Baseline demographic and clinical characteristics as predictors of adverse outcomes to improve management of patients with AF receiving edoxaban: A subanalysis of the ETNA-AF registry

Doralisa Morrone[1], Tze-Fan Chao[2], Cathy Chen[3], Eue-Keun Choi[4], Joris R de Groot[5], Paulus Kirchhof[6,7,8], Ladislav Pecen[9], Hung Fat Tse[10], Martin Unverdorben[3], Raffaele De Caterina[1]

[1]Cardiology Division, Pisa University Hospital and University of Pisa, Pisa, Italy; [2]Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan; [3]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [4]Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Hospital, Seoul, Korea; [5]Department of Cardiology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [6]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK; [7]Department of Cardiology, University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [8]German Center for Cardiovascular Sciences (DZHK), partner site Hamburg/Kiel/Lübeck, Hamburg, Germany; [9]Institute of Computer Science of Academy of Sciences of the Czech Republic, Prague, Czech Republic; [10]Cardiology Division, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China

INTRODUCTION

- Atrial fibrillation (AF) is associated with substantial morbidity and mortality and contributes a substantial burden to societal health and health economics[1,2]
- Identification of characteristics predisposing patients with AF receiving oral anticoagulation to adverse clinical events may improve the management of these patients and help optimise the balance between efficacy and bleeding risk[3]

OBJECTIVE

- To identify clinical parameters associated with cardiovascular (CV) events, including any stroke, in patients with AF receiving edoxaban

METHODS

- The ETNA-AF observational programme prospectively collects data of patients with AF treated with edoxaban
  - This subanalysis included data from patients in Europe (NCT02944019), Japan (UMIN000017011), Korea/Taiwan (NCT02951039), and Thailand (NCT03247569)[4,5]
- A risk prediction model was built and evaluated for 2 dependent variables
  - Composite endpoint 1: CV death, all stroke or systemic embolism or transient ischaemic attack (TIA), myocardial infarction (MI), and venous thromboembolism (VTE)
  - Composite endpoint 2: CV death, all stroke, and MI
- Independent variables used to identify predictors of the composite endpoints at baseline are indicated in **Table 1**

RESULTS

- Overall, 26,580 edoxaban patients were included in the analysis, with 3034 (11.4%) patients aged ≥85 years at baseline (**Table 1**)
- All clinical variables, except smoking history and hepatic impairment, were significant predictors (P <0.05) of both composite endpoints
- Stronger predictors of composite endpoint 1 included history of any stroke/TIA, peripheral arterial disease (PAD), and heart failure (HF), a body mass index (BMI) <18.5 kg/m^2, and a lower creatinine clearance (CrCl) at baseline (all P ≤0.0001; **Figure 1A**)
- The most significant predictors of composite endpoint 2 included a history of ischaemic stroke, PAD, HF, and a BMI <18.5 kg/m^2 (all P ≤0.0001; **Figure 1B**)

CONCLUSIONS

A history of ischaemic stroke or any stroke/TIA, PAD, and HF and a BMI <18.5 kg/m^2 were predictive of a higher risk of the composite endpoints in patients with AF on edoxaban

Most risk factors identified as predictive of the composite endpoints are confirmatory of the CHA_2DS_2-VASc score; lower CrCl and BMI <18.5 kg/m^2 were additional risk factors identified that have not been included in previous risk scores.

This subanalysis of the Global ETNA-AF programme identified additive risk factors of CV events, such as lower CrCl and BMI <18.5kg/m^2, which were not previously included in other risk scores like the CHA_2DS_2-VASc score

Table 1. Baseline demographics and clinical characteristics

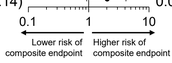
	Global N = 26,580	Europe n = 13,164	Japan n = 10,342	South Korea, Taiwan, and Thailand n = 3074
Age, years, mean (SD)[a]	73.6 (9.7)	73.6 (9.5)	74.2 (10.0)	71.7 (9.6)
Age ≥85 years[a]	3034 (11.4)	1382 (10.5)	1415 (13.7)	237 (7.7)
Sex, male	15,447 (58.1)	7461 (56.7)	6168 (59.6)	1818 (59.1)
Weight, kg, mean (SD)[a]	72.2 (18.2)	80.9 (17.2)	60.1 (12.8)	66.0 (12.4)
BMI				
>30 kg/m^2	4241 (19.4)	3643 (28.9)	347 (5.4)	251 (8.9)
<18.5 kg/m^2[a]	659 (3.0)	116 (0.9)	459 (7.1)	84 (3.0)
CrCl (Cockcroft Gault), mL/min, mean (SD)[a]	69.3 (28.6)	74.3 (30.3)	63.8 (25.7)	62.8 (23.9)
CHA_2DS_2-VASc, mean (SD)	3.26 (1.50)	3.20 (1.43)	3.39 (1.59)	3.13 (1.45)
HAS-BLED, mean (SD)	2.68 (1.06)	2.53 (0.99)	3.01 (1.14)	2.58 (0.99)
Type of AF				
Paroxysmal	13,235 (49.8)	7083 (53.9)	4769 (46.1)	1383 (45.0)
Persistent	5782 (21.8)	3175 (24.2)	1916 (18.5)	691 (22.5)
Long-standing persistent	2785 (10.5)	322 (2.5)	2046 (19.8)	417 (13.6)
Permanent	4748 (17.9)	2559 (19.5)	1610 (15.6)	579 (18.9)
Medical history				
Ischaemic stroke[a]	2875 (10.8)	697 (5.3)	1778 (17.2)	400 (13.0)
Transient ischaemic attack[a]	823 (3.1)	449 (3.4)	309 (3.0)	65 (2.1)
Major bleeding	437 (1.6)	118 (0.9)	252 (2.4)	67 (2.2)
Intracranial haemorrhage	333 (1.3)	62 (0.5)	230 (2.2)	41 (1.3)
Major gastrointestinal bleeding[a]	69 (0.3)	35 (0.3)	16 (0.2)	18 (0.6)
Peripheral artery disease[a]	624 (2.3)	432 (3.3)	170 (1.6)	22 (0.7)
Coronary artery disease[a]	4392 (16.5)	2762 (21.0)	1142 (11.0)	488 (15.9)
Previous myocardial infarction	1000 (3.8)	567 (4.3)	382 (3.7)	51 (1.7)
Previous major or CRNM bleeding	733 (2.8)	255 (1.9)	389 (3.8)	89 (2.9)
Comorbidities				
Chronic obstructive pulmonary disease[a]	1502 (5.7)	1206 (9.2)	147 (1.4)	149 (4.8)
Diabetes mellitus[a]	6217 (23.4)	2881 (21.9)	2431 (23.5)	905 (29.4)
Hypertension	19,864 (74.7)	10,155 (77.1)	7477 (72.3)	2232 (72.6)
Heart failure[a]	5242 (19.7)	2042 (15.5)	2793 (27.0)	407 (13.2)
Hepatic impairment at baseline[a]	118 (0.4)	102 (0.8)	4 (0.0)	12 (0.4)
Renal impairment at baseline	15,341 (70.8)	7549 (64.3)	5544 (78.4)	2248 (78.6)
Alcohol use >2 drinks/day	1089 (5.2)	557 (5.5)	416 (4.9)	116 (4.6)
Currently smoking	1848 (8.4)	823 (7.5)	819 (9.7)	206 (8.0)

Data shown as n (%) unless otherwise indicated. [a]Indicated variable included in the prediction model.
AF, atrial fibrillation; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and sex category (female); CrCl, creatinine clearance; CRNM, clinically relevant nonmajor; HAS-BLED, hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalised ratio, elderly, drug/alcohol usage; SD, standard deviation.

Figure 1. Demographics and clinical characteristics as predictors for (A) composite endpoint 1 (CV death, all stroke or systemic embolism or TIA, MI, and VTE) and (B) composite endpoint 2 (CV death, all stroke, and MI)

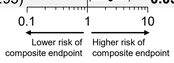
(A)

Predictor	HR (95% CI)	*P*-value
Age	1.03 (1.01, 1.04)	**0.0002**
≥85 years (yes vs no)	1.28 (1.02, 1.62)	**0.03**
Medical history (yes vs no)		
Any stroke and TIA	2.19 (1.86, 2.58)	**<0.0001**
Peripheral artery disease	2.04 (1.55, 2.70)	**<0.0001**
Heart failure	1.39 (1.18, 1.64)	**<0.0001**
Coronary artery disease	1.34 (1.13, 1.58)	**0.0007**
Major or CRNM GI bleeding	1.99 (1.29, 3.08)	**0.002**
COPD	1.32 (1.04, 1.67)	**0.02**
Valvular disease	1.27 (1.06, 1.53)	**0.01**
Diabetes mellitus	1.21 (1.04, 1.42)	**0.02**
BMI <18.5 kg/m^2	1.98 (1.40, 2.78)	**0.0001**
Weight at baseline (kg)	1.01 (1.01, 1.02)	**<0.0001**
CrCl at baseline (mL/min)	0.99 (0.99, 1.00)	**<0.0001**
Smoking history		
Current vs never	1.27 (0.95, 1.70)	0.1
Former vs never	1.09 (0.92, 1.30)	0.3
Unknown vs never	0.79 (0.62, 1.01)	0.06
Hepatic impairment		
Unknown vs no	0.61 (0.35, 1.06)	0.08
Yes vs no	1.96 (0.93, 4.14)	0.08



(B)

Predictor	HR (95% CI)	*P*-value
Age	1.02 (1.01, 1.04)	**0.0009**
≥85 years (yes vs no)	1.34 (1.04, 1.71)	**0.02**
Medical history (yes vs no)		
Ischaemic stroke	2.38 (1.96, 2.89)	**<0.0001**
Peripheral artery disease	2.16 (1.61, 2.90)	**<0.0001**
Heart failure	1.56 (1.31, 1.85)	**<0.0001**
Coronary artery disease	1.35 (1.13, 1.62)	**0.001**
Major or CRNM GI bleeding	2.11 (1.32, 3.38)	**0.002**
COPD	1.43 (1.12, 1.84)	**0.004**
Valvular disease	1.24 (1.02, 1.52)	**0.03**
Diabetes mellitus	1.34 (1.14, 1.59)	**0.0006**
BMI <18.5 kg/m^2	2.06 (1.43, 2.97)	**0.0001**
Weight at baseline (kg)	1.01 (1.01, 1.02)	**<0.0001**
CrCl at baseline (mL/min)	0.99 (0.99, 1.00)	**0.0002**
Hepatic impairment		
Unknown vs no	0.60 (0.33, 1.08)	0.09
Yes vs no	2.34 (1.11, 4.95)	**0.03**



Bold *P*-values are <0.05.
BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRNM, clinically relevant nonmajor; CV, cardiovascular; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischaemic attack; VTE, venous thromboembolism.

Presented at:
European Society of Cardiology 2023, Amsterdam, Netherlands, 25−28 August 2023

REFERENCES

1. Lippi G, et al. *Int J Stroke*. 2021;16(2):217-21.
2. Tanaka Y, et al. *J Am Heart Assoc*. 2021;10(15):e020163.
3. Ganesan AN, et al. *Eur Heart J*. 2016;37(20):1591-602.
4. De Caterina R, et al. *J Clin Med*. 2021;10(4):573.
5. Choi EK, et al. *J Clin Med*. 2021;10(22):5337.

ACKNOWLEDGEMENTS

Medical writing and editorial support were provided by Chuck Blajszczak, PhD, of AlphaBioCom, a Red Nucleus company, and funded by Daiichi Sankyo, Inc.

DISCLOSURES

DM declares fees, honoraria, and research funding from Daiichi Sankyo. **CC** and **MU** are employees of Daiichi Sankyo. **EKC** reports research grants from Daiichi Sankyo and Bristol Myers Squibb/Pfizer. **LP** has received fees and honoraria from Daiichi Sankyo, SOTIO, and Beckman Coulter. **JRdG** reports personal fees from Daiichi Sankyo during the conduct of the study; grants from Abbott, Atricure, Boston Scientific, and Medtronic; personal fees from Atricure, Bayer, Daiichi Sankyo, Johnson & Johnson, Medtronic, Novartis, and Servier; and other support from RhythmCARE outside the submitted work. **PK** declares research support for basic, translational, and clinical research projects from the British Heart Foundation, European Union, German Centre for Cardiovascular Research, Medical Research Council (UK), and several drug and device companies active in atrial fibrillation and has received honoraria from several such companies in the past. **TFC** and **HFT** have nothing to disclose. **RDC** declares fees, honoraria, and research funding received from Sanofi-Aventis, Boehringer Ingelheim, Bayer, Bristol Myers Squibb/Pfizer, Novartis, Merck, Portola, Roche, Guidotti, Menarini, and Daiichi Sankyo.

ETNA-AF Global