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Anticoagulants safety in general practice: one year results from the CACAO multicenter prospective cohort study.

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Aim

Real-world studies on anticoagulants are mostly based on health insurance databases or performed in secondary care.

➡ **Our aim was to compare the occurrence of arterial or venous events, bleedings and deaths between vitamin K antagonist (VKA) and direct oral anticoagulants (DOAC) in a general practice setting**

Methods

* National prospective observational cohort involving 444 general practitioners from January 1st to December 31, 2015
* Participants were aged 18 years or more and have all a non-valvular atrial fibrillation or a thromboembolic indication for anticoagulant. They were selected from the CACAO I study[1], which recruited them consecutively in primary care.
* During the year of follow up, patients were followed as usual by their general practitioner, who collected every three months available data regarding the occurrence of :
  - Arterial or venous events: deep vein thrombosis (DVT), pulmonary embolism (PE), transient ischemic attack (TIA), ischemic stroke, myocardial infarction, and arterial thrombosis of lower limb
  - Bleeding
  - Death

  → All events were adjudicated by an independent committee.
* Incidence rates and Hazard Ratio were calculated with a Cox regression model. In arterial or venous events, as well as in bleeding events, we used Fine and Gray method to calculate absolute risk of events taking into account the competing risk of death. Since this study was observational, we used an adjustment method by propensity score.
* ClinicalTrials.gov protocol Identifier: NCT02376777

Table 1. Characteristics of patients and anticoagulation modalities, given the anticoagulant at the time of inclusion

Characteristics	VKA	DOAC	*P*	Total
Patients, N (%)	1 946 (100.0)	1 136 (100.0)	-	3 082 (100.0)
Age, mean (SD), y	75.0 (11.5)	73.3 (12.3)	***< 0.001***	74.4 (11.8)
Male, N (%)	1 095 (56.3)	594 (52.3)	***0.032***	1 689 (54.8)
BMI >30, N (%), kg/m²	576 (35.7)	336 (34.9)	*0.680*	912 (35.4)
Personal history, N (%)				
Hypertension	1 367 (70.3)	757 (66.6)	***0.037***	2 124 (68.9)
DVT and/or PE	467 (24.0)	186 (16.4)	***< 0.001***	653 (21.2)
Diabetes	469 (24.1)	253 (22.3)	*0.247*	722 (23.4)
Coronary heart disease and/or MI	393 (20.2)	156 (13.7)	***< 0.001***	549 (17.8)
Symptomatic heart failure	336 (17.3)	141 (12.4)	***< 0.001***	477 (15.5)
Stroke and/or TIA	303 (15.6)	172 (15.1)	*0.750*	475 (15.4)
Peripheral arterial disease	220 (11.3)	101 (8.9)	***0.034***	321 (10.4)
Bleeding requiring hospitalization	146 (7.5)	54 (4.8)	***0.003***	200 (6.5)
CHA_2DS_2-VASc ≥2 /Atrial fibrillation, n=2 611, N (%)	1 499 (92.7)	900 (90.5)	***0.050***	2 399 (91.9)
HASBLED >3 / Atrial fibrillation, n=2 611, N (%)	324 (20.0)	111 (11.2)	***< 0.001***	435 (16.7)
Renal impairment (clearance <60 mL/min), N (%)	533 (27.8)	264 (23.2)	***0.016***	797 (25.8)
Normal liver function (AST <3N, ALT <3N AND Bilirubin <2N), N (%)	1 434 (73.7)	875 (77.0)	***0.037***	2 309 (74.9)
Indication for anticoagulation, N (%)				
Non valvular atrial fibrillation	1 619 (83.2)	994 (87.5)	***0.001***	2 613 (84.8)
Treatment of DVT/PE	393 (20.2)	159 (14.0)		552 (17.9)
Timed up and go test as estimated by GP >30 sec, N (%)	229 (11.8)	108 (9.5)	***0.024***	337 (10.9)
Duration of anticoagulation >1 year, N (%)	1 446 (74.3)	582 (51.3)	***<0.001***	2 028 (65.8)
Patient perceived by GP as *not* or *not very* adherent, N (%)	103 (5.4)	76 (6.8)	*0.102*	179 (5.9)
At least one concomitant medication at risk of interaction*, N (%)	1 148 (59.0)	658 (57.9)	*0.561*	1 806 (58.6)
Definitive stop of anticoagulation during the year, n=3 071, N (%)	134 (6.9)	135 (12.0)	***<0.001***	269 (8.8)
At least 1 temporary stop of anticoagulation, n=3 071, N (%)	126 (6.5)	67 (5.9)	*0.536*	193 (6.3)
At least 1 change of anticoagulant class, n=3 071, N (%)	43 (2.2)	45 (4.0)	***0.005***	88 (2.9)

VKA: vitamine-k antagonists, DOA: direct oral anticoagulants, BMI: body mass index, DVT: deep vein thrombosis, PE: pulmonary embolism, MI: myocardial infarction, TIA: transient ischemic attack, BID: twice daily, OD: once daily
**Collected concomitant medications were : statin, amiodarone, antiplatelet, serotonin reuptake inhibitors, fibrate, verapamil, NSAID, quinidine, carbamazepine, tacrolimus, ciclosporin, anticoagulant, systemic antifungal therapy, rifampicin, protease inhibitors*

Results

* 3082 patients were included: 1946 patients (63.1%) had a VKA and 1136 patients (36.9%) had a DOAC.
  11 patients (0.4%) were lost of follow-up during the year.
* Survival analysis at one year (n=3038):
  . 42 patients (1.7%) had an arterial or venous event
  . 151 patients (6.1%) had a bleeding, including 47 (1.9%) major bleedings
  . 105 patients (4.1%) patients died.
* The propensity matching selected 1866 patients (area under ROC curve = 0.675):
  . 935 patients (50.1%) had a VKA and 931 patients (49.9%) had a DOAC.
  . 16 patients were lost of follow-up (0.9%).

Table 2. One-year outcomes in propensity-matched sample, given the anticoagulant class at the time of the outcome

One year outcomes, N (%)	VKA	DOAC	Total	*HR [95%CI]*
At least one arterial or venous event	15 (1.9)	14 (1.9)	29 (1.9)	*1.00 [0.48-2.07]*
Any bleeding	**38 (4.9)**	**55 (7.4)**	**93 (6.1)**	***0.65 [0.43-0.98]***
Major bleeding	8 (1.0)	17 (2.3)	25 (1.6)	*0.45 [0.19-1.03]*
Non major but clinically relevant bleeding	21 (2.7)	22 (2.9)	43 (2.8)	*0.90 [0.50-1.64]*
Minor bleeding	9 (1.1)	16 (2.1)	25 (1.6)	*0.52 [0.23-1.18]*
All-cause death	**40 (5.0)**	**19 (2.5)**	**59 (3.8)**	***1.98 [1.15-3.42]***
Bleeding cause	2 (0.3)	6 (0.8)	8 (0.5)	

VKA, vitamine-k antagonists; DOAC, direct oral anticoagulants; HR, Hazard ratio taking into account the competitive risk with death.

Conclusion

* There was no significant difference between VKA and DOAC groups regarding arterial or venous events and major bleedings.
  VKA group had a lower incidence of overall bleedings and a two times higher incidence of deaths (HR=1.98, IC95% [1.15-3.42]), but this difference was not due to bleeding causes.
* Those results are in line with data from the literature, except regarding overall bleedings, suggesting that **considering all patients' profiles and all bleedings encountered in general practice could moderate results measured in previous cohorts based on databases and/or performed in secondary care, but does not question known safety data on DOAC and VKA.**

1. Frappé P, Cogneau J, Gaboreau Y, Abenhaïm N, Bayen M, Calafiore M, Guichard C, Jacquet JP, Lacoin F, Bertoletti L; CACAO study investigators. Areas of improvement in anticoagulant safety. Data from the CACAO study, a cohort in general practice. PLoS One. 2017:6;12(4):e0175167.

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