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RAPID COMMUNICATION

Kidney disease increases the risk of cardiovascular events in patients with device-detected atrial fibrillation: NOAH-AFNET 6

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Patients with device-detected atrial fibrillation (DDAF) without ECG-documented atrial fibrillation (AF) have a lower rate of stroke than patients with ECG-documented paroxysmal AF,[1,2] possibly due to their relatively low AF burden.[3] Reduced kidney function is associated with higher rates of stroke and cardiovascular events in patients with AF.[4–7] Kidney function is not included in the CHA2DS2-VA score or any other risk score in patients with DDAF. It is not known whether chronic kidney disease (CKD) affects the cardiovascular treatment effects of anticoagulation in patients with DDAF.

This prespecified analysis of the NOAH-AFNET 6 ($n = 2534$ patients) trial compared anticoagulation with edoxaban to no anticoagulation in patients with DDAF at various stages of CKD. The double-blind, double-dummy design of NOAH-AFNET 6 ensured that all patients randomized to edoxaban[1] received the approved dose. Fifty-five per cent of patients randomized to no anticoagulation received low-dose aspirin as part of the randomized treatment. Chronic kidney disease was defined at baseline according to the 2024 Kidney Disease Improving Global Outcomes (KDIGO) criteria[8] as no kidney disease or CKD stage KDIGO G1-G4. Chronic kidney disease Stage G5 patients were excluded from the trial, following the label of edoxaban and other anticoagulants. Exploratory analyses estimated the effect of kidney function as a continuous parameter on cardiovascular outcomes. The efficacy outcome of this analysis was the primary outcome of NOAH-AFNET 6, a composite of stroke, systemic embolism, or cardiovascular death. The safety outcome was the safety outcome of NOAH-AFNET 6, major bleeding according to ISTH criteria or death.[1] The outcomes are reported descriptively as subgroup-specific event numbers, event rates per 100 patient-years and as adjusted cause-specific hazard ratios (HRs) with two-sided 95% confidence intervals (CIs) and corresponding *P*-values. The treatment effects of creatinine on the outcome are presented using a locally estimated scatterplot smoothing (LOESS). The LOESS analysis allows graphic inspection but is merely hypothesis-generating. The impact of CKD on outcome was assessed with cause-specific Cox proportional hazard models with fixed effects for randomized group, sex, age, congestive heart failure history, hypertension history, diabetes mellitus, prior stroke/transient ischaemic attack/systemic thromboembolism, vascular disease history, aspirin intake at baseline, kidney function by estimated glomerular filtration rate (eGFR), and a frailty term for study site. All analyses are exploratory, reflecting the limited power of subgroup analyses, and thus, no adjustment for multiple testing was performed. Results are therefore hypothesis-generating.

Primary outcome events increased with increasing severity of CKD—Stage G1, 9 events/265 patient-years (3.4%); G2, 72/2854 (2.5%); G3a, 59/1245 (4.7%); G3b, 28/540 (5.2%); and G4, 16/147 (10.9%)—which was driven by higher rates of cardiovascular death and systemic embolic events. Of note, total stroke rate was low across all CKD stages (0.7–0.9%/year): G1, 2/265 (0.8%); G2, 25/2854 (0.9%); G3a, 15/1245 (1.3%); G3b, 5/540 (0.9%); and G4, 1/147 (0.7%, ***Figure 1B***, **left panel**). Safety events also increased with increasing severity of CKD, with more major bleeding than death: G1 12/258 (4.6%), G2 110/2870 (3.8%), G3a 78/1232 (6.3%), G3b 46/534 (8.6%), and G4 17/146 (11.6%, ***Figure 1B***, **right panel**). Anticoagulation with edoxaban did not interact with eGFR or CKD groups ($p_{interaction} = 0.50$, and 0.20). A LOESS plot suggests that anticoagulation could be more effective in patients with advanced CKD: event rates increased more in patients randomized to no anticoagulation than in patients randomized to edoxaban than in patients randomized to no anticoagulation (***Figure 1C***, **left panel**). A LOESS plot of the primary safety outcome suggested an increase in event rates with reduced kidney function without differences between treatment groups (***Figure 1C***, **right panel**). A multivariable analysis showed that age [HR 1.057, 95% CI (1.032–1.083); $P < 0.001$] and kidney function [HR 0.985, 95% CI (0.976–0.994); $P < 0.001$] were the strongest predictors of the primary outcome.

This exploratory analysis suggests that eGFR, a widely available blood biomarker, could be useful to refine thromboembolic risk estimation in patients with DDAF. The results are hypothesis-generating but can be used without additional measurements in clinical practice. The analysis also suggests that the approved dose of edoxaban retains its effectiveness across the spectrum of kidney functions tested. The continuous estimation of effect sizes even suggests a stronger effectiveness in patients with reduced kidney function, potentially due to their higher risk of thromboembolic events (**Panel C**). The increased event rate is due to more cardiovascular death, while strokes only increased a bit. This suggests that CKD is at least partially a reflection of overall frailty. The divergence of efficacy and safety LOESS plots supports a possible effect of anticoagulation within the limit of a hypothesis-generating analysis. These findings are consistent with similar analyses of warfarin or of different direct oral anticoagulants[4–7] in patients with ECG-diagnosed AF. Within the limits of a hypothesis-generating analysis, the results may be helpful to refine estimation of thromboembolic risk in selected patients with DDAF and reduced kidney function in context with AF burden (www.afburden.org) and clinical features (https://cordis.europa.eu/project/id/101080189/results).[9,10] Clearly, the findings call for independent, external validation in contemporary patients with DDAF.

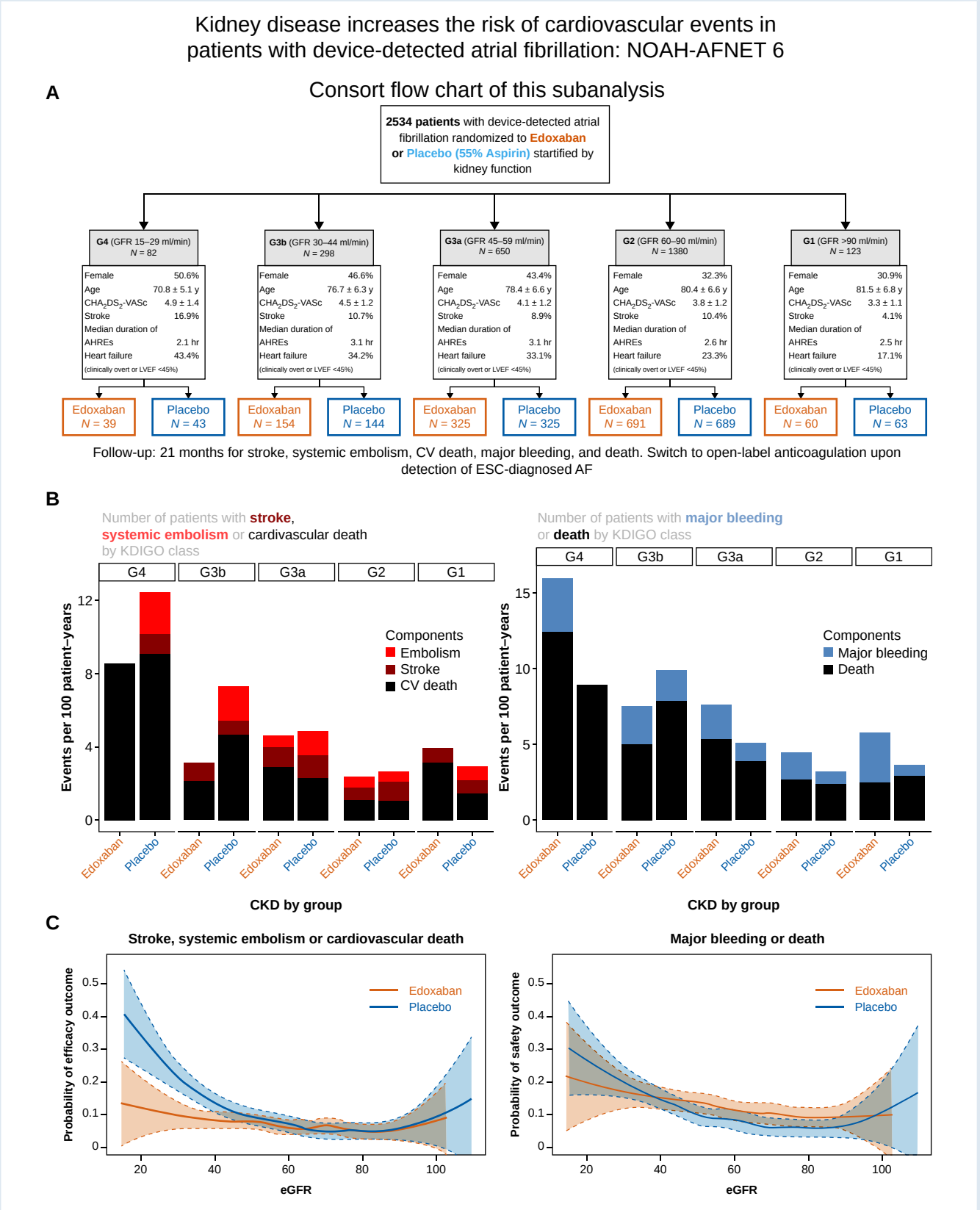

Figure 1 (*A*) CONSORT flow chart of this prespecified secondary analysis of the NOAH-AFNET 6 trial. Displayed are distributions of kidney function and baseline characteristics in each chronic kidney disease (CKD) group [according to KDIGO (Kidney Disease Improving Global Outcomes) definition], including sex, age, CHA2DS2-VASc-Score, previous stroke, median duration of device-detected atrial high-rate episodes (AHRE), and heart failure. **(***B***)** Stacked column plot of efficacy outcomes by CKD stage and randomized group in

(continued)

Figure 1 Continued
NOAH-AFNET 6. Efficacy outcomes (left side) [cardiovascular death (black), stroke (dark red), systemic embolism (lighter red)] by CKD stage and by randomized treatment and safety outcomes [right side, all-cause death (black) and major bleeding (blue)] by CKD stage and by randomized treatment. (*C*) LOESS (locally estimated scatterplot smoothing) plot of the hazard for a primary outcome event (left side) and for a safety outcome (right side) by estimated glomerular filtration rate (eGFR). Blue solid lines show the estimated event rate for patients randomized to placebo, while red solid lines the estimated event rate for patients randomized to edoxaban. Dotted lines indicate 95% confidence intervals. In patients with reduced kidney function (eGFR <30 mL/min/1.73m^2), the curves for the primary efficacy outcome and confidence intervals appear to separate. There was no significant treatment interaction between kidney function and the anticoagulation therapy. The curves for the safety outcome increased in both treatment groups without separation.

Conclusions

Age and eGFR are among the strongest predictors of cardiovascular events, in particular cardiovascular death, in patients with DDAF and clinical stroke risk factors. The effectiveness and safety of anticoagulation with edoxaban in the approved dose are not affected by CKD stage. Pending external validation, eGFR may help to refine cardiovascular risk estimation in selected patients with DDAF and reduced kidney function.

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Data availability

The data underlying these analyses will be made available upon reasonable request in accordance with data protection regulations and respecting the individual consent. Please contact info@kompetenznetz-vorhofflimmern.de

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