# Persistence and predictors for non-persistence to edoxaban therapy in patients with atrial fibrillation: 4-year follow-up data from the ETNA-AF-Europe study

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# BACKGROUND

- Non-persistence to non-vitamin K antagonist oral anticoagulans (NOACs) is associated with increased stroke risk in patients with atrial fibrillation (AF).<sup>1</sup>
- To date, most NOAC persistence studies have been retrospective and often did not include patients receiving edoxaban.
- ETNA-AF-Europe (NCT02944019) was a prospective, observational study conducted in patients with AF receiving edoxaban.<sup>2</sup>
- In the 4-year follow-up of ETNA-AF-Europe, approximately 30% of the patients did not reach the end of the study period due to death, lost-to-followup, withdrawal of consent, transfer to another institution, other or missing.<sup>3</sup>
- Identifying predictors for non-persistence may be useful when considering the design of future studies and help develop strategies to reduce non-persistence in clinical practice.

## PURPOSE

 To define and describe patients who did not reach the end of the study period and patients who were non-persistent to edoxaban during the 4-year follow-up of ETNA-AF-Europe.

## **METHODS**

- In this analysis, patients not reaching the end of the study period and patients who were non-persistent after 4 years of treatment were examined, including patients switching to other NOACs and reasons for discontinuation.
- Non-persistence was defined as the permanent discontinuation of edoxaban and did not include a missed dose or interruption
- Persistence was defined as no permanent discontinuation of edoxaban and may have included a missed dose or interruption
- Baseline predictors for not reaching the end of the study period and baseline predictors for non-persistence with edoxaban treatment during 4 years of follow-up were also examined.
- For backward elimination, the criterion was a p-value of 5%

# RESULTS

### Baseline patient characteristics

- Overall, 13,164 patients were included in the analysis, and 14.3% of patients died during the whole study period.
- Baseline characteristics are presented for patients who: completed the study (N=9417), prematurely discontinued the study (N=3598), and were persistent (N=10,017) or non-persistent (N=3118) at 4 years (Table 1).

### Premature study termination A total of 3598 (27.3%) patients did not reach the end of the

- study period.
  After baseline, and before the 1-year data collection point, 733 (5.6%) of patients had left the study.
- Analogously, a total of 941 (7.1%), 941 (7.1%) and 983 (7.5%) patients did not reach the next (i.e. second, third and fourth year) data collection points, respectively.
- Of patients who prematurely terminated the study, 1878 (52.5%) died, 1088 (30.4%) were lost-to-follow-up, 249 (7.0%) withdrew consent, and 212 (5.9%) transferred to another institution.

#### Persistence

- A total of 9417 (71.5%) patients were classified as completing the study.
- In the first year of follow-up, 11,800 (89.6%) patients were fully persistent. A total of 10,850 (86.8%), 9953 (86.2%) and 9014 (87.1%) were fully persistent during the second, third and fourth years, respectively.
- Of patients who completed the study, 8232 (87.4%) were classified as persistent within the 4 years, and 580 (6.2%) permanently discontinued edoxaban without switching to another NOAC (percentages were based on patients who were still in the study at the beginning of the considered year).

### Table 1. Baseline patient characteristics

	Total (N=13,164)	Completed study (N=9417) <sup>-</sup>	Premature study termination (N=3598) <sup>-</sup>	Persistent at 4 years (n=10,017)†	Non-persistent at 4 years (N=3118)†
Age, years, median (IQR)	75.0 (68.0-80.0)	74.0 (67.0-79.0)	78.0 (71.0-83.0)	74.0 (68.0-79.0)	77.0 (70.0-82.0)
Male	7461 (56.7)	5326 (56.6)	2040 (56.7)	5626 (56.2)	1818 (58.3)
Body mass index, kg/m <sup>2</sup> , median (IQR)	27.3 (24.7-30.7)	27.4 (24.8-30.8)	27.1 (24.2-30.5)	27.4 (24.8-30.8)	27.0 (24.3-30.2)
Creatinine clearance", mL/min, median (IQR)	68.9 (52.7-87.9)	71.8 (56.4-90.0)	60.9 (45.0-79.8)	70.8 (54.9-89.2)	62.8 (46.3-82.3)
Stroke/TIA/SEE	1208 (9.2)	837 (8.9)	365 (10.1)	881 (8.8)	324 (10.4)
Any major bleeding	118 (0.9)	77 (0.8)	40 (1.1)	72 (0.7)	45 (1.4)
CHA <sub>2</sub> DS <sub>2</sub> -VASc, median (IQR) <sup>+1</sup>	3.0 (2.0-4.0)	3.0 (2.0-4.0)	4.0 (3.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)
HAS-BLED, median (IQR) <sup>‡I</sup>	3.0 (2.0-3.0)	2.0 (2.0-3.0)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	3.0 (2.0-3.0)

Persistence is defined as no permanent discontinuation of edoxidan during the considered time period which is from Baseline unit in minimum of (reference start date-1460, date of death, date of premature termination and last wirk date). Furthermore, there are galaxies with a data calculation points, but the last wirks date before the format of of thy ser, as protocal allowed a range of 4-20 months. Data presented as n (%) unless otherwise noted. "Columns for completer and premature discontinuations do not sum up to ball due to missing judgement from investigator. 'A total of 29 patients with documented permanent discontinuation of

code because don't not include the source of the source - missing components are contributing with 0. Modified (HLQ), SAR, Modified (HSQ), SAR, Modified (HS

HAS-BLED, hypertension, CrCI s80mL/min or liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65 years, medication usage predisposing to bleeding or alcohol usage; IQR, interquartilerange; SEE, systemic embolic event; TIA, transient ischaemicatack

# Figure 1. Baseline characteristics associated with (A) premature study termination (excluding deaths) and (B) non-persistence following backwards elimination

(A)	1	HR (95% CI); p-value	(B)		HR (95% CI); p-value
Age <65 years			Age	1	
≥65–74 years	J	1; NA 0.76 (0.64–0.91); 0.0026	<65 years	J	1; NA
≥75–80 years			≥65–74 years	L	0.89 (0.76-1.04); 0.1463
>80 years	1	0.89 (0.73-1.08); 0.2440	≥75–80 years	T.	1.04 (0.87–1.24); 0.6988
Male sex	1	0.87 (0.70-1.08); 0.2037	>80 years		1.36 (1.13–1.64); 0.0012
BMI		1.13 (1.00-1.28); 0.0464	Male sex	<b>T</b>	1.19 (1.08–1.31); 0.0003
<18.5 kg/m <sup>2</sup>		4 04 (4 00 0 07); 0 0040	Body weight		4 04 (4 00 4 05): 0 0000
≥18.5–25.0 kg/m <sup>2</sup>		1.94 (1.23-3.07); 0.0046	<70 kg		1.21 (1.08–1.35); 0.0008
≥25.0–30.0 kg/m <sup>2</sup>	1	1; NA	≥70–80 kg	T.	1; NA
≥30 kg/m <sup>2</sup>	Ť	0.99 (0.86-1.14); 0.0882	≥80–90 kg		1.20 (1.07–1.34); 0.0015
CrCl	Ť	0.99 (0.84-1.17); 0.9170	≥90 kg	•	1.12 (1.00-1.27); 0.0546
<30 mL/min			CrCl		
≥30–50 mL/min	<b>H</b> •	1.58 (1.07–2.34); 0.0211	<30 mL/min		H2.24 (1.80−2.80); <0.0001
≥50-50 mL/min	<b>H</b>	1.27 (1.04–1.57); 0.0217	≥30–50 mL/min		1.47 (1.27–1.71); <0.0001
≥80 mL/min	*	1.10 (0.94–1.28); 0.2443	≥50–80 mL/min	H+H	1.21 (1.08–1.37); 0.0017
Chronic hepatic disease	1	1; NA	≥80 mL/min	<b>†</b>	1; NA
	<b>⊢♦</b> −−1	1.71 (1.16-2.50); 0.0064	CHA <sub>2</sub> DS <sub>2</sub> -VASc score		
Alcohol use (averaged number of daily drinks)			0–1	<b>†</b>	1; NA
None	1	1; NA	24 H	H	0.82 (0.69-0.96); 0.0149
≤1	•	0.88 (0.75-1.02); 0.0946	>4	<b>◆</b>  1	0.89 (0.72-1.09); 0.2646
>1 and ≤2	H	0.72 (0.57-0.90); 0.0043	HAS-BLED score		
>2 and ≤4	•	0.76 (0.53-1.10); 0.1450	0–1	+	1; NA
>4 H	•	0.77 (0.46-1.30); 0.3258	2-4	♦	0.88 (0.74-1.04); 0.1421
Unknown	4	0.97 (0.83-1.12); 0.6515	>4	<b>⊢♦</b> −−1	1.17 (0.85-1.63); 0.3364
AF type			Congestive heart failure	<b>₩</b> H	1.32 (1.20-1.46); <0.0001
Paroxysmal	+	1; NA	Vascular disease	H+H	1.30 (1.14–1.47); <0.0001
Persistent	+	1.01 (0.88-1.16); 0.8929	Chronic hepatic disease	<b>⊢</b> ⊷−i	1.44 (1.11-1.87); 0.0057
Long standing persistent or permanent	<b>e</b> i	1.24 (1.07-1.43); 0.0037	Alcohol use (averaged number of daily drinks	5)	
Smoking			None	+	1; NA
Currently	He H	1.34 (1.08-1.66); 0.0072	≤1	H.	0.98 (0.88-1.09); 0.6816
Current NVAF symptoms	•	0.84 (0.74-0.97); 0.0159	>1 and ≤2	He	0.99 (0.85-1.15); 0.8534
Compliance at baseline as judged by investigator			>2 and ≤4	<b></b>	1.38 (1.13-1.69); 0.0020
Always	•	1; NA	>4	<b>↓↓</b>	1.31 (0.96-1.79); 0.0918
Almost always		1.09 (0.92-1.29); 0.3109	Unknown	<b>I</b>	1.17 (1.06-1.30); 0.0022
Most of the time	<b>⊢</b> •—	1.23 (0.72-2.09); 0.4445	Frailty, perceived	H <b>4</b> 4	1.56 (1.41–1.74); <0.0001
Less than half of the time	•	4.64 (1.49-14.50); 0.0083	COPD	H <b>4</b> H	1.42 (1.27-1.59); <0.0001
Missing/unknown	H <b>4</b> H	1.60 (1.39–1.83); <0.0001	AF type		
No VKA in the 12 months period prior or at baselin	•	1.42 (1.21–1.67); <0.0001	Paroxysmal	1	1; NA
No on going A/R control drug at baseline	<b>●</b> i	1.20 (1.07-1.35); 0.0015	Persistent	1	0.92 (0.84-1.01); 0.0783
			Long standing persistent or permanent	1	1.05 (0.96-1.16); 0.2729
-1	1 3	5	Smoking	T	
· · · · · · · · · · · · · · · · · · ·	$\longrightarrow$		Currently		1.19 (1.03-1.39); 0.0216
Decreased risk of premature termination		premature	Current NVAF symptoms		1.22 (1.03-0.97); 0.0108
			Ablation		1.27 (1.09-1.49); 0.0022
			0	1 2	3
			0	. 4	•

Decreased risk of non-persistence Increased risk of non-persistence

HR for patients with premature study terminations (excluding detates) and non-persistence from cox-model after backwards electron from baseline to 4 years. The criterion for backward elimination was p=0.05. AF, etails feithington, RH, adverse reaction; BMI, bodys-VaSc, heart alliuter, hypertension, age (65-74 years = 2 point; CF years = 2 point; Jadebes, prior storeNTIVSEE (2 points) vascular disease, and sex category (female sex: 1 point; CL confidence interval; COPO, chronic obstructive pulmonary disease; CrGL evanies the category (female sex: 1 point; CL confidence interval; COPO, chronic obstructive pulmonary disease; CrGL evanies the category (female sex: 1 point; CL confidence interval; COPO, chronic obstructive pulmonary disease; CrGL evanies the category (female sex: 1 point; CL confidence interval; COPO, chronic obstructive pulmonary disease; CrGL evanies the category (female sex: 1 point; CL confidence interval; COPO, chronic obstructive pulmoary disease; CrGL evanies the category (female sex: 1 point; CL confidence interval; COPO, chronic obstructive pulmoary disease; CrGL evanies; CL control, CL control, CL control, advective pulmoary disease; CrGL evanies; CL control, CL control, CL control, control, advective; CL control, contr

# CONCLUSIONS

Solution West patients in ETNA-AF-Europe reached the end of the study. Less than a quarter were classified as non-persistent during the 4-year follow-up, and a small number completely stopped anticoagulant therapy

🖌 Male sex, low renal function, chronic hepatic disease and smoking were associated with both treatment discontinuation and non-persistence

· In the first year, 1332 (10.1%) patients had permanently

discontinued treatment. The most common reasons for discontinuation were adverse drug reaction (ADR)/clinical

discontinued treatment. Of these, 13.9% discontinued

· At the end of 4-year follow-up, 3116 patients had

event, while 60.4% were defined as other.

termination (Figure 1A)

Factors associated with premature study

event (16.1%), patient's event (14.2%), and other (52.0%).

because of ADR/clinical event and 9.7% because of patient's

· After backwards elimination, baseline characteristics associated

with higher chance for premature study termination (excluding

death) were: male sex, low body mass index, low renal function.

chronic hepatic disease. long standing persistent/permanent AF.

smoking, low compliance as judged by investigator, vitamin K

antagonist-naïve, and no rate/rhythm control drug at baseline.

Factors associated with non-persistence (Figure 1B)

higher chance for being non-persistent at the end of the study

· After backwards elimination, characteristics associated with

were: increasing age, male sex, body weight, low renal

function, high HAS-BLED score, heart failure, vascular

frailty, chronic obstructive pulmonary disease, smoking,

current NVAF symptoms, and ablation.

disease, chronic hepatic disease, alcohol use, perceived

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