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Apixaban or Vitamin K Antagonists and Aspirin or Placebo According to Kidney Function in Patients With Atrial Fibrillation After Acute Coronary Syndrome or Percutaneous Coronary Intervention

Insights From the AUGUSTUS Trial

BACKGROUND: In the AUGUSTUS trial (An Open-Label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention), apixaban resulted in less bleeding and fewer hospitalizations than vitamin K antagonists, and aspirin caused more bleeding than placebo in patients with atrial fibrillation and acute coronary syndrome or percutaneous coronary intervention treated with a $P2Y_{12}$ inhibitor. We evaluated the risk-benefit balance of antithrombotic therapy according to kidney function.

METHODS: In 4456 patients, the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula was used to calculate baseline estimated glomerular filtration rate (eGFR). The effect of apixaban versus vitamin K antagonists and aspirin versus placebo was assessed across kidney function categories by using Cox models. The primary outcome was International Society on Thrombosis and Haemostasis major or clinically relevant nonmajor bleeding. Secondary outcomes included death or hospitalization and ischemic events (death, stroke, myocardial infarction, stent thrombosis [definite or probable], or urgent revascularization). Creatinine clearance <30 mL/min was an exclusion criterion in the AUGUSTUS trial.

RESULTS: Overall, 30%, 52%, and 19% had an eGFR of >80, >50 to 80, and 30 to 50 mL·min^{-1}·1.73 m^{-2}, respectively. At the 6-month follow-up, a total of 543 primary outcomes of bleeding, 1125 death or hospitalizations, and 282 ischemic events occurred. Compared with vitamin K antagonists, patients assigned apixaban had lower rates for all 3 outcomes across most eGFR categories without significant interaction. The absolute risk reduction with apixaban was most pronounced in those with an eGFR of 30 to 50 mL·min^{-1}·1.73 m^{-2} for bleeding events with rates of 13.1% versus 21.3% (hazard ratio, 0.59; 95% CI, 0.41–0.84). Patients assigned aspirin had a higher risk of bleeding in all eGFR categories with an even greater increase among those with eGFR >80 mL·min^{-1}·1.73 m^{-2}: 16.6% versus 5.6% (hazard ratio, 3.22; 95% CI, 2.19–4.74; *P* for interaction=0.007). The risk of death or hospitalization and ischemic events were comparable to aspirin and placebo across eGFR categories with hazard ratios ranging from 0.97 (95% CI, 0.76–1.23) to 1.28 (95% CI, 1.02–1.59) and from 0.75 (95% CI, 0.48–1.17) to 1.34 (95% CI, 0.81–2.22), respectively.

CONCLUSIONS: The safety and efficacy of apixaban was consistent irrespective of kidney function, compared with warfarin, and in accordance with the overall trial results. The risk of bleeding with aspirin was consistently higher across all kidney function categories.

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Clinical Perspective

What Is New?

- In patients with atrial fibrillation and acute coronary syndrome and percutaneous coronary intervention, apixaban, compared with vitamin K antagonists, displayed a consistent safety and efficacy profile irrespective of kidney function, in accordance with the overall trial.
- Aspirin, relative to placebo, on top of oral anticoagulation and a $P2Y_{12}$ inhibitor, resulted in more bleeding irrespective of kidney function, also consistent with the results of the overall trial.

What Are the Clinical Implications?

- These findings can help clinicians make informed decisions on the antithrombotic therapy in patients with atrial fibrillation and kidney dysfunction with acute coronary syndrome and percutaneous coronary intervention.

Patients with atrial fibrillation (AF) frequently have concomitant coronary artery disease, which can present as an acute coronary syndrome (ACS) or require percutaneous coronary intervention (PCI).[1–3] This introduces difficulties in the clinical management, because oral anticoagulation is preferred for stroke prevention, and dual antiplatelet therapy is preferred for the prevention of acute myocardial infarction and stent thrombosis.[4–6] Unfortunately, the combination of dual antiplatelet therapy and oral anticoagulation often results in excessive bleeding.[7] In past years, randomized clinical trials have shown that the risk of bleeding may be reduced by combining a non–vitamin K antagonist oral anticoagulant with clopidogrel compared with triple therapy with a vitamin K antagonist (VKA) and 2 antiplatelet agents.[8–10] Recently, the AUGUSTUS trial (An Open-Label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) showed that, in patients with AF and ACS or PCI treated with a $P2Y_{12}$ inhibitor, apixaban resulted in less bleeding and fewer hospitalizations than VKA, and that aspirin resulted in more bleeding than placebo, without significant differences in ischemic events.[11] Current international guidelines mirror these findings because the recommended duration of triple therapy has been shortened and, in some instances, even omitted in favor of dual antithrombotic therapy with a non–vitamin K antagonist oral anticoagulant and 1 antiplatelet agent.[12,13] Kidney function, however, plays a major role in the risks of both bleeding and ischemic events, and thus may potentially change the risk-benefit balance of antithrombotic therapy and offer an opportunity to further personalize therapy based on kidney function.[14–17] This prespecified analysis of the AUGUSTUS trial evaluates the different antithrombotic regimens according to baseline kidney function in 4456 patients with AF and ACS or PCI.

METHODS

Study Population and Trial Design

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The trial design and main results of AUGUSTUS have been published previously.[11,18] In brief, AUGUSTUS was a multicenter, 2×2 factorial, randomized clinical trial that compared apixaban with a VKA, and aspirin with placebo, in patients with AF who had a recent ACS and underwent PCI. Patients at least 18 years of age, with AF and planned long-term use of an oral anticoagulant, and recent ACS or PCI with planned use of a $P2Y_{12}$ inhibitor for at least 6 months were randomly assigned by an interactive voice-response system to receive apixaban or VKA and aspirin or matching placebo. Patients with an estimated creatinine clearance <30 mL/min according to the Cockcroft-Gault equation were excluded. A total of 4614 patients were randomly assigned from September 2015 through April 2018 at 492 sites in 33 countries. Of these, 4456 had kidney function reported at baseline. All participants were followed for 6 months.

Written informed consent was obtained from all patients, and institutional review boards for participating institutions approved the trial protocol.

Outcomes

The primary outcome was major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis.[18] International Society on Thrombosis and Haemostasis major bleeding was defined as bleeding that resulted in death, occurred in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or was associated with either a decrease in the hemoglobin level of at least 2 g/dL or a transfusion of at least 2 U of packed red blood cells. Clinically relevant nonmajor bleeding was defined as bleeding that resulted in hospitalization, medical or surgical intervention for bleeding, an unscheduled clinic visit, or a change in physician-directed antithrombotic therapy. Secondary outcomes included the composite of all-cause death or hospitalization and ischemic events (death, stroke, myocardial infarction, stent thrombosis [definite or probable], or urgent revascularization). Bleeding events were assessed from first dose of study drug to 6 months or permanent study drug discontinuation and efficacy events were assessed from randomization to 6 months. All bleeding and ischemic events (except for urgent revascularization) were

independently adjudicated, blinded to randomized group, by the clinical-events classification committee at the Duke Clinical Research Institute.[11,18]

Kidney Function Assessment

From serum creatinine collected at randomization and analyzed locally at each site, the estimated glomerular filtration rate (eGFR) according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)[19] equation ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) was calculated: $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if Black], where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, max indicates the maximum of Scr/κ or 1, and Scr is serum creatinine expressed in mg/dL.

Statistical Analyses

All randomly assigned patients with complete data on age, sex, race, weight, and serum creatinine to estimate baseline kidney function were included in the analysis (n=4456). Patients were classified according to previously used prespecified categories of kidney function[20]: no impairment: >80 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$; mild impairment: >50 to 80 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$; and moderate-severe impairment: 30 to 50 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. In addition, as a sensitivity analysis, kidney function categories according to the National Kidney Foundation practical guidelines were used (≥90 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, 60–89 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$). Given the 2×2 factorial design, parallel analyses were performed to compare 2 randomized antithrombotic regimens: apixaban versus VKA and aspirin versus placebo, respectively. Baseline characteristics of patients were examined by categories of kidney function. Continuous variables were summarized as median (Q1–Q3) or mean (SD) and compared across the groups using ANOVA or the Kruskal-Wallis test. Categorical variables were summarized as n/N (%) and compared across the groups using the Pearson χ^2 test or Fisher exact test.

To assess the effect of apixaban versus VKA on outcomes by kidney function, event rates of each outcome were calculated for patients treated with apixaban or VKA for each kidney function category by using the Kaplan-Meier method. The effect of apixaban versus VKA on each outcome was assessed by using a Cox proportional hazards model that included treatment and kidney function categories, and the interaction between treatment and kidney function category, as well. An identical approach was used to assess the treatment effect of aspirin versus placebo. The results are presented as hazard ratios with 95% CIs by the kidney function categories with an overall *P* value for the interaction (global Wald-type test with 2 degrees of freedom). The proportional hazards assumption was evaluated by using correlation tests based on the weighted Schoenfeld residuals. In sensitivity analyses, the same evaluations were performed using kidney function categories according to the National Kidney Foundation practical guidelines. In a second sensitivity analysis, patients who received low-dose apixaban without meeting the criteria for dose reduction were excluded (n=138). A 2-sided *P* value of <0.05 was considered statistically significant. All the statistical analyses were performed using SAS software, version 9.4 TS1M6 (SAS Institute Inc).

Table 1. Baseline Characteristics of Patients According to Categories of Kidney Function

Characteristics	Overall (N=4456)	>80 mL·min⁻¹·1.73 m⁻² (n=1319)	>50–80 mL·min⁻¹·1.73 m⁻² (n=2306)	30–50 mL·min⁻¹·1.73 m⁻² (n=831)	*P* value
Age, median (Q1–Q3), y	71 (64–77)	67 (61–73)	71 (65–77)	76 (70–81)	<0.001
Female sex, n/N (%)	1301/4456 (29.2)	245/1319 (18.6)	678/2306 (29.4)	378/831 (45.5)	<0.001
Weight, median (Q1–Q3), kg	83.0 (73.5–95.0)	84.0 (74.0–96.0)	83.9 (74.0–95.4)	81.4 (71.0–91.4)	<0.001
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.5)	3.4 (1.4)	3.9 (1.5)	4.8 (1.5)	<0.001
HAS-BLED score, mean (SD)	2.9 (0.9)	2.6 (0.9)	2.8 (0.9)	3.3 (1.0)	<0.001
Prior bleeding, n/N (%)	47/4432 (1.1)	13/1314 (1.0)	20/2295 (0.9)	14/823 (1.7)	0.13
Hypertension, n/N (%)	3949/4456 (88.6)	1122/1319 (85.1)	2064/2306 (89.5)	763/831 (91.8)	<0.001
Heart failure, n/N (%)	1930/4456 (43.3)	472/1319 (35.8)	1009/2306 (43.8)	449/831 (54.0)	<0.001
Diabetes, n/N (%)	1602/4456 (36.0)	472/1319 (35.8)	773/2306 (33.5)	357/831 (43.0)	<0.001
Stroke, transient ischemic attack, or embolism, n/N (%)	609/4428 (13.8)	156/1310 (11.9)	311/2294 (13.6)	142/824 (17.2)	0.002
Previous use of oral anticoagulant, n/N (%)	2210/4456 (49.6)	635/1319 (48.1)	1164/2306 (50.5)	411/831 (49.5)	0.40
Qualifying index event					<0.001
Acute coronary syndrome and percutaneous coronary intervention, n/N (%)	1652/4441 (37.2)	525/1314 (40.0)	840/2296 (36.6)	287/831 (34.5)	
Medically managed acute coronary syndrome, n/N (%)	1083/4441 (24.4)	260/1314 (19.8)	559/2296 (24.3)	264/831 (31.8)	
Elective percutaneous coronary intervention, n/N (%)	1706/4441 (38.4)	529/1314 (40.3)	897/2296 (39.1)	280/831 (33.7)	
Low-dose apixaban, n/N (%)	226/2239 (10.1)	52/655 (7.9)	93/1178 (7.9)	81/406 (20.0)	<0.001
Time in therapeutic range in patients randomly assigned to vitamin K antagonist, median (Q1–Q3)	58.3 (33.1–81.0)	58.8 (33.1–80.8)	58.3 (33.3–81.4)	57.5 (32.1–78.9)	0.86

CHADSVASc indicates congestive heart failure, hypertension, age 75 or older, diabetes, stroke, vascular disease, age 65 or older, sex category; and HAS-BLED, hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage.

RESULTS

Baseline Characteristics, Kidney Function, and Events

The median age was 71 years, 29.2% were women, and the median eGFR was 68.4 mL·min^{-1}·1.73 m^{-2}. The proportion of patients with an eGFR >80 mL·min^{-1}·1.73 m^{-2} was 30%, >50 to 80 mL·min^{-1}·1.73 m^{-2} was 52%, and 30 to 50 mL·min^{-1}·1.73 m^{-2} was 19%, respectively (Table 1). Patients in the group with eGFR 30 to 50 mL·min^{-1}·1.73 m^{-2} were older and had a higher proportion of female sex.

During the trial, a total of 543 primary outcome events (major or clinically relevant nonmajor bleeding), 1125 deaths or hospitalizations, and 222 ischemic events occurred. For all 3 outcomes, event rates increased with declining kidney function (Table 2).

Outcomes of Apixaban Versus VKA According to Kidney Function

In patients receiving apixaban, the rate of major or clinically relevant nonmajor bleeding events was consistently lower, compared with VKA, across all kidney function categories (Table 2). The range of bleeding events varied from 9.7% to 13.1% for patients receiving apixaban, and from 12.2% to 21.3% for those receiving VKA (Table 2). The absolute risk reduction with apixaban, compared with VKA, was greatest in those with kidney function 30 to 50 mL·min^{-1}·1.73 m^{-2} (13.1% versus 21.3%, hazard ratio 0.59 [95% CI, 0.41–0.84]). The lower rate of bleeding with apixaban was evident both for major or clinically relevant nonmajor bleeding and for major bleeding alone (Table 2).

For the efficacy outcomes, death or hospitalization and ischemic events, patients assigned apixaban had lower rates of both outcomes across most kidney function categories (Table 2).

Outcomes of Aspirin Versus Placebo According to Kidney Function

In patients receiving aspirin, the rate of major or clinically relevant nonmajor bleeding was consistently higher, compared with placebo, across all kidney function categories (Table 3). The rate of bleeding ranged from 15.7% to 20.8% for patients randomly assigned to aspirin, and from 5.6% to 13.2% for those randomly assigned to placebo (Table 3). The absolute increase of risk with aspirin, compared with placebo, was even more pronounced in those with preserved kidney function, >80 mL·min^{-1}·1.73 m^{-2} (16.6% versus 5.6%, hazard ratio 3.22 [95% CI, 2.19–4.74]). For major or clinically relevant nonmajor bleeding events, there was a significant interaction for study treatment and kidney function (P=0.007), because the relative risk was

Table 2. Treatment Effect of Apixaban Versus Vitamin K Antagonists on Safety and Efficacy Outcomes by Categories of Kidney Function

Event	No. of events (frequency*) at 6 mo		Hazard ratio (95% CI)	Interaction *P* value
	Apixaban, n (%)	Vitamin K antagonist, n (%)		
International Society on Thrombosis and Haemostasis major or clinically relevant nonmajor bleeding				0.56
>80 mL·min^{-1}·1.73 m^{-2}	59 (9.7)	75 (12.2)	0.77 (0.55–1.08)	
>50–80 mL·min^{-1}·1.73 m^{-2}	121 (10.7)	158 (15.1)	0.68 (0.54–0.86)	
30–50 mL·min^{-1}·1.73 m^{-2}	50 (13.1)	80 (21.3)	0.59 (0.41–0.84)	
International Society on Thrombosis and Haemostasis major bleeding				0.68
>80 mL·min^{-1}·1.73 m^{-2}	15 (2.5)	19 (3.2)	0.74 (0.38–1.45)	
>50–80 mL·min^{-1}·1.73 m^{-2}	35 (3.1)	47 (4.6)	0.67 (0.43–1.03)	
30–50 mL·min^{-1}·1.73 m^{-2}	16 (4.2)	31 (8.4)	0.51 (0.28–0.93)	
Death or hospitalization				0.68
>80 mL·min^{-1}·1.73 m^{-2}	140 (21.8)	172 (26.2)	0.80 (0.64–1.01)	
>50–80 mL·min^{-1}·1.73 m^{-2}	263 (22.6)	293 (26.6)	0.82 (0.70–0.97)	
30–50 mL·min^{-1}·1.73 m^{-2}	123 (31.2)	134 (32.1)	0.92 (0.72–1.18)	
Ischemic events				0.19
>80 mL·min^{-1}·1.73 m^{-2}	34 (5.3)	26 (4.0)	1.37 (0.82–2.27)	
>50–80 mL·min^{-1}·1.73 m^{-2}	70 (6.1)	72 (6.5)	0.91 (0.65–1.26)	
30–50 mL·min^{-1}·1.73 m^{-2}	33 (8.8)	47 (11.4)	0.74 (0.47–1.14)	

*Kaplan-Meier estimates for end points involving mortality or cumulative incidence accounting for the competing risk of death for end points not involving mortality.

Table 3. Treatment Effect of Aspirin Versus Placebo on Safety and Efficacy Outcomes by Categories of Kidney Function

Event	No. of events (frequency*) at 6 mo		Hazard ratio (95% CI)	Interaction *P* value
	Aspirin, n (%)	Placebo, n (%)		
International Society on Thrombosis and Haemostasis major or clinically relevant nonmajor bleeding				0.007
>80 mL·min^{-1}·1.73 m^{-2}	98 (16.6)	35 (5.6)	3.22 (2.19–4.74)	
>50–80 mL·min^{-1}·1.73 m^{-2}	172 (15.7)	110 (10.3)	1.58 (1.24–2.00)	
30–50 mL·min^{-1}·1.73 m^{-2}	79 (20.8)	49 (13.2)	1.67 (1.17–2.37)	
International Society on Thrombosis and Haemostasis major bleeding				0.60
>80 mL·min^{-1}·1.73 m^{-2}	23 (4.0)	11 (1.8)	2.30 (1.12–4.71)	
>50–80 mL·min^{-1}·1.73 m^{-2}	52 (4.8)	34 (3.3)	1.55 (1.01–2.39)	
30–50 mL·min^{-1}·1.73 m^{-2}	26 (7.0)	18 (4.8)	1.48 (0.81–2.70)	
Death or hospitalization				0.22
>80 mL·min^{-1}·1.73 m^{-2}	168 (26.6)	144 (21.6)	1.28 (1.02–1.59)	
>50–80 mL·min^{-1}·1.73 m^{-2}	285 (25.0)	271 (24.1)	1.06 (0.90–1.25)	
30–50 mL·min^{-1}·1.73 m^{-2}	127 (31.4)	130 (31.9)	0.97 (0.76–1.23)	
Ischemic events				0.17
>80 mL·min^{-1}·1.73 m^{-2}	33 (5.2)	27 (4.2)	1.34 (0.81–2.22)	
>50–80 mL·min^{-1}·1.73 m^{-2}	63 (5.5)	79 (7.0)	0.79 (0.57–1.10)	
30–50 mL·min^{-1}·1.73 m^{-2}	35 (9.0)	45 (11.2)	0.75 (0.48–1.17)	

*Kaplan-Meier estimates for end points involving mortality or cumulative incidence accounting for the competing risk of death for end points not involving mortality.

significantly greater in those with kidney function >80 mL·min^{-1}·1.73 m^{-2}.

For the efficacy outcomes of the trial, death or hospitalization, and ischemic events, respectively, the effects of aspirin versus placebo were more comparable across the kidney function categories (Table 3).

For all analyses, the results were consistent without any significant treatment interactions in sensitivity analyses: (1) using alternative kidney function categories (<60, 60–90, >90 mL·min^{-1}·1.73 m^{-2}) according to the National Kidney Foundation Guidelines; (2) omitting those with incorrect dose reduction of apixaban; and (3) for the separate outcomes of all-cause mortality and hospitalization, respectively.

Outcomes According to the 4 Different Treatment Strategies by Kidney Function

Outcomes according to the 4 different treatment strategies were analyzed in relation to kidney function. A triple-therapy strategy with VKA consistently conferred higher rates of bleeding outcomes than the other treatment strategies across kidney function categories (Figure). Double therapy with apixaban consistently conferred lower rates of bleeding outcomes among the studied treatment strategies, irrespective of kidney function (Figure). For the efficacy outcomes, death or hospitalization (Figure B) and ischemic events (Figure C), the patterns were more mixed. However, there seemed to be a trend toward numerically fewer events in patients randomly assigned to dual therapy, in particular, with apixaban. Another pattern worth noting, most evident in those with kidney function 30 to 50 mL·min^{-1}·1.73 m^{-2}, was a signal of higher risk for ischemic events in patients randomly assigned to a dual therapy strategy with VKA (Figure C, lower).

DISCUSSION

The main findings of this prespecified AUGUSTUS analysis were that, first, patients with AF and ACS or PCI, apixaban, compared with VKA, displayed a consistent safety and efficacy profile irrespective of kidney function, in accordance with the overall trial. Second, aspirin, relative to placebo, on top of oral anticoagulation and a $P2Y_{12}$ inhibitor, resulted in more bleeding irrespective of kidney function, consistent with the results of the overall trial.

In previous kidney function substudies from the ARISTOTLE trial, apixaban exhibited beneficial efficacy and safety data, compared with warfarin, irrespective of kidney function.[17] However, the risks associated with dual or triple antithrombotic treatment regarding kidney function in patients with AF and ACS/PCI are less well established. Likewise, the specific assessment of apixaban versus VKA in this setting of patients with AF and ACS/PCI requiring dual or triple antithrombotic treatment has not been described. The study design of the AUGUSTUS trial, with a 2×2 factorial design, randomly assigning patients on $P2Y_{12}$ inhibitor to receive apixaban or VKA, and to receive aspirin or aspirin-placebo, provided a unique opportunity to evaluate

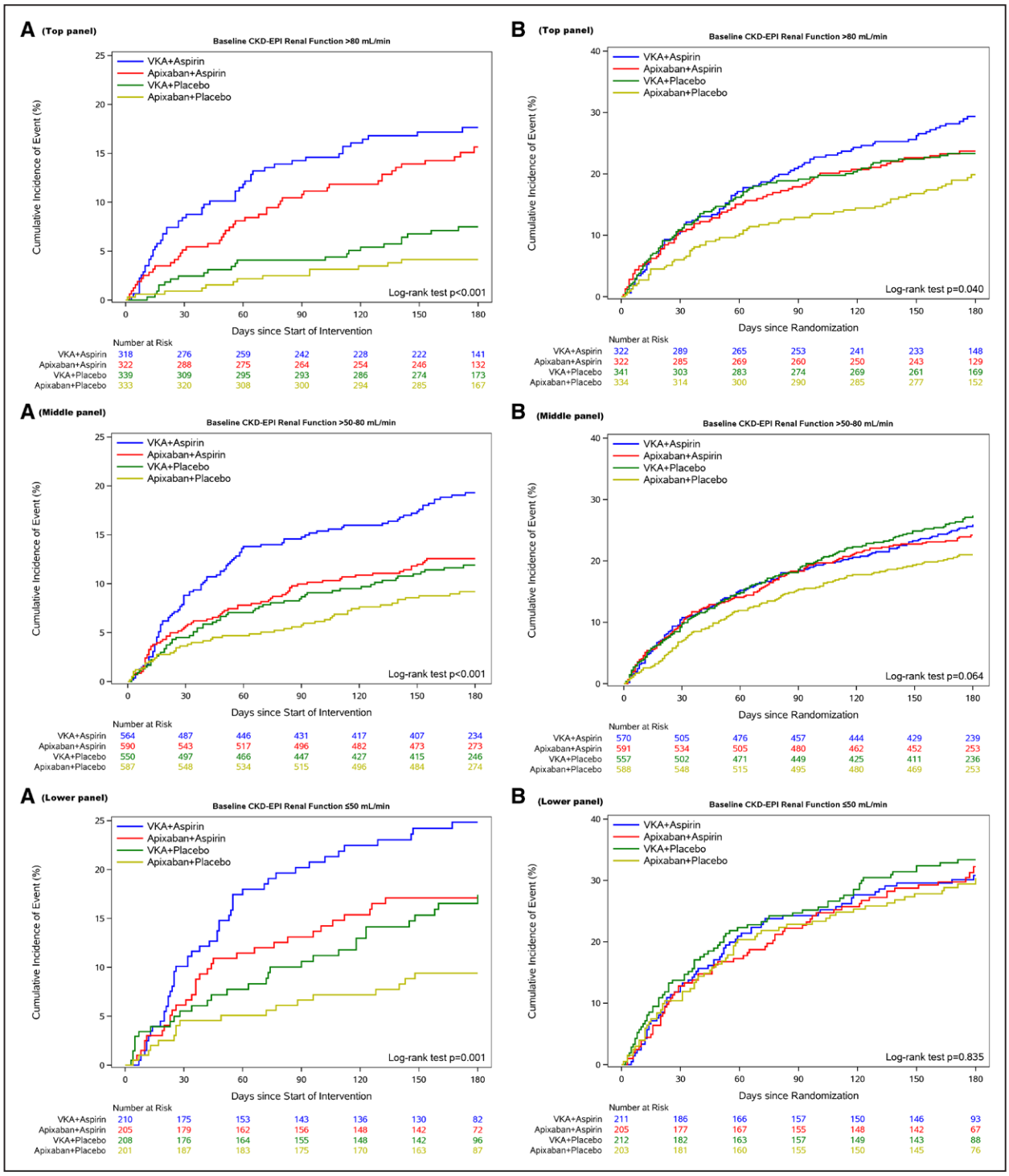

Figure. Outcomes according to 4 different treatment strategies by kidney function for major or clinically relevant nonmajor bleeding, death or hospitalization, and ischemic events.

All participants received a $P2Y_{12}$ inhibitor. **A**, Major or clinically relevant nonmajor bleeding outcomes in 4 treatment strategies by kidney function: >80 mL·min^{-1}·1.73 m^{-2} (**Top**), >50 to 80 mL·min^{-1}·1.73 m^{-2} (**Center**), and 30 to 50 mL·min^{-1}·1.73 m^{-2} (**Bottom**). **B**, Death or hospitalization outcomes in 4 treatment strategies by kidney function: >80 mL·min^{-1}·1.73 m^{-2} (**Top**), >50 to 80 mL·min^{-1}·1.73 m^{-2} (**Center**), and 30 to 50 mL·min^{-1}·1.73 m^{-2} (**Bottom**). **C**, Ischemic events according to 4 treatment strategies by kidney function: >80 mL·min^{-1}·1.73 m^{-2} (**Top**), >50 to 80 mL·min^{-1}·1.73 m^{-2} (**Center**), and 30 to 50 mL·min^{-1}·1.73 m^{-2} (**Bottom**). (*Continued*)

the different antithrombotic strategies according to kidney function. The AUGUSTUS trial showed that, in patients with AF and ACS or PCI treated with a $P2Y_{12}$ inhibitor, apixaban resulted in less bleeding and fewer hospitalizations than VKA, and that aspirin resulted in more bleeding than placebo, without significant differences in ischemic events. The present analyses show that these results were consistent irrespective of kidney

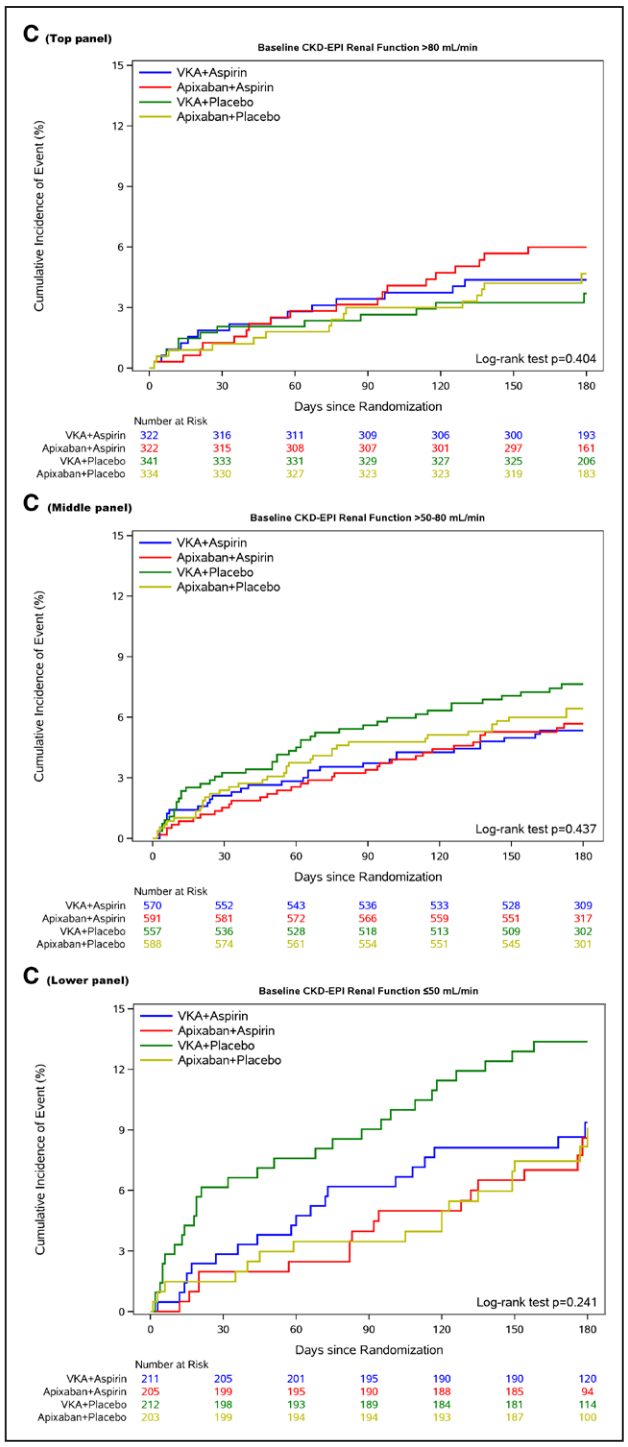

Figure Continued. CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; and VKA, vitamin K antagonist.

function measured at randomization. Thus, the primary safety and efficacy outcomes overall occurred less frequently in patients randomly assigned to apixaban twice daily as compared with VKA, across the kidney function categories. For aspirin, however, in addition to a consistently higher occurrence of major or clinically relevant nonmajor bleeding events across all kidney function categories, a significantly higher relative risk was observed in patients with preserved kidney function (>80 mL·min^{-1}·1.73 m^{-2}). Although this is an unexpected finding and may be attributable to the play of chance, because it was not detected in the sensitivity analysis using the alternative National Kidney Foundation kidney function categories (<60, 60–90, >90 mL·min^{-1}·1.73 m^{-2}).

The incrementally increased risk of bleeding with decreasing kidney function is consistent with prior studies. Several studies have shown that the risk of bleeding and cardiovascular events is higher in patients with AF and kidney dysfunction.[15,17,21,22] In general, the increased bleeding risk in patients with impaired kidney function is considered to be multifactorial and entails factors such as platelet dysfunction, platelet-vessel wall interaction dysfunction, coagulopathy, shear stress by hypertension, and more general factors such as comorbidities, frailty, and polypharmacy.[23–25] The increased risk of bleeding that accompanies triple therapy is also well known and has been identified both in randomized clinical trials, and in less selected patients from large nationwide registries, as well.[7–10] In part, similar findings were recently described from the RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) substudy showing preserved safety of another non–vitamin K antagonist oral anticoagulant, dabigatran, compared with VKA, in patients who have AF with kidney impairment.[26] However, because of the randomized treatment of aspirin versus placebo within the AUGUSTUS trial, the present study provides unique data that add important pieces of information and thus expands current knowledge. The present results show that the increased risk of bleeding with triple therapy is consistent even in non–vitamin K antagonist oral anticoagulant–treated patients (and not limited to VKA therapy) and is not limited only to patients with kidney dysfunction. Furthermore, apixaban, at the dose approved for stroke prevention in patients with AF and despite having a greater extent of kidney metabolism (27% versus 1%),[13] shows preserved safety and efficacy irrespective of kidney dysfunction, compared with VKA, in these high-risk patients. The unique trial design also provides interesting findings regarding patients with kidney dysfunction, who have substantially increased risks for both bleeding and ischemic events. Although based on a subgroup of the trial, and therefore of a hypothesis-generating nature, the present results also indicate that dual therapy with VKA, in particular, may confer higher risk of ischemic events in those with kidney impairment. From the patterns in the event rate, it seems that the first few weeks, in particular, pose a high-risk period for ischemic events in those randomly assigned to VKA therapy and no aspirin with a kidney function 30 to 50 mL·min^{-1}·1.73 m^{-2}. This would be in line with the period usually needed to get a majority of patients with

VKA therapy into therapeutic range.[27] Similar findings have also been reported recently from a risk-benefit analysis from the AUGUSTUS trial that showed that the risk for ischemic events was highest during the first 30 days after an ACS/PCI.[28] Together, these findings provide valuable insights that can help clinicians make informed decisions on the antithrombotic therapy in the setting of AF, ACS/PCI, and kidney dysfunction.

Limitations

Although the present analyses were prespecified in this AUGUSTUS kidney function substudy, the results should be interpreted with caution because the analyses are of exploratory nature based on subgroups with multiple comparisons and limited sample sizes. Serum creatinine was collected and analyzed locally, not centrally, which may affect the precision of the eGFR estimation. Last, outcomes of patients with creatinine clearance <30 mL/min are not known because these patients were not included.

Conclusions

The safety and efficacy of apixaban across kidney function subgroups was consistent with the overall AUGUSTUS trial results as apixaban, on top of a $P2Y_{12}$ inhibitor, confers lower risks of bleeding and death or hospitalization, compared with VKA, irrespective of kidney function. Triple therapy with aspirin, compared with dual therapy, results in a consistently higher risk of bleeding across all kidney function categories. In selected patients, initial triple therapy might confer a reasonable risk-benefit trade-off after ACS and PCI: however, the dual therapy strategy, with apixaban and a $P2Y_{12}$ inhibitor, seems to provide the best overall balance between hemorrhagic and ischemic risk across all kidney function categories.

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