



Intracranial Hemorrhage in Patients with Atrial Fibrillation: Insights from COMBINE-AF

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DukeHealth

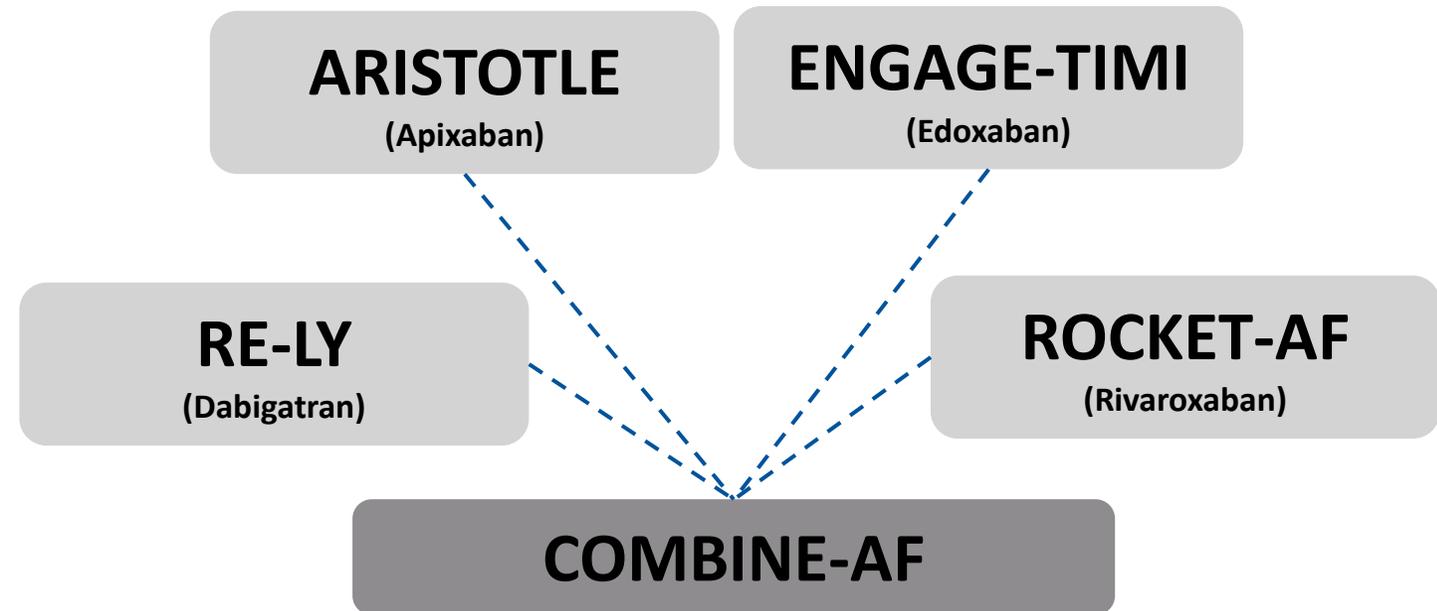


Background

- Observational studies have reported **more** ICH with warfarin than DOAC
- Outcomes data are **limited** by low cumulative events
- COMBINE-AF has unsurpassed amount of CEC-adjudicated, patient-level data from RCTs for the best powered assessment of **rate, risk factors**, and **outcomes of ICH**

Methods

- Patient-level meta-analysis of N=58,634 randomized to standard-dose DOACs or warfarin
- Predictors identified using backward selection algorithm with multivariable Cox prediction model



RE-LY: Connolly et al. NEJM. 2009.
ARISTOTLE: Granger et al. NEJM. 2011.
ENGAGE-TIMI: Giugliano et al. NEJM. 2013.
ROCKET-AF: Patel et al. NEJM. 2011



Study Population (n=58,364)

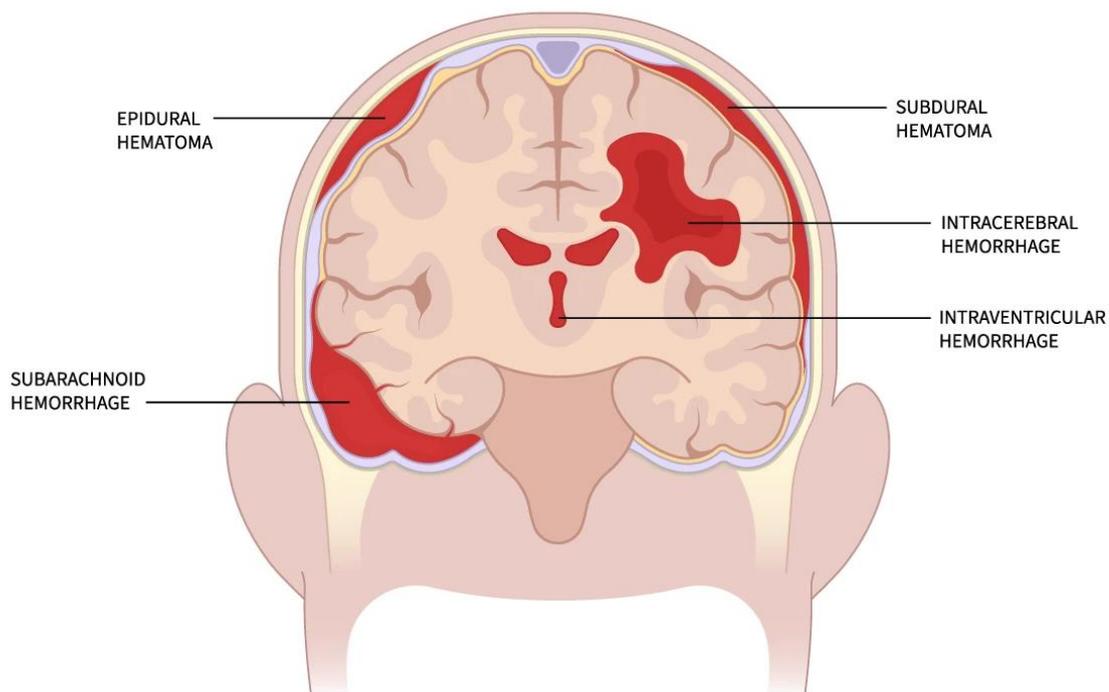
		Intracranial Hemorrhage		
		Yes (n=593)	No (n=58041)	P-value
Female (N,%)		35%	37%	0.2
Age, years		73	70	<0.01
Race (N,%)				<0.01
	White	68%	81%	
	Asian	26%	14%	
	Black	2%	1%	
	Other	4%	4%	
Systolic BP		132	131	0.07
Diastolic BP		79	78	0.4
eGFR		66	76	<0.01
BMI		27	29	<0.01

		Intracranial Hemorrhage		
		Yes (n=593)	No (n=58041)	P-value
Stroke/TIA		40%	29%	<0.01
Antiplatelet		43%	35%	<0.01
CHA ₂ DS ₂ VASc		2.9	2.6	<0.01
Heart Failure		39%	47%	<0.01
History/Risk of Falls		8%	5%	<0.01
Prior GI Bleeding		3%	3%	0.99
Prior Non-GI Bleeding		7%	6%	0.6
HTN		89%	88%	0.6
Smoking		41%	43%	0.3
Diabetes		31%	31%	0.9
CAD		28%	32%	0.07



Location and Mechanism of ICH

INTRACRANIAL HEMORRHAGE



Location of ICH	Number of Events (n)	Case Fatality
INTRACEREBRAL	330	58%
SUBDURAL*	155	35%
UNSPECIFIED	66	42%
SUBARACHNOID	44	46%
HEMORRHAGIC CONVERSION	11	46%
EPIDURAL	1	0%
MISSING	7	-
TOTAL	614	49%

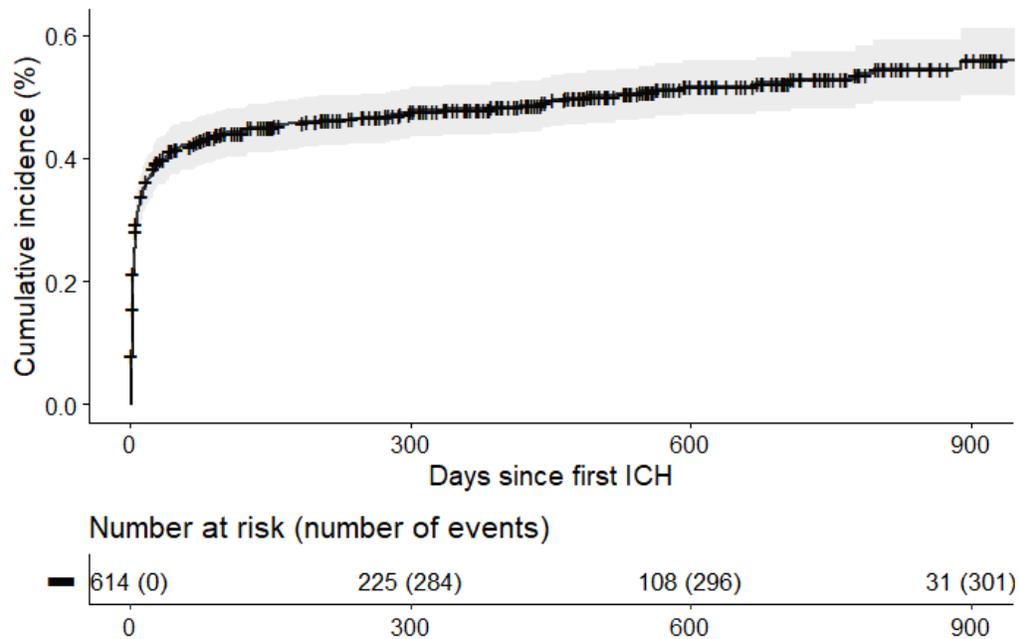
*Patients with both Subdural and Intracerebral were counted only as Subdural

Mechanism of ICH	Number of Events (n)	Case Fatality
SPONTANEOUS	390	54%
TRAUMATIC	124	30%
MISSING	100	53%



Mortality after ICH

All-Cause Mortality after ICH

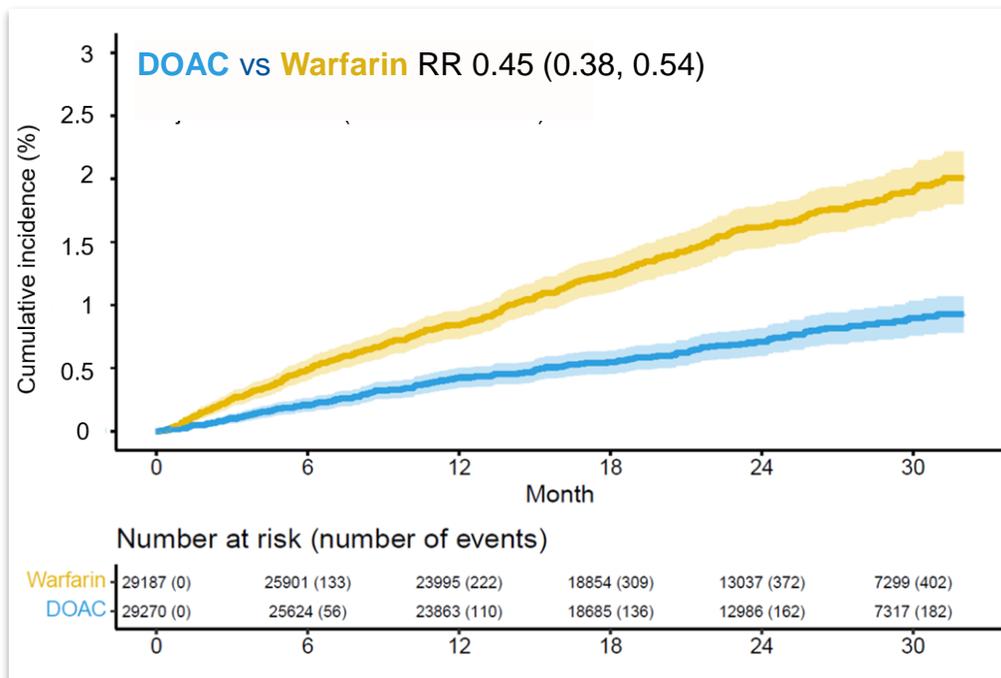


- Mortality after ICH: **49%** over 51 months of follow-up
- Of the post-ICH deaths, a majority occurred within the first **30 days** (80%)
- Of the post-ICH deaths, 18% occurred within **24 hours of presentation**

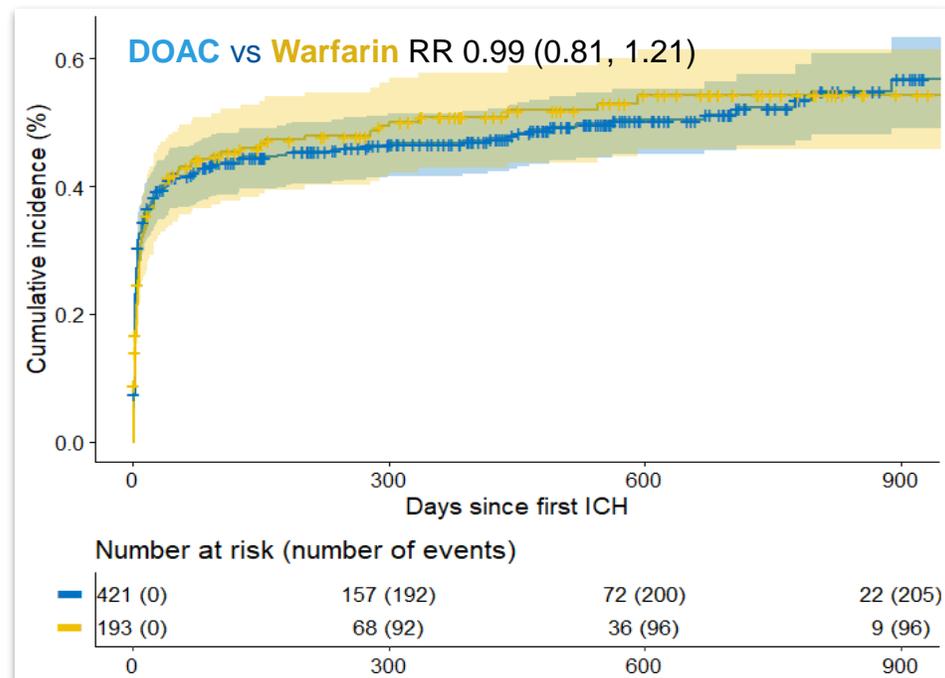


ICH by Anticoagulant

Incidence of ICH by Anticoagulant Type



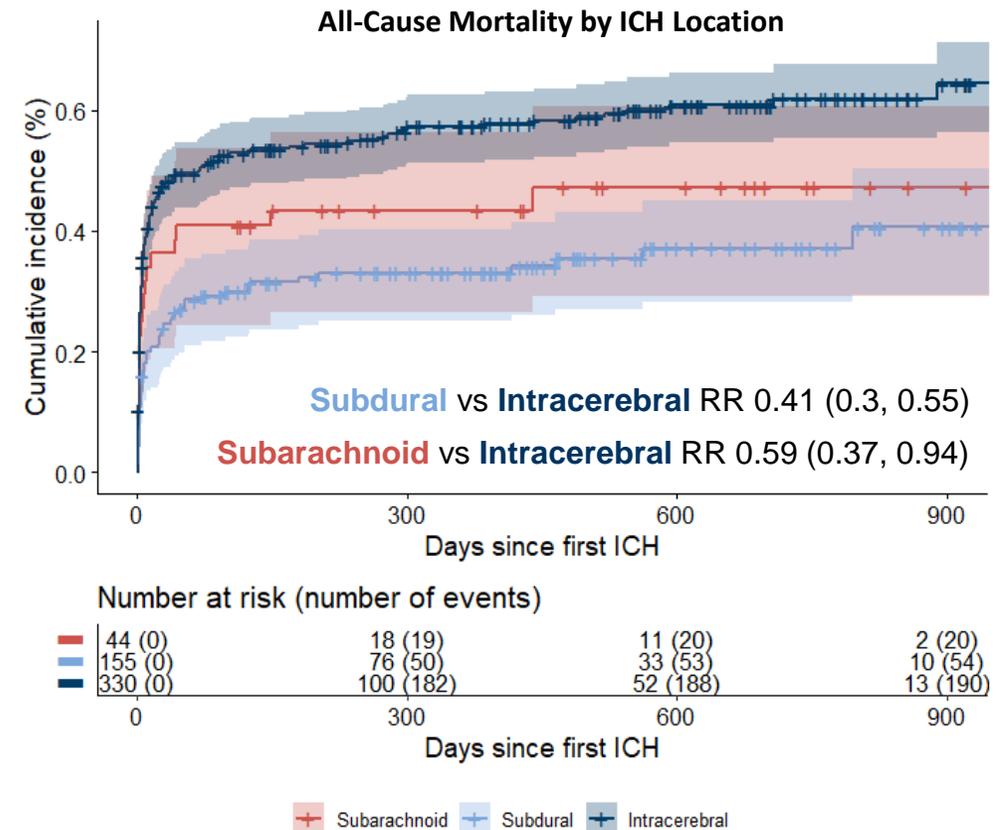
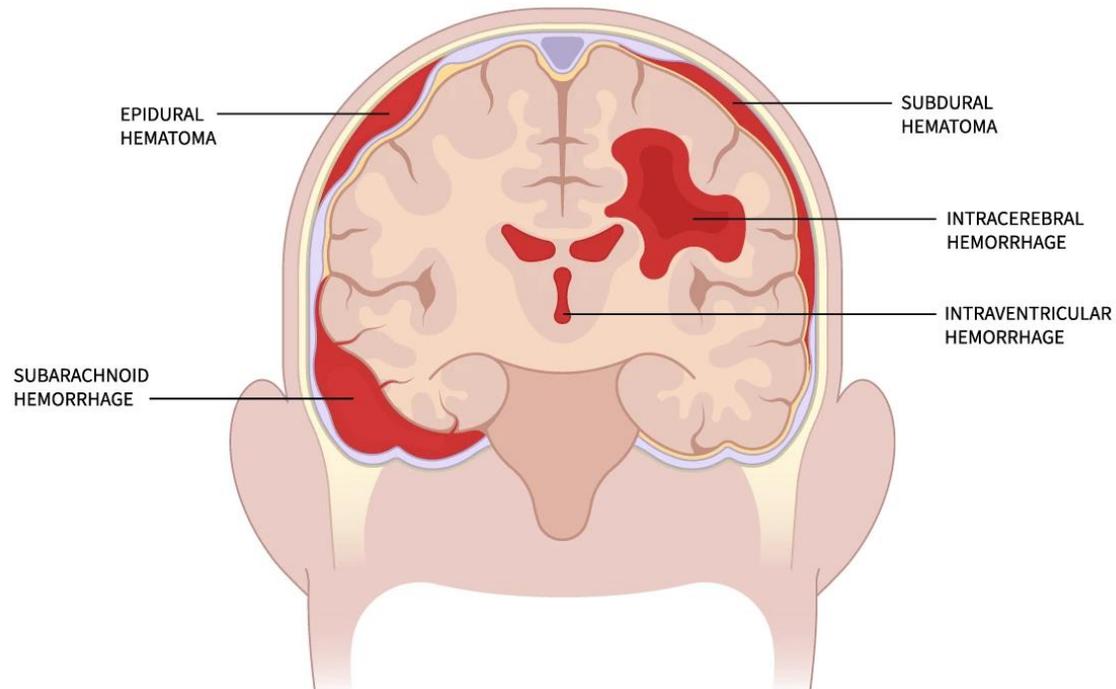
Mortality after ICH by Anticoagulant Type





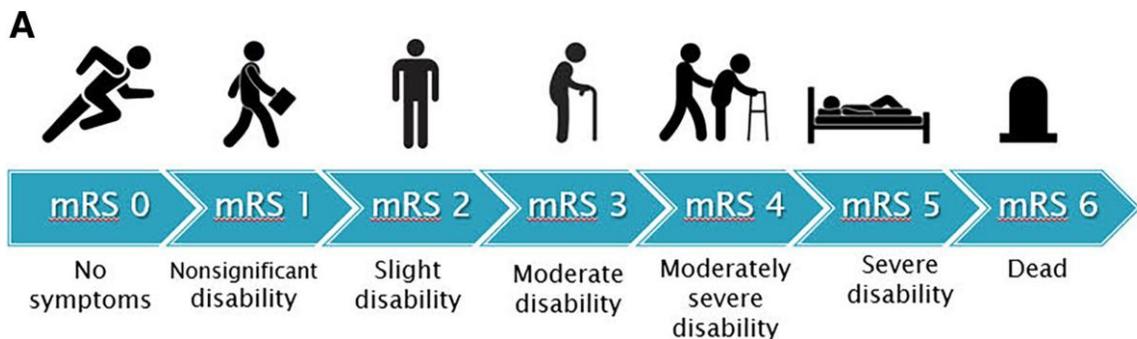
Mortality after ICH by Location

INTRACRANIAL HEMORRHAGE





Debility after ICH (Rankin Score)



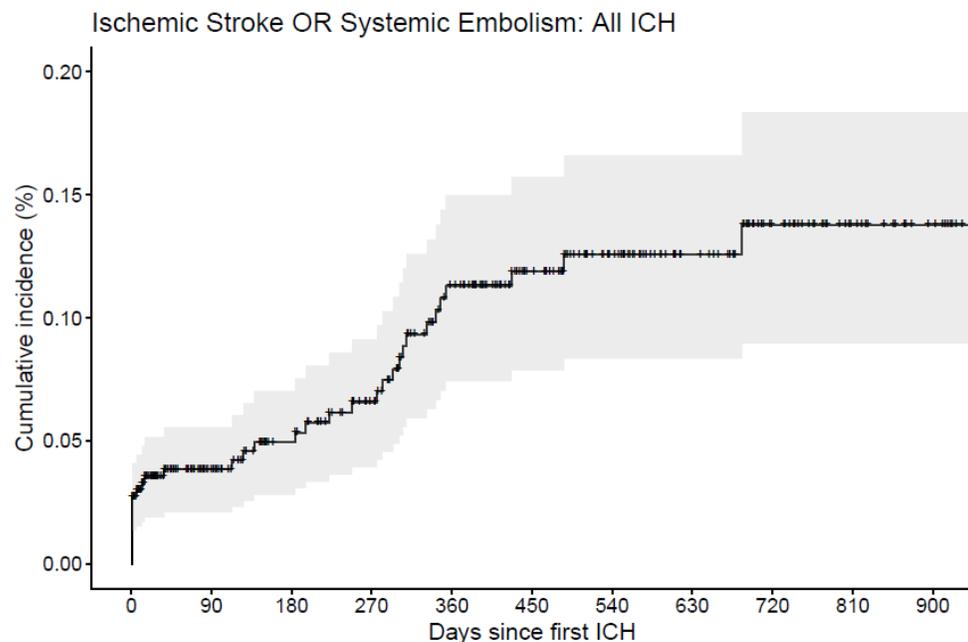
Rankin Score	Grade of Disability
0	No symptoms
1	Able to perform ADLs
2	Perform ADLs, but unable to do previous activities
3	Unable to walk without assistance
4	Needs assistance for bodily needs
5	Constant assistance. Incontinent. 24/7 Nursing care.
6	Dead

Location of ICH	Number of Events (n)	Mean Rankin Score	Proportion of Patients with Rankin Score ≥ 3
INTRACEREBRAL	330	4.6	81%
SUBDURAL*	155	2.8	44%
UNSPECIFIED	66	4.5	100%
SUBARACHNOID	44	3.5	60%
HEMORRHAGIC CONVERSION	11	4	75%
EPIDURAL	1	--	0%
MISSING	7	6	--
TOTAL	614	4.3	76%

Anticoagulant Type	Number of events	Mean Rankin Score	Proportion of Patients with Rankin Score ≥ 3
Warfarin	133	4.3 (2.1)	74%
DOAC	66	4.4 (2.2)	79%
Warfarin vs DOAC p-value	--	0.61	0.62



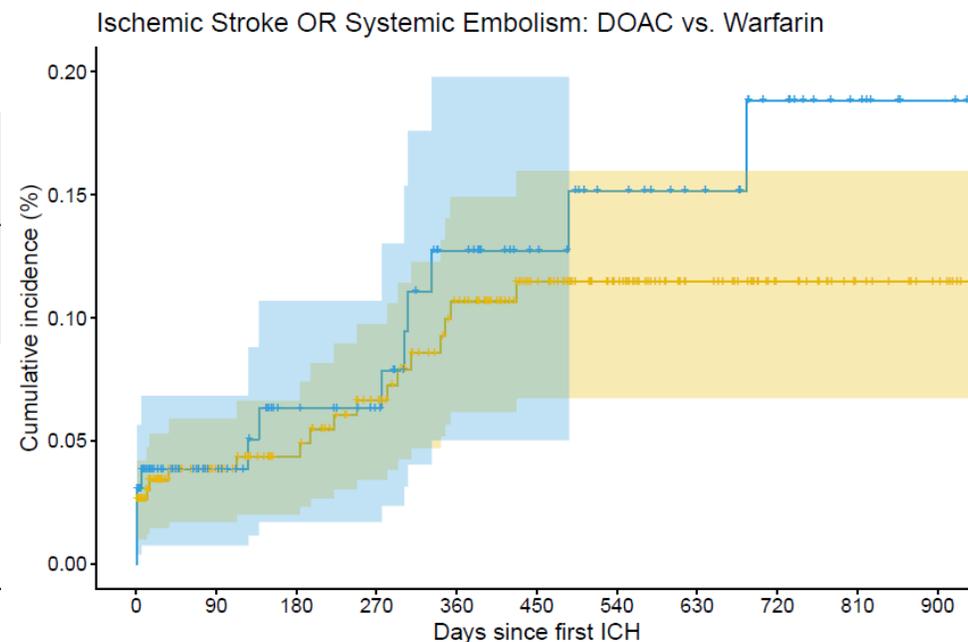
Adverse Events after ICH



Number at risk (number of events)

547 (0)	283 (19)	241 (22)	214 (26)	177 (36)	139 (37)	110 (38)	81 (38)	56 (39)	38 (39)	25 (39)
0	90	180	270	360	450	540	630	720	810	900

— All Patients with ICH



Number at risk (number of events)

Warfarin	383 (0)	198 (13)	172 (14)	152 (18)	127 (24)	101 (25)	79 (25)	55 (25)	37 (25)	26 (25)	18 (25)
DOAC	164 (0)	85 (6)	69 (8)	62 (8)	50 (12)	38 (12)	31 (13)	26 (13)	19 (14)	12 (14)	7 (14)
	0	90	180	270	360	450	540	630	720	810	900

— Warfarin — DOAC



Summary

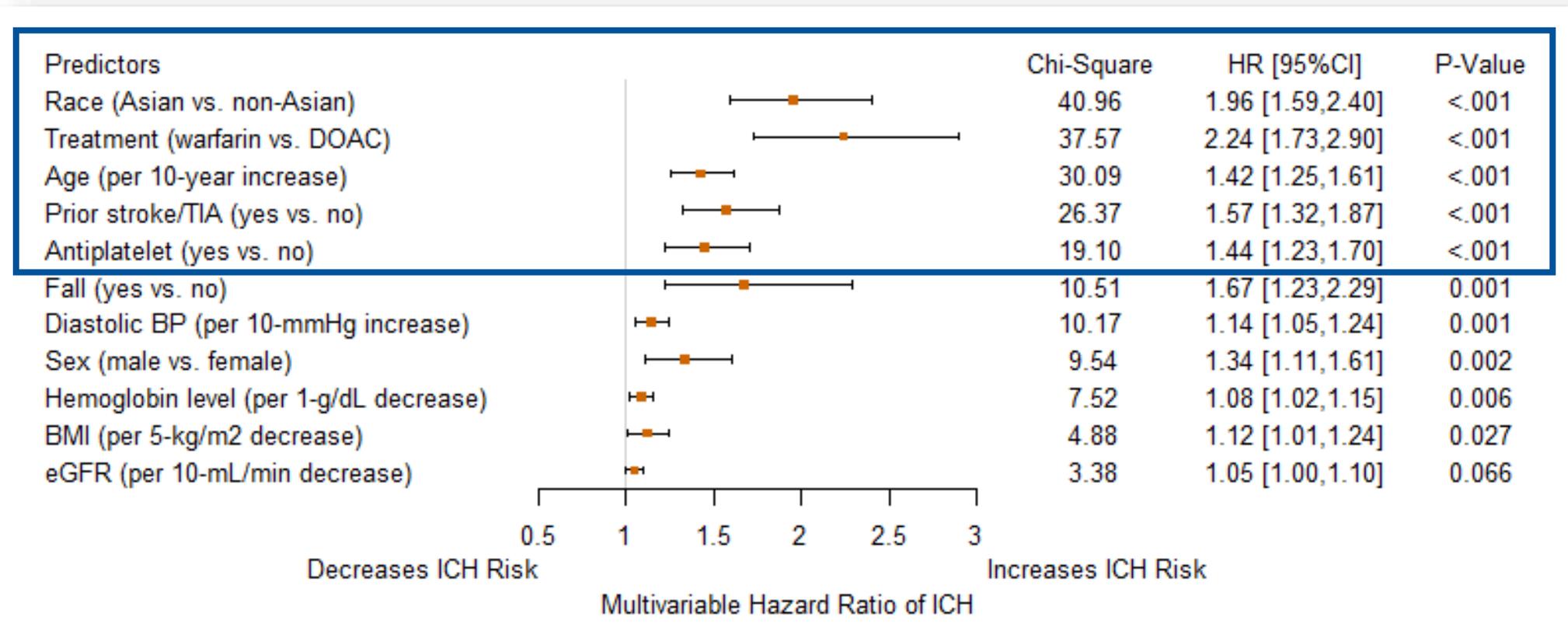
- Post-ICH mortality is **high (49%)**, especially within **first 30 days**
- Risk of ICH is twice as high with Warfarin vs DOAC, mortality is similar **regardless** of anticoagulant
- **Intracerebral ICH** is the most common and most debilitating of all ICH
- **Spontaneous ICH** is more common and associated with higher fatality than traumatic ICH

Extra slides





Predictors of ICH





Adverse Events after ICH

	Event Rate after First All-ICH (95% CI)	Event Rate after First Warfarin-ICH (95% CI)	Event Rate after First DOAC-ICH (95% CI)	Event Rate Ratio of Warfarin-ICH vs DOAC-ICH
Ischemic stroke	9.9 (7.2, 13.6)	9.3 (6.3, 13.7)	11.5 (6.7, 19.8)	0.8 (0.4, 1.6)
Systemic Embolism	0.2 (0.03, 1.7)	0	0.8 (0.1, 5.6)	--
Death	68.5 (61.2, 76.7)	67.4 (58.8, 77.3)	70.9 (58.1, 86.6)	0.9 (0.8, 1.2)
Composite	82.9 (74.4, 92.6)	79.9 (69.9, 91.2)	90.5 (74.6, 109.9)	0.9 (0.7, 1.1)