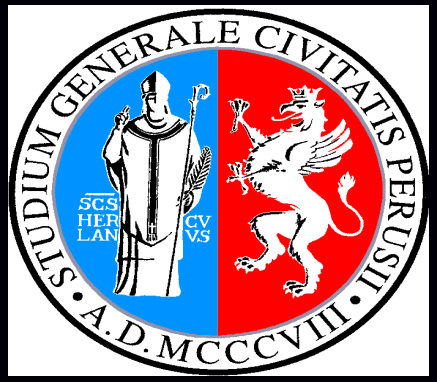
Stroke & AFib:
how many patients can we effectively treat?

Giancarlo Agnelli
Internal & Cardiovascular Medicine - Stroke Unit
University of Perugia, Italy



Stroke & AFib: can we protect more patients?

Giancarlo Agnelli
Internal & Cardiovascular Medicine - Stroke Unit
University of Perugia, Italy

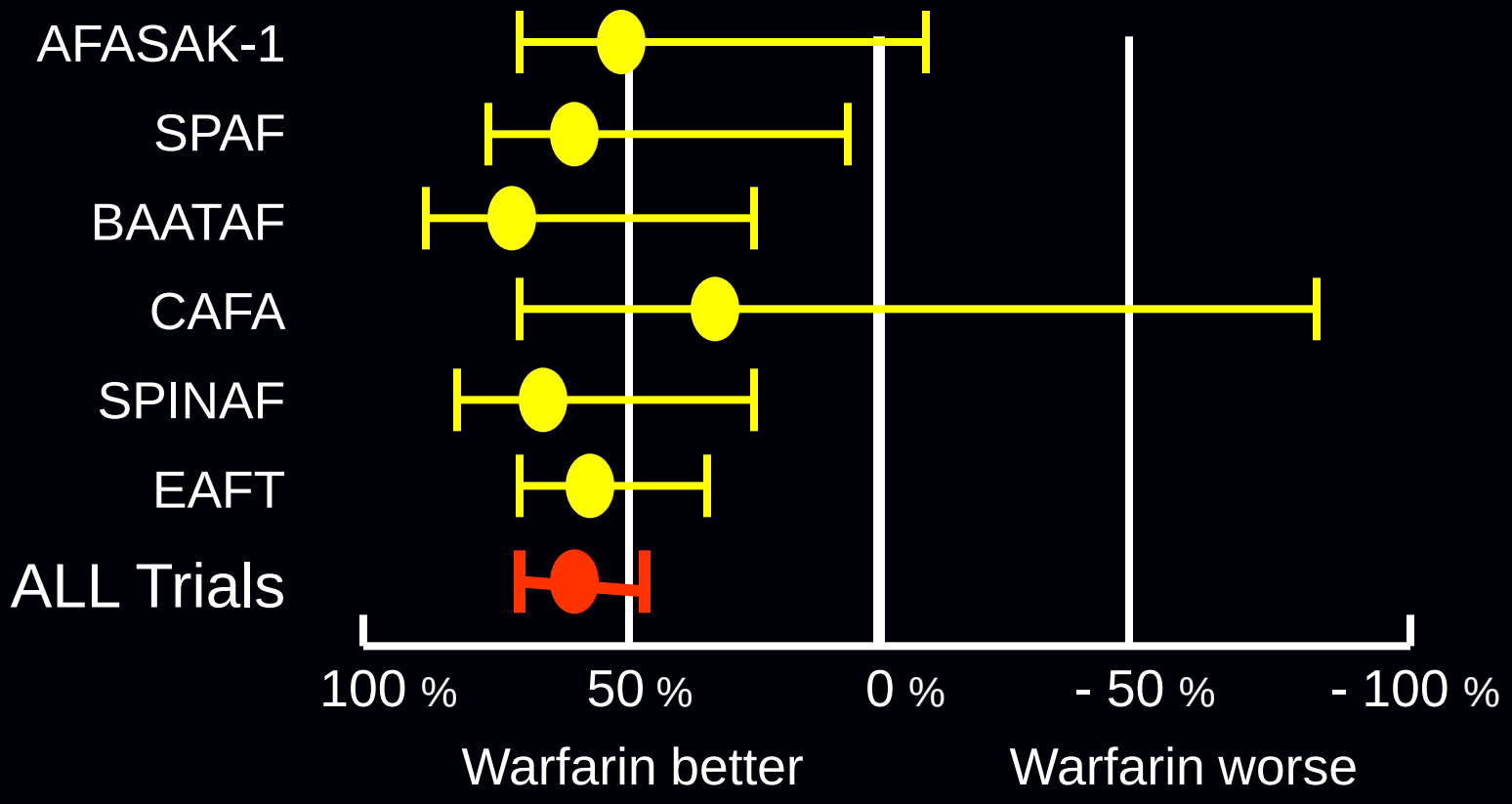
My talk today

- The issue
- The strategies to solve the issue

My talk today

- The issue
- The strategies to solve the issue

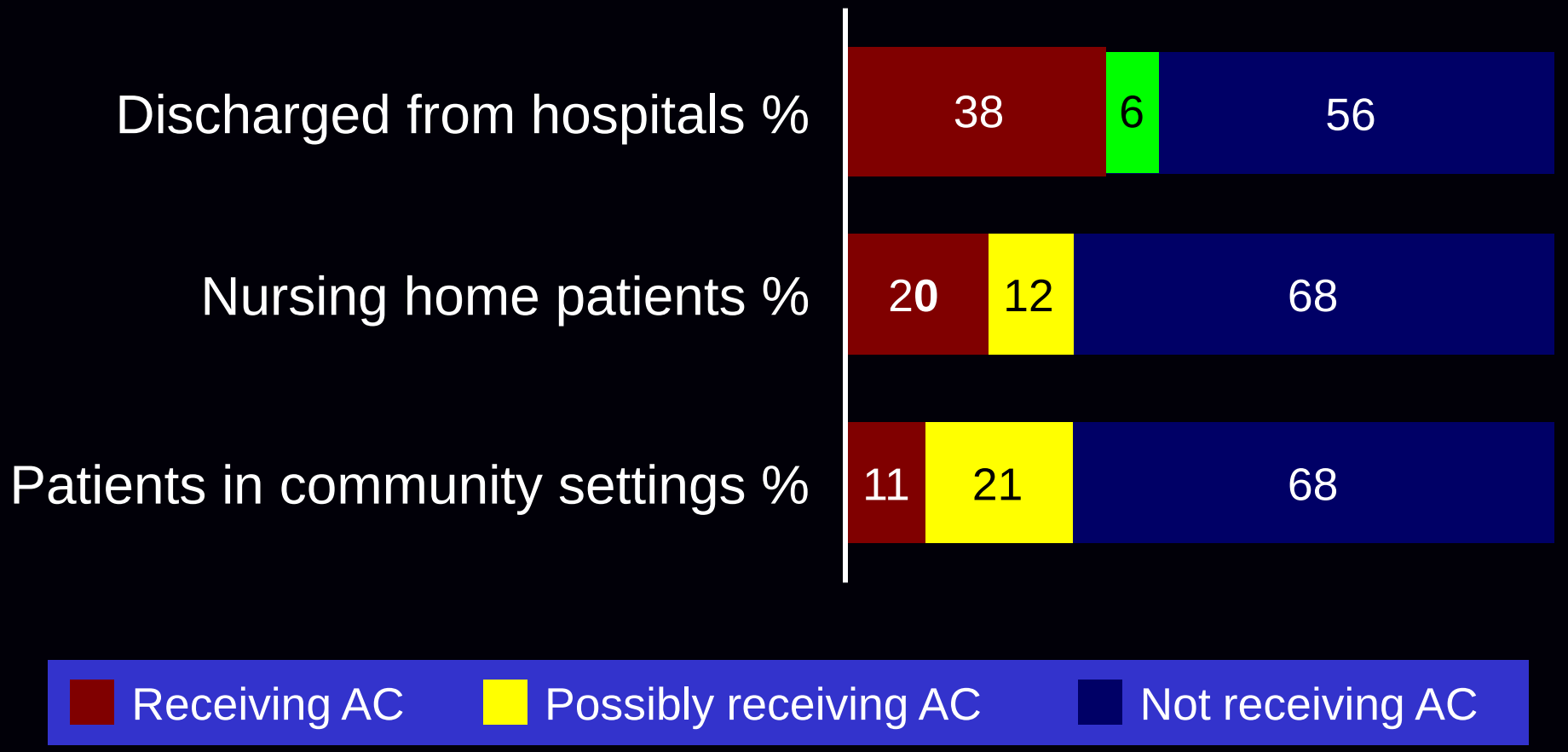
Warfarin in stroke prevention in AF



Relative RR vs. placebo	64% (CI 49–74)
Absolute RR primary	2.7%/yr
Absolute RR secondary	8.4%/yr
NNT primary prevention	37
NNT secondary prevention	12

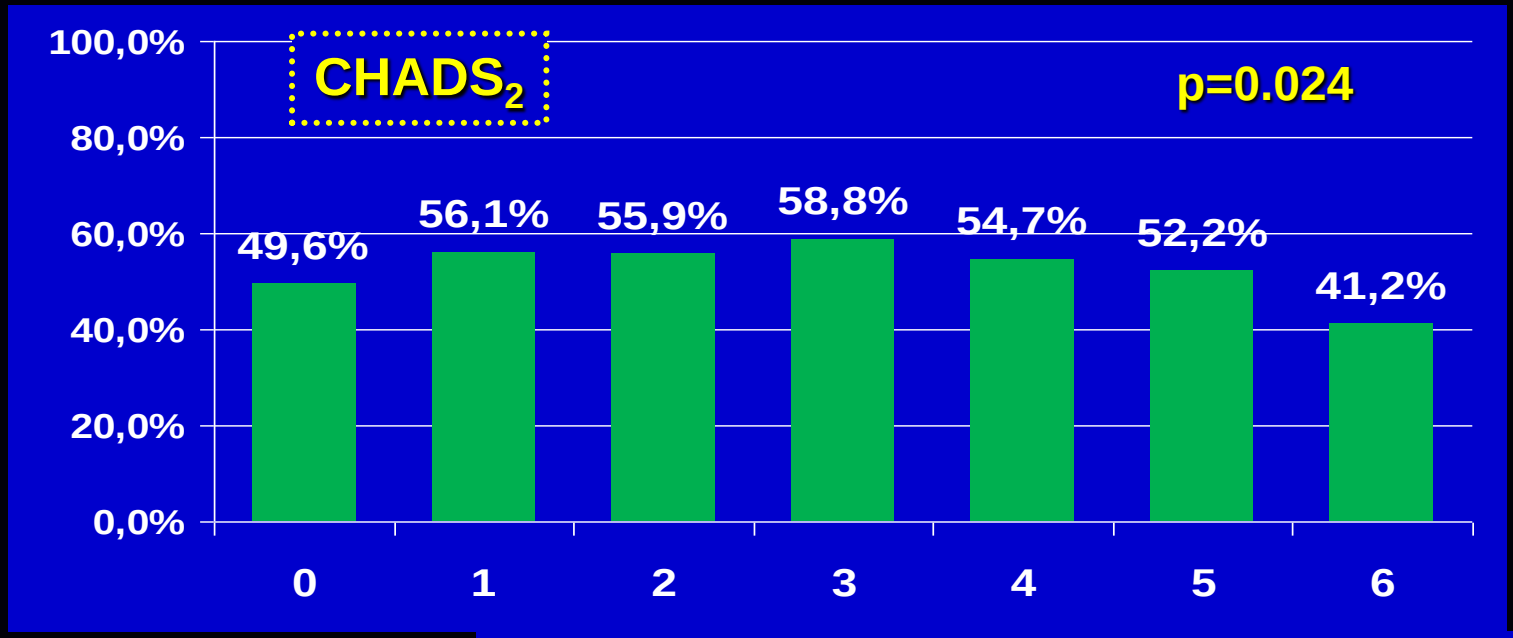
Hart et al., Ann Intern Med 1999

Suboptimal use of AVK in AF

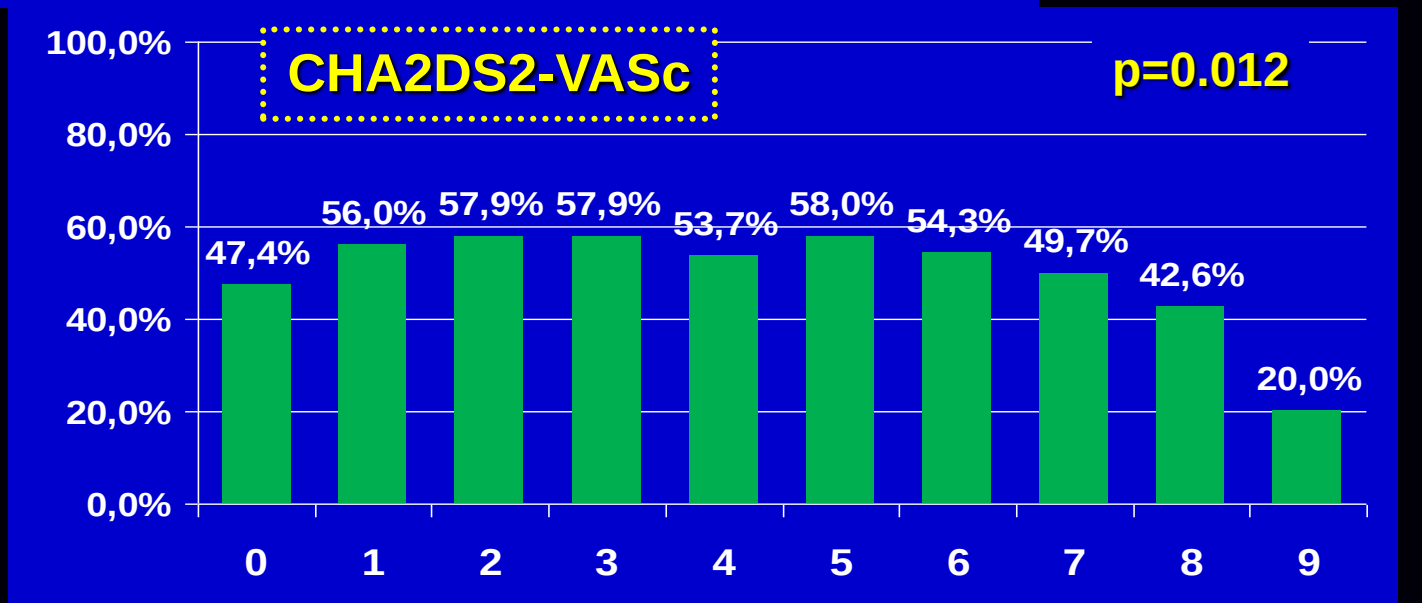


Stafford et al., Circulation 1998

Suboptimal use of AVK in AF



non valvular AF
4.845 pts



AF and cardioembolic stroke

1549 PATIENT WITH ISCHEMIC STROKE

Age (yrs)	75.8±12.8
Known AF (%)	15.8
New diagnosis of AF (%)	4.9

52.1% no treatment
34.9% antiplatelet agents
13% anticoagulants

Only 10.1% adequately treated

Paciaroni & Agnelli, JTH 2005

Warfarin efficacy failure

- 4,785 consecutive patients with ischemic strokes
- 148 (3.1%) had AF and were taking warfarin with an admission INR above 1.8

Multivariable analysis:

- Diabetes (OR 3.8; 95% CI 1.09-13.82)
- Hyperlipidemia (OR 4.5; 95% CI 1.11-18.23)
- Carotid/vertebral atherosclerosis (OR 3.0; 95% CI 1.13-8.41)

- Use of statins was inversely correlated with an ischemic event (OR 0.1; 95% CI 0.06-0.47)

Paciaroni et al., Atherosclerosis 2010

My talk today

- The issue
- The strategies to solve the issue

The strategies to solve the issue

- To identify more patients with silent AFib
- To implement treatment with more practical agents
- To implement treatment with safer agents
- To improve treatment in the “orphan patients”

The strategies to solve the issue

- To identify more patients with silent AFib
- To implement treatment with more practical agents
- To implement treatment with safer agents
- To improve treatment in the “orphan patients”

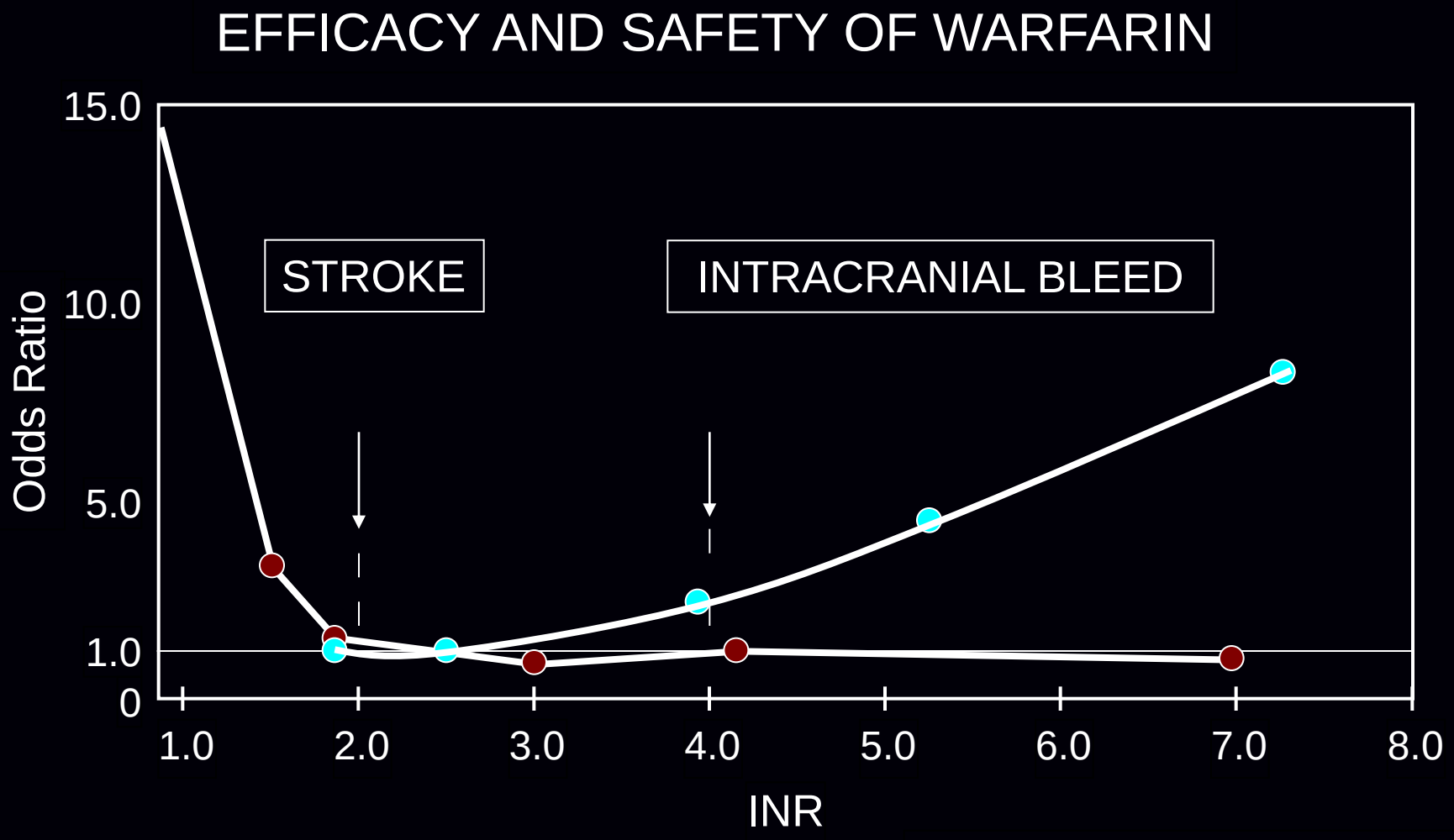
PAFI

	Patients N	Prevalence (%)	AF		ESVEA	
			present	Absent	Present	Absent
Holter ECG	202		14	188	31	171
Sex, M	117 87 F		7 7	110 80	19 12	98 75
Hypertension, n (%)	175	82.2 %	14	-	26	149
Diabetes mellitus, n (%)	27	13.2%	2	12	2	29
Heart failure (EF), n (%)	4	1.96%	-	4	1	30
Stroke/TIA, n (%)	5/5	2.45/2.45	0/2	5/3	4/1	27/30
High cholesterol, n (%)	77	37.7	5	9	11	20
Hypertriglyceridemia, n (%)	37	18.1	2	12	2	29

The strategies to solve the issue

- To identify more patients with silent AFib
- To implement treatment with more practical agents
- To implement treatment with safer agents
- To improve treatment in the “orphan patients”

Proper therapeutic range for INR



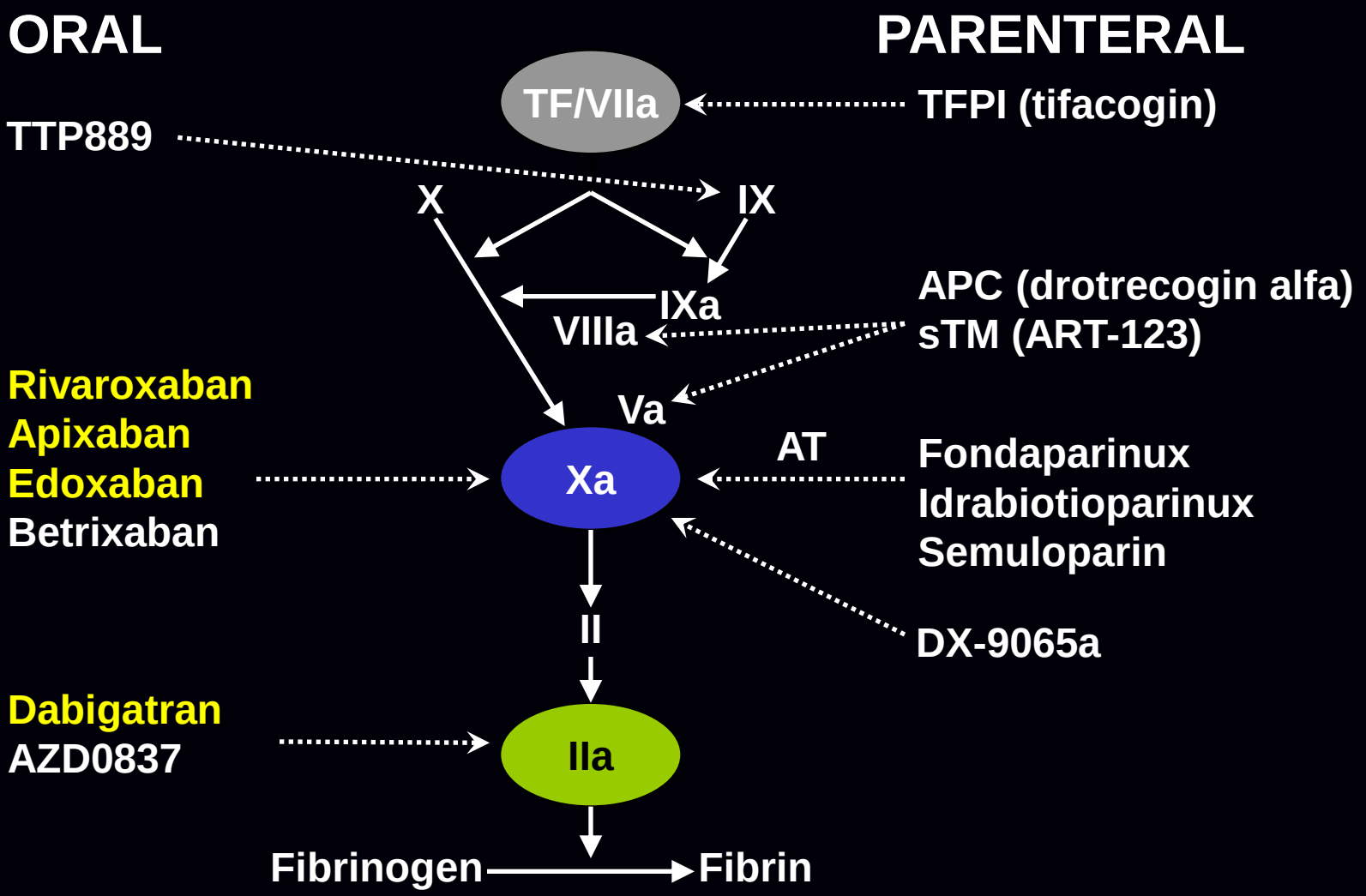
Hylek et al. 1994 and 1996

Time in therapeutic range (TTR) & outcome

Results from SPORTIF III and V

	TTR <60%	TTR 60-75%	TTR >75%
Mortality, %	4.20	1.84	1.69
Major Bleed, %	3.85	1.96	1.58

Phase II-III anticoagulants (year 2012)



NOACs: prevention of stroke in AFib

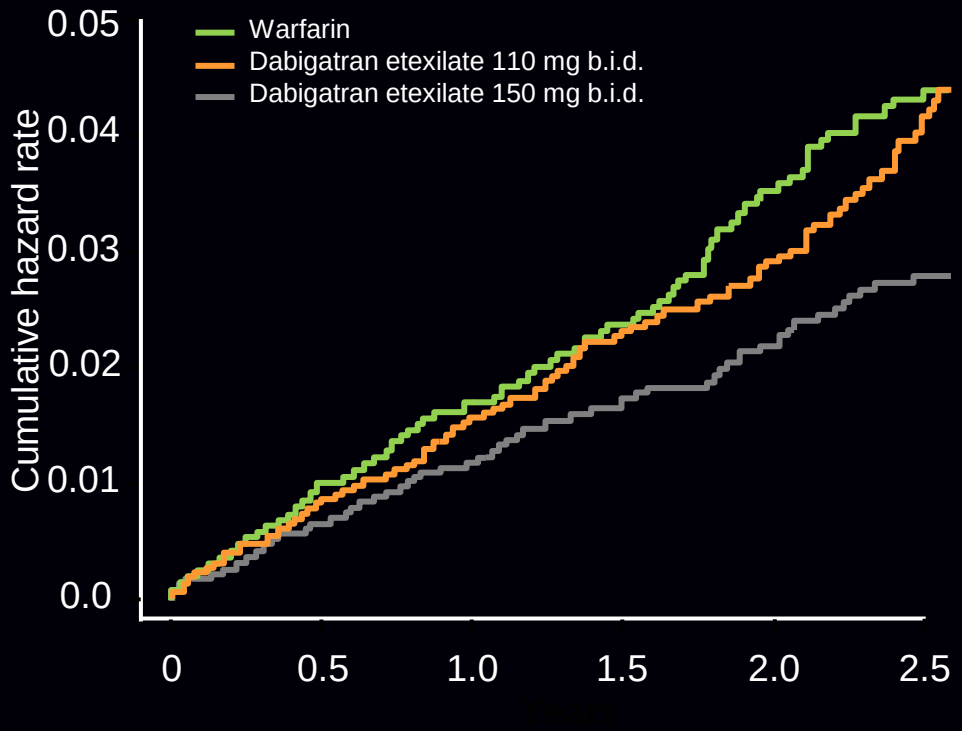
- Rely
- Rocket-AF
- Aristotle

- Averroe

RELY (dabigatran)

–

Stroke/systemic embolism



Bleeding events

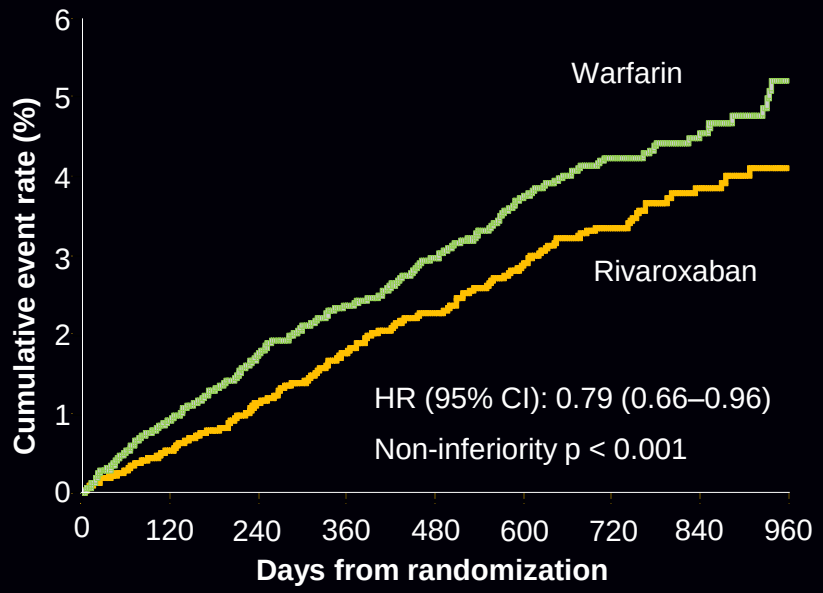
	Dabi. 110 mg (%/y)	Dabi. 150 mg (%/y)	Warf. (%/y)	p, dabi. 110 m mg vs. warf.	p, dabi. 150 mg vs warf.
Patients (n)	6,015	6,076	6,022		
Severe bleeds	2.71	3.11	3.36	0.003	0.31
- life-threatening	1.22	1.45	1.80	< 0.001	0.037
- non-life threatening	1.66	1.88	1.76	0.56	0.47
- gastro-intestinal	1.12	1.51	1.02	0.43	< 0.001

Connolly et al., N Engl J Med. 2009

ROCKET- AF (rivaroxaban)

Stroke and non-CNS embolism*

	Rivaroxaban	Warfarin
Event rate (%/year)	1.71	2.16



Bleeding events

	Rivaroxaban Rate (%/year)	Warfarin Rate (%/year)	p value
Major and clinically relevant non-major	14.91	14.52	0.442
major	3.60	3.45	0.576
clinically relevant non-major	11.80	11.37	0.345

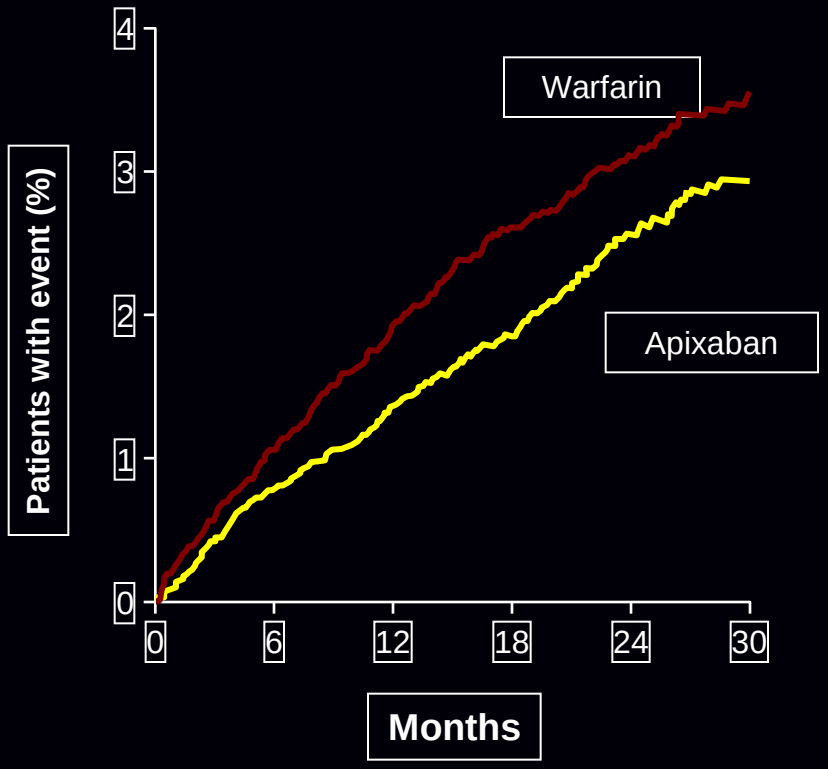
* Based on protocol-compliant, on-treatment population.

Patel et al. N Engl J Med., 2011

ARISTOTLE (apixaban)

Stroke/systemic embolism

Hazard ratio, 0.79 (95% CI, 0.66-0.95); p = 0.01



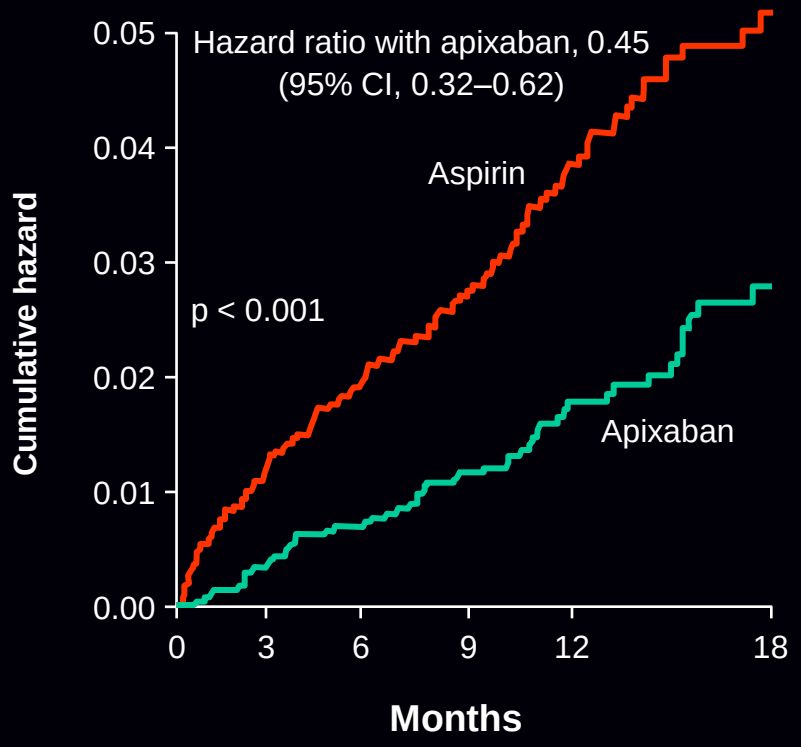
Bleeding events

	Apixaban No. of events (%/yr)	Warfarin No. of events (%/yr)	p value
Patients (n)	9,088	9,052	
Major bleeding (ISTH criteria)	327 (2.13)	462 (3.09)	< 0.001
Major or clinically relevant non-major bleeding	613 (4.07)	877 (6.01)	< 0.001

Granger et al., N Engl J Med. 2011

AVERROES (apixaban)

Stroke/systemic embolism



Bleeding events

	Apixaban No. of events (%/yr)	Aspirin No. of events (%/yr)	p value
Patients (n)	2,808	2,791	
Major bleeding	44 (1.4%)	39 (1.2%)	0.57
Minor bleeding	188	153	0.05

Connolly et al., N Engl J Med. 2011

Good reasons for a non-inferiority study

New agent as effective as but safer (less ICH)

New agent as effective as but cheaper

New agent as effective as but more practical (route of administration, no lab monitoring, in/off procedures)

New agent as effective as but more properly used (more extended use in high risk population)

The strategies to solve the issue

- To identify more patients with silent AFib
- To implement treatment with more practical agents
- To implement treatment with safer agents
- To improve treatment in the “orphan patients”

Proper therapeutic range for INR

Ischemic stroke

Intracerebral bleeding

NOACs for Atrial fibrillation & ICH

		HR	P-value
RELY			
Dabigatran 110 mg	0.12% / yr	0.31	<0.001
Dabigatran 150 mg	0.10% / yr	0.26	<0.001
Warfarin	0.38% / yr		
ROCKET			
Rivaroxaban 20 mg	0.26% / yr	0.59	0.012*
Warfarin	0.44% / yr		
ARISTOTLE			
Apixaban 5 mg	0.24% / yr	0.51	<0.001
Warfarin	0.47% / yr		

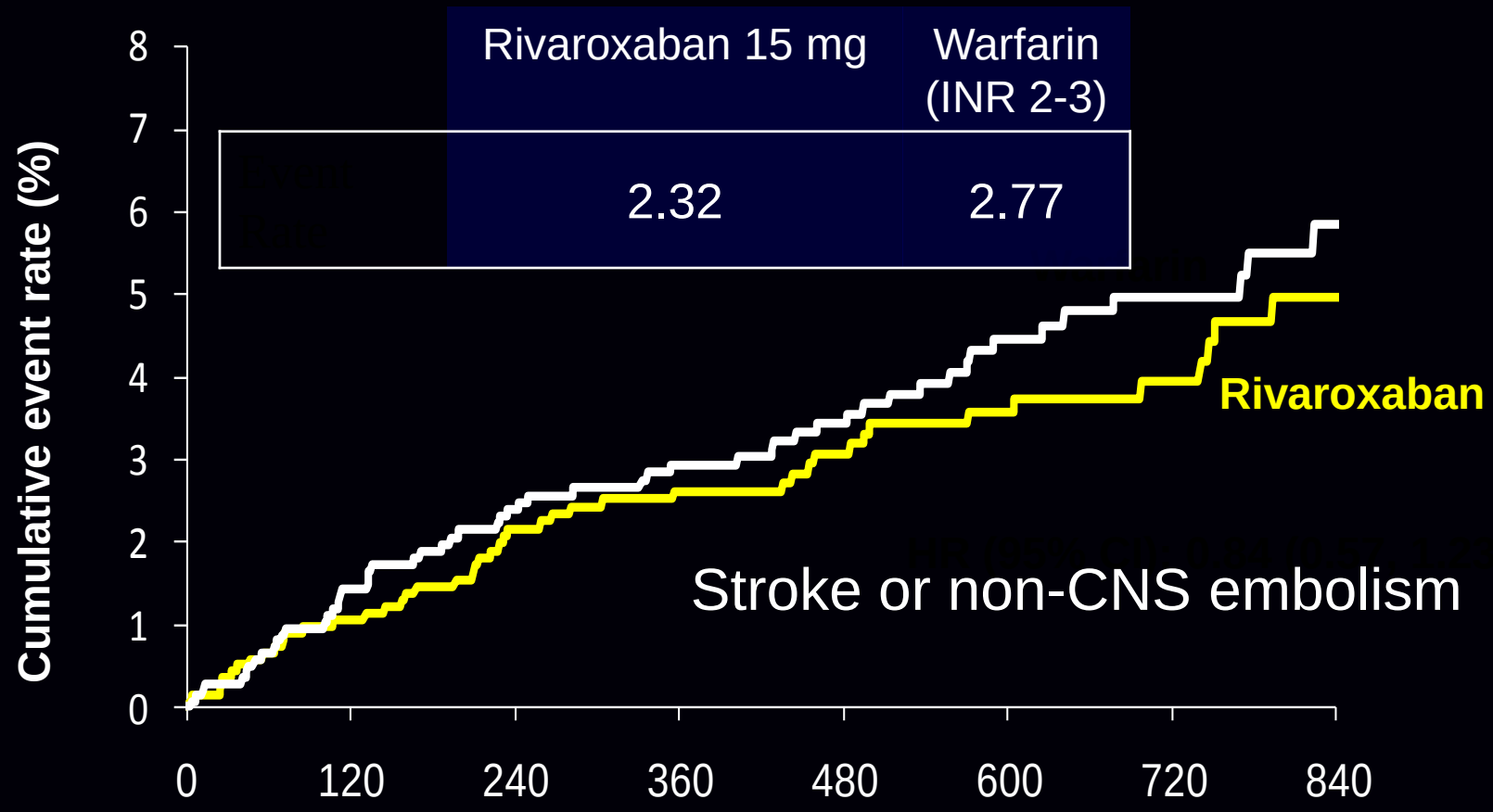
NOACs for Atrial fibrillation & all cause mortality

		HR	p-value
RELY			
Dabigatran 110 mg	3.75% / yr	0.91	0.35
Dabigatran 150 mg	3.64% / yr	0.88	0.051
Warfarin	4.13% / yr		
ROCKET			
Rivaroxaban 20 mg	4.52% / yr	0.92	0.152*
Warfarin	4.91% / yr		
ARISTOTLE			
Apixaban 5 mg	3.52% / yr	0.89	0.01
Warfarin	3.94% / yr	**95% CI 0.89 (0.80, 0.998)** **N=448 events planned, 480 in trial**	

The strategies to solve the issue

- To identify more patients with silent AFib
- To implement treatment with more practical agents
- To implement treatment with safer agents
- To improve treatment in the “orphan patients”

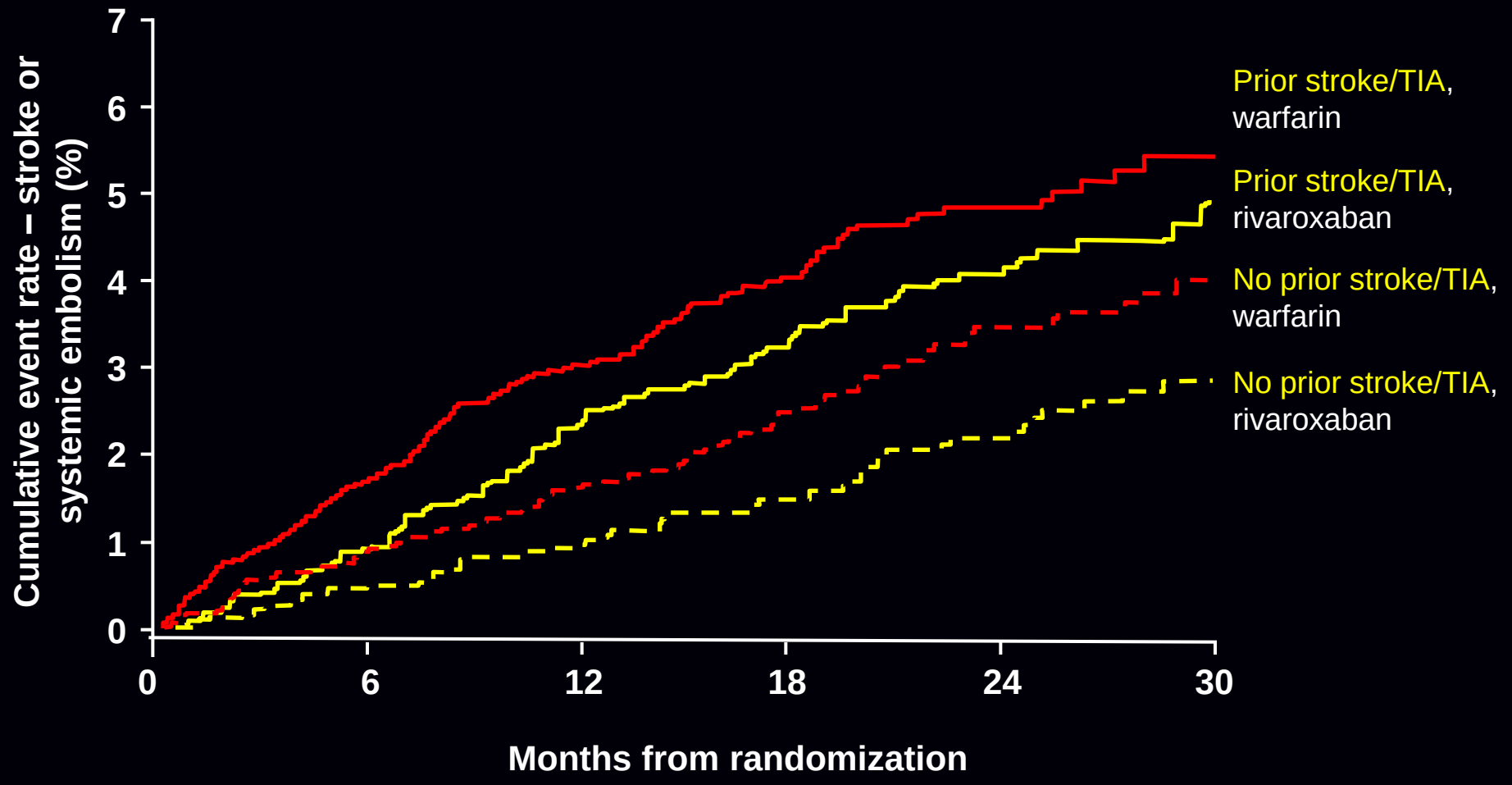
Rocket AF: patients with CrCl 30–49 mL/min



No. at risk:

Rivaroxaban	1434	1226	1103	1027	806	621	442	275
Warfarin	1439	1261	1140	1052	832	656	455	272

Rocket AF: primary efficacy outcome



protocol population, on-treatment

NOACs for AFib: common achievements

All three NOACs are non-inferior to warfarin in reducing the risk of stroke and SSE

All three agents reduce the risk of bleeding (fatal for rivaroxaban, major for apixaban, major at 110 mg for dabigatran) and intracranial hemorrhage

The directionality and magnitude of the mortality reduction is consistent and approximates a RRR of 10% / year

NOACs for AFib: some differences

Dabigatran at a dose of 150 mg was associated with a reduction in ischemic stroke

Rivaroxaban is a once a day drug associated with a lower rate of fatal bleeding

Apixaban was associated with a reduction in all cause mortality

The clinical research itinerary loop