Risk of Fracture in Patients with Nonvalvular Atrial Fibrillation Initiating Direct Oral Anticoagulants *vs* Vitamin K Antagonists

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Background

- It is well known that VKAs can interfere with the biosynthesis of gamma-carboxyglutamic acid proteins in the bone, including osteocalcin and other bone matrix proteins, thus potentially affecting bone metabolism.
- Recently, some studies tried to assess the risk of fracture associated with DOACs compared with VKAs in patients with NVAF, with conflicting results; in fact, no study has included all patients initiating OACs and explored the potential duration-response relation between OACs use and the risk of fracture, accounting for cumulative duration of use.

Aim of the study

To assess the risk of fracture associated with DOACs compared with VKAs among patients with NVAF, using a relevant time-window of exposure accounting for cumulative duration of use.

Methods (I)

- Population-based cohort study;
- data from 3 computerized healthcare databases from the Canadian province of Québec;
- all patients at least 40 years of age, who filled a first prescription for a DOAC (dabigatran, rivaroxaban, or apixaban) or VKA from January 1, 2011 to March 31, 2014, were included;
- exposure to DOACs and VKAs was modelled as a time-varying variable: patients were considered unexposed up to 180 days of cumulative duration of use and exposed thereafter.

Methods (II)

- The primary outcome was a hospitalization with a diagnosis of fracture (admission or primary diagnosis), a composite of hip fracture, vertebral fracture, upper extremity fracture (humerus, forearm, or wrist fracture) and osteoporosis with pathologic fracture;
- secondary outcomes considered the components of the primary outcome separately.

Results (I)

- The final cohort included 10,306 (40.2%) DOACs initiators and 15,357 (59.8%) VKAs initiators;
- new users of DOACs were younger, less likely to have diabetes mellitus, hypertension, CKD, respiratory disease, dementia or stroke;
- overall, 464 fractures occurred during 35,252 person-years of follow-up in the entire cohort, resulting in a crude incidence rate of 13.2 (12.0 -14.4) per 1000 person-years;
- compared with VKA duration ≥ 180 days, use of DOACs for 180 days or greater was associated with a 35% decreased risk of fracture.

Results (II)

- Regarding the type of fracture, DOACs duration ≥ 180 days was associated with a significant decreased rate of hip fracture (crude incidence rates 3.2 vs 8.6 per 1000 person-years) and osteoporosis with pathologic fracture (crude incidence rates 0.4 vs 1.8 per 1000 person-years) compared with VKAs;
- there was no association with upper extremity fracture and vertebral fracture;
- there was no difference in the rate of fracture for shorter duration of use of DOACs (< 180 days) compared with the same short duration of use of VKAs;
- these results were not modified by sex, age, CKD, osteoporosis, history of fracture, history of fracture or falls.

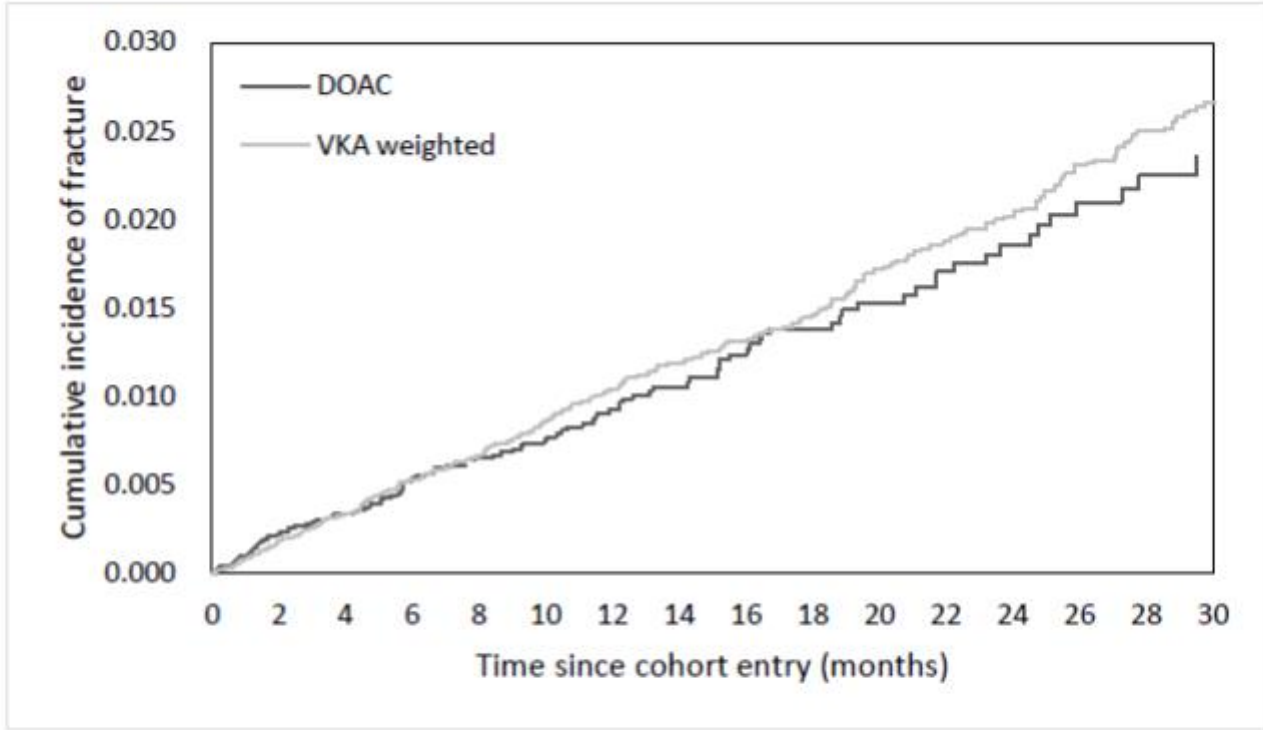

Figure 2. Weighted cumulative incidence curve of fracture events among new users of DOACs and VKAs

Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin-K antagonist

Table 2. Crude and adjusted hazard ratios for the association between DOACs and the risk of fracture

Exposure	Events	Person-years	Incidence rate [a]	Crude HR	Adjusted HR [b] (95% CI)
All fracture					
VKA (≥ 180 days)	183	11930	15.3	1.00 (Ref)	1.00 (Reference)
DOAC (≥ 180 days)	43	5709	7.5	0.49	0.65 (0.46 - 0.91)
VKA (<180 days)	126	8001	15.7	1.00	0.79 (0.52 - 1.19)
DOAC (<180 days)	55	4862	11.3	0.71	0.86 (0.52 - 1.43)
Multiple use	57	4749	12.0	0.78	0.73 (0.52 - 1.03)
Hip fracture					
VKA (≥ 180 days)	103	11930	8.6	1.00 (Ref)	1.00 (Reference)
DOAC (≥ 180 days)	18	5709	3.2	0.36	0.51 (0.31 - 0.86)
VKA (<180 days)	66	8001	8.2	0.98	0.90 (0.52 - 1.55)
DOAC (<180 days)	24	4862	4.9	0.59	0.80 (0.40 - 1.62)
Multiple use	34	4749	7.2	0.84	0.82 (0.53 - 1.27)
Upper extremity fracture					
VKA (≥ 180 days)	27	11930	2.3	1.00 (Ref)	1.00 (Reference)
DOAC (≥ 180 days)	16	5709	2.8	1.24	1.37 (0.73 - 2.57)
VKA (<180 days)	26	8001	3.2	1.76	1.04 (0.42 - 2.58)
DOAC (<180 days)	17	4862	3.5	1.90	1.95 (0.68 - 5.55)
Multiple use	10	4749	2.1	0.96	1.05 (0.52 - 2.11)
Vertebral fracture					
VKA (≥ 180 days)	32	11930	2.7	1.00 (Ref)	1.00 (Reference)
DOAC (≥ 180 days)	7	5709	1.2	0.46	0.62 (0.27 - 1.45)
VKA (<180 days)	21	8001	2.6	0.76	0.51 (0.15 - 1.82)
DOAC (<180 days)	10	4862	2.1	0.59	0.52 (0.15 - 1.77)
Multiple use	6	4749	1.3	0.46	0.34 (0.12 - 1.01)
Other fracture [c]					
VKA (≥ 180 days)	21	11930	1.8	1.00 (Ref)	1.00 (Reference)
DOAC (≥ 180 days)	<5 [d]	-	0.4	0.21	0.24 (0.06 - 1.00)
VKA (<180 days)	13	8001	1.6	0.45	0.25 (0.06 - 1.11)
DOAC (<180 days)	<5 [d]	-	0.8	0.22	0.22 (0.03 - 1.60)
Multiple use	7	4749	1.5	0.71	0.41 (0.13 - 1.31)

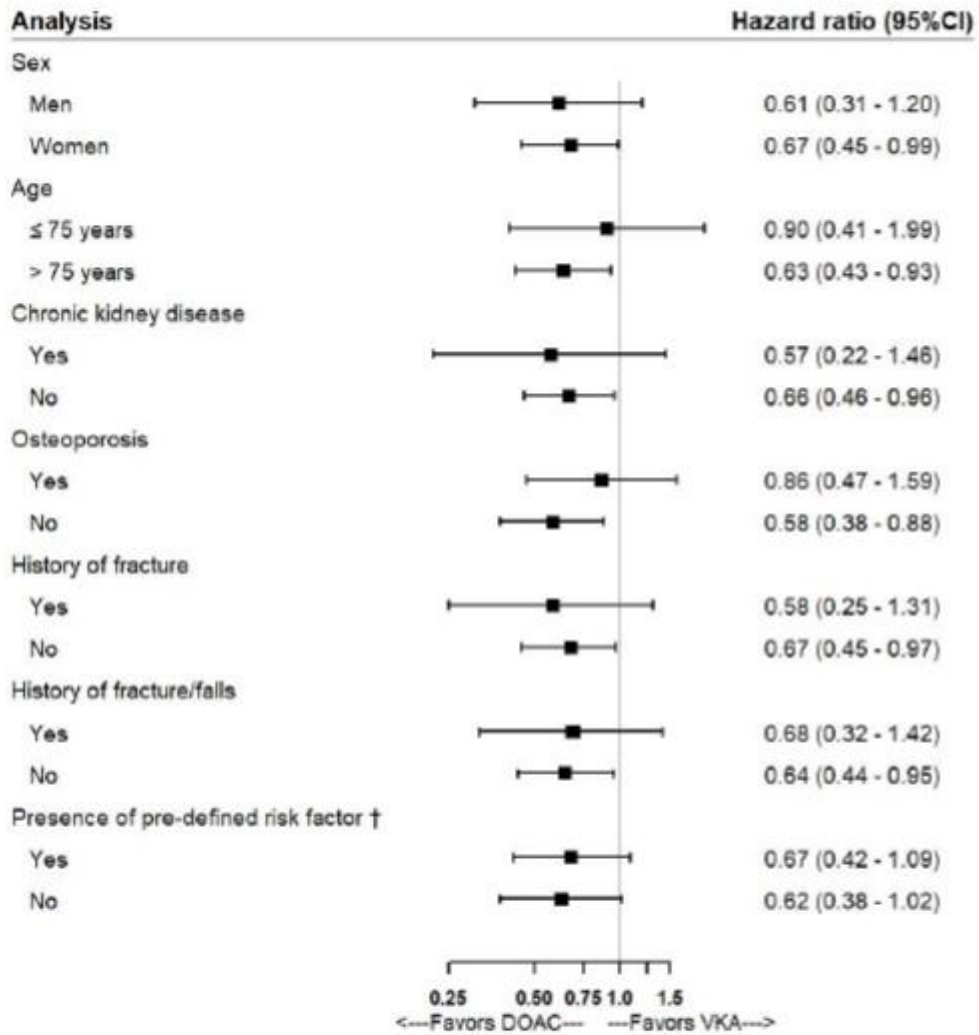

Figure 3. Forest plot showing adjusted hazard ratios and 95% CIs in stratified analyses for the association between DOACs and the risk of fracture

† any risk factor: history of fall, prior fracture, osteoporosis or predisposition to falls

Conclusions

- Compared with VKA, prolonged use of DOACs (≥ 180 days) is associated with a lower risk of fracture, including hip fracture;
- these findings further support the first-line recommendation for DOACs in patients with NVAF, especially for elderly patients initiating lifelong anticoagulation therapy.