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

Igor Diemberger[1], Marianne Gwechenberger[2], Joris J Komen[3], Eva-Maria Fronk[3], Raffaele De Caterina[4], Paulus Kirchhof[5–7]

[1]Department of Medical and Surgical Sciences – DIMEC, University of Bologna, Bologna, Italy; [2]Department of Cardiology, Medical University of Vienna, Vienna, Austria; [3]Daiichi Sankyo Europe GmbH, Munich, Germany; [4]Cardiology Division, Pisa University Hospital, University of Pisa, Pisa, Italy; [5]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK; [6]University Heart and Vascular Centre Hamburg, Hamburg, Germany; [7]German Center for Cardiovascular Sciences (DZHK), partner site Hamburg/Kiel/Lübeck, Germany

BACKGROUND

- Non-persistence to non-vitamin K antagonist oral anticoagulans (NOACs) is associated with increased stroke risk in patients with atrial fibrillation (AF).[1]
- 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.[2]
- 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-follow-up, withdrawal of consent, transfer to another institution, other or missing.[3]
- 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).
- In the first year, 1332 (10.1%) patients had permanently discontinued treatment. The most common reasons for discontinuation were adverse drug reaction (ADR)/clinical event (16.1%), patient's event (14.2%), and other (52.0%).
- At the end of 4-year follow-up, 3116 patients had discontinued treatment. Of these, 13.9% discontinued because of ADR/clinical event and 9.7% because of patient's event, while 60.4% were defined as other.

Factors associated with premature study termination (Figure 1A)

- 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)

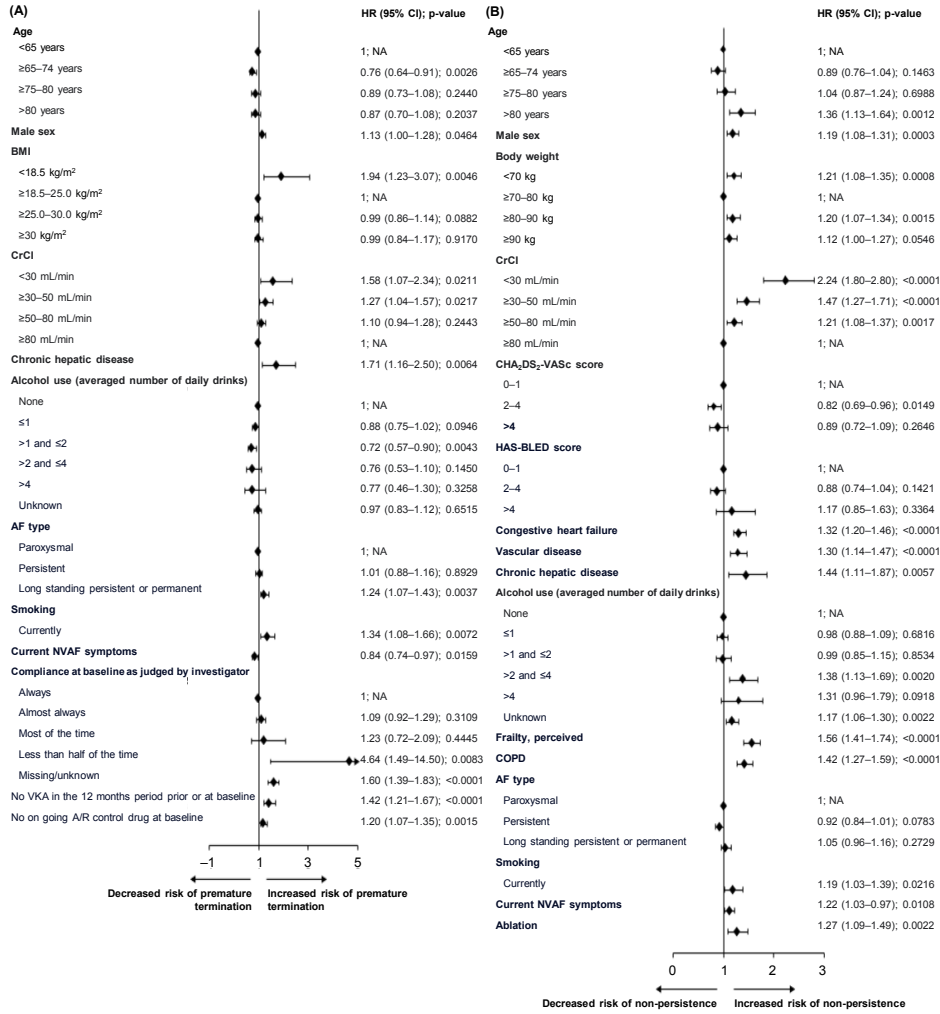
- After backwards elimination, characteristics associated with higher chance for being non-persistent at the end of the study were: increasing age, male sex, body weight, low renal function, high HAS-BLED score, heart failure, vascular disease, chronic hepatic disease, alcohol use, perceived frailty, chronic obstructive pulmonary disease, smoking, current NVAF symptoms, and ablation.

Table 1. Baseline patient characteristics

	Total (N=13,164)	Completed study (N=9417)*	Premature study termination (N=3598)*	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/m², 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_2DS_2-VASc, median (IQR)‡¶	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)‡‖	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 edoxaban during the considered time period which is from Baseline until the minimum of (reference start date+1460, date of death, date of premature termination and last visit date). Furthermore, there are patients with all data collection points, but the last visit took place before the formal end of 4th year, as protocol allowed a range of +/-2 months
Data presented as n (%) unless otherwise noted. *Columns for completer and premature discontinuators do not sum up to total due to missing judgement from investigator. †A total of 29 patients with documented permanent discontinuation of edoxaban, but missing stop data, who could not be assigned as persistent/non-persistent at 4 years and are only presented in total column. **Values out of 5–150 range are considered as missing for creatinine clearance. ‡Derived version, assuming that - when adding up the single components of the score – missing components are contributing with 0. ¶Modified CHA_2DS_2-VASc, ‖Modified HAS-BLED
AF, atrial fibrillation; **CHA_2DS_2-VASc**, heart failure, hypertension, age (65–74 years = 1 point, ≥75 years = 2 points), diabetes, prior stroke/TIA/SEE (2 points), vascular disease, and sex category (female sex: 1 point); **HAS-BLED**, hypertension, CrCl ≤80mL/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**, interquartile range; **SEE**, systemic embolic event; **TIA**, transient ischaemic attack

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



HR for patients with premature study terminations (excluding deaths) and non-persistence from cox-model after backwards selection from baseline to 4 years. The criterion for backward elimination was p=0.05.
AF, atrial fibrillation; **A/R**, adverse reaction; **BMI**, body mass index; **CHA_2DS_2-VASc**, heart failure, hypertension, age (65–74 years = 1 point, ≥75 years = 2 points), diabetes, prior stroke/TIA/SEE (2 points), vascular disease, and sex category (female sex: 1 point); **CI**, confidence interval; **COPD**, chronic obstructive pulmonary disease; **CrCl**, creatinine clearance; **HAS-BLED**, hypertension, CrCl ≤80mL/min or liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65 years, medication usage predisposing to bleeding or alcohol usage; **NVAF**, non-valvular atrial fibrillation; **VKA**, vitamin K antagonist

CONCLUSIONS

- Most 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

Presented at: European Society of Cardiology (ESC) 2024, London, UK, 30 August – 2 September 2024

REFERENCES

1. Holthuis E, et al. *Drugs Real World Outcomes*. 2022;9(4):597–607; 2. De Caterina R, et al. *BMC Cardiovasc Disord*. 2019;19:165; 3. Kirchhof P, et al. *Int J Cardiol*. 2024;132118.

ACKNOWLEDGEMENTS

This ePoster was sponsored by Daiichi Sankyo Europe GmbH, Munich, Germany.
Writing and editorial support were provided by Vicky Hinstridge from inScience Communications, Springer Healthcare Ltd, UK, and funded by Daiichi Sankyo Europe GmbH, Munich, Germany.

ETNA-AF Europe