Safety and efficacy of antithrombotic therapy according to stroke and bleeding risk in patients with atrial fibrillation and acute coronary syndrome or PCI: insights from AUGUSTUS

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Background: The AUGUSTUS trial showed that patients with atrial fibrillation (AF) and acute coronary syndrome (ACS) and/or PCI treated with a P2Y12 inhibitor and apixaban resulted in less bleeding and comparable ischemic events compared with regimens that included a vitamin K antagonist (VKA), aspirin, or both. We assessed the effect of apixaban versus VKA and aspirin versus placebo according to patients' baseline risk of stroke and bleeding.

Methods: AUGUSTUS randomized 4614 patients in a two-by-two factorial design to open label apixaban or VKA and blinded aspirin or placebo. The primary endpoint was major or clinically relevant nonmajor (CRNM) bleeding over 6 months of follow-up. The effects were assessed stratified by baseline CHA2DS2-VASc and HAS-BLED score using Cox proportional hazards models.

Results: 4386 patients were included for this analysis. The median age was 71 (64–77) years, 29.4% were female, 81.7% had a CHA2DS2-VASc score≥3, and 66.8% a HAS-BLED score≥3. As shown in the table, rates of bleeding were lower with apixaban (vs VKA) irrespective of baseline bleeding risk (p-value interaction: 0.23). Aspirin (vs placebo) was associated with increased bleeding irrespective of baseline risk (p-value interaction: 0.88). Apixaban use was associated with a lower risk of death or hospitalization without a significant interaction with stroke risk (p-value of interaction=0.53). No differences were found for ischemic outcomes.

Conclusion: An antithrombotic regimen including a P2Y12 inhibitor and apixaban is associated with less bleeding and hospitalization compared to a regimen with VKA, aspirin, or both with results consistent across CHA2DS2-VASc, and HAS-BLED scores. Our findings support the use of apixaban and a P2Y12 inhibitor without aspirin during the first 6 months for most patients with AF and ACS and/or PCI, regardless of stroke and bleeding risk.

	Risk category	Apixaban (event)	VKA (event)	Hazard ratio (95% CI)	Interaction p-value
Major or CRNM bleeding (HASBLED)	≤2	8.8%	14.4%	0.57 (0.41–0.78)	0.23
	≥3	12.1%	16.3%	0.72 (0.59–0.88)	
Death or hospitalization (CHA2DS2-VASc)	≤2	19.7%	21.5%	0.92 (0.67–1.25)	0.53
	≥3	25.0%	29.2%	0.82 (0.73–0.94)	
		Aspirin (event)	Placebo (event)		
Major or CRNM bleeding (HASBLED)	≤2	15.1%	8.4%	1.86 (1.36–2.56)	0.88
	≥3	17.8%	10.4%	1.81 (1.47–2.23)	
Death or hospitalization (CHA2DS2-VASc)	≤2	21.7%	19.5%	1.09 (0.80–1.49)	0.90
	≥3	27.8%	26.4%	1.07 (0.94–1.21)	