Novel oral anticoagulants in comparison with warfarin

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Direct Oral Anticoagulants & Indications

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- For treatment of deep vein thrombosis (DVT), pulmonary embolism (PE)
- For the reduction in the risk of recurrence of DVT and of PE
- For prophylaxis of DVT or PE in patients undergoing knee or hip replacement surgery or medically ill

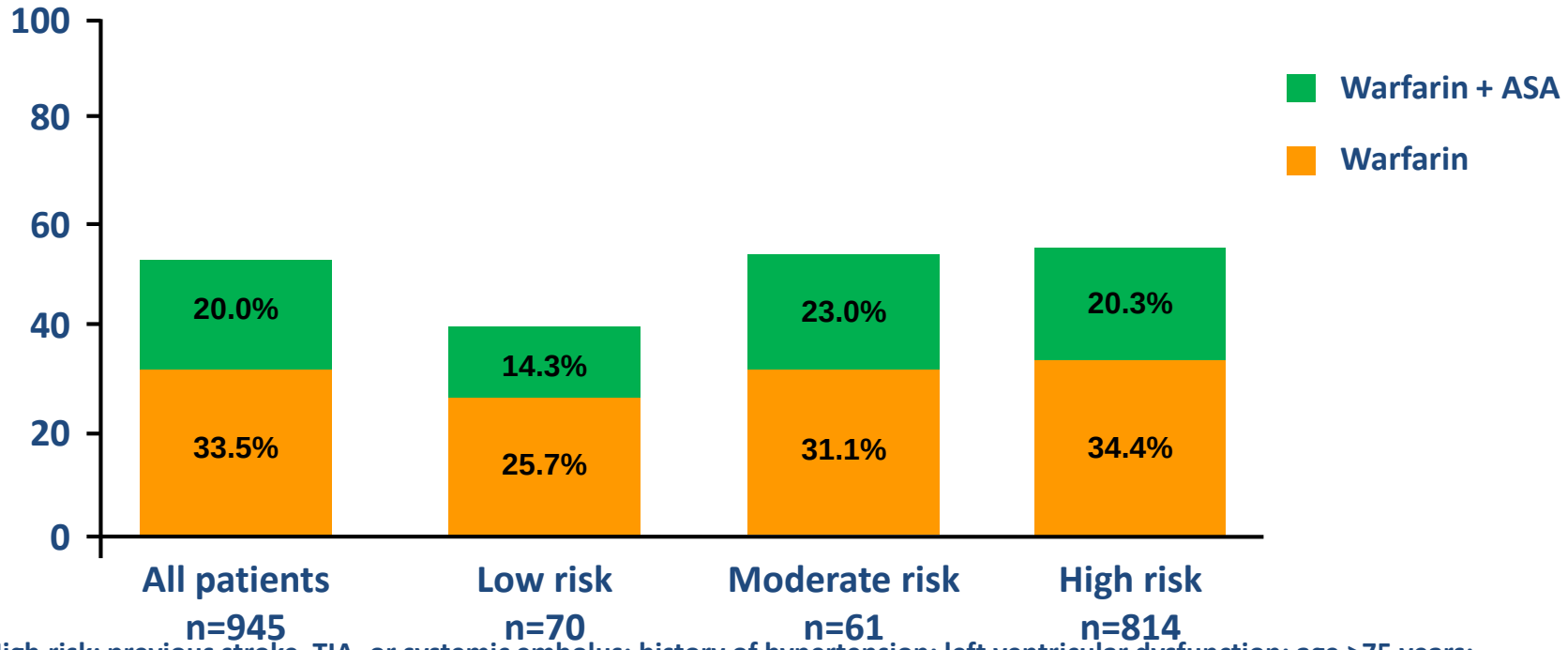
Atrial Fibrillation (AF)

- Common and prevalence increasing[1]
- Epidemiologic association with increased stroke risk firmly established[2]
- Anticoagulant prophylaxis lowers stroke risk[3] However, many patients do not receive effective or optimal management[4]
- Relevant issues for patients, families, providers and health systems
  - Live longer
  - Better quality of life
  - Avoid catastrophic or negative life events

1. Go AS, et al. JAMA 2001;285:2370-2375.
2. Wolf PA, et al. Stroke 1991;22:983–988.
3. Hart RG, et al. Ann Intern Med 1999; 131: 492-501.
4. Go AS, et al. Ann Intern Med 1999 Dec 21;131(12):927-34.

Suboptimal Use of Warfarin:

Management of AF, stratified by risk of stroke



High risk: previous stroke, TIA, or systemic embolus; history of hypertension; left ventricular dysfunction; age >75 years; rheumatic mitral valve disease; or prosthetic heart valve

Moderate risk: 1 risk factor, including age 65–75 years, diabetes mellitus, or coronary artery disease

Low risk: <65 years with no cardiovascular disease

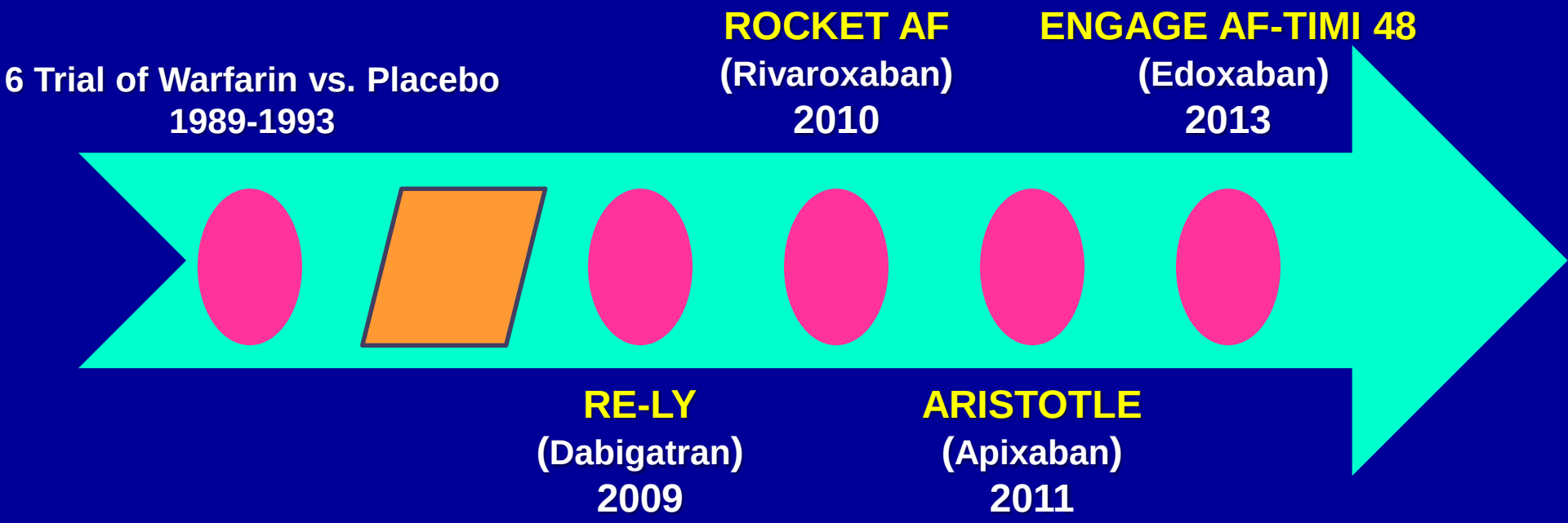
Note: These risk categories are different to 'guideline' risk categories

Waldo *et al, J Am Coll Cardiol.* 2005.

Pivotal Warfarin-Controlled Trials Stroke Prevention in AF

Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients



NOAC Atrial Fibrillation Trials

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
# Randomized	18,113	14,266	18,201	21,105
Dose (mg)	150, 110	20	5	60, 30
Frequency	Twice Daily	Once Daily	Twice Daily	Once Daily
Dose Adjustment	No	20 → 15	5 → 2.5	60 → 30 30 → 15
At Baseline	0	21	5	25
After Randomization	No	No	No	>9%
Target INR (Warfarin)	2.0-3.0	2.0-3.0	2.0-3.0	2.0-3.0
Design	PROBE*	2x blind	2x blind	2x blind

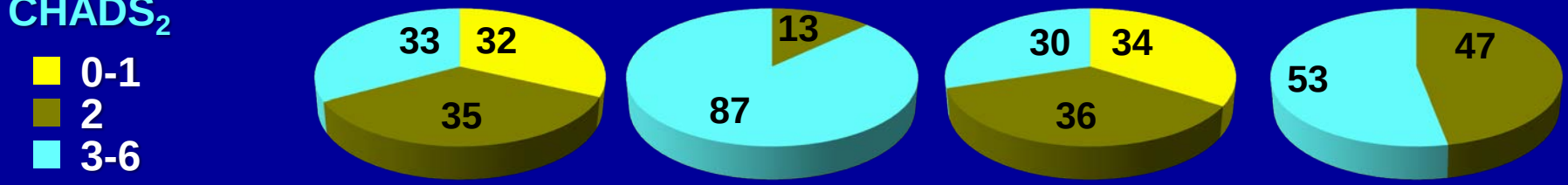
*PROBE = prospective, randomized, open-label, blinded end point evaluation

Connolly SJ, et al. N Engl J Med 2009;361:1139-1151
Patel MR, et al. N Engl J Med 2011;365:883-891
Granger CB, et al. N Engl J Med 2011;365:981-992
Giugliano RP, et al. N Engl J Med 2013; e-pub ahead of print DOI:10.1056/NEJMoa1310907

Baseline Characteristics

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
# Randomized	18,113	14,264	18,201	21,105
Age, years	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	35	38
Paroxysmal AF	32	18	15	25
VKA naive	50	38	43	41
Aspirin Use	40	36	31	29

$CHADS_2$



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Trial Metrics

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
Median Follow-Up, years	2.0	1.9	1.8	2.8
Median TTR	66	58	66	68
Lost to Follow-Up, N	20	32	90	1

***TTR, time in therapeutic range**

Connolly SJ, et al. N Engl J Med 2009;361:1139-1151
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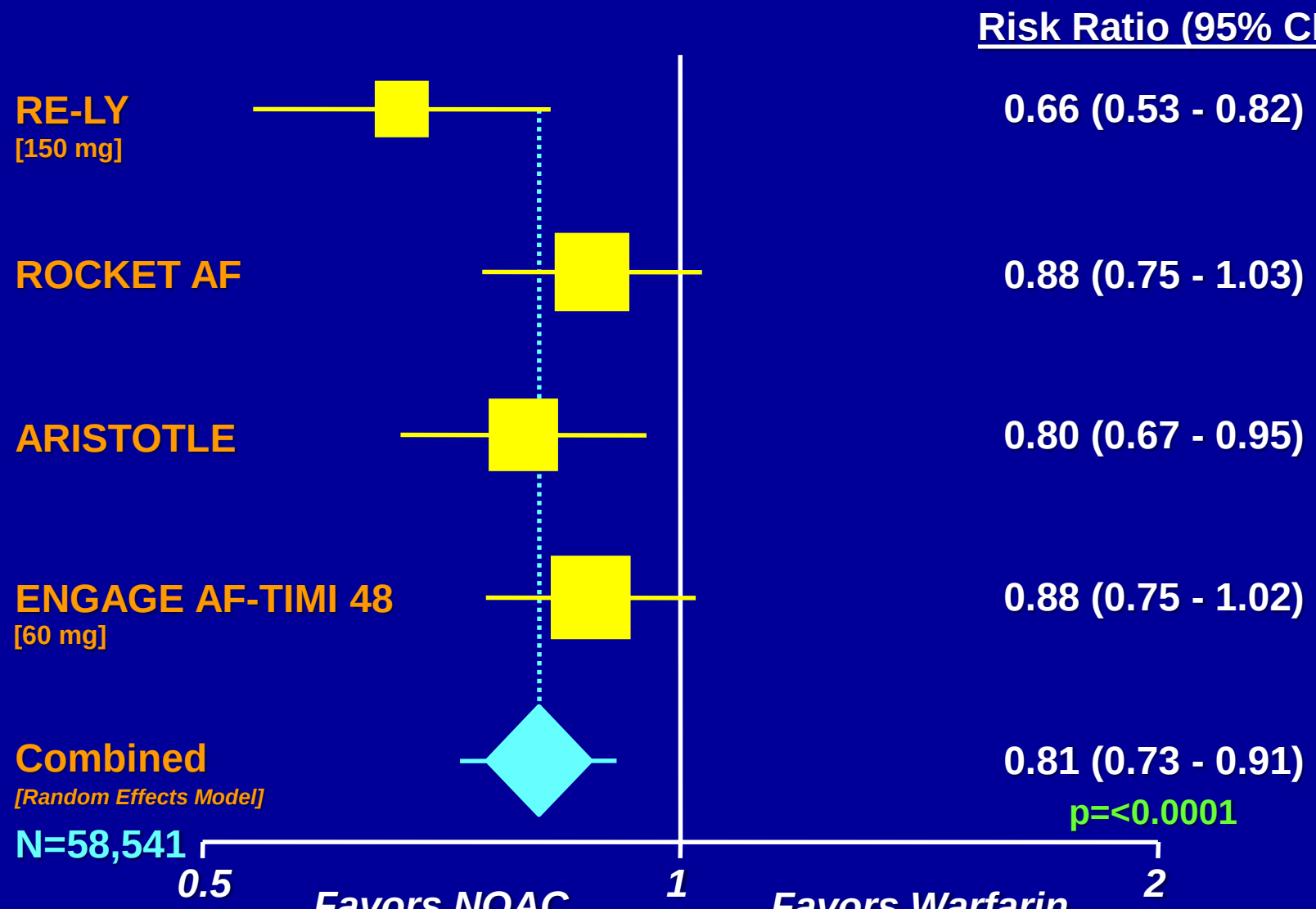
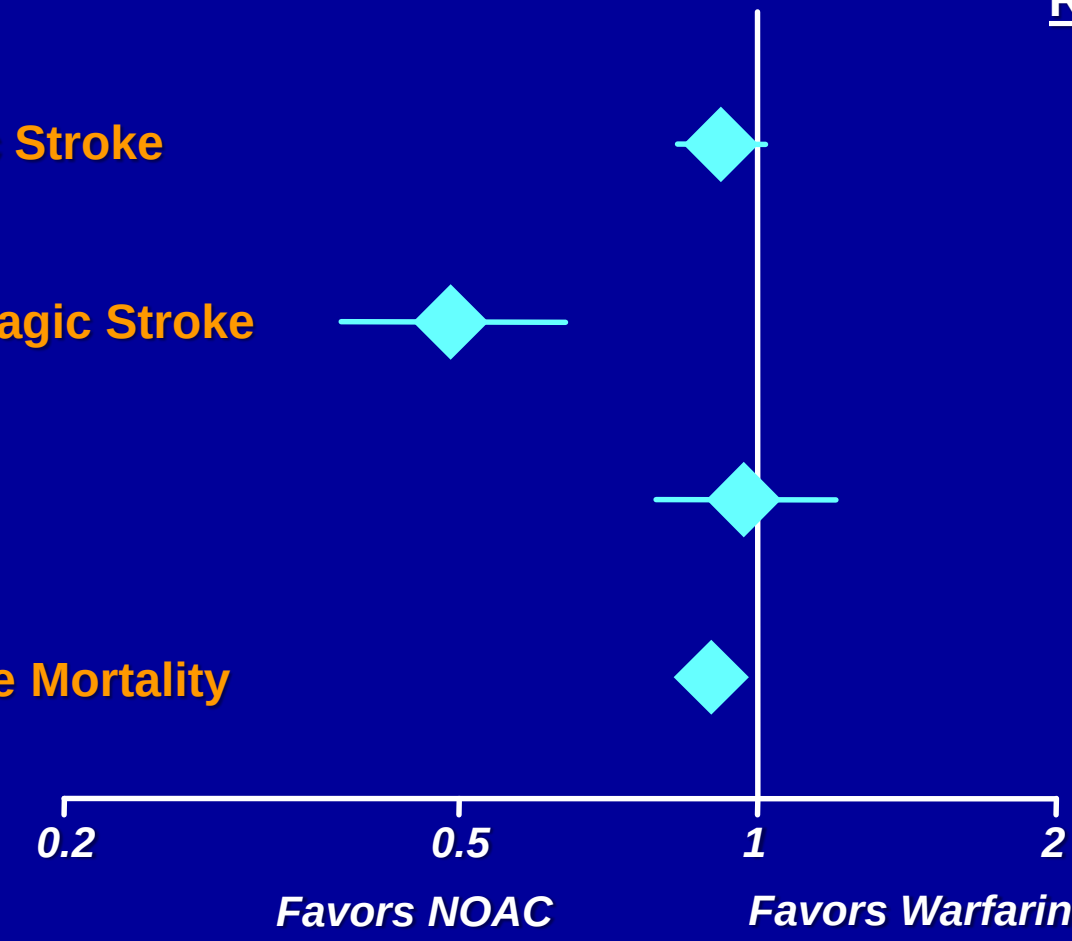
All NOACS: Stroke or Systemic Embolic Events



Ruff CT, et al. Lancet 2013

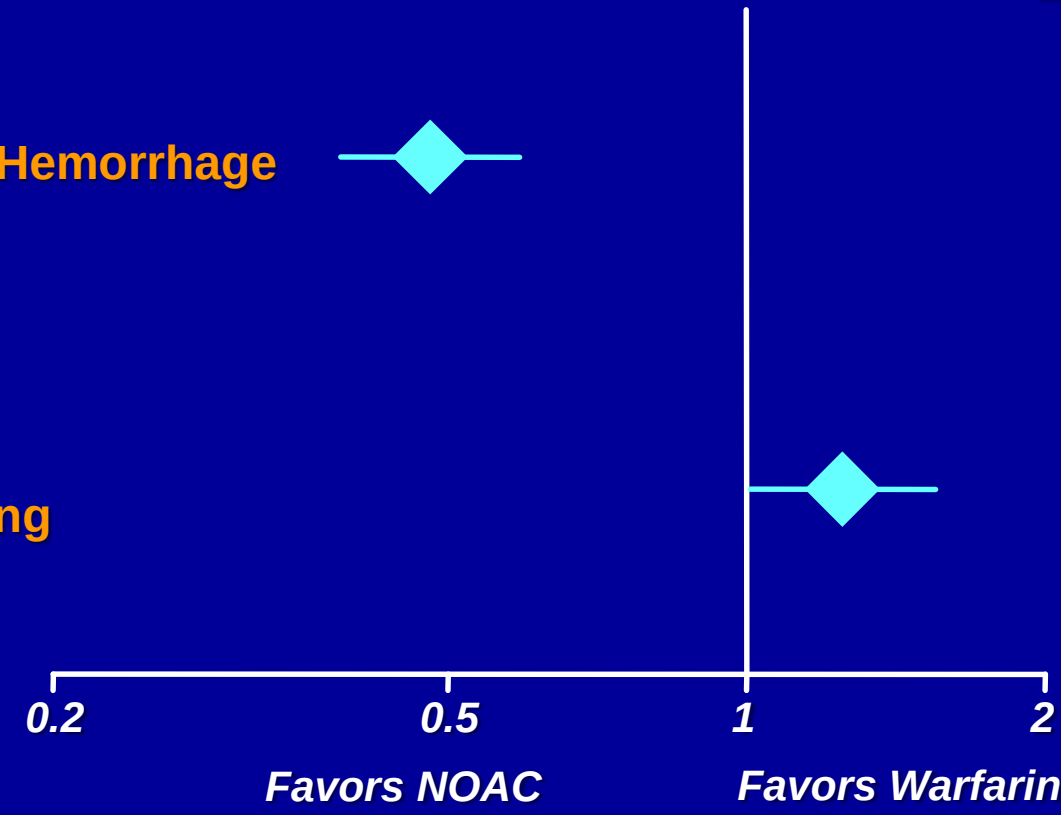
Secondary Efficacy Outcomes



Heterogeneity p=NS for all outcomes

Ruff CT, et al. Lancet 2013

Secondary Safety Outcomes



Heterogeneity
ICH, p=0.22
GI Bleeding, p=0.009

Ruff CT, et al. Lancet 2013

ROCKET-AF Trial
Study Design

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

or
- Stroke, TIA or systemic embolism

Atrial Fibrillation

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind / Double Dummy
(n ~ 14,264)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

Monthly Monitoring
Adherence to standard of care guidelines

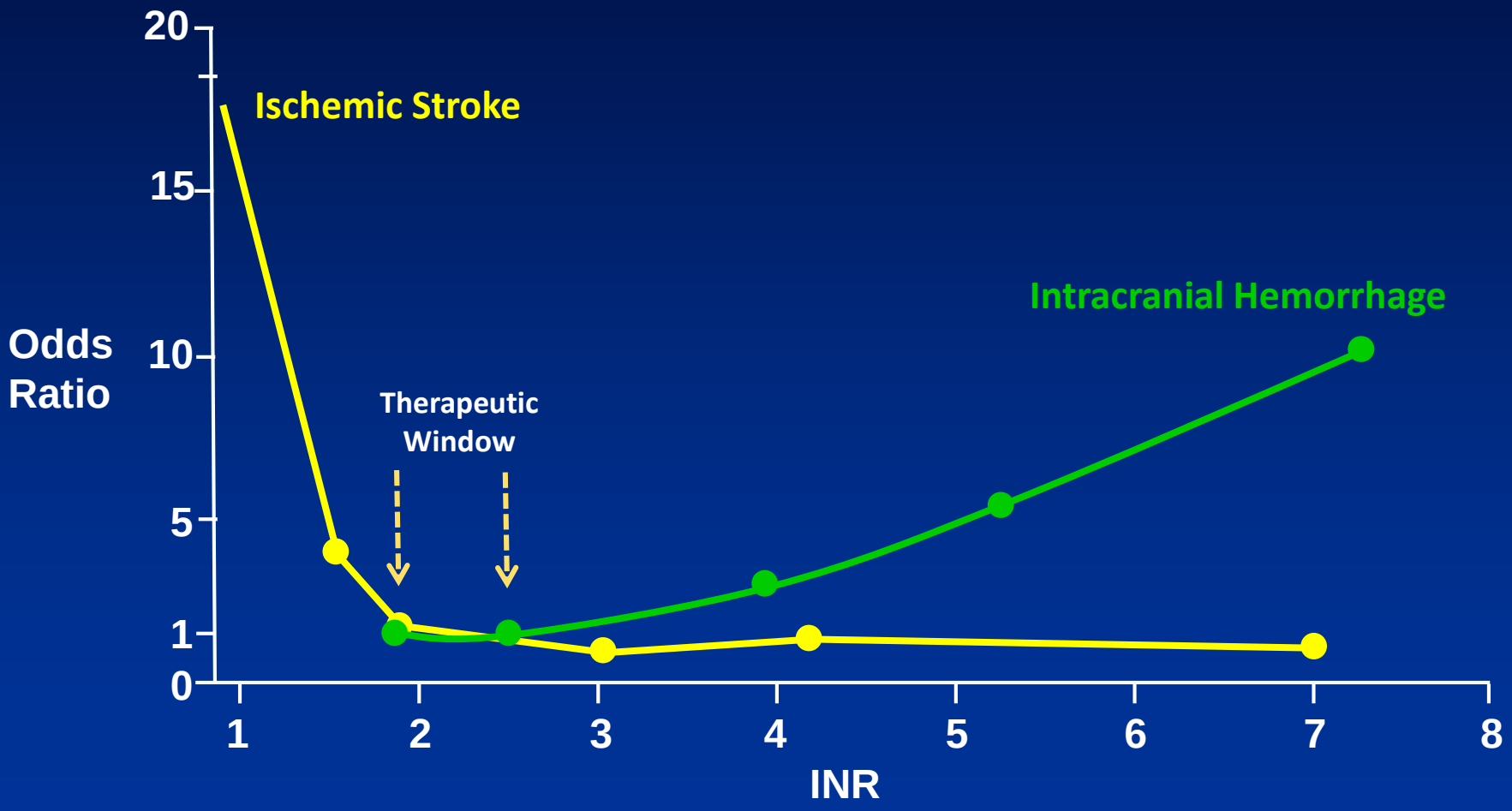
Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior stroke, TIA or systemic embolism and only 2 factors limited to 10%

ROCKET AF Study Investigators. *Am Heart J* 2010; 159: 340.

ROCKET AF

Warfarin: Narrow Therapeutic Window

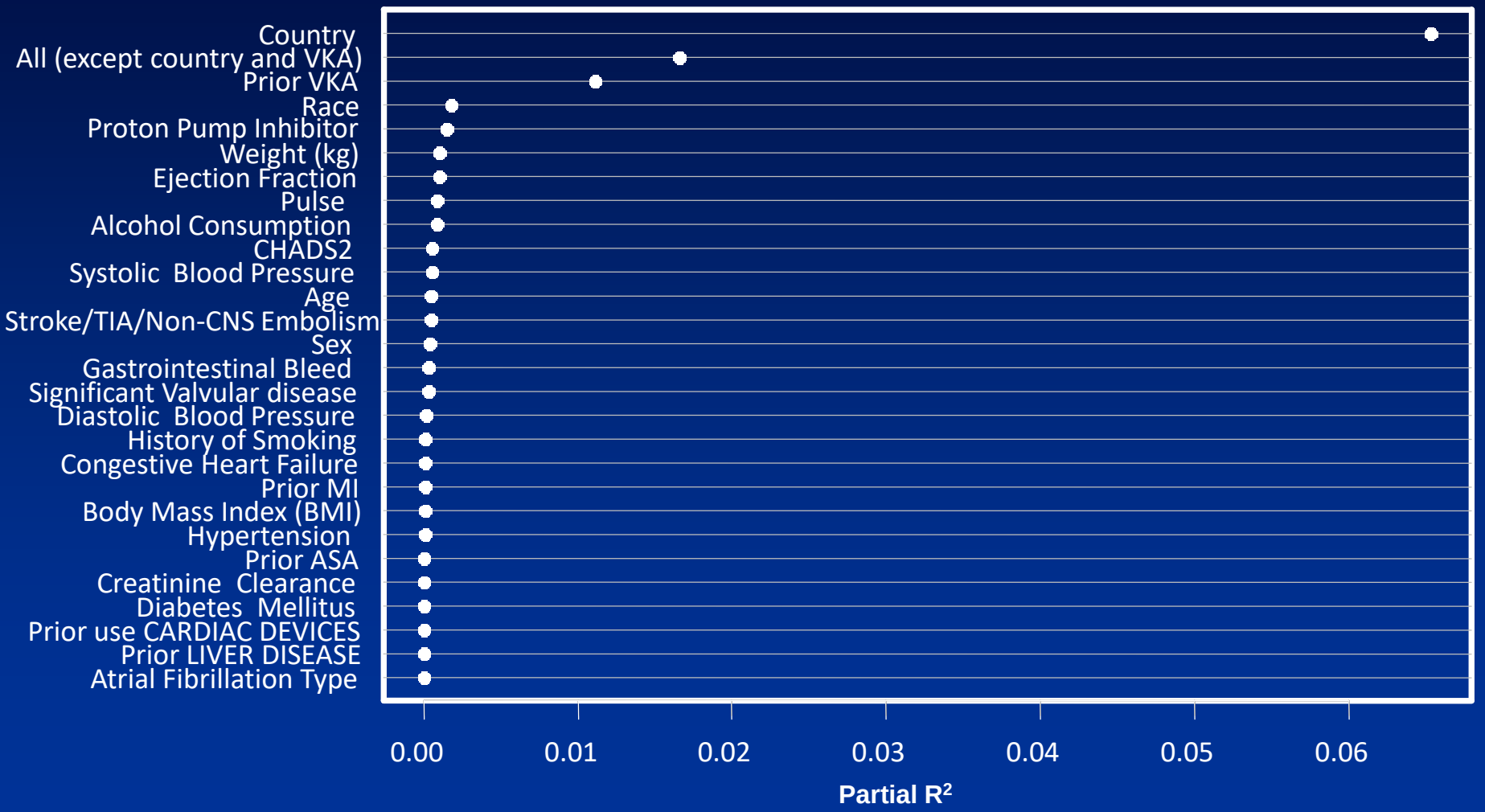


Fuster V. et al. *J Am Coll Cardiol*. 2001;38:1231-1265.

ROCKET-AF Warfarin Group TTR
Safety Population

	Warfarin N=7025	
INR range	Mean	Median (25th, 75th)
<1.5	8.5	2.73 (0.0, 9.0)
1.5 to <1.8	10.4	7.9 (3.5, 14.0)
1.8 to <2.0	10.3	9.1 (5.3, 13.6)
2.0 to 3.0	55.2	57.8 (43.0, 70.5)
>3.0 to 3.2	4.5	4.0 (1.9, 6.5)
>3.2 to 5.0	9.9	7.9 (3.3, 13.8)
>5.0	1.0	0.00 (0.0, 0.5)

Country Strongest Predictor of TTR Regression Model in ROCKET-AF



Ejection fraction is imputed at the median of non-missing values. TTR was transformed to the 1.5 power to improve the model fitting

Benchmarking… Datapoints and Costs

	Chronic Trial (>10,000)	Acute Trial (n=7142)
Type of Trial	Chronic CV (All in)	Acute Heart Failure (Streamlined)
Traditionally Reported SAEs	10,373	964
Triggered Events	10,895	1480
Coded AEs	65,296	386
Concomitant Therapies	332,677	<50,000
Visits	478,001	14,200
eCRF pages	>2.5 million	<200,000
Data Points	>30 million	<3 million
Costs	**+++++++++**	**++**

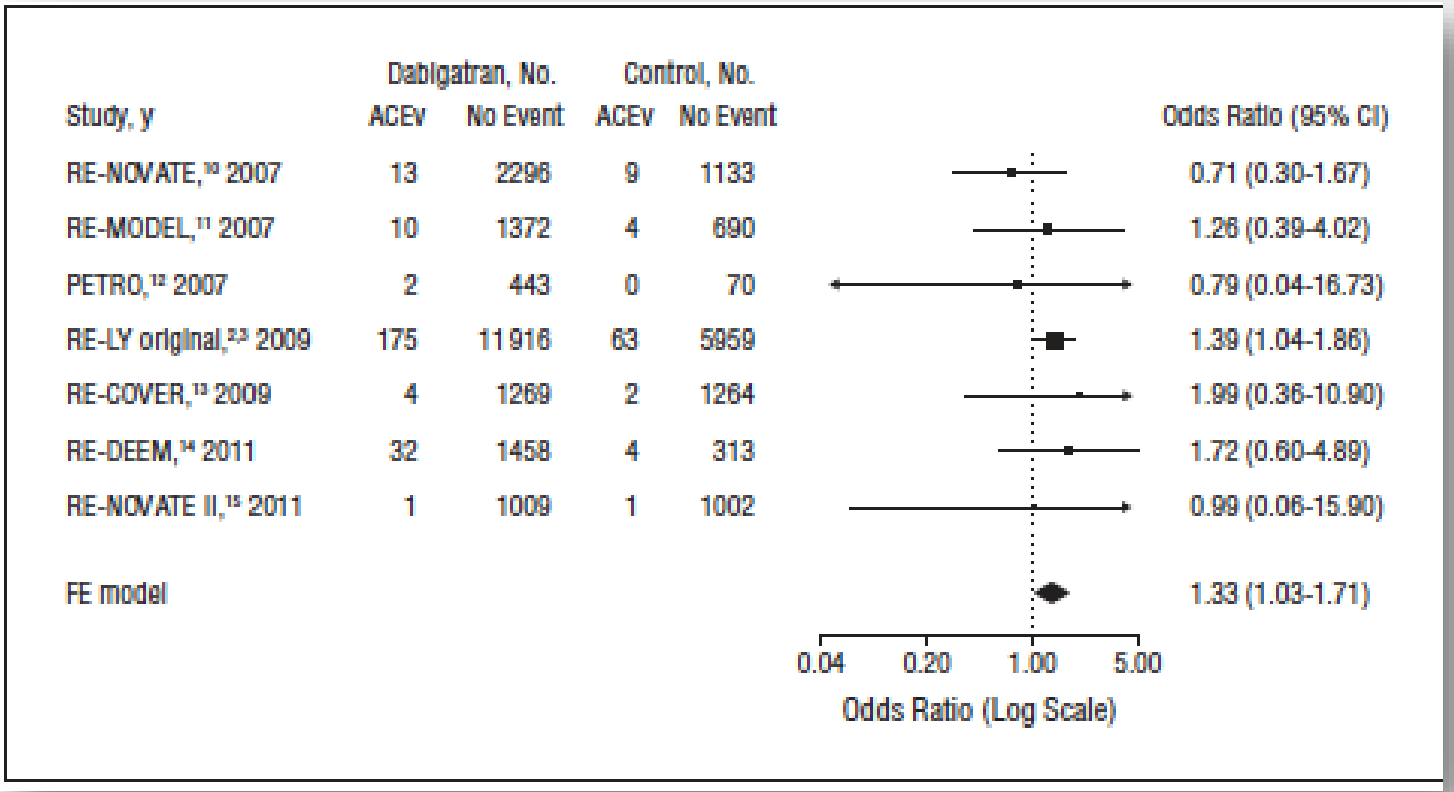
Concerns for Acute Coronary Syndrome?

REVIEW ARTICLE

ONLINE FIRST

Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials



Uchino K et al Archives of Internal Medicine 2012

Sentinel and Real World Evidence

Annals of Internal Medicine

ORIGINAL RESEARCH

Outcomes of Dabigatran and Warfarin for Atrial Fibrillation in Contemporary Practice

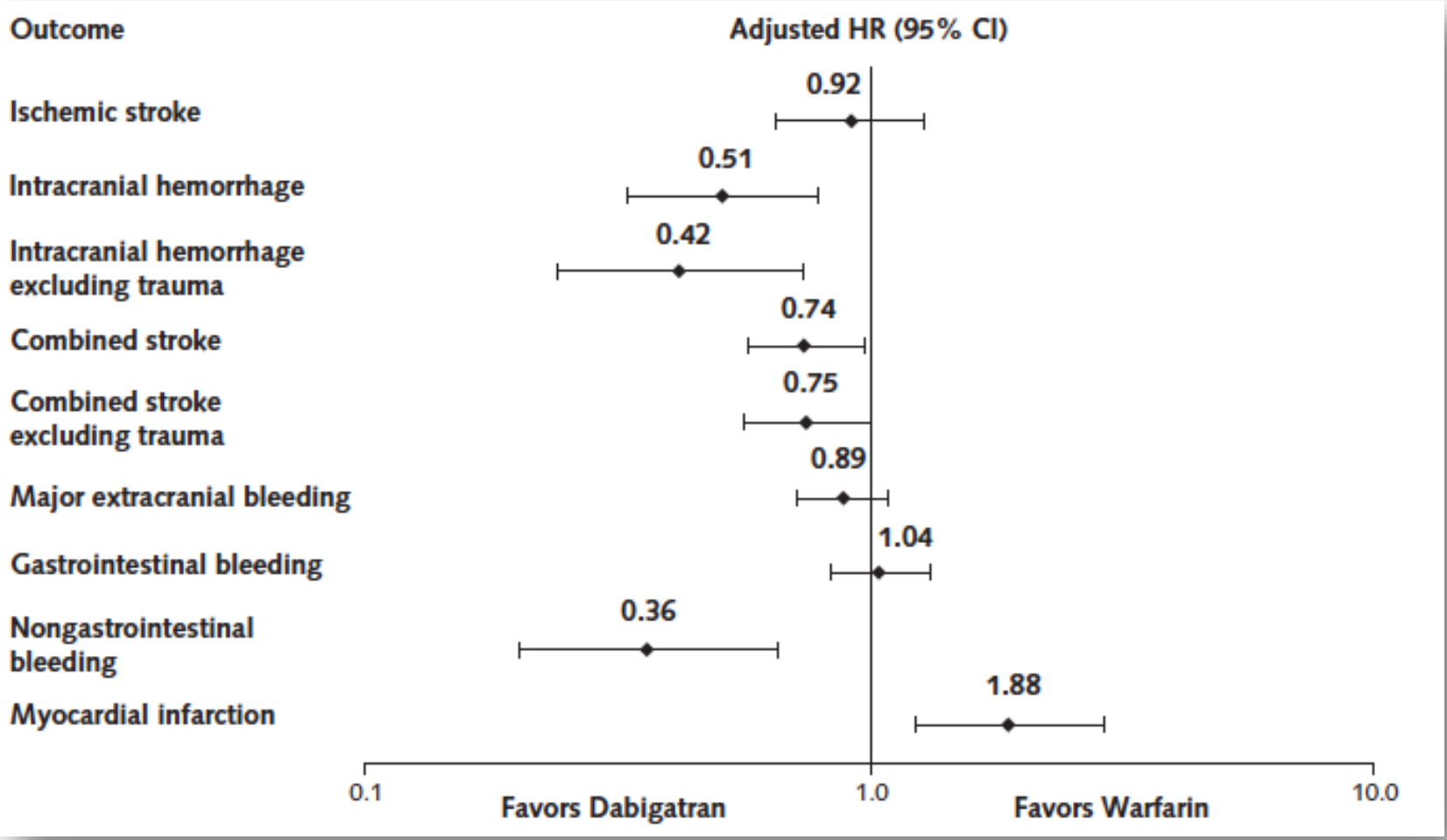
A Retrospective Cohort Study

Alan S. Go, MD; Daniel E. Singer, MD; Sengwee Toh, ScD; T. Craig Cheetham, PharmD, MS; Marsha E. Reichman, PhD; David J. Graham, MD, MPH; Mary Ross Southworth, PharmD; Rongmei Zhang, PhD; Rima Izem, PhD; Margie R. Goulding, PhD; Monika Houstoun, PharmD; Katrina Mott, MS; Sue Hee Sung, MPH; and Joshua J. Gagne, PharmD, ScD

Outcome	Dabigatran (n = 25 289)		Warfarin (n = 25 289)		Incidence Rate Difference per 100 Person-Years (95% CI)
	Patients With Events, n	Incidence Rate per 100 Person-Years	Patients With Events, n	Incidence Rate per 100 Person-Years	
Ischemic stroke	68	0.80	67	0.94	−0.15 (−0.44 to 0.15)
Intracranial hemorrhage	33	0.39	55	0.77	−0.39 (−0.63 to −0.15)
Excluding trauma	18	0.21	38	0.54	−0.32 (−0.52 to −0.13)
Combined stroke	100	1.18	119	1.68	−0.51 (−0.88 to 0.13)
Excluding trauma	85	1.00	102	1.44	−0.44 (−0.79 to −0.09)
Major extracranial bleeding	181	2.12	186	2.63	−0.50 (−0.99 to −0.01)
Gastrointestinal	165	1.93	145	2.05	−0.11 (−0.55 to 0.33)
Nongastrointestinal	16	0.19	41	0.58	−0.39 (−0.59 to −0.19)
Myocardial infarction	66	0.77	30	0.43	0.35 (0.11 to 0.59)

Go AS et al Annals of Internal Medicine 2017

Sentinel and Real World Evidence



……the strength and significance of the association between dabigatran use and MI *varied in sensitivity analyses* and by exposure definition, with hazard ratios ranging from 1.13 (95% confidence interval [CI], 0.78 - 1.64) to 1.43 (95% CI, 0.99 - 2.08).

Go AS et al Annals of Internal Medicine 2017

Discuss

What questions can characterize the utility of any real-world data source and signal reliability before a study is performed?