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ORIGINAL RESEARCH

Apixaban and Limiting Aspirin for Patients With Atrial Fibrillation, Percutaneous Coronary Intervention, and Multimorbidity

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ABSTRACT

BACKGROUND Patients with atrial fibrillation (AF) after an acute coronary syndrome (ACS) and/or undergoing percutaneous coronary intervention (PCI) with multiple comorbidities are at increased risk for bleeding and ischemic events.

OBJECTIVES This post-hoc analysis of AUGUSTUS describes the safety and efficacy of antithrombotic regimens in patients with multimorbidity.

METHODS AUGUSTUS was a 2 × 2 factorial, randomized controlled trial evaluating the safety of apixaban vs vitamin K antagonists (VKA) (open-label) and aspirin vs placebo (double-blind) in patients with AF and ACS and/or PCI treated with a $P2Y_{12}$ inhibitor. Patients were categorized as having no multimorbidity (0-2 comorbidities), moderate multimorbidity (3-4 comorbidities), or high multimorbidity (≥5 comorbidities). The associations between multimorbidity and clinical outcomes and interactions with antithrombotic regimens were tested.

RESULTS Of 4,493 patients (97.4%) with available comorbidity data, 1,897 (42.2%) had no multimorbidity, 2,110 (47%) had moderate, and 486 (10.8%) had high multimorbidity. Patients with moderate (HR: 1.23; 95% CI: 1.02-1.47) and high (HR: 1.98; 95% CI: 1.55-2.54) multimorbidity had higher rates of International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant nonmajor (CRNM) bleeding compared to patients with no multimorbidity. No significant interaction between multimorbidity and apixaban vs vitamin K antagonists was observed for ISTH major bleeding/CRNM ($P_{int} = 0.415$), death or hospitalization ($P_{int} = 0.092$), or death or ischemic event ($P_{int} = 0.299$). Similarly, no significant interaction between multimorbidity and aspirin vs placebo was seen for ISTH major bleeding/CRNM ($P_{int} = 0.261$), death or hospitalization ($P_{int} = 0.646$), or death or ischemic event ($P_{int} = 0.608$).

CONCLUSIONS Our findings support the standard use of apixaban plus a $P2Y_{12}$ inhibitor in patients with AF and ACS/PCI, irrespective of the presence of multimorbidity. (JACC Adv. 2024;3:101335) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AF = atrial fibrillation

CRNM = clinically relevant nonmajor bleeding

DAPT = dual antiplatelet therapy

DOAC = direct oral anticoagulant

ISTH = International Society on Thrombosis and Haemostasis

PCI = percutaneous coronary intervention

VKA = vitamin K antagonists

With a life-time risk of around 1 in 3, atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults and is associated with substantial morbidity and mortality.[1,2] A significant proportion of AF patients exhibit concomitant coronary artery disease with about 10% to 15% of patients undergoing percutaneous coronary intervention (PCI), posing a critical therapeutic dilemma.[3,4] While treatment with oral anticoagulation is the cornerstone in the prevention of thromboembolic events in AF, dual antiplatelet therapy (DAPT) of variable duration is indicated to prevent stent thrombosis and recurrent acute coronary events in patients with an acute coronary syndrome (ACS) and/or undergoing PCI.[5-8] Such patients are at increased risk for both bleeding events owing to combination antithrombotic therapy as well as thromboembolic and coronary ischemic events.

Clinicians therefore need to balance safety and efficacy when deciding on the antithrombotic regimen.[9] In the AUGUSTUS trial, an international, 2 × 2 factorial, randomized controlled trial evaluating the safety and efficacy of apixaban vs vitamin K antagonists (VKA) and aspirin vs placebo in patients with AF and ACS and/or PCI, an antithrombotic regimen consisting of apixaban and a $P2Y_{12}$ inhibitor without aspirin resulted in less bleeding without significant differences in the occurrence of ischemic endpoints as compared to combination therapies with VKA or aspirin.[10]

While increasing age constitutes a major risk factor for AF development, presence of comorbidities further contributes to AF incidence and complications.[11,12] Previously published analyses have investigated the individual influence of body mass index,[13] high baseline bleeding risk,[14] age,[15] diabetes,[16] prior stroke,[17] a history of heart failure,[18] and renal function [19,20] on the effects of double as compared to triple antithrombotic therapy. Data regarding the choice of antithrombotic regimen in patients with multiple comorbid conditions, who may also be frail, requiring both oral anticoagulation and antiplatelet therapy, is lacking. In this post-hoc analysis of AUGUSTUS, we aimed to describe the prevalence of multimorbidity in this population, its relation to outcomes, as well as the effects of choice of antithrombotic regimen on efficacy and safety in this trial cohort.

METHODS

TRIAL DESIGN AND OUTCOMES. The design and main outcomes of the AUGUSTUS trial (NCT02415400) have been reported previously.[10,21] Briefly, AUGUSTUS was a multicenter, 2-by-2 factorial, randomized controlled trial comparing apixaban with VKA and aspirin with placebo in patients with AF who had an ACS or underwent elective PCI on background $P2Y_{12}$ inhibitor treatment. The comparison between apixaban and VKA was open-label, and the comparison between aspirin and placebo was double-blind. The primary outcome was the occurrence of major or clinically relevant nonmajor (CRNM) bleeding over 6 months as defined by the International Society on Thrombosis and Haemostasis (ISTH).[22] Accordingly, major bleeding was defined as any bleeding resulting in death or occurring in a critical organ or bleeding associated with the transfusion of two or more units of packed red cells or a decrease in hemoglobin levels of 2 g/dL. CRNM bleeding was defined as bleeding requiring hospitalization, medical or surgical intervention, an unscheduled clinic visit, or a change in clinician-directed antithrombotic therapy. Secondary outcomes included the composite outcome of death or hospitalization and the composite of death or ischemic events (defined as myocardial infarction, stent thrombosis, urgent revascularization, or stroke). With the exception of urgent revascularization, all events mentioned above were independently and blindly adjudicated by a clinical events classification committee. The trial protocol was approved by the respective ethics committees and institutional review boards, and all patients provided written informed consent before participation in the trial.

POPULATION. Patients aged 18 years or older with paroxysmal, persistent, or permanent AF and planned long-term anticoagulation treatment with a recent ACS or elective PCI requiring background $P2Y_{12}$-inhibitor therapy were eligible for trial participation. Exclusion criteria comprised anticoagulation for reasons other than AF, severe kidney failure, ongoing bleeding or documented coagulopathy, contraindications to any of the trial drugs or $P2Y_{12}$ inhibitors, as well as a history of intracranial

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Prevalence of Selected Comorbidities

	Overall (N = 4,493)	0-2 Comorbidities (n = 1,897)	3-4 Comorbidities (n = 2,110)	5+ Comorbidities (n = 486)
Renal disease	809 (18.0%)	58 (3.1%)	434 (20.6%)	317 (65.2%)
Liver disease	159/4,491 (3.5%)	11/1897 (0.6%)	91/2,109 (4.3%)	57/485 (11.8%)
Congestive heart failure	1,948 (43.4%)	389 (20.5%)	1,171 (55.5%)	388 (79.8%)
Hypertension	3,997 (89.0%)	1,514 (79.8%)	2,005 (95.0%)	478 (98.4%)
Cerebrovascular disease	635 (14.1%)	74 (3.9%)	357 (16.9%)	204 (42.0%)
Diabetes	1,636 (36.4%)	285 (15.0%)	1,003 (47.5%)	348 (71.6%)
Anemia	367/4,462 (8.2%)	20/1,888 (1.1%)	202/2,101 (9.6%)	145/473 (30.7%)
Extreme weight	431/4,473 (9.6%)	48/1,896 (2.5%)	266/2,104 (12.6%)	117/473 (24.7%)
Prior bleeding	101 (2.2%)	11 (0.6%)	39 (1.8%)	51 (10.5%)
Age >80 y	525 (11.7%)	73 (3.8%)	288 (13.6%)	164 (33.7%)
Tobacco use	2,156/4,482 (48.1%)	602/1,892 (31.8%)	1,218/2,105 (57.9%)	336/485 (69.3%)
Alcohol	66 (1.5%)	9 (0.5%)	42 (2.0%)	15 (3.1%)

hemorrhage and a recent or planned coronary artery bypass graft surgery.

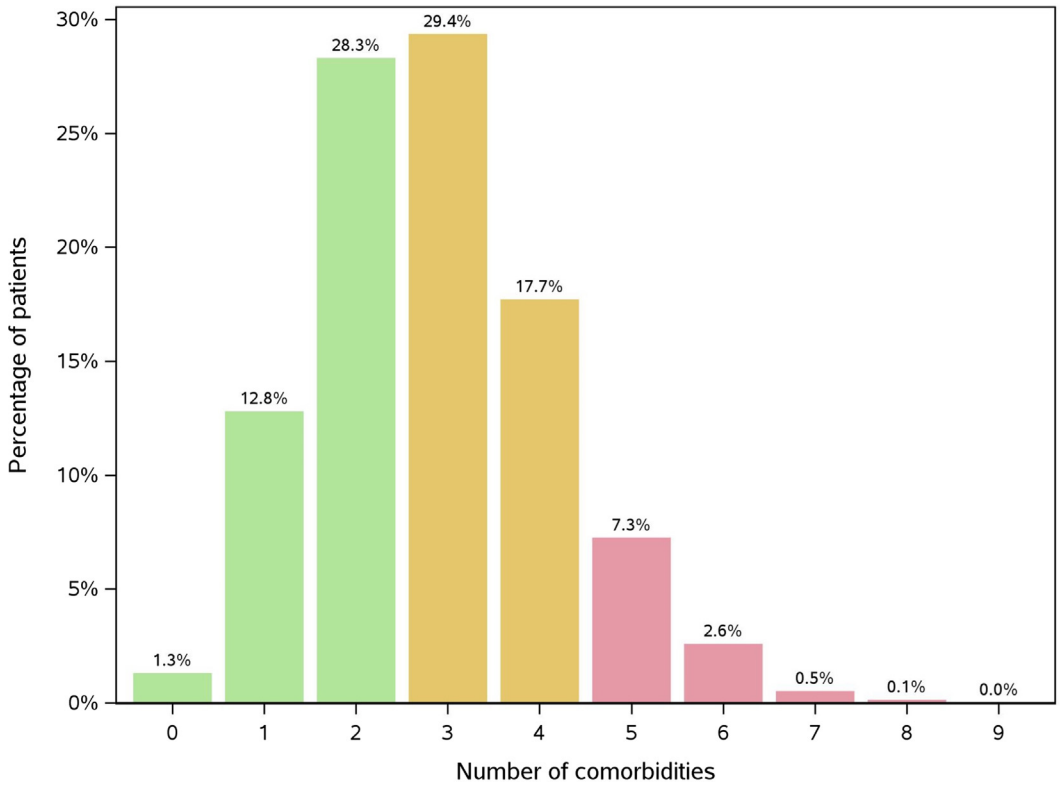
Baseline comorbidities included renal disease (renal insufficiency in medical history; renal disease in HAS-BLED or creatinine ≥1.5 mg/dL), liver disease (liver disease in medical history or liver disease in HAS-BLED), congestive heart failure (congestive heart failure in CHA_2DS_2-VASc), hypertension (hypertension history in CHA_2DS_2-VASc and/or HAS-BLED), cerebrovascular disease (prior stroke, transient ischemic attack, thromboembolism in CHA_2DS_2-VASc and/or stroke history in CHA_2DS_2-VASc), diabetes mellitus (diabetes mellitus in CHA_2DS_2-VASc), anemia (hemoglobin <11 g/dL [WHO moderate definition], in 20 patients hemoglobin was missing but hematocrit available, hematocrit was converted into hemoglobin by dividing by 3), extreme weight (weight <60 kg or >120 kg), prior bleeding (bleeding in medical history and/or in HAS-BLED), older age (age >80 years), tobacco use (current or former cigarette use), and alcohol (current daily use of three or more drinks on average). Patients were classified into three groups according to the number of above-defined comorbidities: No multimorbidity (0-2 comorbidities), moderate multimorbidity (3-4 comorbidities), or high multimorbidity (5 and more comorbidities). Patients with missing data for any of the above-described comorbidities were excluded. All patients with complete data on all comorbidities were included. In addition, we have added 55 patients with missingness in one or more comorbidities by including patients with one comorbidity and only one missing comorbidity in the no multimorbidity group (0-2 comorbidities) and including patients with five comorbidities and any number of missing comorbidities in the high multimorbidity group (5 and more comorbidities).

STATISTICAL ANALYSIS. Continuous variables were summarized as medians and quartiles or mean ± SD as appropriate, and differences across multimorbidity levels were tested with Kruskal-Wallis and analysis of variance (ANOVA) tests. Categorical variables were summarized as frequencies and percentages and compared using chi-square tests. Safety and efficacy endpoints are reported as Kaplan-Meier estimates at 6 months and number of events. HRs comparing multimorbidity levels were derived using the Cox proportional hazard model. Randomized treatment effects (HR and 95% CI) at different multimorbidity levels were estimated using the Cox proportional hazard model with main effects for randomized treatment and multimorbidity level along with their interaction. Absolute risk reductions were estimated as the difference between Kaplan-Meier estimates at different multimorbidity levels. For statistically significant absolute risk reductions, the number needed to treat (harm) was estimated as: 1/(absolute risk reduction). All statistical analyses were performed with SAS System 9.4 (TS1M7).

RESULTS

Of the 4,614 patients enrolled in AUGUSTUS, 4,493 patients (97.4%) had comorbidity data available to allow grouping and were included in the current analysis. Overall, 2,596 (57.8%) patients had multimorbidity of some degree, with 2,110 (47%) presenting with moderate multimorbidity and 486 (10.8%) with high multimorbidity. Table 1 and Figure 1 provide an overview of the distribution of comorbidities according to multimorbidity groups. The most common comorbidities included arterial hypertension (89%), current or former tobacco use (48.1%), congestive heart failure (43.4%), and diabetes mellitus (36.4%).

FIGURE 1 Distribution of Number of Comorbidities Across the AUGUSTUS Population



All comorbidities increased in prevalence across the multimorbidity groups, with pronounced increases in renal disease, congestive heart failure, diabetes, anemia, and tobacco use, while hypertension prevalence was consistently high across subgroups. Patients with high multimorbidity were older and had a higher CHA_2DS_2-VASc score and HAS-BLED score, as compared to patients with moderate multimorbidity and patients without multimorbidity (**Table 2**). The median number of drugs prescribed increased according to multimorbidity groups.

CLINICAL OUTCOMES ACCORDING TO MULTIMORBIDITY. The primary safety outcome of ISTH major or CRNM bleeding occurred significantly more often in patients with high multimorbidity as compared to patients with moderate multimorbidity and patients without multimorbidity (**Table 3**, **Figure 2**). Furthermore, risk estimates for the secondary efficacy outcomes of all-cause death or rehospitalization followed a similar pattern. Risk of all-cause death or ischemic event was particularly pronounced in patients with high multimorbidity as compared to patients without multimorbidity.

EFFECTS OF APIXABAN VS VITAMIN K ANTAGONIST AND ASPIRIN VS PLACEBO IN PATIENTS WITH MULTIMORBIDITY. Treatment with apixaban was associated with a nearly 30% numerical relative risk reduction in the primary bleeding endpoint in patients across the spectrum of multimorbidity (**Figure 3**), with the strongest absolute risk reductions (ARRs) seen in patients with high multimorbidity (6% ARR [−1.7, 13.1]) as compared to patients with moderate multimorbidity (5.9% ARR [2.9, 8.9]) or no multimorbidity (2.7% ARR [−0.17, 5.6]). No significant statistical interaction in relation to treatment with apixaban vs VKA across multimorbidity levels was seen, except for stent thrombosis, where counts were very low (**Figure 3**, Supplemental Table 1A).

In addition, treatment with aspirin as compared to placebo was associated with a relative increase in the primary bleeding endpoint across multimorbidity subgroups (**Figure 3**), with the greatest absolute risk increase of 12.7% (95% CI 5%-20.4%) seen in patients in patients with high multimorbidity, as compared to 5.9% (95% CI: 2.8%-8.9%) and 8% (95% CI: 5.2%-10.9%) in patients with moderate multimorbidity and

TABLE 2 Baseline Characteristics by Comorbidities

	Overall (N = 4,493)	0-2 Comorbidities (n = 1,897)	3-4 Comorbidities (n = 2,110)	5+ Comorbidities (n = 486)	*P* Value
Age, y	70.6 (64.1-77.2)	69.8 (63.4-75.5)	70.7 (64.1-77.5)	75.7 (67.8-82.1)	<0.0001
Female	1,302 (29.0%)	586 (30.9%)	568 (26.9%)	148 (30.5%)	0.0163
Race					0.0170
White	4,074/4,436 (91.8%)	1,709/1,868 (91.5%)	1,921/2,091 (91.9%)	444/477 (93.1%)	
Black	56/4,436 (1.3%)	14/1,868 (0.7%)	31/2,091 (1.5%)	11/477 (2.3%)	
Asian	138/4,436 (3.1%)	69/1,868 (3.7%)	60/2,091 (2.9%)	9/477 (1.9%)	
Other	168/4,436 (3.8%)	76/1,868 (4.1%)	79/2,091 (3.8%)	13/477 (2.7%)	
Serum creatinine (median, 25th-75th)	1.03 (0.88-1.21)	0.99 (0.85-1.13)	1.05 (0.89-1.24)	1.28 (0.97-1.54)	<0.0001
Serum creatinine					<0.0001
<1.5 mg/dl	4,084/4,458 (91.6%)	1,858/1,883 (98.7%)	1,895/2,100 (90.2%)	331/475 (69.7%)	
≥1.5 mg/dl	374/4,458 (8.4%)	25/1,883 (1.3%)	205/2,100 (9.8%)	144/475 (30.3%)	
CHA_2DS_2-VASc score	3.9 ± 1.6	3.1 ± 1.2	4.2 ± 1.4	5.6 ± 1.5	<0.0001
CHA_2DS_2-VASc score group					<0.0001
≤3	1,824/4,403 (41.4%)	1,117/1,814 (61.6%)	673/2,103 (32.0%)	34/486 (7.0%)	
≥4	2,579/4,403 (58.6%)	697/1,814 (38.4%)	1,430/2,103 (68.0%)	452/486 (93.0%)	
HAS-BLED score	2.9 ± 0.9	2.5 ± 0.8	2.9 ± 0.9	3.8 ± 1.0	<0.0001
HAS-BLED score group					<0.0001
≤2	1,503/4,383 (34.3%)	830/1842 (45.1%)	619/2,065 (30.0%)	54/476 (11.3%)	
≥3	2,880/4,383 (65.7%)	1,012/1,842 (54.9%)	1,446/2,065 (70.0%)	422/476 (88.7%)	
LVEF	50 (41-58 [2,755])	52 (45-60 [1,194])	50 (40-57 [1,294])	45 (37-56 [267])	<0.0001
Previous use of oral anticoagulant	2,215 (49.3%)	842 (44.4%)	1,119 (53.0%)	254 (52.3%)	<0.0001
Concomitant P2Y12 inhibitor					0.0561
Clopidogrel	4,058 (90.3%)	1,719 (90.6%)	1,911 (90.6%)	428 (88.1%)	
Ticagrelor	275 (6.1%)	108 (5.7%)	126 (6.0%)	41 (8.4%)	
Prasugrel	49 (1.1%)	29 (1.5%)	16 (0.8%)	4 (0.8%)	
None	111 (2.5%)	41 (2.2%)	57 (2.7%)	13 (2.7%)	
On beta-blockers at randomization	3,255 (72.4%)	1,355 (71.4%)	1,557 (73.8%)	343 (70.6%)	0.1535
On ACE inhibitors/ARBs/ARNI	2,912 (64.8%)	1,184 (62.4%)	1,431 (67.8%)	297 (61.1%)	0.0003
On diuretics	1,398 (31.1%)	384 (20.2%)	764 (36.2%)	250 (51.4%)	<0.0001
Qualifying index event					0.0051
Acute coronary syndrome and PCI	1,675/4,478 (37.4%)	749/1,892 (39.6%)	758/2,102 (36.1%)	168/484 (34.7%)	
Medically managed acute coronary syndrome	1,093/4,478 (24.4%)	461/1,892 (24.4%)	531/2,102 (25.3%)	101/484 (20.9%)	
Elective PCI	1,710/4,478 (38.2%)	682/1,892 (36.0%)	813/2,102 (38.7%)	215/484 (44.4%)	
No. of days from ACS or PCI to randomization	6.6 ± 4.2	6.4 ± 4.1	6.7 ± 4.2	7.1 ± 4.3	0.0042
Apixaban	2,254/4,493 (50.2%)	959/1,897 (50.6%)	1,052/2,110 (49.9%)	243/486 (50.0%)	0.9051
Aspirin	2,252/4,493 (50.1%)	968/1,897 (51.0%)	1,040/2,110 (49.3%)	244/486 (50.2%)	0.5462
Number of drugs taken	9, 6-12	8, 5-11	9, 6-13	10, 6-15	<0.0001

Values are median (25th-75th percentile), n (%), n/N (%), mean ± SD, or median (25th-75th percentile) [N].

ACE = angiotensin converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

patients without multimorbidity. No significant statistical interaction in relation to the effects of aspirin vs placebo on the primary bleeding endpoint as well as the secondary efficacy endpoints across the multimorbidity spectrum was noted (**Figure 3**, Supplemental Table 1B).

DISCUSSION

Among the AUGUSTUS trial population of more than 4,600 patients with AF and ACS and/or PCI, almost 1 in 2 had moderate multimorbidity (3-4 comorbidities) and 1 in 10 had high multimorbidity (5+ comorbidities). Patients with high multimorbidity had a more than 90% higher risk for ISTH major or CRNM bleeding events as well as a 2-fold increased risk of all-cause death or rehospitalization and a 3.5-fold risk for the occurrence of all-cause death or ischemic events. Importantly, outcomes favoring the use of apixaban and single antiplatelet use were preserved across populations with any degree of comorbidity burden. Our findings suggest that a double, apixaban-based antithrombotic therapy including a $P2Y_{12}$ inhibitor without aspirin is safer than double and/or

TABLE 3 Association Between Multimorbidity Group and Endpoints

		Unadjusted	
	KM % [Events]	HR (95% CI)	*P* Value
ISTH major/CRNM bleeding			<0.0001
0-2 comorbidities	11.10 [198]	-	
3-4 comorbidities	13.62 [264]	1.23 (1.02-1.47)	
5 or more comorbidities	21.14 [90]	1.98 (1.55-2.54)	
ISTH major bleeding			<0.0001
0-2 comorbidities	2.33 [41]	-	
3-4 comorbidities	4.94 [94]	2.10 (1.46-3.01)	
5 or more comorbidities	8.86 [37]	3.83 (2.46-5.96)	
Intracranial bleeding			0.0240
0-2 comorbidities	0.17 [3]	-	
3-4 comorbidities	0.49 [9]	2.79 (0.76-10.30)	
5 or more comorbidities	1.26 [5]	7.18 (1.72-30.04)	
All-cause death or rehospitalization			<0.0001
0-2 comorbidities	20.09 [374]	-	
3-4 comorbidities	27.91 [578]	1.44 (1.27-1.64)	
5 or more comorbidities	38.97 [185]	2.17 (1.82-2.59)	
All-cause death or ischemic event			<0.0001
0-2 comorbidities	3.60 [66]	-	
3-4 comorbidities	7.80 [160]	2.20 (1.65-2.93)	
5 or more comorbidities	12.02 [57]	3.52 (2.47-5.00)	
All-cause death			<0.0001
0-2 comorbidities	1.15 [21]	-	
3-4 comorbidities	4.41 [91]	3.78 (2.37-6.01)	
5 or more comorbidities	6.48 [31]	5.66 (3.28-9.78)	
Cardiovascular death			<0.0001
0-2 comorbidities	0.74 [14]	-	
3-4 comorbidities	3.14 [65]	3.95 (2.25-6.93)	
5 or more comorbidities	5.46 [26]	6.96 (3.69-13.14)	
Stroke			0.0202
0-2 comorbidities	0.57 [10]	-	
3-4 comorbidities	0.98 [20]	1.82 (0.85-3.89)	
5 or more comorbidities	1.93 [9]	3.61 (1.47-8.88)	
Myocardial infarction			0.0001
0-2 comorbidities	2.21 [41]	-	
3-4 comorbidities	3.93 [79]	1.78 (1.22-2.60)	
5 or more comorbidities	5.95 [27]	2.77 (1.71-4.48)	
Definite/probable stent thrombosis			0.5528
0-2 comorbidities	0.58 [11]	-	
3-4 comorbidities	0.72 [15]	1.23 (0.57-2.68)	
5 or more comorbidities	1.04 [5]	1.80 (0.62-5.17)	

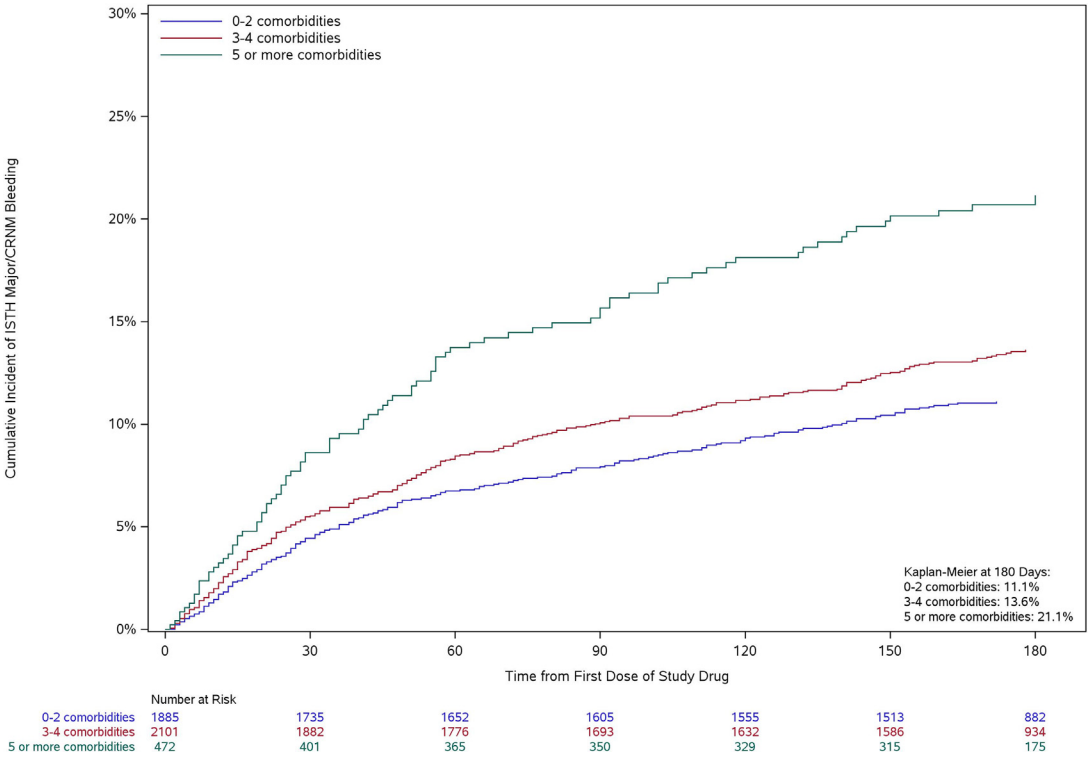
CRNM = clinically relevant nonmajor bleeding; ISTH = International Society on Thrombosis and Haemostasis; KM = Kaplan-Meier.

triple, VKA-based antithrombotic therapy, irrespective of the presence of multimorbidity (**Central Illustration**).

Until recently, clinical practice guidelines recommended "triple therapy" in patients with AF experiencing an ACS and/or undergoing PCI, which typically consisted of a VKA, a $P2Y_{12}$ inhibitor, and aspirin. The rationale for this approach was that oral anticoagulation is superior to DAPT for reducing the risk of stroke, while DAPT is optimal for the prevention of recurrent ACS and stent thrombosis. The downside of this default strategy is an unacceptably high bleeding risk.[9] In the last decade, several randomized controlled trials specifically tested an approach of a direct oral anticoagulant (DOAC) combined with a $P2Y_{12}$ inhibitor as compared to traditional triple therapy. Such a double antithrombotic strategy consistently resulted in lower risk of bleeding while maintaining comparable efficacy outcomes across trials [23,24] and is now recommended as the strategy of choice.[5,6] Elderly, frail patients with multiple chronic conditions and polypharmacy are oftentimes not well represented in clinical trials as they may not fulfill eligibility criteria or are not approached by clinical staff due to anticipated high event rates, which puts the safety and efficacy of such novel strategies in high-risk populations into question.

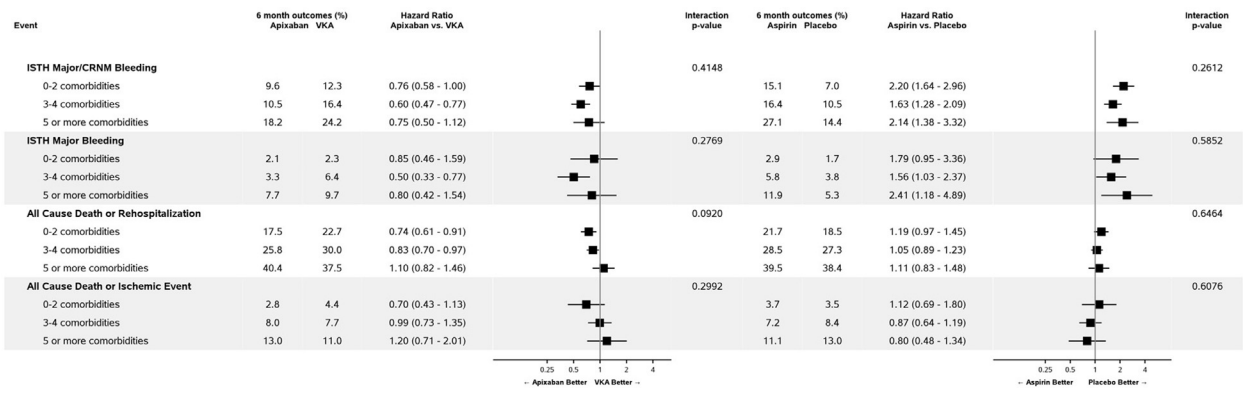
Several secondary and post-hoc analyses of large randomized clinical trials have suggested consistent beneficial effects of treatment with DOACs as compared to VKAs in patients with nonvalvular AF and polypharmacy, multimorbidity, and other high-risk conditions.[25-29] The FRAIL-AF trial suggested an increase in bleeding events when frail patients were switched from a VKA to a DOAC, without any observed beneficial effects on thromboembolic complications.[30] Inclusion criteria in FRAIL-AF comprised an age of 75 years or above and a Groningen Frailty Index of 3 or above, thus including a functionally impaired and phenotypically frail population as compared to several of the above-mentioned analyses that were based on cumulative deficit frailty. Several methodological limitations should be considered when interpreting the results of this small (n = 1,330) open-label trial, which was conducted in a single country and stopped early. The choice of DOAC was left to the discretion of the treating physician, and few patients were prescribed DOACs with a favorable bleeding profile. Further, the mean age in FRAIL-AF was 83 years and the mean CHA_2DS_2-VASc was 4.0; this compares to a median age of 70 and a mean CHA_2DS_2-VASc of 3.9 in AUGUSTUS, with the high multimorbidity group being 76 years old with a CHA_2DS_2-VASc of 5.6. The low rate of hypertension in FRAIL-AF (50% to 55%) is surprising, and the rather late separation of the bleeding curves at around day 90 suggests additional mechanisms at play. Additional trials are warranted to confirm or challenge those findings given that a high percentage of trial participants in the four main cardiovascular outcome trials were switched to DOAC and that no interaction with age or multimorbidity has been documented to date.[31] Functional frailty may be physiologically different, rendering such patients a somewhat

FIGURE 2 **ISTH Major and Clinically Relevant Nonmajor Bleeding by Comorbidity Group**



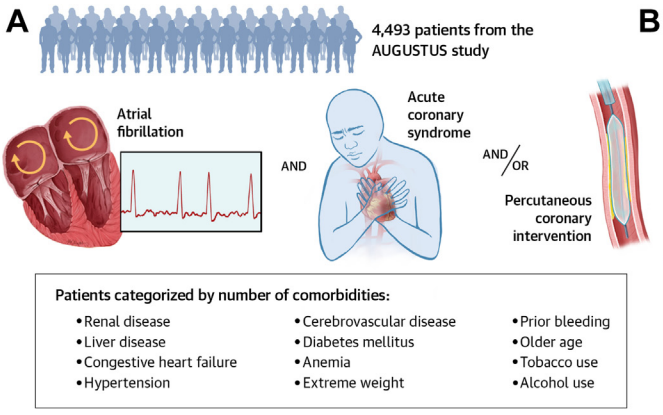
ISTH = International Society on Thrombosis and Haemostasis.

FIGURE 3 **Forrest Plots for the Effects of Apixaban vs VKA and Aspirin vs Placebo on the Primary and Secondary Endpoints According to Multimorbidity Levels**



(Left) Apixaban vs VKA; (right) aspirin vs placebo. CRNM = clinically relevant nonmajor bleeding; ISTH = International Society on Thrombosis and Haemostasis; VKA = vitamin K antagonist.

CENTRAL ILLUSTRATION Apixaban and Limiting Aspirin in Multimorbid Patients



B

ENDPOINT	KM % (events)	HR (95% CI)	*P* value
ISTH major/CRNM bleeding			<.0001
0-2 comorbidities	11.10 (198)	--	
3-4 comorbidities	13.62 (264)	1.23 (1.02-1.47)	
5 or more comorbidities	21.14 (90)	1.98 (1.55-2.54)	
All Cause Death or Rehospitalization			<.0001
0-2 comorbidities	20.09 (374)	--	
3-4 comorbidities	27.91 (578)	1.44 (1.27-1.64)	
5 or more comorbidities	38.97 (185)	2.17 (1.82-2.59)	

C

		Apixaban standard dose	vs Vitamin K antagonist INR 2.0-3.0	Interaction *P* value	Aspirin 81 mg/day	vs Placebo once/day	Interaction *P* value
ISTH major/CRNM bleeding	0-2 comorbidities (n=1,897)	9.6%	12.3% HR: 0.76 (95% CI: 0.58-1.00)	0.42	15.1%	7.0% HR: 2.20 (95% CI: 1.64-2.96)	0.26
	3-4 comorbidities (n=2,110)	10.5%	16.4% HR: 0.60 (95% CI: 0.47-0.77)		16.4%	10.5% HR: 1.63 (95% CI: 1.28-2.09)	
	5 or more comorbidities (n=486)	18.2%	24.2% HR: 0.75 (95% CI: 0.50-1.12)		27.1%	14.4% HR: 2.14 (95% CI: 1.38-3.32)	
All Cause Death or Rehospitalization	0-2 comorbidities (n=1,897)	17.5%	22.7% HR: 0.74 (95% CI: 0.61-0.91)	0.09	21.7%	18.5% HR: 1.19 (95% CI: 0.97-1.45)	0.65
	3-4 comorbidities (n=2,110)	25.8%	30.0% HR: 0.83 (95% CI: 0.70-0.97)		28.5%	27.3% HR: 1.05 (95% CI: 0.89-1.23)	
	5 or more comorbidities (n=486)	40.4%	37.5% HR: 1.10 (95% CI: 0.82-1.46)		39.5%	38.4% HR: 1.11 (95% CI: 0.83-1.48)	

Krychtiuk KA, et al. JACC Adv. 2024;3(11):101335.

(A) Patients with atrial fibrillation, ACS/PCI, and multimorbidity pose a clinical dilemma. (B) Bleeding rates are dramatically increased in such patients. Treatment with apixaban as opposed to VKA (C, left panel) and placebo as compared to aspirin (C, right panel) was superior irrespective of multimorbidity status. ACS = acute coronary syndrome; KM = Kaplan-Meier; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

different population as compared to those identified by convenience approaches in standard clinical trial datasets. In the randomized, placebo-controlled ELDERCARE-AF trial, treatment with very low dose edoxaban at 15 mg when compared with placebo was associated with reduced incidence of stroke or systemic embolism among Japanese AF patients above the age of 80 years and considered ineligible for standard oral anticoagulation regardless of frailty status.[32]

To the best of our knowledge, the present analysis is the first attempt to specifically investigate antithrombotic strategies in multimorbid patients with AF and a recent ACS and/or PCI. Our analysis is based on counts of comorbidities similar to a cumulative deficit approach, and some patients identified as multimorbid will be phenotypically frail while others may not.[33] Still, it provides a reasonable alternative to study a proxy of frailty in clinical trial populations, which often will include healthier populations without available performance-based scores.[34] Based on our stratification, patients in the high multimorbidity group characterized by five or more comorbidities were older, had higher CHA_2DS_2-VASc and HAS-BLED scores, had higher event rates, and were prescribed more drugs as compared to the cohort without multimorbidity, providing some validity to the classification applied.

Patients requiring oral anticoagulation and antiplatelet agents are at higher risk for adverse events as compared to patients with an indication for only one type of antithrombotic therapy.[35] Patients in AUGUSTUS suffered from up to two-threefold higher rates of bleeding as compared to patients in the ARISTOTLE trial, which compared the DOAC apixaban to VKA in patients with nonvalvular AF.[36] In the

present analysis, bleeding rates increased from 11.1% in the group without multimorbidity up to 21.1% in patients with high multimorbidity. In a similar multimorbidity analysis from ARISTOTLE, bleeding rates increased from 4.0% to 5.4%-8.1% across the multimorbidity spectrum.[28] A higher rate of additional endpoints in patients with multimorbidity with high comorbidity counts was also observed. The observed very high event rates during a follow-up period of 6 months underscores the high risk for patients requiring both oral anticoagulation and antiplatelet therapy and highlights the need for an evidence-based approach to therapies.

In the present analysis, no statistical interaction with respect to treatment effects of apixaban as compared to VKA for both the primary bleeding outcome as well as secondary combined endpoints as well as hospitalization, death, stroke, and coronary events was documented across multimorbidity groups. Point estimates of the HR for the primary bleeding events suggest a consistent, numerical, 25% to 40% relative risk reduction across the spectrum of multimorbidity. Patients in the high multimorbidity cohort experienced a 6% absolute risk reduction in the occurrence of the primary bleeding endpoint as compared to 5.9% in the moderate multimorbidity group and 2.7% absolute risk reduction in patients without multimorbidity. One notable exception was the occurrence of stent thrombosis, where a significant interaction *P* value was seen, with a lower apixaban-associated risk of stent thrombosis in the cohort without multimorbidity but a higher risk in patients with a high multimorbidity. With only five stent thromboses observed in the high comorbidity group, the observed findings might be due to chance given the overall trend toward beneficial effects of apixaban. Furthermore, no interaction in relation to aspirin vs placebo was seen for the primary bleeding outcome as well as any secondary outcomes across multimorbidity groups. Importantly, use of aspirin was associated with significant, up to two-fold increases in bleeding events across the multimorbidity spectrum. Patients in the high multimorbidity group experienced a striking 12.7% absolute risk increase in the primary bleeding endpoint, as compared to 5.9% and 8% in patients with moderate multimorbidity and patients without multimorbidity, respectively. Our results therefore suggest that there is no heterogeneity in the antithrombotic treatment effect across multimorbidity, an important finding for decision-making in clinical practice.

STUDY LIMITATIONS. This was a post-hoc analysis and therefore should be considered exploratory. The trial was not designed or powered to detect interactions between randomized treatment arms and outcomes according to the presence of multimorbidity. Therefore, the lack of statistical significance in the interaction tests should be interpreted with caution. Furthermore, we cannot rule out unmeasured confounders that could have impacted outcomes as patients were not randomized according to multimorbidity status. It needs to be noted that AUGUSTUS was only powered for bleeding events and not for any of the secondary ischemic endpoints. The comorbidity analysis was limited to those collected in the case report forms, and no comorbidity information was collected with regard to the presence of malignancy and dementia, as well as additional areas of frailty including mobility, cognition, vision and hearing abilities, physical fitness, and psychosocial factors. In addition, all comorbidities were counted as equal contributors and were not graded by severity. Therefore, our analysis is focused on an accumulation of comorbidities as opposed to phenotypic frailty assessed by comorbidity or frailty scores that incorporate weighing such as the Charlson comorbidity index [37] or the Groningen Frailty Index.[38] Choice of $P2Y_{12}$ inhibitor was left to the clinician's discretion, and clinicians may opt to lower potency drugs in patients with perceived frailty or multimorbidity. However, clopidogrel prescription rates were numerically lower in patients with high multimorbidity.

CONCLUSIONS

Among patients with AF and ACS and/or PCI, multimorbidity is common and strongly associated with an increased risk for adverse clinical outcomes. Although no interaction in relation to the effects of apixaban vs VKA or aspirin vs placebo was seen across the presence or grade of multimorbidity, our findings support the routine use of apixaban and a $P2Y_{12}$ inhibitor without aspirin for this high-risk patient population, especially in the presence of high multimorbidity, where absolute benefits of this regimen are greater.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with AF and previous ACS and/or PCI and multimorbidity are at dramatically increased risk for bleeding and ischemic events. In the AUGUSTUS trial, an antithrombotic regimen consisting of apixaban and a $P2Y_{12}$ inhibitor without aspirin was associated with improved outcomes, irrespective of the presence and degree of multimorbidity. The strongest absolute risk reductions associated with a treatment approach consisting of apixaban and a $P2Y_{12}$ inhibitor without aspirin were seen in patients with a high degree of multimorbidity.

TRANSLATIONAL OUTLOOK: Our results support the preference for a double antithrombotic therapy consisting of the DOAC apixaban and a $P2Y_{12}$ inhibitor as compared to the use of VKA or the use of aspirin in addition to $P2Y_{12}$ inhibitors, irrespective of the presence of multimorbidity. In patients with a high degree of multimorbidity, the risk of bleeding or ischemic events is high, and absolute risk reductions are the strongest when using apixaban and limiting aspirin.

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APPENDIX For supplemental tables, please see the online version of this paper.