Effects of oral anticoagulant therapy in older medical in-patients with atrial fibrillation: a prospective cohort observational study

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Abstract

Background

Uncertainties about efficacy and safety of oral anticoagulant therapy (OAT) among older and frail medical patients with atrial fibrillation (AF) largely contribute to under-prescription of these drugs.

Aims

In this prospective observational cohort study, we investigated mortality, and ischemic and hemorrhagic events, in hospital-discharged older patients with AF.

Methods

Stroke and bleeding risk were evaluated using CHA2DS2-VASC and HAS-BLED scores. Comorbidity, frailty, cognitive and nutritional status and functional autonomy were evaluated using standardized scales. Independent associations between clinical variables, including OAT use, and all-cause mortality, fatal and non-fatal 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.

Results

Of 452 patients included (mean age 81.6 years, 54.9 % women, roughly 30 % cognitively impaired and/or functionally dependent, mean CHA2DS2-VASC and HAS-BLED scores 4.6 and 2.8, respectively), 151 (33.4 %) died during a mean follow-up period of 300.5 days; ischemic and hemorrhagic stroke occurred in 4.0 and 0.4 % of patients, respectively, and major bleedings in 6.2 %.

Discussion

After multivariate analysis, OAT at discharge was associated with lower overall mortality and reduced occurrence of ischemic stroke, the first finding being confirmed in propensity score matched analysis.

Conclusions

Among older vulnerable AF patients with high post discharge death rate, OAT was associated, among other multiple factors, with reduced mortality and lower occurrence of ischemic stroke.

Introduction

Atrial fibrillation (AF) is the most common serious cardiac arrhythmia; both incidence and prevalence of AF increase with advancing age [1, 2]. The most feared consequence of AF is cardio-embolic stroke, carrying an elevated risk of mortality and disability. Although oral anticoagulant drugs have been showed to be effective for prevention of stroke in older patients with AF [3, 4, 5, 6, 7], this therapy is widely underused particularly in the oldest-old. These patients, however, in reason of their high risk of stroke, should derive the greatest benefit from anticoagulant therapy [8, 9, 10, 11]. Advanced age itself, physician's perceived high risk of age-related and fall-related bleeding, and difficulties in monitoring warfarin-based anticoagulant therapy, have been reported among the main factors accounting for under-prescription [9, 10, 11]. Moreover, it has been demonstrated that many hospitalized elderly patients might not be optimal candidates for anticoagulant therapy [8, 12] and that the presence of "geriatric syndromes" is associated with reluctance to prescribe anticoagulant oral drugs [13]. Therefore, despite several studies and meta-analysis suggest that advanced age itself should not prevent prescription of oral anticoagulants in elderly patients, [14, 15, 16, 17], under-prescription of anticoagulants among oldest patients remains a common clinical practice in several contemporary medical settings.

AF in older patients is frequently diagnosed during hospital stay for acute events or exacerbations of chronic diseases. However, elderly in-patients with AF have older age, poorer health and functional status and reduced life-expectancy than patients enrolled in randomized clinical trials [18, 19, 20, 21, 22]. To the best of our knowledge, there is indeed scant evidence of efficacy and safety of anticoagulant therapy in "real-world" older and vulnerable medical in patients with AF [23].

In this prospective cohort study, we aimed to assess overall mortality and fatal and non-fatal ischemic and hemorrhagic events, and their associations with clinical variables including oral anticoagulant therapy, among older AF patients discharged from hospital.

Subjects and methods

The cohort was identified in the period from October 2013 to August 2014 among patients aged ≥65 years with documented history or newly detected AF discharged from the following clinical units: Geriatria e Malattie Metaboliche dell'Osso, Medicina Interna 1U, Medicina Interna 3U, Medicina Interna 4U, Medicina Interna 6, Medicina Interna DEA (A.O.U. Città della Salute e della Scienza, Torino –Molinette), Geriatria (A.O.U. S. Luigi Gonzaga, Orbassano), and Geriatria (A.S.O. S. Croce e Carle, Cuneo). The study was conducted according to the principles of the Declaration of Helsinki Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. Signed informed consent at admission was obtained for all participants and the study was conducted according to the Recommendations Guiding Physicians in Biomedical research Involving Human Subjects.

Data were collected by resident fellows from the section of Geriatrics under the supervision of senior specialists in geriatrics, by means of direct interview and using standardized evaluation protocols. Individual stroke and bleeding risks were evaluated according to the CHA2DS2-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) [24] and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) [25, 26] scores.

Indexes of comorbidity and global physical health (CHARLSON index) [27], cognitive status (SPMSQ, Short Portable Mental Status Questionnaire) [28], and functional autonomy (ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living Scale) [29, 30], at discharge were also included for analysis. Patients were defined not to have cognitive impairment with SPMSQ score 0–2; SPMSQ score of 3–4, 5–7 and ≥8, identified mild, moderate and severe cognitive impairment, respectively. Patients were defined partially or totally dependent in basic daily activities with ADL score of 1–2 and ≥3, respectively. Patients were defined dependent in instrumental daily activities with a IADL score of 9 or less. The risk of depression was evaluated using the Geriatric Depression Scale (GDS) short form [31, 32], with scores ≥7 suggesting the presence of depression. Frailty was evaluated using the Groningen Frailty indicator [33]: scores ≥4 indicate frailty. The risk of malnutrition was evaluated using the Mini Nutritional Assessment (MNA) screening [34], with scores ≤11 suggesting malnutrition. The risk of falls was evaluated through Conley's scale [35], which identifies patients with scores ≥2 at risk of fall events. For each patient height and weight were recorded, and the body mass index (BMI) was calculated; estimated glomerular filtration rate (eGFR) was calculated according to the Cockroft-Gault formula. Date and setting of discharge (home or intermediate-long term care) and antithrombotic therapy at discharge were also recorded.

Follow-up was conducted in the period January–March 2015 through telephone interviews with patients or usual caregivers and through review of medical charts, when available. Death, ischemic and hemorrhagic events, and intervening hospitalizations were investigated. Deaths were assessed from death certificates, patients' hospital records and information from family physicians. Ischemic and hemorrhagic strokes, according to AHA/ASA definition [36], were recorded, as well as other cardiovascular events. Major bleeding was defined according to current international recommendations [37].

Statistical analysis

Absolute and relative frequencies of dichotomous and categorical variables, and either mean and relative distribution or median and 25th–75th percentile of continuous variables were calculated. Descriptive analysis of the sample of patients with AF studied and distribution of the main clinical variables according to prescription of OAT at discharge were performed. The univariate association between variables and death, ischemic and hemorrhagic stroke, and major extra-cranial bleedings was evaluated using Chi-square test. Associations of significant variables from univariate analysis with death, ischemic and hemorrhagic stroke, and major bleedings were then evaluated using a multivariate logistic regression model (forward stepwise method) using SPSSPC+, Spss Inc.

In addition, analysis on clinical outcomes was repeated after adjustment for significant differences in patient baseline characteristics with propensity score matching using a 1:1 nearest-neighbor-

matching algorithm with a ±0.02 caliper and no replacement, yielding 40 propensity score matched observations. In matched sample comparisons were performed with McNemar Test and Chi-square test [38].

Results

Clinical characteristics of the patients studied

During the study period 513 discharged patients with AF and consenting at the study were identified; 61 patients were lost at follow-up or had missing data, leaving a sample of 452 patients for analysis. The main demographic and clinical variables are reported in Table 1. Mean age was 81.6 years, 54.9 % were females. More than half of the cohort had permanent AF (60.0 %), and only 53 patients (11.7 %) had a newly detected AF. Frailty and dependence on IADL were present in 75.4 and 63.7 % of patients, respectively. About one-third of patients was dependent on ADL, and moderate or severe cognitive impairment was present in 29.4 % of patients. Mean CHA2DS2-VASc and HAS-BLED scores were 4.6 ± 1.4 and 2.8 ± 1.0, respectively. OAT was prescribed in 49.8 % of patients (44.7 % oral anticoagulant only, 5.1 % in combination with antiplatelet agents), the vast majority represented by warfarin (85.3 %); 22.6 % of patients were not prescribed any antithrombotic treatment. Variables associated with prescription of OAT at discharge in these patients have been reported in a previous study [12] and included increasing age and CHA2DS2-VASc score, lower HAS-BLED score and burden of comorbidities, and the presence of permanent AF.

Table 1 Demographic and clinical variables of the sample studied (n = 452)

Age, years, m ± sd	81.6 ± 6.6
Age ≥75 years, n (%)	384 (85)
Female, n (%)	248 (54.9)
BMI, kg/m2, m ± sd	25.8 ± 5.4
AF known before admission, n (%)	399 (88.3)
Paroxymal AF, n (%)	137 (30.3)
Persistent AF, n (%)	44 (9.7)
Permanent AF, n (%)	271 (60.0)
CHA2DS2-VASc, m ± sd	4.6 ± 1.4
HAS-BLED, m ± sd	2.8 ± 1.0
HAS-BLED ≥3, n (%)	273 (60.4)

CHARLSON, m ± sd	3.3 ± 2.2
CHARLSON >5, n (%)	79 (17.5)
Bedridden, n (%)	37 (8.2)
Heart failure, n (%)	203 (44.9)
Coronary heart disease, n (%)	121 (26.8)
Peripheral obstructive arteriopathy, n (%)	55 (12.2)
Hypertension, n (%)	340 (75.2)
ADL, m ± sd	1.8 ± 2.2
ADL dependent, n (%)	157 (34.7)
IADL, median (25°–75°)	7 (3–12)
IADL dependent, n (%)	288 (63.7)
SPMSQ, m ± sd	3.2 ± 3.4
Moderate–severe cognitive impairment, n	133 (29.4)
Dementia, n (%)	66 (14.6)
GDS, median (25°–75°)	4 (1–8)
Depression, n (%)	164 (36.3)
Groningen frailty index, median (25°–75°)	7 (4–9)
Frailty, n (%)	341 (75.4)
MNA, m ± sd	8.1 ± 3.4
MNA ≤11, n (%)	352 (77.9)
Conley scale, m ± sd	3.1 ± 2.5
Conley scale ≥2, n (%)	313 (69.2)
eGFR <60 ml/min, n (%)	128 (28.3)
Serum albumin <3 g/dl, n (%)	70 (15.5)
Length of stay, median (25°–75°)	12 (8–19)
Number of drugs at discharge, median (25°–	8 (6–10)
Antithrombotic therapy at discharge	

OAT, n (%)	225 (49.8)
Oral anticoagulant, n (% on OAT)	
Warfarin	192 (85.3)
Dabigatran	19 (8.4)
Rivaroxaban	5 (2.2)
Apixaban	9 (4.0)
Oral anticoagulant only, n (%)	202 (44.7)
Oral antiplatelet only, n (%)	120 (26.5)
Oral anticoagulant + antiplatelet, n (%)	23 (5.1)
Other, n (%)	5 (1.1)
No antithrombotic therapy, n (%)	102 (22.6)

Main outcome clinical events

Table 2 reports fatal and non-fatal clinical events at follow up in the overall sample of patients and according to prescription of OAT at discharge. During a mean follow-up period of 300.5 ± 62.0 days, 151 patients (33.4 %) died. Ischemic stroke occurred in 18 patients (4.0 %), and it was fatal in 6 of them. Hemorrhagic stroke occurred in 2 patients (0.4 %), and it was fatal in 1 of them. Major extra-cranial bleedings occurred in 28 patients (6.2 %) and 7 of them were fatal; minor extra-cranial bleeding events occurred in 35 patients. Compared to patients not receiving anticoagulants, OAT-treated patients had lower mortality, reduced occurrence of ischemic stroke and increased rate of major bleedings. Almost half of the patients were readmitted at least once (49.3 %), most of the times early after discharge (median 3 months).

Table 2 Fatal and non-fatal clinical events of interest at follow-up in the overall sample and according to prescription of OAT at discharge

Clinical events	Overall sample (n = 452)	OAT (n = 225)	No OAT (n = 227)
Overall mortality, n (%)	151 (33.4)	52 (23.1)	99 (43.6)
Fatal Ischemic stroke, n (%)	6 (1.3)	0	6 (2.6)
Fatal Hemorrhagic stroke, n (%)	1 (0.2)	1 (0.4)	0
Fatal Ischemic events, other sites, n (%)	11 (2.4)	5 (2.2)	6 (2.6)
Fatal Extracranial hemorrhagic events, n (%)	7 (1.5)	4 (1.8)	3 (1.3)
Fatal and non-fatal clinical events			
Ischemic stroke, n (%)	18 (4.0)	4 (1.8)	14 (6.2)
Hemorrhagic stroke, n (%)	2 (0.4)	1 (0.4)	1 (0.4)
Ischemic events, other sites, n (%)	21 (4.6)	10 (4.4)	11 (4.8)
Major extracranial hemorrhagic events, n (%)	28 (6.2)	19 (8.4)	9 (4)
Minor extracranial hemorrhagic events, n (%)	35 (7.7)	23 (10.2)	12 (5.3)
Overall ischemic events, n (%)	39 (8.6)	14 (6.2)	25 (11.0)
Overall hemorrhagic events, n (%)	65 (14.4)	43 (19.1)	22 (9.7)
Readmissions, n (%)	223 (49.3)	120 (53.3)	103 (45.4)

OAT oral anticoagulant treatment at discharge

Clinical variables associated with outcome clinical events

At univariate analysis, several clinical variables were found to be associated with mortality and ischemic/hemorrhagic events. Variables significantly associated with fatal and non-fatal clinical events after multivariate analysis are reported in Table 3: beyond dependence on basic activities of daily living, frailty and low serum albumin levels, OAT was associated with a significant reduction of overall mortality and ischemic stroke (relative risk reduction 47 and 75 %, respectively). Both mortality and non-fatal clinical events were associated with increased rate of readmission. Table 4 shows the baseline characteristics and clinical outcomes before and after propensity score matching on 40 propensity score-matched observations, confirming a significant reduction on overall mortality in patients discharged with OAT prescription, regardless of all other significant clinical variables and regardless of association with oral antiplatelet agents.

Table 3 Variables associated with mortality and fatal and non-fatal clinical events: results of multivariate analysis

	β	SE	p	OR
Mortality				
Oral anticoagulant therapy at discharge	−0.6223	0.2281	0.0064	0.5367
ADL ≥2—dependent	0.8625	0.2440	0.0004	2.3691
Groningen ≥4—frailty	1.0194	0.3339	0.0023	2.7716
Serum albumin <3 g/dl	0.7286	0.2936	0.0131	2.0722
Readmission	0.5340	0.2258	0.0180	1.7058
Ischemic stroke				
Oral anticoagulant therapy at discharge	−1.3594	0.6067	0.0250	0.2568
MNA ≤11—at risk of malnutrition	−1.8109	0.5471	0.0009	0.1635
Readmission	1.6421	0.6160	0.0077	5.1658

	β	SE	p	OR
Bedridden	1.9165	0.7256	0.0083	6.7973
Number of falls in the last year	1.4635	0.5572	0.0086	4.3212
Hemorrhagic stroke	–	–	–	–
Major bleeding events				
Readmissions	2.3434	0.6177	0.0001	10.4161
Presence of a caregiver	−0.8652	0.4226	0.0406	0.4210

Table 4

Baseline characteristics and outcome clinical events of the cohorts, before and after propensity score matching by treatment groups (OAT oral anticoagulant treatment at discharge)

	Before propensity score matching			After propensity score matching		
Baseline clinical variables, n (%)	OAT (225)	No OAT (227)	p	OAT (40)	No OAT (40)	p
Age ≥75 years	183 (81.3)	201 (88.5)	0.032	31 (77.5)	33 (82.5)	0.791
Female	125 (55.6)	123 (54.2)	0.77	17 (42.5)	19 (47.5)	0.815
Readmissions	120 (53.3)	103 (45.4)	0.091	18 (45.0)	16 (40.0)	0.824
Number of falls last year ≥1	83 (36.9)	101 (44.5)	0.1	18 (45.0)	20 (50.0)	0.824
Number of drugs ≥5	171 (76.0)	158 (69.6)	0.127	26 (65.0)	27 (67.5)	1.000
Dementia	15 (6.7)	51	0.000	3 (7.5)	8	0.18

	Before propensity score matching			After propensity score matching		
Baseline clinical variables, n (%)	OAT (225)	No OAT (227)	p	OAT (40)	No OAT (40)	p
		(22.5)			(20.0)	
Bedridden	11 (4.9)	26 (11.5)	0.011	3 (7.5)	6 (15.0)	0.508
Heart failure	108 (48.0)	95 (41.9)	0.189	17 (42.5)	15 (37.5)	0.804
Peripheral obstructive arteriopathy	24 (10.7)	31 (13.7)	0.331	5 (12.5)	7 (17.5)	0.727
Hypertension	172 (76.4)	168 (74.0)	0.549	26 (65.0)	25 (62.5)	1.000
Diabetes	74 (32.9)	54 (23.8)	0.032	11 (27.5)	11 (27.5)	1.000
eGFR <60 ml/min	64 (28.4)	64 (28.2)	0.953	8 (20.0)	8 (20.0)	1.000
Serum albumin <3 g/dl	21 (9.3)	49 (21.6)	0.000	8 (20.0)	13 (32.5)	0.267
CHA2DS2-VASc ≥4	179 (79.6)	175 (77.1)	0.525	28 (70.0)	29 (72.5)	1.000
HASBLED ≥3	125 (55.6)	148 (65.2)	0.036	20 (50.0)	19 (47.5)	1.000
CHARLSON index >5	32 (14.2)	47 (20.7)	0.07	9 (22.5)	7 (17.5)	0.791
GDS ≥7—depression	89 (39.6)	75 (33.0)	0.15	15 (37.5)	15 (37.5)	1.000

	Before propensity score matching			After propensity score matching		
Baseline clinical variables, n (%)	OAT (225)	No OAT (227)	p	OAT (40)	No OAT (40)	p
ADL ≥2—dependent	56 (24.9)	101 (44.5)	0.000	10 (25.0)	17 (42.5)	0.144
IADL ≤9—partially or not autonomous	132 (58.7)	156 (68.7)	0.026	8 (20.0)	16 (40.0)	0.057
SPMSQ ≥4—moderate–severe cognitive impairment	50 (22.2)	83 (36.6)	0.001	7 (17.5)	13 (32.5)	0.18
Groningen ≥4—frailty	158 (70.2)	183 (80.6)	0.010	27 (67.5)	31 (77.5)	0.455
MNA ≤11—at risk of malnutrition	166 (73.8)	186 (81.9)	0.037	32 (80.0)	32 (80.0)	1.000
Conley scale ≥2—at risk of falls	147 (65.3)	166 (73.1)	0.073	23 (57.5)	24 (60.0)	1.000
Oral antiplatelet drug	23 (10.2)	120 (52.9)	0.000	14 (35.0)	13 (32.5)	1.000
Clinical outcomes						
Overall mortality	52 (23.1)	99 (43.6)	0.000	7 (17.5)	16 (40.0)	0.049
Ischemic stroke	4 (1.8)	14 (6.2)	0.017	1 (2.5)	3 (7.5)	0.5
Major bleeding events	20 (8.9)	10 (4.4)	0.056	1 (2.5)	0	1.000

Discussion

In older medical in-patients with AF, initiation or continuation of anticoagulant therapy is often a troublesome decision, involving a global evaluation of health and functional status and residual life-expectancy, rather than a simple addition of variables within cardio-embolic and bleeding scales of risk.

Within the intrinsic limitations of a cohort prospective study, we investigated overall mortality and fatal and non-fatal ischemic and hemorrhagic events, and their associations with clinical variables including OAT, among patients with AF. During a mean follow-up period of less than 1 year, one-third of patients died. Despite the high post-discharge overall death rate, use of OATs was significantly associated with reduced overall mortality and lower overall incidence of ischemic stroke, although we were not able to confirm the latter finding in the small subset of 40 propensity score-matched observations.

In this sample, we observed a 6.2 % incidence of ischemic stroke among patients discharged without OAT (most of them receiving antiplatelet therapy): these findings underscore the extremely high age-related risk of ischemic stroke. Interestingly, all ischemic strokes in patients prescribed an OAT were not fatal, compared with a mortality rate of 50 % among those suffering ischemic stroke and not receiving OAT. The magnitude of reduction of ischemic stroke among patients treated with OAT is in keeping with previous studies [1, 3, 4, 5, 6]. Not unexpectedly, major and total bleeding events were more frequent among those receiving OAT compared to untreated patients, but OAT was not associated with an increased rate of mortality and major bleeding events. However, in this setting of frail and vulnerable older patients, the incidence of major bleeding was higher than that reported in a recent national survey on anti-coagulated elderly out-patients [16]. As a whole, despite the increased rates in major bleeding events, our findings suggest a potential mortality and ischemic stroke benefit of OAT also among older and vulnerable patients.

Some limitations of this study must be addressed. The main weakness is the potential for selection bias, which is inherent to the nature of the cohort studied. Patients discharged with OAT 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 two different statistical approaches: firstly, we evaluated which clinical variables independently associated with fatal and non-fatal clinical end-points (mortality and ischemic/hemorrhagic events); secondly, we used a propensity score matching in order to disentangle the effect of anticoagulation from the other variables. However, multivariable analysis and propensity score matching might not account for other unmeasured variables. Further prospective studies and, whether feasible, randomized trials including older and vulnerable patients are needed to confirm these findings. Moreover, the multi-dimensional assessment gathered evidence of survival benefit with OAT use in presence of a well-known set of variables associated with increased death rates among older patients [18] attenuates the selection bias due the higher use of OAT among “healthier” patients. A second flaw of the study is the very small number of pairs evaluated in the propensity score matched analysis. Thirdly, despite most of 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 does not diminish the external validity of

the present findings, which aim to represent the effect of anticoagulant therapy among real-world older patients. The low prevalence of new direct oral anticoagulants use in this sample is likely due to the relatively recent (2013) approval in clinical practice of these drugs in our country and to the regulatory restrictions imposed on their prescription. Therefore, our findings refer mainly to the use of Vitamin K Antagonists which, by the way, are the most prescribed anticoagulant drugs in AF patients [21, 22]. Hopefully, future studies may provide useful information about efficacy and safety of new oral anticoagulants among these patients.

On the other hand, there are some strengths of this study which should be underscored. Present findings originate from patients admitted to different acute medical and geriatric wards from three major hospitals in northwestern Italy, and may be wisely generalized to older in-patients in different hospital medical settings. The population we studied is important for several reasons, including the high AF prevalence, the high post-discharge mortality, the likely under-representation of such patients in prior trials, and the common reluctance to prescribe OAT in such elderly frail patients.

In conclusion, in this prospective cohort study on older AF in-patients, use of OAT was significantly associated, among other multiple factors, with reduced overall mortality and lower incidence of ischemic stroke, and statistical analysis suggests it might be an independent contribution of OAT to these reductions. Our findings have potential relevant clinical implications, being one of the first evidence of the potential clinical benefit of OAT among older and frail medical AF patients, thereby potentially contributing to diminish physicians' reluctance to prescribe anticoagulants in these patients.

Notes

Compliance with ethical standards

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval

The study was conducted according to the principles of the Declaration of Helsinki Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. Signed informed consent at admission was obtained for all participants and the study was conducted according to the Recommendations Guiding Physicians in Biomedical research Involving Human Subjects.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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