


openheart Impact of prior oral anticoagulant use and outcomes on patients from secondary analysis in the AUGUSTUS trial

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ABSTRACT

Objective Managing antithrombotic therapy in patients with atrial fibrillation (AF) and an acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI) is challenging and can be affected by prior oral anticoagulant (OAC) treatment. We examined the relationship between prior OAC use and outcomes in the AUGUSTUS trial.

Methods This prespecified secondary analysis is from AUGUSTUS, an open-label, 2-by-2 factorial, RCT to evaluate the safety of apixaban versus vitamin K antagonist (VKA) and aspirin versus placebo in patients with AF and ACS and/or PCI. The primary endpoint, major or clinically relevant non-major bleeding and clinical outcomes were compared in patients receiving (n=2262) or not receiving (n=2352) an OAC prior to enrolment.

Results Patients with prior OAC use had more comorbidities, higher CHA₂DS₂-VASC and HAS-BLED scores, and were more likely enrolled following elective PCI. There was no difference in major or clinically relevant non-major bleeding with or without prior OAC (30 days: 5.1% vs 5.9% (adjusted HR (aHR) 0.82, 95% CI 0.63 to 1.06); 180 days: 13.5% vs 13.5% (aHR 0.98, 95% CI 0.83 to 1.16)). Patients with prior OAC use had a lower risk of death or ischaemic events (30 days: 1.7% vs 2.8% (aHR 0.61, 95% CI 0.41 to 0.92); 180 days: 5.4% vs 7.6% (aHR 0.70, 95% CI 0.55 to 0.88)). No interactions between randomised treatment (apixaban vs VKA, aspirin vs placebo) and prior OAC status were observed for outcomes, apart from apixaban (vs VKA) being associated with a lower risk of myocardial infarction with prior OAC use (180 days: 2.0% vs 3.7% (aHR 0.56, 95% CI 0.33 to 0.91)).

Conclusions In AUGUSTUS, prior OAC use was associated with fewer ischaemic events but not more bleeding. In patients with AF and ACS and/or undergoing PCI, clinicians can be assured that the trial results can be applied to patients regardless of their prior OAC status.

Trial registration number NCT02415400.

INTRODUCTION

Coronary artery disease and atrial fibrillation (AF) commonly coexist; approximately one

Key questions

What is already known about this subject?

► Managing antithrombotic therapy in patients with atrial fibrillation (AF) and an acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI) is challenging and can be affected by prior oral anticoagulant (OAC) treatment.

What does this study add?

► No interactions between randomised treatment (apixaban vs vitamin K antagonists (VKA), aspirin vs placebo) and prior OAC status were observed for outcomes, apart from apixaban (vs VKA) being associated with a lower risk of myocardial infarction with prior OAC use.

How might this impact on clinical practice?

► In patients with AF and ACS and/or undergoing PCI, clinicians can be assured that the results of the AUGUSTUS trial can be applied to these patients regardless of their prior OAC status when oral antithrombotic therapy is being prescribed at hospital discharge.

in five patients with AF have an acute coronary syndrome (ACS) and/or require percutaneous coronary intervention (PCI).¹⁻³ A consistent finding across four landmark trials⁴⁻⁷ and a subsequent meta-analysis⁸ is that dual antithrombotic therapy, particularly with a non-vitamin K antagonist oral anticoagulant (NOAC) and P2Y₁₂ platelet inhibitor, is associated with a reduction in bleeding in this patient population compared with triple therapy with dual antiplatelet inhibition and an oral anticoagulant (OAC). The largest of these four studies that compared vitamin K antagonists (VKA) with an NOAC was the AUGUSTUS trial (An Open-Label, 2-by-2 Factorial, Randomised, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs

VKA and Aspirin vs Aspirin Placebo in Patients With AF and ACS and/or PCI). AUGUSTUS included patients with AF and either ACS or undergoing elective PCI and showed a lower risk of bleeding and hospitalisation and a similar risk of ischaemic events with an antithrombotic regimen consisting of apixaban and a P2Y12 inhibitor without aspirin compared with regimens that included VKAs, aspirin or both.⁶

Choosing the optimal antithrombotic regimen at hospital discharge is a challenging clinical scenario when patients with AF develop ACS and/or require PCI, especially when prior OAC therapy was used. First, physicians prefer continuing with already established therapies familiar to patients in order to mitigate potential risks of medication errors despite a change in patients' clinical scenario. Second, switching between OAC agents has been associated with an increase in thromboembolic and bleeding events.^{9–13} Third, different baseline characteristics may exist in those patients receiving an OAC prior to developing ACS or requiring elective PCI compared with those not treated with OAC, which may affect subsequent bleeding and ischaemic outcomes.¹

The AUGUSTUS trial uniquely employed a 2-by-2 randomised factorial design (open-label apixaban vs VKA and blinded aspirin vs placebo), in contrast to the other randomised trials in which triple therapy (VKA, aspirin and P2Y12 inhibitor) was the standard of care comparison arm. This allowed assessment of the potential impact of prior OAC therapy without the confounding factor of triple therapy. We, therefore, performed a prespecified subgroup analysis of the AUGUSTUS trial to describe the patient characteristics, clinical events and potential interaction with randomised treatment arms comparing patients with or without prior OAC, with prior OAC separated into those receiving an NOAC or VKA.

METHODS

The AUGUSTUS trial design and results have been published.^{6,14} In brief, AUGUSTUS was an international, randomised, clinical trial with a 2-by-2 factorial design in which patients with AF and recent ACS and/or undergoing PCI and taking a P2Y12 inhibitor were factorially randomised to apixaban or VKA (open-label), and aspirin or aspirin placebo (double-blind) for 6 months. The current prespecified analyses explore outcomes according to whether patients were on OAC or not on OAC prior to enrolment in the trial. Prior OAC included participants receiving therapy prior to the index event and those started on therapy during the index event before randomisation. Patients provided written informed consent before inclusion in the study. There was no patient or public involvement in the design of the study.

Outcome definition

The primary outcome was the first occurrence of International Society on Thrombosis and Haemostasis (ISTH)

major or clinically relevant non-major (CRNM) bleeding. ISTH major bleeding was defined as clinically overt bleeding with a haemoglobin drop of ≥ 2 g/dL, transfusion of ≥ 2 units of packed red cells, or bleeding occurring at a critical site or resulting in death. CRNM bleeding was defined as overt bleeding that did not meet criteria for major bleeding and met ≥ 1 of the following criteria: requires hospitalisation; requires physician-guided medical or surgical intervention or results in unscheduled contact with a physician (visit or telephone call); results in pain or impairment of daily activities; or results in a physician-guided change in antithrombotic therapy. Secondary efficacy outcomes included the composite of death or hospitalisation, and the composite of death or ischaemic events (composite of stroke, myocardial infarction, stent thrombosis (definite or probable) or urgent revascularisation). Other outcomes included ISTH major bleeding and individual components of the composite outcomes. Outcomes were adjudicated according to standard definitions by an independent committee blinded to treatment assignment.

Statistical analyses

Baseline characteristics including demographics, comorbidities, and index event are presented by prior OAC status. Additionally, patients with prior OAC use are subdivided by type of anticoagulant (VKA or NOAC). For patients who reported more than 1 type of anticoagulant, the most recent type is used to group subjects in VKA or NOAC groups. Continuous variables are summarised as median or means and quartiles or SD. Categorical variables are reported as frequencies and percentages. Wilcoxon, t-test, and χ^2 tests were used to compare patients with and without prior OAC use.

For each endpoint, Kaplan-Meier estimates at 30 days and 180 days and number of patients with events are presented by prior OAC status. Unadjusted HRs and 95% CIs were derived using a Cox proportional hazards model with prior OAC status as the only covariate. Adjustment variables used to derive adjusted HRs (AHRs) were: age, sex, race, hypertension, heart failure, diabetes, prior stroke, transient ischaemic attack (TIA) or thromboembolism, qualifying index event and time from index event to randomisation. Separate models were used to estimate the HRs at 30 days and 180 days. Models used to estimate HRs at 30 days included events from randomisation up to 30 days. Models used to estimate HRs at 180 days included events from randomisation up to 180 days. In a separate analysis, patients on prior OAC were divided by type of OAC and HRs were derived comparing prior NOAC and prior VKA vs no OAC.

Randomised comparisons by prior OAC status

For each endpoint, Kaplan-Meier estimates at 30 days and 180 days and number of patients with events are presented by randomised arm and prior OAC. Separate tables for the 2 factorial randomised comparisons are presented: apixaban versus warfarin and aspirin vs placebo. Additionally,

descriptive results for the four treatment combinations (apixaban + aspirin, apixaban + placebo, warfarin + aspirin and warfarin + placebo) are presented.

HRs and 95% CIs comparing randomised treatments were derived from Cox proportional hazards models including prior OAC status, randomised treatment and their interaction. Similar analyses dividing the patients with prior OAC use by type of OAC are presented. The proportional hazard assumption was tested in all Cox models using scaled Schoenfeld residuals without clinically relevant deviations observed. All analyses were performed at Duke Clinical Research Institute using SAS System V.9.4 (TS1M6) (SAS Institute).

RESULTS

Of 4614 patients enrolled in the trial, 2262 (49%) had prior OAC use and 2352 (50.1%) did not. Patients with prior OAC use were older, more likely to be male, and have a history of hypertension, diabetes, congestive heart failure, stroke, TIA and thromboembolism, translating into higher CHA₂DS₂-VAS_c and HAS-BLED scores (table 1). The prior OAC group was further separated into those on prior NOAC or VKA with baseline characteristics shown in the first 2 columns of table 1. The most common qualifying events in the prior OAC and non-prior OAC groups were elective PCI and PCI due to ACS, respectively (table 1). OAC use before the index event was 66.5% among those with prior OAC use, with the remaining patients starting simultaneously with the index event, but prior to randomisation. Prior OAC use included VKA in 46% and NOAC in 54% (online supplemental table 1).

Prior OAC Compared with No OAC

Prior OAC users and those with no prior OAC use had similar rates of the primary outcome of ISTH major or CRNM bleeding at 30 days (5.1% vs 5.9%; aHR 0.82, 95% CI 0.63 to 1.06) and 180 days (13.5% vs 13.5%; aHR 0.98, 95% CI 0.83 to 1.16). Secondary safety outcome rates were also similar between groups. All-cause death or ischaemic events were lower in those with prior OAC use at 30 days (1.7% vs 2.8%; aHR 0.61, 95% CI 0.41 to 0.92) and 180 days (5.4% vs 7.6%; aHR 0.70, 95% CI 0.55 to 0.88). Cardiovascular deaths at 180 days were lower with prior OAC use (1.9% vs 2.9%; aHR 0.61, 95% CI 0.42 to 0.90). The remainder of secondary efficacy outcomes were numerically lower in the prior OAC group (table 2A). The outcomes comparing patients on prior NOAC with no prior OAC and prior VKA with no prior OAC are presented in table 2B.

Apixaban versus VKA randomisation

For the primary endpoint, there was no interaction between prior OAC status and randomised comparison between apixaban or VKA, with apixaban associated with lower rates of ISTH major/CRNM bleeding (table 3A). Similar trends were seen in secondary endpoints with the exception of myocardial infarction where an interaction

was demonstrated. Myocardial infarction was reduced at 30 days with apixaban (apixaban 0.51% vs VKA 1.41%; HR 0.36, 95% CI 0.12 to 0.92) and 180 days (apixaban 1.98% vs VKA 3.65%; HR 0.55, 95% CI 0.33 to 0.91) compared with warfarin in those with prior OAC use with no difference in myocardial infarction in those not on prior OAC.

Aspirin versus aspirin placebo randomisation

There was no interaction between prior OAC status and aspirin compared with aspirin placebo in the randomised arms for any endpoint (table 3B). The incidence of the primary outcome at 30 days in patients with prior OAC use was 7.1% with aspirin compared with 2.9% with placebo (HR 2.49, 95% CI 1.65 to 3.75), and in those with no prior OAC use was 7.8% with aspirin compared with 4.0% with placebo (HR 1.98, 95% CI 1.38 to 2.83). The incidence of the primary outcome at 180 days in patients with prior OAC use was 17.0% with aspirin compared with 9.6% with placebo (HR 1.91, 95% CI 1.50 to 2.44), and in those with no prior OAC use was 17.3% with aspirin compared with 9.5% with placebo (HR 1.88, 95% CI 1.48 to 2.39).

Prior NOAC, prior VKA and no prior OAC comparison by randomised arm

The Kaplan-Meier event rates and HRs with assessment for interaction between those with no prior OAC, prior NOAC and prior VKA are presented for apixaban compared with VKA and aspirin compared with placebo in figure 1 (online supplemental tables 2A and 2B). There was no interaction found for the primary endpoint at 30 days or 180 days between no prior OAC, prior NOAC and prior VKA with either the randomisation to apixaban compared with VKA or aspirin compared with placebo (online supplemental tables 2A and 2B). Myocardial infarction occurred less frequently in those previously on an NOAC randomised to apixaban vs VKA at 30 days (0.48% vs 2.01%; HR 0.24, 95% CI 0.16 to 0.84) and 180 days (1.47% vs 3.89%; HR 0.82, 95% CI 0.17 to 0.77) (figure 1 and online supplemental table 2A).

DISCUSSION

In this prespecified subgroup analysis of the AUGUSTUS trial, we explored patient characteristics, clinical events and potential interaction with randomised treatment arms comparing patients with or without prior OAC use. The main findings of this study are (1) despite increased comorbidities and associated higher HAS-BLED scores, patients on prior OAC had similar 30-day and 180-day incidence of the primary endpoint of ISTH major or CRNM bleeding, including after adjustment for these and other baseline characteristic differences; (2) apixaban was associated with lower rates of the primary endpoint compared with VKA regardless of prior OAC use and (3) aspirin was associated with a higher incidence of the primary endpoint compared with placebo regardless of prior OAC use. Accordingly, clinicians can be assured

Table 1 Baseline characteristics by prior oral anticoagulation status at randomisation

Characteristic	Prior OAC			No prior OAC	P value†
	NOAC (N=1227)	VKA (N=1033)	Any OAC* (N=2262)	(N=2352)	
Age, median (25th, 75th), years	71, 64–77	71, 65–77	71, 65–77	70, 64–77	0.040
Female sex, no (%)	336 (27.4)	276 (26.7)	613 (27.1)	724 (30.8)	0.006
Race, no/No (%)					0.018
White	1120/1208 (92.7)	960/1031 (93.1)	2082/2241 (92.9)	2102/2316 (90.8)	
Black	14/1208 (1.2)	12/1031 (1.2)	26/2241 (1.2)	33/2316 (1.4)	
Asian	35/1208 (2.9)	32/1031 (3.1)	67/2241 (3.0)	73/2316 (3.2)	
Other	39/1208 (3.2)	27/1031 (2.6)	66/2241 (2.9)	108/2316 (4.7)	
Serum creatinine, median (25th, 75th), mg/dL	1.0, 0.9–1.2	1.0, 0.9–1.2	1.0, 0.9–1.2	1.0, 0.9–1.2	0.020
Serum creatinine, no/No (%)					0.56
<1.5 mg/dL	1114/1210 (92.1%)	938/1024 (91.6%)	2054/2236 (91.9%)	2098/2296 (91.4%)	
≥1.5 mg/dL	96/1210 (7.9%)	86/1024 (8.4%)	182/2236 (8.1%)	198/2296 (8.6%)	
CHA ₂ DS ₂ -VASc score, mean (SD)	4.0 (1.5)	4.1 (1.6)	4.0 (1.5)	3.8 (1.6)	<0.001
HAS-BLED score, mean (SD)	2.9 (0.9)	2.9 (1.0)	2.9 (1.0)	2.8 (0.9)	<0.001
Hypertension leading to medication use, no (%)	1104 (90.0%)	923 (89.4%)	2029 (89.7%)	2044 (86.9%)	0.003
Heart failure, no (%)	546 (44.5%)	510 (49.4%)	1056 (46.7%)	917 (39.0%)	<0.001
Diabetes mellitus, no (%)	472 (38.5%)	399 (38.6%)	872 (38.5%)	806 (34.3%)	0.003
Stroke, TIA, or thromboembolism, no/No (%)	171/1218 (14.0%)	173/1027 (16.8%)	344/2247 (15.3%)	289/2334 (12.4%)	0.004
Concomitant P2Y12 inhibitor, no (%)					<0.001
Clopidogrel	1123 (91.5%)	985 (95.4%)	2110 (93.3%)	2055 (87.4%)	
Ticagrelor	66 (5.4%)	25 (2.4%)	91 (4.0%)	189 (8.0%)	
Prasugrel	15 (1.2%)	6 (0.6%)	21 (0.9%)	30 (1.3%)	
None	23 (1.9%)	17 (1.6%)	40 (1.8%)	78 (3.3%)	
Qualifying index event, no/No (%)					<0.001
ACS and PCI	418/1223 (34.2%)	294/1031 (28.5%)	712/2256 (31.6%)	1002/2339 (42.8%)	
Medically managed ACS	216/1223 (17.7%)	305/1031 (29.6%)	521/2256 (23.1%)	576/2339 (24.6%)	
Elective PCI	589/1223 (48.2%)	432/1031 (41.9%)	1023/2256 (45.3%)	761/2339 (32.5%)	
Days from ACS or PCI to randomisation, mean (SD)	6.7 (4.3)	7.0 (4.2)	6.8 (4.3)	6.4 (4.1)	0.001
On OAC prior to index event, no/No (%)	827/1227 (67.4%)	677/1033 (65.5%)	1505/2262 (66.5%)	–	–

For patients reporting more than one type of anticoagulant, the most recent type is used.

*Two patients reported prior oral anticoagulant use but information about the type of anticoagulant was not reported; they were included in the 'any OAC' group.

†P value compares 'any OAC' versus 'no prior OAC' columns.

ACS, acute coronary syndrome; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Table 2A Association between prior oral anticoagulant use and endpoints

Endpoint	Prior OAC		Unadjusted			Adjusted*		
	Yes KM% (events)	No KM% (events)	HR (95% CI) Prior OAC Yes vs No	P value	HR (95% CI) Prior OAC Yes vs No	P value		
Primary endpoint								
ISTH major/CRNM bleeding								
At 30 days	5.1 (111)	5.9 (131)	0.87 (0.67 to 1.12)	0.27	0.82 (0.63 to 1.06)	0.13		
At 180 days	13.5 (282)	13.5 (288)	1.004 (0.85 to 1.18)	0.96	0.98 (0.83 to 1.16)	0.80		
ISTH major bleeding								
At 30 days	1.2 (30)	1.8 (39)	0.79 (0.49 to 1.27)	0.33	0.65 (0.39 to 1.07)	0.093		
At 180 days	4.2 (86)	4.3 (90)	1.00 (0.74 to 1.34)	0.99	0.90 (0.66 to 1.22)	0.48		
Intracranial bleeding								
At 30 days	0.00 (0)	0.2 (4)	–	–	–	–		
At 180 days	0.5 (10)	0.4 (9)	1.13 (0.46 to 2.79)	0.79	0.96 (0.38 to 2.40)	0.92		
Definite/probable stent thrombosis								
At 30 days	0.5 (11)	0.7 (16)	0.71 (0.33 to 1.53)	0.38	0.73 (0.33 to 1.59)	0.43		
At 180 days	0.6 (14)	0.8 (18)	0.801 (0.40 to 1.61)	0.53	0.81 (0.40 to 1.66)	0.57		
All-cause death or rehospitalisation								
At 30 days	9.2 (208)	10.8 (250)	0.86 (0.71 to 1.030)	0.099	0.86 (0.71 to 1.04)	0.11		
At 180 days	26.3 (585)	25.4 (580)	1.04 (0.93 to 1.17)	0.46	1.02 (0.90 to 1.14)	0.80		
All-cause death or ischaemic event								
At 30 days	1.7 (38)	2.8 (65)	0.60 (0.40 to 0.90)	0.012	0.61 (0.41 to 0.92)	0.019		
At 180 days	5.4 (119)	7.6(171)	0.72 (0.57 to 0.91)	0.006	0.70 (0.55 to 0.88)	0.003		
Cardiovascular death								
At 30 days	0.6 (13)	0.9 (20)	0.67 (0.33 to 1.35)	0.26	0.70 (0.34 to 1.42)	0.32		
At 180 days	1.9 (43)	2.9 (67)	0.67 (0.46 to 0.98)	0.04	0.61 (0.42 to 0.90)	0.013		
Stroke								
At 30 days	0.2 (4)	0.4 (9)	0.46 (0.14 to 1.49)	0.19	0.53 (0.16 to 1.74)	0.29		
At 180 days	0.8 (16)	1.0 (23)	0.71 (0.38 to 1.35)	0.29	0.74 (0.39 to 1.43)	0.37		
Myocardial infarction								
At 30 days	0.9 (21)	1.7 (39)	0.55 (0.33 to 0.94)	0.029	0.59 (0.34 to 1.01)	0.053		
At 180 days	2.8 (61)	4.0 (89)	0.72 (0.52 to 0.99)	0.044	0.73 (0.53 to 1.02)	0.065		

HRs in the 'at 30 days' rows include events from randomisation to 30 days. HRs in the 'at 180 days' rows include events from randomisation to 180 days.

*Adjusted by age, sex, race, hypertension, heart failure, diabetes, prior stroke, TIA or thromboembolism, qualifying index event and time from index event to randomisation.

CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; KM, Kaplan-Meier; OAC, oral anticoagulation; TIA, transient ischaemic attack.

that the results of the AUGUSTUS trial can be applied to these patients regardless of their prior OAC status when oral antithrombotic therapy is being prescribed at hospital discharge.

In AUGUSTUS, OAC use prior to enrolment was more common in patients with comorbidities and those enrolled following elective PCI. Despite increased comorbidities and the associated increased HAS-BLED scores in patients with prior OAC use, this group did not have an increased 30-day or 180-day incidence of the combined

primary endpoint (ISTH major or CRNM bleeding) or the secondary safety endpoint (ISTH major bleeding or intracranial bleeding) in the unadjusted or adjusted analysis. Prior OAC use was associated with fewer ischaemic events, with the combined outcome of all-cause death or ischaemic events (composite of stroke, myocardial infarction, stent thrombosis (definite or probable), or urgent revascularisation) reduced by 39% at 30 days and 30% at 180 days after adjusting for baseline differences. Further stratification of prior OAC group into those

Table 2B Association between type of prior oral anticoagulant use and endpoints

Endpoint	Prior NOAC	Prior VKA	No prior OAC	NOAC vs no OAC	VKA vs no OAC	P value
	KM% (events)	KM% (events)	KM% (events)	Adj. HR (95% CI)*	Adj. HR (95% CI)*	
Primary endpoint						
ISTH major/CRNM bleeding						
At 30 days	5.1 (60)	5.1 (51)	5.9 (131)	0.80 (0.58 to 1.10)	0.84 (0.60 to 1.17)	0.33
At 180 days	12.8 (144)	14.2 (137)	13.5 (288)	0.93 (0.76 to 1.14)	1.03 (0.83 to 1.27)	0.70
ISTH major bleeding						
At 30 days	1.1 (13)	1.7 (17)	1.8 (39)	0.48 (0.24 to 0.95)	0.84 (0.47 to 1.51)	0.11
At 180 days	3.8 (41)	4.7 (45)	4.3 (90)	0.78 (0.53 to 1.15)	1.02 (0.71 to 1.48)	0.39
Intracranial bleeding						
At 30 days	0.0 (0)	0.0 (0)	0.2 (4)	---	---	---
At 180 days	0.5 (5)	0.6 (5)	0.4 (9)	0.91 (0.30 to 2.76)	1.01 (0.33 to 3.07)	0.98
Definite/probable stent thrombosis						
At 30 days	0.7 (8)	0.3 (3)	0.7 (16)	0.92 (0.39 to 2.17)	0.47 (0.14 to 1.63)	0.49
At 180 days	0.7 (9)	0.5 (5)	0.8 (18)	0.92 (0.41 to 2.08)	0.67 (0.25 to 1.82)	0.73
All-cause death or rehospitalisation						
At 30 days	10.1 (124)	8.1 (83)	10.8 (250)	0.92 (0.74 to 1.15)	0.77 (0.60 to 0.99)	0.12
At 180 days	27.6 (332)	24.6 (251)	25.4 (580)	1.07 (0.93 to 1.22)	0.95 (0.82 to 1.11)	0.40
All-cause death or ischaemic event						
At 30 days	2.0 (25)	1.3 (13)	2.8 (65)	0.74 (0.46 to 1.18)	0.46 (0.25 to 0.85)	0.03
At 180 days	5.5 (66)	5.2 (53)	7.6 (171)	0.74 (0.56 to 0.96)	0.65 (0.47 to 0.88)	0.009
Cardiovascular death						
At 30 days	0.6 (7)	0.6 (6)	0.9 (20)	0.69 (0.29 to 1.66)	0.70 (0.28 to 1.77)	0.61
At 180 days	2.0 (24)	1.9 (19)	2.9 (67)	0.67 (0.42 to 1.06)	0.55 (0.33 to 0.93)	0.04
Stroke						
At 30 days	0.2 (2)	0.2 (2)	0.4 (9)	0.48 (0.10 to 2.26)	0.58 (0.12 to 2.76)	0.57
At 180 days	1.0 (11)	0.5 (5)	1.0 (23)	1.01 (0.49 to 2.11)	0.47 (0.185 to 1.25)	0.29
Myocardial infarction						
At 30 days	1.2 (15)	0.6 (6)	1.7 (39)	0.76 (0.41 to 1.39)	0.37 (0.16 to 0.89)	0.08
At 180 days	2.7 (32)	2.9 (29)	4.0 (89)	0.73 (0.48 to 1.09)	0.74 (0.48 to 1.13)	0.18

HRs in the 'at 30 days' rows include events from randomisation to 30 days. HRs in the 'at 180 days' rows include events from randomisation to 180 days.

*Adjusted by age, sex, race, hypertension, heart failure, diabetes, prior stroke, TIA or thromboembolism, qualifying index event and time from index event to randomisation.

CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; KM, Kaplan-Meier; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

treated previously with an NOAC or VKA confirmed no difference in the primary endpoint, although those with a prior NOAC compared with no prior OAC had a 52% lower risk of ISTH major bleeding at 30 days which was not seen in those on prior VKA compared with NOAC (table 2B). The difference in all-cause death or ischaemic events at 30 days was 64% lower in the prior VKA group compared with the no prior OAC group and 35% lower at 180 days.

The most robust comparison in this current analysis is between the randomised arms of the study. The primary endpoint of ISTH major or CRNM bleeding at 180 days was reduced by 30% with apixaban compared with VKA in both those with or without prior OAC use at the time of randomisation (table 3A). Similarly, randomisation to aspirin compared with placebo was associated with a doubling of the primary endpoint in both those with and without prior OAC therapy. These findings were

Table 3A Association between randomised treatment (apixaban vs VKA) and endpoints by prior oral anticoagulant status

Endpoint	Prior oral anticoagulant=Yes			Prior oral anticoagulant=No			Interaction p value
	Apixaban KM % (events)	VKA KM % (events)	HR* (95% CI) Apixaban vs VKA	Apixaban KM % (events)	VKA KM % (events)	HR* (95% CI) Apixaban vs VKA	
Primary endpoint							
ISTH major/CRNM bleeding							
At 30 days	4.4 (51)	5.7 (58)	0.77 (0.53 to 1.12)	4.2 (45)	7.5 (86)	0.56 (0.39 to 0.80)	0.23
At 180 days	11.3 (127)	15.6 (152)	0.70 (0.56 to 0.89)	10.9 (113)	15.6 (173)	0.67 (0.53 to 0.85)	0.787
ISTH major bleeding							
At 30 days	1.0 (12)	1.7 (17)	0.62 (0.30 to 1.29)	1.3 (14)	2.1 (24)	0.63 (0.32 to 1.21)	0.98
At 180 days	3.4 (38)	4.7 (45)	0.70 (0.45 to 1.07)	3.0 (31)	5.2 (57)	0.58 (0.37 to 0.89)	0.54
Intracranial bleeding							
At 30 days	0.0 (0)	0.0 (0)	---	0.1 (1)	0.3 (3)	0.36 (0.04 to 3.49)	---
At 180 days	0.2 (2)	0.8 (7)	0.25 (0.05 to 1.18)	0.3 (3)	0.5 (6)	0.53 (0.13 to 2.11)	0.47
Definite/probable stent thrombosis							
At 30 days	0.3 (3)	0.8 (8)	0.33 (0.09 to 1.26)	0.7 (8)	0.7 (8)	1.11 (0.42 to 2.95)	0.16
At 180 days	0.3 (4)	1.0 (10)	0.36 (0.11 to 1.14)	0.9 (10)	0.7 (8)	1.38 (0.55 to 3.50)	0.07
All-cause death or Rehospitalisation							
At 30 days	8.7 (103)	9.9 (105)	0.86 (0.66 to 1.13)	9.5 (105)	11.9 (145)	0.80 (0.62 to 1.03)	0.69
180 days	24.9 (293)	27.9 (292)	0.86 (0.73 to 1.01)	22.9 (247)	27.8 (333)	0.80 (0.68 to 0.94)	0.49
All-cause death or Ischaemic event							
At 30 days	1.2 (14)	2.3 (24)	0.52 (0.27 to 1.00)	2.4 (26)	3.2 (39)	0.73 (0.45 to 1.20)	0.41
At 180 days	4.9 (58)	5.9 (61)	0.86 (0.60 to 1.22)	7.9 (83)	7.3 (88)	1.04 (0.77 to 1.42)	0.41
Cardiovascular death							
At 30 days	0.4 (5)	0.8 (8)	0.56 (0.18 to 1.71)	0.7 (8)	1.0 (12)	0.74 (0.30 to 1.80)	0.70
At 180 days	2.0 (23)	1.9 (20)	1.07 (0.59 to 1.93)	3.0 (33)	2.8 (34)	1.07 (0.66 to 1.73)	0.99
Stroke							
At 30 days	0.1 (1)	0.3 (3)	0.30 (0.03 to 2.86)	0.3 (3)	0.5 (6)	0.55 (0.14– to 2.21)	0.65
At 180 days	0.6 (7)	0.9 (9)	0.69 (0.26 to 1.86)	0.6 (6)	1.4 (17)	0.39 (0.15 to 0.99)	0.40
Myocardial infarction							
At 30 days	0.5 (6)	1.4 (15)	0.36 (0.14 to 0.92)	1.6 (18)	1.7 (21)	0.94 (0.50 to 1.77)	0.09
At 180 days	2.0 (23)	3.7 (38)	0.56 (0.33 to 0.91)	4.7 (48)	3.4 (41)	1.30 (0.86 to 1.97)	0.01

*HRs in the 'at 30 days' rows include events from randomisation to 30 days. HRs in the 'at 180 days' rows include events from randomisation to 180 days.

CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; KM, Kaplan-Meier; VKA, vitamin K antagonist.

consistent whether the prior OAC was an NOAC or VKA. Myocardial infarction was the only secondary endpoint with a significant interaction in events with patients on a prior NOAC having a 70% lower incidence at 30 days and a 64% lower incidence at 180 days when randomised to apixaban compared with VKA. However, we did not adjust for multiple comparisons, including for individual endpoints such as myocardial infarction, which was not part of the primary outcome.

Several large-scale observational studies and subgroup analyses have assessed the impact of initiating an NOAC or VKA in populations that were previously naïve to OAC therapy or alternatively switching from VKA to an NOAC.^{3 9 10 12 15–17} An analysis from the French medico-administrative databases demonstrated no difference in 90-day bleeding or thromboembolic complications in OAC-naïve matched patients initiated on VKA, dabigatran or rivaroxaban.¹⁵ Additionally, there was no

Table 3B Association between randomised treatment (aspirin vs placebo) and endpoints by prior oral anticoagulant status

Endpoint	Prior oral anticoagulant=Yes			Prior oral anticoagulant=No			Interaction p value
	Aspirin KM % (events)	Placebo KM % (events)	HR* (95% CI) Aspirin vs placebo	Aspirin KM % (events)	Placebo KM % (events)	HR* (95% CI) Aspirin vs Placebo	
Primary Endpoint							
ISTH major/CRNM bleeding							
At 30 days	7.1 (78)	2.9 (32)	2.49 (1.65 to 3.76)	7.8 (87)	4.0 (45)	1.98 (1.38 to 2.83)	0.41
At 180 days	17.0 (179)	9.6 (100)	1.91 (1.50 to 2.44)	17.3 (185)	9.5 (101)	1.88 (1.48 to 2.39)	0.93
ISTH major bleeding							
At 30 days	1.8 (19)	0.9 (10)	1.91 (0.89 to 4.12)	2.7 (30)	1.0 (11)	2.77 (1.39 to 5.52)	0.48
At 180 days	4.8 (49)	3.3 (34)	1.50 (0.97 to 2.33)	5.5 (58)	3.0 (31)	1.93 (1.25 to 2.99)	0.43
Intracranial bleeding							
At 30 days	0.0 (0)	0.0 (0)	---	0.2 (2)	0.2 (2)	1.01 (0.14 to 7.15)	---
At 180 days	0.3 (3)	0.6 (6)	0.51 (0.127 to 2.035)	0.5 (5)	0.4 (4)	1.29 (0.35 to 4.79)	0.34
Definite/Probable stent thrombosis							
At 30 days	0.4 (4)	0.6 (7)	0.57 (0.17 to 1.95)	0.4 (4)	1.0 (12)	0.33 (0.11 to 1.03)	0.52
At 180 days	0.5 (5)	0.8 (9)	0.56 (0.19 to 1.66)	0.5 (6)	1.0 (12)	0.500 (0.19 to 1.33)	0.89
All-cause death or rehospitalisation							
At 30 days	9.9 (111)	8.6 (97)	1.15 (0.88 to 1.51)	11.7 (136)	9.8 (114)	1.20 (0.94 to 1.54)	0.81
At 180 days	26.4 (292)	26.2 (293)	1.01 (0.86 to 1.18)	27.0 (307)	23.9 (273)	1.16 (0.98 to 1.36)	0.24
All-cause death or ischaemic event							
At 30 days	1.4 (16)	2.0 (22)	0.73 (0.38 to 1.38)	2.2 (25)	3.4 (40)	0.62 (0.38 to 1.03)	0.71
At 180 days	5.2 (57)	5.6 (62)	0.93 (0.65 to 1.33)	6.9 (78)	8.2 (93)	0.84 (0.62 to 1.13)	0.66
Cardiovascular death							
At 30 days	0.7 (8)	0.4 (5)	1.60 (0.52 to 4.90)	0.5 (6)	1.2 (14)	0.43 (0.16 to 1.11)	0.079
At 180 days	2.0 (22)	1.9 (21)	1.10 (0.61 to 1.98)	2.6 (30)	3.2 (37)	0.81 (0.50 to 1.32)	0.45
Stroke							
At 30 days	0.1 (1)	0.3 (3)	0.33 (0.04 to 3.21)	0.5 (6)	0.3 (3)	2.00 (0.50 to 8.01)	0.19
At 180 days	0.7 (8)	0.8 (8)	1.00 (0.38 to 2.67)	1.1 (12)	1.0 (11)	1.10 (0.48 to 2.48)	0.89
Myocardial infarction							
At 30 days	0.6 (7)	1.2 (14)	0.50 (0.20 to 1.24)	1.1 (13)	2.2 (26)	0.50 (0.26 to 0.97)	0.99
At 180 days	2.4 (26)	3.1 (35)	0.75 (0.45 to 1.23)	3.7 (41)	4.4 (48)	0.85 (0.56 to 1.30)	0.69

*HRs in the 'at 30 days' rows include events from randomisation to 30 days. HRs in the 'at 180 days' rows include events from randomisation to 180 days.

CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; KM, Kaplan-Meier; VKA, vitamin K antagonist.

difference in bleeding outcomes in patients sustained on VKA (n=10705) and those switched (n=6705) either to dabigatran or rivaroxaban.¹⁶

Consistent with the current analysis, prior OAC users in the RE-DUAL PCI (Randomised Evaluation of Dual Anti-thrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular AF Undergoing PCI) trial, were more likely to be older and have higher CHA₂DS₂-VAS_c and HAS-BLED scores.¹⁷ Although limited by smaller sample size and an imbalance of

warfarin (61% of prior OAC) and NOAC (39% of prior OAC) use, there was no interaction between all prior OAC usage and the trial's primary endpoint (ISTH major or CRNM bleeding). Although the authors appropriately acknowledged the small sample size and caution associated with interpretation, in RE-DUAL PCI the prior NOAC group had no reduction in the primary endpoint between dabigatran dual therapy and warfarin triple therapy. Specifically, in those with prior NOAC, the primary endpoint was 7.9% with dabigatran 110 mg dual

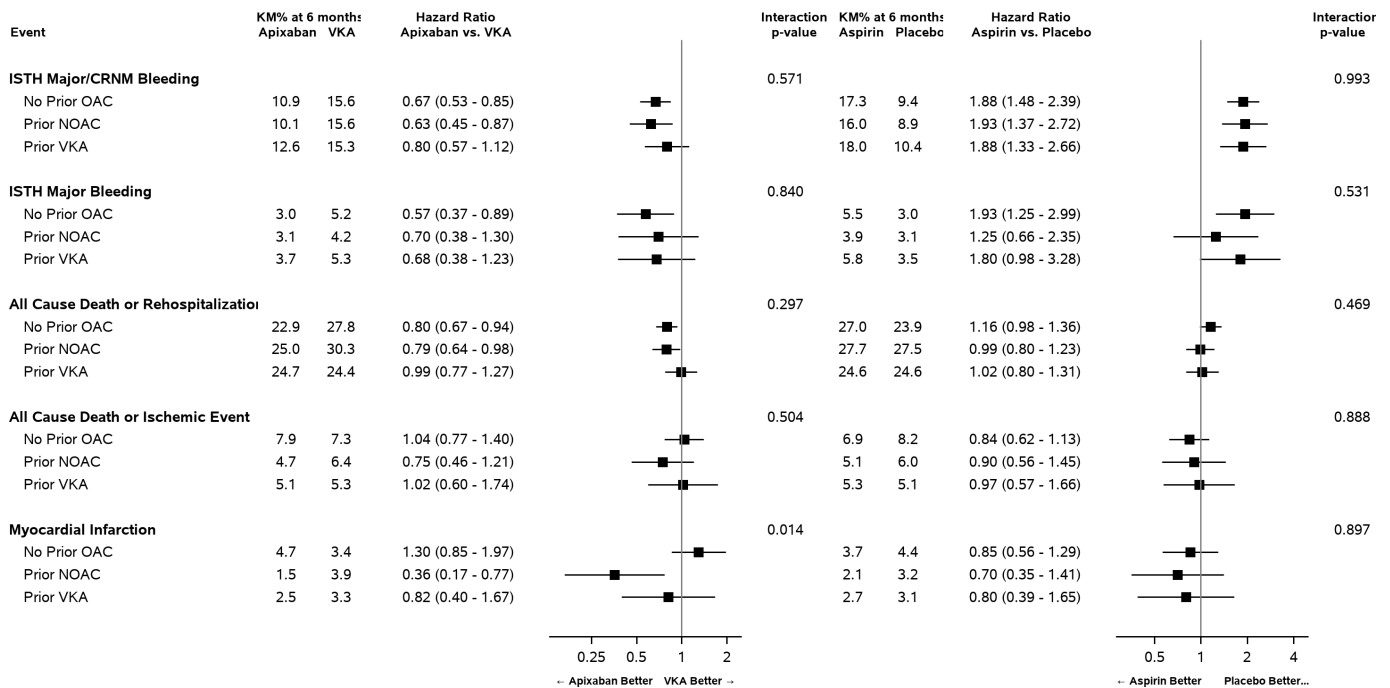


Figure 1 Kaplan-Meier event rates, HRs with assessment for interaction between no prior OAC, prior NOAC and prior VKA for apixaban compared with VKA and aspirin compared with aspirin placebo. ISTH, vitamin K antagonists; KM, Kaplan-Meier; NOAC, non-vitamin K antagonist OAC; OAC, oral anticoagulant; VKA, vitamin K antagonists.

therapy compared with 5.6% with warfarin triple therapy (HR 1.37, 95% CI -0.55 to 3.41) and 2.6% with dabigatran 150mg dual therapy compared with 4.7% with warfarin triple therapy (HR 0.55, 95% CI 0.11 to 2.83). In the AUGUSTUS trial, the lower rate of the primary endpoint (ISTH major or CRNM bleeding) with apixaban compared with VKA was consistent in those with or without prior OAC use and in the 3-way comparison between prior NOAC, prior VKA and no prior OAC.

Limitations

The AUGUSTUS study was not powered nor designed to assess the impact of prior OAC use in patients at the time of randomisation. Further, AUGUSTUS enrolled patients with ACS with or without PCI, a unique feature of this study but the differences in baseline characteristics (eg, greater proportion of those with elective PCI in the prior OAC subgroup), together with unmeasured confounders, could contribute to the observed associated outcome differences, despite robust attempts at multivariable adjustment. Accordingly, interpretation of the findings beyond the primary endpoint should be undertaken with caution.

CONCLUSION

Although patients enrolled in AUGUSTUS with prior OAC use, compared with those without prior OAC use, had increased comorbidities with associated higher CHA₂DS₂-VASc and HAS-BLED scores, they had no increased risk of bleeding complications and lower risk of ischaemic complications. In patients with AF and ACS and/or elective PCI, clinicians can be assured that the

results of the AUGUSTUS trial can be applied to patients regardless of their prior OAC status.

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