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ORIGINAL RESEARCH

Impact of renal function on edoxaban antithrombotic therapy in patients with atrial fibrillation and stable coronary artery disease: a prespecified analysis of the EPIC-CAD trial

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ABSTRACT

BACKGROUND: Renal function is a critical factor of ischaemic and bleeding risks in patients with atrial fibrillation (AF) receiving antithrombotic therapy.

AIMS: This study aimed to evaluate the impact of renal dysfunction in patients with AF and stable coronary artery disease (CAD) undergoing antithrombotic therapy.

METHODS: The Edoxaban Versus Edoxaban With antiPlatelet Agent In Patients With Atrial Fibrillation and Chronic Stable Coronary Artery Disease (EPIC-CAD) trial randomised patients to edoxaban monotherapy or dual antithrombotic therapy (edoxaban plus a single antiplatelet agent). In this prespecified analysis, patients were stratified by creatinine clearance into low (<50 mL/min) or high (≥50 mL/min) groups according to edoxaban dose-reduction criteria. The primary endpoint was net adverse clinical events (NACE: death from any cause, myocardial infarction, stroke, systemic embolism, urgent revascularisation, or major/clinically relevant non-major bleeding) at 12 months.

RESULTS: Of 1,040 randomised patients, 252 (24.2%) had low creatinine clearance; these patients were older and had more comorbidities compared with the 788 patients (75.8%) with high creatinine clearance. Patients with low creatinine clearance experienced higher risks of NACE (hazard ratio [HR] 1.72, 95% confidence interval [CI]: 1.19-2.49; p=0.004), ischaemic events (HR 2.70, 95% CI: 1.09-6.70; p=0.032), and bleeding (HR 1.54, 95% CI: 1.01-2.34; p=0.046). At 12 months, edoxaban monotherapy reduced NACE compared with dual therapy in both the low (12.1% vs 21.7%, HR 0.52, 95% CI: 0.28-0.98; p=0.042) and high creatinine clearance groups (5.2% vs 14.5%, HR 0.40, 95% CI: 0.25-0.65; p<0.001), with no interaction (p for interaction=0.53).

CONCLUSIONS: In patients with AF and stable CAD, edoxaban monotherapy led to a lower risk of primary NACE than dual antithrombotic therapy, regardless of renal function. (ClinicalTrials.gov: NCT03718559)

KEYWORDS: anticoagulant; atrial fibrillation; coronary artery disease; creatinine clearance; haemorrhage; ischaemia; renal function

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Impaired renal function and the presence of chronic kidney disease (CKD) are well known to markedly increase the risks of both ischaemic and bleeding events[1,2]. Therefore, renal function is a crucial factor for the optimal selection of antithrombotic therapy for patients with atrial fibrillation (AF) or coronary artery disease (CAD)[3,4]. Given that reduced renal clearance leads to increased drug concentrations and a heightened risk of bleeding events[5,6], dose adjustment of direct oral anticoagulants (DOACs) is essential in patients with AF and impaired renal function. Furthermore, since impaired renal function negatively influences platelet activity, potentially exacerbating the simultaneous risk of bleeding and ischaemic complications[7], the presence of renal dysfunction or CKD is a well-known risk factor for high bleeding risk in patients with known CAD[8]. While choosing antithrombotic therapy for patients with both AF and CAD is challenging[9,10], the task of optimally balancing the risks of ischaemic and bleeding complications becomes much more complicated when impaired renal function is present.

The Edoxaban Versus Edoxaban With antiPlatelet Agent In Patients With Atrial Fibrillation and Chronic Stable Coronary Artery Disease (EPIC-CAD) study was a randomised trial comparing edoxaban monotherapy with dual antithrombotic therapy (edoxaban plus a single antiplatelet agent) in patients with AF and stable CAD[11]. Given that the EPIC-CAD trial employed a creatinine clearance threshold of 50 mL/min as the criterion for edoxaban dose reduction, it provides a reasonable framework for assessing the impact of renal dysfunction on randomised antithrombotic treatment strategies and their clinical outcomes. Therefore, this prespecified analysis of EPIC-CAD data aims to enhance the interpretation of the trial's findings based on the status of renal function. Therefore, we examined clinical outcomes according to the randomised antithrombotic strategy (edoxaban monotherapy vs dual antithrombotic therapy) and the category of renal dysfunction in patients with concomitant AF and CAD.

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Impact on daily practice

Patients with atrial fibrillation and stable coronary artery disease who have impaired renal function face substantially higher risks of bleeding and net adverse clinical events. In this analysis, edoxaban monotherapy consistently reduced net adverse outcomes compared with dual antithrombotic therapy across all levels of renal function, without increasing ischaemic events. These findings support a monotherapy-first approach as a practical and safe antithrombotic strategy even in patients with reduced kidney function.

Methods

STUDY DESIGN AND PATIENT POPULATION

The trial design, methods, and primary outcomes of the EPIC-CAD study have been described previously[12]. In brief, EPIC-CAD was a multicentre, open-label, adjudicator-masked, randomised trial conducted at 18 hospitals in South Korea between May 2019 and September 2022. A total of 1,040 patients with high-risk AF (CHA_2DS_2-VASc score ≥2) and stable CAD (either revascularised or managed medically) were randomly assigned in a 1:1 ratio to receive either edoxaban monotherapy or dual antithrombotic therapy (edoxaban plus a single antiplatelet agent). Stable CAD was defined as one of the following: (1) chronic coronary syndrome treated with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at least 6 months prior to enrolment; (2) acute coronary syndrome treated with PCI or CABG at least 12 months prior to enrolment; or (3) anatomically confirmed CAD (≥50% stenosis of a major epicardial coronary artery on cardiac catheterisation or coronary computed tomography angiography) managed with medical therapy alone. Key exclusion criteria included contraindications for antithrombotic drugs, such as severe coexisting conditions or a high risk of bleeding; a history of intracranial haemorrhage; presence of prosthetic heart valves or moderate-to-severe mitral stenosis; and severe hepatic or renal dysfunction (creatinine clearance <15 mL/min).

The trial was approved by the investigational review board or ethics committee at each participating institution, and all patients provided written informed consent before enrolment. The trial was registered at ClinicalTrials.gov: NCT03718559.

RANDOMISATION, TRIAL REGIMENS, AND CATEGORY OF RENAL DYSFUNCTION

Enrolled patients were randomly assigned to receive either standard-dose edoxaban monotherapy (60 mg once daily) or dual antithrombotic therapy, comprising standard-dose edoxaban plus a single antiplatelet agent (either aspirin or a $P2Y_{12}$ inhibitor, at the discretion of the treating physician), for 12 months. Dose adjustment of edoxaban to 30 mg once daily was indicated in patients with a creatinine clearance of 15-50 mL/min (as calculated with the Cockcroft-Gault formula), a body weight of ≤60 kg, and the use of certain P-glycoprotein inhibitors.

Based on the edoxaban dose-reduction criteria, this prespecified subgroup analysis categorised study participants into low creatinine clearance (<50 mL/min) versus high creatinine clearance (≥50 mL/min) renal function groups. Further analyses within the high creatinine clearance groups distinguished between normal (creatinine clearance of 50-95 mL/min) and extra-normal (creatinine clearance >95 mL/min) levels. Sensitivity analyses, in accordance with the National

Abbreviations

AF	atrial fibrillation	**DOAC**	direct oral anticoagulant	**MI**	myocardial infarction
CABG	coronary artery bypass grafting	**eGFR**	estimated glomerular filtration rate	**PCI**	percutaneous coronary intervention
CAD	coronary artery disease	**ISTH**	International Society on Thrombosis and Haemostasis	**SAP**	statistical analysis plan
CKD	chronic kidney disease				

Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines[13], were also performed using estimated glomerular filtration rate (eGFR), categorising patients into low (eGFR <60 mL/min/1.73 m^2, stages 3-4) and normal (eGFR ≥60 mL/min/1.73 m^2, stages 1-2) renal function groups.

OUTCOMES

The primary outcome of the study was net adverse clinical events (i.e., efficacy and safety outcomes), defined as a composite of death from any cause, myocardial infarction (MI), stroke, systemic embolism, unplanned urgent revascularisation, or major/clinically relevant non-major bleeding (as defined by the International Society on Thrombosis and Haemostasis [ISTH])[14], at 12 months after randomisation. Secondary efficacy outcomes included the individual components of the primary outcome, a composite of major ischaemic events (death from any cause, MI, ischaemic stroke, or systemic embolism), and a composite of any ischaemic event (death from any cause, MI, ischaemic stroke, systemic embolism, or unplanned urgent revascularisation). Secondary safety outcomes included a composite of major/clinically relevant non-major bleeding, major bleeding, clinically relevant non-major bleeding, and any bleeding event. Prespecified, standard definitions were used to assess clinical outcomes[11]. All clinical outcomes were adjudicated by an independent clinical events committee, whose members were unaware of the trial-group assignments.

Follow-up assessments were performed at baseline, and at 6 and 12 months after randomisation. At each visit, data on clinical events and concomitant cardiovascular medications were systematically collected. Survival status was cross validated using the Korean National Health Insurance database.

STATISTICAL ANALYSIS

The full statistical analysis plan (SAP), including the sample size calculation for EPIC-CAD, has been previously published[11]. Subgroup analysis by renal function was prespecified in both the trial protocol and the SAP. Baseline characteristics and procedural data were compared between groups using the Student's t-test for continuous variables and the χ^2 or Fisher's exact test for categorical variables.

For comparisons between creatinine clearance <50 mL/min and ≥50 mL/min, propensity score (PS) matching was performed using a 1:1 nearest-neighbour algorithm with a calliper width of 0.2 of the standard deviation of the logit of the PS, to minimise selection bias and potential confounding. Model discrimination was evaluated using the C-statistic (0.946), and calibration was assessed with the Hosmer-Lemeshow test (χ^2=8.177; degrees of freedom=8; p=0.42). Balance between groups was evaluated using standardised mean differences (SMDs), with values <0.1 indicating negligible imbalance. The outcomes were compared by use of Cox proportional hazards regression with robust standard errors that accounted for the clustering of matched pairs.

All analyses were conducted on an intention-to-treat basis. Outcomes of patients randomised to the two antithrombotic strategies (edoxaban monotherapy versus dual antithrombotic therapy) were evaluated according to the creatinine clearance level. Time-to-event estimates for clinical outcomes were obtained using Kaplan-Meier estimates and compared with the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. The proportional hazards assumption was tested for each outcome using Schoenfeld residuals and visual inspection[15]. Differences in cumulative incidence and corresponding 95% CIs for trial outcomes at 12 months were calculated using Kaplan-Meier estimates and Greenwood standard errors[16]. Interactions between the randomised antithrombotic strategy and the category of renal function were also tested. Also, the non-linear association between creatinine clearance values (as a continuous variable) and the 12-month predicted probability of adverse outcomes was evaluated using a restricted cubic spline function. Results were visualised by plotting the predicted 12-month probability of adverse outcome versus the creatinine clearance level. No imputation methods were used to infer missing values of baseline variables.

All reported p-values are two-sided. A p-value of <0.05 was considered statistically significant for all tests. No adjustments were made for multiple testing; thus, all findings of the present study must be interpreted as exploratory, given the potential for type I error arising from multiple comparisons. All statistical analyses were performed by independent statisticians using commercially available software (SAS, version 9.4 [SAS Institute] and R, version 4.6.1 [R Foundation for Statistical Computing]).

Results

STUDY POPULATION AND BASELINE CHARACTERISTICS

Between 14 May 2019 and 19 September 2022, a total of 1,040 patients were enrolled in the EPIC-CAD trial across 18 sites in South Korea. Of the 1,040 patients randomised in the EPIC-CAD trial, 252 patients (24.2%) had low creatinine clearance (<50 mL/min), and 788 patients (75.8%) had high creatinine clearance (≥50 mL/min). Among the patients with low creatinine clearance, 128 (50.8%) were assigned to edoxaban monotherapy and 124 (49.2%) to dual antithrombotic therapy. In the high creatinine clearance group, 396 patients (50.3%) were assigned to edoxaban monotherapy and 392 (49.7%) to dual antithrombotic therapy **(Figure 1)**.

Baseline characteristics of patients according to the levels of creatinine clearance are presented in **Table 1** and **Supplementary Table 1**. Compared with patients with high creatinine clearance (≥50 mL/min), those with low creatinine clearance (<50 mL/min) were older, more likely to be female, had a lower body weight, exhibited a higher prevalence of clinical comorbidities, and had higher mean CHA_2DS_2-VASc (5.4±1.5 vs 4.0±1.4) and HAS-BLED scores (2.4±0.8 vs 2.1±0.8). Within each creatinine clearance subgroup, the baseline characteristics of patients were mostly well balanced between the randomised antithrombotic strategies of edoxaban monotherapy and dual antithrombotic therapy **(Supplementary Table 2)**.

TREATMENT AND FOLLOW-UP

Details regarding the antithrombotic regimens administered before or after randomisation are summarised in **Supplementary Table 3**. Before randomisation, 47.2% of the patients in the low creatinine clearance group received dual antithrombotic therapy, 44.4% received oral anticoagulants

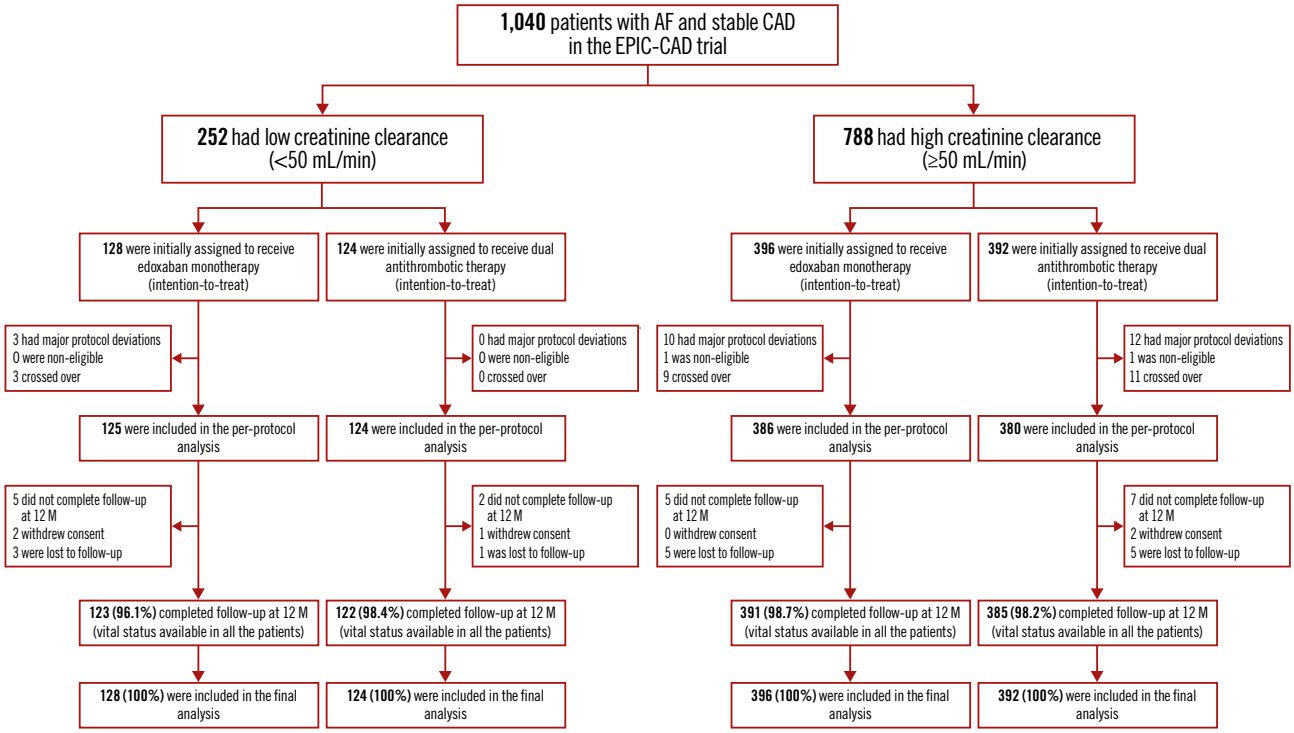


Figure 1. *Enrolment, randomisation, and follow-up stratified by the status of renal function. Renal function was stratified into low (<50 mL/min) or high (≥50 mL/min) creatinine clearance groups. Patients were randomly assigned in a 1:1 ratio to receive edoxaban monotherapy or dual antithrombotic therapy consisting of edoxaban plus a single antiplatelet agent (either aspirin or a $P2Y_{12}$ inhibitor), and propensity score matching was performed to minimise baseline imbalances. Propensity-matched groups were generated based on clinically relevant baseline characteristics, including age, sex, body weight, comorbidities (diabetes, hypertension, hyperlipidaemia, heart failure), cardiovascular history, and concomitant medications. AF: atrial fibrillation; CAD: coronary artery disease; EPIC-CAD: Edoxaban Versus Edoxaban With antiPlatelet Agent In Patients With Atrial Fibrillation and Chronic Stable Coronary Artery Disease*

alone, and 7.5% received a single antiplatelet agent. This pattern was similar for patients in the high creatinine clearance group. After randomisation, most patients started their assigned antithrombotic treatment, irrespective of the creatinine clearance category. Details regarding trial regimens and concomitant cardioactive medication use at randomisation and during follow-up are provided in **Supplementary Table 4**.

CLINICAL OUTCOMES

BY CREATININE CLEARANCE LEVELS

Primary and secondary outcomes were assessed at 12 months in 98.2% of all patients **(Figure 1)**. Data regarding vital status were obtained for all patients. Crude and adjusted clinical outcomes stratified by the level of creatinine clearance are summarised in **Table 2**, **Supplementary Table 5**, and **Figure 2**. As expected, the incidence of the primary net adverse clinical events at 12 months was significantly higher in the low creatinine clearance group than in the high creatinine clearance group in both the crude and PS-matched analyses **(Figure 2)**. However, the cumulative incidence of major ischaemic events at 12 months was significantly higher in the low creatinine clearance group than in the high creatinine clearance group in the crude analysis, whereas this difference was no longer significant in the PS-matched analysis. The incidence of major/clinically relevant non-major bleeding was higher in the low creatinine clearance group. Major bleeding events were also more frequent in the low creatinine clearance group than in the high creatinine clearance group.

BY RANDOMISED ANTITHROMBOTIC STRATEGY AND RENAL FUNCTION

The primary and secondary outcomes according to the randomised antithrombotic strategy, stratified by creatinine clearance levels, are presented in **Table 3**, **Supplementary Table 6**, and **Figure 3**. In the low creatinine clearance group, the incidence of the primary net adverse events at 12 months was significantly lower with edoxaban monotherapy than with dual antithrombotic therapy (12.1% vs 21.7%, respectively; HR 0.52, 95% CI: 0.28-0.98; p=0.04). Similarly, in the high creatinine clearance group, the incidence of the primary net adverse events was also lower with edoxaban monotherapy compared to dual antithrombotic therapy (5.2% vs 14.5%; HR 0.40, 95% CI: 0.25-0.65; p<0.001). Thus, no significant interaction was observed between the randomised antithrombotic strategy and the creatinine clearance category (p for interaction=0.53) **(Central illustration)**.

Table 1. Baseline characteristics of patients stratified by renal function status.

Baseline characteristics	Before PS matching				After PS matching[d]		
	Low creatinine clearance (n=252)	High creatinine clearance (n=788)	*p*-value	SMD	Low creatinine clearance (n=99)	High creatinine clearance (n=99)	SMD
Age, years	78.7±6.3	70.0±7.6	<0.001	1.247	75.7±6.2	76.2±6.3	0.074
Male sex	158 (62.7)	644 (81.7)	<0.001	0.435	58 (58.6)	55 (55.6)	0.061
Weight, kg	62.1±10.3	70.8±10.8	<0.001	0.822	60.3±9.6	60.3±10.4	0.002
Body mass index[a], kg/m^2	24.1±3.2	25.8±3.2	<0.001	0.515	23.4±3.2	23.9±3.8	0.139
Diabetes mellitus	120 (47.6)	301 (38.2)	0.008	0.191	37 (37.4)	34 (34.3)	0.063
Hypertension	206 (81.7)	639 (81.1)	0.82	0.017	80 (80.8)	80 (80.8)	<0.001
Hyperlipidaemia or statin use	235 (93.3)	737 (93.5)	0.88	0.011	90 (90.9)	91 (91.9)	0.036
Current smoker	13 (5.2)	74 (9.4)	0.04	0.164	6 (6.1)	5 (5.1)	0.044
Previous myocardial infarction	48 (19.0)	123 (15.6)	0.20	0.091	12 (12.1)	11 (11.1)	0.032
Congestive heart failure	65 (25.8)	140 (17.8)	0.005	0.195	19 (19.2)	21 (21.2)	0.050
History of cerebrovascular disease	56 (22.2)	98 (12.4)	<0.001	0.261	15 (15.2)	15 (15.2)	<0.001
History of peripheral artery disease	28 (11.1)	50 (6.3)	0.01	0.170	4 (4.0)	5 (5.1)	0.049
Creatinine clearance, mL/min[b]	40.4±7.3	74.9±19.1	<0.001	2.387	42.0±6.4	64.6±15.8	1.879
Type of atrial fibrillation			0.63	0.035			0.081
Paroxysmal	136 (54.0)	439 (55.7)			55 (55.6)	51 (51.5)	
Persistent or permanent	116 (46.0)	349 (44.3)			44 (44.4)	48 (48.5)	
CHA_2DS_2-VASc score[c]			<0.001	1.038			0.029
Mean	5.4±1.5	4.0±1.4			4.8±1.4	4.8±1.4	
Median	6 (4-6)	4 (3-5)			5 (4-6)	5 (4-6)	
Actual dose of edoxaban			<0.001	1.471			0.048
60 mg	33 (13.1)	565 (71.7)			23 (23.2)	21 (21.2)	
30 mg	219 (86.9)	223 (28.3)			79 (79.8)	81 (81.8)	

Values are mean±SD, n (%), or median (IQR). Percentages may not add up to 100% due to rounding. [a]The body mass index is the weight in kilograms divided by the square of the height in metres. [b]Creatinine clearance was assessed using the Cockcroft-Gault formula. [c]The CHA_2DS_2-VASc score is a clinical tool used to assess the risk of stroke among people with atrial fibrillation. Scores are weighted based on the presence of congestive heart failure, hypertension, diabetes mellitus, and vascular disease; a history of stroke or transient ischaemic attack; age (65-74 years or ≥75 years); and sex. Scores range from 0 to 9, with higher scores indicating a greater risk[28]. [d]Propensity-matched groups were generated based on clinically relevant baseline characteristics, including age, sex, body weight, comorbidities (diabetes, hypertension, hyperlipidaemia, heart failure), cardiovascular history, and concomitant medication. IQR: interquartile range; PS: propensity score; SD: standard deviation; SMD: standardised mean difference

In both groups of low or high creatinine clearance category, the cumulative incidence of major or any ischaemic events did not significantly differ between the edoxaban monotherapy and dual antithrombotic therapy groups. Regardless of creatinine clearance levels, the cumulative incidence of major/clinically relevant non-major bleeding at 12 months was significantly lower with edoxaban monotherapy than with dual antithrombotic therapy. The cumulative incidence of major bleeding at 12 months was significantly lower with edoxaban monotherapy than with dual antithrombotic therapy in the low creatinine clearance group; however, this trend was not significant in the high creatinine clearance group **(Figure 3)**. Detailed information regarding the severity of bleeding, stratified by bleeding criteria and sites, is summarised in **Supplementary Table 7**. No significant interaction was observed between the randomised antithrombotic strategy and the creatinine clearance category with respect to major ischaemic events (p for interaction=0.65), any ischaemic event (p for interaction=0.69), major/clinically relevant non-major bleeding (p for interaction=0.78), and major bleeding (p for interaction=0.30).

SENSITIVITY ANALYSES

The outcomes of analyses performed, stratified by normal (creatinine clearance 50-95 mL/min) and extra-normal (creatinine clearance >95 mL/min) levels, are summarised and illustrated in **Supplementary Table 8** and **Supplementary Figure 1**, respectively. In patients with creatinine clearance of 50-95 mL/min, the incidence of primary net adverse events, major bleeding, or clinically relevant non-major bleeding was significantly lower with edoxaban monotherapy compared with dual antithrombotic therapy. However, this difference

Table 2. Primary and key secondary outcomes at 1 year in patients stratified by creatinine clearance of 50 mL/min.

Outcomes	Before PS matching				After PS matching			
	Low creatinine clearance (n=252)	High creatinine clearance (n=788)	HR (95% CI)	*p*-value	Low creatinine clearance (n=99)	High creatinine clearance (n=99)	HR (95% CI)	*p*-value
Net adverse clinical events[a]	39 (17.0)	74 (9.8)	1.72 (1.19-2.49)	0.004	17 (18.5)	4 (4.8)	3.53 (1.24-10.07)	0.018
Composite major ischaemic events[b]	8 (3.5)	8 (1.1)	2.70 (1.09-6.70)	0.032	2 (2.2)	1 (1.0)	2.02 (0.19-21.99)	0.564
Major bleeding or clinically relevant non-major bleeding	30 (13.3)	63 (8.2)	1.54 (1.01-2.34)	0.046	13 (14.4)	2 (2.0)	4.37 (1.16-16.43)	0.029
Major bleeding	13 (5.7)	15 (2.0)	2.80 (1.37-5.74)	0.005	7 (8.2)	0 (0)	NE	-

Values are the number of patients with events (estimated percentages), calculated using Kaplan-Meier survival analysis of data from the intention-to-treat population; therefore, the reported percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons; consequently, inferences drawn from these intervals may not be reproducible. Kaplan-Meier event rates and Cox proportional hazard ratios were adjusted for age, sex, weight, diabetes mellitus, current smoking status, congestive heart failure, cerebrovascular disease, peripheral artery disease, and prior coronary revascularisation. [a]Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, stroke, systemic thromboembolic event, unplanned urgent revascularisation, or major/clinically relevant non-major bleeding (according to the International Society on Thrombosis and Haemostasis definition). A p-value<0.001 indicated the superiority of edoxaban monotherapy over dual antithrombotic therapy. [b]The composite of major ischaemic events was defined as a composite of death from any cause, myocardial infarction, ischaemic stroke, or systemic embolism. CI: confidence interval; HR: hazard ratio; NE: not estimable; PS: propensity score

was not observed in patients with creatinine clearance >95 mL/min. Sensitivity analyses using an eGFR cutoff of 60 mL/min/1.73 m^2 showed results that were consistent with the overall findings **(Supplementary Table 9, Supplementary Figure 2)**. In a sensitivity analysis restricted to patients with high creatinine clearance and receiving a 60 mg dose of edoxaban, the results were consistent with the primary findings **(Supplementary Table 10)**: edoxaban monotherapy was associated with a lower risk of the primary net adverse clinical events, major bleeding, or clinically relevant non-major bleeding compared with dual antithrombotic therapy. Using a linear model, the probability of the primary outcome substantially increased with lower baseline creatinine clearance, and this association was consistent across each stratum of the edoxaban monotherapy and dual antithrombotic therapy groups, with no significant interaction (p for interaction=0.37) **(Supplementary Figure 3)**.

Discussion

In this prespecified secondary analysis of the EPIC-CAD trial, we evaluated the comparative outcomes of different antithrombotic strategies (edoxaban monotherapy vs dual antithrombotic therapy) in patients with high-risk AF and stable CAD according to their renal function status. The key findings are summarised as follows: (1) patients with lower creatinine clearance were older, had a lower body weight, and had a higher risk of clinical comorbidities associated with an increased risk of ischaemic and bleeding events; (2) the incidences of primary net adverse events, major/clinically relevant bleeding events, and major bleeding events were generally higher in patients with low creatinine clearance than in those with high creatinine clearance; (3) the 12-month rate of primary net adverse events was significantly lower with edoxaban monotherapy than with dual antithrombotic therapy in both the low and high creatinine clearance groups **(Central illustration)**. This observation was driven mainly by a lower incidence of bleeding events. Despite the low number of ischaemic outcomes, the incidences of ischaemic events and mortality were similar in the randomised antithrombotic groups; and (4) overall findings were consistent across various categories of renal function.

In contemporary clinical practice, renal function is a key determinant in selecting optimal antithrombotic therapy due to the increased risks of both ischaemic and bleeding events in patients with AF, CAD, or both conditions[1,2,17,18]. Such detrimental effects of renal dysfunction on ischaemic or bleeding complications were also evident in the current analysis of the EPIC-CAD trial. Also, we observed that edoxaban monotherapy was associated with a lower incidence of the primary net adverse clinical events compared with dual antithrombotic therapy in patients with either reduced or normal creatinine clearance. This key finding was mainly driven by a lower incidence of clinically relevant bleeding events without a corresponding increase in ischaemic events. Prior studies have reported that DOAC underdosing was associated with an increased risk of ischaemic events in patients with reduced renal function (i.e., low creatinine clearance), despite a lower incidence of bleeding events[19-22]. In the present study, the creatinine clearance cutoff of <50 mL/min was prespecified in this analysis and corresponds to the approved criterion for edoxaban dose reduction. Although the creatinine clearance cutoff of <50 mL/min reflects a pharmacokinetic threshold for edoxaban dose adjustment rather than a conventional prognostic boundary, sensitivity analyses using eGFR <60 mL/min/1.73 m^2 yielded consistent results, supporting the robustness of our findings. From a clinical viewpoint, our findings suggest that edoxaban monotherapy was associated with a lower risk of primary net adverse clinical events and bleeding events compared with dual antithrombotic therapy, irrespective of baseline renal function. While no statistically significant difference in ischaemic events was observed between the treatment

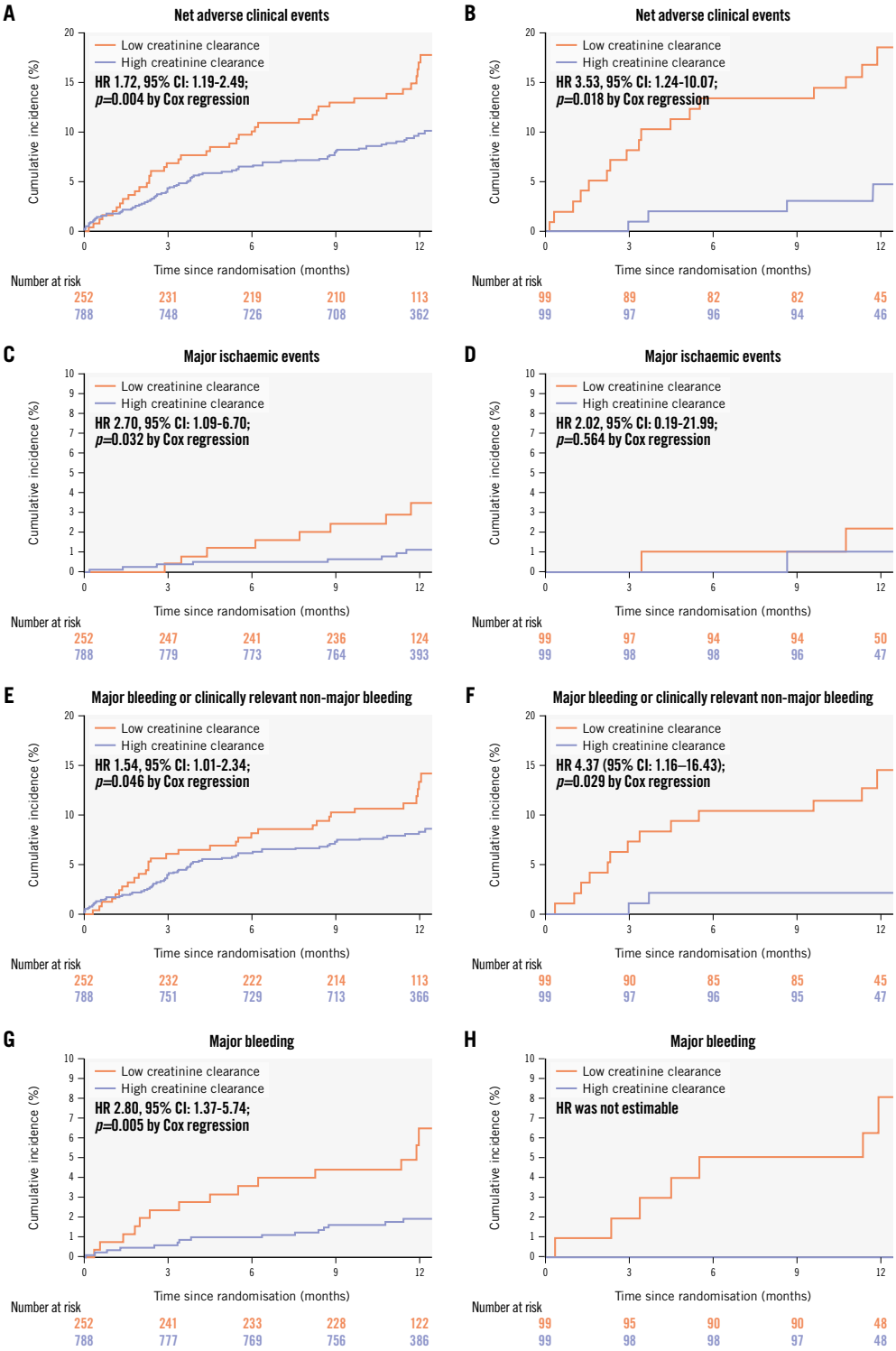


Figure 2. *Time-to-event curves for clinical outcomes stratified by creatinine clearance of 50 mL/min. Renal function was stratified into low (<50 mL/min) or high (≥50 mL/min) creatinine clearance groups. Primary outcome refers to the net adverse outcome, which includes death from any cause, myocardial infarction, stroke, systemic embolism, unplanned emergency procedures, and major/clinically significant non-major bleeding. Secondary outcomes included major ischaemic events, major/clinically significant non-major bleeding, and major bleeding. The percentages for events were calculated using Kaplan-Meier estimates and compared with Cox regression tests. Propensity-matched groups were generated based on clinically relevant baseline characteristics, including age, sex, body weight, comorbidities (diabetes, hypertension, hyperlipidaemia, heart failure), cardiovascular history, and concomitant medications. A, C, E, G) Results from the unmatched cohort; (B, D, F, H) outcomes after propensity score matching. CI: confidence interval; HR: hazard ratio*

Table 3. Primary and key secondary outcomes at 1 year in patients stratified by creatinine clearance and randomisation strategy.

Outcomes	Low creatinine clearance (n=252)				High creatinine clearance (n=788)				
	Edoxaban monotherapy (n=128)	Dual antithrombotic therapy (n=124)	HR (95% CI)	*p*-value	Edoxaban monotherapy (n=396)	Dual antithrombotic therapy (n=392)	HR (95% CI)	*p*-value	p-int
Net adverse clinical events[a]	14 (12.1)	25 (21.7)	0.52 (0.28-0.98)	0.04	20 (5.2)	54 (14.5)	0.40 (0.25-0.65)	<0.001	0.53
Composite major ischaemic events[b]	4 (3.3)	4 (3.6)	1.00 (0.26-3.90)	>0.99	4 (1.1)	4 (1.2)	1.54 (0.43-5.50)	0.50	0.65
Major bleeding or clinically relevant non-major bleeding	8 (7.3)	22 (19.2)	0.37 (0.17-0.79)	0.01	15 (3.9)	48 (12.7)	0.32 (0.18-0.55)	<0.001	0.78
Major bleeding	2 (2.4)	11 (9.2)	0.17 (0.04-0.76)	0.02	4 (1.0)	11 (3.0)	0.44 (0.15-1.28)	0.133	0.30

Values are the number of patients with events (estimated percentages), calculated using Kaplan-Meier survival analysis of data from the intention-to-treat population; therefore, the reported percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons; consequently, inferences drawn from these intervals may not be reproducible. [a]Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, stroke, systemic thromboembolic event, unplanned urgent revascularisation, or major/clinically relevant non-major bleeding (according to the International Society on Thrombosis and Haemostasis definition). A p-value of <0.001 indicated the superiority of edoxaban monotherapy over dual antithrombotic therapy. [b]The composite of major ischaemic events was defined as the occurrence of any of the following: death from any cause, myocardial infarction, ischaemic stroke, or systemic embolism. CI: confidence interval; HR: hazard ratio; p-int: p for interaction

strategies, these ischaemic comparisons should be considered exploratory given the low event rates and limited statistical power.

A substudy of the Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients With Stable Coronary Artery Disease Study (AFIRE), which used a similar eGFR cutoff value of 50 mL/min, reported that impaired renal function (eGFR <50 mL/min) was associated with bleeding events when recurrent events were considered. Moreover, the bleeding risk remained high over time in patients with decreased renal function[23]. However, comparative outcomes of randomised antithrombotic strategies stratified by renal function were not reported. In the current study, the detrimental effect of renal dysfunction on bleeding events and net adverse clinical events was more remarkable. Furthermore, the superior effect of edoxaban monotherapy over dual antithrombotic therapy with regard to primary net adverse events and clinically relevant bleeding events was consistent across patients with or without decreased renal function. From a clinical perspective, these findings can directly inform decision-making regarding optimal antithrombotic therapy in patients with high-risk AF and concomitant CAD, especially those with reduced kidney function.

Interestingly, previous reports have suggested that patients with creatinine clearance >95 mL/min may exhibit decreased plasma concentrations of edoxaban, which potentially reduce the drug efficacy[24,25]. In an explorative analysis of the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial[26], the relative efficacy of higher-dose edoxaban in preventing thromboembolic events, compared with warfarin, was lower in patients with creatinine clearance >95 mL/min. Nevertheless, the primary net clinical outcome remained favourable for higher-dose edoxaban, with persistently lower rates of major bleeding than warfarin.

Limitations

The present study has several limitations. First, as a subgroup analysis of a prospective randomised controlled trial, the present study was limited by a relatively small sample size and reduced statistical power. Accordingly, the findings should be considered exploratory, and further prospective studies are warranted to confirm these observations. Second, although patients with creatinine clearance <50 mL/min were a prespecified subgroup of interest for the original EPIC-CAD trial, no adjustment for multiple testing was made; therefore, the findings should not be used to infer definitive treatment effects. Third, randomisation in the EPIC-CAD trial was not stratified by baseline renal function. Although baseline characteristics were generally balanced between the randomised treatment groups within the creatinine clearance strata, residual confounding due to unmeasured factors may remain in this subgroup analysis. Accordingly, treatment effects may be partly confounded despite multivariable adjustment. Fourth, renal function was assessed only at baseline in the present analysis, and serial reassessment of creatinine clearance during follow-up was not available. Given the dynamic nature of renal function in elderly and comorbid patients with AF, some degree of misclassification may have occurred, which could attenuate the observed differences between the treatment strategies. Lastly, the present study was conducted exclusively in an East Asian population, who are known to exhibit a higher bleeding

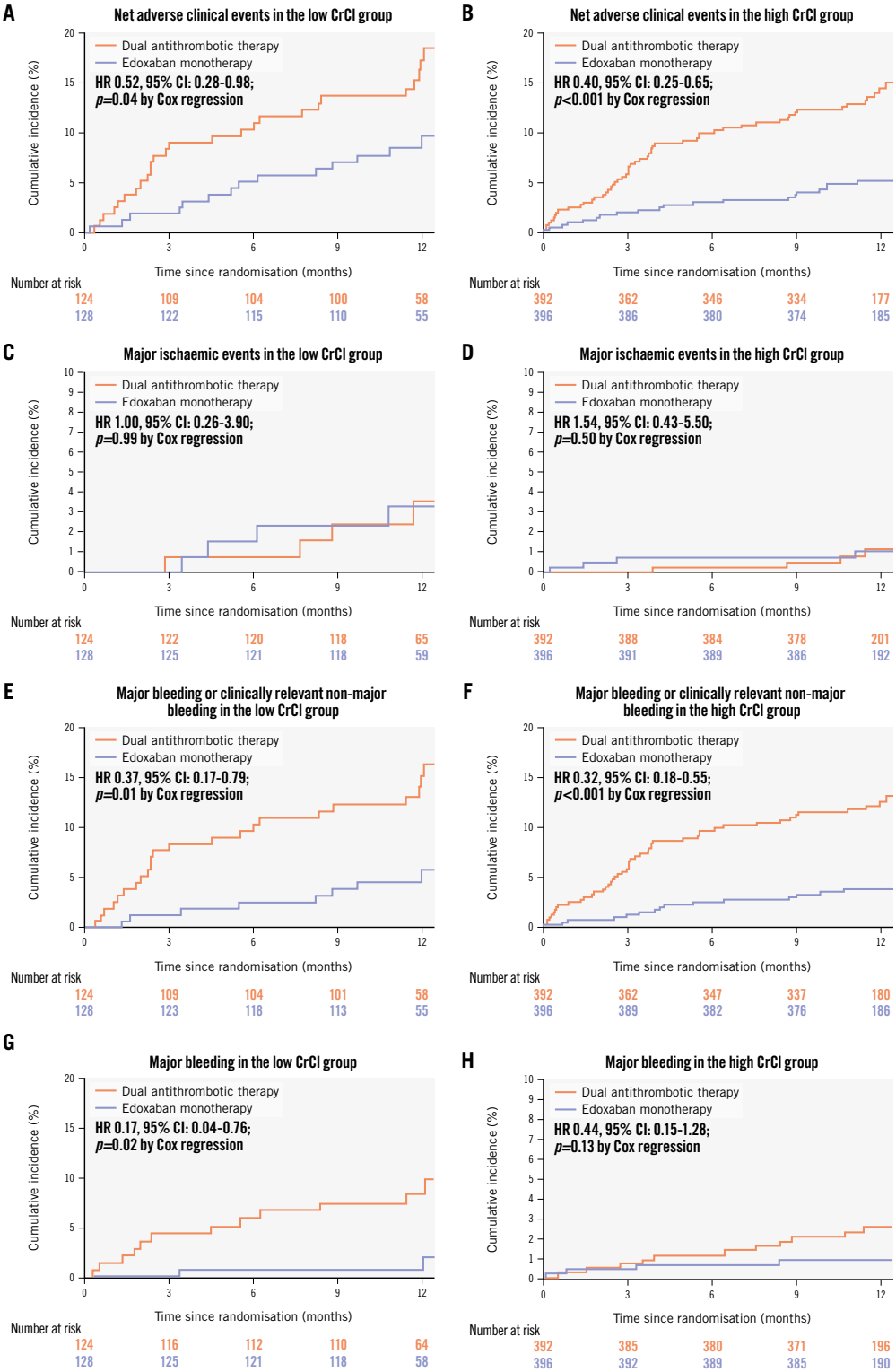
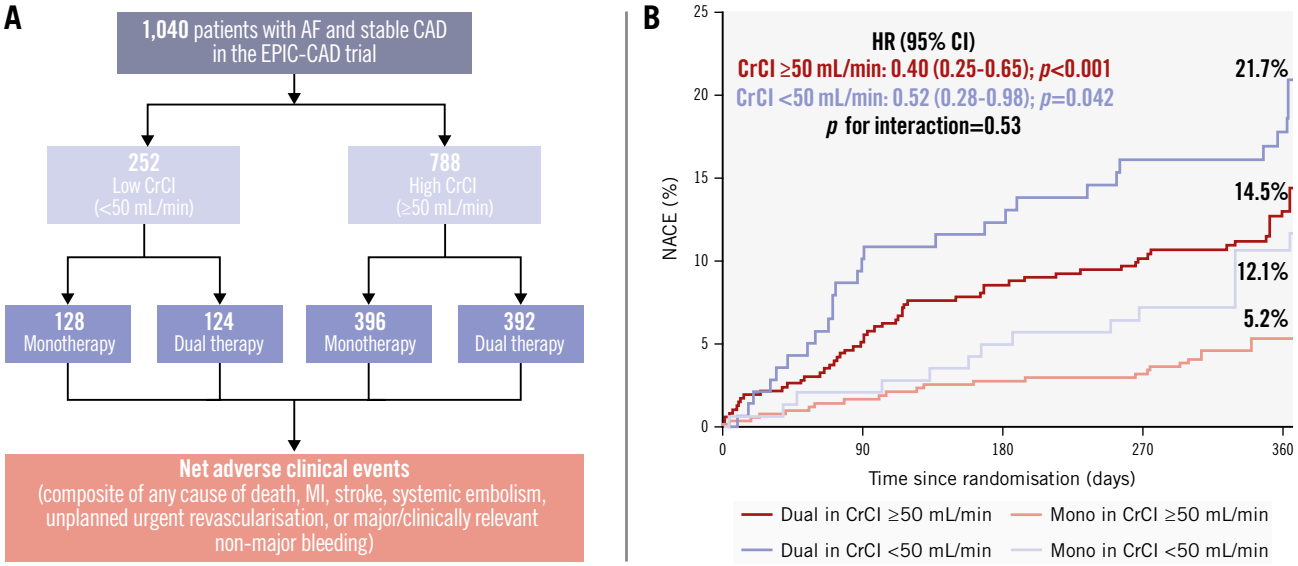


Figure 3. *Time-to-event curves for the primary composite outcome stratified by creatinine clearance level and randomised follow-up strategy. Renal function was stratified into low (<50 mL/min) or high (≥50 mL/min) creatinine clearance groups. Primary outcome refers to the net adverse outcome, which includes death from any cause, myocardial infarction, stroke, systemic embolism, unplanned emergency procedures, and major/clinically significant non-major bleeding. Secondary outcomes included major ischaemic events, major/clinically significant non-major bleeding, and major bleeding. The percentages of events were calculated using Kaplan-Meier estimates and were compared with Cox regression tests. A, C, E, G) Results from the low creatinine clearance groups; (B, D, F, H) outcomes from the high creatinine clearance groups. CI: confidence interval; CrCl: creatinine clearance; HR: hazard ratio*

EuroIntervention Central Illustration

Impact of creatinine clearance on the antithrombotic therapeutic strategy in patients with AF and stable CAD: findings from the EPIC-CAD trial.



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A) Patient distribution in the study; (B) time-to-event curves for the incidence of NACE according to dual or monotherapy and high or low creatinine clearance. AF: atrial fibrillation; CAD: coronary artery disease; CI: confidence interval; CrCl: creatinine clearance; EPIC-CAD: Edoxaban Versus Edoxaban With antiPlatelet Agent In Patients With Atrial Fibrillation and Chronic Stable Coronary Artery Disease; HR: hazard ratio; MI: myocardial infarction; NACE: net adverse clinical events

risk phenotype and distinct pharmacodynamic responses to DOACs compared with Western populations, a phenomenon often referred to as the "East Asian paradox"[27]. These ethnic and demographic differences, including lower body weight and a different balance between ischaemic and bleeding risks, may influence both the safety and efficacy profiles of antithrombotic strategies. Accordingly, the generalisability of our findings to Western populations should be interpreted with caution, and further studies in more diverse, non-East Asian cohorts are warranted to confirm the external validity of these observations.

Conclusions

In this prespecified secondary analysis of the EPIC-CAD trial, impaired renal function was significantly associated with an increased risk of primary net adverse clinical events and major/clinically relevant bleeding events. Nevertheless, the benefit of edoxaban monotherapy over dual antithrombotic therapy, including reductions in the primary net outcome and bleeding events, was consistent irrespective of renal function status, with no evidence of an excess in ischaemic events.

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Conflict of interest statement

D.-W. Park has received research grants from the Cardiovascular Research Foundation, Daewoong Pharmaceutical, and Daiichi Sankyo. G.-B. Nam has received research grants from the Cardiovascular Research Foundation, Daewoong Pharmaceutical, and Daiichi Sankyo. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Additional baseline characteristics of patients stratified by creatinine clearance of 50 mL/min.

Supplementary Table 2. Baseline characteristics of patients based on randomised antithrombotic strategy stratified by renal function status.

Supplementary Table 3. Antithrombotic therapy before and after randomisation.

Supplementary Table 4. Relevant cardiac-related medications at randomisation and during follow-up.

Supplementary Table 5. Other secondary outcomes at 1 year in patients stratified by creatinine clearance of 50 mL/min.

Supplementary Table 6. Other secondary outcomes at 1 year in patients stratified by creatinine clearance of 50 mL/min and randomised antithrombotic strategy.

Supplementary Table 7. Details of bleeding events in the studied patients (overall study period).

Supplementary Table 8. Primary and secondary outcomes at 1 year in patients according to creatinine clearance of 95 mL/min and randomised antithrombotic strategy among the high creatinine clearance group.

Supplementary Table 9. Primary and secondary outcomes at 1 year in patients stratified by estimated glomerular filtration rate of 60 mL/min/1.73 m^2 and randomised antithrombotic strategy.

Supplementary Table 10. Clinical outcomes in patients with high creatinine clearance receiving the 60 mg edoxaban dose according to the antithrombotic strategy.

Supplementary Figure 1. Time-to-event curves for clinical outcomes stratified by creatinine clearance of 95 mL/min and randomised antithrombotic strategy in patients with creatinine clearance ≥50 mL/min.

Supplementary Figure 2. Time-to-event curves for clinical outcomes stratified by estimated glomerular filtration rate of 60 mL/min/1.73 m^2 and randomised antithrombotic strategy in patients.

Supplementary Figure 3. One-year probability of the primary outcome as a function of baseline creatinine clearance level.

Data availability statement.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-01274

Supplementary data

Table of contents

Supplementary Table 1. Additional baseline characteristics of patients stratified by creatinine clearance of 50 mL/min.

	Before PS matching				After PS matching		
	Low Creatinine-clearance	**High Creatinine-clearance**	***P value***	***SMD***	**Low Creatinine-clearance**	**High Creatinine-clearance**	***SMD***
Additional baseline characteristics							
Systolic blood pressure, mmHg	130.0±16.8	129.2±16.2	0.48	0.05	127.6±16.1	130.5±17.2	0.18
Diastolic blood pressure, mmHg	73.1±10.8	74.5±10.7	0.08	0.13	72.3±9.8	73.4±9.7	0.12
History of systemic embolism, n (%)	1 (0.4)	1 (0.1)	0.43	0.05	0 (0.0)	0 (0.0)	<0.001
Details of previous cerebrovascular disease, n (%)			0.28	0.33			<0.001
Ischemic stroke	53 (94.6)	84 (85.7)			15 (100.0)	15 (100.0)	
Hemorrhagic stroke	0 (0.0)	2 (2.0)			0 (0.0)	0 (0.0)	
Unspecified	3 (5.4)	12 (12.2)			0 (0.0)	0 (0.0)	
CHA_2DS_2-VA score			<0.001	0.96			0.01
Mean	5.1±1.3	3.8±1.4			4.4±1.2	4.4±1.3	
Median (IQR)	5 (4–6)	4 (3–5)			4 (3–5)	4 (3–5)	
$CHADS_2$ score [b]			<0.001	0.72			0.01

Mean	2.8±1.3	1.9±1.1			2.3±1.2	2.3±1.1	
Median (IQR)	3 (2–4)	2 (1–2)			2 (2–3)	2 (2–3)	
HAS-BLED score [c]			<.0001	0.49			0.12
Mean	2.4±0.8	2.1±0.8			2.3±0.7	2.2±0.7	
Median (IQR)	2 (2–3)	2 (2–3)			2 (2–3)	2 (2–3)	
Previous or concomitant PPI use, n (%)	31 (12.3)	102 (12.9)	0.79	0.02	16 (16.2)	12 (12.1)	0.12
Indication for dose adjustment of edoxaban, n (%)[d]	233 (92.5)	113 (14.3)	<0.001	2.52	80 (80.8)	79 (79.8)	0.03
Initial clinical presentation for coronary disease, n (%)			0.01	0.19			0.02
Chronic coronary syndrome	173 (68.7)	606 (76.9)			77 (77.8)	76 (76.8)	
Acute coronary syndrome	79 (31.3)	182 (23.1)			22 (22.2)	23 (23.2)	
Unstable angina	31 (12.3)	59 (7.5)	0.04	0.20	10 (10.1)	12 (12.1)	0.07
NSTEMI	23 (9.1)	55 (7.0)	0.04		7 (7.1)	7 (7.1)	
STEMI	25 (9.9)	68 (8.6)	0.04		5 (5.1)	4 (4.0)	
Obstructive coronary artery disease, n (%) [e]	68 (27.0)	289 (36.7)	0.005	0.21	39 (39.4)	34 (34.3)	0.11
Previous coronary revascularization, n (%)	184 (73.0)	499 (63.3)			60 (60.6)	65 (65.7)	
Previous percutaneous coronary intervention	164 (65.1)	462 (58.6)	0.07	0.13	56 (56.6)	61 (61.6)	0.10
Previous CABG, n (%)	28 (11.1)	49 (6.2)	0.01	0.18	6 (6.1)	5 (5.1)	0.04

History of major bleeding, n (%)	6 (2.4)	3 (0.4)	0.01	0.17	2 (2.0)	0 (0.0)	0.20
History of gastrointestinal bleeding, n (%)	12 (4.8)	16 (2.0)	0.02	0.15	3 (3.0)	2 (2.0)	0.06
Previous open-heart surgery, n (%)	6 (2.4)	16 (2.0)	0.74	0.02	1 (1.0)	3 (3.0)	0.14
Previous left atrial appendage closure, n (%)	3 (1.2)	3 (0.4)	0.16	0.09	0 (0.0)	0 (0.0)	<0.001
Previous radiofrequency ablation, n (%)	62 (24.6)	220 (27.9)	0.30	0.08	25 (25.3)	24 (24.2)	0.02
Alcohol use history, n (%)			0.01	0.22			0.20
No	182 (72.2)	488 (61.9)			70 (70.7)	77 (77.8)	
Mild (0–8 units/week)	68 (27.0)	283 (35.9)			28 (28.3)	22 (22.2)	
Abuse (>8 units/week)	2 (0.8)	17 (2.2)			1 (1.0)	0 (0.0)	
Total number of coronary revascularizations, median (IQR)	1 (1–1)	1 (1–1)	0.18	0.18	1 (1–1)	1 (1–2)	0.28
Disease extent, n (%)			<0.001	0.39			0.44
1-vessel disease	102 (40.5)	426 (54.1)			51 (51.5)	49 (49.5)	
2-vessel disease	68 (27.0)	194 (24.6)			20 (20.2)	25 (25.3)	
3-vessel disease	55 (21.8)	103 (13.1)			21 (21.2)	16 (16.2)	
Left main disease alone	0 (0.0)	4 (0.5)			0 (0.0)	2 (2.0)	
Left main plus 1-vessel disease	2 (0.8)	17 (2.2)			0 (0.0)	2 (2.0)	

Left main plus 2-vessel disease	11 (4.4)	17 (2.2)			5 (5.1)	1 (1.0)	
Left main plus 3-vessel disease	14 (5.6)	27 (3.4)			2 (2.0)	4 (4.0)	
Chronic total occlusion, n (%)	44 (17.5)	91 (11.5)	0.02	0.17	9 (9.1)	9 (9.1)	<0.001
Median time from last revascularization — months	64.0 (31.0–128.5)	50.0 (26.0–105.0)	0.04	0.18	44.5 (25.0 - 105.5)	51.0 (27.0 - 108.0)	0.16
PCI	55.0 (29.0–114.5)	49.0 (26.0–101.0)	0.21	0.10	41.5 (24.5 - 99.5)	47.0 (26.0 - 100.0)	0.14
CABG	133.0 (62.5–186.0)	78.0 (37.5–156.0)	0.26	0.24	66.0 (29.0 - 127.0)	116.0 (41.0 - 188.0)	0.55
Median time from last angiogram in medically treated patient — months[a]	13.9 (5.3–24.4)	9.7 (1.2–20.4)	0.01	0.21	13.6 (3.3 - 22.3)	14.6 (1.4 - 28.6)	0.13
Left ventricular ejection fraction	57.8±9.2	58.0±9.3	0.81	0.02	59.5±8.7	59.0±9.6	0.05

* Plus–minus values are means ± SD. Percentages may not add up to 100% due to rounding.

CABG, coronary artery bypass grafting; CT, computed tomography; IQR, interquartile range; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

[a] Time from last coronary angiography

[b] The CHADS2 score is a clinical tool used to assess the risk of stroke among persons with atrial fibrillation. Scores are weighted based on the presence of congestive heart failure, hypertension, and diabetes mellitus; age ≥75 years; and a history of stroke or transient ischemic attack. Scores range from 0 to 6, with higher scores indicating a greater risk.

[c] The HAS-BLED score is a clinical tool used to assess the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy. Scores are weighted based on the presence of hypertension, abnormal renal function, and abnormal liver function; a history of stroke or bleeding; the labile international normalized ratio; age ≥65 years; and the use of medications or consumption of alcohol at a level that increases the risk of bleeding. Scores range from 0 to 9, with higher scores indicating a greater risk.

[d] Indications for adjustment of the edoxaban dose included a creatinine-clearance rate of ≤50 mL/min, a body weight of ≤60 kg, and concomitant therapy with a P-glycoprotein inhibitor.

[e] Obstructive coronary artery disease was managed with the use of medical therapy alone and was confirmed anatomically as ≥50% stenosis in major epicardial vessels on coronary angiography and on coronary computed tomographic angiography.

Supplementary Table 2. Baseline characteristics of patients based on randomised antithrombotic strategy stratified by renal function status.

	Low Creatinine-clearance (n=252)			High Creatinine-clearance (n=788)		
Baseline characteristics	**Edoxaban Monotherapy (n=128)**	**Dual Antithrombotic Therapy (n=124)**	***P value***	**Edoxaban Monotherapy (n=396)**	**Dual Antithrombotic Therapy (n=392)**	***P value***
Age, years	78.2±6.6	79.1±6.0	0.26	69.6±7.2	70.3±8.0	0.16
Male sex, n (%)	79 (61.7)	79 (63.7)	0.74	317 (80.1)	327 (83.4)	0.22
Weight, kg	61.6±10.1	62.6±10.6	0.46	70.7±11.0	70.9±10.6	0.74
Body mass index[a]	24.0±3.1	24.1±3.4	0.80	25.8±3.3	25.7±3.2	0.54
Diabetes mellitus, n (%)	65 (50.8)	55 (44.4)	0.31	159 (40.2)	142 (36.2)	0.26
Hypertension, n (%)	100 (78.1)	106 (85.5)	0.13	323 (81.6)	316 (80.6)	0.73
Hyperlipidemia or statin use, n (%)	121 (94.5)	114 (91.9)	0.41	369 (93.2)	368 (93.9)	0.69
Current smoker, n (%)	6 (4.7)	7 (5.6)	0.73	31 (7.8)	43 (11.0)	0.13
Previous myocardial infarction, n (%)	27 (21.1)	21 (16.9)	0.40	52 (13.1)	71 (18.1)	0.05
Congestive heart failure, n (%)	30 (23.4)	35 (28.2)	0.39	66 (16.7)	74 (18.9)	0.42
History of cerebrovascular disease, n (%)	25 (19.5)	31 (25.0)	0.30	52 (13.1)	46 (11.7)	0.55

History of peripheral artery disease, n (%)	11 (8.6)	17 (13.7)	0.20	22 (5.6)	28 (7.1)	0.36
Creatinine-clearance, mL/min [b]	40.5±7.2	40.3±7.4	0.83	75.6±20.5	74.2±17.6	0.28
Type of atrial fibrillation, n (%)			0.63			0.96
Paroxysmal	71 (55.5)	65 (52.4)		221 (55.8)	218 (55.6)	
Persistent or permanent	57 (44.5)	59 (47.6)		175 (44.2)	174 (44.4)	
CHA_2DS_2-VASc score [c]			0.54			0.74
Mean	5.4±1.5	5.5±1.4		4.0±1.4	4.0±1.3	
Median (IQR)	6 (4–6)	6 (5–7)		4 (3–5)	4 (3–5)	
CHA_2DS_2-VA score			0.46			0.48
Mean	5.0±1.4	5.2±1.3		3.8±1.4	3.8±1.3	
Median (IQR)	5 (4–6)	5 (4–6)		4 (3–5)	4 (3–5)	
$CHADS_2$ score [d]			0.46			0.80
Mean	2.7±1.3	2.9±1.3		1.9±1.1	1.9±1.1	
Median (IQR)	3 (2–4)	3 (2–4)		2 (1–3)	2 (1–2)	
HAS-BLED score [e]			0.13			0.97
Mean	2.4±0.7	2.5±0.8		2.1±0.8	2.1±0.8	
Median (IQR)	2 (2–3)	3 (2–3)		2 (2–3)	2 (2–3)	

Obstructive coronary artery disease, n (%) [f]	40 (31.2)	28 (22.6)	0.12	148 (37.4)	141 (36.0)	0.68
Previous coronary revascularization, n (%)	88 (68.8)	96 (77.4)		248 (62.6)	251 (64.0)	
Previous percutaneous coronary intervention	78 (60.9)	86 (69.4)	0.16	230 (58.1)	232 (59.2)	0.75
Previous CABG, n (%)	17 (13.3)	11 (8.9)	0.27	24 (6.1)	25 (6.4)	0.85
Previous or concomitant PPI use, n (%)	12 (9.4)	19 (15.3)	0.15	47 (11.9)	55 (14.0)	0.37
Indication for dose adjustment of edoxaban, n (%)[g]	115 (89.8)	118 (95.2)	0.11	63 (15.9)	50 (12.8)	0.21

Plus–minus values are means ± SD. Percentages may not add up to 100% due to rounding. CABG, coronary artery bypass grafting; IQR, interquartile range; and PPI, proton-pump inhibitor.

[a] The body mass index is the weight in kilograms divided by the square of the height in meters.

[b] Creatinine-clearance was assessed using the Cockcroft–Gault formula.

[c] The CHA2DS2-VASc score is a clinical tool used to assess the risk of stroke among persons with atrial fibrillation. Scores are weighted based on the presence of congestive heart failure, hypertension, diabetes mellitus, and vascular disease; a history of stroke or transient ischemic attack; age (65–74 years or ≥75 years); and sex. Scores range from 0 to 9, with higher scores indicating a greater risk.

[d] The CHADS2 score is a clinical tool used to assess the risk of stroke among persons with atrial fibrillation. Scores are weighted based on the presence of congestive heart failure, hypertension, and diabetes mellitus; age ≥75 years; and a history of stroke or transient ischemic attack. Scores range from 0 to 6, with higher scores indicating a greater risk.

[e] The HAS-BLED score is a clinical tool used to assess the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy. Scores are weighted based on the presence of hypertension, abnormal renal function, and abnormal liver function; a history of stroke or bleeding; the labile

international normalized ratio; age ≥65 years; and the use of medications or consumption of alcohol at a level that increases the risk of bleeding. Scores range from 0 to 9, with higher scores indicating a greater risk.

[f] Obstructive coronary artery disease was managed with the use of medical therapy alone and was confirmed anatomically as ≥50% stenosis in major epicardial vessels on coronary angiography and on coronary computed tomographic angiography.

[g] Indications for adjustment of the edoxaban dose included a creatinine-clearance rate of ≤50 mL/min, a body weight of ≤60 kg, and concomitant therapy with a P-glycoprotein inhibitor.

Supplementary Table 3. Antithrombotic therapy before and after randomisation.

	Low Creatinine-clearance			High Creatinine-clearance		
	Edoxaban Monotherapy	**Dual Antithrombotic Therapy**	***P value***	**Edoxaban Monotherapy**	**Dual Antithrombotic Therapy**	***P value***
Prior history of antithrombotic drugs[a]						
By medication, n (%)						
baseline aspirin	28 (21.9)	31 (25.0)	0.56	98 (24.7)	112 (28.6)	0.23
baseline clopidogrel	38 (29.7)	51 (41.1)	0.06	113 (28.5)	123 (31.4)	0.38
baseline cilostazol	1 (0.8)	2 (1.6)	0.62	0 (0.0)	3 (0.8)	0.12
baseline sarpogrelate	1 (0.8)	3 (2.4)	0.36	5 (1.3)	3 (0.8)	0.73
baseline warfarin	5 (3.9)	1 (0.8)	0.21	4 (1.0)	5 (1.3)	0.75
baseline edoxaban	63 (49.2)	63 (50.8)	0.80	197 (49.7)	203 (51.8)	0.57
baseline rivaroxaban	21 (16.4)	23 (18.5)	0.65	62 (15.7)	61 (15.6)	0.97
baseline apixaban	17 (13.3)	18 (14.5)	0.78	59 (14.9)	47 (12.0)	0.23
baseline dabigatran	10 (7.8)	9 (7.3)	0.87	28 (7.1)	38 (9.7)	0.18
By strategy, n (%)			0.19			0.18

None	2 (1.6)	0 (0.0)		5 (1.3)	6 (1.5)	
baseline antiplatelet only	9 (7.0)	10 (8.1)		42 (10.6)	32 (8.2)	
baseline anticoagulation only	63 (49.2)	49 (39.5)		190 (48.0)	168 (42.9)	
baseline dual	54 (42.2)	65 (52.4)		159 (40.2)	186 (47.4)	
Study drug regimens after randomization, n (%)						
Actual dose of edoxaban						
60 mg	24 (18.8)	9 (7.3)	0.01	293 (74.0)	272 (69.4)	0.15
appropriate dose	11 (45.8)	4 (44.4)	1.00	289 (98.6)	269 (98.9)	1.00
inappropriate overdose	13 (54.2)	5 (55.6)		4 (1.4)	3 (1.1)	
weight ≤ 60 kg	0 (0.0)	0 (0.0)		3 (1.0)	3 (1.1)	1.00
creatinine clearance < 50 mL/min	13 (54.2)	5 (55.6)	1.00	0 (0.0)	0 (0.0)	
concomitant P-glycoprotein inhibitors	2 (8.3)	0 (0.0)	1.00	2 (0.7)	0 (0.0)	0.50
30 mg	104 (81.3)	115 (92.7)	0.01	103 (26.0)	120 (30.6)	0.15
appropriate dose	102 (98.1)	113 (98.3)	1.00	59 (57.3)	47 (39.2)	0.01
weight ≤ 60 kg	55 (52.9)	53 (46.1)	0.32	57 (55.3)	43 (35.8)	0.004
creatinine clearance < 50 mL/min	102 (98.1)	113 (98.3)	1.00	5 (4.9)	4 (3.3)	0.74
concomitant P-glycoprotein inhibitors	4 (3.8)	10 (8.7)	0.14	3 (2.9)	3 (2.5)	1.00

inappropriate underdose	2 (1.9)	2 (1.7)	1.00	44 (42.7)	73 (60.8)	0.01
Type of antiplatelet agents			<0.001			<0.001
Aspirin	0 (0.0)	80 (64.5)		1 (0.3)	239 (61.0)	
Clopidogrel	1 (0.8)	44 (35.5)		1 (0.3)	151 (38.5)	

* Numbers (percentages) are from the intention-to-treat analysis.

[a] Previous use of antithrombotic regimens before randomization, which was discontinued before the patients underwent randomization for the trial

Supplementary Table 4. Relevant cardiac-related medications at randomisation and during follow-up.

Drug	Low Creatinine-clearance			High Creatinine-clearance		
	Edoxaban Monotherapy	**Dual Antithrombotic Therapy**	***P value***	**Edoxaban Monotherapy**	**Dual Antithrombotic Therapy**	***P value***
At randomization, n (%)						
Edoxaban	128 (100.0)	124 (100.0)	-	396 (100.0)	392 (100.0)	-
Antiplatelet agent	1 (0.8)	124 (100.0)	<0.001	2 (0.5)	390 (99.5)	<0.001
Beta-blocker	71 (55.5)	61 (49.2)	0.32	234 (59.1)	213 (54.3)	0.18
Calcium channel blocker	15 (11.7)	13 (10.5)	0.76	55 (13.9)	71 (18.1)	0.11
ACE inhibitor or ARB	86 (67.2)	81 (65.3)	0.75	224 (56.6)	216 (55.1)	0.68
Statin	110 (85.9)	112 (90.3)	0.28	368 (92.9)	360 (91.8)	0.56
Class I antiarrhythmics[a]	19 (14.8)	17 (13.7)	0.80	70 (17.7)	70 (17.9)	0.95
Class III antiarrhythmics[b]	30 (23.4)	29 (23.4)	0.99	71 (17.9)	70 (17.9)	0.98
Proton pump inhibitors	12 (9.4)	19 (15.3)	0.15	47 (11.9)	55 (14.0)	0.37
Digoxin	6 (4.7)	7 (5.6)	0.73	11 (2.8)	9 (2.3)	0.67
6 months after randomization, n (%)						

Edoxaban	115 (95.8)	118 (98.3)	0.45	373 (96.6)	363 (96.0)	0.66
Antiplatelet agent	2 (1.7)	112 (93.3)	<0.001	5 (1.3)	352 (93.1)	<0.001
Beta-blocker	64 (53.3)	63 (52.5)	0.90	230 (59.6)	212 (56.1)	0.33
Calcium channel blocker	14 (11.7)	14 (11.7)	1.00	50 (13.0)	69 (18.3)	0.04
ACE inhibitor or ARB	85 (70.8)	77 (64.2)	0.27	220 (57.0)	222 (58.7)	0.63
Statin	106 (88.3)	109 (90.8)	0.53	366 (94.8)	359 (95.0)	0.92
Class I antiarrhythmics	16 (13.3)	22 (18.3)	0.29	84 (21.8)	82 (21.7)	0.98
Class III antiarrhythmics	28 (23.3)	26 (21.7)	0.76	64 (16.6)	66 (17.5)	0.75
Proton pump inhibitors	18 (15.0)	20 (16.7)	0.72	41 (10.6)	63 (16.7)	0.02
Digoxin	6 (5.0)	6 (5.0)	1.00	11 (2.8)	10 (2.6)	0.86
12 months after randomization, n (%)						
Edoxaban	107 (96.4)	106 (93.8)	0.37	362 (96.3)	353 (95.7)	0.67
Antiplatelet agent	4 (3.6)	96 (85.0)	<0.001	15 (4.0)	325 (88.1)	<0.001
Beta-blocker	58 (52.3)	58 (51.3)	0.89	222 (59.0)	202 (54.7)	0.24
Calcium channel blocker	14 (12.6)	12 (10.7)	0.66	48 (12.8)	67 (18.3)	0.04
ACE inhibitor or ARB	76 (68.5)	71 (62.8)	0.38	213 (56.6)	222 (60.2)	0.33
Statin	101 (91.0)	102 (90.3)	0.85	357 (94.9)	349 (94.6)	0.82

Class I antiarrhythmics	17 (15.3)	16 (14.3)	0.83	86 (22.9)	82 (22.4)	0.86
Class III antiarrhythmics	28 (25.2)	25 (22.3)	0.61	62 (16.5)	60 (16.4)	0.96
Proton pump inhibitors	19 (17.1)	22 (19.5)	0.65	41 (10.9)	53 (14.4)	0.16
Digoxin	5 (4.5)	7 (6.2)	0.57	12 (3.2)	8 (2.2)	0.39

* Numbers (percentages) are based on the intention-to-treat analysis. During the regular follow-up period, patients who were unable to attend outpatient clinic visits were assessed via telephone interviews for adverse clinical events; however, for these patients, precise information regarding concomitant cardiovascular medications was not available.

ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker.

[a] Class I antiarrhythmics were flecainide or propafenone.

[b] Class III antiarrhythmics were amiodarone, dronedarone, or sotalol.

Supplementary Table 5. Other secondary outcomes at 1 year in patients stratified by creatinine clearance of 50 mL/min.

Outcomes	Before PS matching				After PS matching			
	Low Creatinine-clearance (n=252)	High Creatinine-clearance (n=788)			Low Creatinine-clearance (n=99)	High Creatinine-clearance (n=99)		
	No. of patients (estimated %)		HR (95% CI)	*P value*	No. of patients (estimated %)		HR (95% CI)	*P value*
Efficacy								
Death, any cause	5 (2.3)	1 (0.1)	8.47 (1.69–42.49)	0.009	17 (18.5)	4 (4.8)	3.53 (1.24–10.07)	0.02
Death, CV cause	2 (0.8)	1 (0.1)	7.58 (0.76–75.63)	0.08				
Death, non-CV cause	3 (1.5)	0	9.38 (0.98–90.14)	0.05	1 (1.1)	0	NE	
Stroke, any	4 (1.6)	7 (0.9)	NR[a]		0	0	NE	
Stroke, ischemic	3 (1.2)	5 (0.7)	1.61 (0.40–6.42)	0.50	1 (1.1)	0	NE	
Stroke, hemorrhagic	1 (0.4)	2 (0.3)	1.57 (0.14–17.35)	0.71	2 (2.1)	1 (1.0)	NR	
Myocardial infarction	0	2 (0.3)	NR		1 (1.0)	1 (1.0)	1.03 (0.07–16.18)	0.99
Unplanned urgent revascularization	3 (1.2)	10 (1.4)	1.30 (0.41–4.13)	0.66	1 (1.0)	0	NE	

Composite any ischemic events[b]	10 (4.3)	16 (2.2)	2.05 (0.99–4.28)	0.06	4 (4.2)	2 (2.7)	2.03 (0.37–11.18)	0.42
Safety[c]								
Clinically relevant nonmajor bleeding	19 (8.4)	51 (6.7)	1.17 (0.70–1.96)	0.54	8 (8.3)	2 (2.0)	2.60 (0.63–10.82)	0.19
Any bleeding	43 (18.5)	105 (13.9)	1.34 (0.95–1.88)	0.10	17 (18.6)	6 (6.1)	2.04 (0.89– 4.67)	0.09
Intracranial hemorrhage	2 (0.8)	3 (0.4)	2.12 (0.35–12.67)	0.41	1 (1.0)	0	NE	
GI hemorrhage	7 (2.9)	14 (1.9)	NR	-	2 (2.1)	2 (2.0)	NR	

The number of patients with events and estimated percentages were calculated using Kaplan–Meier survival analysis of data from the intention-to-treat population; therefore, the reported percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons; consequently, inferences drawn from these intervals may not be reproducible. Kaplan–Meier event rates and cox proportional hazard ratios were adjusted for age, sex, weight, diabetes mellitus, current smoking status, congestive heart failure, cerebrovascular disease, peripheral artery disease, and prior coronary revascularization. CI, denotes confidence interval; CV, cardiovascular; GI, gastrointestinal; HR, hazard ratio; NR, not reported

[a] Hazard ratios were NR for outcomes that did not satisfy the proportional-hazards assumption.

[b] The composite of any ischemic events was defined post hoc as the occurrence of any of the following: death from any cause, myocardial infarction, ischemic stroke, systemic embolism, or unplanned urgent revascularization.

[c] Bleeding events were assessed primarily using the ISTH definition and further classified based on the criteria of the Bleeding Academic Research Consortium and Thrombolysis in Myocardial Infarction.

Supplementary Table 6. Other secondary outcomes at 1 year in patients stratified by creatinine clearance of 50 mL/min and randomised antithrombotic strategy.

Outcomes	Low Creatinine-clearance (n=252)				High Creatinine-clearance (n=788)				
	Edoxaban Monotherapy (n=128)	Dual Antithrombotic Therapy (n=124)			Edoxaban Monotherapy (n=396)	Dual Antithrombotic Therapy (n=392)			
	no. of patients (estimated %)		HR (95% CI)	*P value*	no. of patients (estimated %)		HR (95% CI)	*P value*	P-Int
Efficacy									
Death, any cause	3 (2.6)	2 (2.0)	1.69 (0.29–9.77)	0.56	0	1 (0.3)	1.09 (0.07–17.74)	0.95	0.79
Death, CV cause	2 (1.6)	0	3.92 (0.19–80.05)	0.38	0	1 (0.3)	0.44 (0.01–26.22)	0.69	0.37
Death, non-CV cause	1 (1.0)	2 (2.0)	0.78 (0.06–9.74)	0.85	0	0	NA		
Stroke, any	1 (0.8)	3 (2.5)	NR[b]		6 (1.6)	1 (0.3)	NR		
Stroke, ischemic	1 (0.8)	2 (1.7)	0.49 (0.04–5.44)	0.56	4 (1.1)	1 (0.3)	4.86 (0.57–41.65)	0.15	0.16
Stroke, hemorrhagic	0	1 (0.8)	0.33 (0.01–20.27)	0.59	2 (0.5)	0	4.94 (0.10–248.90)	0.42	0.35
Myocardial infarction	0	0	NA		0	2 (0.6)	NR		

Unplanned urgent revascularization	2 (1.6)	1 (0.8)	1.01 (0.16–6.59)	0.99	5 (1.3)	5 (1.5)	1.00 (0.28–3.52)	>0.99	0.99
Composite any ischemic events[d]	6 (4.9)	4 (3.6)	1.19 (0.37–3.80)	0.77	9 (2.4)	7 (2.1)	1.61 (0.62–4.18)	0.32	0.69
Safety[e]									
Clinically relevant nonmajor bleeding	6 (4.9)	13 (11.8)	0.52 (0.21–1.30)	0.16	12 (3.1)	39 (10.2)	0.30 (0.16–0.55)	<0.001	0.32
Any bleeding	15 (12.9)	28 (24.0)	0.53 (0.29–0.96)	0.04	34 (9.0)	71 (18.8)	0.46 (0.31–0.68)	<0.001	0.71
Intracranial hemorrhage	0	2 (1.6)	0.19 (0.01–7.08)	0.37	2 (0.5)	1 (0.3)	1.65 (0.15–18.06)	0.683	0.33
GI hemorrhage	3 (2.5)	4 (3.3)	NR		5 (1.3)	9 (2.4)	NR		

The number of patients with events and estimated percentages were calculated using Kaplan–Meier survival analysis of data from the intention-to-treat population; therefore, the reported percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons; consequently, inferences drawn from these intervals may not be reproducible. CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; HR, hazard ratio; NA, not available; NR, not reported, P-Int, P-for-interaction

[a] Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, stroke, systemic thromboembolic event, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding (according to the International Society on Thrombosis and Haemostasis [ISTH] definition). A P value of <0.001 indicated the superiority of edoxaban monotherapy over dual antithrombotic therapy.

[b] Hazard ratios were NR for outcomes that did not satisfy the proportional-hazards assumption.

[c] The composite of major ischemic events was defined as the occurrence of any of the following: death from any cause, myocardial infarction, ischemic stroke, or systemic embolism.

[d] The composite of any ischemic events was defined post hoc as a composite of death from any cause, myocardial infarction, ischemic stroke, systemic embolism, or unplanned urgent revascularization.

[e] Bleeding events were assessed primarily using the ISTH definition and further classified based on the criteria of the Bleeding Academic Research Consortium and Thrombolysis in Myocardial Infarction.

Supplementary Table 7. Details of bleeding events in the studied patients (overall study period).

Bleeding Classification	Low Creatinine-clearance			High Creatinine-clearance		
	Edoxaban Monotherapy	Dual Antithrombotic Therapy	*P value*	Edoxaban Monotherapy	Dual Antithrombotic Therapy	*P value*
By severity (ISTH criteria), n (%)[a]						
Major bleeding	2 (1.6)	12 (9.7)	0.005	5 (1.3)	11 (2.8)	0.125
Clinically relevant non major bleeding	7 (5.5)	13 (10.5)	0.141	13 (3.3)	41 (10.5)	<0.001
Clinically irrelevant minor bleeding	11 (8.6)	7 (5.6)	0.364	22 (5.6)	31 (7.9)	0.187
By severity (BARC criteria), n (%)						
Type 1	11 (8.6)	7 (5.6)	0.364	22 (5.6)	31 (7.9)	0.187
Type 2	7 (5.5)	12 (9.7)	0.206	11 (2.8)	41 (10.5)	<0.001
Type 3a	0 (0.0)	7 (5.6)	0.006	3 (0.8)	7 (1.8)	0.222
Type 3b	0 (0.0)	2 (1.6)	0.241	1 (0.3)	1 (0.3)	1.000
Type 3c	2 (1.6)	4 (3.2)	0.441	2 (0.5)	3 (0.8)	0.685
By severity (TIMI criteria), n (%)						
Major	2 (1.6)	6 (4.8)	0.167	3 (0.8)	4 (1.0)	0.724

Minor	0 (0.0)	7 (5.6)	0.006	2 (0.5)	7 (1.8)	0.106
Requiring medical attention	7 (5.5)	11 (8.9)	0.294	13 (3.3)	40 (10.2)	0.001
Minimal	11 (8.6)	9 (7.3)	0.695	22 (5.6)	32 (8.2)	0.147
By site (Major bleeding by ISTH criteria), n (%)						
Intracranial hemorrhage	0 (0.0)	2 (1.6)	0.241	2 (0.5)	1 (0.3)	1.000
Intraocular bleeding	2 (1.6)	2 (1.6)	1.000	0 (0.0)	2 (0.5)	0.247
Pericardial bleeding	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (0.3)	0.498
Hemoptysis or respiratory tract bleeding	0 (0.0)	2 (1.6)	0.241	1 (0.3)	1 (0.3)	1.000
Gastrointestinal bleeding	0 (0.0)	3 (2.4)	0.118	2 (0.5)	3 (0.8)	0.685
Genitourinary bleeding	0 (0.0)	2 (1.6)	0.241	0 (0.0)	1 (0.3)	0.498
Musculoskeletal bleeding	0 (0.0)	2 (1.6)	0.241	0 (0.0)	2 (0.5)	0.247
By site (Clinically relevant nonmajor bleeding by ISTH criteria), n (%)						
Hemoptysis or respiratory tract bleeding	0 (0.0)	2 (1.6)	0.241	5 (1.3)	4 (1.0)	1.000
Epistaxis	1 (0.8)	1 (0.8)	1.000	1 (0.3)	15 (3.8)	<0.001
Pharyngeal or intraoral bleeding	1 (0.8)	0 (0.0)	1.000	0 (0.0)	6 (1.5)	0.015
Gastrointestinal bleeding	3 (2.3)	1 (0.8)	0.622	3 (0.8)	4 (1.0)	0.724
Genitourinary bleeding	2 (1.6)	3 (2.4)	0.680	4 (1.0)	7 (1.8)	0.354

Musculoskeletal bleeding	0 (0.0)	2 (1.6)	0.241	0 (0.0)	4 (1.0)	0.061
Subcutaneous bleeding	0 (0.0)	3 (2.4)	0.118	1 (0.3)	5 (1.3)	0.122
Others	0 (0.0)	1 (0.8)	0.492	0 (0.0)	1 (0.3)	0.498
By site (Clinically irrelevant minor bleeding by ISTH criteria), n (%)						
Conjunctival bleeding	1 (0.8)	1 (0.8)	1.000	1 (0.3)	0 (0.0)	1.000
Hemoptysis or respiratory tract bleeding	0 (0.0)	0 (0.0)	-	1 (0.3)	5 (1.3)	0.122
Epistaxis	0 (0.0)	3 (2.4)	0.118	4 (1.0)	7 (1.8)	0.354
Pharyngeal or intraoral bleeding	1 (0.8)	2 (1.6)	0.618	4 (1.0)	3 (0.8)	1.000
Gastrointestinal bleeding	2 (1.6)	0 (0.0)	0.498	2 (0.5)	2 (0.5)	1.000
Genitourinary bleeding	6 (4.7)	0 (0.0)	0.030	3 (0.8)	4 (1.0)	0.724
Musculoskeletal bleeding	1 (0.8)	1 (0.8)	1.000	2 (0.5)	1 (0.3)	1.000
Subcutaneous bleeding	1 (0.8)	2 (1.6)	0.618	5 (1.3)	13 (3.3)	0.054
Others	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (0.3)	0.498

* Numbers (percentages) are based on the intention-to-treat analysis. The listed percentages were estimated as the ratio of the numerator and denominator.

BARC denotes Bleeding Academic Research Consortium, ISTH International Society on Thrombosis and Haemostasis, and TIMI Thrombolysis in Myocardial Infarction.

[a] The severity of bleeding events is primarily assessed using the ISTH definition. Bleeding events were also assessed based on the BARC and TIMI definitions.

Supplementary Table 8. Primary and secondary outcomes at 1 year in patients according to creatinine clearance of 95 mL/min and randomised antithrombotic strategy among the high creatinine clearance group.

	Normal Creatinine-clearance				Extra-normal Creatinine-clearance				
Outcomes	**Edoxaban Monotherapy**	**Dual Antithrombotic Therapy**	**HR (95% CI)**	***P value***	**Edoxaban Monotherapy**	**Dual Antithrombotic Therapy**	**HR (95% CI)**	***P value***	**P for interactio**
Primary outcome									
Net adverse clinical events[a]	15 (4.4)	50 (15.1)	0.30 (0.18–0.52)	<0.001	5 (10.6)	4 (9.3)	1.67 (0.49–5.70)	0.41	0.01
Secondary outcomes									
Efficacy									
Death, any cause	0	1 (0.3)	0.27 (0.00–25.61) [d]	0.58	0	0	NA		
Death, CV cause	0	1 (0.3)	0.33 (0.00–84.93) [d]	0.70	0	0	NA		
Death, non-CV cause	0	0	NA		0	0	NA		
Stroke, any	6 (1.8)	1 (0.3)	NR[a]		0	0	NA		

Stroke, ischemic	4 (1.2)	1 (0.3)	3.53 (0.44–28.44)	0.24	0	0	NA		
Stroke, hemorrhagic	2 (0.6)	0	4.90 (0.07–355.94) [d]	0.47	0	0	NA		
Myocardial infarction	0	2 (0.7)	NR		0	0	NA		
Unplanned urgent revascularization	3 (0.9)	5 (1.7)	0.64 (0.15–2.76)	0.55	2 (4.3)	0	4.80 (0.17–133.71) [d]	0.36	0.28
Composite major ischemic events[c]	4 (1.2)	4 (1.3)	1.15 (0.29–4.52)	0.84	0	0	NA		
Composite any ischemic events[b]	7 (2.1)	7 (2.3)	1.10 (0.39–3.10)	0.86	2 (4.3)	0	6.92 (0.30–157.28) [d]	0.23	0.27
Safety|[c]									
Major bleeding or clinically relevant nonmajor bleeding	11 (3.2)	44 (13.1)	0.24 (0.13–0.46)	<0.001	4 (8.4)	4 (9.3)	1.18 (0.32–4.40)	0.80	0.03
Major bleeding	2 (0.6)	9 (2.7)	0.22 (0.05–1.02)	0.05	2 (4.2)	2 (4.8)	1.20 (0.20–7.41)	0.84	0.16

Clinically relevant nonmajor bleeding	9 (2.7)	36 (10.7)	0.25 (0.12–0.49)	<0.001	3 (6.3)	3 (6.7)	0.93 (0.19–4.60)	0.93	0.14
Any bleeding	29 (8.8)	65 (19.4)	0.42 (0.28–0.64)	<0.001	5 (10.5)	6 (13.8)	0.94 (0.30–2.91)	0.91	0.19
Intracranial hemorrhage	2 (0.6)	1 (0.3)	1.66 (0.12–22.60)	0.71	0	0	NA		
GI hemorrhage	4 (1.2)	8 (2.3)	NR		1 (2.1)	1 (2.6)	NR		

The number of patients with events and estimated percentages were calculated using Kaplan–Meier survival analysis of data from the intention-to-treat population; therefore, the reported percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons; consequently, inferences drawn from these intervals may not be reproducible. CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; HR, hazard ratio; NA, not available; NR, not reported

[a] Hazard ratios were NR for outcomes that did not satisfy the proportional-hazards assumption.

[b] The composite of any ischemic events was defined post hoc as a composite of death from any cause, myocardial infarction, ischemic stroke, systemic embolism, or unplanned urgent revascularization.

[c] Bleeding events were assessed primarily using the ISTH definition and further classified based on the criteria of the Bleeding Academic Research Consortium and Thrombolysis in Myocardial Infarction.

[d] Hazard ratios were derived from Firth's penalized Cox regression model

Supplementary Table 9. Primary and secondary outcomes at 1 year in patients stratified by estimated glomerular filtration rate of 60 mL/min/1.73 m^2 and randomised antithrombotic strategy.

	Low Renal Function (eGFR < 60 mL/min/1.73 m^2, n=255)				Low Renal Function (eGFR ≥ 60 mL/min/1.73 m^2, n=785)				
Outcomes	**Edoxaban Monotherapy (n=121)**	**Dual Antithrombotic Therapy (n=134)**	**HR (95% CI)**	***P value***	**Edoxaban Monotherapy (n=403)**	**Dual Antithrombotic Therapy (n=382)**	**HR (95% CI)**	***P value***	**P-for-interaction**
Primary outcome									
Net adverse clinical events[a]	6 (5.2)	22 (17.9)	0.29 (0.12–0.72)	0.01	28 (7.3)	57 (15.7)	0.49 (0.32–0.75)	<0.001	0.31
Secondary outcomes									
Efficacy									
Death, any cause	1 (1.0)	2 (1.8)	0.46 (0.04–5.27)	0.53	0	1 (0.3)	3.10 (0.32–29.89)	0.33	0.26
Death, CV cause	0	0	NA		0	1 (0.3)	1.58 (0.12–21.59)	0.73	0.91
Death, non-CV cause	1 (1.0)	2 (1.8)	0.41 (0.03–6.14)	0.52	0	0	NA		
Stroke, any	1 (0.8)	1 (0.8)	NR[b]		6 (1.6)	1 (0.3)	NR		
Stroke, ischemic	0	0	NA		4 (1.1)	1 (0.3)	1.88 (0.47–7.50)	0.37	1.00

Stroke, hemorrhagic	1 (0.8)	1 (0.8)	1.12 (0.06–20.76)	0.94	2 (0.5)	0	2.84 (0.05–176.71)	0.62	0.72
Myocardial infarction	0	1 (1.0)	NR		0	2 (0.6)	NR		
Unplanned urgent revascularization	0	3 (3.0)	0.16 (0.01–3.79)	0.26	5 (1.3)	5 (1.5)	1.61 (0.46–5.61)	0.46	0.18
Composite major ischemic events[c]	1 (1.0)	3 (2.8)	0.35 (0.04–3.39)	0.37	4 (1.1)	4 (1.2)	1.75 (0.59–5.23)	0.32	0.21
Composite any ischemic events[d]	1 (1.0)	5 (4.8)	0.21 (0.02–1.84)	0.16	9 (2.4)	7 (2.1)	2.24 (0.92–5.44)	0.08	0.05
Safety[e]									
Major bleeding or clinically relevant nonmajor bleeding	5 (4.2)	17 (13.2)	0.32 (0.12–0.86)	0.02	15 (3.9)	48 (12.7)	0.34 (0.20–0.55)	<0.001	0.92
Major bleeding	1 (0.8)	8 (6.4)	0.13 (0.02–1.07)	0.06	4 (1.0)	11 (3.0)	0.39 (0.15–1.00)	0.05	0.36
Clinically relevant nonmajor bleeding	4 (3.4)	11 (8.3)	0.39 (0.13–1.24)	0.11	12 (3.1)	39 (10.2)	0.34 (0.19–0.60)	<0.001	0.81
Any bleeding	14 (11.9)	25 (19.9)	0.62 (0.33–1.17)	0.14	34 (9.0)	71 (18.8)	0.44 (0.30–0.65)	<0.001	0.37

Intracranial hemorrhage	1 (0.8)	1 (0.8)	1.12 (0.08–16.30)	0.93	2 (0.5)	1 (0.3)	0.57 (0.05–6.22)	0.64	0.71
GI hemorrhage	2 (1.7)	6 (4.7)	NR		5 (1.3)	9 (2.4)	NR		

The number of patients with events and estimated percentages were calculated using Kaplan–Meier survival analysis of data from the intention-to-treat population; therefore, the reported percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons; consequently, inferences drawn from these intervals may not be reproducible. CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; HR, hazard ratio; NA, not available; NR, not reported

[a] Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, stroke, systemic thromboembolic event, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding (according to the International Society on Thrombosis and Haemostasis [ISTH] definition). A P value of <0.001 indicated superiority of edoxaban monotherapy over dual antithrombotic therapy.

[b] Hazard ratios were NR for outcomes that did not satisfy the proportional-hazards assumption.

[c] The composite of major ischemic events was defined as the occurrence of any of the following: death from any cause, myocardial infarction, ischemic stroke, or systemic embolism.

[d] The composite of any ischemic events was defined post hoc as a composite of death from any cause, myocardial infarction, ischemic stroke, systemic embolism, or unplanned urgent revascularization.

[e] Bleeding events were assessed primarily using the ISTH definition and further classified based on the criteria of the Bleeding Academic Research Consortium and Thrombolysis in Myocardial Infarction.

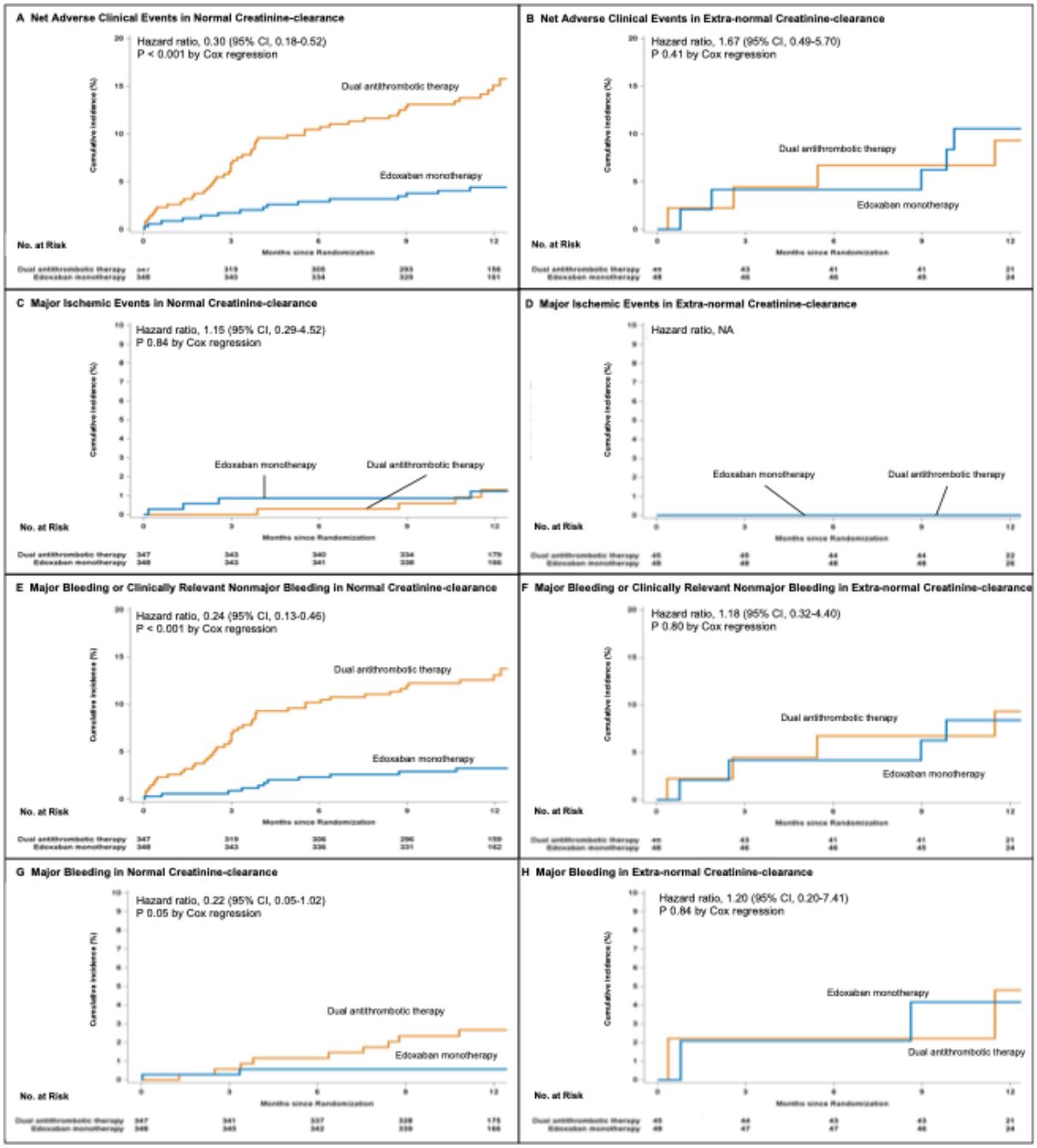
Supplementary Table 10. Clinical outcomes in patients with high creatinine clearance receiving the 60 mg edoxaban dose according to the antithrombotic strategy.

	Edoxaban monotherapy (n=293)	**Dual antithrombotic therapy (n=272)**		
Outcomes	**No. of patients (estimated %)**		**HR (95% CI)**	***P value***
Net adverse clinical events[a]	17 (5.9)	42 (16.3)	0.41 (0.24–0.69)	<0.001
Composite major ischemic events[b]	3 (1.1)	3 (1.3)	1.49 (0.36–6.26)	0.582
Major bleeding or clinically relevant nonmajor bleeding	12 (4.2)	37 (14.1)	0.31 (0.17–0.57)	<0.001
Major bleeding	3 (1.0)	9 (3.5)	0.39 (0.12-1.26)	0.115

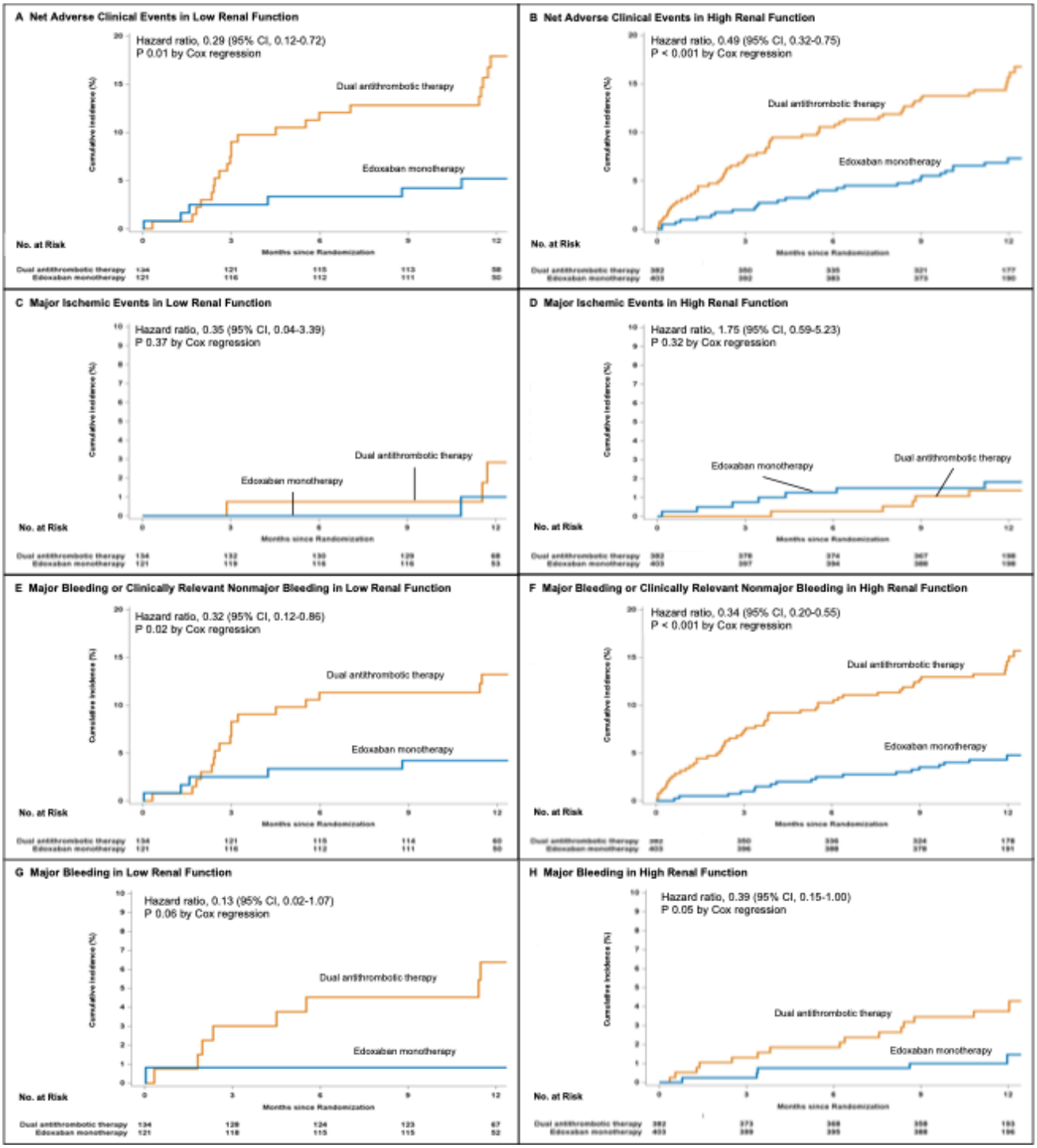
The number of patients with events and estimated percentages were calculated using Kaplan–Meier survival analysis of data from the intention-to-treat population; therefore, the reported percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons; consequently, inferences drawn from these intervals may not be reproducible. Kaplan–Meier event rates and cox proportional hazard ratios were adjusted for age, sex, weight, diabetes mellitus, current smoking status, congestive heart failure, cerebrovascular disease, peripheral artery disease, and prior coronary revascularization. aHR, denotes adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

[a] Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, stroke, systemic thromboembolic event, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding (according to the International Society on Thrombosis and Haemostasis [ISTH] definition). A P value <0.001 indicated the superiority of edoxaban monotherapy over dual antithrombotic therapy.

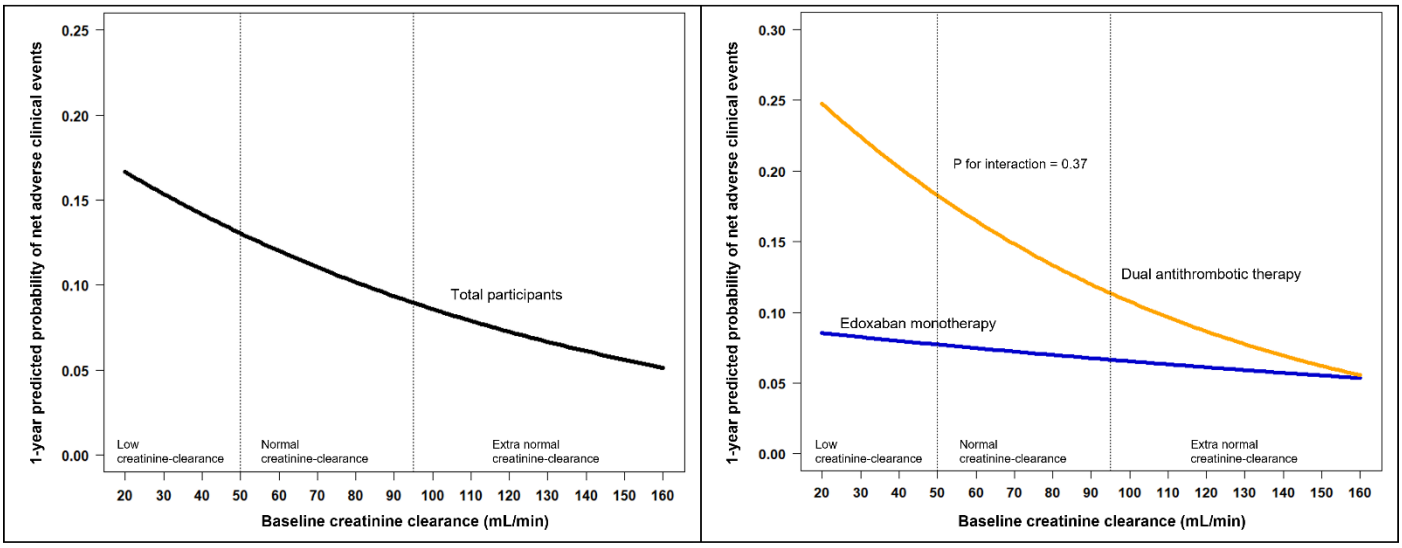
[b] The composite of major ischemic events was defined as a composite of death from any cause, myocardial infarction, ischemic stroke, or systemic embolism.



Supplementary Figure 1. Time-to-event curves for clinical outcomes stratified by creatinine clearance of 95 mL/min and randomised antithrombotic strategy in patients with creatinine clearance ≥50 mL/min.



Supplementary Figure 2. Time-to-event curves for clinical outcomes stratified by estimated glomerular filtration rate of 60 mL/min/1.73 m^2 and randomised antithrombotic strategy in patients.



Supplementary Figure 3. One-year probability of the primary outcome as a function of baseline creatinine clearance level.

Left panel: A nonlinear inverse relationship was observed between baseline creatinine clearance and the predicted 1-year risk of net adverse clinical events (composite of death, myocardial infarction, stroke, systemic embolism, unplanned revascularization, and major or clinically relevant nonmajor bleeding), estimated using a restricted cubic spline model.

Right panel: When stratified by randomized treatment strategy, patients receiving dual antithrombotic therapy (edoxaban plus single antiplatelet agent; orange line) demonstrated a markedly higher predicted risk of net adverse events at lower levels of creatinine clearance, compared with those receiving edoxaban monotherapy (blue line). The predicted event rate for edoxaban monotherapy remained relatively consistent across the range of creatinine clearance values. No significant interaction was observed between renal function and treatment strategy (*P* for interaction = 0.37).

Data availability statement.

The data regarding this article will be shared by the corresponding author upon reasonable request.