Apixaban o Warfarin e Aspirina o Placebo dopo sindrome coronarica acuta o angioplastica percutanea nei pazienti con fibrillazione atriale e storia di pregresso ictus ischemico, attacco ischemico transitorio o evento tromboembolico

Analisi *post hoc* del trial AUGUSTUS

Background

- Recent trials and meta-analyses demonstrated the benefit of a dual pathway strategy with a P2Y12 inhibitor coupled with an oral anticoagulant in patients with atrial fibrillation and acute coronary syndrome and/or recent percutaneous coronary intervention.
- In the AUGUSTUS trial apixaban resulted in less bleeding and fewer hospitalizations than vitamin K antagonist (VKA), and aspirin resulted in more bleeding than placebo.
- Patients with history of stroke, transient ischemic attack (TIA) or thromboembolism (TE) may be at increased risk for both ischemic and bleeding risk.

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Apixaban or Warfarin and Aspirin or Placebo After Acute Coronary Syndrome or Percutaneous Coronary Intervention in Patients With Atrial Fibrillation and Prior Stroke

A Post Hoc Analysis From the AUGUSTUS Trial

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Aim

- To determine the efficacy and safety of apixaban or VKA and aspirin or placebo according to prior stroke, transient ischemic attack, or thromboembolism.

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Methods

- In this prospective, multicenter, 2-by-2 factorial, randomized clinical trial, post hoc parallel analyses were performed to compare randomized treatment regimens according to presence or absence of prior stroke/TIA/TE using Cox proportional hazards models.
- Patients with AF, recent ACS or PCI, and planned use of P2Y12 inhibitors for 6 months or longer were included; 33 patients with missing data about prior stroke/TIA/TE were excluded.

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Patients baseline characteristics

	No./total No. (%)			
	Overall (n = 4581)	Prior stroke/TIA/TE (n = 633)	No prior stroke/TIA/TE (n = 3948)	*P* value
Age, median (IQR), y	71 (64-77)	72 (66-78)	70 (64-77)	<.001
Female sex	1329/4581 (29.0)	183/633 (28.9)	1146/3948 (29.0)	.95
Male sex	3252/4581 (71.0)	450/633 (71.1)	2802/3948 (71.0)	
Race and ethnicity[a]				.17
American Indian and Alaska Native	16/4524 (0.4)	3/624 (0.5)	13/3900 (0.3)	
Asian	140/4524 (3.1)	20/624 (3.2)	120/3900 (3.1)	
Black	59/4524 (1.3)	14/624 (2.2)	45/3900 (1.2)	
White	4152/4524 (91.8)	570/624 (91.3)	3582/3900 (91.8)	
Other	157/4524 (3.5)	17/624 (2.7)	140/3900 (3.6)	
Serum creatinine, mg/dL				.61
<1.5	4128/4504 (91.7)	565/620 (91.1)	3563/3884 (91.7)	
≥1.5	376/4504 (8.3)	55/620 (8.9)	321/3884 (8.3)	
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.6)	5.9 (1.4)	3.6 (1.3)	<.001
HAS-BLED score, mean (SD)	2.9 (0.9)	3.7 (1.0)	2.7 (0.9)	<.001
Prior bleeding	50/4561 (1.1)	16/632 (2.5)	34/3929 (0.9)	<.001
Hypertension leading to medication use	4073/4581 (88.9)	576/633 (91.0)	3497/3948 (88.6)	.07
Heart failure	1973/4581 (43.1)	301/633 (47.6)	1672/3948 (42.4)	.01
Diabetes	1678/4581 (36.6)	264/633 (41.7)	1414/3948 (35.8)	.004
Concomitant P2Y12 inhibitor at randomization				.09
Clopidogrel	4142/4469 (92.7)	557/615 (90.6)	3585/3854 (93.0)	
Prasugrel	49/4469 (1.1)	8/615 (1.3)	41/3854 (1.1)	
Ticagrelor	278/4469 (6.2)	50/615 (8.1)	228/3854 (5.9)	
Previous use of oral anticoagulant	2247/4581 (49.1)	344/633 (54.3)	1903/3948 (48.2)	.004
Qualifying index event				.38
ACS and PCI	1705/4564 (37.4)	222/629 (35.3)	1483/3935 (37.7)	
Medically managed ACS	1095/4564 (24.0)	163/629 (25.9)	932/3935 (23.7)	
Elective PCI	1764/4564 (38.7)	244/629 (38.8)	1520/3935 (38.6)	
No. of days from ACS or PCI to randomization, mean (SD)	6.6 (4.2)	7.0 (4.2)	6.6 (4.2)	.006
Reduced-dose apixaban (2.5 mg) in patients randomized to receive apixaban	227/2274 (10.0)	37/324 (11.4)	190/1950 (9.7)	.35

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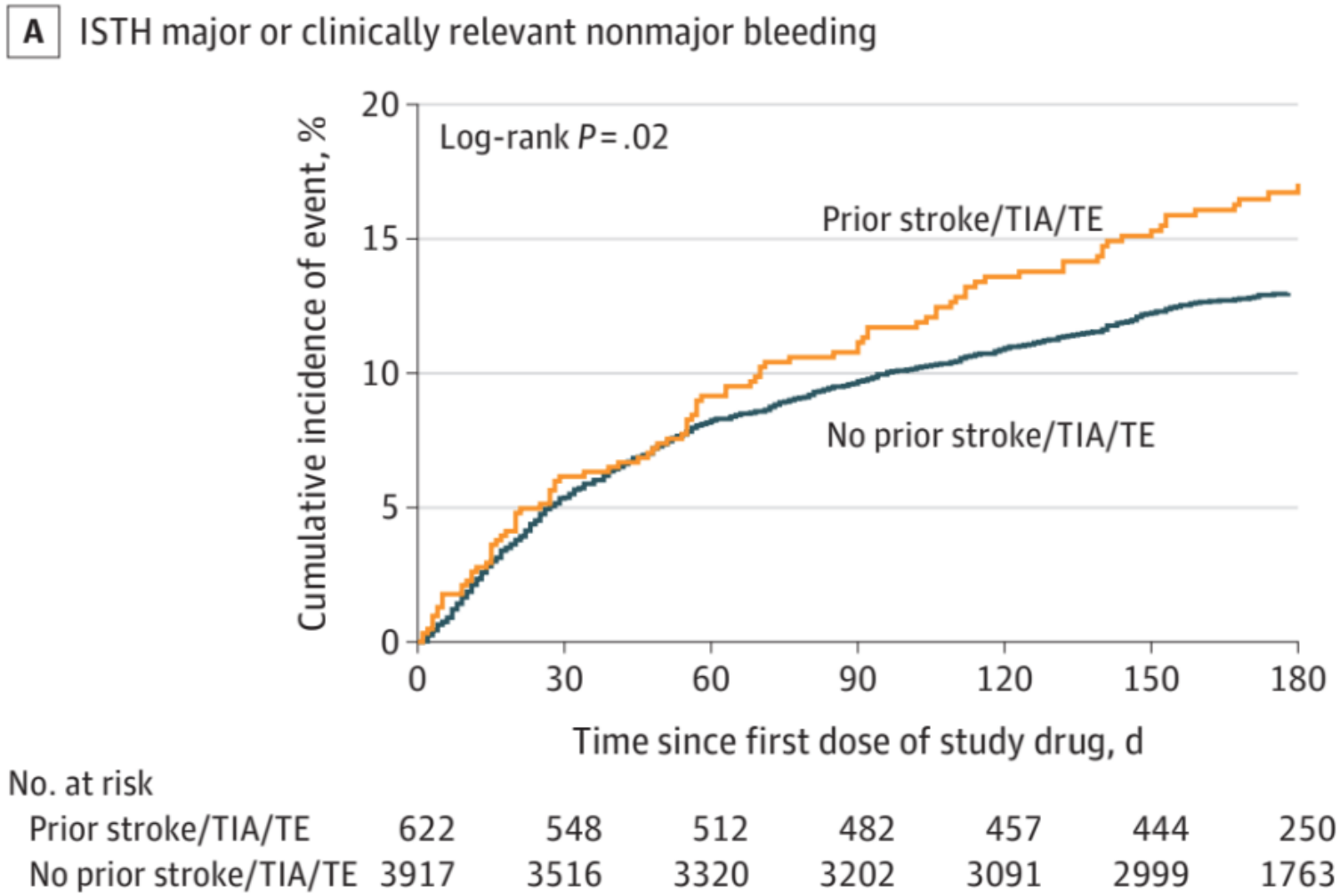
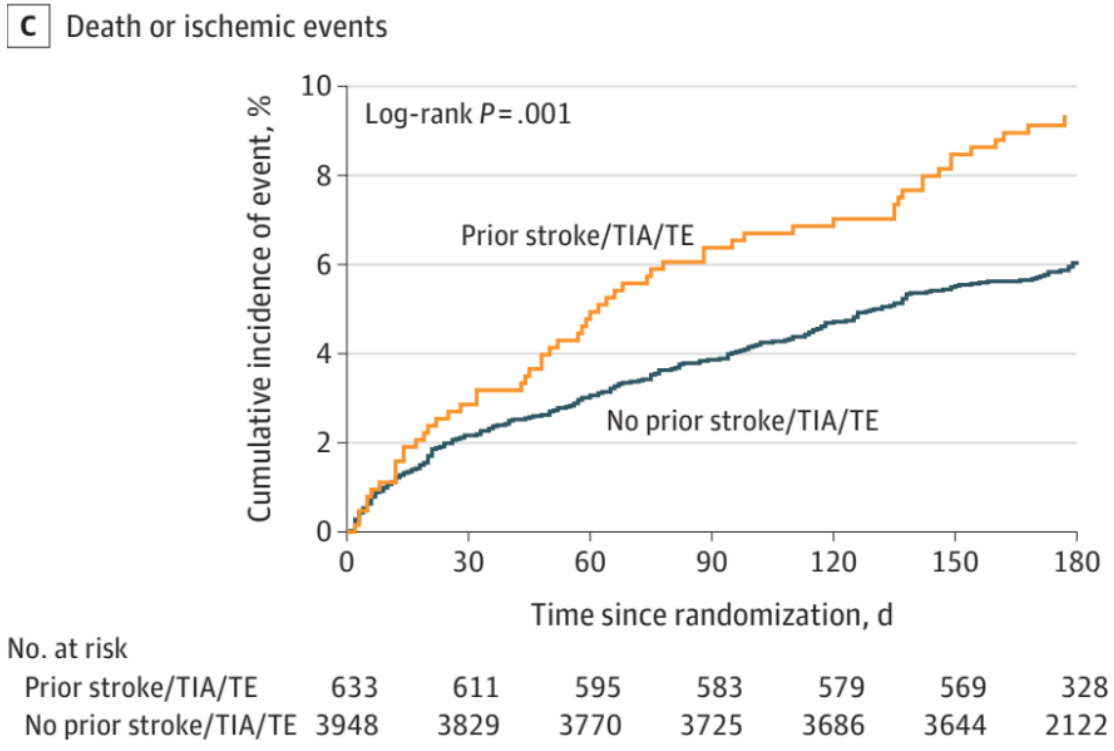
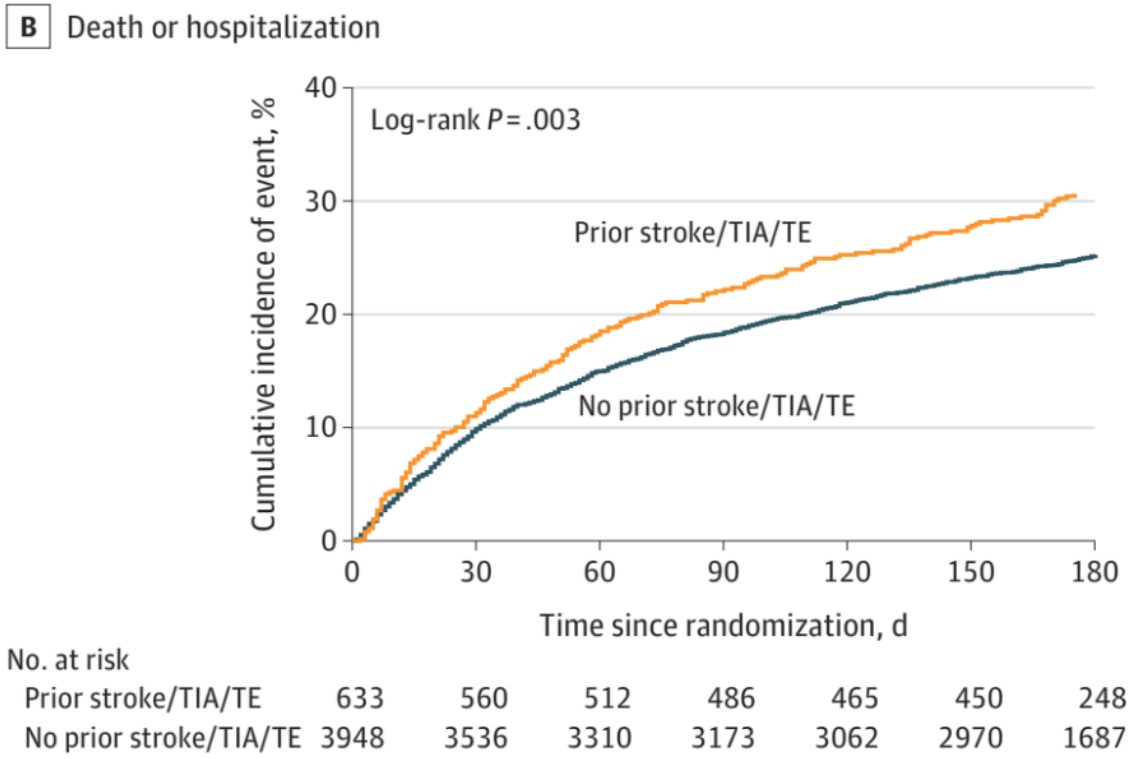
Kaplan-Meier curves for bleeding events



Kaplan-Meier curves for death, hospitalization and ischemic events





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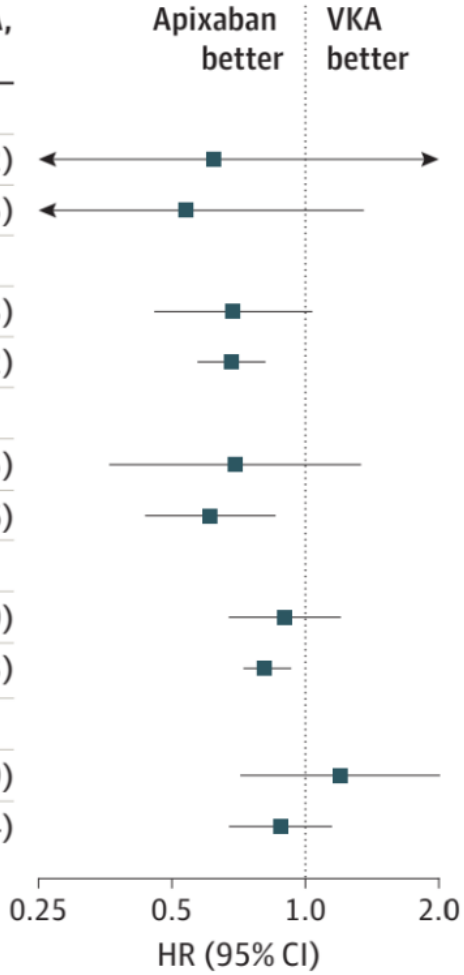
Treatment effect of apixaban vs VKA

Event	No. of events (%)		Apixaban vs VKA, HR (95% CI)	Interaction *P* value
	Apixaban	VKA		
Ischemic stroke				.85
Prior stroke/TIA/TE	4 (1.3)	6 (2.0)	0.63 (0.18-2.22)	
No prior stroke/TIA/TE	7 (0.4)	13 (0.7)	0.54 (0.22-1.35)	
ISTH major or CRNM bleeding				.97
Prior stroke/TIA/TE	42 (13.9)	52 (19.9)	0.69 (0.46-1.03)	
No prior stroke/TIA/TE	197 (10.7)	272 (15.0)	0.68 (0.57-0.82)	
ISTH major bleeding				.73
Prior stroke/TIA/TE	16 (5.3)	19 (7.4)	0.70 (0.36-1.35)	
No prior stroke/TIA/TE	53 (2.9)	83 (4.6)	0.61 (0.43-0.86)	
Death or hospitalization				.56
Prior stroke/TIA/TE	95 (29.6)	95 (31.6)	0.90 (0.68-1.19)	
No prior stroke/TIA/TE	444 (23.1)	528 (27.3)	0.82 (0.72-0.93)	
Death or ischemic events				.31
Prior stroke/TIA/TE	32 (10.0)	26 (8.6)	1.19 (0.71-1.99)	
No prior stroke/TIA/TE	109 (5.8)	123 (6.4)	0.88 (0.68-1.14)	



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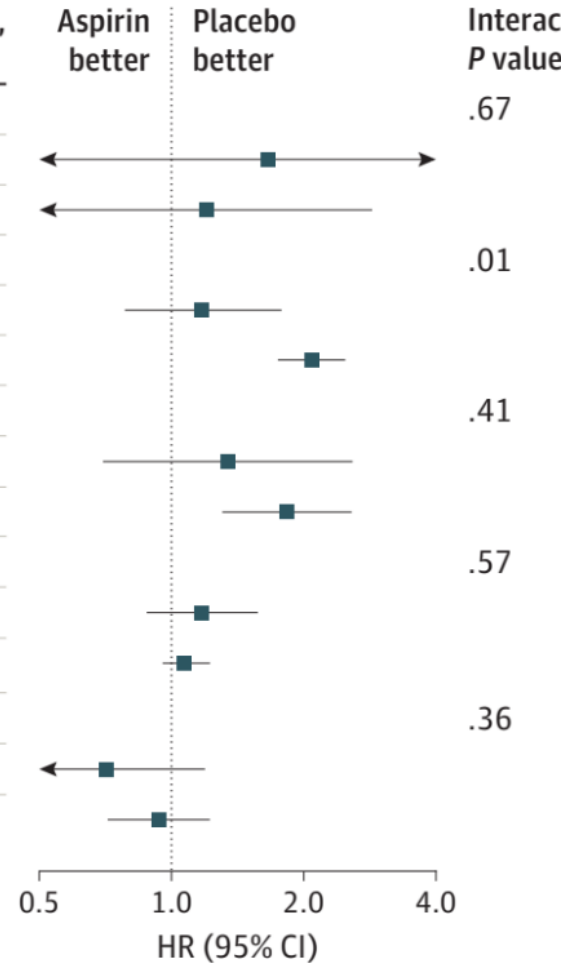
Treatment effect of aspirin vs placebo

Event	No. of events (%) Aspirin	Placebo	Aspirin vs placebo, HR (95% CI)	Interac *P* value
Ischemic stroke				.67
Prior stroke/TIA/TE	6 (2.1)	4 (1.2)	1.68 (0.48-5.97)	
No prior stroke/TIA/TE	11 (0.6)	9 (0.5)	1.21 (0.50-2.91)	
ISTH major or CRNM bleeding				.01
Prior stroke/TIA/TE	47 (17.3)	46 (15.9)	1.18 (0.79-1.76)	
No prior stroke/TIA/TE	315 (17.1)	155 (8.5)	2.10 (1.73-2.54)	
ISTH major bleeding				.41
Prior stroke/TIA/TE	18 (6.7)	16 (5.8)	1.34 (0.69-2.61)	
No prior stroke/TIA/TE	89 (4.9)	49 (2.7)	1.84 (1.30-2.61)	
Death or hospitalization				.57
Prior stroke/TIA/TE	95 (32.6)	95 (28.8)	1.18 (0.89-1.56)	
No prior stroke/TIA/TE	504 (26.0)	468 (24.4)	1.08 (0.95-1.22)	
Death or ischemic events				.36
Prior stroke/TIA/TE	23 (7.9)	35 (10.7)	0.71 (0.42-1.20)	
No prior stroke/TIA/TE	112 (5.8)	120 (6.3)	0.93 (0.72-1.21)	



JAMA Cardiol. 2022 Jul 1;7(7):682-689.

Limitations

- Only aggregate of stroke/TIA/TE, not individual components.
- Ethnic and racial minority groups were underrepresented.
- Post hoc analysis.

JAMA Cardiol. 2022 Jul 1;7(7):682-689.

Conclusions

The safety and efficacy of apixaban compared with VKA was consistent with the AUGUSTUS findings, irrespective of prior stroke/TIA/TE.

Aspirin increased major or CRNM bleeding, particularly in patients without prior stroke/TIA/TE.

Although aspirin may have some benefit in patients with prior stroke, our findings support the use of apixaban and a P2Y12 inhibitor without aspirin for the majority of patients with AF and ACS and/or PCI, regardless of prior stroke/TIA/TE status.

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