View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Archivio della Ricerca - Università di Pisa

Title: Risk of bone fractures among users of oral anticoagulants: an administrative database cohort study

Authors:

Ersilia Lucenteforte [a], PhD ScD; Alessandra Bettiol [a], ScD; Niccolò Lombardi [a], PharmD PhD; Alessandro Mugelli [a], Prof MD; Alfredo Vannacci [a*], PhD MD.

Affilitations:

[a] Department of Neurosciences, Psychology, Pharmacology and Child Health (NEUROFARBA), University of Florence, Florence, Italy

***Corresponding author:** Alfredo Vannacci, MD, PhD

Department of Neurosciences, Psychology, Pharmacology and Child Health (NEUROFARBA), University of Florence, Florence, Italy

viale Gaetano Pieraccini, 6 – 50139, Florence, Italy

e-mail: alfredo.vannacci@unifi.it

Financial support information: This study was funded by a research grant from the AIFA (the Italian Medicines Agency), Rome, Italy. The funder of the study had no role in the collection, analysis and interpretation of data, nor in the writing of the report, nor in the decision to submit the article for publication.

Keywords: bone fracture; anticoagulant; adverse drug reaction; pharmacovigilance.

Word count: 582

Background

Warfarin is a traditional oral anticoagulant for stroke prevention in patients with Non Valvular Atrial Fibrillation (NVAF). The novel oral anticoagulants (NOACs), firstly dabigatran (directly targeting the enzymatic activity of thrombin) and then rivaroxaban, apixaban and edoxaban (targeting the enzymatic activity of factor Xa), have been approved for use in patients with NAVF. Although several studies have reported the possible association between warfarin and an increased risk of osteoporotic fracture (1-4), only one population-based cohort study was conducted to compare the risk of dabigatran and warfarin, showing a lower risk for dabigatran compared with warfarin (5). In addition, a pre-specific analysis of a phase 3 clinical trial indicated that edoxaban is a valid alternative to warfarin in patients at increased risk of falling (6). On the other hand, no study was conducted on the risk of bone fractures among other direct Xa inhibitors.
The aim of the present study was to investigate the occurrence of osteoporotic fracture with warfarin, dabigatran and direct Xa inhibitors (rivaroxaban and apixaban).

Material and Methods

A cohort study was performed on administrative databases of the Florence Metropolitan Area. All patients treated with oral anticoagulants (OACs) in the year 2015 were included. The first date of OACs prescription in the year was considered as the index date. Since the index date, all patients were followed until the occurrence of fracture, death, change of OACs treatment, or end of data availability (December 31st, 2015). Occurrence of fracture during follow-up was evaluated both from hospital discharge records and emergency departments admissions, considering all records with a diagnosis of hip or vertebral fracture in primary or secondary diagnosis fields (ICD9-CM code 820.x or 805.x). For each treatment, the rate of fracture/100 person/year was estimated. Moreover, the Hazard Ratio (HR) of fracture was calculated for patients exposed to NOACs (dabigatran or direct Xa inhibitors) compared to warfarin users, using a multivariate cox models adjusted for gender, age and pattern of OACs use (incident or non-incident). Edoxaban was not considered in this study, since it entered the Italian marked in the second half of 2015 and poor data were available. Data analysis was performed using the software STATA version 13; statistical significance was considered with a p-value <0.05.

Results

Among 16,850 patients treated with OACs, 77.7% used warfarin, 14.5% used direct Xa inhibitos, and 7.6% used dabigatran (**table 1**). Overall, the majority of subjects were men (51.09%), aged 75 or more (67.22), and non-incident users (76.71%). Distribution of gender, age and pattern of use significantly differed among OACs.

Table 1: Distribution of general characteristics among users of oral anticoagulant

	TOTAL No. (%)	WARFARIN No. (%)	DIRECT Xa INHIBITORS No. (%)	DABIGATRAN No. (%)	p-value[a]
Number	16,850	13,091	2,474	1,285	
Gender					
Male	8,608 (51.09)	6,769 (51.71)	1,195 (48.30)	644 (50.12)	.0027
Female	8,242 (48.91)	6,322 (48.29)	1,279 (51.70)	641 (49.88)	
Age					
≥75 years	11,327 (67.22)	8,735 (66.73)	1,718 (69.44)	874 (68.02)	<.0001
<75 years	5,523 (32.78)	4,356 (33.27)	756 (30.56)	411 (31.98)	
Pattern of use					
Incident use	3,925 (23.29)	2,420 (18.49)	1,169 (47.25)	336 (26.15)	<.0001
Non-incident use	12,925 (76.71)	10,671 (81.51)	1,305 (52.75)	949 (73.85)	

[a] p-value from chi-square test.

For OAC users overall, rate of fractures per 100 person years was 1.58 [1.37 – 1.81] (**table 2**). Comparing NOACs with warfarin, no significant difference emerged in their association with fractures (HR of 1.04 [0.68 – 1.59] for direct Xa inhibitors; 0.96 [0.56 – 1.63] for dabigatran). Among warfarin users, the occurrence of fractures was significantly higher among female subjects (106/4658.68 events/person years and 47/5052.33 events/person years for women and men, respectively; p <0.0001) and patients aged ≥75 years (19/3309.55 events/person years and 134/6401.46 events/person years for people aged ≥75 and <75, respectively; p <0.0001). On the other hand, among users of direct Xa inhibitors or dabigatran, occurrence of fractures did not significantly differ among genders or age classes. In all OACs groups, occurrence of fractures was comparable among different strata of pattern of use.

Table 2: Number of Events, Rate and Hazard Ratio, with corresponding 95% confidence Intervals (95% CIs) for fractures among users of oral anticoagulants

	N events / person years	**Rate per 100 person years [95% CI]**	**HR[a] [95% CI]**
OACs	194/12432.89	1.58 [1.37 – 1.81]	
WARFARIN, overall	153/9711.01	1.58 [1.34 – 1.85]	1 (reference)
Male	47/5052.33	0.93 [0.70 – 1.24]	-
Female	106/4658.68	2.28 [1.88 – 2.75]	-
p-value	<.0001		
≥75 years	134/6401.46	2.09 [1.76 – 2.48]	-
< 75 years	19/3309.55	0.57 [0.37 – 0.90]	-
p-value	<.0001		
Incident use	15/1166.83	1.29 [0.78 – 2.13]	-
Non-incident use	138/8544.19	1.62 [1.37 – 1.91]	-
p-value	0.401		
DIRECT Xa INHIBITORS, overall	26/1579.42	1.64 [1.12 – 2.42]	1.04 [0.68 – 1.59]
Male	9/780.33	1.15 [0.60 – 2.21]	1.28 [0.62 – 2.64]
Female	17/799.09	2.13 [1.32 – 3.42]	0.94 [0.56 – 1.59]
p-value	0.137		0.332
≥75 years	26/1085.51	2.40 [1.63 – 3.52]	1.19 [0.78 – 1.83]
< 75 years	-	-	-
p-value			
Incident use	6/508.99	1.18 [0.53 – 2.62]	0.82 [0.31 – 2.12]
Non-incident use	20/1070.43	1.87 [1.21 – 2.90]	1.12 [0.70 – 1.79]
p-value	0.329		0.578
DABIGATRAN, overall	15/969.88	1.55 [0.93 –2.57]	0.96 [0.56 – 1.63]
Male	5/488.50	1.02 [0.43 – 2.46]	1.17 [0.46 – 2.93]
Female	10/481.39	2.07 [1.11 – 3.86]	0.88 [0.46 – 1.68]
p-value	0.200		0.680
≥75 years	14/658.15	2.13 [1.26 – 3.59]	1.01 [0.58 – 1.75]
< 75 years	1/311.73	0.32 [0.05 – 2.28]	0.57 [0.08 – 4.25]
p-value	0.027		0.690
Incident use	3/156.75	1.91 [0.62 – 5.93]	1.40 [0.41 – 4.86]
Non-incident use	12/813.13	1.48 [0.84 – 2.60]	0.90 [0.50 – 1.62]
p-value	0.661		0.669

[a] HR calculated using cox models adjusted for gender, age and pattern of use (incident use, yes/no)

Discussion

OACs is an inevitable treatment, and the choice of whether using warfarin or one of new OACs is still debated. Recently, it has been proposed that osteoporotic fractures could be a crucial factor in the choice between dabigatran or warfarin, since an increased risk in the latter compared to the former was reported (5). Data from our study do not confirm differences in risk, and provided further evidence of the lack of such

effect for other OACs (i.e., direct Xa inhibitors). Additional evidence is needed in order to assess the importance of considering the possible risk of fractures during the process of choosing and prescribing OACs. Nevertheless, female and elderly subjects appear to have a higher rate of fractures, with a difference that was statistically significant with respect to warfarin.

Acknowledgments

The authors would like to thank Dr. Daniela Balzi (Epidemiology Unit, Florence Local Health Unit) who provided data. The corresponding author listed everyone who contributed significantly to the work. This study was funded by a research grant from the AIFA (the Italian Medicines Agency), Rome, Italy. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data of the study and had final responsibility for the decision to submit for publication.

Conflicts of interest: none.

References

1. Sugiyama T, Kugimiya F, Kono S, Kim YT, Oda H. Warfarin use and fracture risk: an evidence-based mechanistic insight. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(3):1231-2.

2. Caraballo PJ, Heit JA, Atkinson EJ, Silverstein MD, O'Fallon WM, Castro MR, et al. Long-term use of oral anticoagulants and the risk of fracture. Archives of internal medicine. 1999;159(15):1750-6.

3. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Archives of internal medicine. 2006;166(2):241-6.

4. Rejnmark L, Vestergaard P, Mosekilde L. Fracture risk in users of oral anticoagulants: a nationwide case-control study. International journal of cardiology. 2007;118(3):338-44.

5. Lau WC, Chan EW, Cheung CL, Sing CW, Man KK, Lip GY, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation. Jama. 2017;317(11):1151-8.

6. Steffel J, Giugliano RP, Braunwald E, Murphy SA, Mercuri M, Choi Y, et al. Edoxaban Versus Warfarin in Atrial Fibrillation Patients at Risk of Falling: ENGAGE AF-TIMI 48 Analysis. . J Am Coll Cardiol. 2016 Sep 13;68(11):1169-1178.