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Thromboembolic Events in the Angiotensin II for the Treatment of High-Output Shock Phase 3 Trial

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Background

- Angiotensin II is an effective vasopressor, particularly in patients with disrupted renin-angiotensin system function
- Mechanistic and preclinical experiments suggest angiotensin II induces plasminogen activator-inhibitor 1 and may promote platelet activation
- The clinical impact of thrombotic effects of angiotensin II in patients with shock remains uncertain



Methods

- **Objective:** To assess the timing and incidence of thromboembolic events with angiotensin II in shock
- **Design:** Post-hoc analysis of ATHOS-3 trial
- **Analysis:** Cause-specific Cox hazards regression for probability of surviving without a thromboembolic event within 28-days

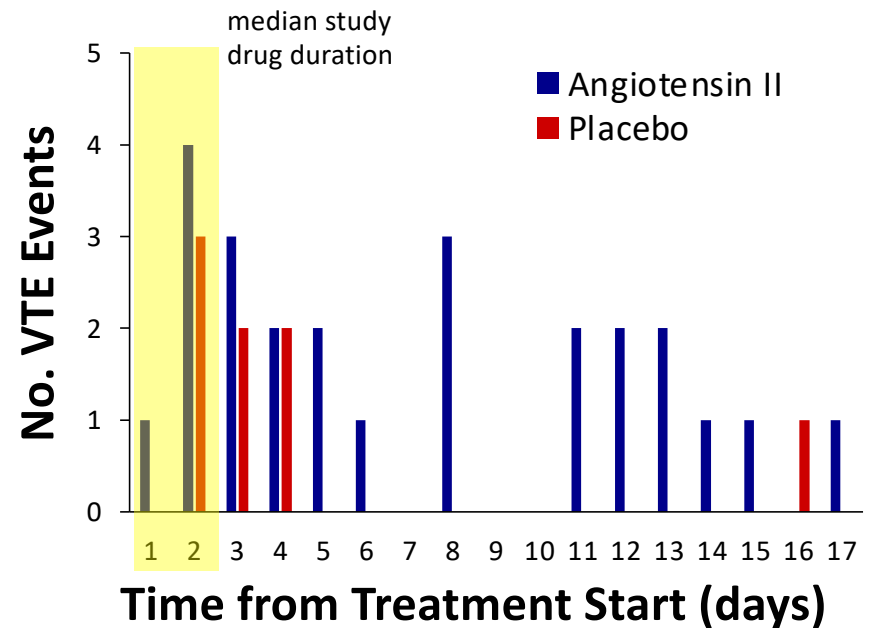
Results

	Ang II (n = 163)		Placebo (n = 158)	
	No TE (n = 142)	TE (n = 21)	No TE (n = 150)	TE (n = 8)
Age, years	63 (22-89)	63 (27-89)	65 (22-89)	66 (57-89)
Male sex	78 (55%)	14 (67%)	97 (65%)	6 (75%)
APACHE II score	27 (9-52)	31 (18-54)	28 (12-51)	32 (20-38)
NED, mcg/kg/min	0.33 (0.08-1.72)	0.31 (0.12-2.58)	0.34 (0.05-3.80)	0.39 (0.24-1.25)
Primary MAP outcome	96 (68%)	18 (86%)	32 (21%)	5 (63%)

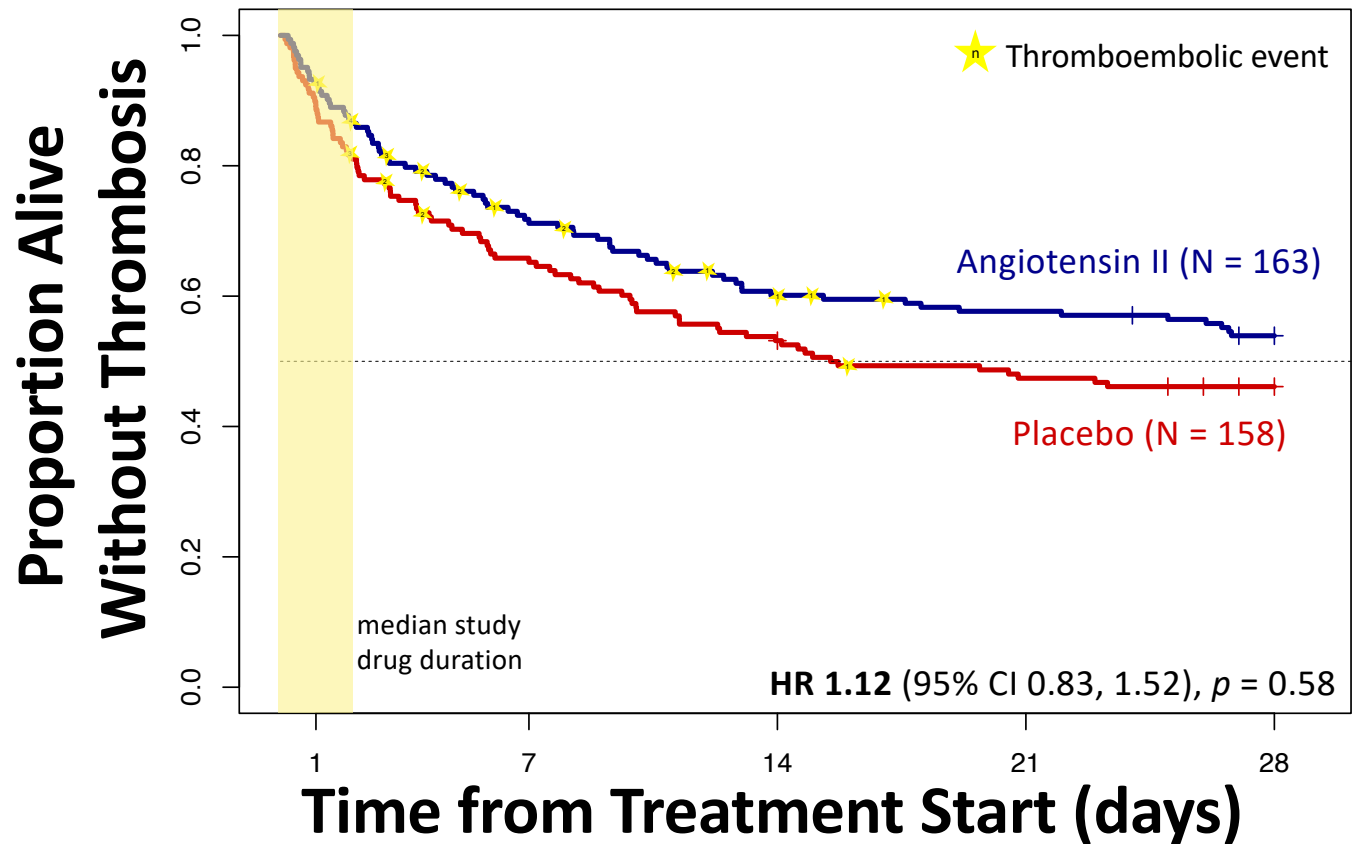
	Ang II (n = 163)	Placebo (n = 158)	p-value
28-day follow-up done	88 (54%)	72 (46%)	0.13
Total days in ICU	1918	1676	--
Total days in hospital	2570	2166	--
Total days alive	2974	2533	--
Observable days alive	28 (6-28)	17 (5-28)	0.08

Characteristics of Thrombotic Events

	Ang II (n = 21)	Placebo (n = 8)	p-value
Within 3d study drug stop	12 (57)	7 (88)	0.12
Time to first diagnosis, d	5 (3-11)	3 (2-4)	0.14
Event severity			0.34
Grade 1-2	12 (57)	3 (38)	
Grade 3-4	9 (43)	5 (62)	



Survival without thrombosis



Conclusions

- Angiotensin II recipients had numerically more observable days alive than placebo in the ATHOS-3 trial
- Thromboembolic events in angiotensin II recipients tended to occur later, with nearly half more than 3 days after study drug discontinuation
- Probability of surviving without a thromboembolic event was similar between groups



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