Efficacia e sicurezza di diversi regimi antitrombotici del trial AUGUSTS in base ai punteggi di rischio HAS-BLED e CHA_2DS_2- VASc

Background

- Approximately 20%-30% of patients with atrial fibrillation (AF) have concomitant coronary artery disease
- Patients with AF who have an acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI) have an indication for both anticoagulation and dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor, but the risk of bleeding complications with triple antithrombotic ttherapy can be unacceptably high.
- Recent clinical trials have demonstrated that double antithrombotic therapy with a $P2Y_{12}$ inhibitor plus a direct oral anticoagulant (DOAC) provides an optimal balance in protecting against ischemic events while avoiding major bleeding in many patients; however, there may be subgroups of patients with higher or lower bleeding or thromboembolic risk that benefit from more potent antithrombotic therapy.

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Antithrombotic Therapy in Patients With Atrial Fibrillation After Acute Coronary Syndromes or Percutaneous Intervention

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Objective

- The authors assessed the safety and efficacy of antithrombotic regimens according to HAS-BLED and CHA2DS2-VASc scores in AUGUSTUS (The Open-Label, 2 x 2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention).

J Am Coll Cardiol 2022;79:417–427

Methods

- In AUGUSTUS, 4614 patients were randomized in a 2-by-2 factorial design to open-label apixaban or VKA and blinded aspirin or placebo.
- The primary endpoint was major or clinically relevant nonmajor bleeding over 6 months of follow-up.
- Cox proportional hazard models were used to assess treatment effects by baseline HAS-BLED (≤2 vs ≥3) and CHA_2DS_2-VASc (≤2 vs ≥3) scores.
- Nonprespecified, post hoc analysis

J Am Coll Cardiol 2022;79:417–427

Patient Characteristics Stratified by Stroke and Bleeding Risk

J Am Coll Cardiol 2022;79:417–427

	Overall (N = 4,386)	CHA_2DS_2-VASc		HAS-BLED	
		≤2 (n = 803)	≥3 (n = 3,583)	≤2 (n = 1,455)	≥3 (n = 2,931)
Age, y	71 (64, 77)	62 (57, 65)	73 (67, 78)	63 (59, 70)	73 (68, 79)
Women	1,289/4,386 (29.4)	32/803 (4.0)	1,257/3,583 (35.1)	330/1,455 (22.7)	959/2,931 (32.7)
Race					
White	4,018/4,339 (92.6)	704/787 (89.5)	3,314/3,552 (93.3)	1,324/1,439 (92.0)	2,694/2,900 (92.9)
Black	56/4,339 (1.3)	3/787 (0.4)	53/3,552 (1.5)	19/1,439 (1.3)	37/2,900 (1.3)
Asian	102/4,339 (2.4)	30/787 (3.8)	72/3,552 (2.0)	42/1,439 (2.9)	60/2,900 (2.1)
Native American	13/4,339 (0.3)	5/787 (0.6)	8/3,552 (0.2)	3/1,439 (0.2)	10/2,900 (0.3)
Other	150/4,339 (3.5)	45/787 (5.7)	105/3,552 (3.0)	51/1,439 (3.5)	99/2,900 (3.4)
Serum creatinine					
<1.5 mg/dL	3,946/4,311 (91.5)	743/790 (94.1)	3,203/3,521 (91.0)	1,351/1,430 (94.5)	2,595/2,881 (90.1)
≥1.5 mg/dL	365/4,311 (8.5)	47/790 (5.9)	318/3,521 (9.0)	79/1,430 (5.5)	286/2,881 (9.9)
Prior bleeding	47/4,368 (1.1)	3/799 (0.4)	44/3,569 (1.2)	4/1,451 (0.3)	43/2,917 (1.5)
Hypertension	3,984/4,386 (90.8)	621/803 (77.3)	3363/3,583 (93.9)	1,118/1,455 (76.8)	2,866/2,931 (97.8)
Heart failure	1,949/4,386 (44.4)	188/803 (23.4)	1,761/3,583 (49.1)	654/1,455 (44.9)	1,295/2,931 (44.2)
Diabetes mellitus	1,633/4,386 (37.2)	104/803 (13.0)	1,529/3,583 (42.7)	476/1,455 (32.7)	1,157/2,931 (39.5)
Stroke, TIA, or thromboembolism	619/4,386 (14.1)	0/803 (0.0)	619/3,583 (17.3)	78/1,455 (5.4)	541/2,931 (18.5)
HAS-BLED	3 (2, 3)	2 (2, 3)	3 (3, 4)	–	–
CHA_2DS_2-VASc	4 (3, 5)	–	–	3 (2,4)	4 (3, 5)

Patient Management Stratified by Stroke and Bleeding Risk

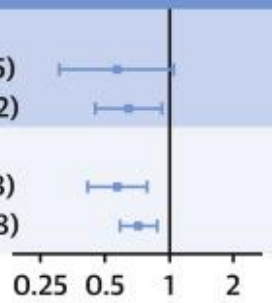
	Overall (N = 4,386)	CHA_2DS_2-VASc		HAS-BLED	
		≤2 (n = 803)	≥3 (n = 3,583)	≤2 (n = 1,455)	≥3 (n = 2,931)
Qualifying index event					
Acute coronary syndrome and PCI	1,617/4,373 (37.0)	326/800 (40.8)	1,291/3,573 (36.1)	521/1,448 (36.0)	1,096/2,925 (37.5)
Medically managed acute coronary syndrome	1,070/4,373 (24.5)	163/800 (20.4)	907/3,573 (25.4)	400/1,448 (27.6)	670/2,925 (22.9)
Elective PCI	1,686/4,373 (38.6)	311/800 (38.9)	1,375/3,573 (38.5)	527/1,448 (36.4)	1,159/2,925 (39.6)
Number of days from ACS or PCI to randomization	6 (3, 10)	5 (2, 10)	6 (3, 10)	6 (3, 10)	6 (3, 10)
Low-dose apixaban (2.5 mg twice daily) in patients randomized to apixaban	216/2,178 (9.9)	25/414 (6.0)	191/1,764 (10.8)	54/722 (7.5)	162/1,456 (11.1)
Concomitant $P2Y_{12}$ inhibitor at randomization					
Clopidogrel	3,970/4,281 (92.7)	708/785 (90.2)	3,262/3,496 (93.3)	1,298/1,403 (92.5)	2,672/2,878 (92.8)
Prasugrel	46/4,281 (1.1)	19/785 (2.4)	27/3,496 (0.8)	23/1,403 (1.6)	23/2,878 (0.8)
Ticagrelor	265/4,281 (6.2)	58/785 (7.4)	207/3,496 (5.9)	82/1,403 (5.8)	183/2,878 (6.4)
Previous use of oral anticoagulant	2,171/4,386 (49.5)	345/803 (43.0)	1,826/3,583 (51.0)	681/1,455 (46.8)	1,490/2,931 (50.8)
Time in therapeutic range (VKA only)	58.5 (33.6-80.8)	58.0 (34.5-79.2)	58.8 (33.5-81.2)	58.1 (34.2-79.2)	58.9 (33.3-81.7)
Discontinued anticoagulant prematurely	565/4,325 (13.1)	78/793 (9.8)	487/3,532 (13.8)	155/1,438 (10.8)	410/2,887 (14.2)
Discontinued antiplatelet prematurely	674/4,333 (15.6)	85/794 (10.7)	589/3,539 (16.6)	167/1,441 (11.6)	507/2,892 (17.5)

J Am Coll Cardiol 2022;79:417–427

Treatment Effect of Antithrombotic Regimens on Bleeding Events

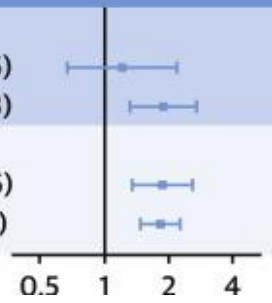
A

	Number (Rate) of Events at 6 Months Apixaban	VKA	HR (95% CI)	Interaction *P* Value
ISTH major bleeding				0.722
≤2	16 (2.3%)	27 (4.0%)	0.57 (0.30-1.05)	
≥3	50 (3.7%)	72 (5.6%)	0.64 (0.45-0.92)	
ISTH major or CRNM bleeding				0.230
≤2	61 (8.8%)	98 (14.4%)	0.57 (0.41-0.78)	
≥3	165 (12.1%)	214 (16.3%)	0.72 (0.59-0.88)	



B

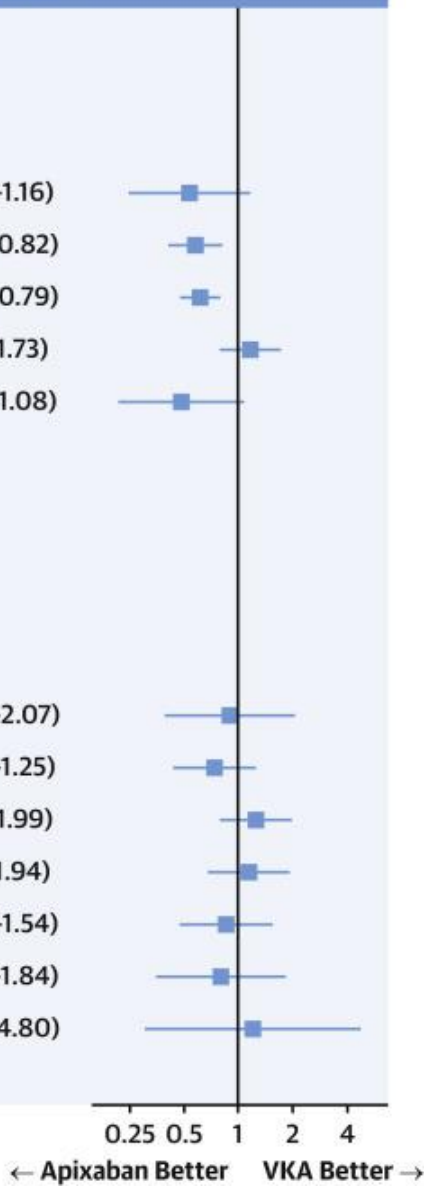
	Number (Rate) of Events at 6 Months Aspirin	Placebo	HR (95% CI)	Interaction *P* Value
ISTH major bleeding				0.205
≤2	24 (3.6%)	21 (3.0%)	1.20 (0.67-2.16)	
≥3	78 (5.9%)	43 (3.4%)	1.88 (1.30-2.73)	
ISTH major or CRNM bleeding				0.881
≤2	102 (15.1%)	59 (8.4%)	1.86 (1.36-2.56)	
≥3	239 (17.8%)	137 (10.4%)	1.81 (1.47-2.23)	



- The treatment effect of **(A)** apixaban vs VKA and **(B)** aspirin vs placebo on ISTH major and major or CRNM bleeding by HAS-BLED category.
- There was no treatment effect interaction by baseline bleeding risk for the comparison of apixaban vs VKA or placebo vs aspirin; patients randomized to apixaban and placebo had a lower risk of major and CRNM bleeding regardless of baseline bleeding risk.

J Am Coll Cardiol 2022;79:417–427

Event/Risk Score	KM% at 6 Months [Events] Apixaban	VKA	HR (95% CI) Apixaban vs VKA
ISTH Major or CRNM Bleeding			
HAS-BLED			
0 (N = 2)	0.0 [0]	--	--
1 (N = 258)	7.7 [10]	14.4 [17]	0.53 (0.24-1.16)
2 (N = 1,195)	9.1 [51]	14.4 [81]	0.58 (0.41-0.82)
3 (N = 1,975)	10.9 [101]	17.0 [152]	0.61 (0.48-0.79)
4 (N = 761)	15.6 [55]	13.3 [45]	1.17 (0.79-1.73)
5 (N = 169)	12.1 [9]	24.9 [17]	0.48 (0.21-1.08)
6 (N = 24)	0.0 [0]	0.0 [0]	--
7 (N = 2)	0.0 [0]	--	--
Death or Ischemic Events			
CHA_2DS_2-VASc			
1 (N = 168)	1.2 [1]	2.4 [2]	--
2 (N = 635)	3.4 [11]	3.7 [11]	0.90 (0.39-2.07)
3 (N = 997)	4.7 [23]	6.6 [33]	0.74 (0.44-1.25)
4 (N = 1,083)	8.0 [40]	6.1 [33]	1.25 (0.79-1.99)
5 (N = 805)	7.6 [30]	6.7 [25]	1.14 (0.67-1.94)
6 (N = 428)	9.8 [20]	11.0 [24]	0.86 (0.48-1.54)
7 (N = 197)	10.0 [10]	12.4 [11]	0.80 (0.35-1.84)
8 (N = 63)	14.3 [4]	12.4 [4]	1.20 (0.30-4.80)
9 (N = 10)	0.0 [0]	16.7 [1]	--

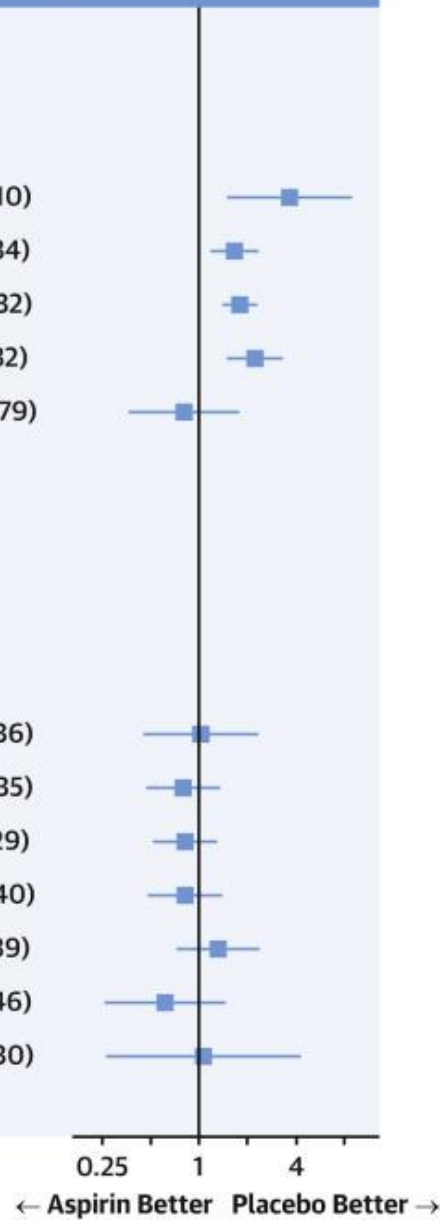


Treatment Effect of Antithrombotic Regimens on Bleeding or Ischemic Events

- The treatment effect of apixaban vs VKA on bleeding and death or ischemic events by HAS-BLED and CHA2DS2-VASc scores.
- There was no treatment effect interaction by baseline bleeding or stroke risk for the comparison of apixaban vs VKA (P for trend = 0.14)

J Am Coll Cardiol 2022;79:417–427

Event/Risk Score	KM% at 6 Months [Events] Aspirin	Placebo	HR (95% CI) Aspirin vs Placebo
ISTH Major or CRNM Bleeding			
HAS-BLED			
0 (N = 2)	--	0.0 [0]	--
1 (N = 258)	16.9 [21]	4.9 [6]	3.67 (1.48-9.10)
2 (N = 1,195)	14.7 [81]	9.2 [53]	1.66 (1.18-2.34)
3 (N = 1,975)	17.4 [161]	10.2 [90]	1.80 (1.39-2.32)
4 (N = 761)	19.8 [67]	9.9 [34]	2.21 (1.47-3.32)
5 (N = 169)	16.1 [11]	18.1 [13]	0.80 (0.36-1.79)
6 (N = 24)	0.0 [0]	0.0 [0]	--
7 (N = 2)	0.0 [0]	0.0 [0]	--
Death or Ischemic Events			
CHA_2DS_2-VASc			
1 (N = 168)	1.2 [1]	2.5 [2]	--
2 (N = 635)	3.5 [11]	3.6 [11]	1.02 (0.44-2.36)
3 (N = 997)	5.0 [24]	6.4 [32]	0.80 (0.47-1.35)
4 (N = 1,083)	6.3 [33]	7.7 [40]	0.81 (0.51-1.29)
5 (N = 805)	6.8 [24]	7.6 [31]	0.82 (0.48-1.40)
6 (N = 428)	11.5 [26]	9.1 [18]	1.32 (0.73-2.39)
7 (N = 197)	8.6 [8]	13.4 [13]	0.61 (0.26-1.46)
8 (N = 63)	13.7 [4]	12.9 [4]	1.08 (0.27-4.30)
9 (N = 10)	0.0 [0]	20.0 [1]	--



Treatment Effect Of Antithrombotic Regimens on Bleeding or Ischemic Events

- The treatment effect of aspirin vs placebo on bleeding and death or ischemic events by HAS-BLED and CHA2DS2-VASc scores.
- There was no treatment effect interaction by baseline bleeding or stroke risk for the comparison of placebo vs aspirin (*P* for trend = 0.47).

J Am Coll Cardiol 2022;79:417–427

Treatment Effect of Antithrombotic Regimens on Death or Ischemic Events

A

	Number (Rate) of Events at 6 Months Apixaban	VKA	HR (95% CI)	Interaction *P* Value
Stroke				
≤2	0 (0.0%)	0 (0.0%)		
≥3	13 (0.8%)	25 (1.4%)	0.52 (0.27-1.02)	
Death or ischemic events				0.737
≤2	12 (3.0%)	13 (3.4%)	0.85 (0.39-1.87)	
≥3	127 (7.4%)	131 (7.4%)	0.98 (0.77-1.25)	
Death or hospitalization				0.531
≤2	80 (19.7%)	81 (21.5%)	0.92 (0.67-1.25)	
≥3	435 (25.0%)	513 (29.2%)	0.82 (0.73-0.94)	

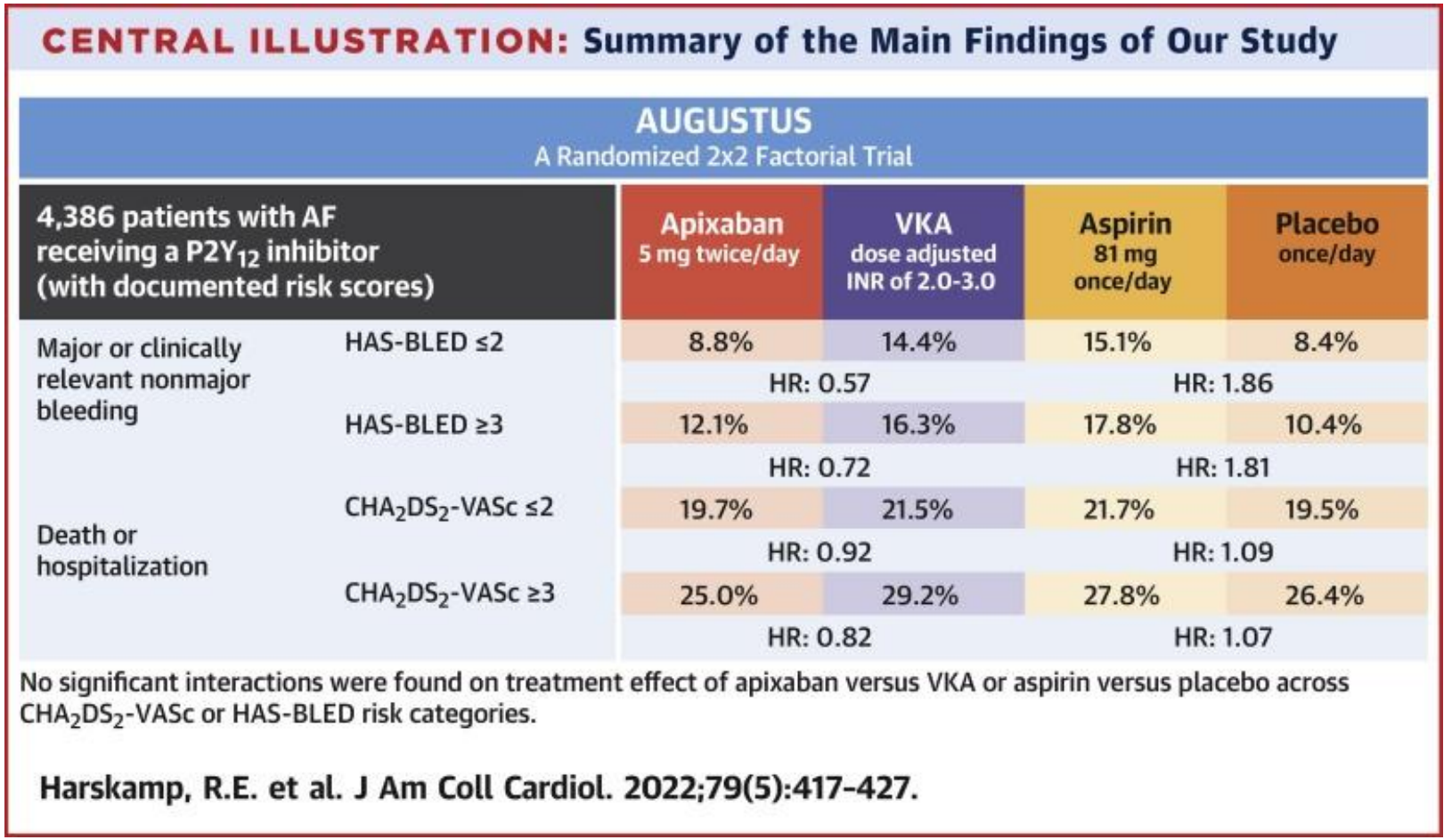
B

	Number (Rate) of Events at 6 Months Aspirin	Placebo	HR (95% CI)	Interaction *P* Value
Stroke				
≤2	0 (0.0%)	0 (0.0%)		
≥3	20 (1.2%)	18 (1.0%)	1.12 (0.59-2.12)	
Death or ischemic events				0.881
≤2	12 (3.0%)	13 (3.4%)	0.92 (0.42-2.03)	
≥3	119 (6.9%)	139 (7.9%)	0.87 (0.68-1.11)	
Death or hospitalization				0.903
≤2	84 (21.7%)	77 (19.5%)	1.09 (0.80-1.49)	
≥3	483 (27.8%)	465 (26.4%)	1.07 (0.94-1.21)	

- The treatment effect of **(A)** apixaban vs VKA and **(B)** aspirin vs placebo on stroke, death or ischemic events, and death or hospitalization by CHA_2DS_2-VASc category.
- There was no treatment effect interaction by baseline stroke risk for the comparison of apixaban vs VKA (p for trend = 0.84) or placebo vs aspirin (*P* for trend = 0.80).

J Am Coll Cardiol 2022;79:417–427

Summary of the main findings



CENTRAL ILLUSTRATION: Summary of the Main Findings of Our Study

AUGUSTUS
A Randomized 2x2 Factorial Trial

4,386 patients with AF receiving a $P2Y_{12}$ inhibitor (with documented risk scores)		Apixaban 5 mg twice/day	VKA dose adjusted INR of 2.0-3.0	Aspirin 81 mg once/day	Placebo once/day
Major or clinically relevant nonmajor bleeding	HAS-BLED ≤2	8.8%	14.4%	15.1%	8.4%
		HR: 0.57		HR: 1.86	
	HAS-BLED ≥3	12.1%	16.3%	17.8%	10.4%
		HR: 0.72		HR: 1.81	
Death or hospitalization	CHA_2DS_2-VASc ≤2	19.7%	21.5%	21.7%	19.5%
		HR: 0.92		HR: 1.09	
	CHA_2DS_2-VASc ≥3	25.0%	29.2%	27.8%	26.4%
		HR: 0.82		HR: 1.07	

No significant interactions were found on treatment effect of apixaban versus VKA or aspirin versus placebo across CHA_2DS_2-VASc or HAS-BLED risk categories.

Harskamp, R.E. et al. J Am Coll Cardiol. 2022;79(5):417-427.

Limitations

- AUGUSTUS trial was not powered to detect interactions between study medications and outcomes according to HAS-BLED or CHA_2DS_2-VASc subgroups.
  - This should be particularly emphasized for ischemic events, including stroke.
- AUGUSTUS trial had a numerically lower TTR for patients who received VKA compared with other RCT of stroke prevention.
- $P2Y_{12}$ inhibitor choice was open-label and at investigator discretion, and clinicians could theoretically have used higher-potency $P2Y_{12}$ inhibitors in patients at lower risk of bleeding, introducing confounding by indication.
  - Clopidogrel was used in >90% of patients irrespective of bleeding risk.
- AUGUSTUS randomized patients a median of 6 days (maximum of 14 days) after the qualifying ACS or PCI event, and these findings may not apply to patients very shortly after an ACS or PCI event.

J Am Coll Cardiol 2022;79:417–427

Conclusions

- An antithrombotic regimen including apixaban is associated with less bleeding and hospitalization compared with a regimen with VKA or aspirin, independent of HAS-BLED and CHA_2DS_2-VASc scores.
- These findings support the use of apixaban (and possibly other DOACs) and a $P2Y_{12}$ inhibitor without aspirin for most patients with AF and ACS and/or undergoing PCI, regardless of baseline bleeding and stroke risk.

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