European Journal of Internal Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Use of oral anticoagulant drugs in older patients with atrial fibrillation in internal medicine wards

ARTICLE INFO

Keywords:
Atrial fibrillation
Oral anticoagulant drugs
Prescription rate
Elderly

Atrial fibrillation (AF) is independently associated with a higher risk of morbidity and mortality, in particular with an increased risk of thromboembolic events [1]. Use of oral anticoagulant (OAC) drugs reduces the risk of stroke and systemic embolism, as well as mortality among patients with AF [1].

In recent years, the non-vitamin K antagonist oral anticoagulants (NOACs) have been proved to be at least as effective and safer than warfarin, the most widely used VKA [2], such that NOACs are the recommended choice in many patients [1]. Notwithstanding, the number of untreated patients is still relevant [3]. In particular, in the clinical setting of internal medicine and geriatric wards, previous data showed that elderly hospitalized patients with AF were largely not prescribed with OAC [4] or treated in a non-guideline adherent manner [5]. After NOACs have been marketed, a significant increase in OAC uptake was recorded, but a substantial portion of patients still does not receive the appropriate treatment based on their cardioembolic risk [3,6]. In particular, scarce data are available about NOACs use in the non-cardiologic setting. Furthermore, elderly AF patients are less likely prescribed with OAC compared to the younger ones [5,7], even though the net clinical benefit of OAC treatment in these patients has been demonstrated [8].

With the aim to provide evidences about use of OAC and NOACs in older hospitalized patients, we here report data about the retrospective observational phase of the "Simulation-Based Technologies to Improve the Appropriate Use of Oral Anticoagulants in Hospitalized Elderly Patients with Atrial Fibrillation" (SIM-AF) Trial. The SIM-AF is a cluster randomized controlled trial aimed at increasing the rate of OAC prescription in elderly (≥65 years) AF patients admitted to 32 Italian Internal Medicine and Geriatric wards through a simulation-based e-learning educational intervention (ClinicalTrials.gov #NCT03188211). In this retrospective pre-intervention phase, we analysed the medical records of 328 older patients (50.9% females) between October 2016 and May 2017. Median [IQR] age was 83 [78–87] years, with 48 patients (14.6%) in the 65–74 years stratum, 143 (43.6%) and 137 (41.8%) respectively in 75–84 years and ≥85 years strata. Patients enrolled had both high baseline thromboembolic and bleeding risk. Indeed, median [IQR] CHA_2DS_2-VASc was 5 [4–6] and median [IQR] HAS-BLED was 3 [2–4]. Polypharmacy (i.e. ≥5 drugs) was reported in most of the patients (258 patients, 78.7%), with a median [IQR] number of drugs of 7 [5–9]. Overall, 55 (16.8%) patients were prescribed with antiplatelet drugs [33 (10.1%) of which treated exclusively with antiplatelet drugs], while 221 (67.4%) patients were prescribed with OAC.

Baseline characteristics according to the use of OAC at baseline are reported in the Table 1. Compared to those not prescribed with OAC, those prescribed had a higher body mass index (BMI) ($p = .028$), reported a clinical history more burdened with heart failure ($p = .032$) but with a lower prevalence of previous major bleeding ($p < .001$). Patients not prescribed with OAC were more likely diagnosed with dementia compared to those prescribed with OAC ($p = .001$). The HAS-BLED score was lower in patients prescribed with OAC when compared to those not prescribed ($p = .003$). Using a multivariable logistic model, we found that BMI was independently associated with OAC prescription (hazard ratio [HR]: 1.09, 95% confidence interval [CI]: 1.02–1.17), while smoking habit (HR: 0.47, 95% CI: 0.25–0.89), previous major bleeding (HR: 0.11, 95% CI: 0.05–0.25) and diagnosis of dementia (HR: 0.43, 95% CI: 0.23–0.80) were inversely associated with OAC use.

Overall, NOACs were more prevalent (51.6%) than VKA (48.4%). Among the four NOACs available, apixaban was the most widely used (46.5%), followed by rivaroxaban (26.3%), dabigatran (16.7%) and edoxaban (10.5%). Among the NOACs users, 64 (56.1%) patients were treated with a low-dose regimen.

Our data underlined how a significant change occurred in OAC prescription in elderly AF patients. Previous data from the "REgistro POliterapie SIMI" (REPOSI) register showed that in 2008 cohort the overall rate of OAC prescription was 36.4% [4], that then increased up to 47.7% in the 2012–2014 cohort [5]. Our data, coming from a very similar cohort, showed a 20% increase in rate of OAC prescription. Notwithstanding, the prevalence of AF patients not treated with any antithrombotic drug was still high, as well as the use of antiplatelet drugs.

Major bleeding and other factors associated with a higher perceived frailty, such as the concurrent diagnosis of dementia, were inversely associated with OAC use. Thus, our data are consistent with the results pointed out from the PREFER-AF (Prevention of thromboembolic events – European Registry in Atrial Fibrillation) study, which showed that, among very elderly AF patients, higher age, prior bleeding, paroxysmal AF, chronic liver disease and difficulties with self-care (likely related to an overall impaired functional and cognitive state) were inversely associated with OAC prescription [9]. Likewise, the positive association between BMI and use of OAC was previously reported among general

https://doi.org/10.1016/j.ejim.2018.04.006
Received 3 April 2018; Received in revised form 5 April 2018; Accepted 6 April 2018

Table 1
Baseline characteristics according to the use of oral anticoagulant drugs.

	No OAC	OAC	p
	N = 107	*N* = 221	
Age, *years* (median [IQR])	84 [79–88]	83 [77–87]	0.068
Age classes, n (%)			0.290
65–74 years	11 (10.3)	37 (16.7)	
75–84 years	48 (44.9)	95 (43.0)	
≥85 years	48 (44.9)	89 (40.3)	
Female sex, n (%)	61 (57.0)	106 (48.0)	0.124
Living status, n (%)			0.340
Alone	9 (8.5)	10 (4.5)	
Family	73 (68.9)	162 (73.6)	
Institutionalized	24 (22.6)	48 (21.8)	
Marital status, n (%)			0.162
Alone	11 (10.4)	15 (6.9)	
Married	45 (42.5)	116 (53.2)	
Divorced/widowed	50 (47.2)	87 (39.9)	
Scholar status, n (%)			0.394
None/primary	44 (41.5)	106 (48.2)	
Secondary	55 (51.9)	105 (47.7)	
High degree	7 (6.6)	9 (4.1)	
History of falls, n (%)	24 (22.4)	37 (16.7)	0.215
Current smoking, n (%)	29 (27.1)	37 (16.7)	0.028
Alcohol use, n (%)	12 (11.2)	30 (13.6)	0.549
CrCl, mL/min (median [IQR]) 297	44.4 [30.1–60.5]	44.9 [31.8–63.6]	0.541
CrCl classes, n (%) 297			0.562
≥60 mL/min	23 (24.7)	62 (30.4)	
30–59 mL/min	48 (51.6)	101 (49.5)	
< 30 mL/min	22 (23.7)	41 (20.1)	
BMI, kg/m^2 (median [IQR]) 300	24.2 [22.2–27.2]	25.5 [22.9–28.7]	0.028
SBP, mmHg (median [IQR]) 325	120 [110−130]	120 [110–130]	0.366
DBP, mmHg (median [IQR]) 325	70 [60–75]	70 [60–80]	0.813
Type of AF, n (%)			0.517
Paroxysmal	31 (29.0)	59 (26.7)	
Persistent	54 (50.5)	125 (56.6)	
Permanent	12 (11.2)	25 (11.3)	
Unknown	10 (9.3)	12 (5.4)	
Stroke/TIA, n (%)	27 (25.2)	41 (18.6)	0.162
Hypertension, n (%)	82 (76.6)	173 (78.3)	0.737
Diabetes mellitus, n (%)	29 (27.1)	60 (27.1)	0.993
Chronic kidney disease, n (%)	52 (49.1)	99 (45.0)	0.491
Neoplasm, n (%)	21 (19.6)	40 (18.1)	0.739
Pulmonary disease, n (%)	34 (31.8)	66 (29.9)	0.724
Heart failure, n (%)	53 (49.5)	137 (62.0)	0.032
Acute coronary syndrome, n (%)	14 (13.1)	37 (16.7)	0.391
Previous major bleeding, n (%)	27 (25.2)	10 (4.5)	< 0.001
Dementia, n (%)	34 (31.8)	35 (15.8)	0.001
Depression, n (%)	15 (14.0)	33 (14.9)	0.826
Polypharmacy, n (%)	87 (81.3)	171 (77.4)	0.415
HAS-BLED (median [IQR])	3 [2–4]	3 [2–3]	0.003
CHA_2DS_2-VASc (median [IQR])	5 [4–6]	5 [4–6]	0.283

Legend: BMI, body mass index; CrCl, creatinine clearance; DBP, diastolic blood pressure; IQR, interquartile range; OAC, oral anticoagulant; SBP, systolic blood pressure; TIA, transient ischemic attack.

AF cohorts [6].

The observation that NOACs were more likely prescribed than VKA, was in line with other data reported from large observational studies on AF patients [10]. Nevertheless, we were here able to provide this evidence in the context of older AF patients, outside the setting of cardiology practices.

In conclusion, our data showed that even though a significant increase in rate of OAC prescription in older AF patients was observed overtime in the context of internal medicine setting a significant proportion of older frail patients were still untreated. Further analyses will be performed in order to specifically assess the appropriateness of OAC prescription in this cohort of patients. Finally, results from the SIM-AF trial will likely provide deeper insights in this clinically relevant issue.

Sources of funding

This study is supported by an unrestricted grant from Bristol Myers Squibb/Pfizer Alliance, within the European Thrombosis Investigator-Initiated Research Program (ERISTA) (Grant No. BMS ISR #CV 185-483).

Disclosures of interest

MP reports consulting fees from Boehringer Ingelheim; all other authors have no conflict of interest to declare.

Appendix A. Investigators and co-authors of the SIMulation-based technologies to improve the appropriate use of oral anticoagulants in hospitalized elderly patients with Atrial Fibrillation (SIM-AF) Trial

Steering Committee: Paola Santalucia [*Principal Investigator*], Valter Monzani, Maura Marcucci, Stefania Antoniazzi, Silvano Bosari, Pier Mannuccio Mannucci (*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico*, *Milano*); Carlotta Franchi [*Co-Principal Investigator*], Alessandro Nobili (*IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"*, *Milano*).

Study Coordination and Clinical Data Monitoring: Carlotta Franchi (*IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"*, *Milano*); *Stefania Antoniazzi* (*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico*, *Milano*).

Clinical Cases Contents: Paola Santalucia, Barbara *Brignolo*, *Pier Mannuccio Mannucci* (*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico*, *Milano*); Marco Proietti (*IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"*, *Milano*).

Clinical Cases Development: *Accurate Srl*, *Parma.*

Database and Electronic Case Report Form (E-CRF) Implementation: Enrico Nicolis (*IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"*, *Milano*).

Statistical Analysis: *Ilaria Ardoino* (*IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"*, *Milano*).

Investigators: Luigi M. Fenoglio, Remo Melchio (*Azienda Ospedaliera Santa Croce e Carle di Cuneo - Medicina Interna*); Fabrizio Fabris, Maria Teresa Sartori (*Azienda Ospedaliera Universitaria di Padova - Clinica Medica I*); Roberto Manfredini, Alfredo De Giorgi, Fabio Fabbian (*Azienda Ospedaliero-Universitaria di Ferrara - Arcispedale S. Anna - Clinica Medica*); Gianni Biolo, Michela Zanetti, Nicola Altamura (*Azienda Sanitaria Universitaria Integrata di Trieste*, *Ospedale di Cattinara - Clinica Medica*); Carlo Sabbà, Patrizia Suppressa, (*Azienda Ospedaliero-Universitaria Policlinico di Bari - Medicina Interna*); Francesco Bandiera, Carlo Usai (*Azienda Ospedaliero-Universitaria di Sassari - Medicina Interna*); Giovanni Murialdo, Francesca Fezza, Alessio Marra, Francesca Castelli, Federico Cattaneo, Valentina Beccati (*Ospedale Policlinico San Martino*, *Genova - Clinica di Medicina Interna 2*); Giovanni di Minno, Antonella Tufano, Paola Contaldi (*Azienda Ospedaliera Universitaria Federico II di Napoli - Medicina Interna*); Graziana Lupattelli, Vanessa Bianconi (*Ospedale "Santa Maria della Misericordia"*, *S. Andrea delle Fratte di Perugia - Medicina Interna*); Domenica Cappellini, Cinzia Hu, Francesca Minonzio (*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano - Medicina Interna*); Silvia Fargion, Larry Burdick, Paolo Francione (*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano - Medicina Interna ad Indirizzo Metabolico*); Flora Peyvandi, Raffaella Rossio, Giulia Colombo (*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano - Ematologia non tumorale e Coagulopatie*); Valter Monzani, Giuliana Ceriani (*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano - Medicina Interna ad Alta*

Intensità Di Cura); Tiziano Lucchi, Barbara Brignolo (*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano – Geriatria*); Dario Manfellotto, Irene Caridi (*Ospedale San Giovanni Calibita Fatebenefratelli di Roma - Medicina Interna*); Gino Roberto Corazza, Emanuela Miceli, Donatella Padula, Giacomo Fraternale (*IRCCS Fondazione Policlinico San Matteo di Pavia - Clinica Medica I*); Luigina Guasti, Alessandro Squizzato, Andrea Maresca (*Ospedale di Circolo e Fondazione Macchi, Azienda Socio-Sanitaria Territoriale Sette-Laghi, Varese, Università degli Studi dell'Insubria Varese - Medicina Interna 1*); Nicola Lucio Liberato, Tiziana Tognin (*Azienda Socio-Sanitaria Territoriale di Pavia Ospedale Civile "C. Mira" di Casorate Primo - Medicina Interna*); Renzo Rozzini, Francesco Baffa Bellucci (*Fondazione Poliambulanza Istituto Ospedaliero di Brescia – Geriatria*); Maurizio Muscaritoli, Alessio Molfino, Enrico Petrillo (*Dipartimento di Medicina Clinica, Sapienza Università di Roma, Policlinico Umberto I di Roma - Medicina Interna e Nutrizione Clinica*); Maurizio Dore, Francesca Mete, Miriam Gino (*Ospedale degli Infermi Di Rivoli - Medicina Generale*); Francesco Franceschi, Maurizio Gabrielli (*Fondazione Policlinico Universitario "Agostino Gemelli" di Roma - Medicina D'Urgenza e Pronto Soccorso*); Francesco Perticone, Maria Perticone (*Azienda Ospedaliero Universitaria "Mater Domini" di Catanzaro – Geriatria*); Marco Bertolotti, Chiara Mussi (*Nuovo Ospedale Civile S. Agostino Estense di Modena - Geriatria e Post-Acuzie Geriatria*); Claudio Borghi, Enrico Strocchi (*Azienda Ospedaliero Universitaria - Policlinico S·Orsola-Malpighi di Bologna - Medicina Interna*); Marilena Durazzo, Paolo Fornengo (*Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino - Presidio Molinette, Medicina Interna 3*); Franco Dallegri, Luciano Carlo Ottonello, Kassem Salam, Lara Caserza (*Ospedale Policlinico San Martino, Genova - Medicina Interna*); Mario Barbagallo, Giovanna Di Bella (*Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo – Geriatria*); Giorgio Annoni, Adriana Antonella Bruni (*Ospedale S·Gerardo di Monza, Azienda Socio-Sanitaria Territoriale di Monza, Clinica Geriatrica Università degli Studi di Milano-Bicocca - Clinica Geriatrica*); Patrizio Odetti, Alessio Nencioni, Fiammetta Monacelli, Armando Napolitano (*Ospedale Policlinico San Martino, Genova - Clinica Geriatrica*); Antonio Brucato, Anna Valenti (*Ospedale Papa Giovanni XXIII di Bergamo - Medicina Interna*); Pietro Castellino, Luca Zanoli, Marco Mazzeo (*Azienda Ospedaliero-Universitaria "Policlinico-Vittorio Emanuele" di Catania - Medicina Interna*).

References

[1] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur. Heart J. 2016;37:2893–962.

[2] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–62.

[3] Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational research Programme on atrial fibrillation (EORP-AF) long-term general registry. Europace 2017 Sep;14. [Epub ahead of print].

[4] Marcucci M, Iorio A, Nobili A, Tettamanti M, Pasina L, Marengoni A, et al. Factors affecting adherence to guidelines for antithrombotic therapy in elderly patients with atrial fibrillation admitted to internal medicine wards. Eur. J. Intern. Med. 2010;21:516–23.

[5] Proietti M, Nobili A, Raparelli V, Napoleone L, Mannucci PM, Lip GYH, et al. Adherence to antithrombotic therapy guidelines improves mortality among elderly patients with atrial fibrillation: insights from the REPOSI study. Clin. Res. Cardiol. 2016;105:912–20.

[6] Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J. Am. Coll. Cardiol. 2017;69:2475–84.

[7] Lubitz SA, Bauer KA, Benjamin EJ, Besdine RW, Forman DE, Gurol ME, et al. Stroke prevention in atrial fibrillation in older adults: existing knowledge gaps and areas for innovation: a summary of an American Federation for Aging research seminar. J. Am. Geriatr. Soc. 2013;61:1798–803.

[8] Patti G, Lucerna M, Pecen L, Siller-Matula JM, Cavallari I, Kirchhof P, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: a sub-analysis from the PREFER in AF (PREvention oF thromboembolic events-European registry in atrial fibrillation). J. Am. Heart Assoc. 2017;6:e005657.

[9] Hanon O, Vidal J-S, Le Heuzey J-Y, Kirchhof P, De Caterina R, Schmitt J, et al. Oral anticoagulant use in octogenarian European patients with atrial fibrillation: a sub-analysis of PREFER in AF. Int. J. Cardiol. 2017;232:98–104.

[10] Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener H-C, Dubner SJ, et al. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF registry phase 2. J. Am. Coll. Cardiol. 2017;69:777–85.

Marco Proietti[a,b], Stefania Antoniazzi[c,d], Valter Monzani[e], Paola Santalucia[c,f], Carlotta Franchi[g,*], on behalf of SIM-AF Investigators[1]

[a] *Department of Neuroscience, Laboratory of Quality Assessment of Geriatric Therapies and Services, IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy*

[b] *Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom*

[c] *Scientific Direction, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

[d] *Department of Biomedical and Clinical Sciences, Clinical Pharmacology Unit, ASST Fatebenefratelli – Sacco University Hospital, University of Milan, Milan, Italy*

[e] *Department of Emergency Medicine, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy*

[f] *IRCCS Centro Neurolesi Bonino Pulejo - Ospedale Piemonte, Messina, Italy*

[g] *Unit of Pharmacoepidemiological Research in Older People, IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy*

E-mail address: carlotta.franchi@marionegri.it

[*] Corresponding author at: Unit of Pharmacoepidemiological Research in Older People, IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Via Giuseppe La Masa 19, 20156 Milan, Italy.

[1] Reported in Appendix.