant bleeding, which includes major and clinically relevant non-major bleeding events; and 3) major bleeding, which includes only major bleeding events.

To address the issue of competing risk of death and bleeding, we also defined a composite outcome which included death and clinically relevant bleeding.

1.5. Statistical analysis

The sociodemographic and clinical characteristics of study participants were compared according to the presence of any bleeding events and/or mortality using analysis of variance for continuous variables and the $\chi 2$ test for categorical variables.

In the analysis of the composite outcome of death and clinically relevant bleeding, we carried out a logistic regression analysis in which several potentially confounding variables were controlled for. Model 1 controlled for age, sex, race, and education. Model 2 additionally controlled for patient's history of bleeding, heart failure, carotid artery disease, peripheral vascular disease, hypertension, diabetes, anemia, lung disease, renal disease, and the placement of an implantable device. Model 3 further controlled for HASBLED score, systolic blood pressure, anticoagulation use, and antiplatelet use.

The association of geriatric conditions with all-cause mortality and bleeding events was also examined using these outcomes as separate end points by logistic regression analysis. In analyses with death as the outcome, model 1 controlled for age, sex, race, and education. Model 2 additionally adjusted for patient's history of bleeding, heart failure, peripheral vascular disease, hypertension, diabetes, anemia, lung disease, renal disease, implantable device, and anxiety. Because confounders in the analysis with bleeding as the outcome may differ from those in the analysis with death as the outcome, we built different multivariable models for bleeding endpoints: model 1 controlled for age, sex, and race. Model 2 additionally adjusted for education, history of bleeding, and HASBLED score. Model 3 additionally adjusted for systolic blood pressure, anticoagulation use, and antiplatelet use. We additionally

introduced the variable of time in the therapeutic range as a surrogate for quality of anticoagulation control to model 3 among participants on warfarin.

Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

2. Results

2.1. Study population

A total of 1,244 participants completed their baseline examination. At 1 year, 1,097 (96.5%) individuals attended the follow up visit and 44 patients (3.9%) had died since the time of the baseline examination. At the baseline interview, study participants were on average 75.3 (±7.0) years old and 47.9% were women. Physical, cognitive, and psychosocial impairment were relatively common: frailty (13.3%), hearing impairment (35.4%), visual impairment (33.3%), cognitive impairment (40.6%), depressive symptoms (27.4%), and social isolation (13.0%).

Table 1 summarizes the baseline characteristics of the 1,137 individuals according to the composite outcome of death or development of a clinically relevant bleeding episode (major + clinically relevant non-major) at 1 year. Individuals who developed the composite outcome (n = 122, 10.7%) were more likely to be female and frail than participants who did not experience this endpoint. These individuals were also more likely to have a history of major bleeding, heart failure, carotid disease, diabetes, anemia, renal disease, and an implantable cardiac device. They were more likely to have been treated with Plavix and had higher CHADSVASC and HASBLED scores as compared with individuals who did not develop the composite outcome.

2.2. Study end points and follow up

At 1 year, 44 (3.9%) individuals had died. Major bleeding occurred in 25 (2.2%) individuals, clinically relevant non-major bleeding in 56 (4.9%), and minor bleeding in 585 (51.5%). There were 2 (0.2%) bleeding-related deaths.

2.3. Geriatric conditions and composite outcome (death or clinically relevant bleeding)

In examining the prognostic value of geriatric conditions in relation to death or clinically relevant bleeding during the first year of study follow up, a greater risk of the composite outcome was observed in individuals with cognitive impairment (14.5% versus 8.2%), depressive symptoms (15.8% versus 8.8%), frailty (23.2% versus 8.8%), and social isolation (16.2% versus 9.9%) than among those without these conditions. After adjusting for several demographic characteristics and comorbidities of prognostic importance, depression, frailty and social isolation remained significantly associated with all-cause mortality or clinically relevant bleeding (Table 2).

We also examined whether the use of anti-depressants was associated with a worse clinical outcome. There were 200 (17.6%) participants who reported taking anti-depressants. The use of anti-depressants was not associated with the composite endpoint of death or bleeding (p = 0.70).

2.4. Geriatric conditions and all-cause mortality

We next examined the association of the 6 geriatric conditions and all-cause mortality during the first year of study follow up. A greater risk of dying was observed in individuals with cognitive impairment (6.1% versus 2.4%), depressive symptoms (6.4% versus 2.9%), frailty (10.6% versus 2.8%), and social isolation (7.4% versus 3.3%) than among those without these conditions. After adjusting for several demographic characteristics and comorbidities, social isolation remained significantly associated with 1-year mortality (Table 3).

2.5. Geriatric conditions and bleeding

Bleeding outcomes were examined in a systemic manner: clinically relevant bleeding, any bleeding, and major bleeding were assessed separately.

We first examined this association in relation to clinically relevant bleeding events (major + clinically relevant non-major). A significantly higher risk of clinically relevant bleeding was observed in individuals with depressive symptoms (9.9% versus 6.5%) and frailty (13.9% versus 6.4%) than among those without these conditions. After adjusting for a variety of patient demographic, clinical, and treatment characteristics, depressive symptoms and frailty remained significantly associated with an increased risk of a clinically relevant bleeding episode (Table 4).

We also examined any bleeding as the outcome (major + clinically relevant non-major bleeding + minor bleeding). Consistent with our previous finding, depressive symptoms and frailty were significantly associated with the development of any bleeding episode during the following year after adjusting for several potentially confounding variables (Supplementary material: Tables S1).

Lastly, major bleeding was the most severe but least common (2.3%) bleeding outcome. None of the geriatric conditions was significantly associated with major bleeding in the multivariable adjusted regression models (Supplementary material: Tables S2).

Since age may impact the association between various geriatric conditions and clinical outcomes, we performed stratified analyses according to age (<75 years old versus $\geq$ 75 years old). There was no material difference in the association between geriatric conditions and the composite endpoint of clinically relevant bleeding and death by age with the exception of the factor of visual impairment. Specifically, vision impairment was significantly associated with the composite endpoint of clinically relevant bleeding and death in older (>=75 years) participants (adjusted OR 1.93, 95% CI: 1.05–3.55) but not in younger participants (<75 years) (adjusted OR 0.99, 95% CI: 0.50–1.95) (Supplementary material: Tables S3).

Since the quality of anticoagulation can be related to bleeding and death, we additionally introduced the variable of time in the therapeutic range to regression model 3 in Table 2 among participants on warfarin. After controlling for this additional variable, depression (OR 1.48, 95% CI 0.79–2.75), frailty (OR 1.63, 95% CI 0.75–3.57), and social isolation (OR 1.92, 95% CI 0.85–4.34) were no longer significantly associated with the composite endpoint of bleeding and death.

3. Discussion

In a large cohort of older persons with AF, 86% of whom were treated with oral anticoagulants, we systematically measured several physical, cognitive, and psychosocial conditions that are common in older men and women with AF. We showed that depressive symptoms, frailty, and social isolation were associated with an increased risk of dying or experiencing clinically relevant bleeding in older patients with AF during our 1-year follow-up period. When death and bleeding events were examined separately, social isolation was associated with all-cause mortality while depressive symptoms and frailty were associated with the development of clinically relevant bleeding.

Table 1
Characteristics of older adults with atrial fibrillation according to death or clinically relevant bleeding episode within 1 year.

		Overall	Death or clinically relevant bleed		P value
		(n = 1137)	Yes (n = 122)	No (n = 1015)	
Age		75.3 (7.0)	76.2 (7.0)	75.2 (7.0)	0.11
	65–74 years	586 (51.5%)	54 (44.3%)	532 (52.4%)	0.23
	75–84 years	412 (36.2%)	50 (41.0%)	362 (35.7%)	
	>85 years	139 (12.2%)	18 (14.8%)	121 (11.9%)	
Female		545 (47.9%)	45 (36.9%)	500 (49.3%)	<0.01
Non-Hispanic white		976 (85.9%)	99 (81.2%)	877 (86.5%)	0.11
Education	< College graduate	629 (56.1%)	69 (57.0%)	560 (56.0%)	0.83
	>= College	492 (43.9%)	52 (43.0%)	440 (44.0%)	
Site	Massachusetts	892 (78.5%)	87 (71.3%)	805 (79.3%)	0.05
Insurance	Commercial/HMO/PPO	209 (18.4%)	18 (14.8%)	191 (18.8%)	0.44
	Medicare	816 (71.8%)	94 (77.1%)	722 (71.1%)	
	Other	108 (9.5%)	10 (8.2%)	98 (9.7%)	
Frailty	Frail (>= 3 criteria)	151 (13.3%)	35 (28.7%)	116 (11.4%)	<0.001
	Pre-frail (1 or 2 criteria)	602 (53.0%)	67 (54.9%)	535 (52.7%)	
Smoking	Never	538 (47.3%)	53 (43.4%)	485 (47.8%)	0.65
	Ever	567 (50.0%)	65 (53.3%)	502 (49.5%)	
Bleeding history	Major bleeding	212 (18.7%)	39 (32.0%)	173 (17.0%)	<0.001
	Gastrointestinal bleeding	122 (57.6%)	27 (69.2%)	95 (54.9%)	0.1
	Bleeding requiring transfusion	37 (17.6%)	9 (23.7%)	28 (16.3%)	0.29
	Intracranial bleeding	13 (6.2%)	3 (7.9%)	10(5.8%)	0.63
Medical history	Alcohol use	362 (31.8%)	40 (32.8%)	322 (31.7%)	0.81
	Anemia	356 (31.3%)	50 (41.0%)	306 (30.2%)	<0.05
	Carotid disease	122 (10.7%)	21 (17.2%)	101 (10.0%)	<0.05
	Myocardial infarction	217 (19.1%)	25 (20.5%)	192 (18.9%)	0.68
	Dyslipidemia	914 (80.4%)	103 (84.4%)	811 (79.9%)	0.22
	Hypertension	1024 (90.1%)	107 (87.7%)	917 (90.3%)	0.37
	Heart failure	416 (36.6%)	69 (56.6%)	347 (34.2%)	<0.001
	Implanted cardiac device	380 (33.4%)	60 (49.2%)	320 (31.5%)	<0.001
	Lung disease	287 (25.2%)	39 (32.0%)	248 (24.4%)	0.08
	Peripheral vascular disease	161 (14.2%)	20 (16.4%)	141 (13.9%)	0.46
	Renal disease	317 (27.9%)	44 (36.1%)	273 (26.9%)	<0.05
Medical history	Stroke	112 (9.9%)	12 (9.8%)	100 (9.9%)	0.99
	Type 2 diabetes	309 (27.2%)	54 (44.3%)	255 (25.1%)	<0.001
Anti-platelet	Aspirin	400 (35.2%)	49 (40.2%)	351 (34.6%)	0.23
	Clopidogrel	70 (6.2%)	13 (10.7%)	57 (5.6%)	<0.05
Anticoagulant		976 (85.9%)	109 (89.3%)	867 (85.4%)	0.24
Type of Oral anticoagulant*	Direct oral anticoagulant	420 (43.0%)	42 (38.2%)	378 (43.6%)	0.28
	Warfarin	557 (57.0%)	68 (61.8%)	489 (56.4%)	
CHADSVASC		4.4 (1.6)	4.8 (1.7)	4.3 (1.6)	<0.01
HASBLED		3.2 (1.1)	3.4 (1.1)	3.2 (1.1)	<0.05
Creatinine (milligrams per deciliter)		1.1 (0.5)	1.3 (0.9)	1.1 (0.5)	<0.01
Hemoglobin (grams per deciliter)		13.1 (1.8)	12.9 (2.0)	13.2 (1.8)	0.16
Platelet ($\times 10^9$ per liter)		210.2 (71.0)	213.5 (84.5)	209.8 (69.2)	0.63
Time in therapeutic range (in warfarin users)		0.49 (0.42)	0.51 (0.42)	0.49 (0.42)	0.65

Data were presented as n (%) or mean (standard deviation).
*among those on anticoagulants.

Table 2
Associations between geriatric conditions and mortality or clinically relevant bleeding at 1 year among patients with atrial fibrillation.

				Odds ratio			
			Death or clinically relevant bleed	Unadjusted	Model 1	Model 2	Model 3
Cognitive impairment	Yes	462 (40.6%)	67 (14.5%)	1.91 (1.31, 2.79)	1.82 (1.20, 2.77)	1.45 (0.94, 2.24)	1.47 (0.95,2.28)
	No	675 (59.4%)	55 (8.2%)	Reference			
Depression	Yes	311 (27.4%)	49 (15.8%)	1.93 (1.31, 2.85)	2.14 (1.43, 3.18)	1.93 (1.28, 2.93)	1.94 (1.28, 2.95)
	No	826 (72.7%)	73 (8.84%)	Reference			
Frailty	Yes	151 (13.3%)	35 (23.2%)	3.12 (2.01, 4.83)	3.53 (2.21, 5.62)	2.54 (1.55, 4.17)	2.55 (1.55, 4.19)
	No	986 (86.7%)	87 (8.8%)	Reference			
Hearing impairment	Yes	402 (35.4%)	42 (10.5%)	0.96 (0.64, 1.42)	0.84 (0.55, 1.27)	0.85 (0.55, 1.30)	0.84 (0.55, 1.29)
	No	735 (64.6%)	80 (10.9%)	Reference			
Social isolation	Yes	148 (13.0%)	24 (16.2%)	1.76(1.08, 2.86)	1.77 (1.08,2.90)	1.66 (1.00,2.78)	1.69 (1.01,2.84)
	No	989 (87.0%)	98 (9.9%)	Reference			
Vision impairment	Yes	294 (25.9%)	39 (13.3%)	1.40 (0.93, 2.10)	1.40 (0.92,2.13)	1.29 (0.84, 1.99)	1.28 (0.83, 1.98)
	No	843 (74.1%)	83 (9.9%)	Reference			

Model 1 adjusted for age, sex, race, education; Model 2 additionally adjusted for bleeding history, heart failure, carotid artery disease, peripheral arterial disease, hypertension, diabetes, anemia, chronic obstructive lung disease, renal disease and prior implantable cardiac device; Model 3 additionally adjusted for HAS-BLED score, systolic blood pressure, anticoagulation use, and antiplatelet use.

Table 3
Associations between geriatric conditions and 1-year mortality among older adults with atrial fibrillation.

				Odds ratio (95% confidence interval)		
			Death	Unadjusted	Model 1	Model 2
Cognitive impairment	Yes	462 (40.6%)	28 (6.1%)	2.66 (1.42, 4.97)	2.12 (1.05, 4.26)	1.53 (0.74, 3.17)
	No	675 (59.4%)	16 (2.4%)		Reference	
Depression	Yes	311 (27.4%)	20 (6.4%)	2.30 (1.25, 4.22)	2.44 (1.31, 4.57)	1.39 (0.64, 3,02)
	No	826 (72.7%)	24 (2.9%)		Reference	
Frailty	Yes	151 (13.3%)	16 (10.6%)	4.06 (2.14, 7.69)	3.87 (1.96, 7.65)	1.87 (0.89, 3.92)
	No	986 (86.7%)	28 (2.8%)		Reference	
Hearing impairment	Yes	402 (35.4%)	13 (3.2%)	0.76 (0.39, 1.47)	0.59 (0.29, 1.20)	0.60 (0.29, 1.23)
	No	735 (64.6%)	31 (4.2%)		Reference	
Social isolation	Yes	148 (13.0%)	11 (7.4%)	2.33 (1.15, 4.71)	2.24 (1.09, 4.60)	2.57 (1.19, 5.55)
	No	989 (87.0%)	33 (3.3%)		Reference	
Vision impairment	Yes	294 (25.9%)	14 (4.8%)	1.36 (0.71, 2.59)	1.27 (0.65, 2.49)	1.09 (0.54, 2.19)
	No	843 (74.1%)	30 (3.6%)		Reference	

Model 1 adjusted for age, sex, race, and education. Model 2 additionally adjusted for history of bleeding, heart failure, peripheral vascular disease, hypertension, diabetes, anemia, lung disease, renal disease, implantable device, and anxiety.

Table 4
Associations between geriatric conditions and clinically relevant bleeding at 1 year among older adults with atrial fibrillation.

				Odds ratio (95% confidence interval)			
			Clinically relevant bleeding*	Unadjusted	Model 1	Model 2	Model 3
Cognitive impairment	Yes	436 (39.7%)	40 (9.2%)	1.53 (0.97, 2.41)	1.49 (0.91, 2.43)	1.50 (0.90, 2.49)	1.50 (0.90, 2.49)
	No	663 (60.3%)	41 (6.2%)	Reference			
Depression	Yes	294 (26.8%)	29 (9.9%)	1.59 (0.99, 2.55)	1.75 (1.08, 2.84)	1.82 (1.12, 2.98)	1.79 (1.09, 2.93)
	No	805 (73.2%)	52 (6.5%)	Reference			
Frailty	Yes	137 (12.5%)	19 (13.9%)	2.34 (1.35, 4.05)	2. 68 (1.51, 4.75)	2.94 (1.62, 5.35)	2.83 (1.55, 5.17)
	No	962 (87.5%)	62 (6.4%)	Reference			
Hearing impairment	Yes	391 (35.6%)	30 (7.7%)	1.07 (0.67, 1.71)	0.99 (0.61, 1.61)	0.99 (0.61, 1.61)	0.96 (0.59, 1.57)
	No	708 (64.4%)	51 (7.2%)	Reference			
Social isolation	Yes	139 (12.7%)	15 (10.8%)	1.64 (0.91, 2.96)	1.65 (0.91, 3.00)	1.69 (0.92, 3.08)	1.73 (0.94, 3.17)
	No	960 (87.3%)	66 (6.9%)	Reference			
Vision impairment	Yes	284 (25.8%)	27 (9.5%)	1.48 (0.91, 2.40)	1.50 (0.92, 2.45)	1.48 (0.90, 2.42)	1.45 (0.88, 2.38)
	No	815 (74.2%)	54 (6.6%)	Reference			

Model 1 adjusted for age, sex, race; Model 2 additionally adjusted for education, bleeding history, and HASBLED score; Model 3 additionally adjusted for systolic blood pressure, anticoagulation use, and antiplatelet use.
*Clinically relevant bleeding is defined as self-reported major bleeding, bleeding related death, and clinical related non-major bleeding.

To ensure the efficacy and safety of anticoagulation in the management of patients with AF, patient participation including adequate compliance, lifestyle adjustment, and frequent monitoring are required. Impairments in physical, cognitive, and psychosocial domains pose challenges in this regard. However, reports examining their associations with bleeding [5,15] have been sporadic. To our knowledge this is the first evaluation of the association between geriatric conditions to bleeding in a contemporary cohort of older men and women with AF, the majority of whom were anticoagulated with warfarin and direct oral anticoagulants.

Physical, cognitive, and psychosocial impairments as well as AF are common in older individuals. There has been increasing awareness about the prognostic value of these impairments in individuals with AF [4,16]. For example, depression has been associated with an increased risk of dying in patients with coexisting AF and heart failure [17] as well as among patients with AF seen in a primary care setting [18]. More recent studies have shown a greater risk of dying among patients with AF who were frail both in an ambulatory-based AF registry [15] and in patients after undergoing AF ablation [19]. In addition, social isolation has an additive risk on mortality to depression [17] in patients with AF and heart failure. Our findings are in agreement with these previous reports.

We observed that socially isolated individuals had a more than 2-fold higher risk of dying at one year than those who were well supported socially. This association was strengthened after accounting for several comorbidities and patient's socio-demographic characteristics. Social isolation has been previously associated with poor clinical outcomes in patients with acute myocardial infarction [20] and heart failure [21]. This may be partly because patients with better social support are more likely adhere to prescribed medical therapy [22] and embrace lifestyle modifications such as diet change, exercise, and weight loss [23]. Further studies should examine whether various types of interventions (e.g., telephone check-in, lifestyle coaching, and help in transportation for clinic visit) lessen the detrimental effects of social isolation among older patients with AF.

The finding that frail and depressed individuals were more likely to have developed clinically relevant bleeding can facilitate an open and frank discussion about the risks and benefits associated with anticoagulation initiation among older patients with AF. This finding is also consistent with our prior work that depressive symptoms were associated with high perceived anticoagulation burden [16].

More than one-half of individuals in our study developed minor bleeding. This was much higher than the rate of nuisance bleeding (14.8 events per 100 person-years) reported in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry [24]. The discrepancy may be explained by the different ascertainment methods applied. In ORBIT-AF, nuisance bleeding was ascertained from medical records and defined as minor bleeding that did not require medical attention. Our structured questionnaire likely has higher sensitivity in capturing minor bleeding not documented in medical records. Although minor bleeding is an important patient-reported outcome, it should not lead to changes in a patient's anticoagulation plan.

4. Study strengths and limitations

Our study has several strengths. First, we used validated instruments to assess the presence of several geriatric conditions, namely cognition, frailty, social support, and presence of depressive symptoms. Our study population is geographically diverse and contemporary with a balanced prescription of direct oral anticoagulants and warfarin. Also, participants have a high degree of comorbidity, reflecting a 'real-world' population one would expect to see in daily practice and making the results more generalizable. Also, bleeding events were graded according to the International Society on Thrombosis scale [14]. Lastly, mortality was systematically adjudicated from medical records. Several limitations should, however, be kept in mind in the interpretation of our study results. Bleeding events were ascertained from scripted interviews with patients and were not adjudicated from medical records. Therefore, the bleeding events could be subjected to recall bias. We planned to report the adjudicated outcomes in future publications as they become available. Secondly, the study was not an inception cohort and patients with bleeding complication at the beginning of anticoagulation may have been lost, thus the bleeding rate may have been underestimated. Thirdly, quality of anticoagulation control is important and can be related to bleeding and death. In fact, adjusting the time in the therapeutic range attenuated the association between geriatric condition and composite endpoint of bleeding and death. This finding was somewhat expected as the quality of anticoagulation is more likely to be a mediator rather than a confounder of the observed association (geriatric impairment → poor anticoagulation quality → more bleeding and death). Therefore, adjusting for this factor would likely attenuate the association under study. Because this is an observational study, we cannot establish causation and residual confounding by other factors may have affected our study results.

5. Conclusion

Among older patients with AF recruited from the ambulatory setting, social isolation was associated with an increased risk of dying over our one-year follow-up period and clinically relevant bleeding was more common in individuals with depressive symptoms and frailty. Assessing physical, cognitive, and psychosocial limitations in older patients with AF helps identify individuals at high risk for poor clinical outcomes who may require increased surveillance or tailored management. It also facilitates risk and benefit discussions of anticoagulation therapy among older patients with AF.

Acknowledgements

Financial Disclosure: This work was supported by grant R01HL126911 from the National Heart, Lung, and Blood Institute. DDM's time was also supported by grants R01HL137734, R01HL137794, R01HL13660, and R01HL141434, also from the National Heart, Lung and Blood Institute.

Declaration of Competing Interest: DDM has received research grant support from Apple Computer, Bristol-Myers Squibb, Boeringher-Ingelheim, Pfizer, Samsung, Philips Healthcare, Biotronik, has received consultancy fees from Bristol-Myers Squibb, Pfizer, Flexcon, Boston Biomedical Associates, and has inventor equity in Mobile Sense Technologies, Inc. (CT). The remaining authors have no conflicts of interest.

Author Contributions: Weijia Wang affirms that he has listed everyone who contributed significantly to the work. All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscript Submitted to Biomedical Journals. All authors had substantial contributions in conception and design, acquisition of data, or analysis and interpretation of data; in drafting the article of revising it critically for important intellectual content; and in final approval of the version to be published.

Sponsor's role: The sponsor had no role in study concept and design, acquisition of subjects and/or data, collection, analysis, and interpretation of the data, or preparation of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100739.

References

[1] E.J. Benjamin, P.A. Wolf, R.B. D'Agostino, H. Silbershatz, W.B. Kannel, D. Levy, Impact of atrial fibrillation on the risk of death: the Framingham Heart Study, Circulation 98 (10) (1998) 946–952.
[2] A.J. Camm, P. Kirchhof, G.Y.H. Lip, et al., Guidelines for the management of atrial fibrillationThe Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC), Eur. Heart J. 31 (19) (2010) 2369–2429, https://doi.org/10.1093/eurheartj/ehq278.
[3] E.M. Hylek, A.S. Go, Y. Chang, et al., Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation, N. Engl. J. Med. 349 (11) (2003) 1019–1026, https://doi.org/10.1056/NEJMoa022913.
[4] J.S. Saczynski, S.R. Sanghai, C.I. Kiefe, et al., Geriatric elements and oral anticoagulant prescribing in older atrial fibrillation patients: SAGE-AF, J. Am. Geriatr. Soc. (2019), Published online October 1, doi:10.1111/jgs.16178.
[5] C. Baumgartner, D. Fan, M.C. Fang, et al., Anxiety, depression, and adverse clinical outcomes in patients with atrial fibrillation starting warfarin: cardiovascular research network WAVE study, J. Am. Heart. Assoc. 7 (8) (2018), https://doi.org/10.1161/JAHA.117.007814.
[6] D.D. McManus, C. Kiefe, D. Lessard, et al., Geriatric conditions and prescription of vitamin K antagonists vs. direct oral anticoagulants among older patients with atrial fibrillation: SAGE-AF, Front Cardiovasc Med. 6 (2019), https://doi.org/10.3389/fcvm.2019.00155.
[7] G.Y.H. Lip, R. Nieuwlaat, R. Pisters, D.A. Lane, H.J.G.M. Crijns, Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation, Chest 137 (2) (2010) 263–272, https://doi.org/10.1378/chest.09-1584.
[8] L.P. Fried, C.M. Tangen, J. Walston, et al., Frailty in older adults: evidence for a phenotype, J. Gerontol. A Biol. Sci. Med. Sci. 56 (3) (2001) M146–156.
[9] Z.S. Nasreddine, N.A. Phillips, V. Bédirian, et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, J. Am. Geriatr. Soc. 53 (4) (2005) 695–699, https://doi.org/10.1111/j.1532-5415.2005.53221.x.
[10] J.S. Saczynski, S.K. Inouye, J. Guess, et al., The Montreal cognitive assessment: creating a crosswalk with the mini-mental state examination, J. Am. Geriatr. Soc. 63 (11) (2015) 2370–2374, https://doi.org/10.1111/jgs.13710.
[11] A.J. Mitchell, A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment, J. Psychiatr. Res. 43 (4) (2009) 411–431, https://doi.org/10.1016/j.jpsychires.2008.04.014.
[12] C.D. Sherbourne, A.L. Stewart, The MOS social support survey, Soc. Sci. Med. 32 (6) (1991) 705–714.
[13] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (9) (2001) 606–613.
[14] S. Schulman, C. Kearon, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients, J. Thromb. Haemost. 3 (4) (2005) 692–694, https://doi.org/10.1111/j.1538-7836.2005.01204.x.
[15] M. Madhavan, D.N. Holmes, J.P. Piccini, et al., Association of frailty and cognitive impairment with benefits of oral anticoagulation in patients with atrial fibrillation, Am. Heart J. 211 (2019) 77–89, https://doi.org/10.1016/j.ahj.2019.01.005.
[16] W. Wang, J. Saczynski, D. Lessard, et al., Physical, cognitive, and psychosocial conditions in relation to anticoagulation satisfaction among elderly adults with atrial fibrillation: The SAGE-AF study, J. Cardiovasc. Electrophysiol. 30 (11) (2019) 2508–2515, https://doi.org/10.1111/jce.14176.
[17] N. Frasure-Smith, F. Lespérance, M. Habra, et al., Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibrillation and heart failure, Circulation 120 (2) (2009) 134–140, https://doi.org/10.1161/CIRCULATIONAHA.109.851675, 3p following 140.
[18] P. Wändell, A.C. Carlsson, D. Gasevic, L. Wahlström, J. Sundquist, K. Sundquist, Depression or anxiety and all-cause mortality in adults with atrial fibrillation–A cohort study in Swedish primary care, Ann. Med. 48 (1–2) (2016) 59–66, https://doi.org/10.3109/07853890.2015.1132842.
[19] H. Kundi, P.A. Noseworthy, L.R. Valsdottir, et al., Relation of frailty to outcomes after catheter ablation of atrial fibrillation, Am. J. Cardiol. (2020), https://doi.org/10.1016/j.amjcard.2020.01.049.

[20] W. Ruberman, E. Weinblatt, J.D. Goldberg, B.S. Chaudhary, Psychosocial influences on mortality after myocardial infarction, N. Engl. J. Med. 311 (9) (1984) 552–559, https://doi.org/10.1056/NEJM198408303110902.
[21] E. Friedmann, S.A. Thomas, F. Liu, P.G. Morton, D. Chapa, S.S. Gottlieb, Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality, Am. Heart J. 152 (5) (2006) 940.e1–940.e8, https://doi.org/10.1016/j.ahj.2006.05.009.
[22] M.R. DiMatteo, Social support and patient adherence to medical treatment: a meta-analysis, Health Psychol. 23 (2) (2004) 207–218, https://doi.org/10.1037/0278-6133.23.2.207.
[23] M.W. Verheijden, J.C. Bakx, C. van Weel, M.A. Koelen, W.A. van Staveren, Role of social support in lifestyle-focused weight management interventions, Eur. J. Clin. Nutr. 59 (1) (2005) S179–S186, https://doi.org/10.1038/sj.ejcn.1602194.
[24] E.C. O'Brien, D.N. Holmes, L.E. Thomas, et al., Prognostic significance of nuisance bleeding in anticoagulated patients with atrial fibrillation, Circulation 138 (9) (2018) 889–897, https://doi.org/10.1161/CIRCULATIONAHA.117.031354.