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# **Effects of Oral Anticoagulant Therapy in Medical Inpatients $\geq 65$ Years With Atrial Fibrillation**

## **Effects of Oral Anticoagulant Therapy in Medical Inpatients $\geq 65$ Years With Atrial Fibrillation**

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In this retrospective cohort observational study, we investigated mortality, ischemic, and hemorrhagic events in patients  $\geq 65$  years with atrial fibrillation consecutively discharged from an Acute Geriatric Ward in the period 2010 to 2013. Stroke and bleeding risk were evaluated using CHA<sub>2</sub>DS<sub>2</sub>-VASC (congestive heart failure/left ventricular dysfunction, hypertension, aged  $\geq 75$  years, diabetes mellitus, stroke/transient ischemic attack/systemic embolism, vascular disease, aged 65 to 74 years, gender category) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) scores. Comorbidity, cognitive status, and functional autonomy were evaluated using standardized scales. Independent associations among clinical variables, including use of vitamin K antagonist–based oral anticoagulant therapy (OAT), all-cause mortality, and fatal and nonfatal ischemic and hemorrhagic events, were evaluated. Further clinical outcomes comparison between patients treated with OAT and those untreated was performed after adjustment for significant differences in patient baseline characteristics with propensity score matching. Of 980 patients discharged (mean age 83 years, 60% women, roughly 30% cognitively impaired or functionally dependent, mean CHA<sub>2</sub>DS<sub>2</sub>-VASC and HAS-BLED scores 4.8 and 2.1, respectively), 505 (51.5%) died during a mean follow-up period of 571 days; ischemic and hemorrhagic stroke occurred in 82 (12.3%) and 13 patients (1.3%), respectively, and major bleedings in 43 patients (4.4%). Vitamin K antagonists' use was independently associated with reduced mortality (odds ratio 0.524) and with a nonsignificant reduction in incidence of ischemic stroke, without excess in bleeding risk. Similar findings were observed in the 2 propensity score–matched cohorts of patients. In conclusion, among vulnerable patients with atrial fibrillation  $\geq 65$  years with high post-discharge death rate, OAT was associated, among other multiple factors, with reduced mortality.

Incidence and prevalence of atrial fibrillation (AF) increase with advancing age.<sup>1</sup> Although oral anticoagulant therapy (OAT) has been showed to be effective for prevention of cardioembolic stroke in older patients with AF,<sup>2, 3, 4, 5, 6</sup> this therapy is widely underused particularly in the oldest old, who should derive the greatest benefit from anticoagulant therapy.<sup>7, 8, 9, 10, 11</sup> AF in patients aged  $\geq 65$  years is frequently diagnosed during hospital stay, and it has been demonstrated that many of these hospitalized patients might not be optimal candidates for anticoagulant therapy,<sup>7, 11, 12</sup> in reason of older age, poorer health conditions, greater number of co-morbidities, worse functional autonomy, and reduced life expectancy than those enrolled in randomized clinical trials with anticoagulants.<sup>13, 14, 15, 16</sup> Moreover, there is scant evidence of efficacy and safety of OAT in real-world medical in patients aged  $\geq 65$  years with AF.<sup>17</sup> In this retrospective cohort study, we aimed to assess overall mortality and fatal and nonfatal ischemic and hemorrhagic events and their associations with clinical variables, including OAT, in inpatients with AF aged  $\geq 65$  years.

## Methods

Patients  $\geq 65$  years discharged in the period 2010 to 2013 from the Acute Geriatric Ward (AGW) at the Città della Salute e della Scienza-Molinette (a university teaching hospital in Turin, Northern Italy) with a primary or secondary diagnosis of AF (code 427.31 of the *International Classification of Diseases*, Ninth Revision [ICD-9]) were identified from the electronic discharge database. Data were collected by 4 geriatric postgraduate students who reviewed the electronic discharge charts under the supervision of 2 senior geriatricians.

AF was defined paroxysmal, persistent or permanent, according to current international recommendations. Individual stroke and bleeding risk were evaluated according to the CHA<sub>2</sub>DS<sub>2</sub>-VASC (congestive heart failure/left ventricular dysfunction, hypertension, aged  $\geq 75$  years, diabetes mellitus, stroke/transient ischemic attack/systemic embolism, vascular disease, aged 65 to 74 years, gender category)<sup>18</sup> and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly)<sup>19</sup> scores.

Antithrombotic therapy at discharge was recorded according to the following classes: OAT only, single-antiplatelet therapy, double-antiplatelet therapy, combined double or triple anticoagulant-antiplatelet therapy, and "other," mainly represented by low-molecular weight heparin. Since in most of the study period in our country, new direct oral anticoagulants were yet not available through the National Health Service, and in this study, OAT included only vitamin K antagonists (VKAs).

In our AGW, all discharge electronic records include several standardized scales that are part of the Comprehensive Geriatric Assessment. Therefore, indexes of co-morbidity and global physical health (Charlson co-morbidity index),<sup>20</sup> cognitive status (Short Portable

Mental Status Questionnaire [SPMSQ]),<sup>21</sup> and functional autonomy (Activities of Daily Living [ADL]; Instrumental Activities of Daily Living Scale)<sup>22, 23</sup> at discharge were also included for analysis. Patients were defined not to have cognitive impairment with SPMSQ scores 0 to 2 and of 3 to 4, 5 to 7, and  $\geq 8$ , identified mild, moderate, and severe cognitive impairment, respectively. Patients were defined partially or totally dependent in basic daily activities with ADL score of 1 to 2 and  $\geq 3$ , respectively. Patients were defined dependent in instrumental daily activities with an Instrumental Activities of Daily Living Scale score of  $\leq 9$  of 14. For each patient, creatinine and hemoglobin value at discharge were also recorded. Follow-up was conducted in the period September to October 2014 by the same 4 geriatric postgraduate students under the supervision of a senior geriatrician through telephone interview with patients or usual caregivers in patients living at home and through review of medical charts in patients resident in long-term facilities. Death, ischemic and hemorrhagic events, and switch of antithrombotic treatment were investigated. Among patients reporting any hospitalization or suspected clinical event of interest, a thorough review of clinical documentation, medical charts, inpatient hospital discharges, and death certificate was performed by a senior geriatrician. Death and its causes were assessed from death certificates, patients' hospital records, and information from general practitioners or family physicians.

Ischemic and hemorrhagic strokes according to American Heart Association/American Stroke Association definition<sup>24</sup> were recorded. We categorized bleeding events as major and minor events. Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a decrease in hemoglobin level of  $\geq 20$  g/L or leading to transfusion of  $\geq 2$  units of whole-blood or red cells, and/or bleeding causing patient's hospitalization according to current international recommendations.<sup>25</sup>

The study was conducted according to the principles of the Declaration of Helsinki Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001, and according to the Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects.

Absolute and relative frequencies of dichotomous and categorical variables and mean and relative distribution of continuous variables were calculated. Associations between variables and fatal and nonfatal clinical end points (death, ischemic and hemorrhagic stroke, and major extracranial bleedings) were evaluated using ANOVA, chi-square test, and Mann-Whitney test and then using a logistic regression model (forward stepwise method) to evaluate significant independent associations. In addition, a propensity score matching using a 1:1 nearest neighbor–matching algorithm with a  $\pm 0.01$  caliper and no replacement (yielding 201 propensity score–matched observations) was used to evaluate clinical outcomes after adjustment for significant differences in patient baseline characteristics. Matched sample comparisons were performed with McNemar test, paired *t* test, and Wilcoxon test.<sup>26</sup>

## Results

Of the 4,072 admissions from the emergency department, 422 patients (10.4%) died in hospital, yielding a sample of 3,650 patients discharged from AGW. AF was present in 1,078 (29.5%) of these patients, and 98 had incomplete data and were excluded, leaving a sample of 980 patients eligible for analysis (Figure 1).

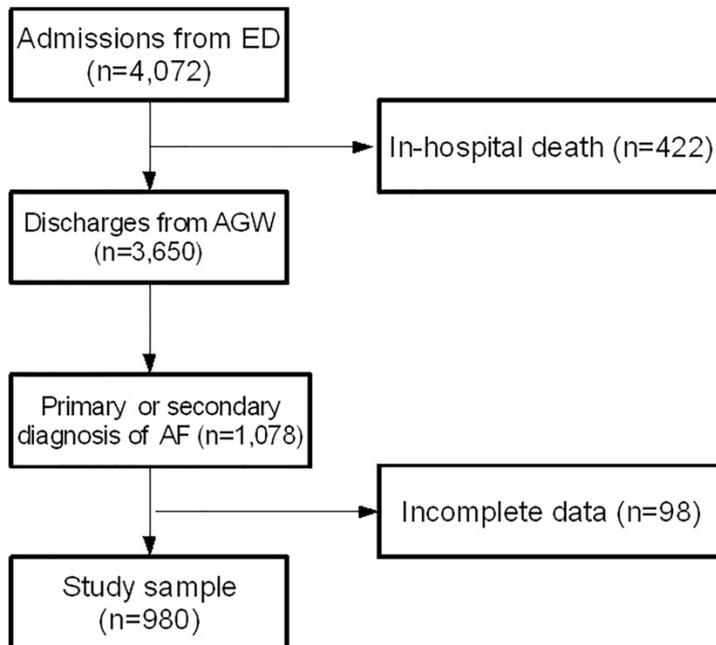


Figure 1. Flow chart of patients enrollment. ED = emergency department.

Table 1 reports main clinical characteristics of patients studied. Mean age was 83 years and 60% were women, most of the patients had known and permanent AF, with mean CHA2DS2-VASC and HAS-BLED scores of 4.8 and 2.1, respectively. Roughly 1/3 of patients had moderate-to-severe cognitive impairment or were functionally dependent in daily activities. Mean Charlson co-morbidity index and daily number of drugs assumed were 7.4 and 8, respectively. OAT at discharge was prescribed in 384 patients (39.1%), whereas 40.3% were discharged with antiplatelet drugs only, and 10% of subjects did not receive any antithrombotic therapy. Prescription of VKAs at discharge was independently associated with younger age, permanent/persistent AF, home versus long-term facility discharge, higher hemoglobin levels and CHA2DS2-VASC score, lower ADL score (better functional autonomy), and greater number of drugs at discharge.

Table 1. Demographic and clinical variables in the total sample of patients studied (980)

Age (years, m±sd)	83.4±6.7
Female gender	593 (60.5%)
Length of stay (median days [25°-75°])	8 (5-12)
CHA <sub>2</sub> DS <sub>2</sub> -VASC (m±sd)	4.8±1.4
HAS-BLED (m±sd)	2.1±0.9
Atrial fibrillation known before admission	810 (82.7%)
Permanent atrial fibrillation	720 (73.5%)
Charlson comorbidity index (m±sd)	7.4±2.1
ADL dependent	263 (26.8%)
IADL dependent	366 (37.3%)
Moderate-severe cognitive impairment	303 (31.0%)
Home-discharge	792 (81.8%)
Intermediate or long-term care discharge	188 (18.2%)
Number of therapeutic drugs at discharge (m±sd)	8.0±2.8
Hemoglobin (g/dl, m±sd)	11.9±2.0
Creatinine (mg/dl, median [25°-75°])	1.06 (0.9-1.4)
<b>Antithrombotic therapy at discharge:</b>	
Oral anticoagulant only	346 (35.3%)
Oral antiplatelet	369 (37.7%)
Double antiplatelet	25 (2.6%)
Low Molecular Weight Heparin	88 (9.0%)
Oral anticoagulant + antiplatelet	38 (3.8%)
None	114 (11.6%)
<b>Antithrombotic therapy at follow-up:</b>	
Oral anticoagulant only	347 (35.4%)
Oral antiplatelet	378 (38.6%)
Double antiplatelet	17 (1.7%)
Low Molecular Weight Heparin	93 (9.5%)
Oral anticoagulant + antiplatelet	31(3.2%)
None	114 (11.6%)

ADL= activities of daily living; CHA<sub>2</sub>DS<sub>2</sub>-VASC = congestive heart failure/left ventricular dysfunction, hypertension, aged ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack/systemic embolism, vascular disease, aged 65-74 years, sex category; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; IADL = instrumental activities of daily living scale.

Outcome clinical events during the period of observation are reported in Table 2. During a mean follow-up period of 571 days, more than half of patients died; main causes of death included pneumonia, sepsis and infections, myocardial infarction, neoplasms, heart failure, respiratory diseases, falls and trauma, dementia, cachexia, and renal failure. Ischemic stroke occurred in 82 patients (12.3%), and it was fatal in 40 of them. Hemorrhagic stroke occurred in 13 patients, and it was fatal in 11 of them. Major extracranial bleedings occurred in 43 patients, and 2 of them were fatal; minor extracranial bleeding events occurred in 44 patients. All-cause and ischemic stroke–related deaths occurred in 36.5% and 2.9% of patients treated with VKAs and in 61.2% and 4.9% of patients not receiving OAT. At the time of follow-up interview or of clinical events, 378 of 384 patients were still following the anticoagulant therapy prescribed at discharge.

Table 2. Outcome events at follow-up in the total sample of patients studied, and according to the prescription of oral anticoagulant therapy at discharge

Clinical events	Overall sample	Oral anticoagulants	
		YES	NO
Follow-up (days, m±sd)	571±446.3		
All-cause hospitalization, median (25°-75°)	1 (0.0-2.0)	1 (0-2)	1 (0-1)
Ischemic stroke	82 (8.4%)	22 (6.8%)	60 (10.1%)
Hemorrhagic stroke	13 (1.3%)	6 (1.6%)	7 (1.3%)
Ischemic events, other sites	43 (4.4%)	15 (3.9%)	28 (4.7%)
Major extracranial hemorrhagic events	43 (4.4%)	18 (4.7%)	25 (4.2%)
Minor extracranial hemorrhagic events	44 (4.5%)	18 (4.7%)	26 (4.4%)
Overall ischemic events	125 (12.8%)	41 (8.4%)	88 (14.8%)
Overall hemorrhagic events	100 (10.2%)	41 (10.7%)	59 (9.9%)
<b>Fatal clinical events</b>			
Fatal ischemic stroke	40 (4.1%)	11 (2.9%)	29 (4.9%)
Fatal hemorrhagic stroke	11 (1.1%)	4 (1.0%)	7 (1.2%)
Fatal ischemic events, other sites	15 (1.5%)	5 (1.3%)	10 (1.8%)
Fatal extracranial hemorrhagic events	2 (0.2%)	0	2 (0.3%)
Overall mortality	505 (51.5%)	140 (36.5%)	365 (61.2%)

Several clinical variables were found to be associated with mortality and ischemic/hemorrhagic events at univariate analysis. After multivariate analysis, increasing age, co-morbidity index and creatinine levels, functional dependence, and discharge-to-intermediate or long-term facilities were independently associated with overall mortality,

whereas use of VKAs was independently associated with reduced mortality rate (Table 3). History of dementia, increasing CHAD2S2-VASC score, and hemoglobin levels were independently associated with incidence of ischemic stroke, whereas no independent associations were found between hemorrhagic stroke and clinical variables investigated. Table 4 lists baseline clinical variables and outcome events before and after propensity score matching on 201 propensity score–matched observations, confirming significantly reduced overall mortality in patients treated with OAT.

Table 3. Clinical variables associated with overall mortality and non-fatal events: results of multivariate analysis

	<b>p Value</b>	<b>OR (95% CI)</b>
<b>Mortality</b>		
Intermediate or long-term care facility discharge	.0003	2.29 (1.47 - 3.57)
Creatinine	.0137	1.37 (1.07 - 1.75)
Charlson comorbidity index	.000	1.19 (1.11 - 1.28)
Anticoagulant therapy at discharge	.0000	0.52 (0.39 – 0.71)
Functional dependence in ADL	.0020	1.60 (1.19 – 2.16)
Age	.0000	1.07 (1.04 – 1.09)
<b>Ischemic stroke</b>		
CHAD2S2VASC	.0040	1.27 (1.08 - 1.49)
Hemoglobin level	.0016	1.20 (1.07 – 1.35)
Dementia	.0007	2.43 (1.46 – 4.05)
Hemorrhagic stroke	-	-
<b>Major Bleeding events</b>		
Female gender	.0163	0.45 (0.24 – 0.86)
Known atrial fibrillation	.0036	0.34 (0.16 – 0.70)
Permanent atrial fibrillation	.0407	1.73 (1.02 - 2.93)
HAS-BLED	.0053	1.35 (1.09 – 1.66)
Hemoglobin level	.0255	0.83 (0.17 – 4.14)
Re-hospitalizations	.0050	1.15 (1.04 – 1.28)

ADL= activities of daily living; CHA<sub>2</sub>DS<sub>2</sub>-VASC = congestive heart failure/left ventricular dysfunction, hypertension, aged ≥75 years, diabetes mellitus, stroke/transient ischemic attack/systemic embolism, vascular disease, aged 65-74 years, sex category; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly.

Table 4. Baseline characteristics and outcome clinical events of the cohorts, before and after propensity score matching by treatment group

Baseline clinical variables	Before propensity score matching			After propensity score matching		
	Oral Anticoagulant Therapy		p Value	Oral Anticoagulant Therapy		p Value
	YES (n=384)	NO (n=596)		YES (n=201)	NO (n=201)	
Age ( years)	81.8± 6.1	84.7±6.8	0.000	83.7±5.8	83.6±6.7	0.943
Female gender	230 (59.9%)	363 (60.9%)	0.753	117 (58.2%)	114 (56.7%)	0.267
Length of stay (mg/dl, median [25°-75°])	7 (4-12)	8 (5-13)	0.162	8 (5-14)	8 (5-12)	0.128
ADL dependent	165 (42.9%)	384 (64.4%)	0.000	114 (56.7%)	114 (56.7%)	0.999
IADL dependent	238 (52.0%)	455 (76.4%)	0.000	146 (72.6%)	146 (72.6%)	0.999
Moderate-severe cognitive impairment	179 (46.6%)	117 (19.6%)	0.000	111 (55.2%)	114 (56.7%)	0.852
Charlson comorbidity index (m±sd)	7.0±2.0	7.6± 2.2	0.000	7.3±2.0	7.3±2.3	0.774
CHA <sub>2</sub> DS <sub>2</sub> -VASc (m±sd)	4.9±1.3	4.7±1.4	0.252	4.9±1.3	4.7±1.4	0.257
HAS-BLED (m±sd)	2.0 (1-2)	2.0 (2-3)	0.000	2.0 (1-3)	2.0 (1-3)	0.306
Hemoglobin (g/dl, m±sd)	12.3±1.9	11.7±2.1	0.000	12.0±1.9	12.0±2.0	0.849
Creatinine (mg/dl, median [25°-75°])	1.02 (0.88-1.41)	1.1 (0.9-1.5)	0.000	1.1 (0.87-1.42)	1.1 (0.9-1.57)	0.262
Home-discharge	349 (90.9%)	444 (74.5%)	0.001	172 (85.6%)	169 (84.1%)	0.771
Permanent atrial fibrillation	319 (83.1%)	401 (67.3%)	0.001	147 (73.1%)	144 (71.6%)	0.822
<b>Clinical outcomes</b>						
Overall mortality	140 (36.5%)	365 (61.2%)	0.000	90 (44.8%)	120 (59.7%)	0.008
Ischemic stroke	22 (6.8%)	60 (10.1%)	0.075	17 (8.5%)	19 (9.5%)	0.864
Hemorrhagic stroke	6 (1.6%)	7 (1.3%)	0.776	3 (1.5%)	1 (0.5%)	0.625
Major extracranial hemorrhagic events	18 (4.7%)	25 (4.2%)	0.861	11 (5.5%)	8 (4.0%)	0.629

ADL= activities of daily Living; CHA<sub>2</sub>DS<sub>2</sub>-VASC = congestive heart failure/left ventricular dysfunction, hypertension, aged ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack/systemic embolism, vascular disease, aged 65-74 years, sex category; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; IADL, instrumental activities of daily living scale.

## Discussion

Within the intrinsic limitations of a retrospective cohort study, we assessed safety and efficacy of VKA-based OAT in frail co-morbid patients aged  $\geq 65$  years with AF. Despite the high post-discharge overall death rate observed, use of VKAs was associated with reduced overall mortality and no significant excess in bleeding events, although we were not able to detect a significant reduction in incidence of ischemic stroke. In keeping with a very recent study on AF outpatients aged  $\geq 85$  years,<sup>27</sup> our findings demonstrated that the use of VKAs was associated with significant lower mortality in the entire study population and in the smaller propensity-matched cohort. Although the rate of embolic events appeared affected by the use of VKAs in the total population, use of VKAs did not prove to be an independent predictor of reduced embolic events by statistical analysis of the whole cohort or in the smaller propensity-matched groups, probably because of the few cases of stroke during the short period of observation. However, the magnitude of reduction observed in incidence of ischemic stroke in patients treated with VKAs compared with untreated patients is in keeping with previous studies.<sup>2, 3, 4, 5</sup> Moreover, incidence of fatal ischemic strokes was also roughly halved in patients treated with VKAs. Finally, also the incidence of major bleeding in VKA-treated patients is quite similar to the bleeding rates reported in a recent national survey on anticoagulated elderly patients.<sup>28</sup>

As a whole, these findings provide encouraging evidence of potential clinical benefit of OAT also in co-morbid and vulnerable patients  $\geq 65$  years with AF. The population we studied is important for several reasons, including the high AF prevalence, the high post-discharge mortality, the under-representation of such patients in previous trials of OAT for AF, the common reluctance to prescribe OAT, and the scant evidence of benefit of anticoagulation in such elderly frail patients. In our view, present findings have clinical implications, potentially contributing to reduce physicians' reluctance to prescribe anticoagulants in these patients.

Some limitations of this study must be addressed. The main weakness is clearly the potential for selection bias, which is inherent to the retrospective and observational nature of the cohort studied. Compared with patients not treated with oral anticoagulants, those discharged with VKAs are younger and have better functional and health status, conditions that are known to correlate with better survival. To mitigate this potential bias, we did not use a conventional analysis based on a comparison of outcomes between oral anticoagulant-treated and untreated patients, but 2 different statistical approaches: first, we evaluated which clinical variables independently associated with fatal and nonfatal clinical end points (mortality and ischemic/hemorrhagic events); second, we used a propensity score matching to disentangle the effect of anticoagulation from the other variables. However, despite these precautions and the comprehensive geriatric assessment, multivariable analysis and propensity score matching might not account for other unknown or unmeasured influential variables. Further prospective studies and, whether

feasible, randomized trials including older and vulnerable patients are needed to confirm these findings. Moreover, the multidimensional assessment gathered evidence of survival benefit with the use of VKAs in the presence of a well-known set of variables associated with increased death rates in older patients (age, co-morbidities, functional dependence, high serum creatinine levels, and facility discharge)<sup>13</sup> reinforces the reliability of our findings and attenuates the selection bias because of the higher use of VKAs in “healthier” patients. Second, present findings originate from patients admitted to a single acute geriatric unit of a large teaching hospital in Northern Italy. As previous studies demonstrated a close similarity of patients admitted to the geriatric unit with those admitted to acute medical wards of the same hospital,<sup>11, 14, 29</sup> it is likely that these findings may be wisely generalized to inpatients aged  $\geq 65$  years in different hospital medical settings. Moreover, recent observational studies reported very similar clinical findings and high post-discharge death rates in medical inpatients  $\geq 65$  years.<sup>30</sup> As in other retrospective studies, despite most of the patients were still on prescribed anticoagulant treatment at the follow-up interview or at the censored event, we could not evaluate therapeutic adherence and time in therapeutic range in patients receiving warfarin. However, in our view, this limitation does not diminish the external validity of present findings, which aim to represent the effect of OAT in older real-world patients rather than in the more comfortable setting of randomized trial with strictly monitored patients. Finally, as stated, direct oral anticoagulants were not available in our country until 2013; therefore, our findings refer to use of VKAs that, by the way, are at the moment the most prescribed anticoagulant drugs in patients with AF.<sup>15, 16</sup> Current and future observational studies may provide useful information about efficacy and safety of new direct oral anticoagulants in these frail medical patients  $\geq 65$  years with AF.

## Disclosures

The authors have no conflicts of interest to disclose.

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