Low rate of worsening renal function after 2 years of treatment with edoxaban in patients from the ETNA-AF-Europe study

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Funding Acknowledgement: Type of funding sources: Private company. Main funding source(s): Daiichi Sankyo Europe GmbH

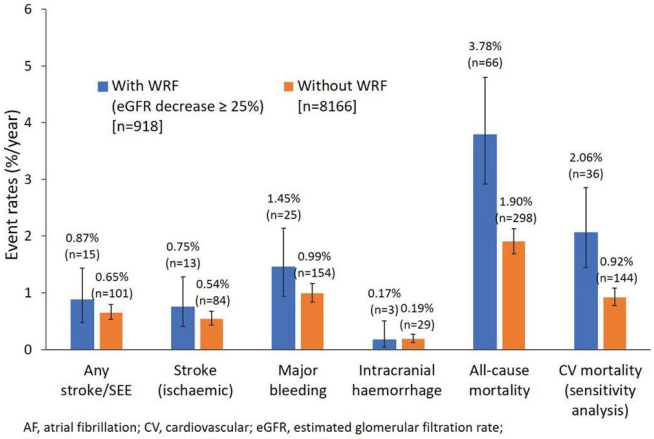
Background: Use of vitamin K antagonists (VKAs) is associated with a crude event rate of 23% per year for worsening renal function (WRF). Although non-vitamin K antagonist oral anticoagulants (NOACs) have been associated with a lower risk of longitudinal decline in renal function compared with VKAs, available evidence on renal function decline in patients using NOACs is still limited. Furthermore, renal function is a dose reduction criterion for NOACs, which poses an important question about how physicians should treat patients whose renal function worsens over time.
Purpose: To evaluate the degree of renal function decline in AF patients treated with edoxaban after 2 years of follow-up, and to investigate clinical outcomes of patients with vs without WRF in the ETNA-AF-Europe study.
Methods: ETNA-AF-Europe is a multinational, multicentre, observational, post-authorisation safety study conducted in 825 sites in 10 European countries. Results are based on a data snapshot taken on 26th October 2020 which include data up to 2 years of follow-up. Patients were excluded from the analysis population if data to calculate estimated glomerular filtration rate [eGFR] were not available for at least one of the follow-up timepoints of 1-year and 2-year. We categorised patients (n=9084) into two subgroups: 1) those with WRF (i.e. ≥25% decline in eGFR from baseline; n=918), and 2) those without WRF (n=8166). eGFR was estimated using the Cockcroft-Gault formula. Baseline characteristics and annualised event rates including 95% confidence intervals were analysed using descriptive analyses.
Results: Of the 13,417 patients in ETNA-AF-Europe who were included in the 2-year follow-up analysis, 9084 were included in this subgroup analysis, of whom 56.2% were male. Baseline eGFR were similar between patients with and without WRF when comparing across the different renal function categories (Table 1). The majority of the edoxaban-treated patients did not experience WRF (89.9%) during the 2 years of follow-up. The proportion of patients with WRF (10.1%) were older, more often frail and had higher rates of underlying comorbidities, such as diabetes, hypertension and heart failure (Table 1). Patients with WRF had higher annualised event rates of all-cause and cardiovascular death than those without (3.78% vs 1.90% and 2.06% vs 0.92%, respectively). Major bleeding and stroke rates were low, but numerically higher in patients with renal worsening compared to those without WRF (Figure 1). Intracranial haemorrhage rates remained low (0.17% vs 0.19%; Figure 1) in both subgroups.
Conclusions: This subgroup analysis provides real-world evidence for a low risk of WRF in AF patients treated with edoxaban over a 2-year period. Patients with WRF had higher mortality than those without, as well as numerically higher major bleeding and stroke rates. Importantly, intracranial haemorrhage rates remained low irrespective of WRF.

Table 1: Baseline characteristics of edoxaban-treated AF patients with or without worsening renal function during a 2-year follow-up period

	With WRF [n=918]	Without WRF [n=8166]
Edoxaban dose at baseline		
60 mg, OD	655 (71.4)	6194 (75.9)
30 mg, OD	263 (28.6)	1972 (24.1)
Overall adherence to SmPC		
Recommended edoxaban dose at baseline	755 (82.2)	6806 (83.3)
Non-recommended edoxaban dose at baseline	163 (17.8)	1360 (16.7)
Male	445 (48.5)	4662 (57.1)
Age [years]	75.7 ± 9.1	73.7 ± 9.3
Weight [kg]	78.6 ± 17.2	80.8 ± 17.1
Body Mass Index [kg/m^2]	28.1 ± 5.2	28.1 ± 5.1
Recalc. eGFR* (CG formula) [ml/min/1.73m^2]	76.2 ± 33.3	73.8 ± 29.5
≥ 80	357 (38.9)	2885 (35.3)
50; 80	369 (40.2)	3571 (43.7)
30; 50	167 (18.2)	1509 (18.5)
15; 30	25 (2.7)	200 (2.4)
<15	0 (0.0)	1 (0.0)
Recalc. CHA_2DS_2-VASc†	3.7 ± 1.4	3.2 ± 1.4
Recalc. mod. HASBLED‡	2.7 ± 1.1	2.6 ± 1.1
Type of atrial fibrillation		
Paroxysmal	428 (46.7)	4324 (53.0)
Persistent	254 (27.7)	2001 (24.5)
Long-standing persistent	22 (2.4)	204 (2.5)
Permanent	213 (23.2)	1623 (19.9)
Perceived Frailty	164 (17.9)	924 (11.3)
History of		
Diabetes mellitus	257 (28.0)	1819 (22.3)
Hypertension	769 (83.8)	6301 (77.2)
Heart failure (derived)	205 (22.3)	1151 (14.1)
Peripheral artery disease	34 (3.7)	281 (3.4)
Coronary heart disease	210 (22.9)	1734 (21.2)
Ischaemic stroke	61 (6.6)	497 (6.1)
Any bleeding	34 (3.7)	272 (3.3)
Valvular disease	199 (21.7)	1315 (16.1)

Data are presented as mean ± standard deviation for continuous variables or as number (%) for categorical variables. *GFR was estimated by Cockcroft-Gault formula. †Not including complex vascular plaque, and the score was based on derived heart failure; ‡Not including labile INR, alcohol use was defined as ≥1 unit/day, and defining the presence or absence of renal or hepatic disease was left to the discretion of the physician. CG, Cockcroft-Gault; CRNM, clinically relevant non-major; eGFR, estimated glomerular filtration rate; OD, once daily; WRF, worsening renal function.

Figure 1. Effect of worsening renal function on annualised event rates of clinical outcomes in edoxaban-treated patients at 2-years follow-up.



AF, atrial fibrillation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; SEE, systemic embolic event; WRF, worsening renal function