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ORIGINAL RESEARCH ARTICLE

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Concomitant Use of Direct Oral Anticoagulants and Antiepileptic Drugs: A Prospective Cohort Study in Patients with Atrial Fibrillation

Michela Giustozzi[1] · Matteo Mazzetti[2] · Maurizio Paciaroni[1] · Giancarlo Agnelli[1] · Cecilia Becattini[1] · Maria Cristina Vedovati[1]

Background

- European guidelines do not recommend the use of carbamazepine, levetiracetam, phenobarbital, phenytoin,topiramate and valproic acid in patients taking direct oral anticoagulants (DOACs).
- These recommendations are based on expert opinions, DOAC summary of product characteristics and on animal or in vitro studies.
- Little is known regarding the clinical relevance of the interaction between DOACs and antiepileptic drugs (AEDs).

Aim of the study

- The aim of the study was to evaluate the incidence of thromboembolic and bleeding events in a cohort of patients with non-valvular AF concurrently treated with AEDs and DOACs.

Methods

- Consecutive patients with non-valvular AF treated with DOACs and AEDs were prospectively included in on-going prospective cohorts from 2014 to December 2018 .
- The patients were prospectively observed until January 2020.
- The primary effectiveness outcome was the composite of ischaemic stroke, transient ischaemic attack (TIA) and systemic embolism (SE).
- The primary safety outcome was major bleeding (MB).

Results (I)

- 91 patients.
- Mean age was 78 ± 9.5 years, 45 (49.5%) patients were female and 44 (48%) had a previous stroke or TIA.
- 41 (45%) were on treatment with levetiracetam, 20 (22%) with valproic acid, 11 (12%) with phenobarbital, 10 (11%) with carbamazepine and 9 patients (10%) with other AEDs.
- Median follow-up was 17.5 ± 14.5 months.

Results (II)

- During the study period, ischaemic stroke/TIA/SE occurred in 9 patients (5.7% patient-year).
- No differences were observed in terms of risk of ischaemic stroke between patients treated with enzyme-inducing AEDs and patients treated with other AEDs (log-rank = 0.342).
- MB occurred in 3 patients (1.9% patient-year).

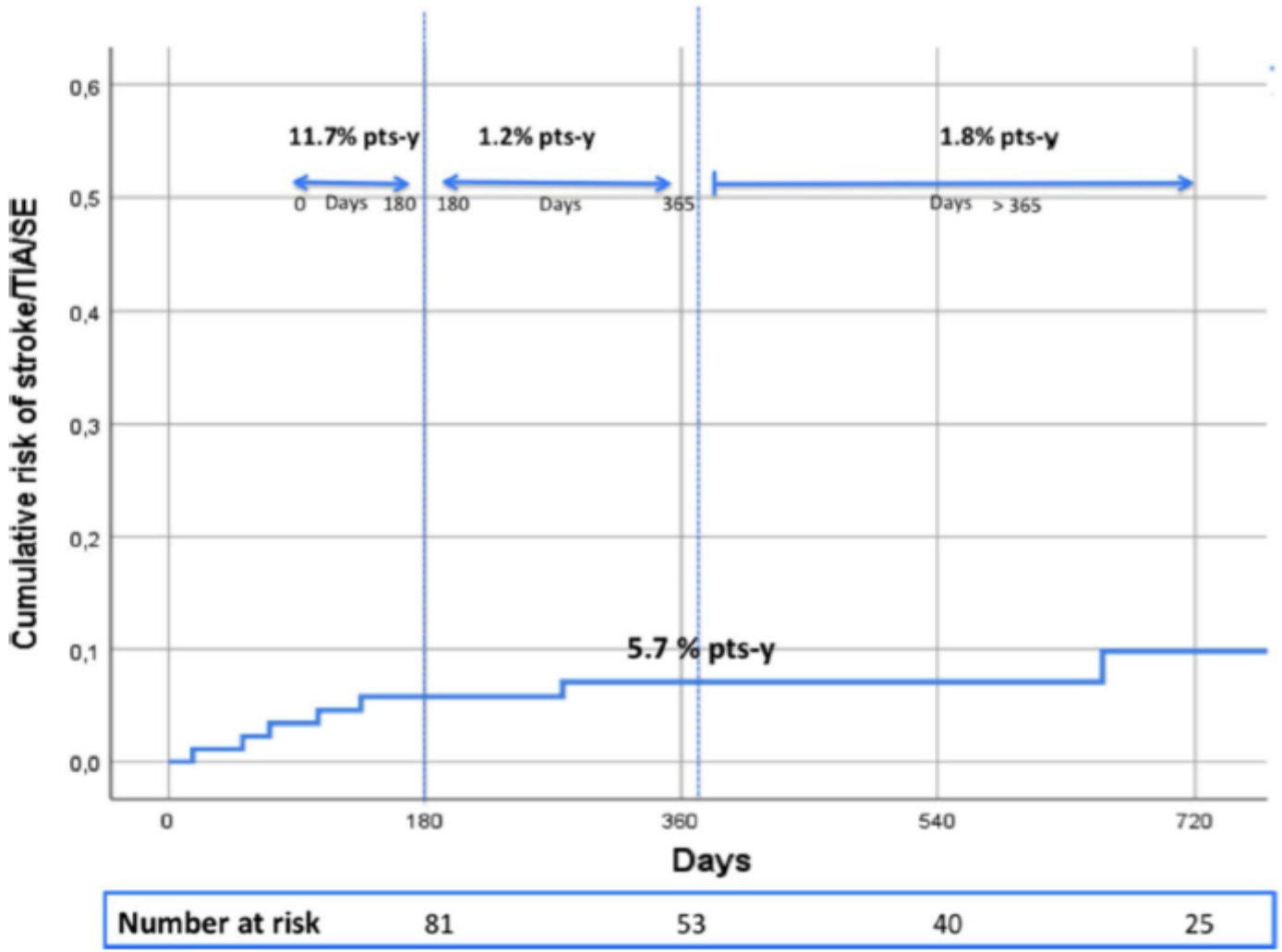

Fig. 1 Risk and incidence rates of ischaemic stroke/TIA/SE. *pts-y* patient-year, *SE* systemic embolism, *TIA* transient ischaemic attack

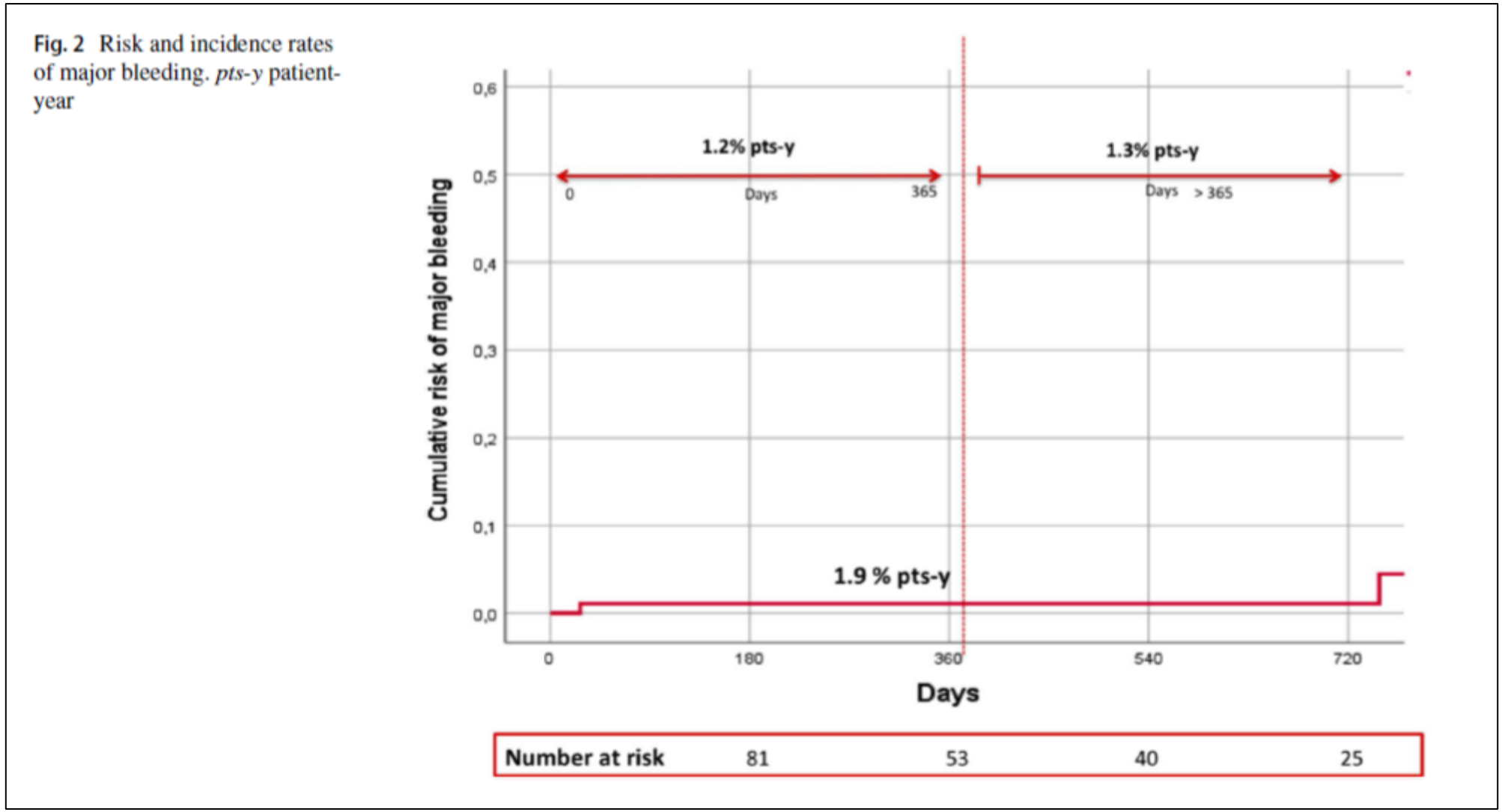

Fig. 2 Risk and incidence rates of major bleeding. *pts-y* patient-year

Table 3 Main characteristics of the study patients with thromboembolic events

Pt. ID	Age, years	Sex	CHA_2DS_2-VASc score	Previous stroke	Type of DOAC	Type of AED	Type of event	Fatal event	Time to event (days)
1	75	F	4	No	Rivaroxaban 20 mg	Carbamazepine 400 mg bid	Ischaemic stroke	No	786
2	75	F	6	Yes	Apixaban 5 mg bid	Valproic acid 500 mg	TIA	No	105
3	77	F	5	Yes	Apixaban 5 mg bid	Levetiracetam 250 mg bid	Ischaemic stroke	No	17
4	81	M	5	Yes	Apixaban 5 mg bid	Levetiracetam 500 bid	Ischaemic stroke	No	52
5	87	F	7	Yes	Apixaban 2.5 mg bid	Carbamazepine 400 mg bid	Ischaemic stroke	No	947
6	90	M	2	No	Rivaroxaban 15 mg	Levetiracetam 500 mg bid	Ischaemic stroke	No	277
7	82	M	3	No	Dabigatran 110 mg bid	Levetiracetam 250 mg bid	Ischaemic stroke	Yes	655
8	88	F	8	Yes	Rivaroxaban 15 mg	Fenobarbital 100 mg + levetiracetam 250 mg bid	Ischaemic stroke	Yes	135
9	93	F	7	Yes	Rivaroxaban 15 mg	Fenobarbital 100 mg	Ischaemic stroke	Yes	71

AED anti-epileptic drug, *DOAC* direct oral anticoagulant, *F* female, *M* male, *TIA* transient ischaemic attack, *bid* twice daily

Conclusions

- In this prospective study, patients with non-valvular AF treated with DOACs and antiepileptic drugs appear to have a relatively high rate of thromboembolic events.
- These findings suggest that the interaction between AEDs and DOACs might be of high clinical relevance.
- Indeed, caution is needed when prescribing AEDs to patients on concomitant treatment with DOACs.