

## Letters to the Editor

### Increased Risk of Bleeding in Elderly Patients Treated With Oral Anticoagulants and Angiotensin-Converting Enzyme Inhibitors



#### To the Editor:

Information about bleeding events (BEs) in patients on non-vitamin K antagonist oral anticoagulants (NOACs) is derived from clinical trials, in which participants do not share the characteristics of real-life older populations. Also, knowledge about adverse reactions to NOACs is restricted to few interactions with medications—mostly infrequently used in older populations—that share common metabolic pathways.<sup>1</sup> We assessed the correlates of BEs in a cohort of 101 patients aged 65+ with nonvalvular atrial fibrillation who were prescribed NOACs at the geriatric service of the Catholic University, Rome, from February 2017, to January 2018, and followed for a median of 11 months (Table 1).

The percent population attributable risk (PAR) was calculated as  $100 \times (Px \times [\text{odds ratio (OR)} - 1]) / (1 + (Px \times [\text{OR} - 1]))$ .

Forty-nine participants took apixaban, 29 dabigatran, 15 rivaroxaban, and 8 edoxaban. BEs occurred in 12 participants; 2 required transfusions, and 1 died from gastrointestinal bleeding.

Use of angiotensin-converting enzyme inhibitors (ACEIs) was recorded in 26 subjects: 15 ramipril, 7 enalapril, 2 perindopril, 1 captopril, and 1 zofenopril.

No differences were found in incident BEs when comparing single NOACs (all  $P > 0.700$ ).

ACEIs were taken by 7 of 12 (58%) participants with incident BEs and by 19 of 89 (21%) patients without BEs ( $P = 0.011$ ). In logistic regression, use of ACEIs was associated with BEs in crude model (OR = 5.16; 95% CI, 1.47–18.09;  $P = 0.010$ ); adjusting for age and sex (OR = 5.65; 95% CI, 1.56–20.51;  $P = 0.008$ ); and adjusting for age, sex, serum creatinine, and HAS-BLED score (OR = 5.73; 95% CI, 1.54–21.32;  $P = 0.009$ ).

Kaplan–Meier analysis indicated that the risk of bleeding was significantly increased among participants on ACEIs. Increasing ACEIs dosages were associated with increasing risk of bleeding ( $\chi^2 = 8.94$ ; log-rank  $P = 0.030$ ). The effect of single agents could not be analyzed because of insufficient statistical power.

The PAR of bleeding for treatment with ACEIs was 21%. Our results indicate that, in older patients on NOACs, use of

ACEIs is associated with increased risk of bleeding in a dose-dependent manner. This finding is of interest, as ACEIs are frequently prescribed for older patients with atrial fibrillation. In this study, the PAR indicated that switching patients treated with ACEIs to alternative drugs would reduce the occurrence of bleeding by 21%. ACEIs might increase the risk of bleeding associated with NOACs by interfering with CES-1 metabolism<sup>2</sup> or through their anticoagulant and antiplatelet effects.<sup>3</sup> More simply, NOACs kinetics might be altered by ACEIs because these agents frequently induce subclinical impairment of renal function in older populations.<sup>4</sup> The interaction of ACEIs with NOACs deserves further investigation by large, dedicated databases.

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#### Disclosures

The authors have no conflicts of interest to disclose.

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**Table 1. Main characteristics of participants according to the occurrence of bleeding**

	N (%), mean $\pm$ SD, or n (%) or median (IQR)		<i>P</i> value
	Patients with bleeding (N = 12)	Patients without bleeding (N = 89)	
Age, yrs	83 $\pm$ 5	83 $\pm$ 7	0.746
Sex (female)	8 (67)	53 (60)	0.759
MMSE	21 $\pm$ 10	24 $\pm$ 6	0.405
GFR	94.5 $\pm$ 31.7	58.2 $\pm$ 31.1	0.204
Hemoglobin (g/dL)	11.8 $\pm$ 1.6	12.4 $\pm$ 1.7	0.286
Platelets ( $\times 10^3/\mu\text{L}$ )	226 $\pm$ 48	226 $\pm$ 103	0.993
CHA <sub>2</sub> DS <sub>2</sub> -VASC score	5 $\pm$ 1	5 $\pm$ 2	0.663
HAS-BLED score	3 (3-4)	3 (2-4)	0.504
Impairment in ADLs	6 (50)	42 (47)	0.999
Impairment in IADLs	6 (50)	53 (54)	0.548
Diabetes	1 (8)	18 (20)	0.455
Hypertension	11 (92)	75 (84)	0.688
Cerebrovascular disease	4 (33)	32 (36)	0.999
Falls over the last year	3 (25)	28 (31)	0.751
Previous use of anticoagulants	2 (17)	16 (18)	0.999
Fall risk score	2 (1-4)	2 (1-3)	0.423
Total number of drugs	6 (4-8)	5 (1-6)	0.134
ACEIs	7 (58)	19 (21)	0.011
ARBs	1 (8)	23 (26)	0.285
$\beta$ -Blockers	9 (75)	48 (54)	0.221
Calcium antagonists	1 (8)	13 (15)	0.999
Antisecretives/Antacids	10 (83)	50 (56)	0.116
Diuretics	9 (75)	44 (49)	0.128
Antiplatelets	1 (8)	15 (17)	0.685
Psychotropic drugs	3 (25)	15 (17)	0.444
Orthostatic hypotension	1 (8)	1 (1)	0.225
Severe osteoarthritis	4 (33)	18 (20)	0.288
Dizziness	1 (8)	5 (6)	0.541

Impairment in ADLs: Impairment in 1 or more Katz's Activities of Daily Living. Impairment in IADLs: Impairment in 2 or more Lawton and Brody's Instrumental Activities of Daily Living. Fall risk score: calculated in the ENGAGE AF-TIMI 48 study. ATC codes C09A (ACEIs) and C09B (ACEIs, associations), ATC codes C09C (ARBs) and C09D (ARBs, associations).

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; GFR, glomerular filtration rate; MMSE, Mini-Mental State Examination test.