Rivaroxaban (XARELTO®)

Cardiovascular and Renal Drugs Advisory Committee

September 8, 2011

Introduction

Gary R. Peters, M.D.
Vice President, Cardiovascular Development
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Sponsor Presentation

• Introduction	**Gary R. Peters, M.D.** *Vice President , Cardiovascular Development* *J&J PRD*
• Medical Landscape and ROCKET AF Study Design	**Kenneth W. Mahaffey, M.D.** *Co-Director, DCRI CV Research* *Director, DCRI CEC Group*
• ROCKET AF Efficacy	**Robert M. Califf, M.D.** *Vice Chancellor Clinical Research,* *Duke University Medical Center* *Director, Duke Translational Medicine Institute*
• ROCKET AF Safety	**Christopher C. Nessel, M.D.** *Senior Director, Clinical Research* *J&J PRD*
• Benefit Risk Balance, Key Issues and Conclusions	**Robert M. Califf, M.D.**

Experts Available to Advisory Committee

- **Paul Watkins, M.D.** — *Director, Hamner - University of North Carolina Institute for Drug Safety Sciences*
- **Jeffrey Weitz, M.D.** — *Canada Research Chair in Thrombosis, McMaster University*

Proposed Indication

Rivaroxaban is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Basis for Rivaroxaban Approval: ROCKET AF

- Well designed and executed double-blind study
- Robustly non-inferior efficacy
- Superior efficacy on treatment
- Similar safety to warfarin
  - Similar discontinuation and bleeding rates
  - Fewer of the most important bleeding events (critical organ and/or fatal)

Important Points for Today

- Warfarin group time in therapeutic range (TTR) 55%
  - Biomarker with high variability and not validated for cross study comparisons
  - Country and patient characteristics account for observed TTR
  - Little relationship between TTR and treatment effect at the center or region level
- Warfarin therapy well managed based on observed event rates
- Increase in post-treatment thrombotic events
  - Resulted from study specific transition process
  - Transition plan has been developed to overcome gaps in anticoagulation

Rivaroxaban
First Oral Direct Factor Xa Inhibitor

- Direct, selective, competitive Factor Xa inhibitor
- Inhibits free and clot-associated Factor Xa activity
- Inhibits thrombin generation

Rivaroxaban
Clinical Pharmacology Summary

- Predictable PK and PD properties
- High oral bioavailability when given with food
- Multiple routes of elimination
- Limited drug-drug interaction potential
- No need for routine coagulation monitoring

Rivaroxaban
Phase 3 Clinical Development Programs

Indication ***Program***	**Number Randomized Subjects (study status)**
VTE prophylaxis after THR/TKR† *RECORD*	12,729 (complete)
Secondary prevention after ACS *ATLAS ACS TIMI 51*	15,079 (ongoing)
VTE prophylaxis in hospitalized medically ill *MAGELLAN*	8,101 (complete)
VTE treatment and secondary prevention *EINSTEIN (DVT and PE)*	9,145 (PE ongoing)
Stroke and embolism prevention in atrial fibrillation *ROCKET AF and J-ROCKET*	**15,544 (complete)**
Total (December 31, 2010 safety cutoff)	**60,598**

† **FDA Approved July 1, 2011**

Medical Landscape and ROCKET AF Study Design

Kenneth W. Mahaffey, M.D.
Co-Director, DCRI CV Research
Director, DCRI CEC Group

Atrial Fibrillation (AF)

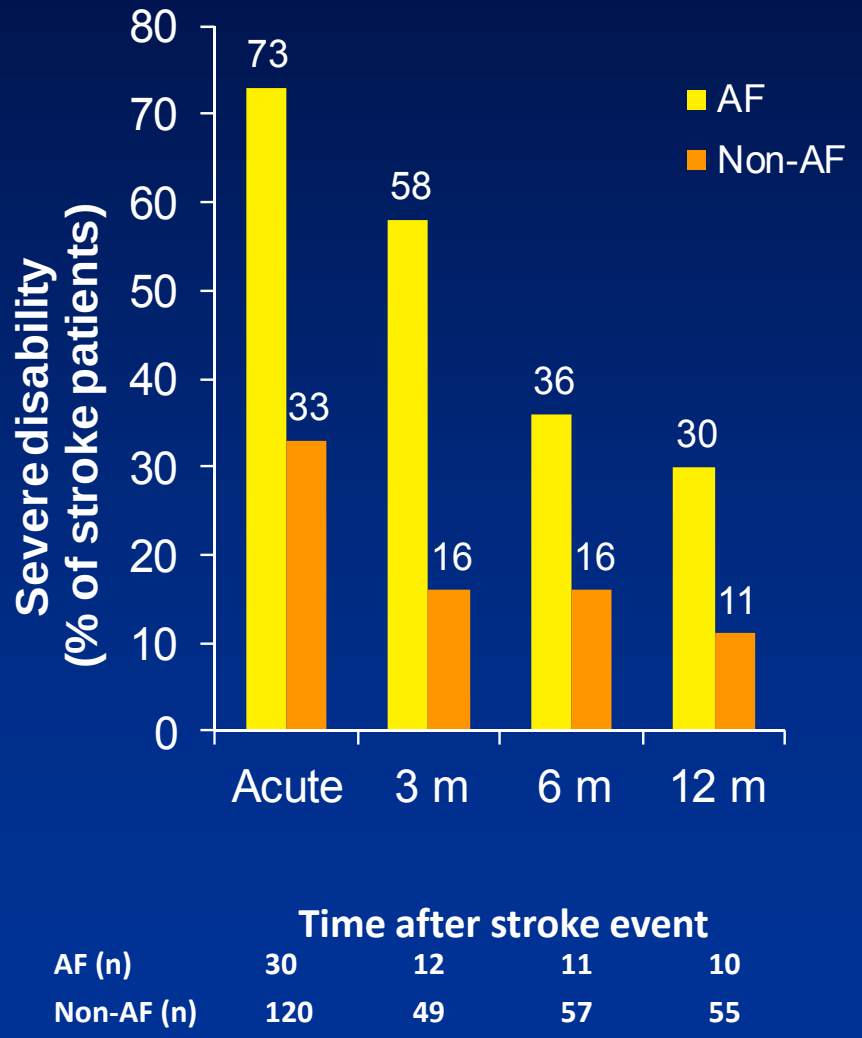
- Common and prevalence increasing[1]
- Association with increased stroke risk firmly established[2]
- Anticoagulant prophylaxis lowers stroke risk[3] however, many patients do not receive effective or optimal management[4]
- Novel oral anticoagulants may offer stroke protection comparable to VKAs with additional clinical benefits

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.

AF-Related Stroke

Greater disability compared to non-AF related stroke[1]

- higher mortality (AF vs no AF = 1.84)[1]
- larger infarcts (52 vs. 16 ml, p=0.05)[2]
- more severe hemorrhagic transformation (29 vs. 5%, p=0.002 for parenchymal hematomas)[2]



AF (n)	30	12	11	10
Non-AF (n)	120	49	57	55

1. Lin HJ, et al. Stroke 1996 Oct;27(10):1760-4.
2. Tu HT, et al. Cerebrovasc Dis 2010;30(4):389-95.

ACC/AHA/ESC 2006 Guidelines and ACCF/AHA/HRS 2011 Focused Update

Risk category	Recommended prophylaxis
No risk factors	Aspirin 81–325 mg daily
One moderate-risk factor	Aspirin 81–325 mg daily, or warfarin, alternative dabigatran (NVAF)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin, alternative dabigatran (NVAF)

Less validated/weaker risk factors

- **Female gender**
- **Age 65 to 74 years**
- **Coronary artery disease**
- **Thyrotoxicosis**

Moderate-risk factors

- **Age ≥ 75 years**
- **Hypertension**
- **Heart failure**
- **LVEF ≤ 35%**
- **Diabetes mellitus**

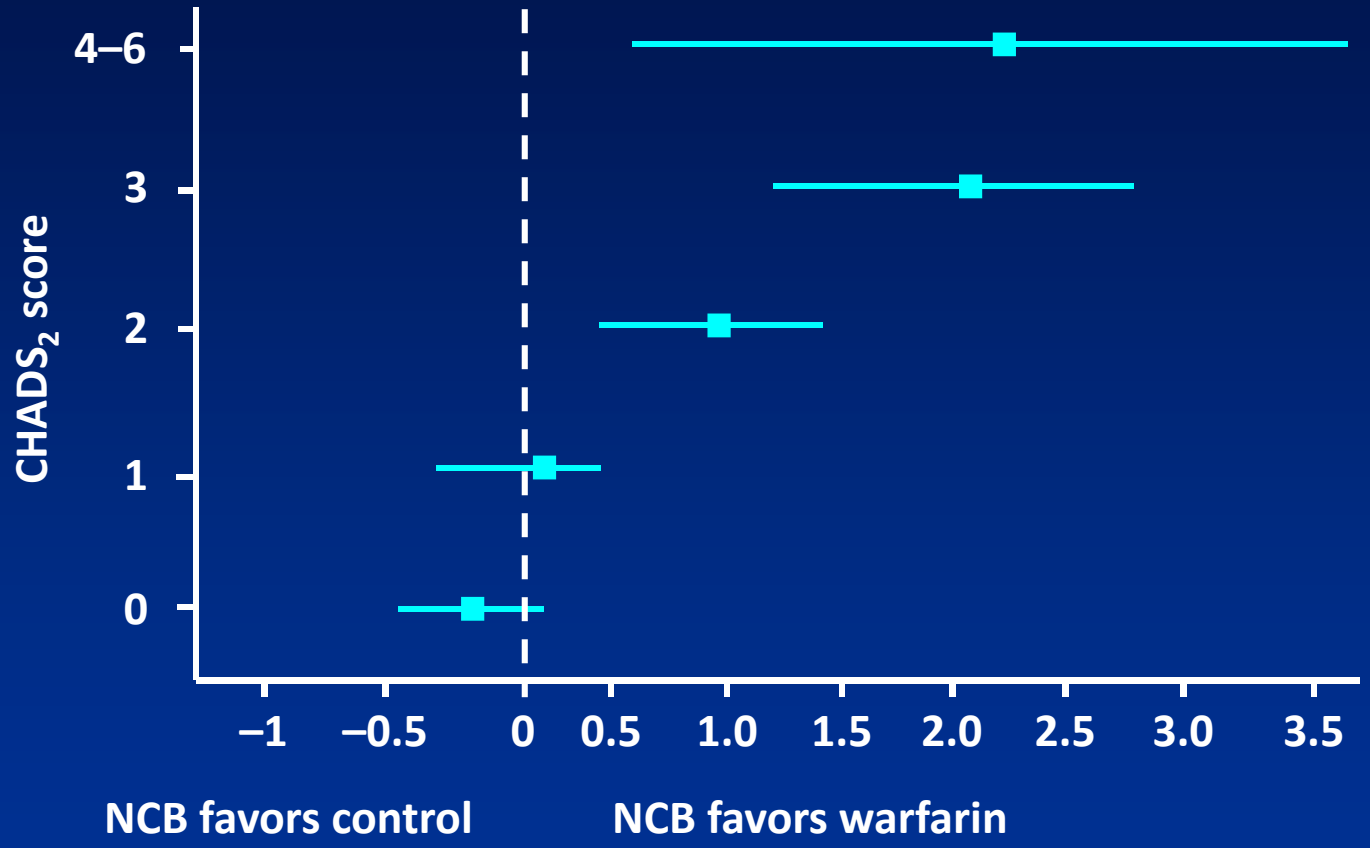
High-risk factors

- **Previous stroke, TIA or embolism**
- **Mitral stenosis**
- **Prosthetic heart valve**

NVAF = non-valvular atrial fibrillation

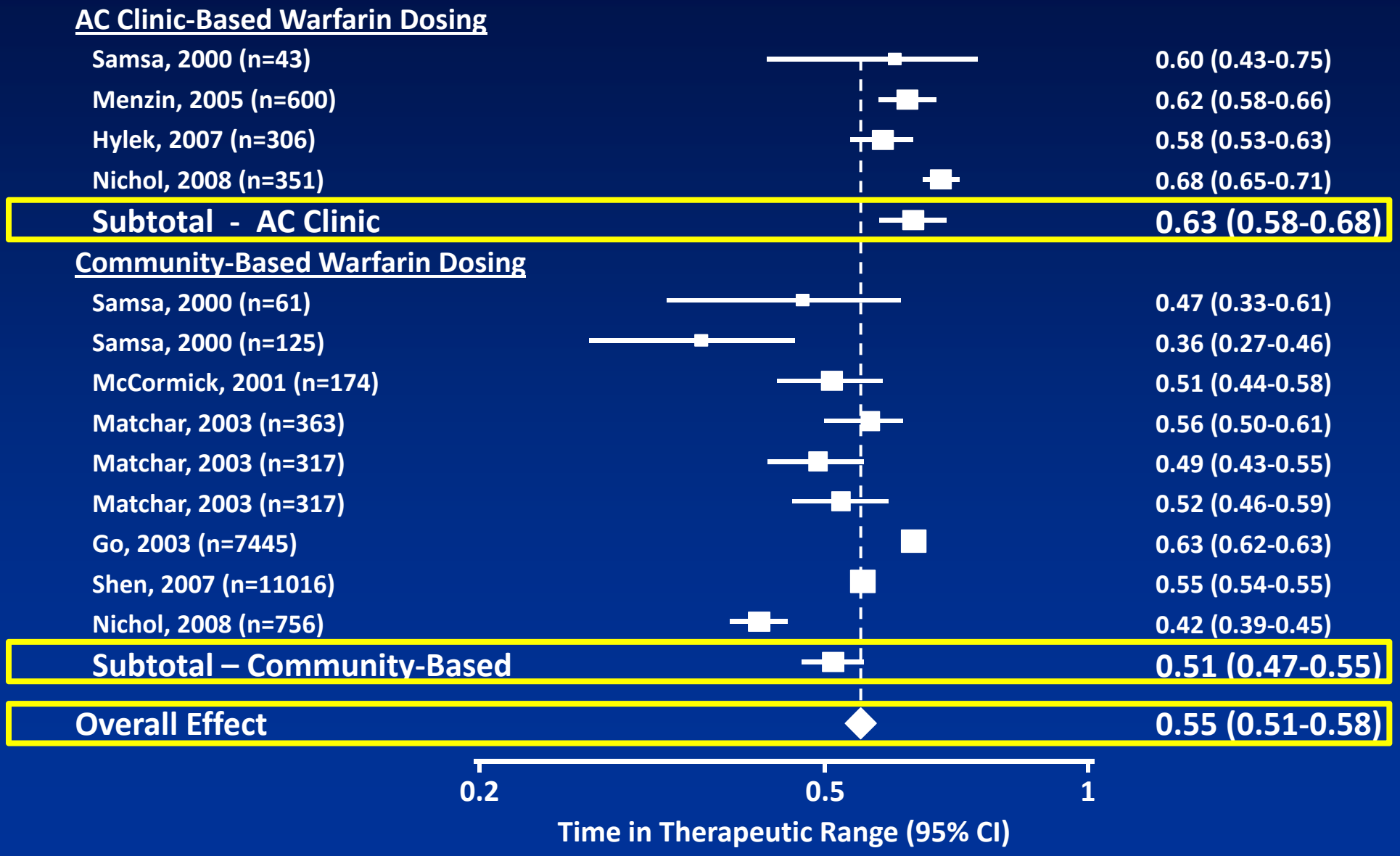
Wann LS, et al. J Am Coll Cardiol. 2011 Mar 15;57(11):1330-7.
Wann LS, et al. Circulation. 2011 Mar 15;123(10):1144-50.
Fuster V, et al. Circulation. 2006 Aug 15;114(7):e257-354.

Stroke Risk and Anticoagulant Benefit ATRIA Study



NCB = Net clinical benefit (ischemic stroke, systemic emboli , ICH)
$CHADS_2$ = Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA
Adapted from Singer DE, et al. Ann Intern Med 2009;151:297–305.

Systematic US Overview
Percentage of INR Time In Therapeutic Range



Baker W, et al. J Manag Care Pharm 2009; 15: 244-252.

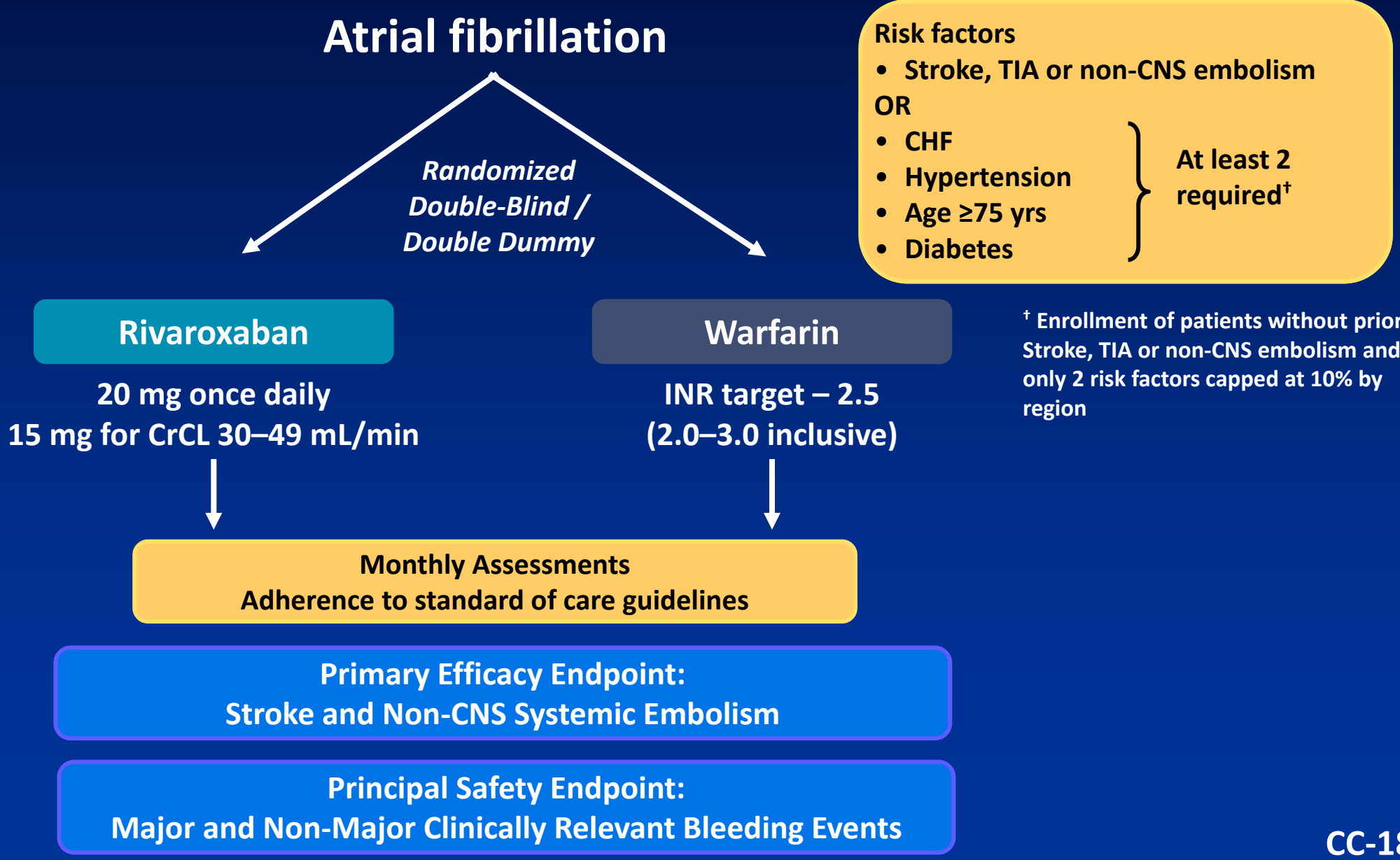
ROCKET AF

Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation

Primary Hypothesis:

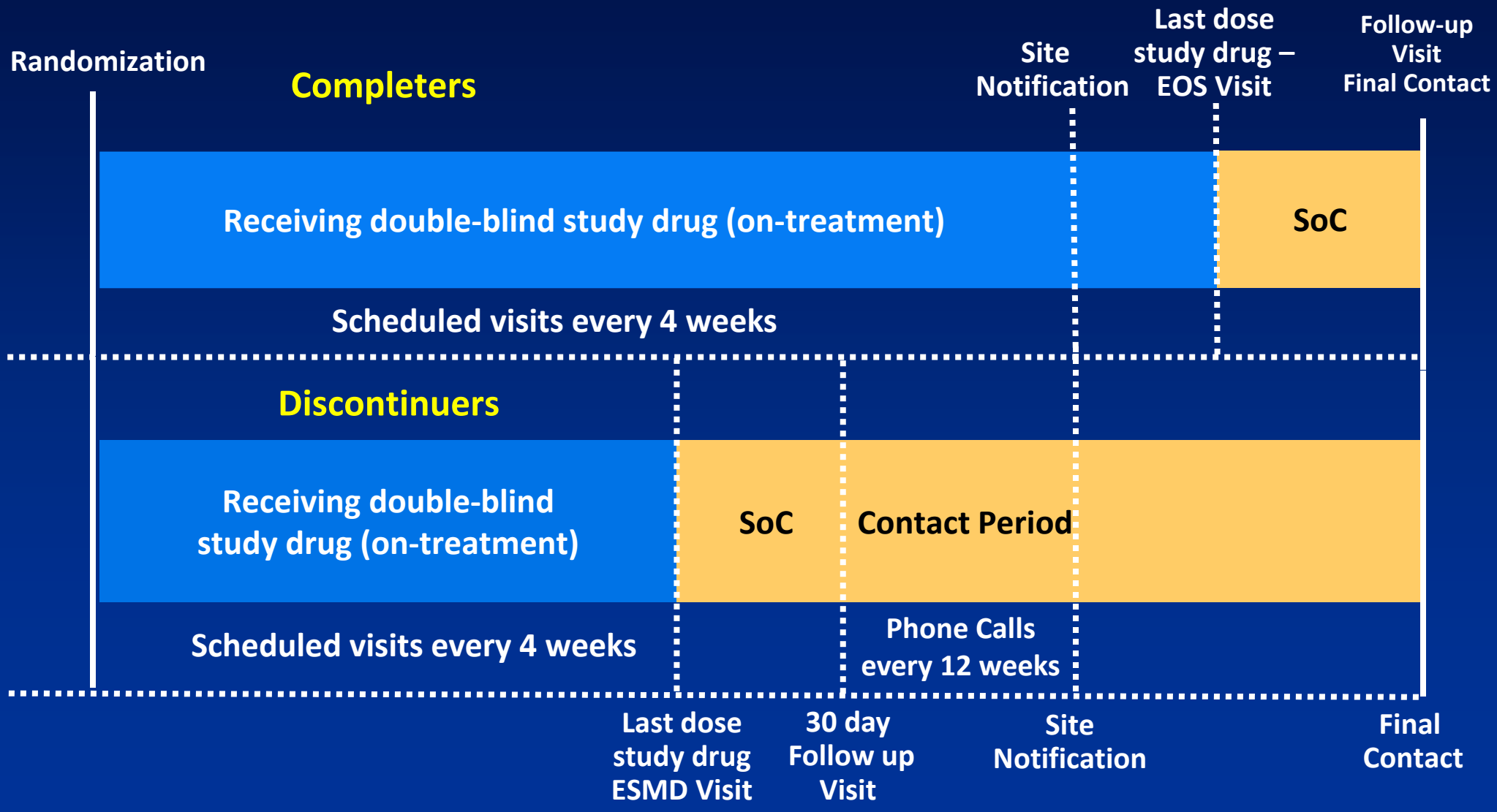
Rivaroxaban is non-inferior to warfarin in the prevention of the composite endpoint of stroke and non-CNS systemic embolism in subjects with non-valvular atrial fibrillation

ROCKET AF Study Design



† Enrollment of patients without prior Stroke, TIA or non-CNS embolism and only 2 risk factors capped at 10% by region

Study Design



SoC=Standard of Care; EOS = End of Study; ESMD = Early Study Medication Discontinuation

Blinded INR Measurements

Subject A:
- Warfarin
- Rivaroxaban placebo

Subject B:
- Rivaroxaban
- Warfarin placebo

Blood sample

Modified commercial POC INR monitor

Encoded value

- Subject No. A
- Dose of warfarin

- Subject No. B
- Dose of warfarin placebo

True PT-INR

Sham PT-INR

Warfarin dose determined by site investigator

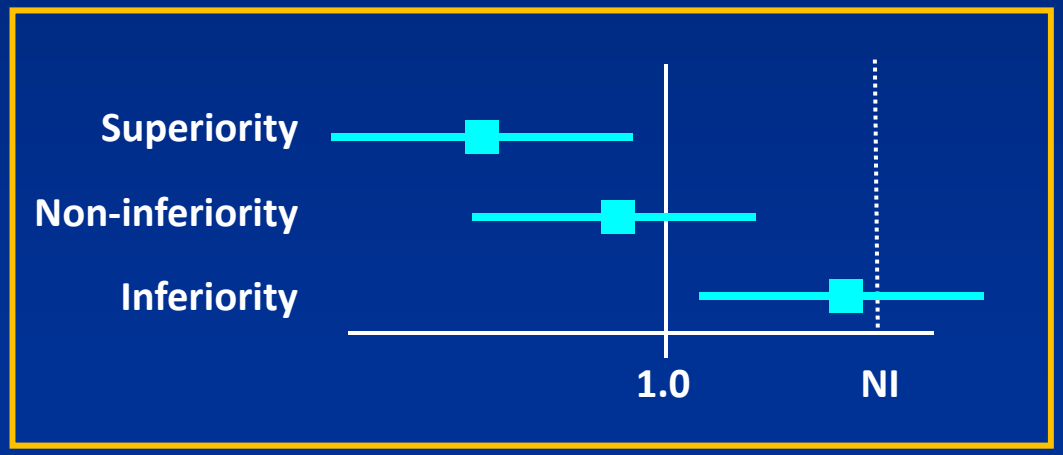
POC = Point of Care
ROCKET AF trial

INR Management

- Global target INR 2.5 with allowable range 2.0 to 3.0
  - No specific warfarin dosing protocol provided
  - Each site managed INR according to local standards
  - Continued education provided regarding the importance of keeping INR 2.0-3.0
- Mandated monthly study visits, 35 day drug supply at each visit
- Unblinded assistance for safety was available

Statistical Considerations

- Warfarin event rate ~2.3 per 100 pt-years
- Non-inferiority margin of 1.46 (FDA 1.38) based on 50% preservation of warfarin effect used in Hart† overview
- Type 1 error 0.05 (2-sided)
- ~14,000 patients with 405 per-protocol events
- Power:
  - >95% power for margin = 1.46
  - 90% power for margin = 1.38



†Hart RG, et al. Ann Intern Med. 1999 Oct 5;131(7):492-501.

Definitions: Populations

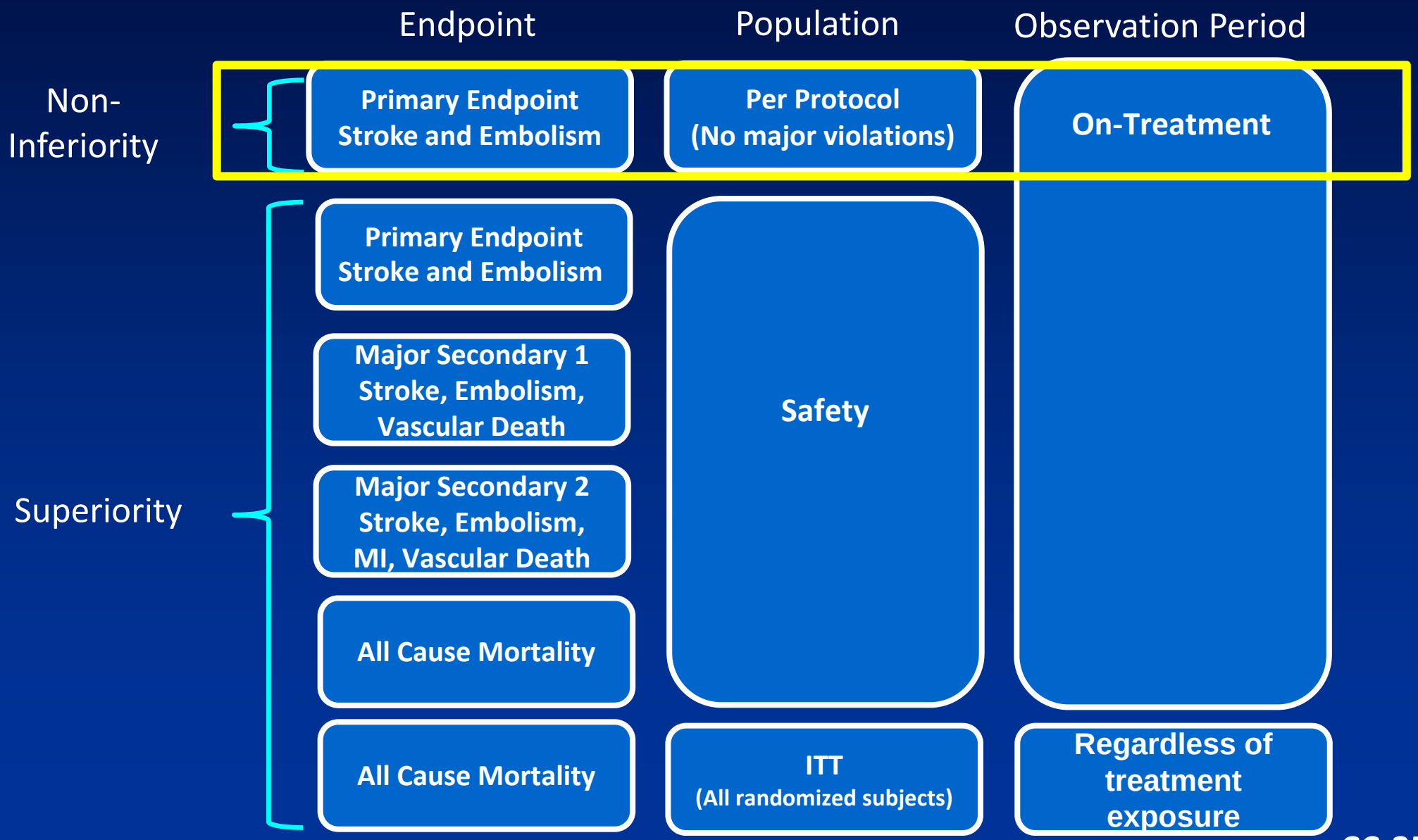
	Participants N (%)
• Intent-to-Treat Population (ITT) all unique participants randomized to treatment	14,264 (100)
• Safety Population all participants in ITT population who received at least 1 dose of study medication (analogous to mITT population)	14,236 (99.8)
• Per-protocol Population (PP) all participants in safety population who did not have (pre-defined) major protocol violations	14,054 (98.5)

Note: All efficacy analyses excluded data from Site 042012. Therefore, the ITT, safety, and per protocol populations excluded 50 rivaroxaban and 43 warfarin subjects.

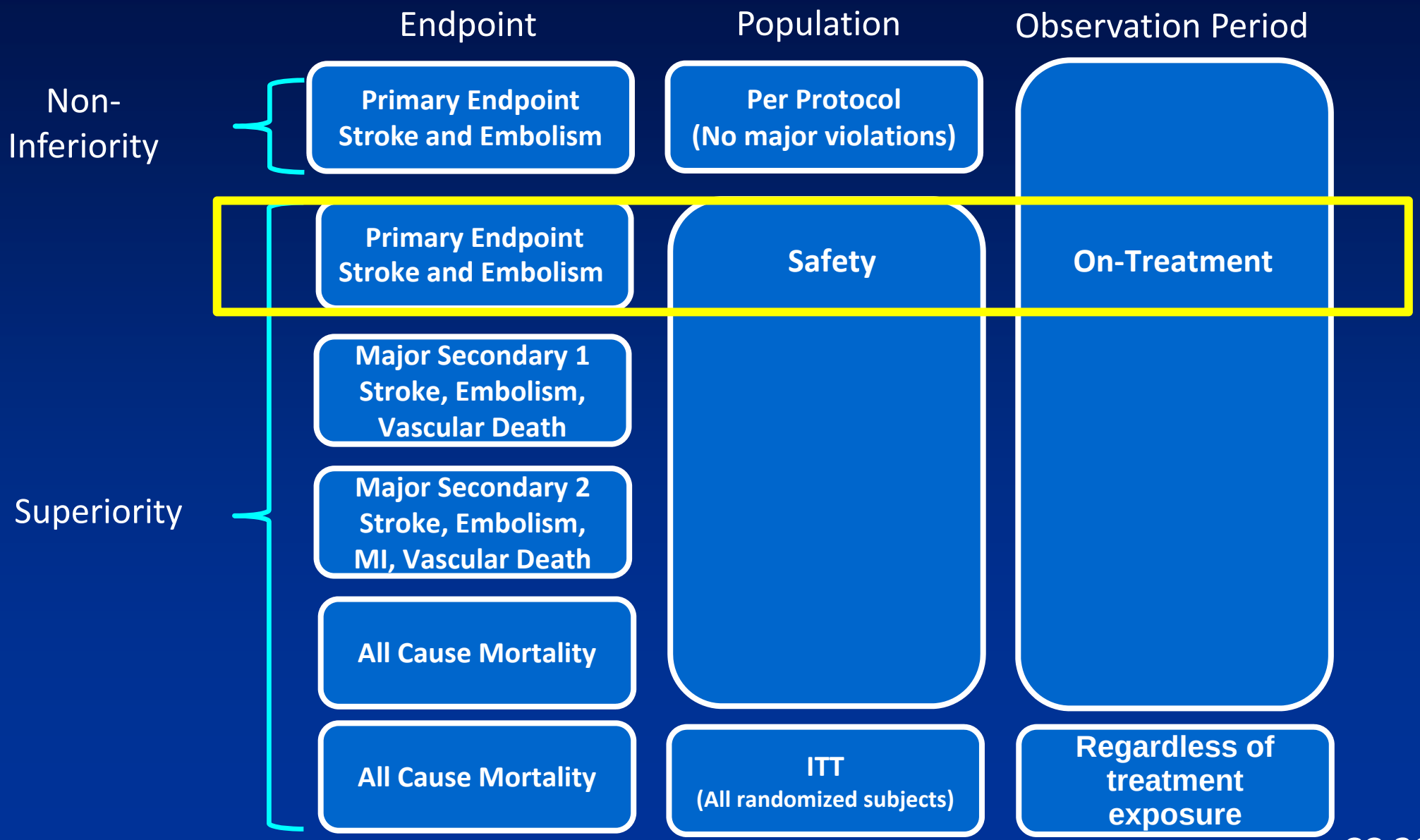
Definitions: Observation Periods

- On-treatment: up to last dose of study drug plus 2 days
- Up to site notification: up to the date of notification that required number of endpoints had been met
- Up to follow-up visit: up to time of post-treatment visit (~30 days after the last dose of study drug)
- Regardless of treatment exposure: all of the above plus data up to the last study contact for prematurely discontinued subjects who were followed by telephone

SAP Pre-specified Closed Hierarchical Testing Procedure



SAP Pre-specified Closed Hierarchical Testing Procedure



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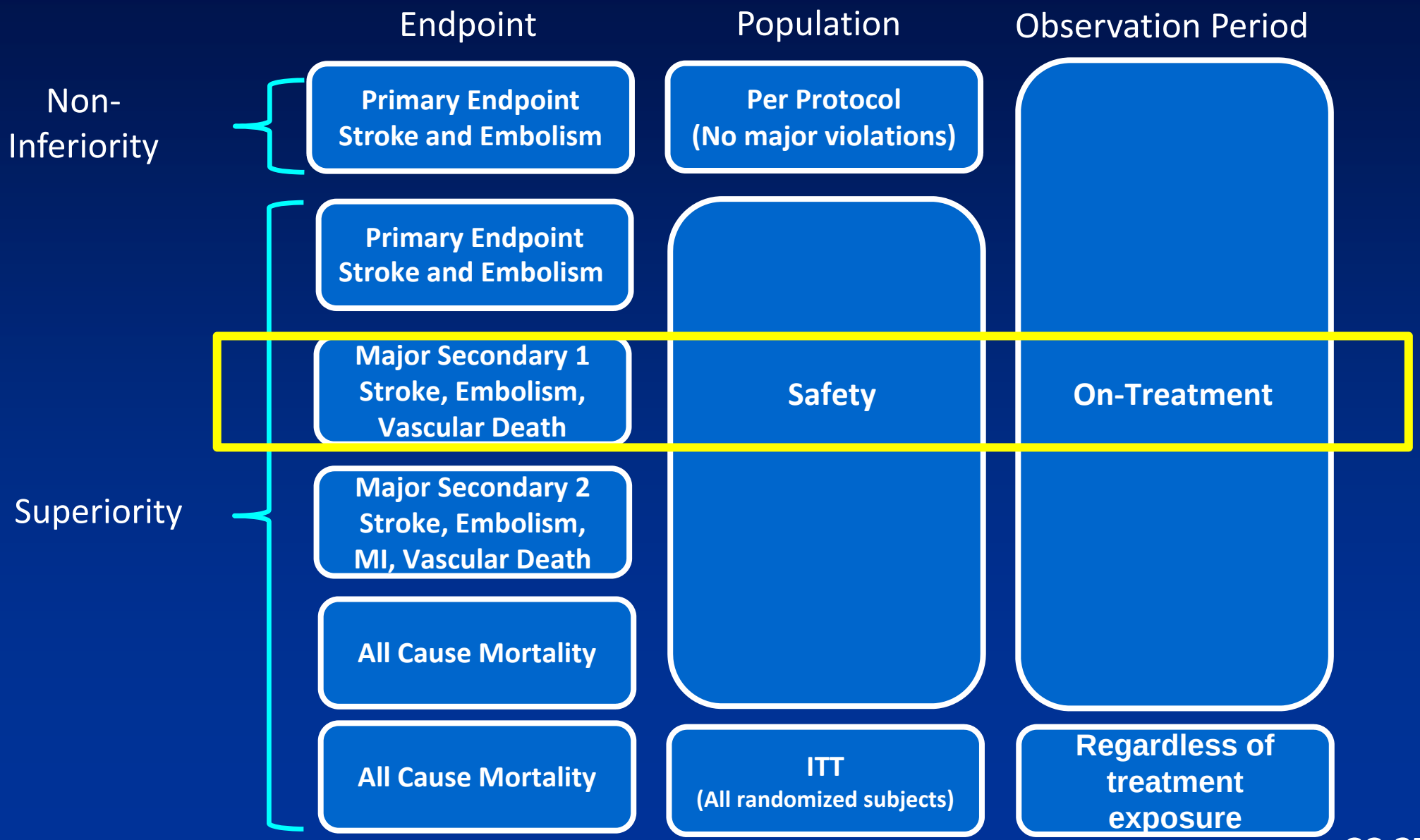

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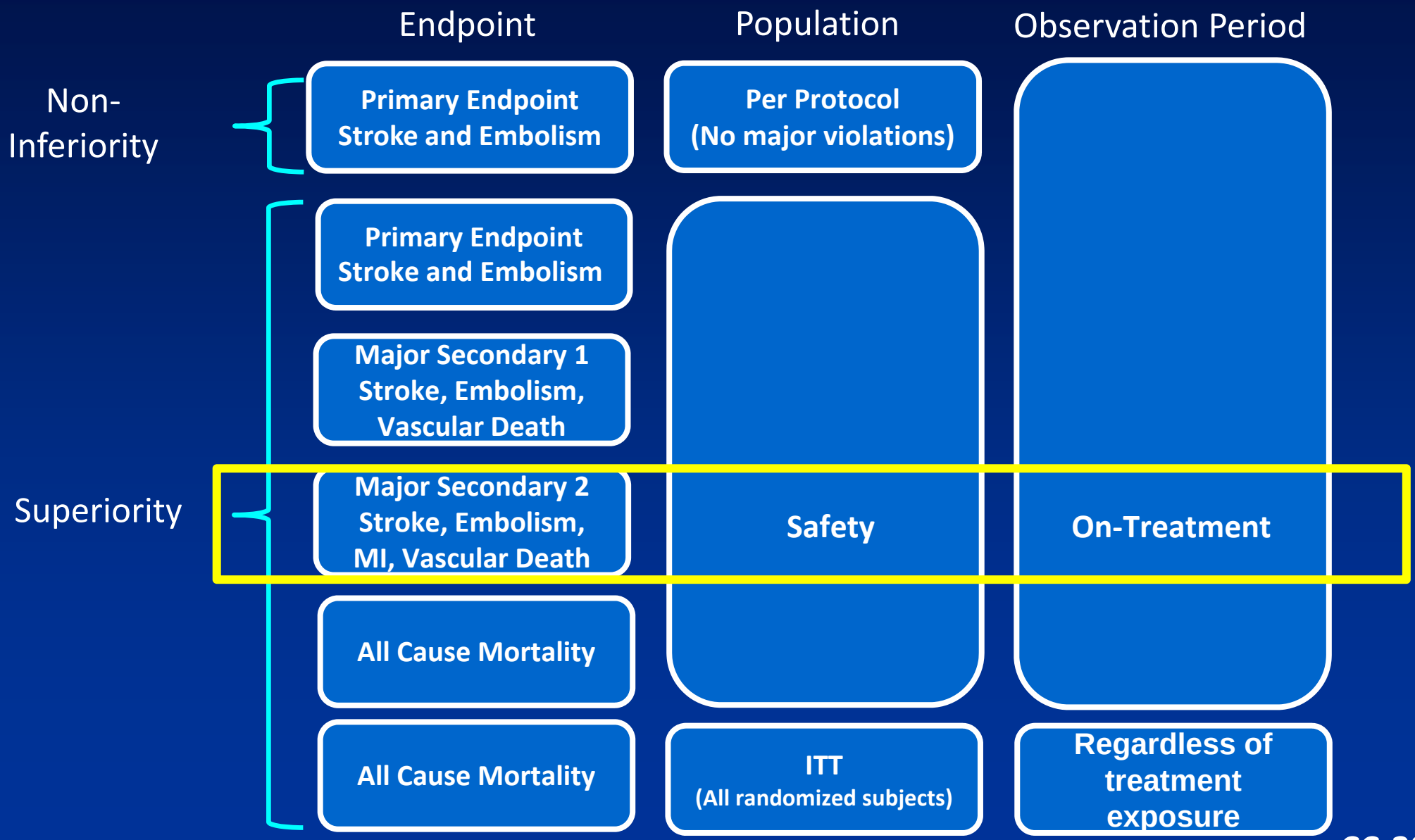

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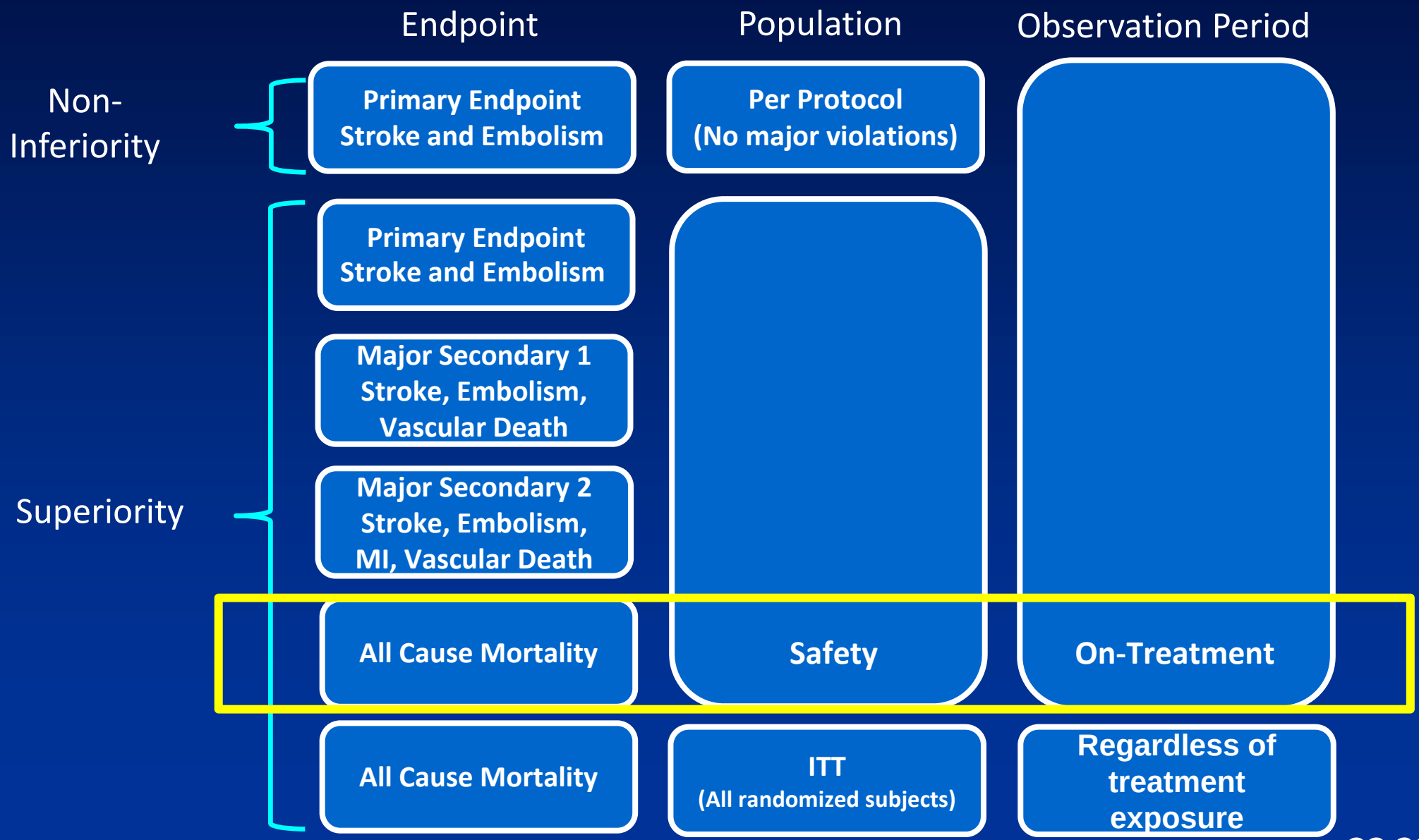

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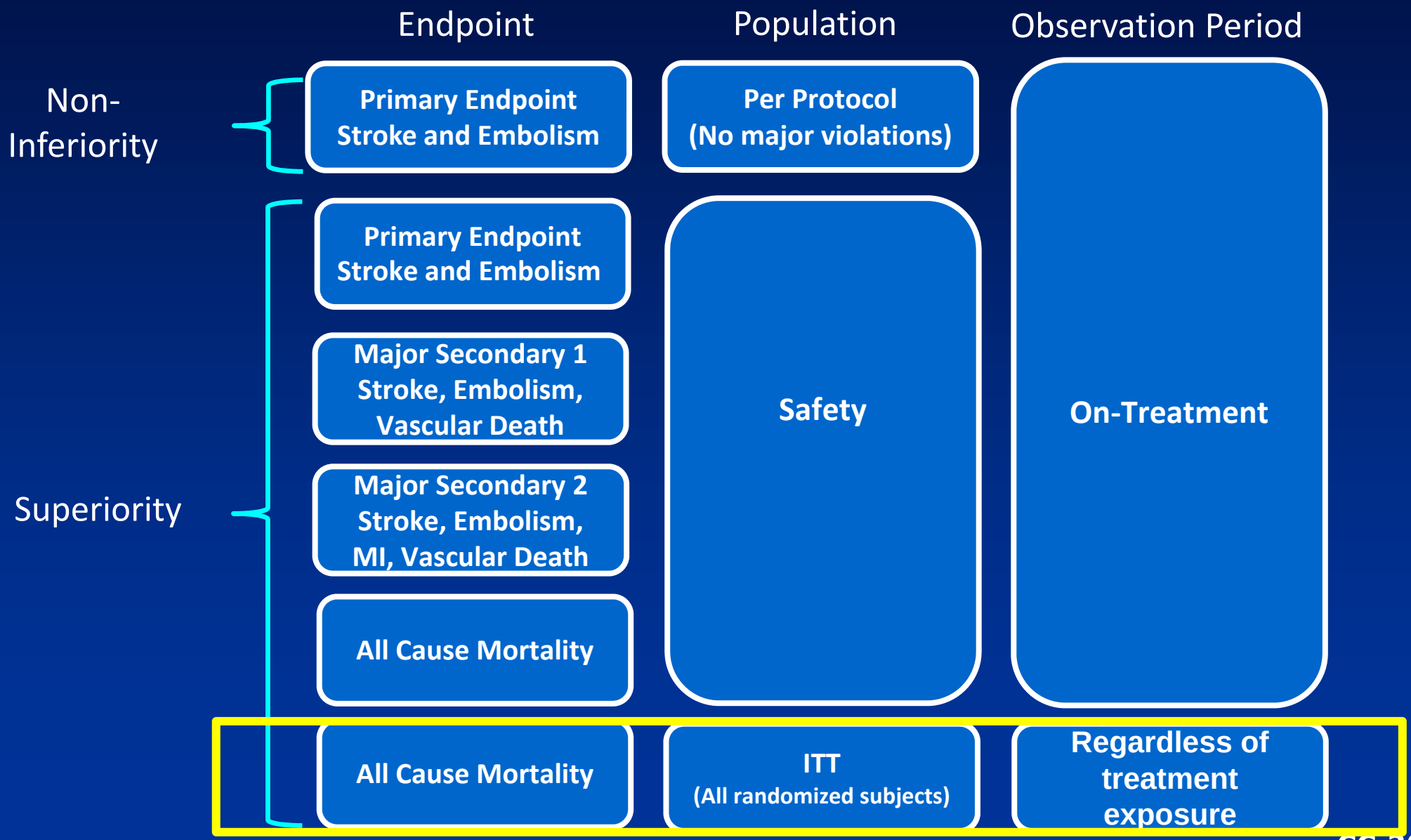


Additional Analyses

- Primary efficacy endpoint† in ITT population
- Key secondary outcomes in ITT population
  - Vascular death, stroke, non-CNS embolism
  - Vascular death, stroke, non-CNS embolism, MI
- Individual components of primary and key secondary endpoints
- Primary efficacy endpoint in ITT population on-treatment‡

†stroke and non-CNS systemic embolism
‡ Analysis not pre-specified
ROCKET AF trial

Study Design and Analysis Plan Summary

- Large global double-blind clinical trial
  - Practice guidelines and local standard of care drove therapy
  - High stroke risk population with other comorbidities
  - Rigorous event ascertainment
- Multiple pre-specified analyses
  - Hierarchical testing to preserve type 1 error
  - Per-Protocol is the standard for non-inferiority testing
  - ITT through end of study is standard for superiority testing
    - On-Treatment analyses performed due to expected high rate of discontinuations with long-term follow-up

ROCKET AF: Efficacy

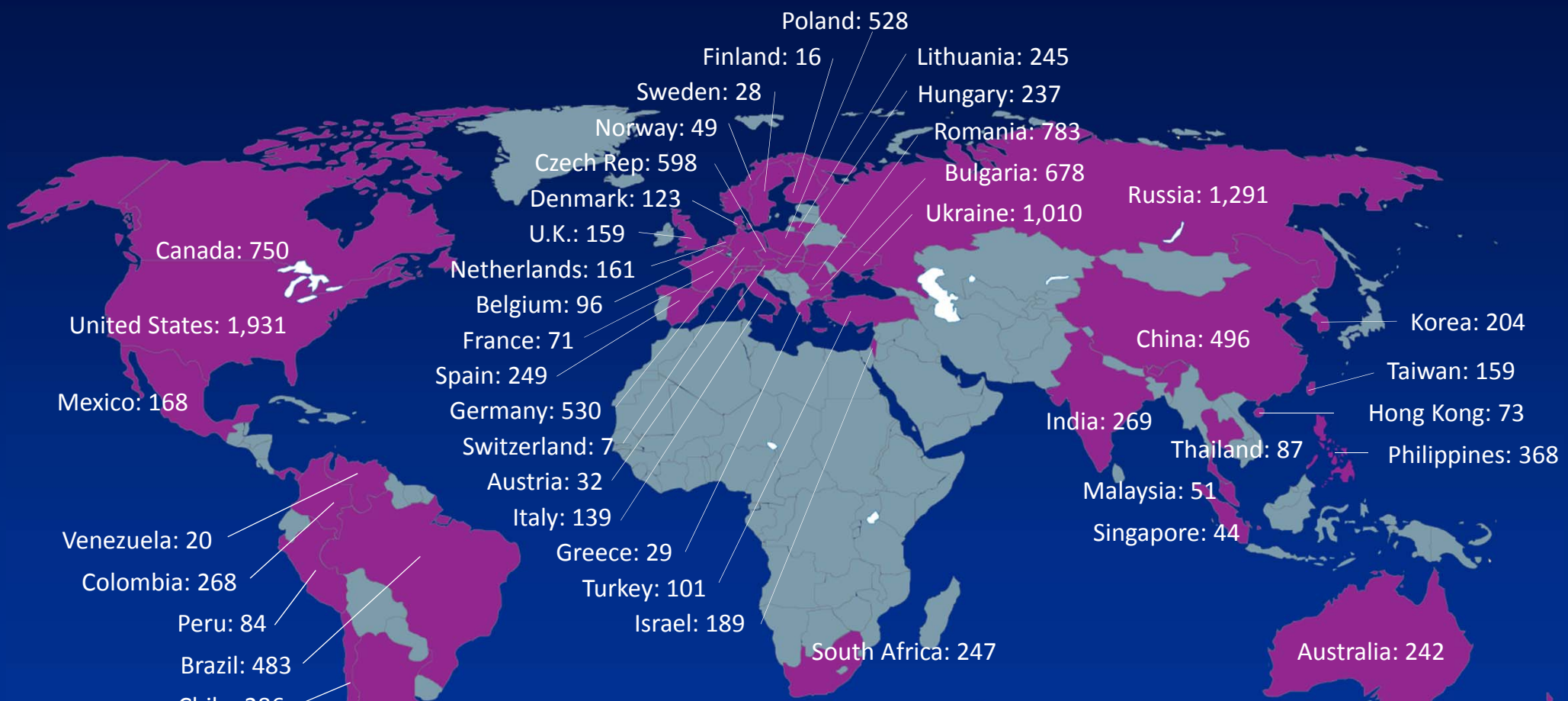
Robert M. Califf, M.D.

Vice Chancellor Clinical Research,
Duke University Medical Center
Director, Duke Translational Medicine Institute

Efficacy – Key Points

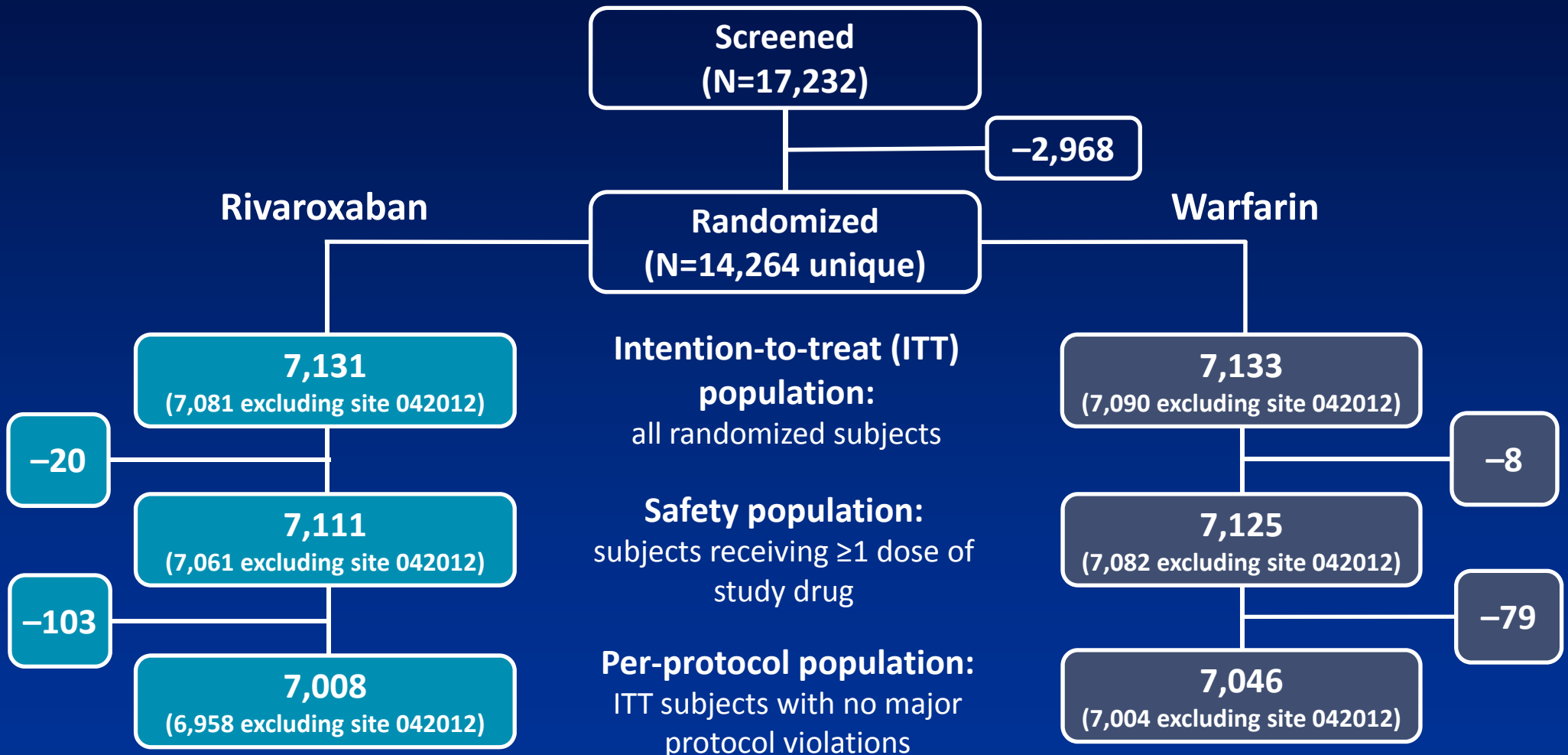
- Rivaroxaban is
  - Non-inferior to warfarin (all populations and observation periods)
  - Superior to warfarin while on treatment (all populations)
- Substantial reduction in hemorrhagic strokes
- Consistent results across subgroups and for secondary endpoints

Enrollment – 14,264 Participants from 1,187 Sites in 45 Countries



Region	Rivaroxaban	Warfarin	Total
North America	1339	1342	2681
Latin America	940	938	1878
West Europe	1046	1050	2096
East Europe	2751	2749	5500
Asia Pacific	1055	1054	2109

Study Populations

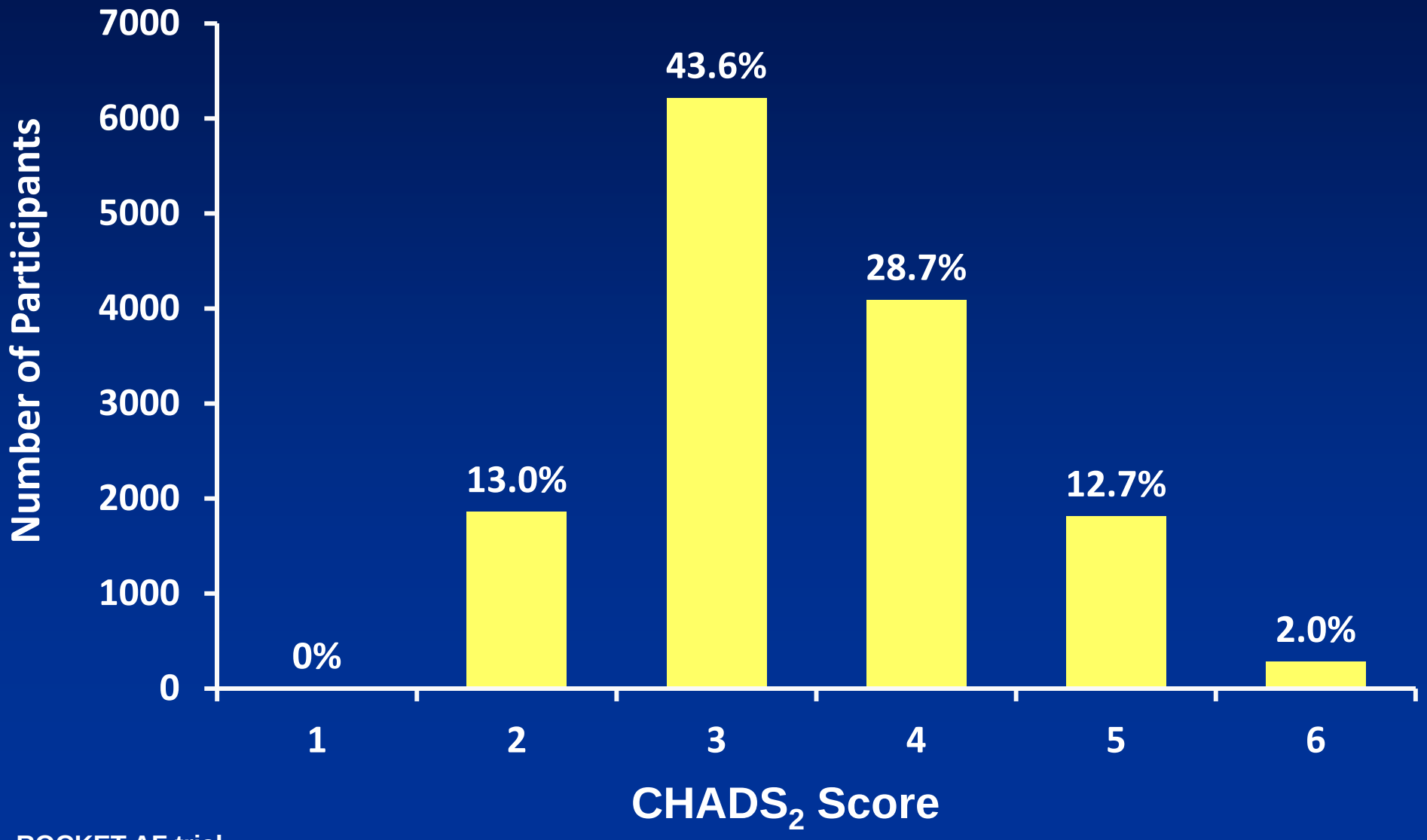


All efficacy analyses excluded data from Site 042012. Therefore, the ITT, safety, and per protocol populations excluded 50 rivaroxaban and 43 warfarin subjects.

Stroke Risk Factors – Intended Enrichment
ITT Population

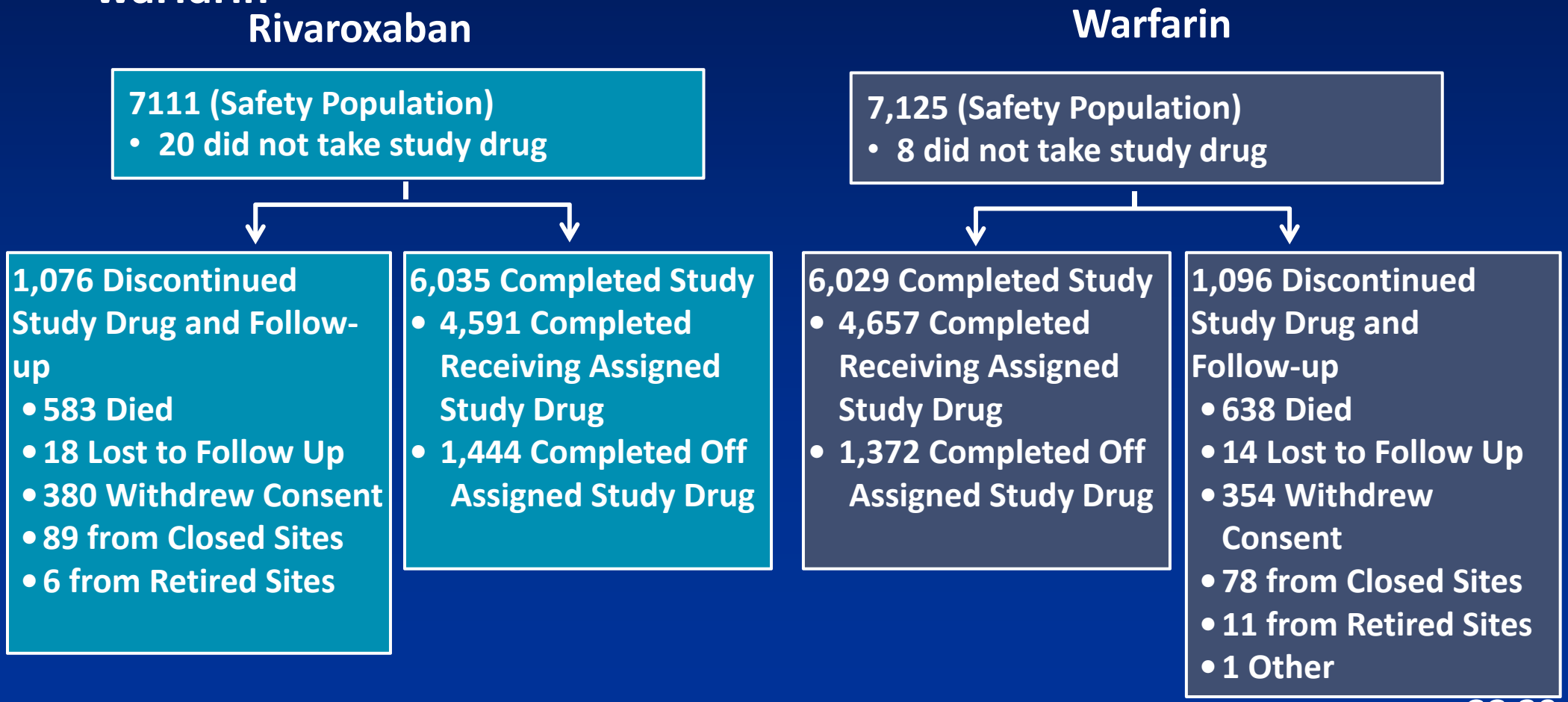
	Rivaroxaban N=7131 %	Warfarin N=7133 %
CHF	62.7	62.3
Hypertension	90.3	90.8
Age ≥ 75	43.8	43.6
Diabetes	40.4	39.5
Prior Stroke/TIA/Non-CNS Embolism	54.9	54.6
Prior MI	16.6	18.0

Baseline $CHADS_2$ Score
ITT Population



Participant Disposition with Detail

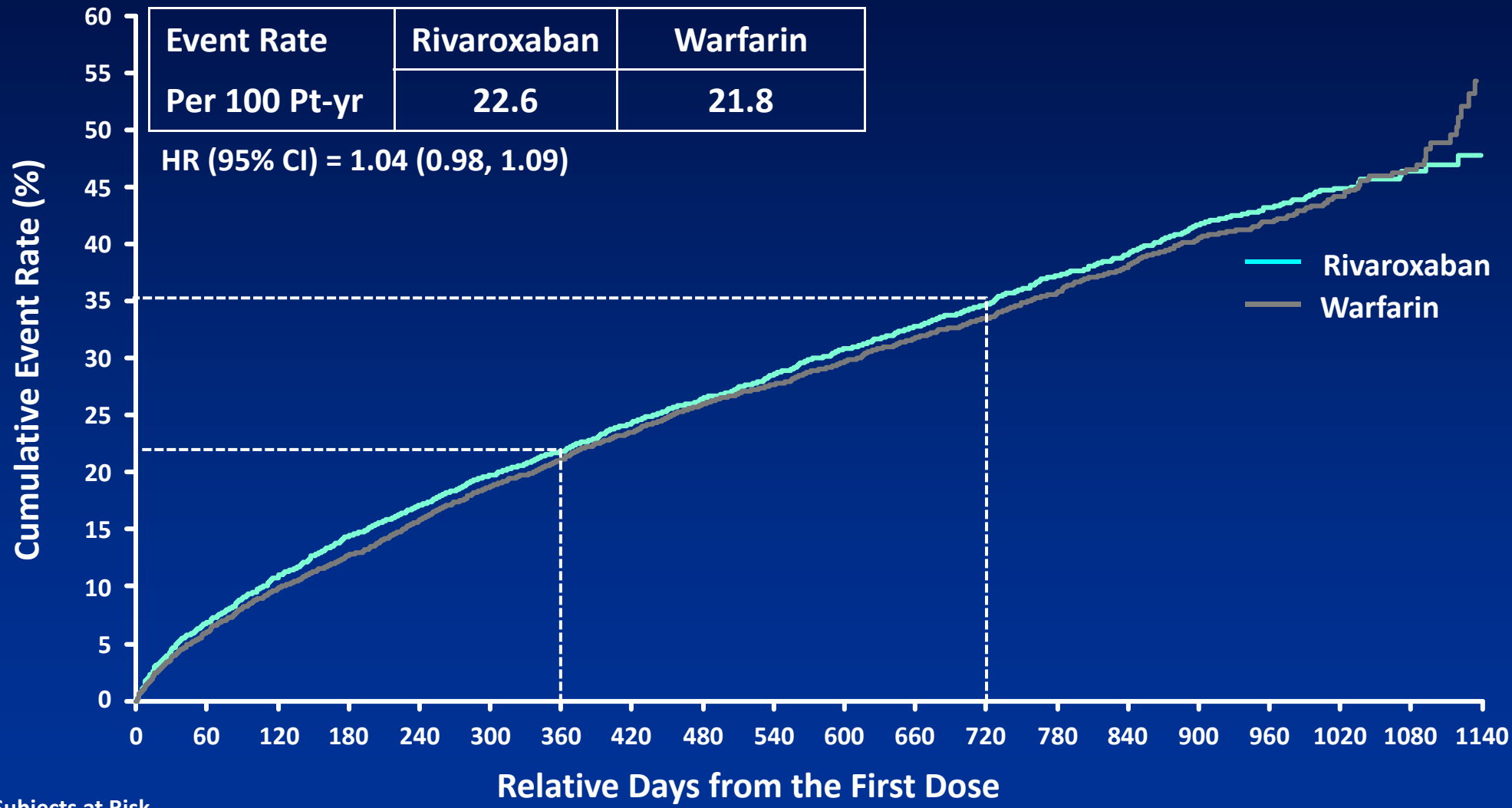
Ratios of missing follow-up time for subjects with 'Lost Follow up' and 'Withdrew consent' are 4.0% for rivaroxaban and 3.5% for warfarin



Early Study Medication Discontinuation
Safety Population

Event Rate	Rivaroxaban	Warfarin
Per 100 Pt-yr	22.6	21.8

HR (95% CI) = 1.04 (0.98, 1.09)



No. Subjects at Risk

Rivaroxaban	7111	6627	6342	6089	5896	5708	5558	5144	4463	4001	3452	2937	2512	1991	1495	1057	636	307	141	44
Warfarin	7125	6700	6426	6222	6003	5790	5624	5225	4512	4074	3522	3005	2571	2019	1530	1062	644	323	147	38

ROCKET AF trial

Pre-specified Statistical Testing Hierarchy

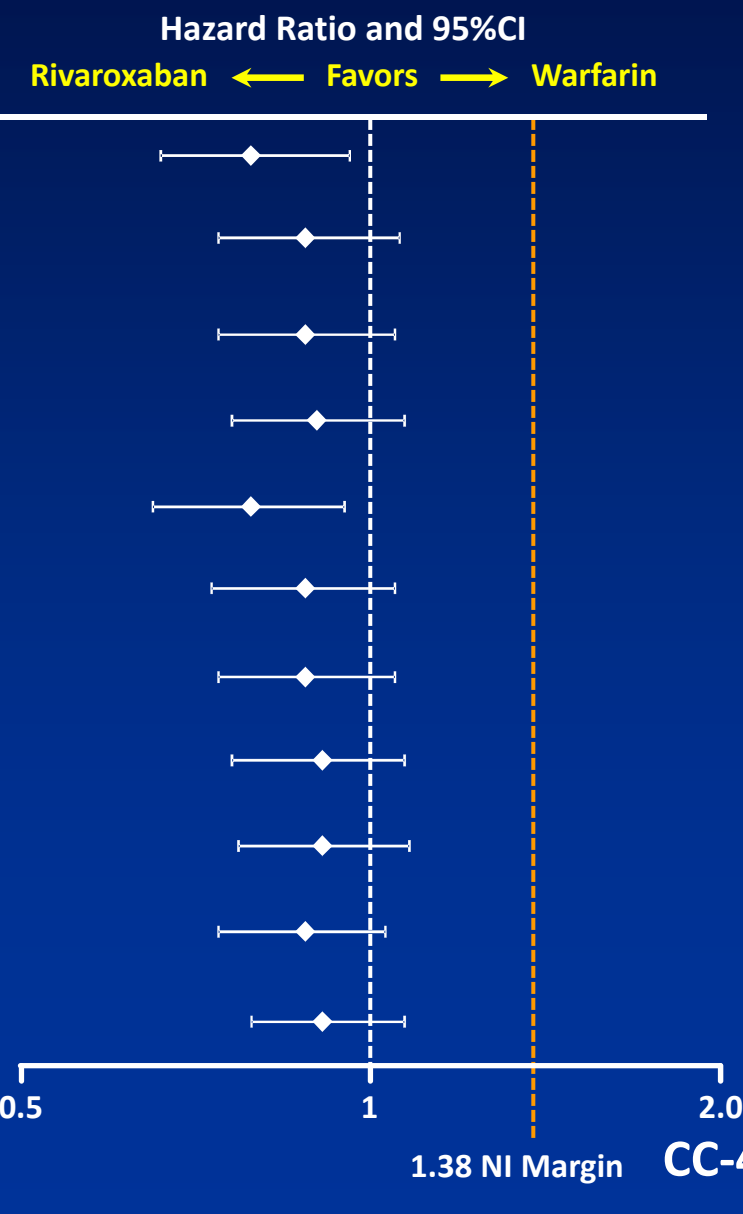
Endpoint	Population/ Data Scope	Rivaroxaban Rate/ 100 pt-yrs	Warfarin Rate/ 100 pt-yrs	HR (95% CI)	p-value
Primary Efficacy[†]	Per-Protocol/ On-Treatment	1.71	2.16	0.79 (0.66,0.96)	<0.001 (non-inferiority)

[†]Stroke and non-CNS Systemic Embolism

ROCKET AF trial

Robust Non-Inferiority
Primary Efficacy Endpoint† Additional Analyses

	Rivaroxaban n/N (%)	Warfarin n/N (%)
Per Protocol, On-Treatment	188/6958 (2.70)	241/7004 (3.44)
Per Protocol, Last Dose Plus 7 Days	219/6958 (3.15)	253/7004 (3.61)
Per Protocol, Last Dose Plus 14 Days	233/6958 (3.35)	269/7004 (3.84)
Per Protocol, Last Dose Plus 30 Days	247/6958 (3.55)	279/7004 (3.98)
Safety, On-Treatment	189/7061 (2.68)	243/7082 (3.43)
Safety, Last Dose Plus 7 Days	220/7061 (3.12)	255/7082 (3.60)
Safety, Last Dose Plus 14 Days	235/7061 (3.33)	271/7082 (3.83)
Safety, Last Dose Plus 30 Days	251/7061 (3.55)	281/7082 (3.97)
ITT – Follow-Up Visit	257/7081 (3.63)	285/7090 (4.02)
ITT – Site Notification	269/7081 (3.80)	306/7090 (4.32)
ITT – Regardless of Treatment Exposure	293/7081 (4.14)	320/7090 (4.51)



†Stroke and non-CNS systemic embolism

ROCKET AF trial

Pre-specified Statistical Testing Hierarchy

Endpoint	Population/ Data Scope	Rivaroxaban Rate/ 100 pt-yrs	Warfarin Rate/ 100 pt-yrs	HR (95% CI)	p-value
Primary Efficacy†	Per-Protocol/ On-Treatment	1.71	2.16	0.79 (0.66,0.96)	<0.001 (non-inferiority)
⇩					
Primary Efficacy†	Safety/ On-Treatment	1.70	2.15	0.79 (0.65,0.95)	0.015 (superiority)

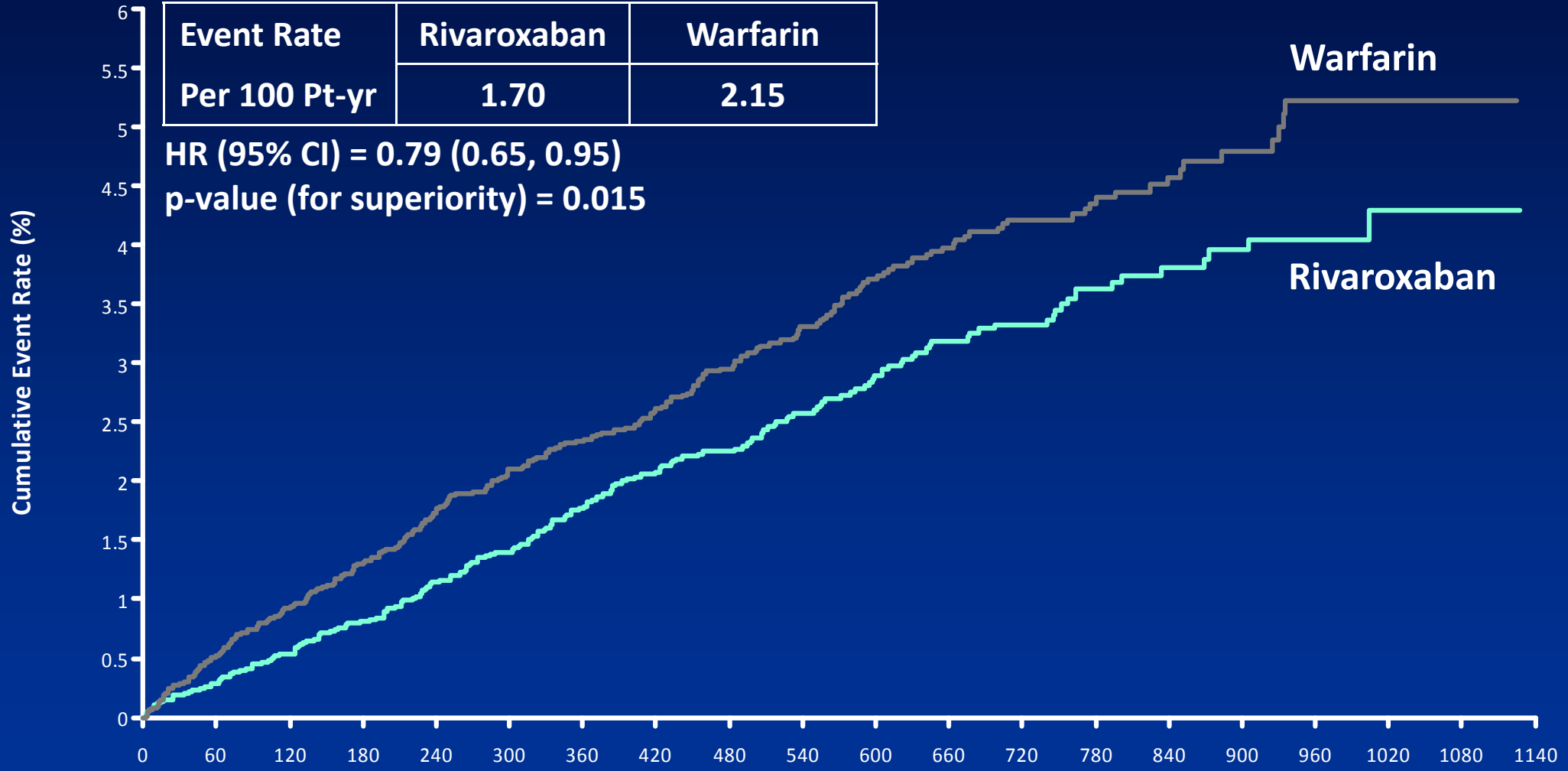
†Stroke and non-CNS Systemic Embolism

ROCKET AF trial

Time to First Primary Efficacy Endpoint
Safety/On-Treatment

Event Rate	Rivaroxaban	Warfarin
Per 100 Pt-yr	1.70	2.15

HR (95% CI) = 0.79 (0.65, 0.95)
p-value (for superiority) = 0.015



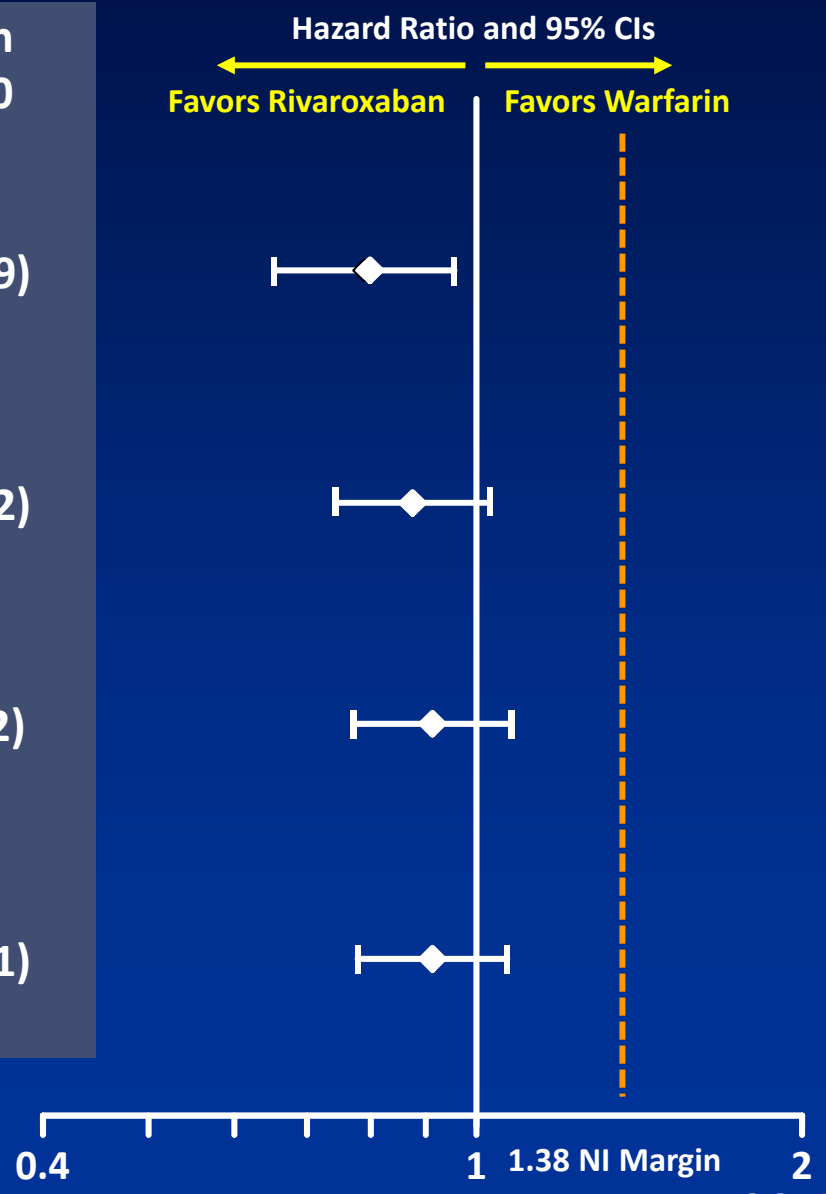
No. Subjects at Risk

Rivaroxaban	7061	6586	6298	6056	5866	5688	5544	5162	4471	4004	3456	2945	2514	2005	1519	1072	644	307	143	46
Warfarin	7082	6663	6394	6182	5974	5767	5604	5235	4515	4071	3520	3010	2568	2035	1552	1069	662	326	150	38

ROCKET AF trial

Primary Efficacy Endpoint
ITT Population Analyses

	Rivaroxaban N = 7081 n (%)	Warfarin N = 7090 n (%)
ITT-On-Treatment	189 (2.67)	240 (3.39)
ITT - Site Notification	269 (3.80)	306 (4.32)
ITT - Follow-Up Visit	257 (3.63)	285 (4.02)
ITT - Regardless of Treatment Exposure	293 (4.14)	320 (4.51)

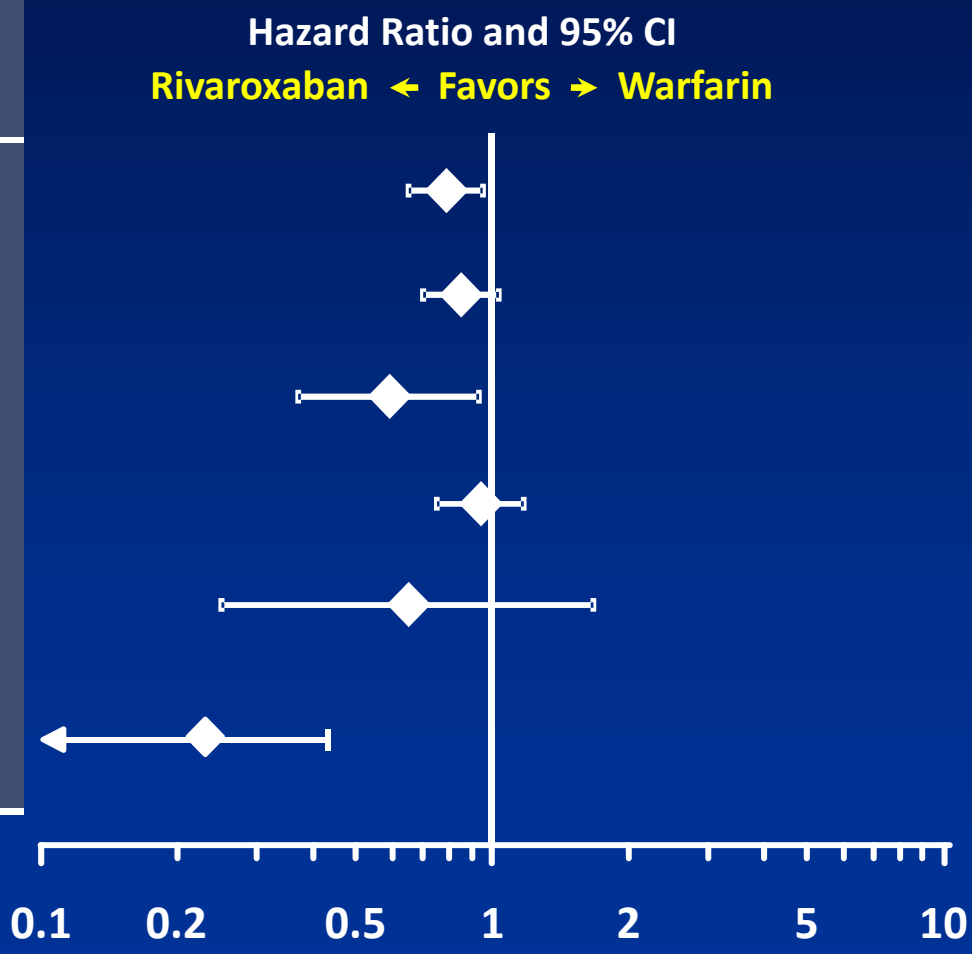


ROCKET AF trial

Efficacy: Primary Endpoint Components, Subgroups and Secondary Endpoints

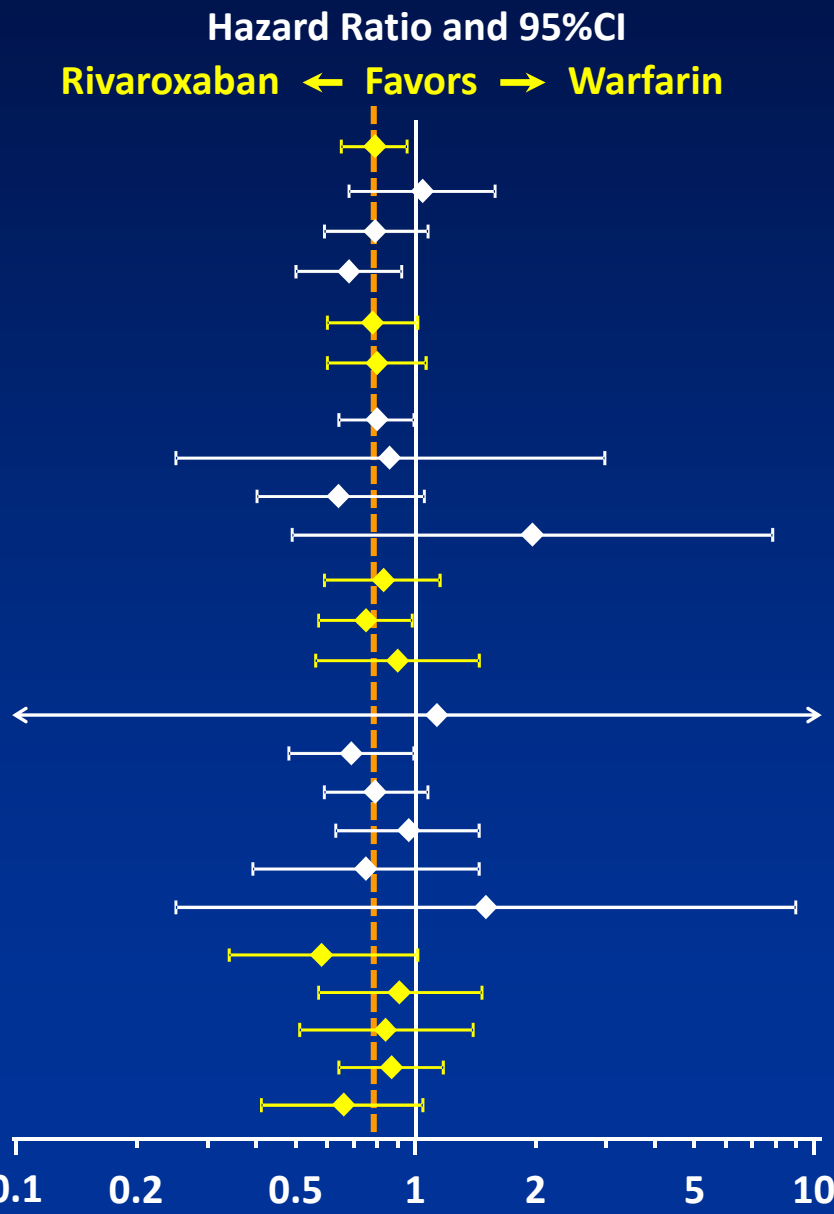
Primary Efficacy Endpoint Components
Safety/On-Treatment

	Rivaroxaban N=7061 n (%)	Warfarin N=7082 n (%)
Primary Efficacy Endpoint	189 (2.68)	243 (3.43)
Total Strokes	184 (2.61)	221 (3.12)
Primary Hemorrhagic	29 (0.41)	50 (0.71)
Primary Ischemic	149 (2.11)	161 (2.27)
Unknown	7 (0.10)	11 (0.16)
Non-CNS Systemic Embolism	5 (0.07)	22 (0.31)



ROCKET AF trial

Primary Efficacy Endpoint - Selected Subgroups
Safety/On-Treatment



Overall

Age (<65; 65 to 75; >75 years)

Sex (Male; Female)

Race (White; Black; Asian; Other)

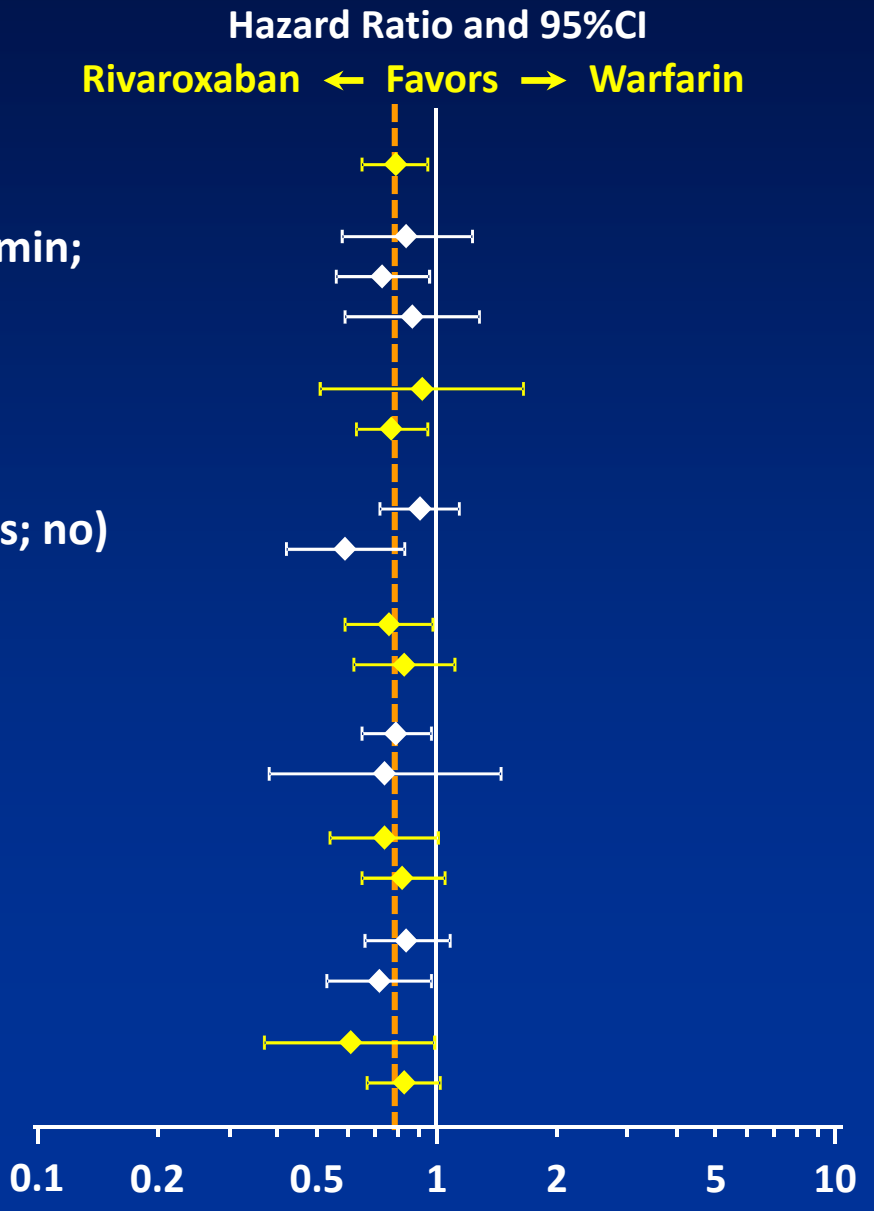
Weight (≤70; >70 to 90; >90 kg)

BMI (≤ 18.5 kg/m^2; >18.5-≤ 25 kg/m^2; >25-≤30 kg/m^2; >30-≤35 kg/m^2; >35-≤40 kg/m^2; >40 kg/m^2)

Region (North America; Latin America; West Europe; East Europe; Asia Pacific)

ROCKET AF trial

Primary Efficacy Endpoint - Selected Subgroups
Safety/On-Treatment



ROCKET AF trial

Secondary Efficacy Endpoints
Safety/On-Treatment

Endpoints	Rivaroxaban N= 7061 n (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7082 n (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin HR (95% CI)	Rivaroxaban vs. Warfarin p-value
Secondary Efficacy Endpoint 1†	346 (4.90)	3.11	410 (5.79)	3.63	0.86 (0.74,0.99)	0.034*
Secondary Efficacy Endpoint 2††	433 (6.13)	3.91	519 (7.33)	4.62	0.85 (0.74,0.96)	0.010*
Myocardial Infarction	101 (1.43)	0.91	126 (1.78)	1.12	0.81 (0.63,1.06)	0.121
All Cause Mortality	208 (2.95)	1.87	250 (3.53)	2.21	0.85 (0.70,1.02)	0.073
Vascular Death	170 (2.41)	1.53	193 (2.73)	1.71	0.89 (0.73,1.10)	0.289
Non-vascular Death	21 (0.30)	0.19	34 (0.48)	0.30	0.63 (0.36,1.08)	0.094
Unknown Death	17 (0.24)	0.15	23 (0.32)	0.20	0.75 (0.40,1.41)	0.370

†Secondary Efficacy Endpoint 1: Stroke, non-CNS Embolism, Vascular Death

†† Secondary Efficacy Endpoint 2: Stroke, non-CNS Embolism, Vascular Death, and MI

* Statistically significant at 0.05 (two-sided)

Efficacy Summary

- ROCKET AF was a double-blind study in a high stroke risk population
- Rivaroxaban is
  - Non-inferior to warfarin (all populations and observation periods)
  - Superior to warfarin while on treatment (all populations)
- Substantial reduction in hemorrhagic strokes
- Consistent results across subgroups and for secondary endpoints

ROCKET AF: Safety

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Johnson & Johnson Pharmaceutical

Research and Development , L.L.C.

Major Bleeding

- Clinically **overt** bleeding associated with:
  - Fall in hemoglobin ≥ 2 g/dL, or
  - Transfusion of ≥ 2 units of packed red blood cells or whole blood, or
  - Bleeding into critical anatomic site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
  - Fatal outcome

Non-Major Clinically Relevant Bleeding

- Overt bleeding not meeting the criteria for major bleeding but requiring
  - Medical intervention
  - Unscheduled contact (visit or telephone) with a physician
  - Interruption of study treatment (temporary or permanent)
  - Associated with discomfort or that which impairs activities of daily living

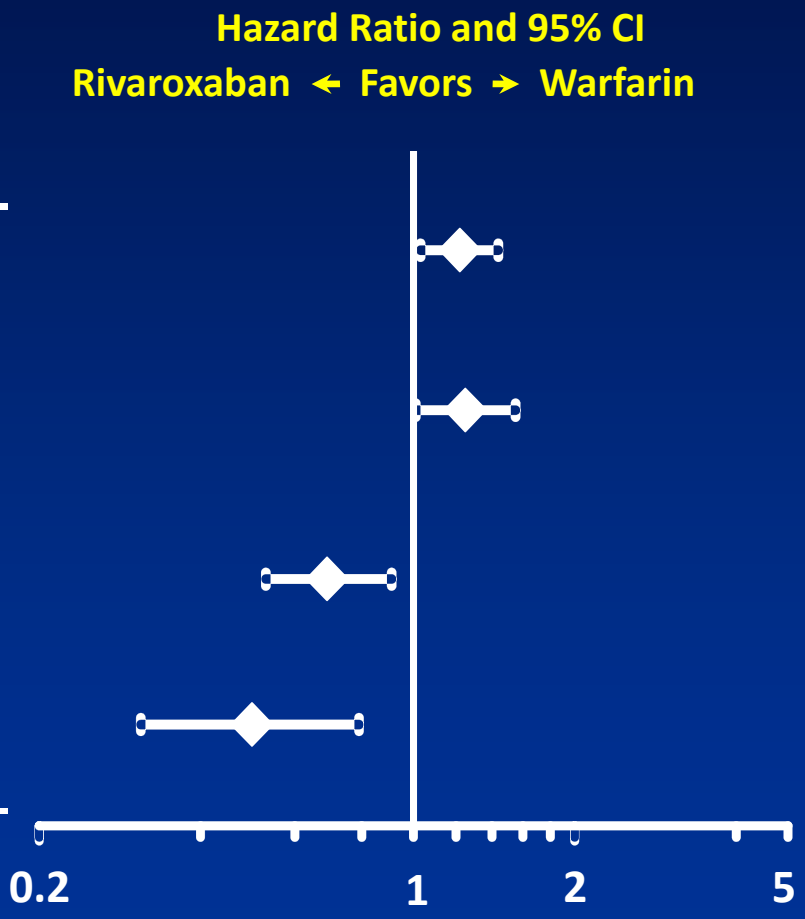
Principal Safety Endpoint†
Safety/On-Treatment

Bleeding	Rivaroxaban N=7111 n (rate)	Warfarin N=7125 n (rate)	HR (95% CI)	p-value
Principal Safety Endpoint	1475 (14.91)	1449 (14.52)	1.03 (0.96, 1.11)	0.442
Major	395 (3.60)	386 (3.45)	1.04 (0.90, 1.20)	0.576
NMCR	1185 (11.80)	1151 (11.37)	1.04 (0.96, 1.13)	0.345

†composite of major and non-major clinically relevant bleeding events
Rate = number of events per 100 patient-years
n = subjects with events; NMCR = non-major clinically relevant
ROCKET AF trial

Major Bleeding Events
Safety/On-Treatment

	Rivaroxaban N=7111 n (rate)	Warfarin N=7125 n (rate)	Hazard Ratio and 95% CI
Hemoglobin drop ≥2 g/dL	305 (2.77)	254 (2.26)	1.22 (1.03,1.44)
Transfusion	183 (1.65)	149 (1.32)	1.25 (1.01,1.55)
Critical Organ/Site	91 (0.82)	133 (1.18)	0.69 (0.53,0.91)
Death	27 (0.24)	55 (0.48)	0.50 (0.31,0.79)



Rate = number of events per 100 patient-years; n = subjects with events
Critical organ/site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal

ROCKET AF trial

Major Bleeding with Blood Transfusion ≥4 Units†
Safety/On-Treatment

		Rivaroxaban N=395 n (rate)	Warfarin N=386 n (rate)	Rivaroxaban vs. Warfarin HR (95%CI)
Total no. Subjects receiving transfusion ≥4 units for a Major Bleeding Event		64 (0.57)	64 (0.57)	1.01 (0.72,1.43)
Mucosal	Gastrointestinal-Upper	43	36	
	Gastrointestinal-Lower	6	11	
	Other mucosal	9	1	
Other Sites	Hematoma	2	4	
	Other non-mucosal	5	12	

†pRBC or whole blood
N=number of subjects with major bleeding events
Rate = number of events per 100 patients-years

ROCKET AF trial

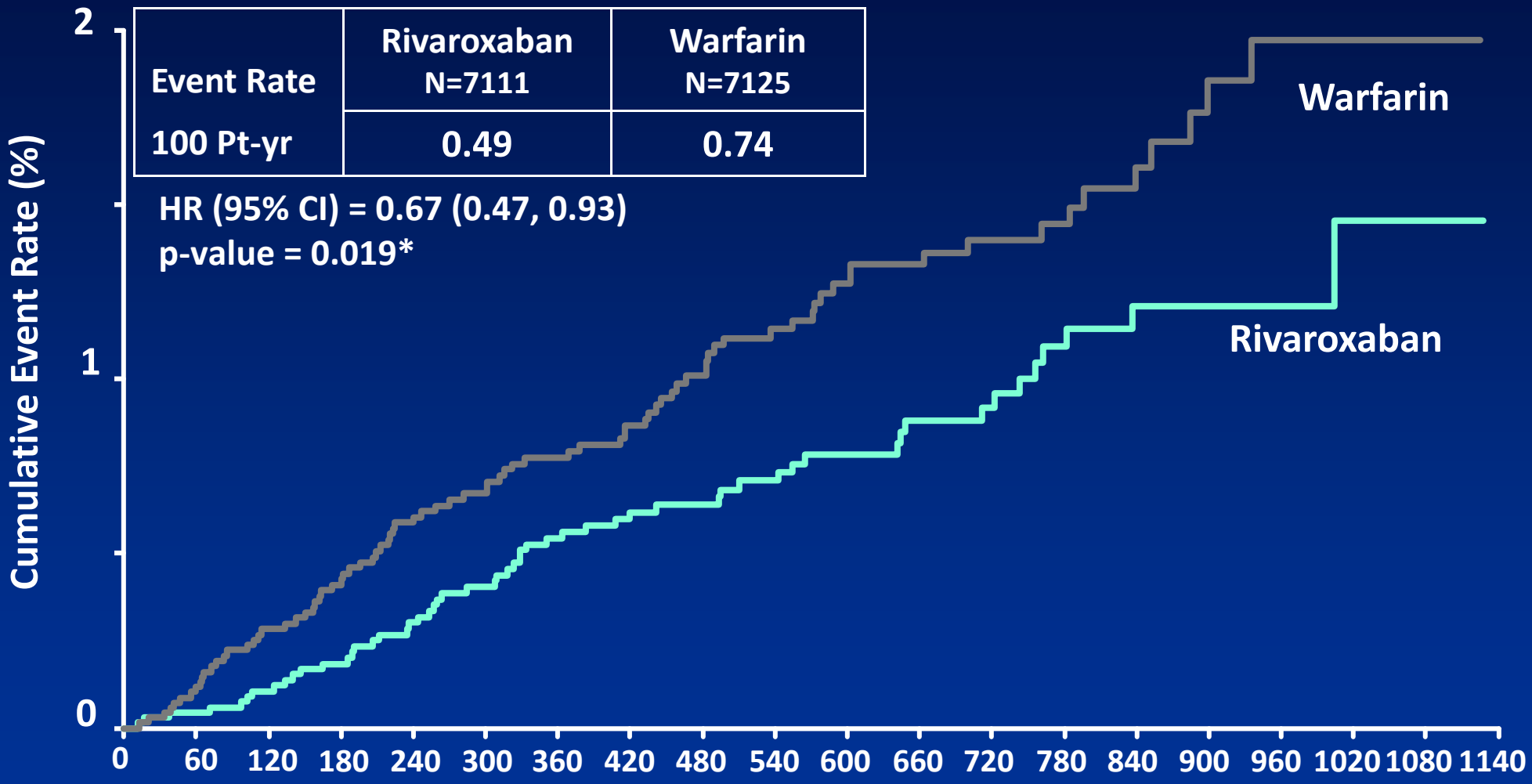
Intracranial Hemorrhage

- ICH included intracerebral bleeding (intraparenchymal, intraventricular) and subdural hematoma, subarachnoid hemorrhage, and epidural hematoma
  - Each ICH was adjudicated as a bleeding event and also to determine if met criteria for a primary hemorrhagic stroke
- Hemorrhagic strokes were included in both the primary efficacy and principal safety endpoints

Time to First Intracranial Hemorrhage
Safety/On-Treatment

Event Rate	Rivaroxaban N=7111	Warfarin N=7125
100 Pt-yr	0.49	0.74

HR (95% CI) = 0.67 (0.47, 0.93)
p-value = 0.019*



Number of Subjects at risk										
Rivaroxaban	6635	6093	5711	5176	4009	2947	2006	1074	308	46
Warfarin	6707	6222	5795	5256	4083	3016	2040	1070	326	38

* not adjusted for multiplicity
ROCKET AF trial

Intracranial Hemorrhage
Safety/On-Treatment

	Rivaroxaban N=7111 n (%)	Warfarin N=7125 n (%)
Intracranial Hemorrhage (ICH)	55 (0.77)	84 (1.18)
Primary Hemorrhagic Stroke	29 (0.41)	50 (0.70)
Primary Ischemic Stroke with Hemorrhagic Conversion	5 (0.07)	6 (0.08)
All Other ICH	21 (0.30)	28 (0.39)

n = subjects with events

ROCKET AF trial

Major Bleeding Events with Fatal Outcome
Safety/On-Treatment

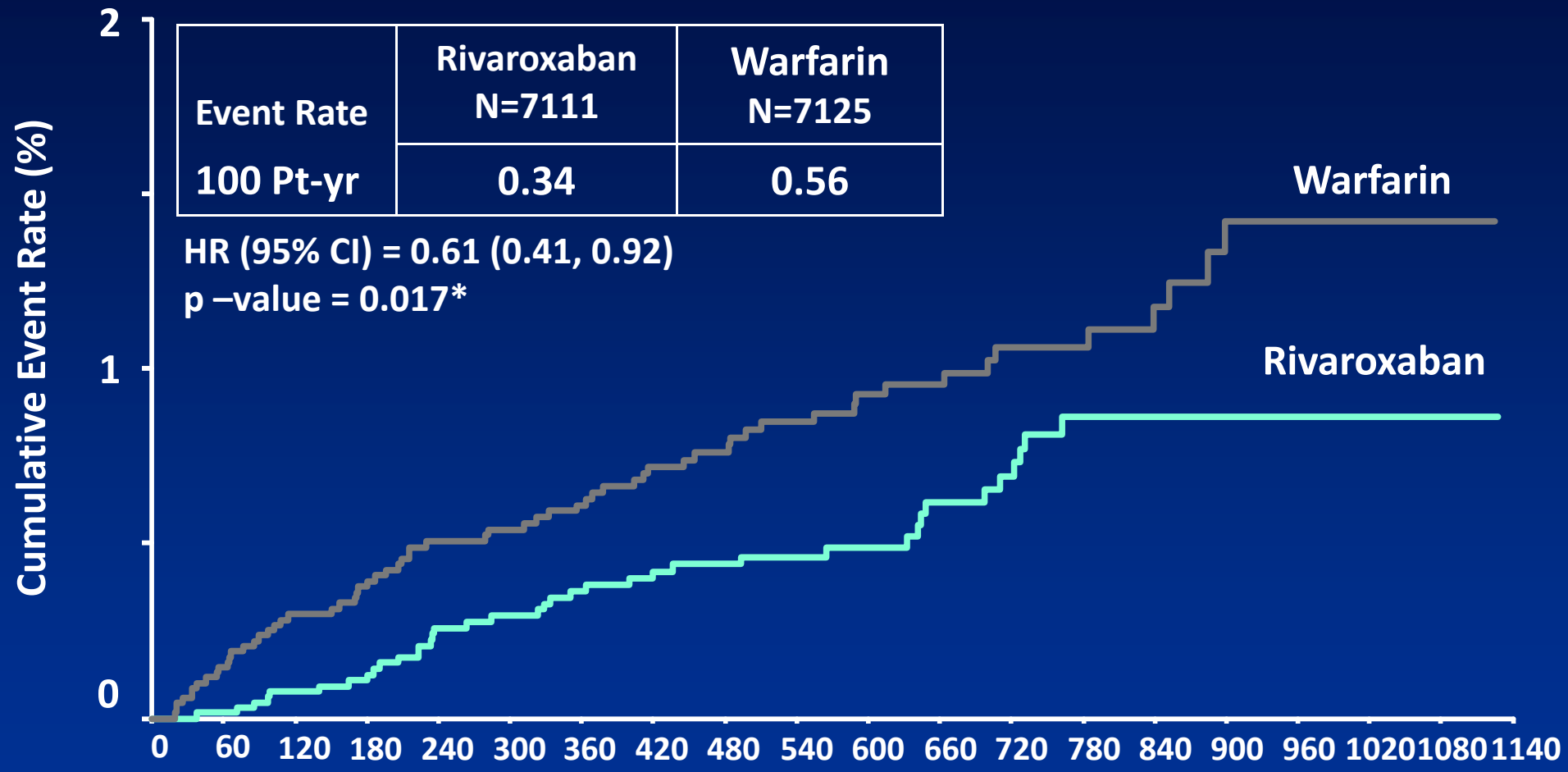
Bleeding Site	Rivaroxaban n/J (%)	Warfarin n/J (%)
Total no. subjects with major bleeding events with fatal outcome†	27/395 (6.84)	55/386 (14.25)
Intracranial	24/55 (43.64)	42/84 (50.00)
Gastrointestinal – Upper	1/151 (0.66)	3/104 (2.88)
Gastrointestinal – Lower	0/49	2/32 (6.25)
Other	2/151 (1.32)	8/181 (4.42)

†As adjudicated by the CEC
n = subjects who died; J = number of subjects with major bleeding site

Time to Fatal Bleeding†
Safety/On-Treatment

Event Rate	Rivaroxaban N=7111	Warfarin N=7125
100 Pt-yr	0.34	0.56

HR (95% CI) = 0.61 (0.41, 0.92)
p –value = 0.017*



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Rivaroxaban	6635	6094	5711	5176	4009	2947	2007	1074	308	46
Warfarin	6707	6224	5795	5256	4083	3016	2040	1070	326	38

† Using Broad definition
* not adjusted for multiplicity
ROCKET AF trial

Fatal Bleeding Events
Safety/On-Treatment

Fatal Bleeding	Rivaroxaban N=7111 n (rate)	Warfarin N=7125 n (rate)	Rivaroxaban vs. Warfarin HR (95% CI)	p-value
Using Broad Definition	38 (0.34)	63 (0.56)	0.61 (0.41,0.92)	0.017*
Using Narrow Definition	21 (0.19)	43 (0.38)	0.50 (0.29,0.84)	0.008*
Using CEC Major Bleed Category Death	27 (0.24)	55 (0.48)	0.50 (0.31, 0.79)	0.003*

Rate = number of events per 100 patient-years
n = subjects with events
* not adjusted for multiplicity

ROCKET AF trial

Adverse Events Summary
Safety/Treatment-Emergent

	Rivaroxaban N=7111 n (%)	Warfarin N=7125 n (%)	Rivaroxaban Minus Warfarin Diff (%) 95% CI (%)
Total no. of Subjects with Adverse Events	5791 (81.44)	5810 (81.54)	-0.11 (-1.38, 1.17)
Serious Adverse Events	2489 (35.00)	2598 (36.46)	-1.46 (-3.04, 0.11)
Adverse Events Leading to Permanent Study Drug Discontinuation	1043 (14.67)	1004 (14.09)	0.58 (-0.58,1.73)
Adverse Events with Outcome of Death	319 (4.49)	387 (5.43)	-0.95 (-1.66, -0.23)

Safety Summary

- Compared with warfarin, rivaroxaban shows
  - Similar major bleeding event rates with
    - More events associated with transfusion and/or hemoglobin decrease (primarily gastrointestinal tract)
    - Fewer of the most important bleeding events (critical organ and/or fatal)
  - Similar rates of AEs, SAEs, and premature discontinuations
  - Fewer AEs with outcome of death

ROCKET AF: Benefit Risk Balance, Key Issues and Conclusions

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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.

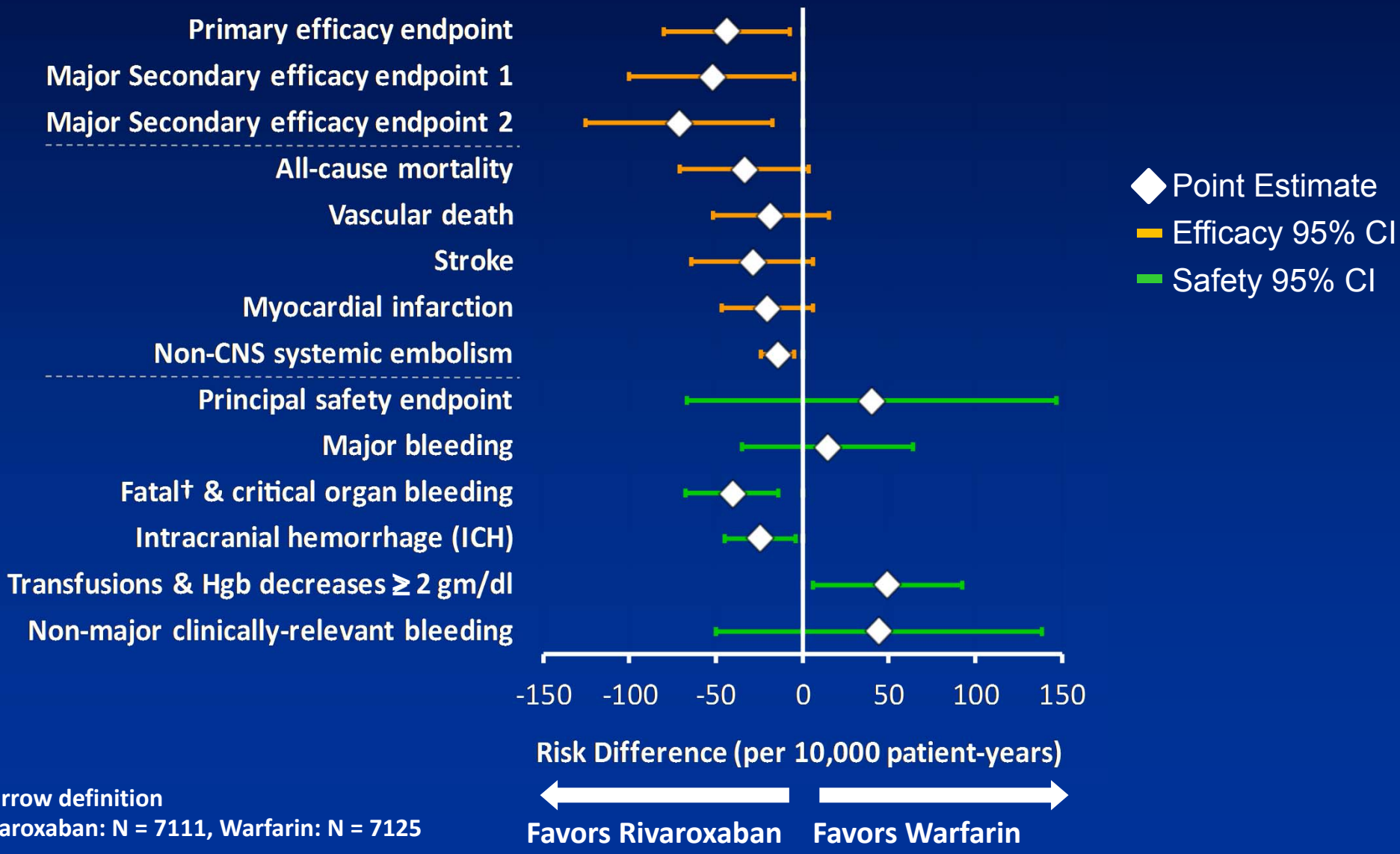
Warfarin and Atrial Fibrillation

- Proven benefits
  - Reduction in stroke and arterial embolus
- Proven risks
  - Bleeding, especially intracranial bleeding
  - Other miscellaneous toxicities
  - Inconvenience (diet, monitoring, etc.)
- Failure to use treatment in situations in which it is known to be effective
  - Doctors—concerned about bleeding
  - Patients—concerned about complexity, bleeding

ROCKET AF

- Double-blind global trial in a high-risk population
- Primary intention–find an alternative to warfarin
- Plan was to move on to superiority testing if non-inferiority was demonstrated
- Understood from the beginning that high-risk population would lead to significant discontinuation with attendant analytical issues
- Careful measurement of a broad range of adverse events to look for signals of risk other than bleeding

Risk Differences for Composite Endpoints and Components Safety/On-Treatment



†Narrow definition
Rivaroxaban: N = 7111, Warfarin: N = 7125

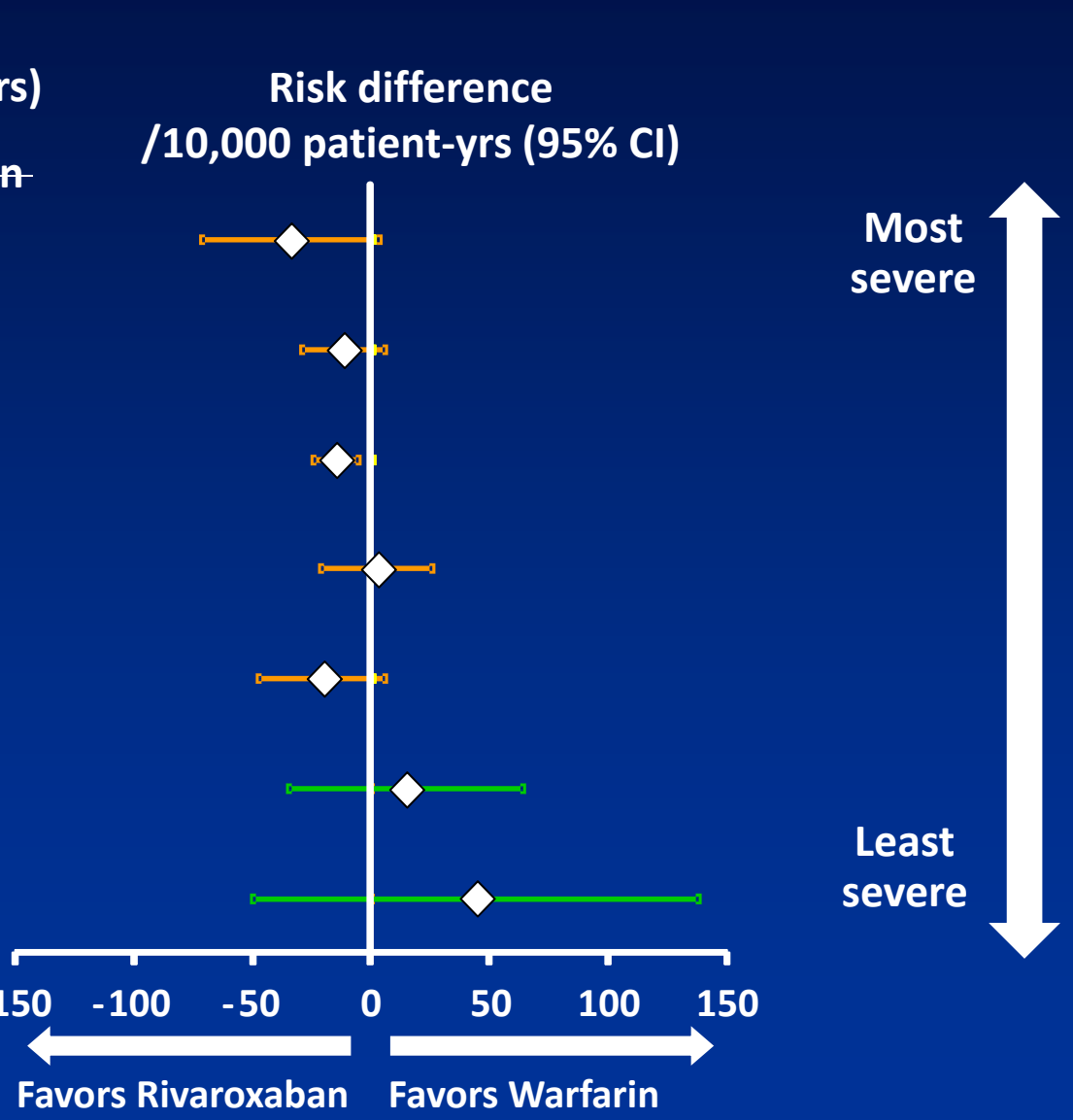
ROCKET AF Trial

What do Patients and Doctors Want?

- Long history of studies of preferences related to anticoagulation in general
- Generally patients and doctors rate outcomes in the following order
  - Death
  - Disabling stroke
  - Non-disabling stroke
  - Myocardial infarction
  - Major bleed
  - Minor bleed

ROCKET AF: Risk Differences by Clinical Severity/Impact†
All Patients
Safety/On-Treatment

Endpoint	# of Events (/10,000 patient-years) Rivaroxaban n	Warfarin
All-cause mortality	188	222
Disabling stroke	38	50
Non-CNS systemic embolism	4	19
Non-disabling stroke	79	77
Myocardial infarction	91	112
Major bleeding	360	345
Non-major clinically-relevant bleeding	1180	1137



† Endpoints in order of health state utility, a value that reflects preference for health states relative to perfect health and death. Values from Tufts' CEA registry.

Benefit Risk Summary

Rivaroxaban has a favorable benefit risk balance compared with warfarin

- Benefits
  - Non-inferior for stroke or systemic embolism prevention by all analyses; superior while on treatment
  - Lower rate of intracranial and fatal bleeding
  - Benefits in categories most valued by patients and doctors
  - Once daily oral fixed dose, no INR monitoring, limited potential for drug/food interactions
- Risk
  - Increase in the rate of blood transfusions and $\geq$2 gm/dL falls in hemoglobin concentration
- No significant difference in major bleeding overall

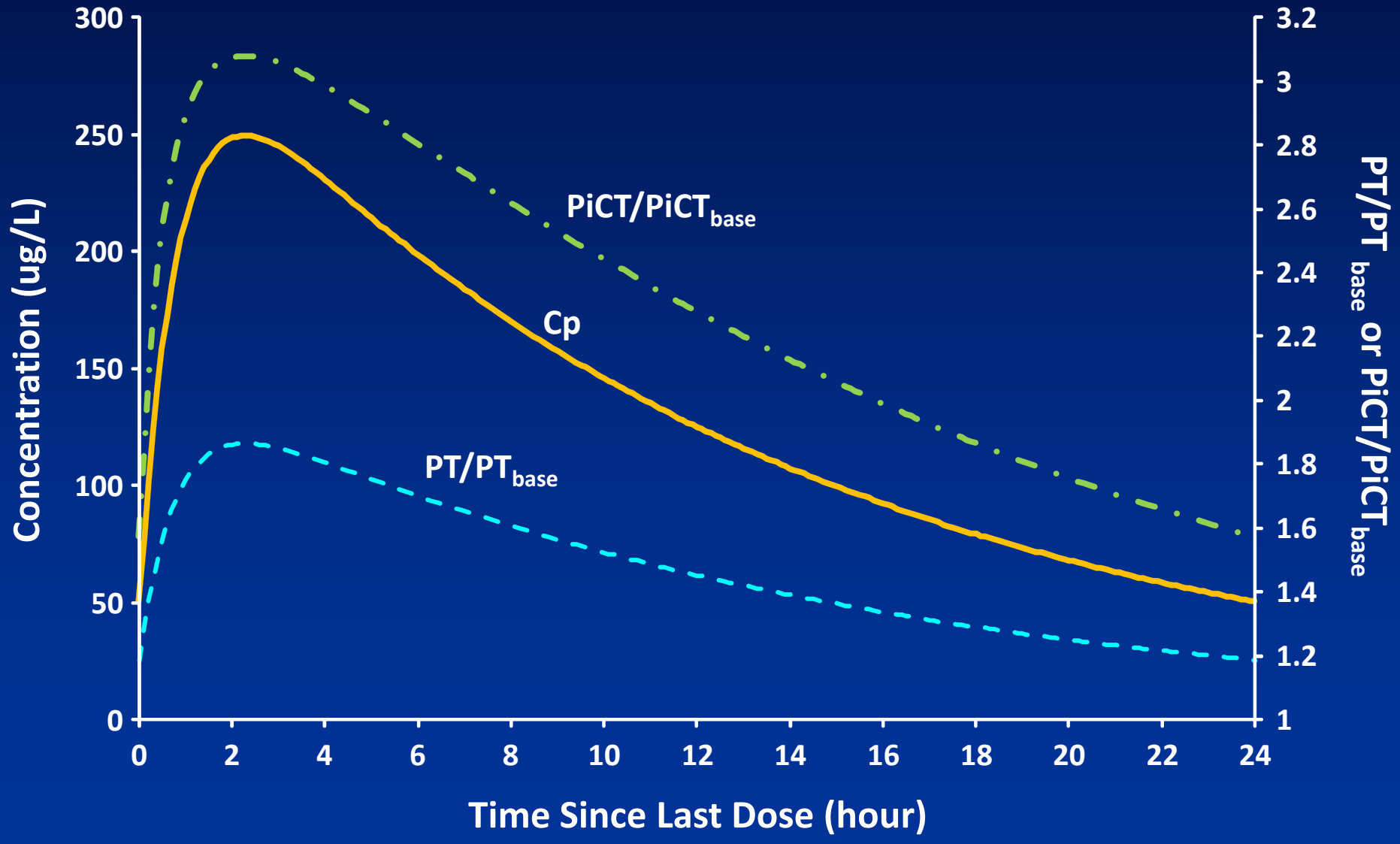
Key Questions Raised in the FDA Review

- Dose and regimen selection
- Events after study drug discontinuation
- Time in therapeutic range (TTR)
- Approval standard in 2011

ROCKET AF Dose Selection

- Phase 2 Deep Vein Thrombosis treatment data
  - Total daily dose range 20 mg to 60 mg
  - Flat dose response for efficacy
  - Shallow dose response for bleeding
  - Once vs. twice daily dosing similar results
- Coagulation system modeling for warfarin efficacy
- Pharmacodynamic effects at trough with once daily dosing in Phase 1

ROCKET AF Population PK/PD Model Steady State Rivaroxaban 20 mg Dose



Once vs. Twice Daily Rivaroxaban Dosing Phase 2 Studies 20 mg Total Daily Dose

	Efficacy		Bleeding	
Indication	20 mg qd n/N (%)	10 mg bid n/N (%)	20 mg qd n/N (%)	10 mg bid n/N (%)
DVT Prevention*	9/106 (8.5)	12/101 (11.9)	6/139 (4.3)	3/133 (2.3)
DVT Treatment**	3/115 (2.6)	2/100 (2.0)	1/135 (0.7)	2/119 (1.7)
ATLAS ACS	16/304 (5.3)	20/307 (6.5)	48/301 (16.0)	41/302 (13.6)

*Cross-study comparison between two of the 4 Phase 2 studies
** Cross-study comparison between the two Phase 2 studies

Dose and Regimen Selection Summary

- Modeling consistent with good choice of dose
- Phase 2 data supported either once or twice daily dosing
  - Once daily dosing clinically preferred
  - Better adherence with once daily dosing
- The dose tested achieved the desired results

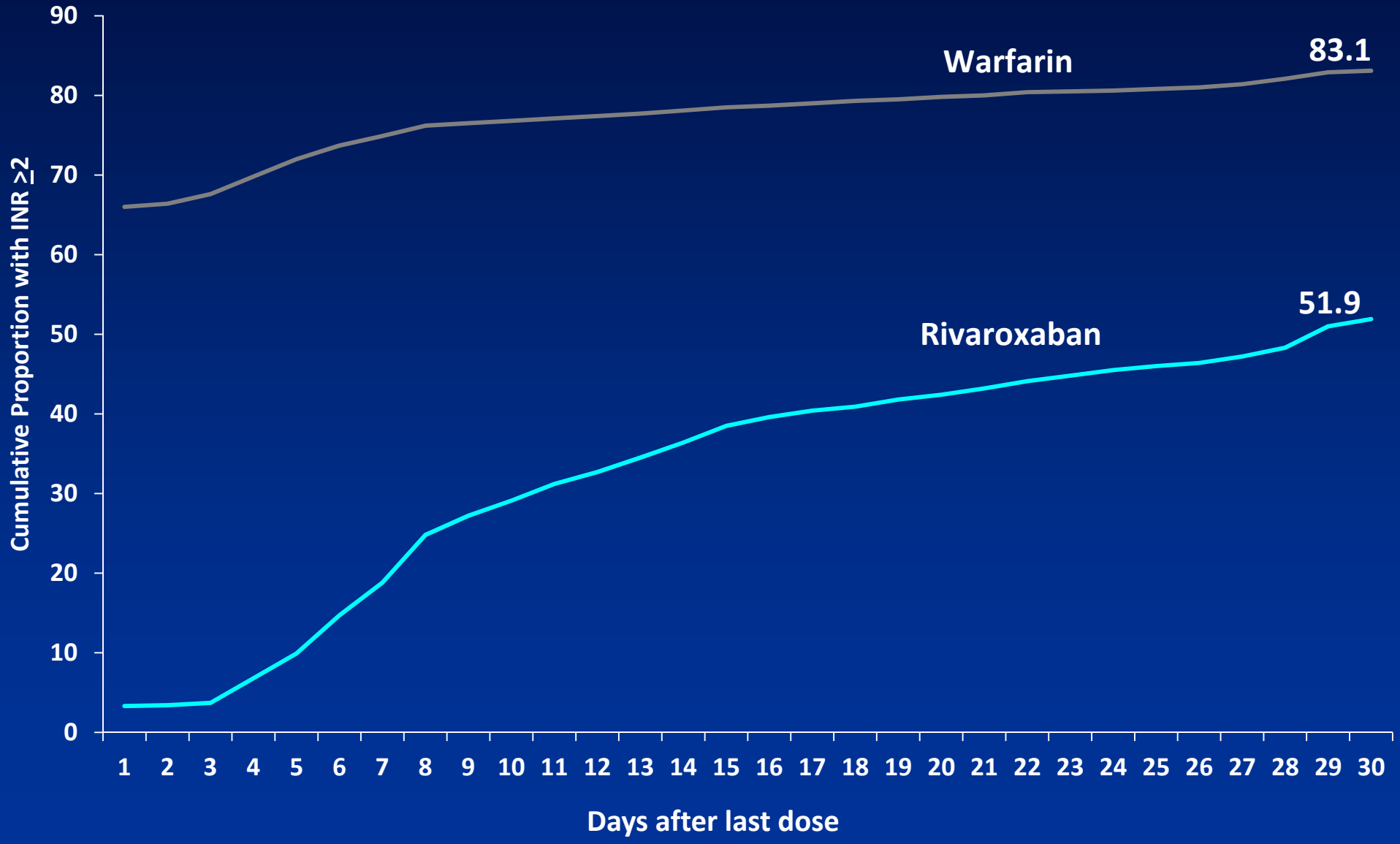
Thrombotic Events after Discontinuation of Study Drug

Study Specific End of Treatment Transition

- To maintain study blind
  - Started VKA at expected maintenance dose
  - No overlap with blinded study drug
  - No INRs for 3 days
  - Heparin bridging therapy allowed but infrequently used
- Impact
  - Imbalance in anticoagulation between treatment groups
- Other options considered but not implemented based on feedback from IDMC review of early discontinuer event rates during the study

Cumulative Proportion Subjects with INR ≥2 Who Completed and Transitioned to VKA

Safety/Days 1 to 30 after the Last Dose



ROCKET AF trial

Post-Therapy Primary Efficacy Endpoint Events
Safety/Days 3 to 30 after the Last Dose

	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	n/N	Event Rate (per 100 pt-yrs)	n/N	Event Rate (per 100 pt-yrs)	HR (95% CI)	p-value
All Participants	64/6843	12.63	42/6807	8.36	1.51 (1.02,2.23)	0.037
Completed Study Medication	22/4587	6.42	6/4652	1.73	3.72 (1.51,9.16)	0.004
Early Study Medication Discontinuation	42/2256	25.60	36/2155	23.28	1.10 (0.71,1.72)	0.663
Temporary interruptions ≥3 days during study†	9/3734	6.20	8/4511	5.05	1.27 (0.49,3.31)	0.617

† From last dose plus 3 days to 3 days after resumption
n=number of interruptions

ROCKET AF trial

Post-Therapy Primary Endpoint plus MI and Vascular Death Endpoint Events

Safety/Days 3-30 after the Last Dose

	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	n/N	Event Rate (per 100 pt-yrs)	n/N	Event Rate (per 100 pt-yrs)	HR (95% CI)	p-value
All Participants	162/6843	31.99	161/6807	32.08	1.00 (0.80,1.24)	0.987
Completed Study Medication	31/4587	9.05	14/4652	4.03	2.24 (1.19,4.20)	0.012
Early Study Medication Discontinuation	131/2256	80.01	147/2155	95.28	0.84 (0.67,1.07)	0.154
Temporary interruptions ≥3 days during study†	17/3735	11.73	18/4511	11.39	1.08 (0.56,2.10)	0.821

† From last dose plus 3 days to 3 days after resumption

n=number of interruptions

ROCKET AF trial

Comparison with Estimated Untreated Event Rate for ROCKET AF Patient Population

- Untreated event rate based on baseline $CHADS_2$ score
  - Original $CHADS_2$: 7.5 per 100 patient-years[1]
  - ATRIA: 5.4 per 100 patient-years [2]
- Observed event rate 6.42 within this range
- Ischemic stroke after transition to VKA
  - 73% with last INR before event <2.0

[1]Gage BF, et al. JAMA. 2001 Jun 13;285(22):2864-70.
[2]Go AS, et al. JAMA. 2003 Nov 26;290(20):2685-92

Overlapping Therapy Recommended for Transition in Clinical Practice

- Maintain continuous anticoagulation
  - Apply same principle as for LMWH to VKA
  - Overlap VKA with rivaroxaban until INR >2.0 at rivaroxaban trough
- Supported by
  - Clinical pharmacology data
  - Experience of overlapping VKA and rivaroxaban at randomization

Summary: Events after Discontinuation

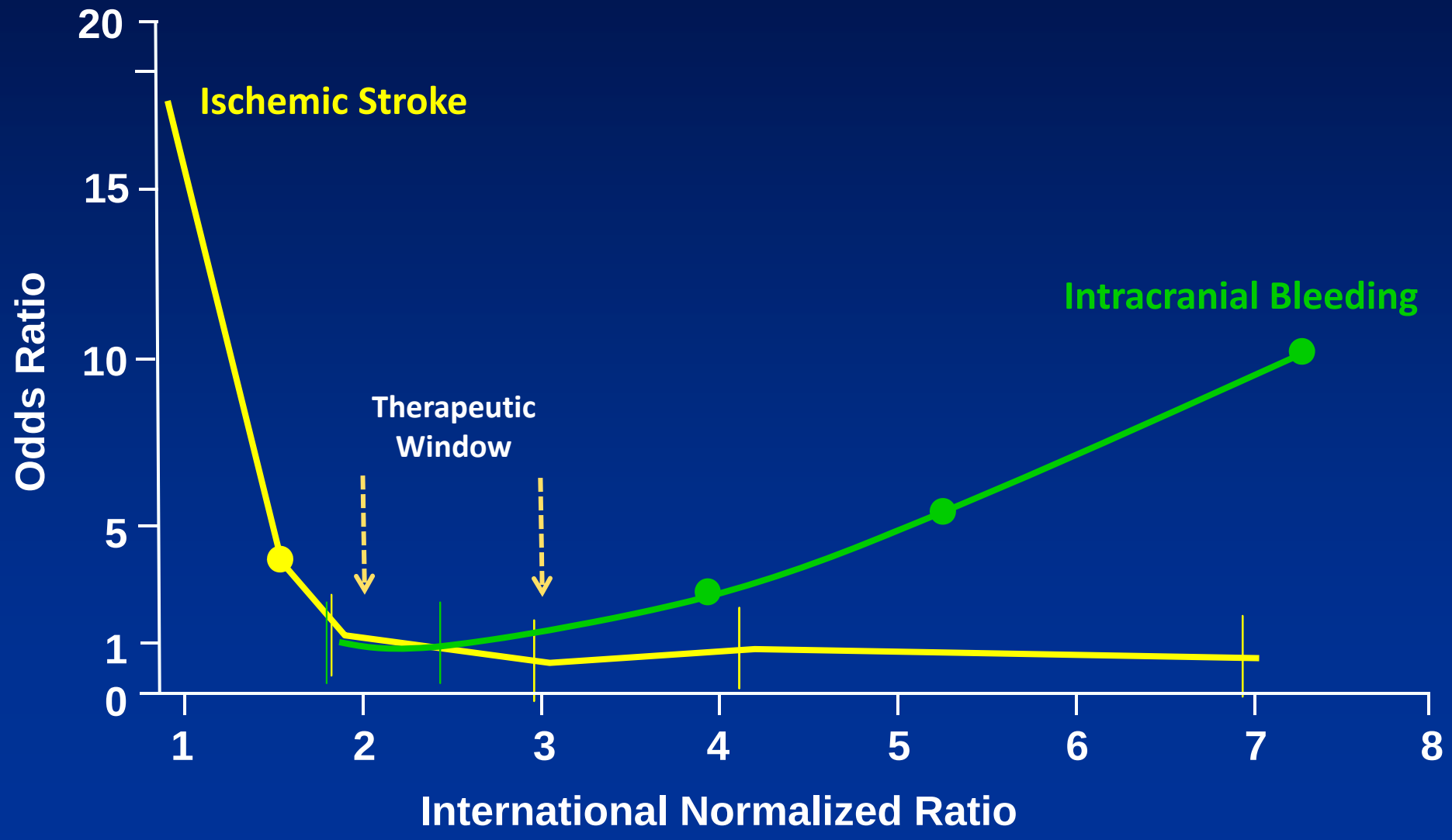
- No excess events in midst of trial
  - Early permanent discontinuation
  - Temporary treatment interruptions
- Excess events at end of trial with rivaroxaban
  - Associated with an imbalance in anticoagulation due to study specific procedures
  - Transition plan has been developed based on pharmacodynamic modeling

Time in Therapeutic Range (TTR)

TTR – Key Points

- TTR is a useful biomarker and quality measure for practice, but it is not a surrogate for anticoagulant benefit risk balance
- ROCKET AF TTR was consistent with standards for use of warfarin considering
  - More complex patients have lower TTR
  - Regional variations are well documented and reproducible
- There is no evidence that TTR affected the benefit risk balance of rivaroxaban compared with warfarin

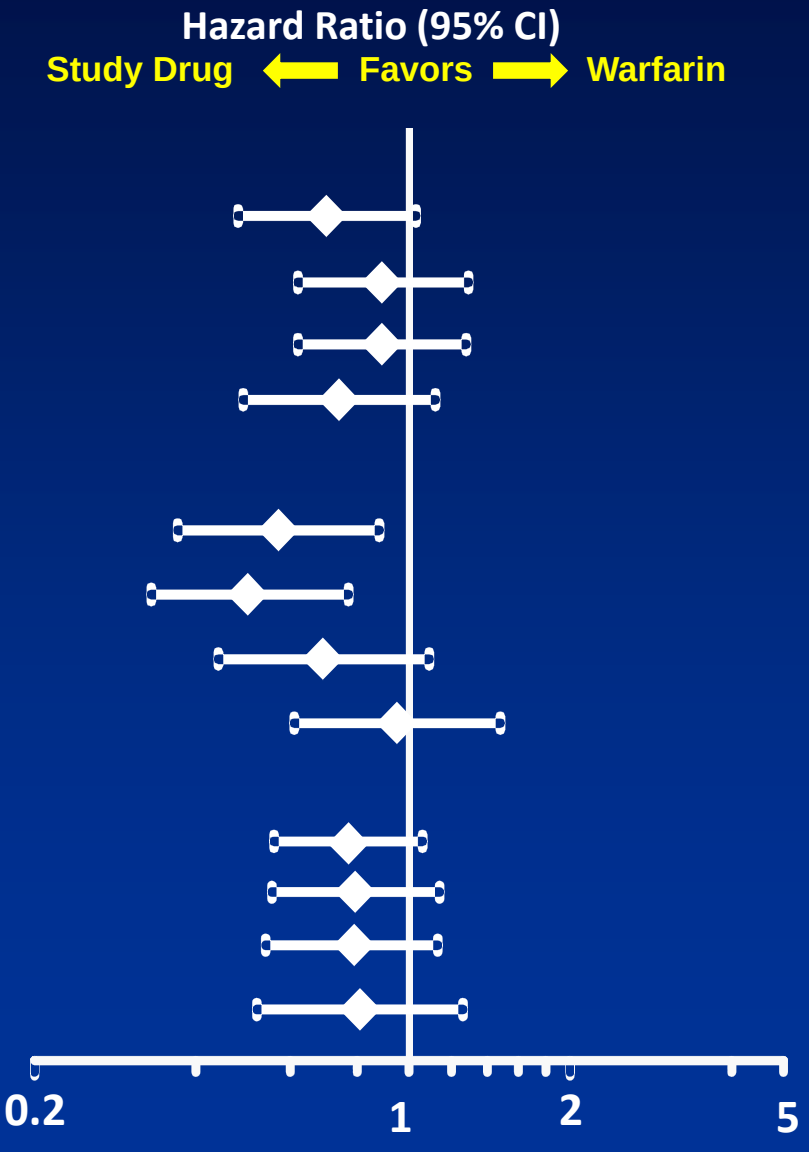
INR: A Useful Quality Measure



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

Primary Efficacy Endpoint by Center TTR ROCKET AF/RE-LY/ARISTOTLE

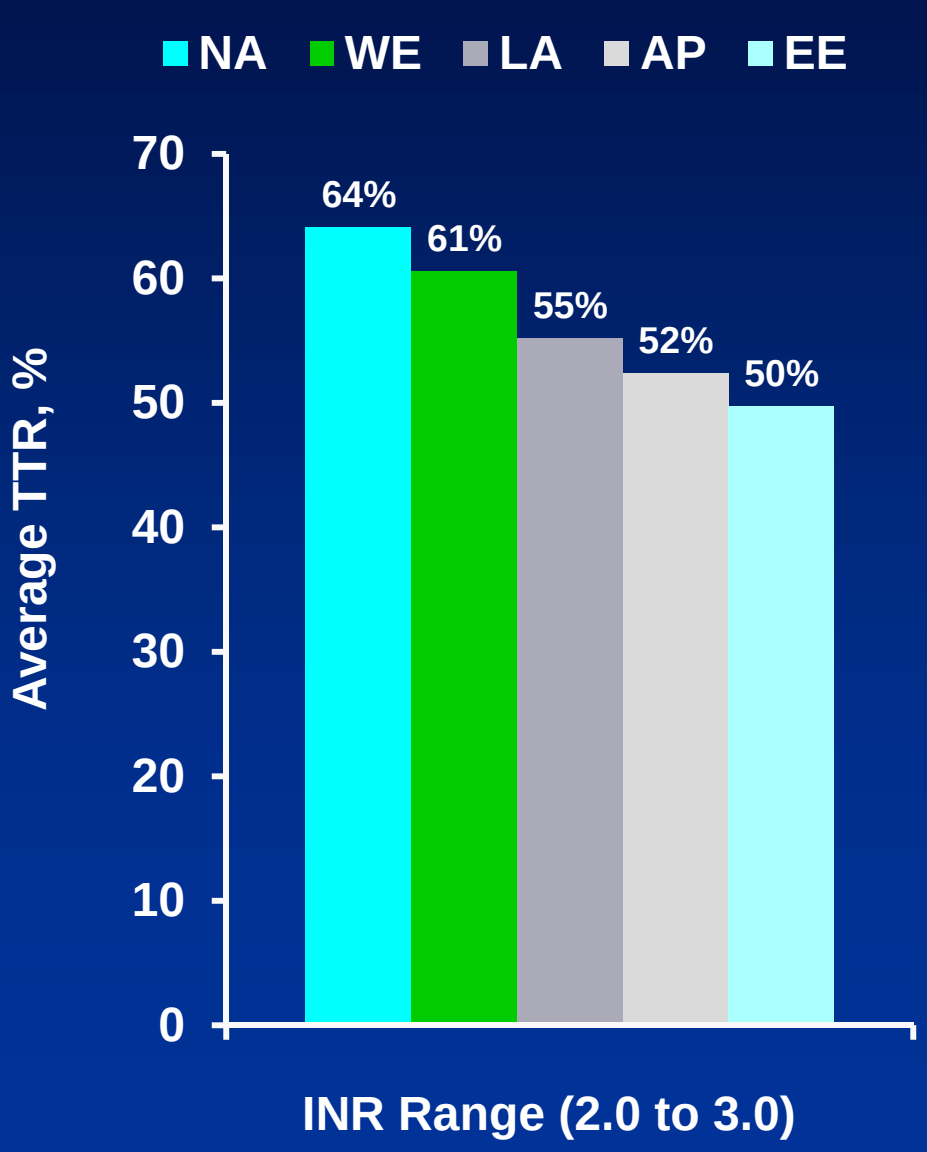
	Treatment Group n/J (rate)	Warfarin n/J (rate)	p-value (interaction)
ROCKET AF			0.736
0.00-50.62%	45/1735 (1.77)	62/1689 (2.53)	
50.71-58.54%	53/1746 (1.94)	63/1807 (2.18)	
58.63-65.71%	54/1734 (1.90)	62/1758 (2.14)	
65.74-100.0%	37/1676 (1.33)	55/1826 (1.80)	
RE-LY (Dabigatran 150 mg)[†]			0.20
<57.1%	32/1509 (1.1)	54/1504 (1.92)	
57.1–65.5%	32/1526 (1.04)	62/1514 (2.06)	
65.5–72.6%	31/1484 (1.04)	45/1487 (1.51)	
>72.6%	38/1514 (1.27)	40/1509 (1.34)	
ARISTOTLE[‡]			0.29
< 58.0%	70/2266 (1.75)	88/2252 (2.28)	
58.0–65.7%	54/2251 (1.30)	68/2278 (1.61)	
65.7–72.2 %	51/2256 (1.21)	65/2266 (1.55)	
> 72.2 %	36/2266 (0.83)	44/2251 (1.02)	

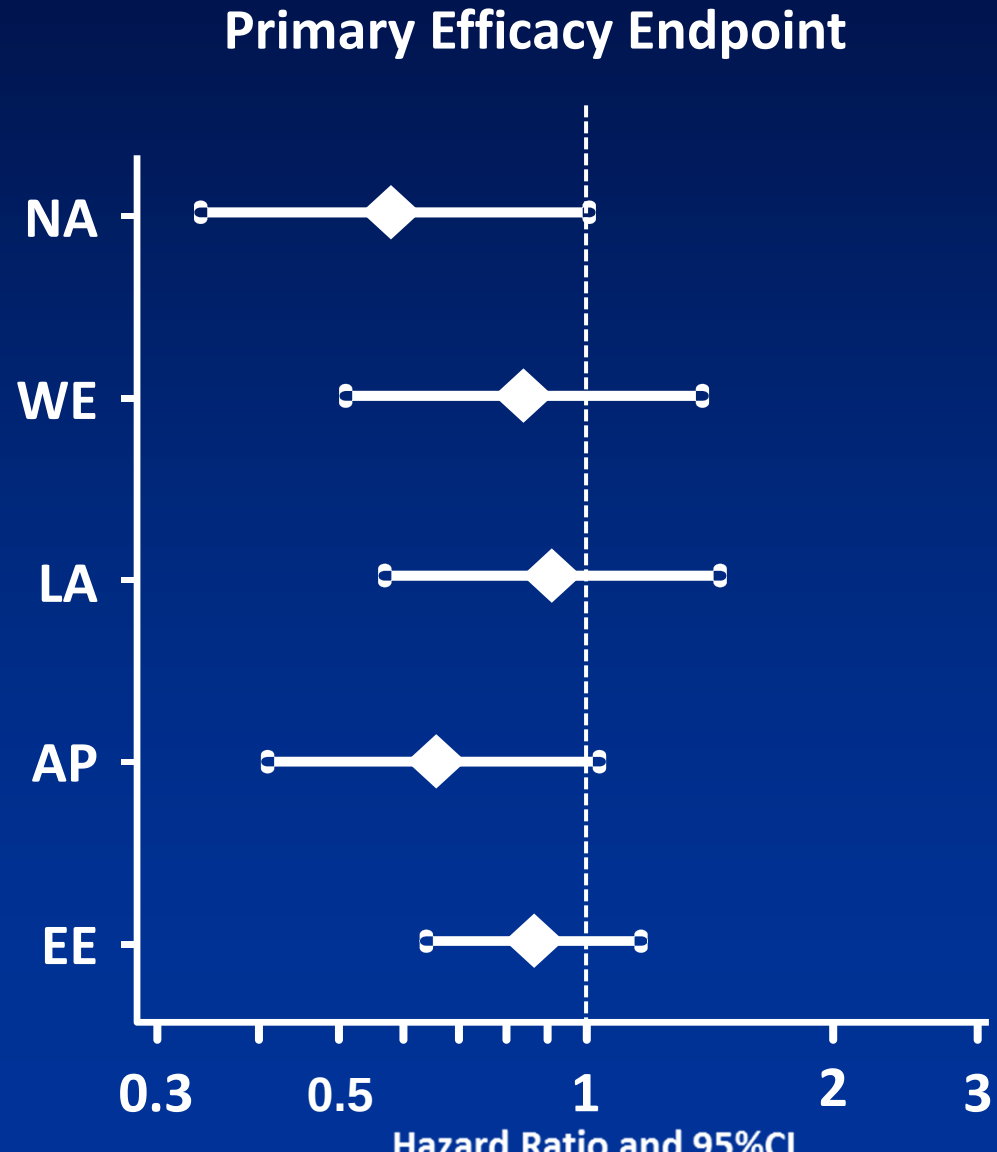


[†]Wallentin L, et al. Lancet 2010;376:975–983.
[‡]Granger, CB. Results of the ARISTOTLE Trial. ESC, France, August, 2011

Rate = number of events per 100 patient-years
n = subjects with events; J = number of subjects in each subgroup

Across Regions with Various Levels of INR Control, Treatment Efficacy is Preserved





ROCKET AF trial

Warfarin Primary Efficacy Event Rates Across Studies by $CHADS_2$ Score

			$CHADS_2$ =2	$CHADS_2$ ≥3	Prior Stroke
Study	TTR	Mean $CHADS_2$ Score	Primary Efficacy Rate	Primary Efficacy Rate	Primary Efficacy Rate
ROCKET AF	55%	3.5	1.7	2.6	2.9
RE-LY[†] (2009)	64%	2.1	1.4	2.7	2.7
ARISTOTLE[‡] (2011)	62%	2.1	1.4	2.8	3.2

[†]Wallentin L, et al. Lancet 2010;376:975–983.
[‡]Granger, CB. Results of the ARISTOTLE Trial. ESC, France, August, 2011
Rate = per 100 patient years

TTR Was Measured Using Conventional Methods

How is TTR Calculated for Individual Patients (iTTR)?

- Rosendaal method was pre-specified for ROCKET AF
  - Linear interpolation of INR values
  - Conservative approach
    - Interruption > 7 days excluded

ROCKET AF Warfarin Group TTR
Safety Population

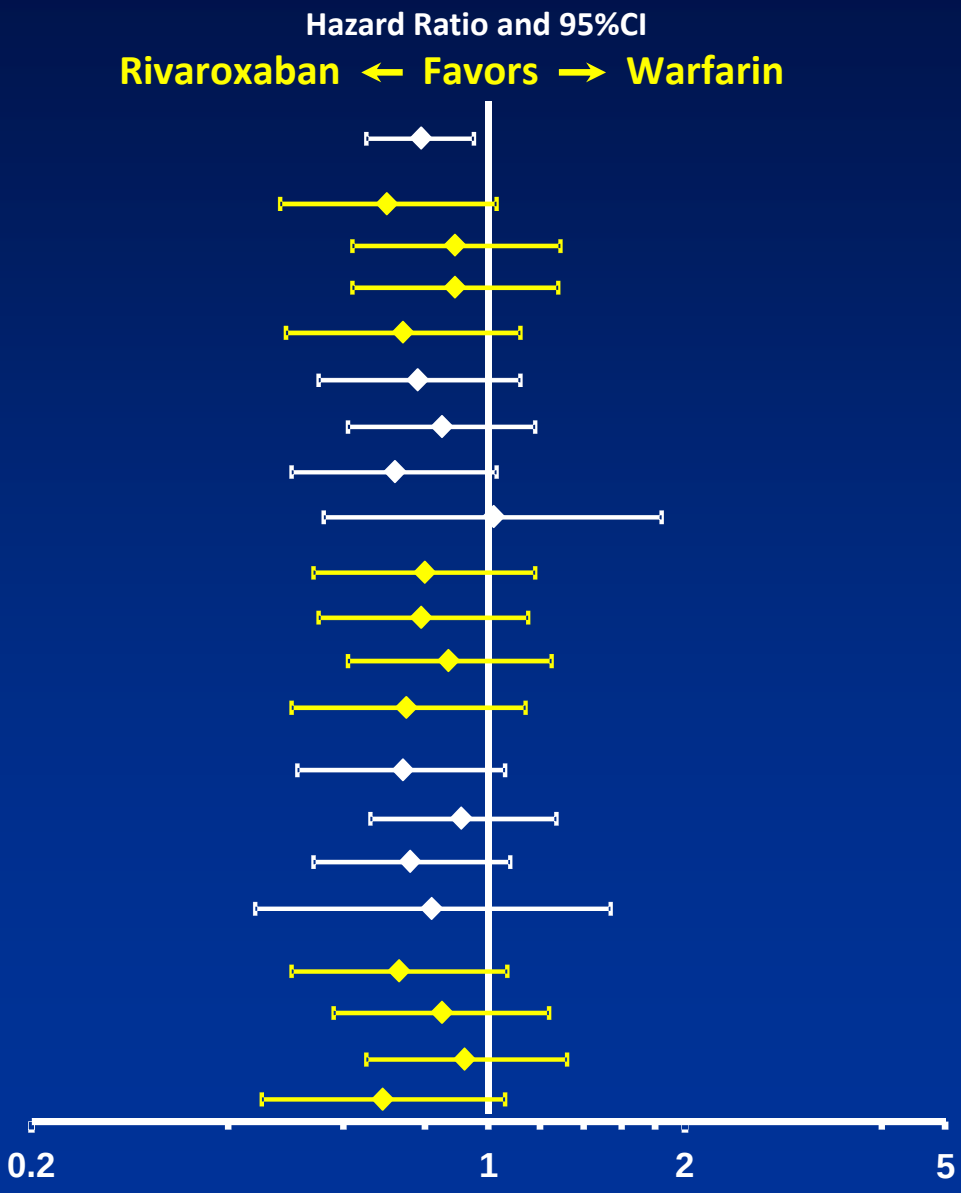
	Warfarin N=7025	
INR range	Mean	Median (25th, 75th)
<1.5	8.5	2.73 (0.0, 9.0)
1.5 to <1.8	10.4	7.9 (3.5, 14.0)
1.8 to <2.0	10.3	9.1 (5.3, 13.6)
2.0 to 3.0	55.2	57.8 (43.0, 70.5)
>3.0 to 3.2	4.8	4.0 (1.9, 6.5)
>3.2 to 5.0	9.9	7.9 (3.3, 13.8)
>5.0	1.0	0.00 (0.0, 0.5)

How is TTR Calculated for a Center (cTTR)?

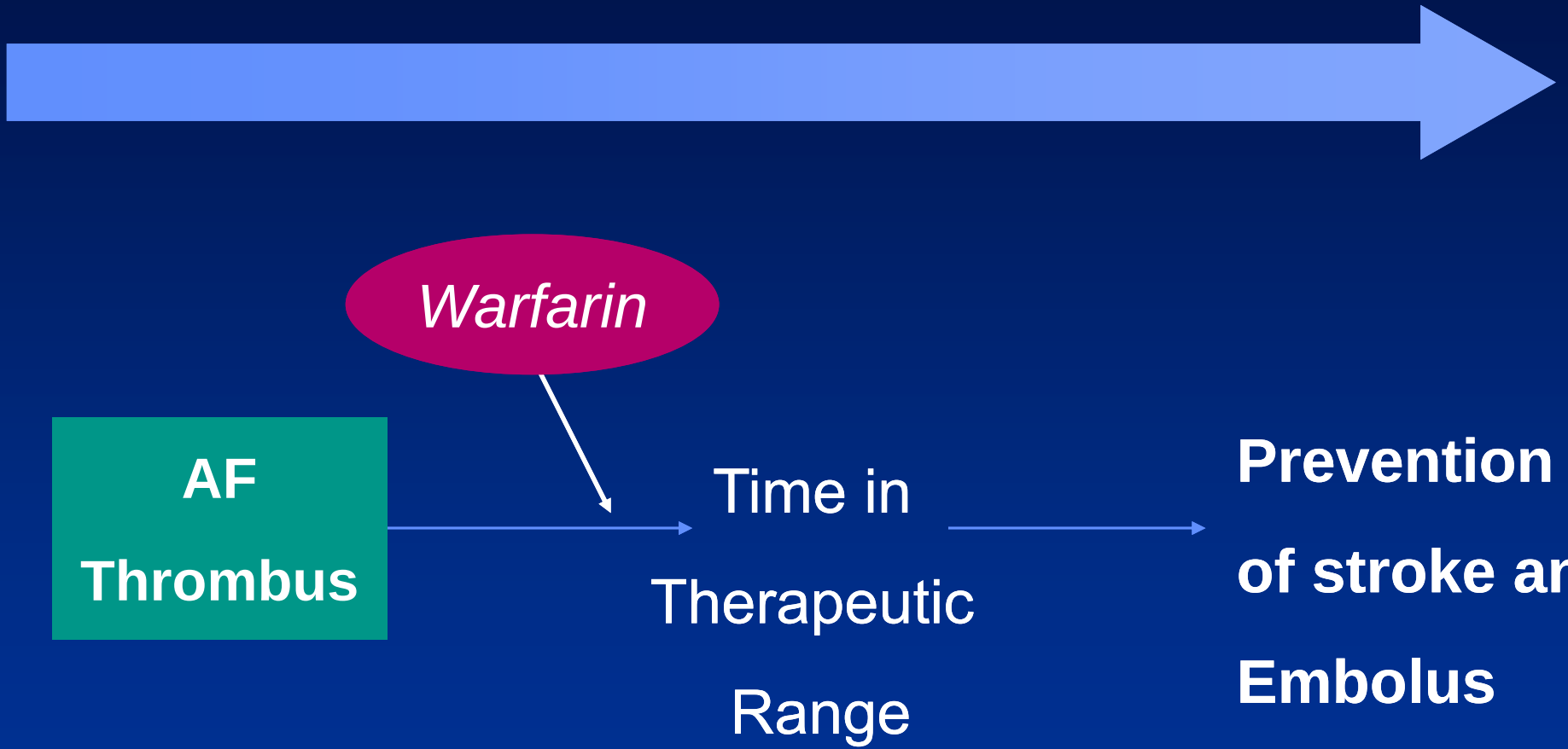
- Total time in range for all patients divided by total amount of time on warfarin for all patients at the center
  - This weights a patient's contribution to cTTR as a function of time on warfarin
- FDA used method of Connolly which averages the TTR without considering time on warfarin
- Caveat
  - Some centers have very few participants
  - Some centers have no or few events

Hazard Ratios (95% CI) for Primary Efficacy Endpoint According Center TTR (Safety on treatment) – Consistency Across Imputation Methods

Imputation Method	Quartile Method	
Study CSR	Overall	
Study CSR – TTR (Pre-planned)	Subject balanced	quartile 1
		quartile 2
		quartile 3
		quartile 4
FDA – TTRE	center balanced	quartile 1
		quartile 2
		quartile 3
		quartile 4
FDA - TTRE	subject balanced	quartile 1
		quartile 2
		quartile 3
		quartile 4
Study – iTTR	center balanced	quartile 1
		quartile 2
		quartile 3
		quartile 4
Study - iTTR	Subject balanced	quartile 1
		quartile 2
		quartile 3
		quartile 4

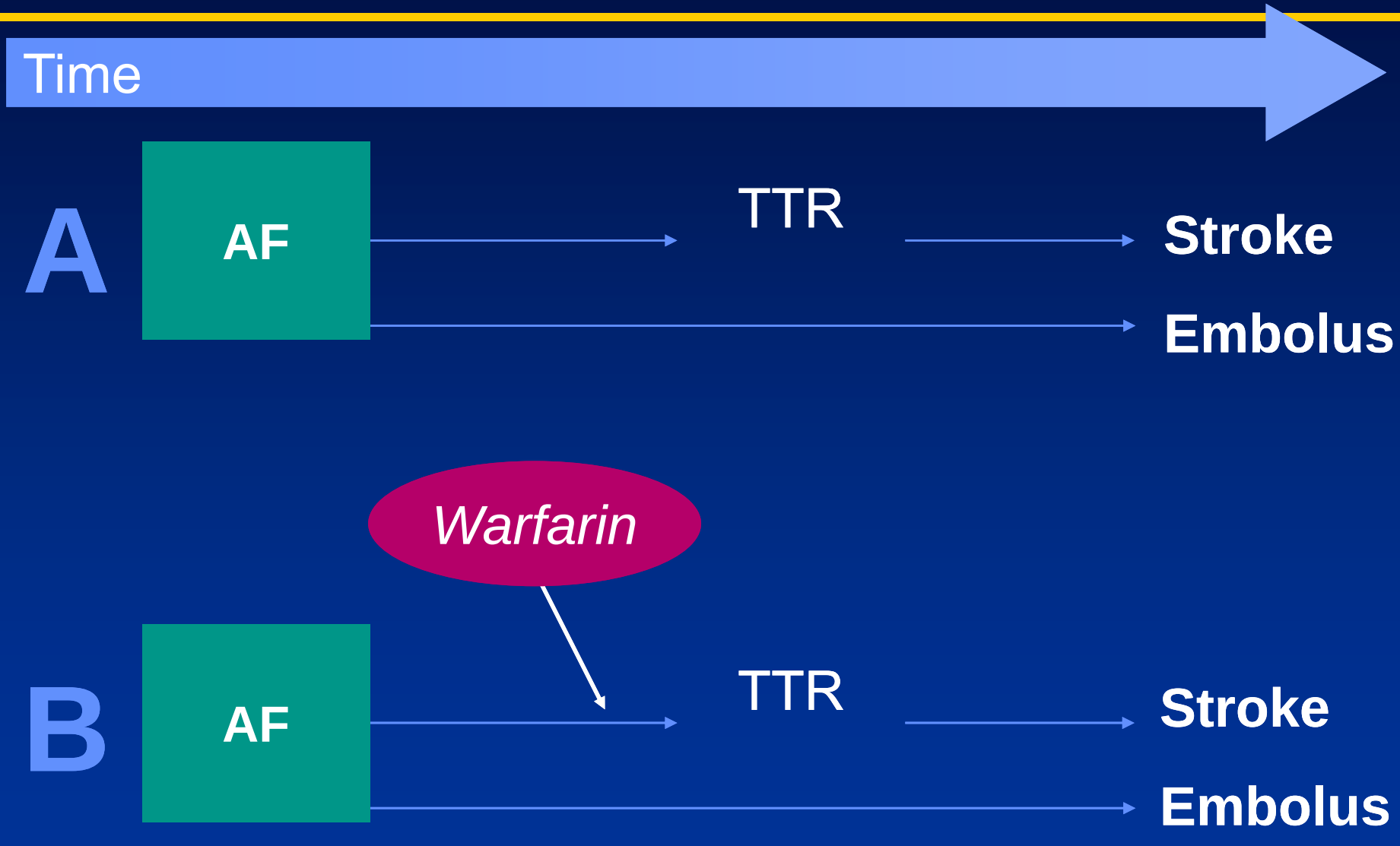


TTR as a Biomarker for Warfarin Effect



Fleming TR, Demets DL. Annals Int Med 1997; 126 (8):667.

Thrombus is not only cause of stroke/embolus (e.g., atherosclerosis)



Fleming TR, Demets DL. Annals Int Med 1997; 126 (8):667.

Poor Relationship between Estimated TTRs and Event Rates in the Studies Used for ROCKET AF Design

Study	PT Ratio or TTR	VKA (warfarin) events/pt yrs(%)	Placebo events/pt yrs(%)	Risk Reduction Ratio (95% CI)
AFASAK (Petersen 1989)	42 %	9/413 (2.18)	21/398 (5.28)	0.41 (0.19,0.89)
SPAF (McBride 1991)	71%	8/260 (3.08)	20/244 (8.20)	0.38 (0.17,0.84)
BAATAF (Kistler 1990)	83%	3/487 (0.62)	13/435 (2.99)	0.21 (0.06,0.72)
CAFA (Connolly 1991)	44%	7/237 (2.95)	11/241 (4.56)	0.65 (0.26,1.64)
SPINAF (Ezekowitz 1992)	56%	9/489 (1.84)	24/483 (4.97)	0.37 (0.17,0.79)
EAFT (Koudstaal 1993)	59%	21/507 (4.14)	54/405 (13.3)	0.31(0.19,0.51)
Pooled		**57/2393(2.38)**	**143/2206 (6.44)**	**0.36 (0.24,0.53)**

Jackson K, et al. Am Heart J, 2008;155:829-40

TTR Does Not Accurately Predict Benefit-Risk Balance

- Uncertainty in the measurement itself
- Warfarin has protean effects on biology
- Comparative treatments have effects not mediated through same mechanisms as warfarin
- Stroke caused by atherosclerosis and hemorrhage as well as clot
- Characteristics of AF, inflammation and other disease manifestations are important as well as status of anticoagulation

Conclusion

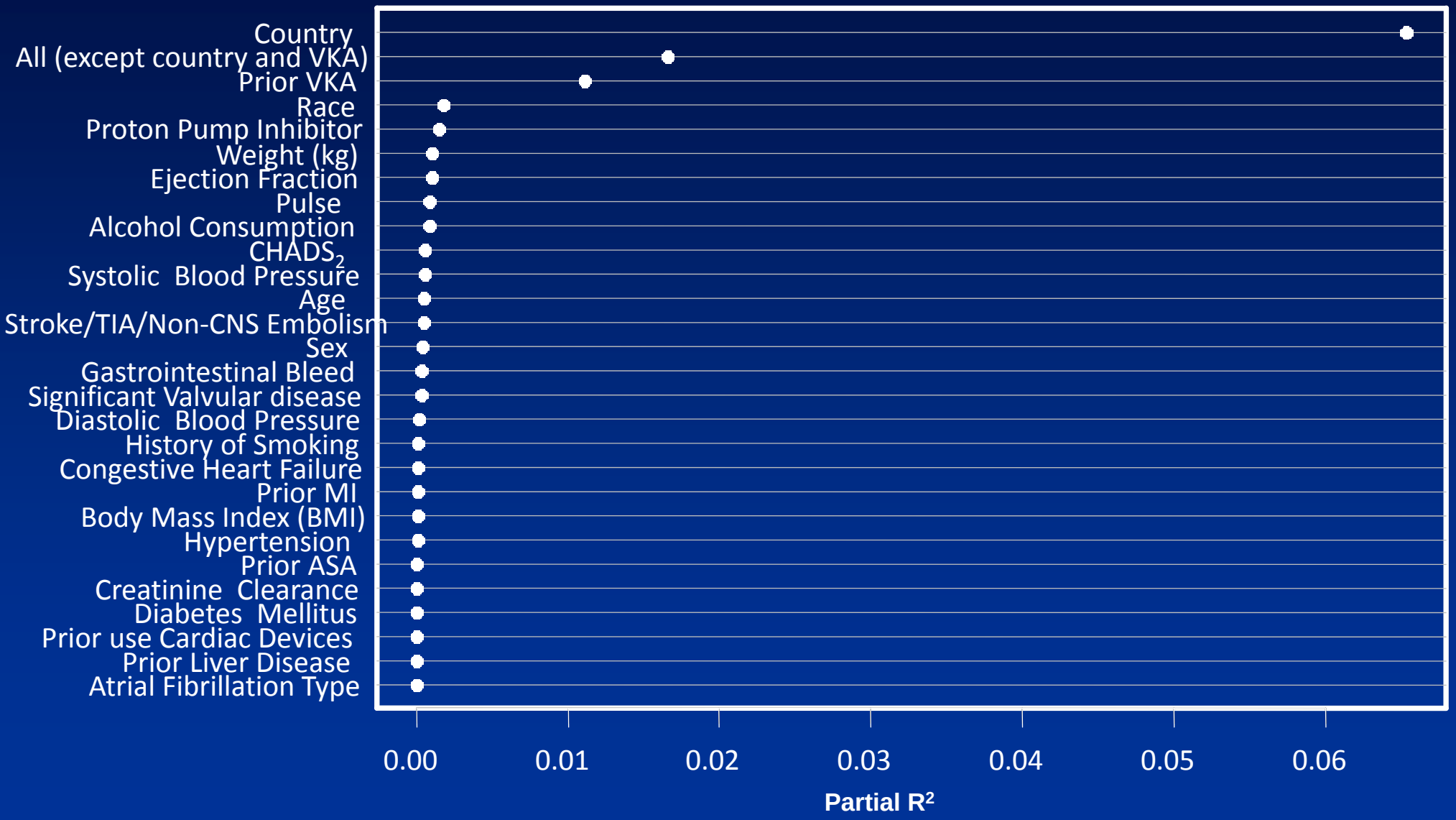
- TTR is a useful measure for quality improvement
- TTR is not a valid surrogate

ROCKET AF TTR in Context

What Determines TTR?

- Prior VKA Use
- Patient Characteristics
  - Gender
  - Age
  - Co-morbidities
- Frequency of INR Testing
- Patient adherence
- Structural factors in practice
  - Anticoagulation Clinic
- Region and Country
  - Cultural/Social Factors
  - Poverty, Logistical Factors

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

ROCKET AF Trial

Baseline Characteristics Stratified by cTTR in Warfarin Treated Subjects

ROCKET AF Center TTR	<50.7%	50.9 – 58.4%	58.5 – 65.7%	>65.7%
$CHADS_2$ Score 3-6	89.4%	89.4%	87.5%	81.6%
Prior Stroke	35.3%	33.6%	36.2%	32.1%
Heart Failure	71.4%	69.4%	61.1%	48.8%

ARISTOTLE† Center TTR	<58.0%	58.0–65.7%	65.7–72.2%	≥72.2%
$CHADS_2$ Score 3-6	32.6%	31.1%	30.0%	27.0%
Prior stroke	13.4%	12.0%	11.5%	9.8%
Heart failure	41.8%	36.5%	27.2%	16.4%

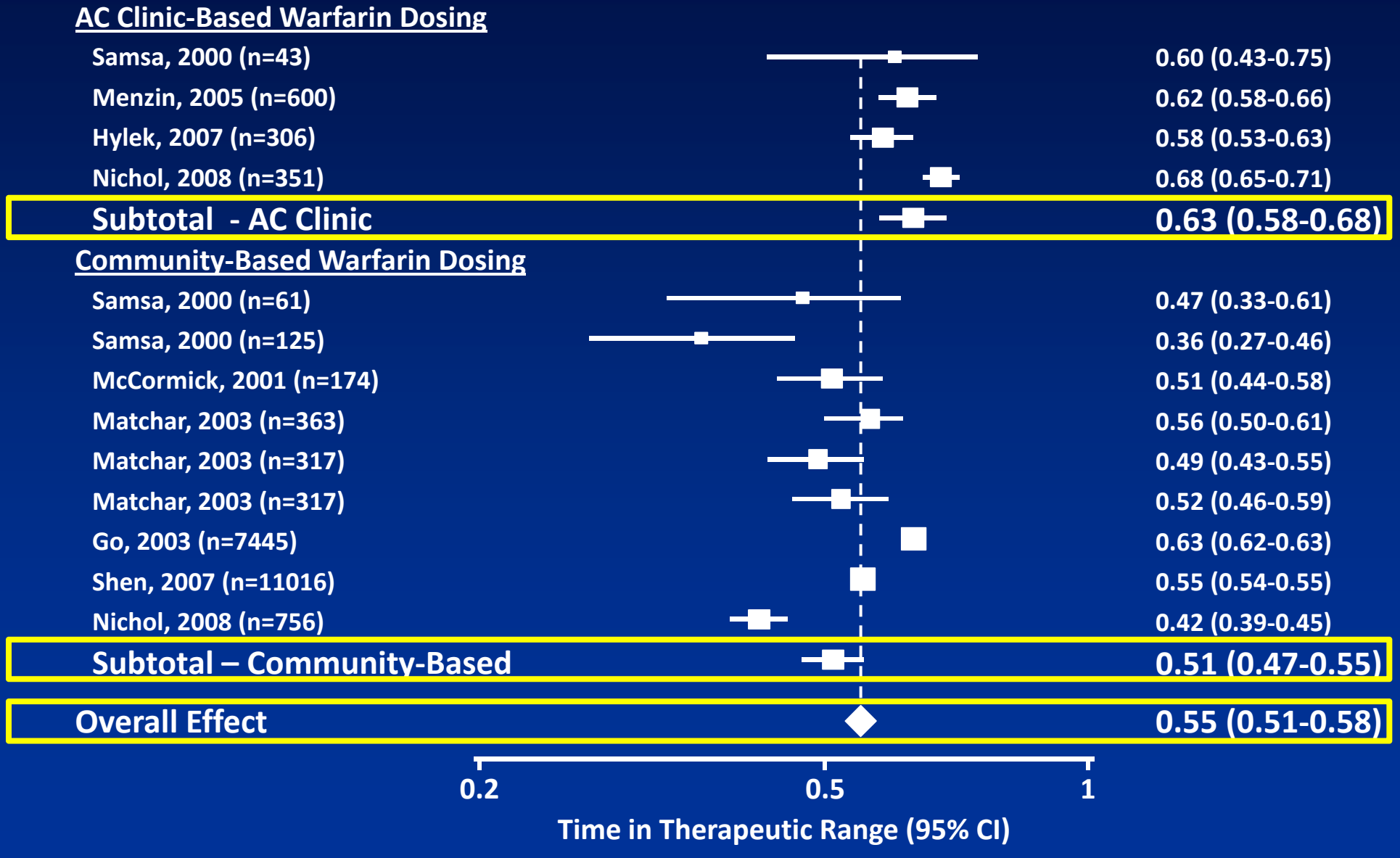
† Granger, CB on behalf of the ARISTOTLE Investigators and Committees. "Apixaban versus Warfarin in Patients with Atrial Fibrillation: Results of the ARISTOTLE Trial". European Society of Cardiology Congress, Paris, France, August 28, 2011.

Key Selected Predictors of Lower TTR

	Number of Patients (%)	Unadjusted % TTR Effect (95% CI)	Adjusted % TTR Effect (95% CI)
Female	1984 (1.9)	-5.5 (-5.9 to -5.0)	-2.9 (-3.9 to -2.0)
Number of non-warfarin medications			
8-11	33,393 (32.0)	-3.6 (-3.7 to -3.4)	-1.8 (-2.1 to -1.5)
12-15	17,915 (17.1)	-7.3 (-7.4 to -7.1)	-3.2 (-3.6 to -2.8)
Number of hospitalizations			
2	6261 (6.0)	-8.5 (-8.8 to -8.3)	-5.1 (-5.7 to -4.5)
≥ 4	4213 (4.0)	-14.9 (-15.2 to -14.6)	-9.4 (-10.1 to -8.7)
Lowest socioeconomic status	20,482 (19.6)	-4.0 (-4.2 to -3.8)	-1.5 (-2.0 to -1.1)
Chronic kidney disease	14,806 (14.2)	-4.4 (-4.6 to -4.3)	-1.6 (-2.0 to -1.2)
Coronary artery disease	53,114 (50.8)	-1.4 (-1.5 to -1.2)	-0.6 (-0.9 to -0.3)
Diabetes	41,863 (40.1)	-2.1(-2.2 to -2.0)	-1.0 (-1.3 to -0.7)
Heart failure	34,229 (32.8)	-3.6 (-3.7 to -3.5)	-1.0 (-1.3 to -0.7)
Hypertension	87,776 (84.0)	+0.0 (-0.2 to 0.1)	+ 1.0 (0.7 to 1.4)

Note: during the experienced period, that is, any time after the first 6 months of warfarin therapy
Adapted from Rose AJ, et al. J Thromb Haemost 2010;8:2182-91

A Systematic US Overview
INR Time In Therapeutic Range Is 55%



Baker W et al. J Manag Care Pharm 2009; 15: 244-252.

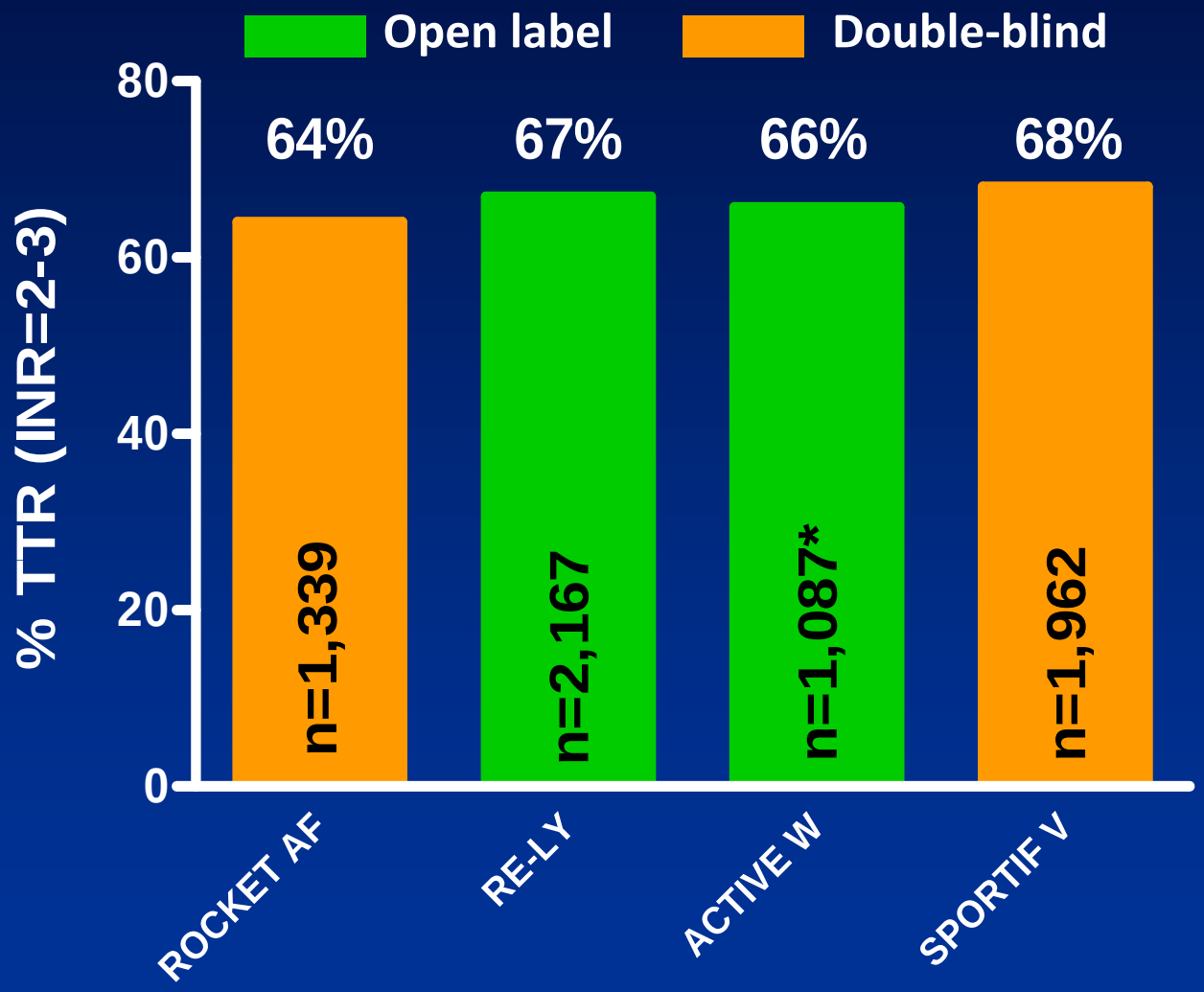
How Well is Warfarin Managed in the US? The Quest Diagnostics Database of Laboratory Tests

- Includes all 50 states, queried for all outpatient INR testing for patients ≥ 18 years of age with AF or VTE
- 187,574 individual patients (74% with AF)
- 3,493,443 actual INR measurements

Category	INR	Number of Measurements	%
Subtherapeutic	<1.5	255,285	9.5%
Low Intensity Therapeutic	1.5 – <2.0	618,126	23%
Therapeutic	2.0-3.0	1,357,843	50.6%
Mild Supratherapeutic	>3.0 – 4.0	328,676	12.2%
Supratherapeutic	>4.0	125,470	4.7%

Dlott J et al. "Anticoagulant Management of Atrial Fibrillation In the United States; Findings from a Large National Database of Clinical Test Results". American Society of Hematology, Orlando, Florida, December 7, 2010

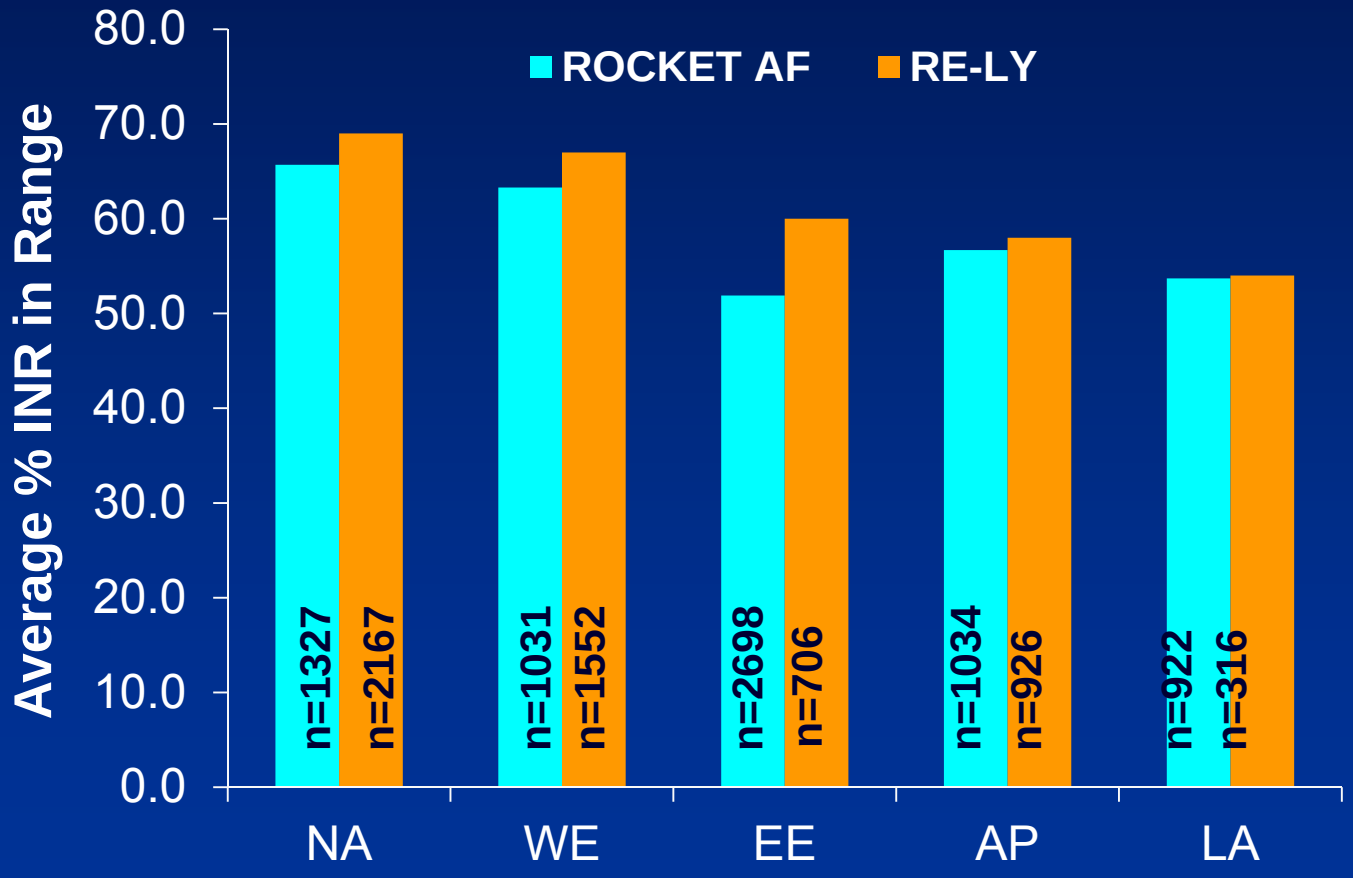
North American TTR



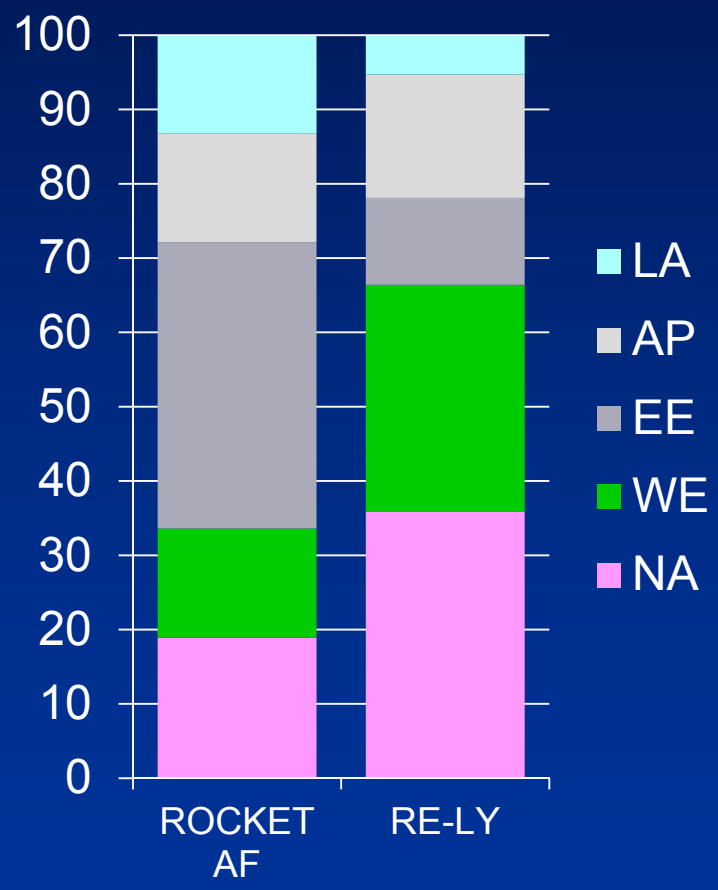
*North America Warfarin Population is Estimated as 50% of Canada + US Total Population
ROCKET AF data are from the Safety population; RE-LY Sponsor's Briefing Document FDA 27Aug2010;
ACTIVE W Connolly et al., CIRC, 2008;118; SPORTIF V Albers et al., JAMA, 2005;293

TTR Results (Warfarin) By Region – ROCKET AF and RE-LY Are Similar

	ROCKET AF	RE-LY
Mean TTR	56%*	64%



Percent of Subjects Within the Study

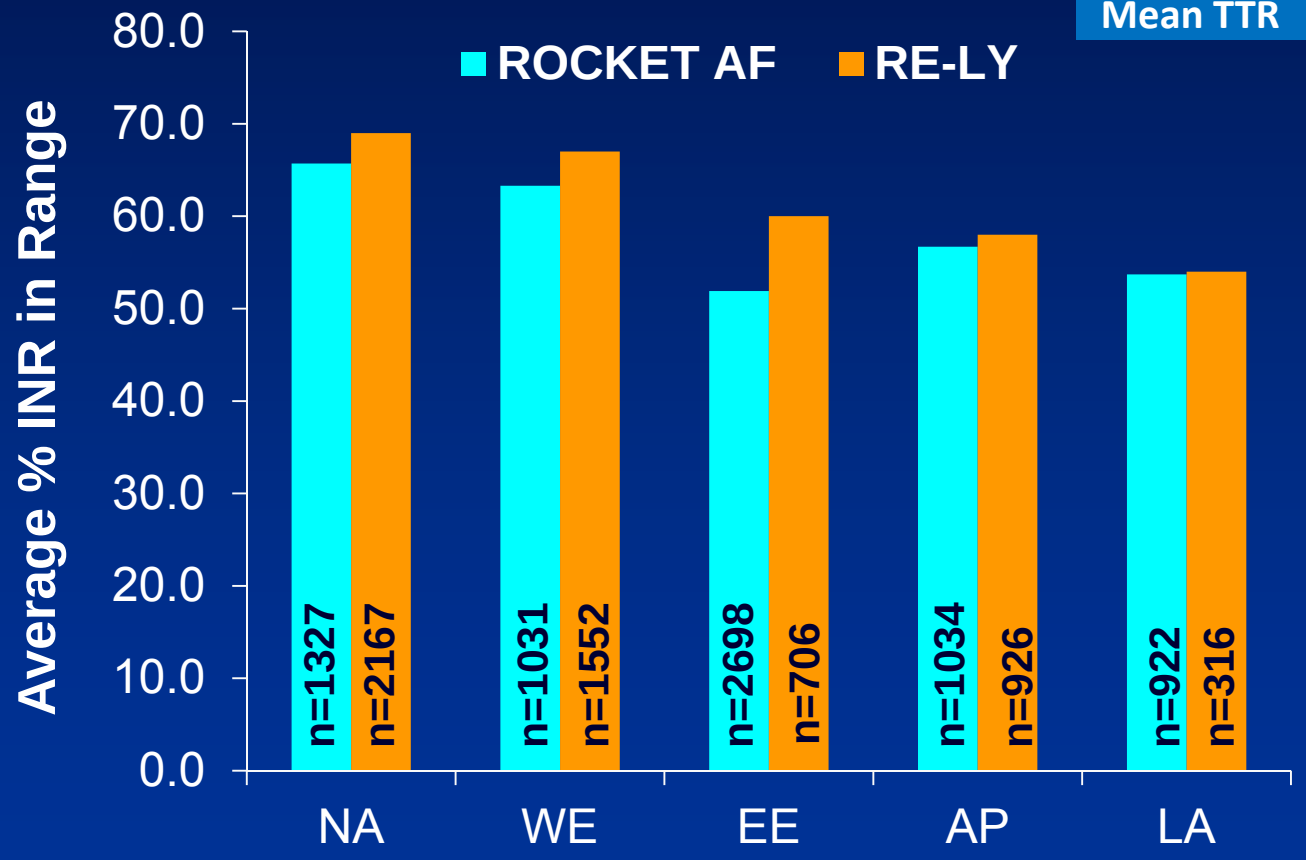


*ROCKET AF TTR was based on RE-LY imputation

Wallentin L, et al. Lancet 2010; 376: 975–83

TTR Results (Warfarin) By Region – (ROCKET AF vs. RE-LY – Simple Approach)

	ROCKET AF (weighted per RE-LY population)	RE-LY
Mean TTR	61.2%*	64.7%



*ROCKET AF TTR was based on RE-LY imputation, and then weighted by RE-LY population

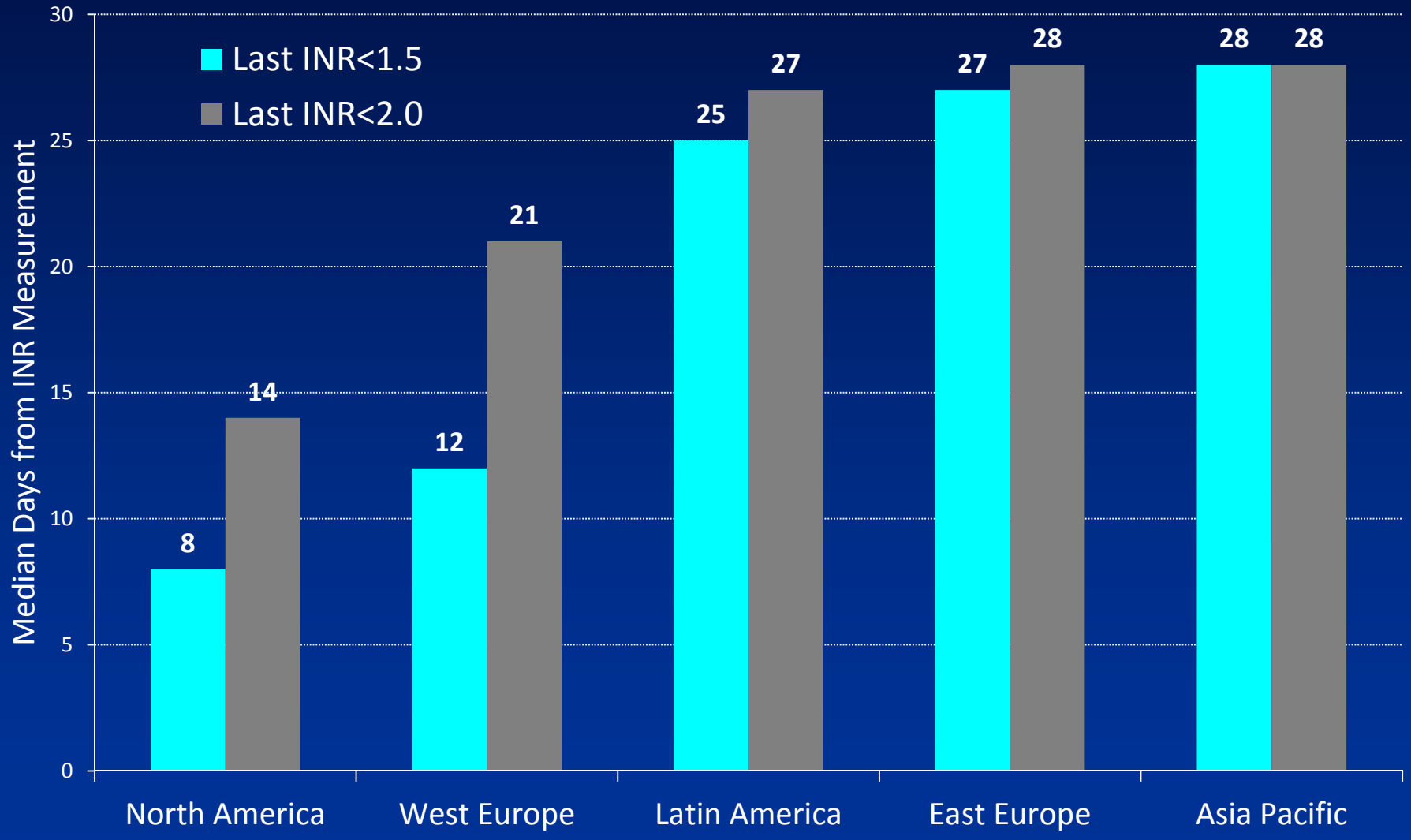
Wallentin L, et al. Lancet 2010; 376: 975–83

Conclusion

- TTR in ROCKET AF was similar to recent trials
  - Considering higher risk population
  - Considering regional distribution of patients enrolled
- TTR in ROCKET AF was similar to other trials in North America despite higher risk population
- TTR in ROCKET AF was
  - Better than global practice
  - Similar to standard US practice for the trial overall
  - Better than US practice for North American subset

Do we Have Direct Evidence of Effect of Cultural Factors on TTR in ROCKET AF?

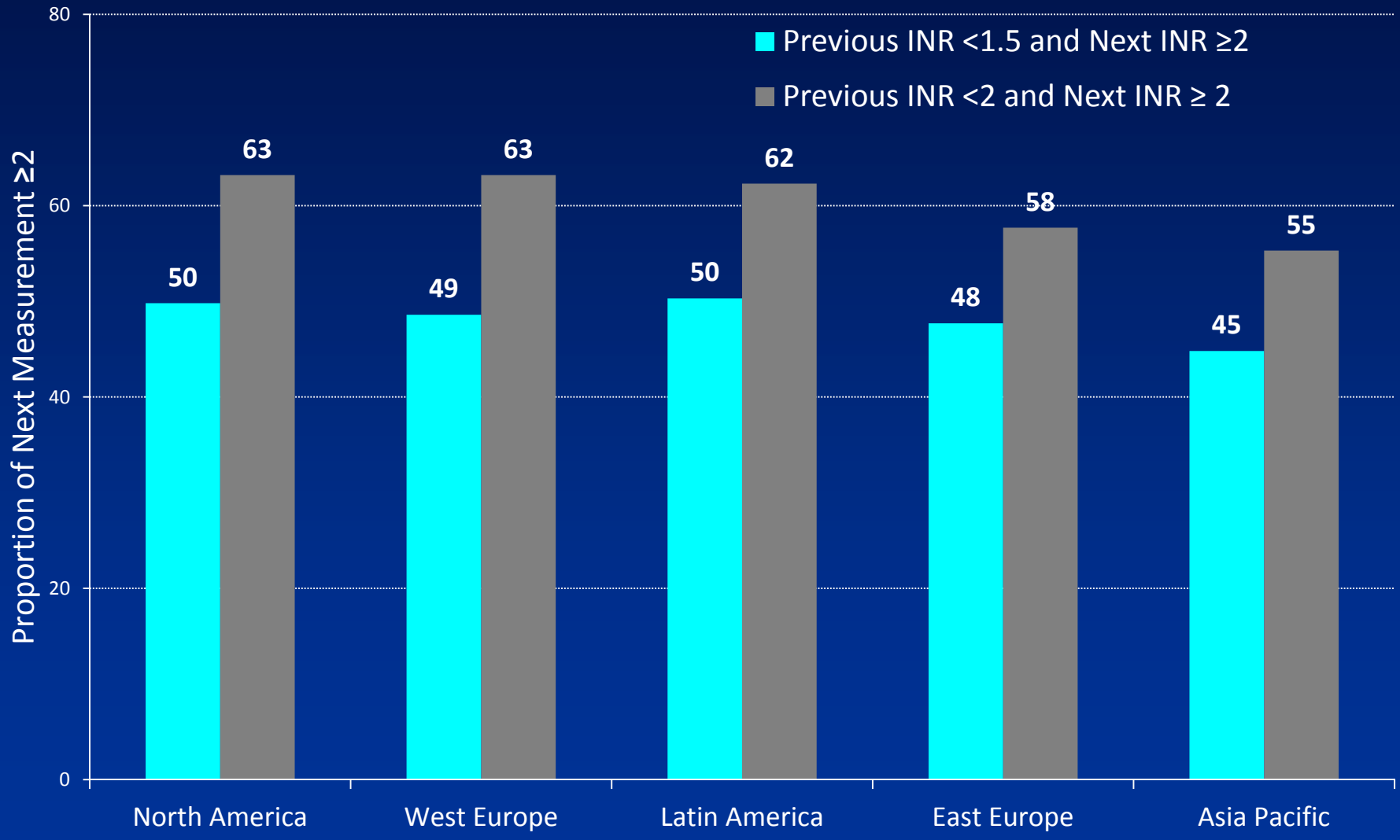
Median Days to Next Measurement after Low INR by Region – Warfarin Subjects



Note: INR measurements for the first 3 weeks on treatment excluded

ROCKET AF Trial

Proportion of INR Measurements ≥ 2 after Low INR by Region – Warfarin Subjects



Note: INR measurements for the first 3 weeks on treatment excluded
ROCKET AF Trial

Conclusion

- There is variation by region in timing between out of range value and next INR, but most dose adjustments are appropriate
- This induces an “artificial” lowering of TTR in areas with longer delay to INR measurement
- Evidence of modest under-dosing in Eastern Europe and Asia

Effect of Rivaroxaban vs. Warfarin is NOT Dependent on cTTR

Similar Treatment Effect for Primary Efficacy Endpoint (cTTR Pre-Specified Analysis)

Center TTR	Rivaroxaban N= 7061 n	Rivaroxaban Event Rate (100 pt-yr)	Warfarin N= 7082 n	Warfarin Event Rate (100 pt-yr)
0.00-50.62%	45	1.77	62	2.53
50.71-58.54%	53	1.94	63	2.18
58.63-65.71%	54	1.90	62	2.14
65.74-100.0%	37	1.33	55	1.80

Treatment by Quartile p-value: 0.736

ROCKET AF Trial

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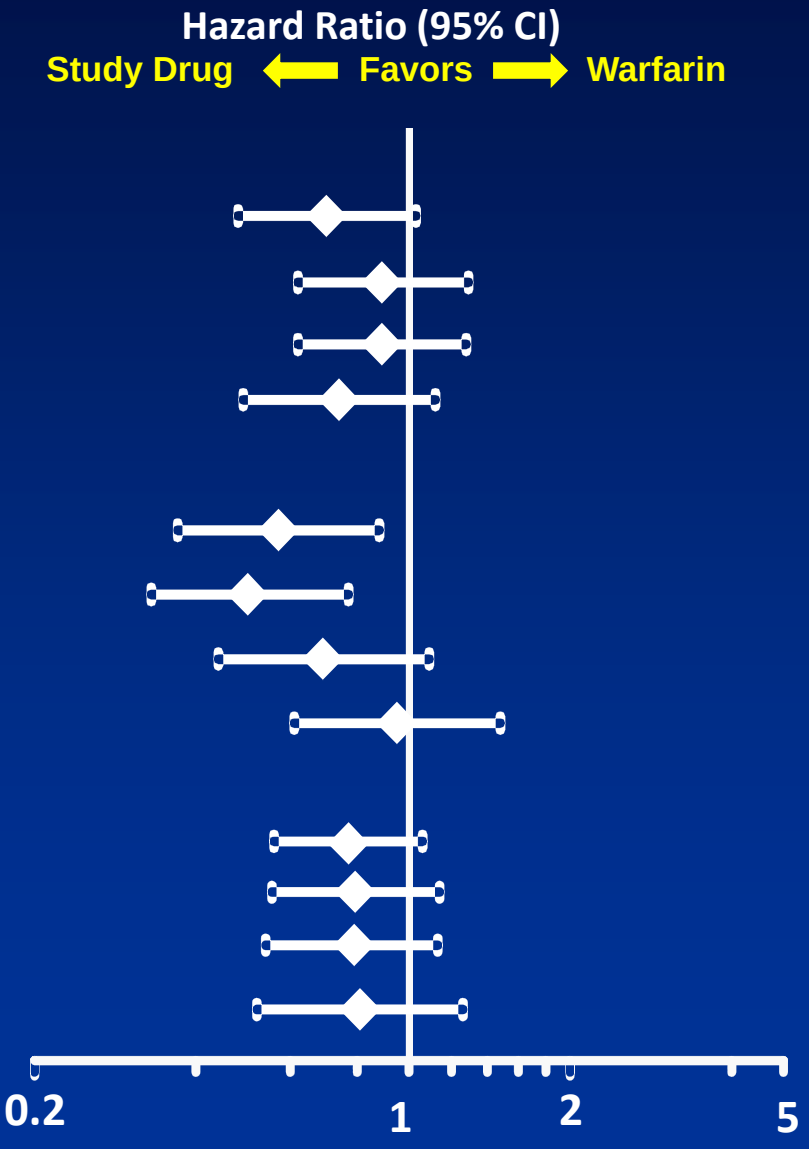
Primary Efficacy Endpoint by Center TTR ROCKET AF/RE-LY/ARISTOTLE

	Treatment Group n/J (rate)	Warfarin n/J (rate)	p-value (interaction)
ROCKET AF			0.736
0.00-50.62%	45/1735 (1.77)	62/1689 (2.53)	
50.71-58.54%	53/1746 (1.94)	63/1807 (2.18)	
58.63-65.71%	54/1734 (1.90)	62/1758 (2.14)	
65.74-100.0%	37/1676 (1.33)	55/1826 (1.80)	
RE-LY (Dabigatran 150 mg)[†]			0.20
<57.1%	32/1509 (1.1)	54/1504 (1.92)	
57.1–65.5%	32/1526 (1.04)	62/1514 (2.06)	
65.5–72.6%	31/1484 (1.04)	45/1487 (1.51)	
>72.6%	38/1514 (1.27)	40/1509 (1.34)	
ARISTOTLE[‡]			0.29
< 58.0%	70/2266 (1.75)	88/2252 (2.28)	
58.0–65.7%	54/2251 (1.30)	68/2278 (1.61)	
65.7–72.2 %	51/2256 (1.21)	65/2266 (1.55)	
> 72.2 %	36/2266 (0.83)	44/2251 (1.02)	



[†]Wallentin L, et al. Lancet 2010;376:975–983.
[‡]Granger, CB. Results of the ARISTOTLE Trial. ESC, France, August, 2011

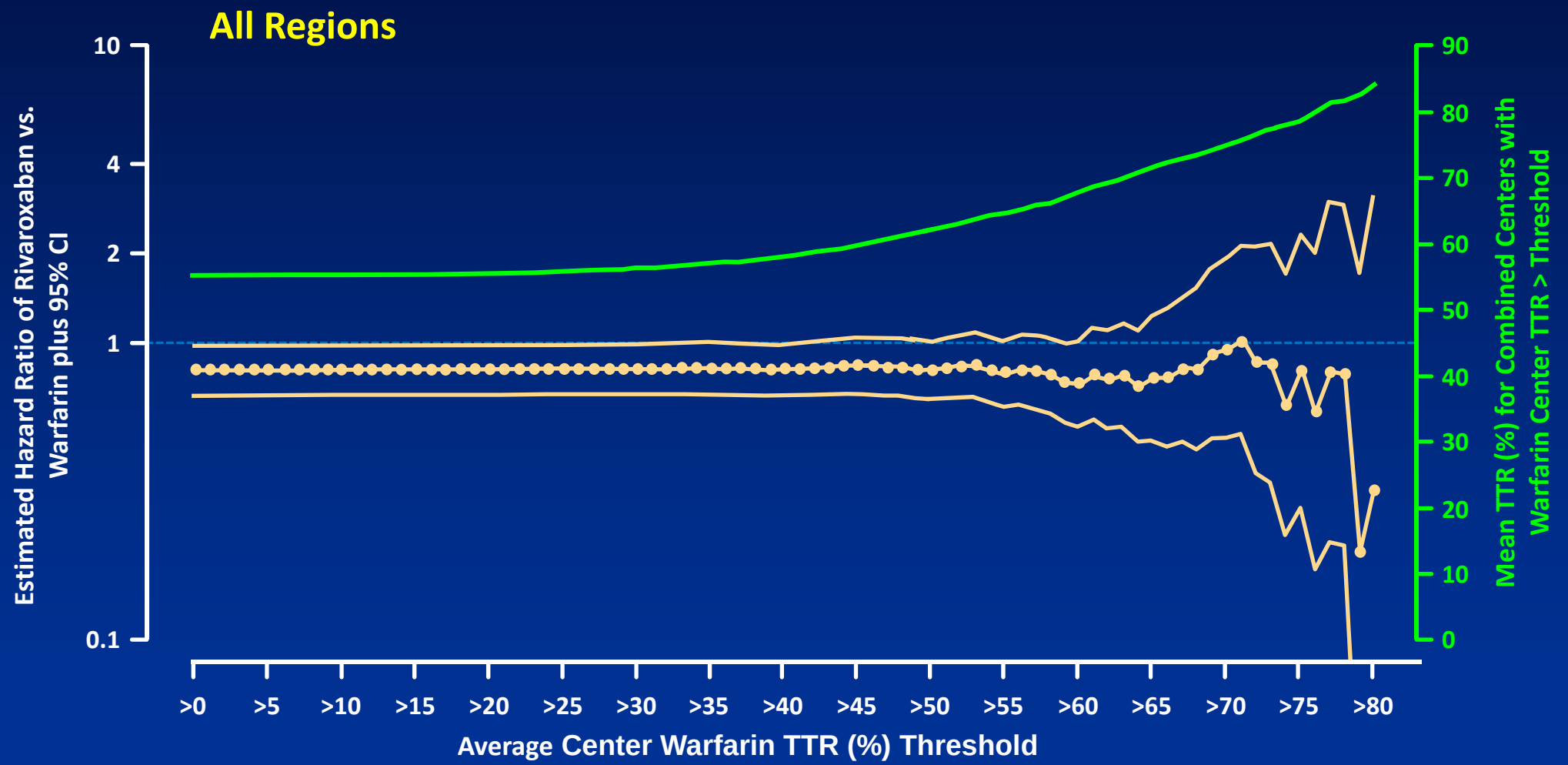
Rate = number of events per 100 patient-years
n = subjects with events; J = number of subjects in each subgroup

CC-120

Quartile Analysis Could Hide Results that May Be Evident when ALL the Data are Viewed

Primary Efficacy Endpoint HR for Center Average Warfarin TTR > Threshold

Safety/On-Treatment



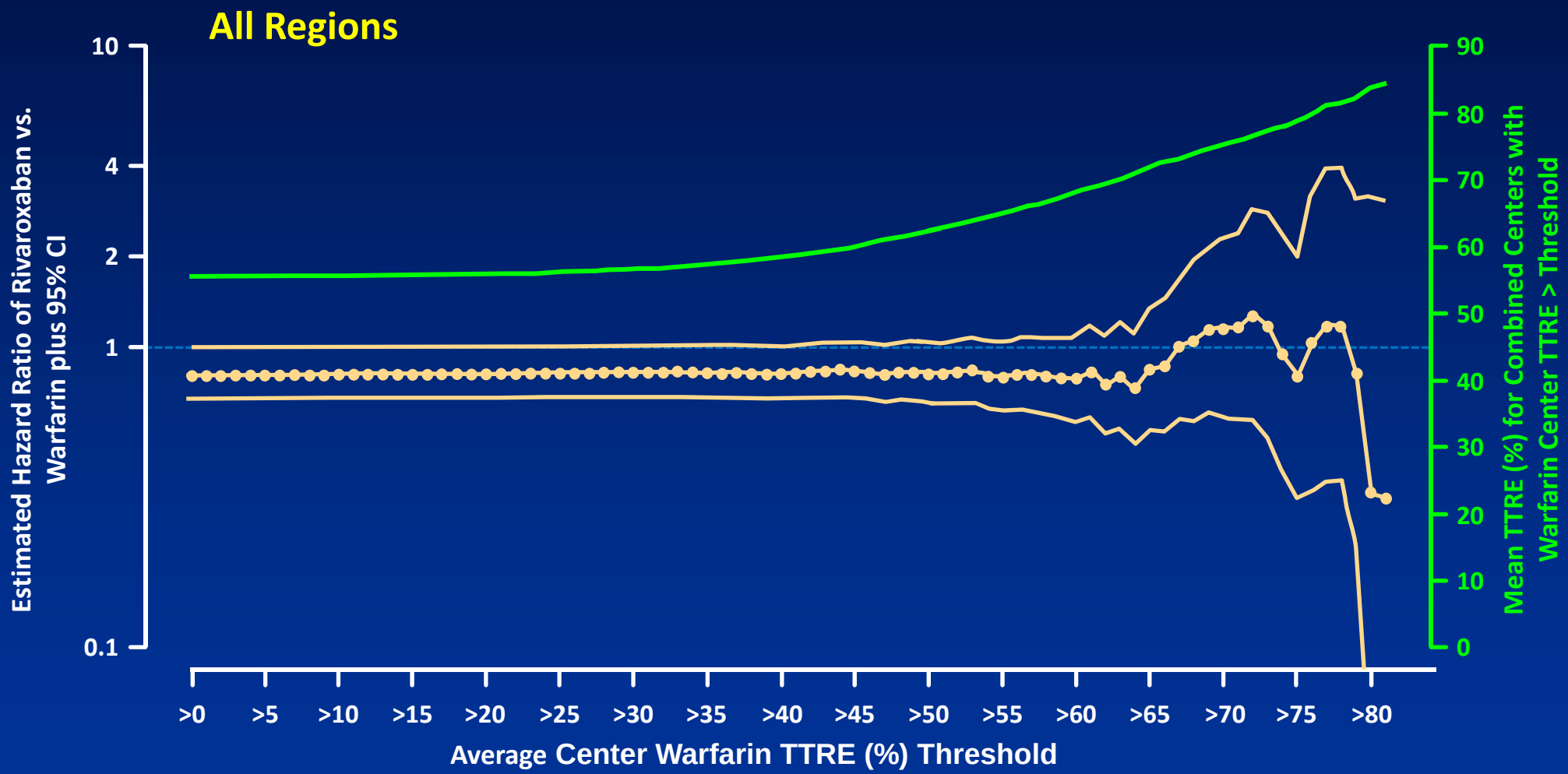
Total Number of Subjects/Total Number of Events:

13958	13940	13920	13904	13840	13651	13468	13054	12341	11090	9235	7366	5032	2951	1687	744	184
431	431	430	428	428	424	417	401	381	339	286	226	145	69	32	14	4

Note: Only centers with calculable average Warfarin center TTR from safety evaluable subjects (excluding site 042012) were used.
ROCKET AF trial.

Primary Efficacy Endpoint HR for Center Average Warfarin TTRE (FDA Method) > Threshold

Safety/On-Treatment

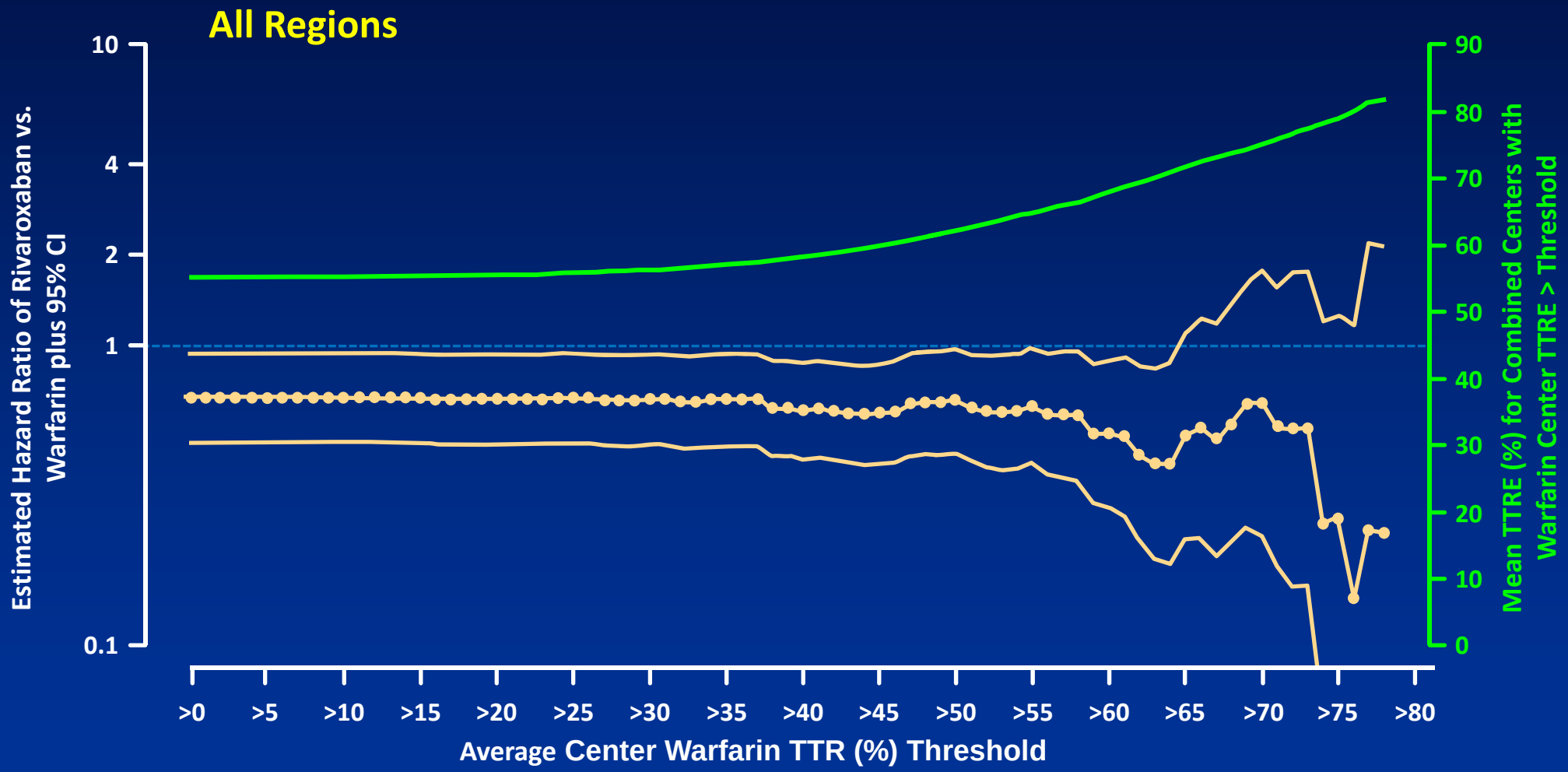


Total Number of Subjects/Total Number of Events:

13958	13940	13920	13904	13827	13651	13485	13122	12422	11163	9411	7418	5101	2989	1703	805	197
431	431	430	428	428	424	418	405	385	347	291	225	148	72	33	18	4

Note: Only centers with calculable average Warfarin center TTR from safety evaluable subjects (excluding site 042012) were used.
ROCKET AF trial.

ICH for Center Average Warfarin TTR > Threshold
Safety/On-Treatment



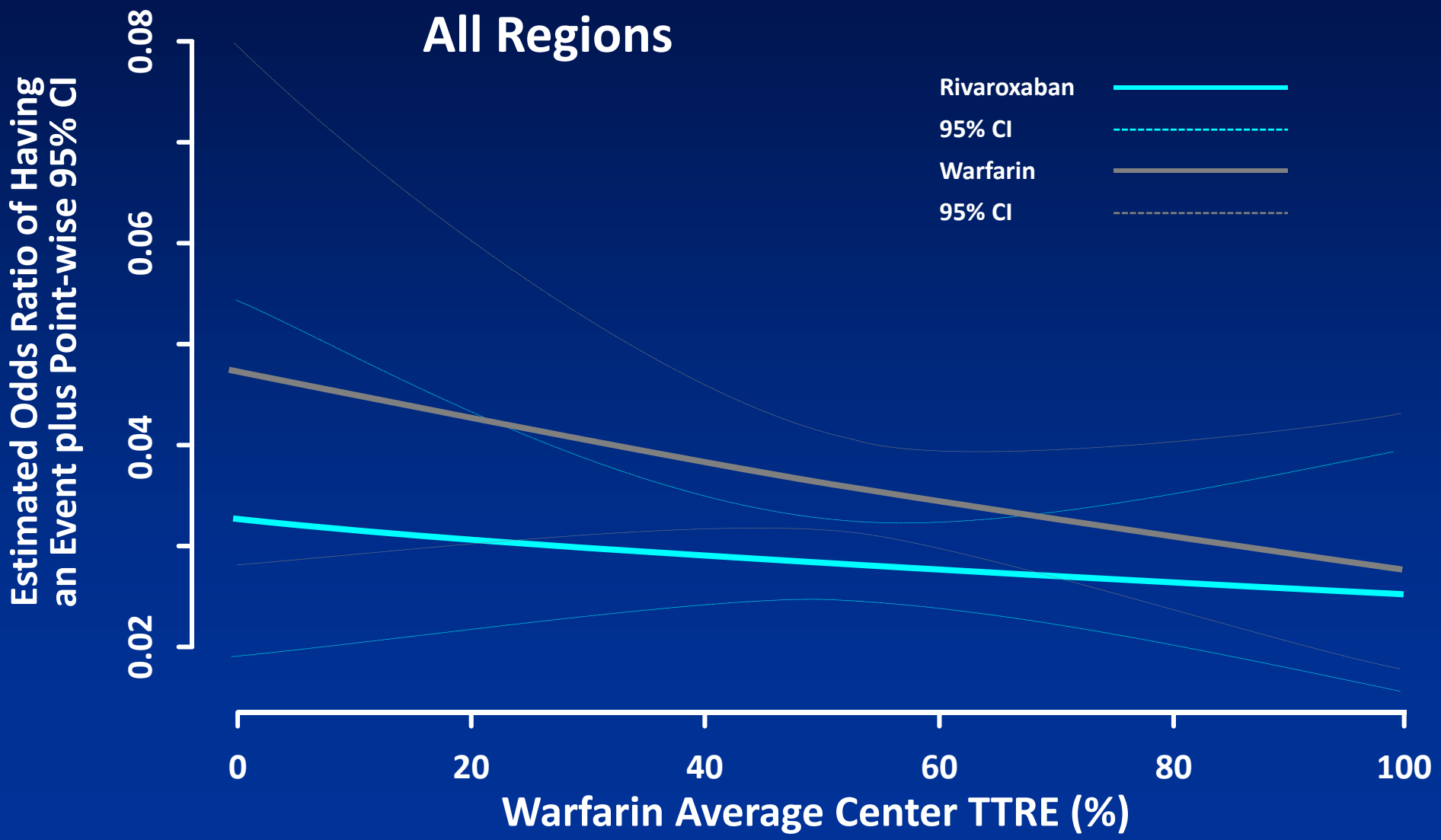
Total Number of Subjects/Total Number of Events:

14051	14033	14013	13997	13933	13744	13561	13147	12434	11183	9328	7366	5032	2951	1687	744
138	138	138	138	137	136	134	127	123	114	103	84	57	29	16	10

Note: Only centers with calculable average Warfarin center TTR from safety evaluable subjects (excluding site 042012) were used.
ROCKET AF trial.

CC-124

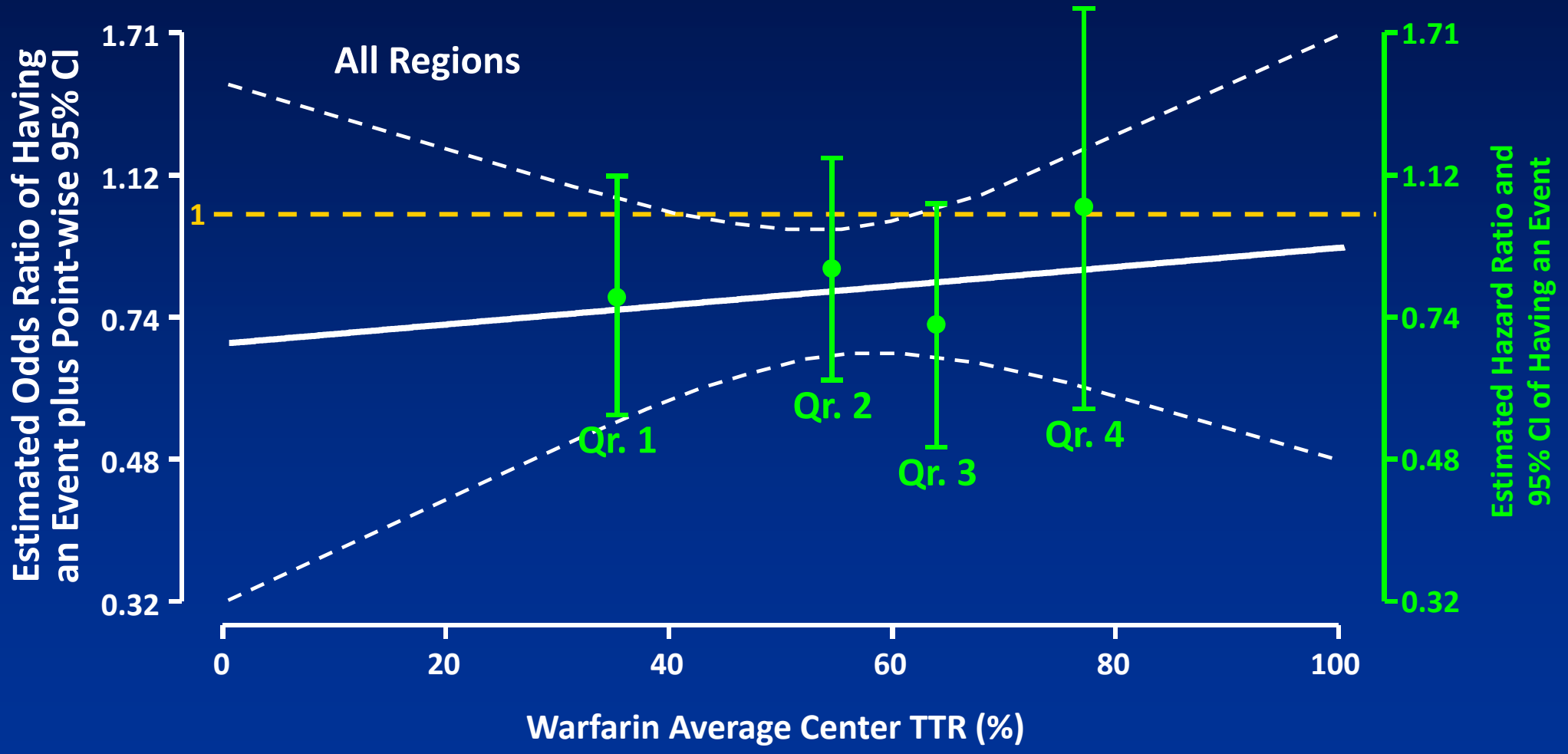
Primary Efficacy Endpoint Predicted Odds Ratio of Having an Event for Center TTRE – Connolly 2008 Method Safety/On-Treatment



Note: Average Warfarin center TTRE was used as the TTRE value for all Rivaroxaban and Warfarin subjects in that center.
ROCKET AF trial

Predicted Odds Ratio of Having an Event Randomization to First Primary Efficacy Endpoint

Safety/On-Treatment



Note: Average Warfarin center TTRE was used as the TTRE value for all Rivaroxaban and Warfarin subjects in that center.
Hazard Ratio and 95% CI were obtained from Warfarin Center TTRE Equal Center Number Quartile Analysis.

Conclusion

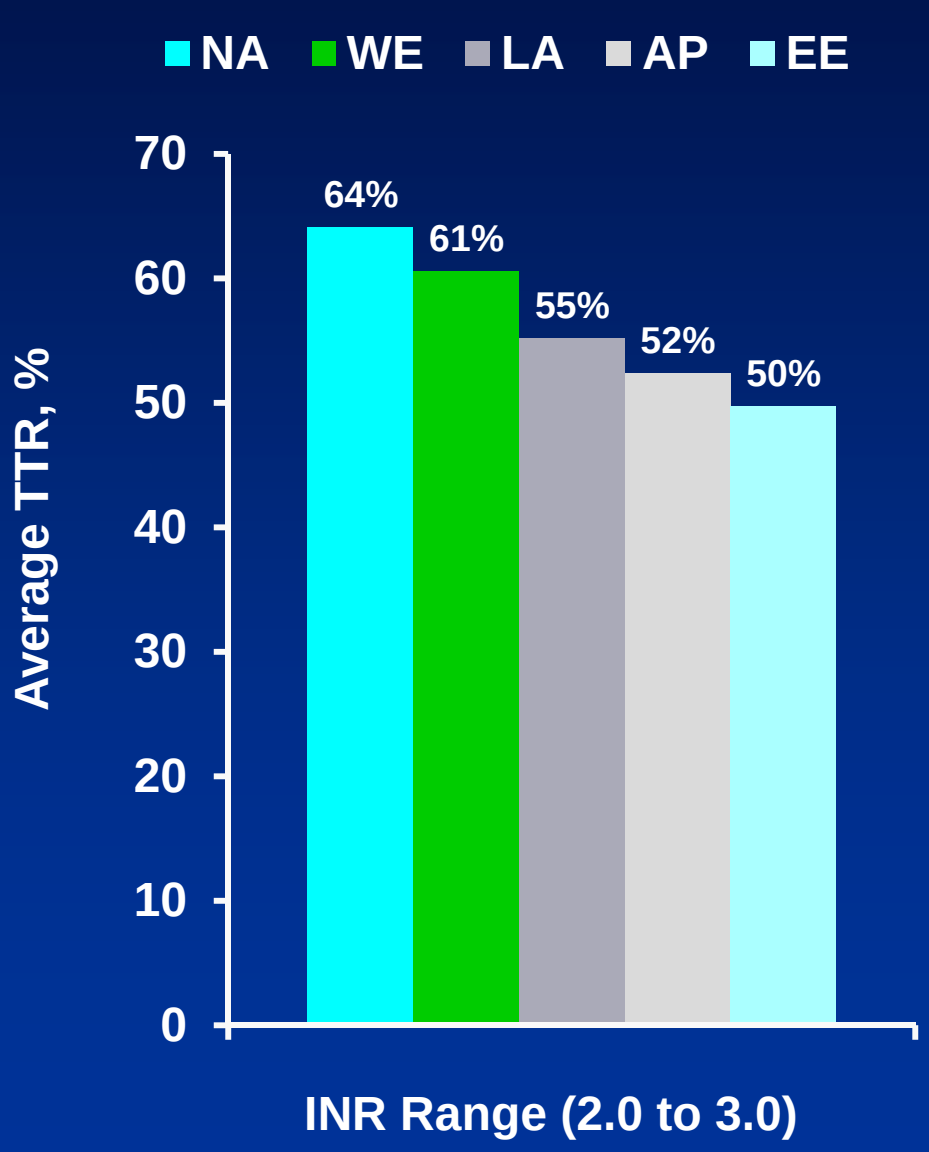
- When all the results are displayed, there is no evidence that cTTR is a significant predictor of the comparison of rivaroxaban and warfarin

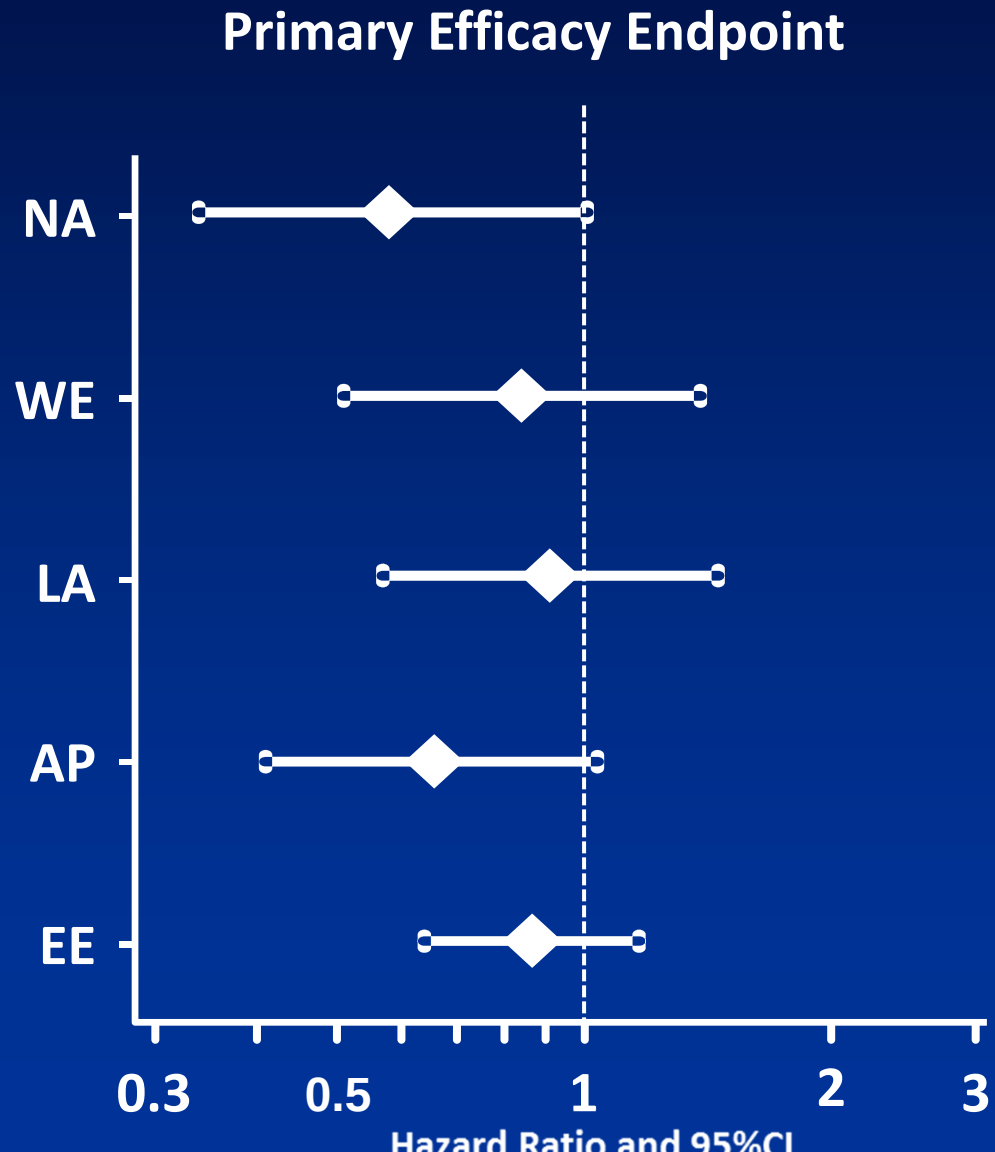
North America

- Recent trials have highlighted that US or NA results frequently differ quantitatively or qualitatively with the rest of world

Across Regions with Various Levels of INR Control, Treatment Efficacy is Preserved

Safety/On-Treatment





ROCKET AF Trial

CC-129

Conclusion

- North American centers had the best TTR results and the most favorable estimate of rivaroxaban effect on the primary endpoint

Event Rates as a Measure of Quality of Anticoagulation

Warfarin Primary Efficacy Event Rates Across Studies by $CHADS_2$ Score

			$CHADS_2$ =2	$CHADS_2$ ≥3	Prior Stroke
Study	TTR	Mean $CHADS_2$ Score	Primary Efficacy Rate	Primary Efficacy Rate	Primary Efficacy Rate
ROCKET AF	55%	3.5	1.7	2.6	2.9
RE-LY[†] (2009)	64%	2.1	1.4	2.7	2.7
ARISTOTLE[‡] (2011)	62%	2.1	1.4	2.8	3.2

[†]Wallentin L, et al. Lancet 2010;376:975–983.
[‡]Granger, CB. Results of the ARISTOTLE Trial. ESC, France, August, 2011
Rate = per 100 patient years

Conclusion

- Warfarin event rates in ROCKET AF were similar to other recent trials when patients with similar risk are compared

Key Points: Relevance of TTR to Interpretation of ROCKET AF Results

- No relationship between treatment effect and center TTR in ROCKET AF or two other contemporary trials
- Best TTR observed in NA with most favorable estimate of treatment effect for rivaroxaban
- Risk adjusted warfarin event rates comparable to other contemporary trials indicating well managed warfarin therapy

Approval Standard in 2011

- ROCKET AF primary objective met
  - Robust non-inferiority to warfarin
- Indirect comparisons for treatment effects are not reliable

Cross-Study Comparisons

- Cross study comparisons are hazardous but common
- ROCKET AF and RE-LY
  - Different drugs
  - Different study designs
  - Different patient populations
  - Different regions

Overall Conclusions

- ROCKET AF was a definitive double-blind study comparing rivaroxaban with warfarin that shows
  - Robust non-inferior efficacy for all analyses
  - Superior efficacy on treatment
  - Favorable safety profile with a reduction in ICH and fatal bleeding events
- Rivaroxaban is a proven alternative to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Stroke Outcome
Safety/On Treatment

Stroke Outcome	Rivaroxaban N= 7061 n (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7082 n (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)	p-value
Total Strokes	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70,1.03)	0.092
Death	47 (0.67)	0.42	67 (0.95)	0.59	0.71 (0.49,1.03)	0.075
Disabling	43 (0.61)	0.39	57 (0.80)	0.50	0.77 (0.52,1.14)	0.188
Non-disabling	88 (1.25)	0.79	87 (1.23)	0.77	1.03 (0.76,1.38)	0.863
Missing Rankin	7 (0.10)	0.06	12 (0.17)	0.11	0.59 (0.23,1.50)	0.271

Summary of Primary Ischemic Stroke by Outcome

Safety Population/On Treatment, Up to Last Dose plus 7 and 30 Days

	Rivaroxaban N=7061 n %	Rivaroxaban N=7061 n %	Rivaroxaban N=7061 n %	Warfarin N=7082 n (%)	Warfarin N=7082 n (%)	Warfarin N=7082 n (%)
Stroke Type/Outcome	On Treatment	Up to Last Dose + 7 days	Up to Last Dose + 30 days	On Treatment	Up to Last Dose + 7 days	Up to Last Dose + 30 days
Stroke	149 (2.11)	173 (2.45)	193 (2.73)	161 (2.27)	171 (2.41)	193 (2.73)
Death	26 (0.37)	34 (0.48)	38 (0.54)	28 (0.40)	32 (0.45)	37 (0.52)
Disabling	37 (0.52)	47 (0.67)	55 (0.78)	50 (0.71)	50 (0.71)	56 (0.79)
Non-disabling	79 (1.12)	84 (1.19)	90 (1.27)	75 (1.06)	81 (1.14)	90 (1.27)
Missing Rankin	7 (0.10)	8 (0.11)	10 (0.14)	9 (0.13)	9 (0.13)	11 (0.16)

Note: Subjects may have more than one stroke event with different outcome.
Note: Stroke outcome is based on investigator's assessment of modified Rankin scale score.

ROCKET AF trial

INR Monitoring

- Only use point-of-care device
- Monitoring occur as clinically indicated, but at least every 4 weeks
- Unblinded INR monitor
  - Consult with an unblinded physician at DCRI
  - Answering potential questions and identify systemic pattern of behavior
- IDMC regular review of INR monitoring and aggregated report of INR values
  - Balancing the goals of maintaining the blind and achieving good INR control
- Letters and related site communications were sent periodically to all investigators reminding them of the need to maintain INRs within the target range

ROCKET. Feedback to Sites on the Importance of INR Control.

- In an effort to prevent inadvertent un-blinding, no information on INR control in warfarin subjects was shared with the site.
  - By design, individual sites were not advised on specific dosing or management of the subject on warfarin.
  - The only time that an individual site was contacted was if that site was clearly not adjusting. This occurred at only 3 sites. The critical importance of improving INR control was reiterated to the investigators either by telephone or by letter.
- At each investigator meeting, investigators were reminded that the target INR range was 2.0 to 3.0.
- A letter was sent out twice to investigators emphasizing the importance of maintaining appropriate therapeutic INRs.
- INR control was discussed in 3 of the 12 quarterly newsletters that were sent to sites.
- No site was closed specifically because of poor INR control subjects.

Primary Efficacy Endpoint
ITT/Regardless of Treatment Exposure

Endpoint	Rivaroxaban N=7081 n (rate)	Warfarin N=7090 n (rate)	Rivaroxaban vs. Warfarin HR (95% CI)	p-value
Primary Efficacy Endpoint	293 (2.20)	320 (2.40)	0.91 (0.78,1.07)	0.263
Total Strokes	277 (2.07)	295 (2.21)	0.94 (0.80,1.10)	0.443
Primary Hemorrhagic	37 (0.27)	57 (0.42)	0.65 (0.43,0.98)	0.041*
Primary Ischemic	226 (1.69)	220 (1.64)	1.03 (0.85,1.24)	0.783
Unknown Stroke	20 (0.15)	20 (0.15)	1.00 (0.54,1.86)	0.998
Non-CNS Systemic Embolism	20 (0.15)	27 (0.20)	0.74 (0.42,1.32)	0.309

rate = number of events per 100 patient-years
Note: * Statistically significant at nominal 0.05 (two-sided)
ROCKET AF Trial

Recurrent Major Bleeding Events

Safety/On-Treatment

	Rivaroxaban N=7111 n (%)	Warfarin N=7125 n (%)
Total no. subjects with Major Bleeding Events	395 (5.55)	386 (5.42)
Subjects with 1 Major Bleeding Event	361 (5.08)	361 (5.07)
Subjects with 2 Major Bleeding Events	32 (0.45)	25 (0.35)
Subjects with 3 Major Bleeding Events	2 (0.03)	0 (0.00)

ROCKET AF trial
n = subjects with events

Summary of Strokes by Type and Sub-Type

Safety/On-Treatment

Stroke Type Sub-Type	Rivaroxaban (N=7061) n (%)	Warfarin (N=7082) n (%)
Primary Ischemic Stroke	149 (2.11)	161 (2.27)
Cardioembolic	28 (0.40)	21 (0.30)
Non-cardioembolic	15 (0.21)	23 (0.32)
Uncertain	106 (1.50)	118 (1.67)
Primary Hemorrhagic Stroke	29 (0.41)	50 (0.71)
Intraparenchymal	27 (0.38)	47 (0.66)
Intraventricular	12 (0.17)	29 (0.41)
Unknown	7 (0.10)	11 (0.16)

Primary Efficacy Endpoint (Stroke/Embolism)

Safety/On Treatment

Endpoints	Rivaroxaban N= 7061 n (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7082 n (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)	Rivaroxaban vs. Warfarin p-value
Primary Efficacy Endpoint	189 (2.68)	1.70	243 (3.43)	2.15	0.79 (0.65,0.95)	0.015*
Total Strokes	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70,1.03)	0.092
Primary Hemorrhagic Stroke	29 (0.41)	0.26	50 (0.71)	0.44	0.59 (0.37,0.93)	0.024*
Primary Ischemic Stroke	149 (2.11)	1.34	161 (2.27)	1.42	0.94 (0.75,1.17)	0.581
Unknown Stroke Type	7 (0.10)	0.06	11 (0.16)	0.10	0.65 (0.25,1.67)	0.366
Non-CNS Systemic Embolism	5 (0.07)	0.04	22 (0.31)	0.19	0.23 (0.09,0.61)	0.003*

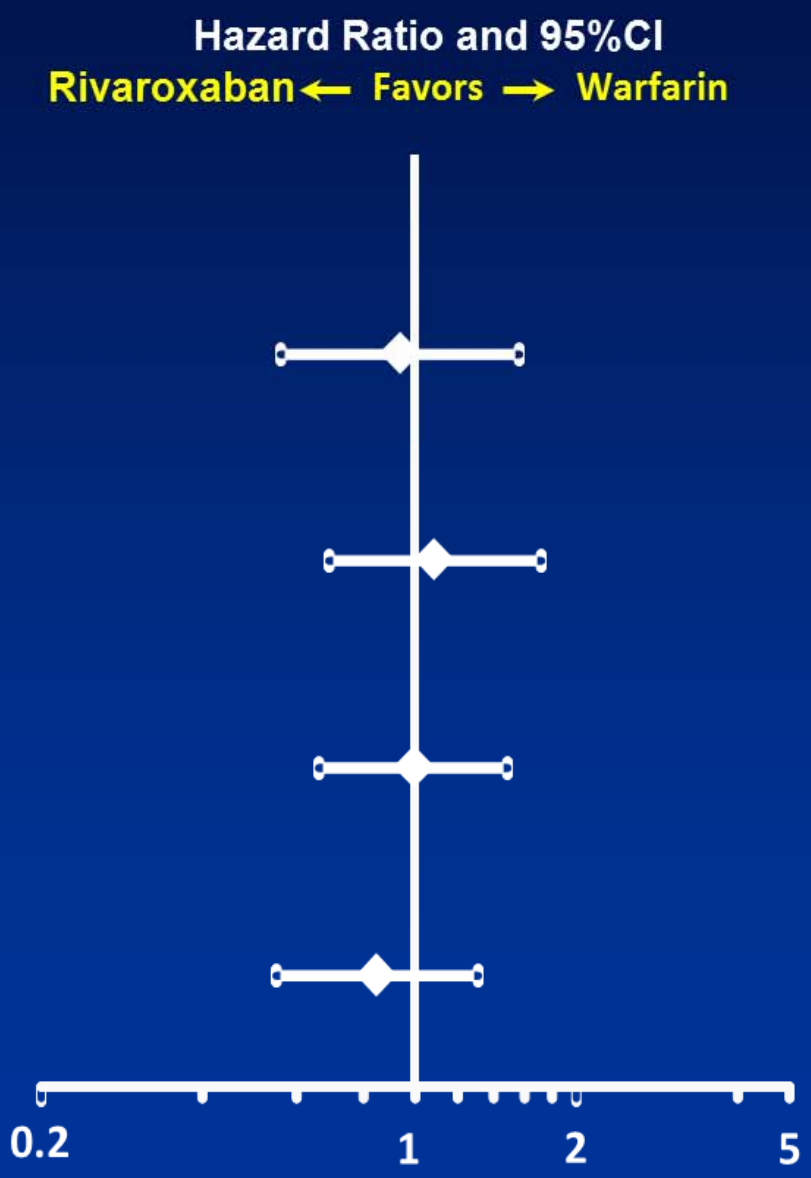
- Statistically significant at nominal 0.05 (two-sided)
- Rate = number of events per 100 patient-years

ROCKET AF trial

Treatment Comparisons for the Ischemic Stroke (Adjudicated by CEC) (up to Last Dose Plus 2 Days) According to Center Quartile Time Below Range (INR<2) (Imputed)

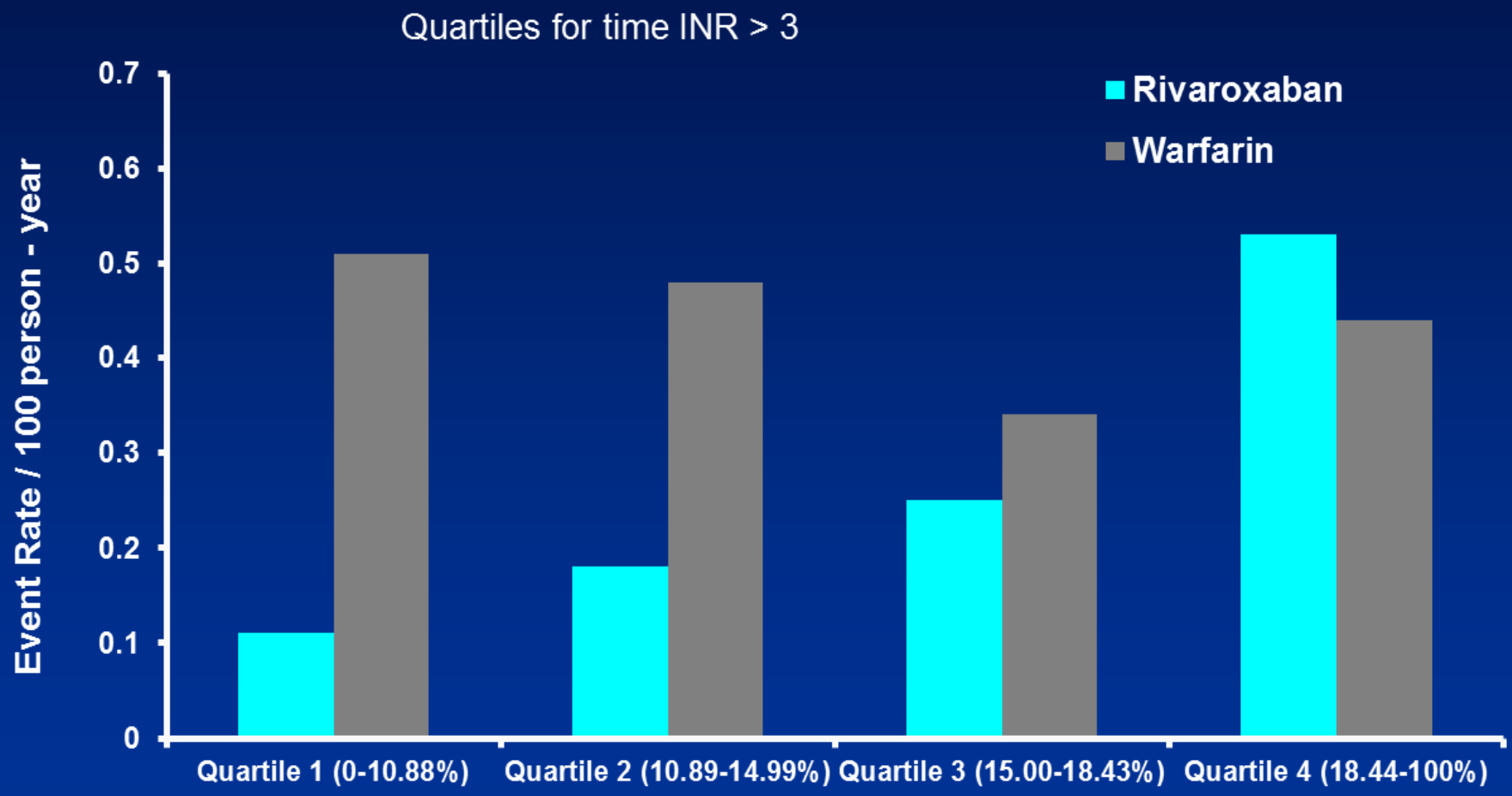
	Rivaroxaban		Warfarin	
Center TTR	N= 7061 n/J	Event Rate (100 pt-yr)	N= 7082 n/J	Event Rate (100 pt-yr)
0.0-17.6%	27/1667	0.97	32/1807	1.05
17.6-24.9%	38/1725	1.37	36/1762	1.26
24.9-34.1%	46/1740	1.70	48/1775	1.71
34.2-100%	38/1759	1.44	44/1736	1.7

Treatment by Quartile p-value : 0.886

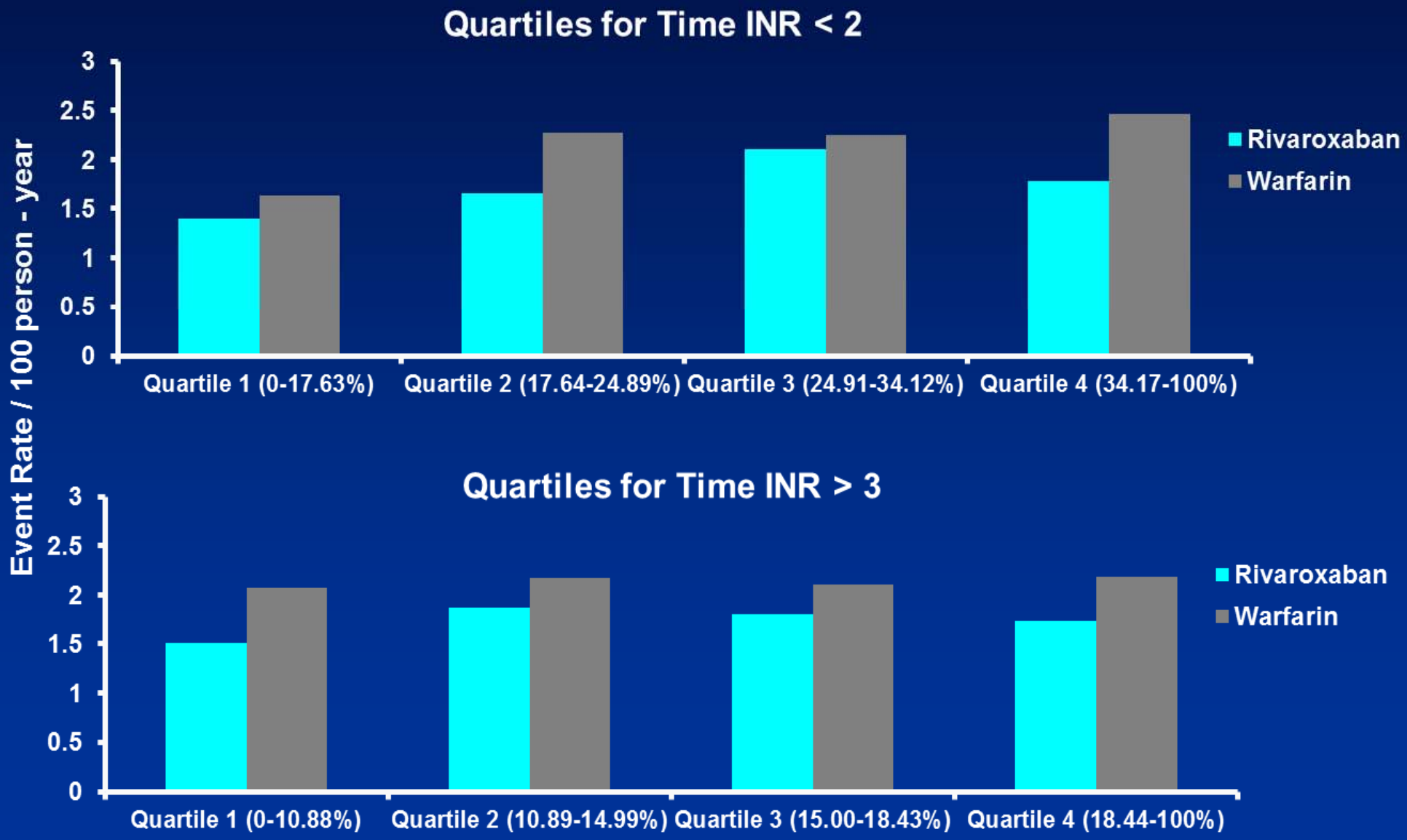


n=number of subjects with event ; J=number of subjects in subgroup

Treatment Comparisons for Hemorrhagic Stroke (Adjudicated by CEC) (up to Last Dose Plus 2 Days) According to Center Quartile Time Above Range (Imputed)



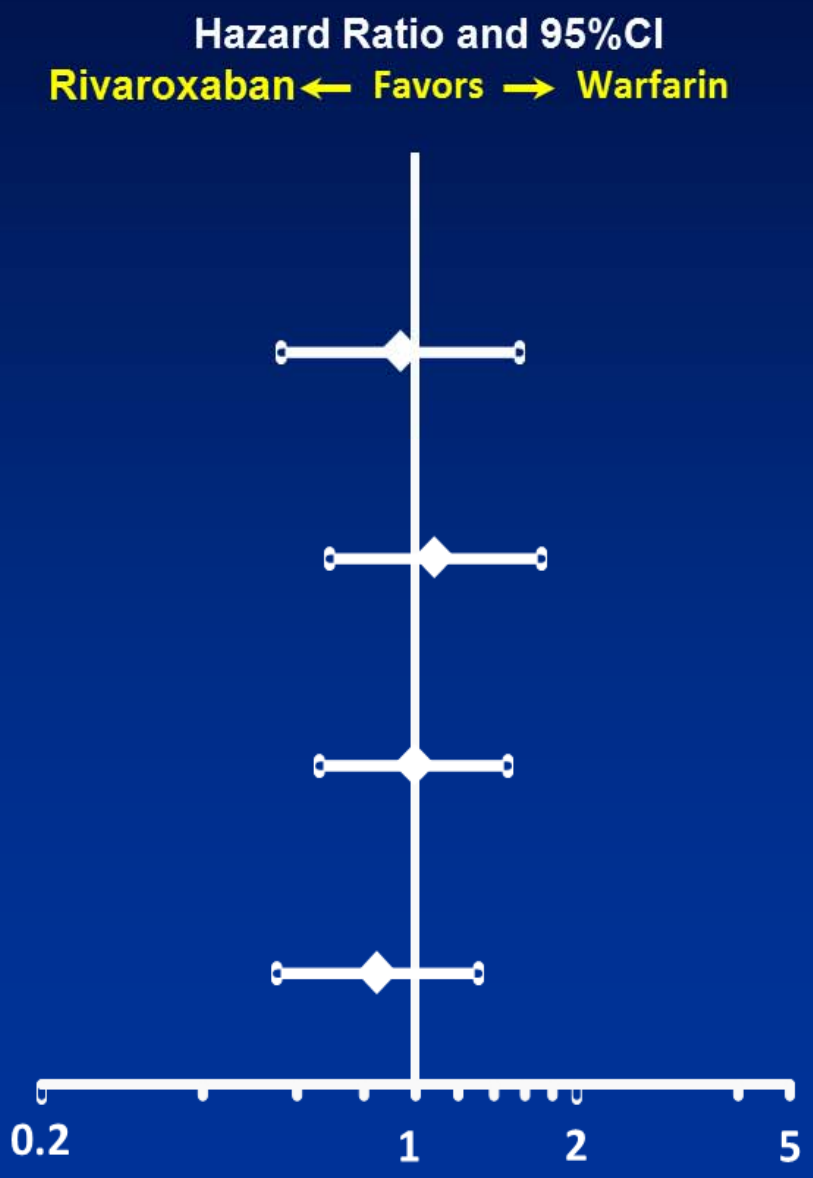
Treatment Comparisons for the Primary Efficacy Endpoint (Adjudicated by CEC) (up to Last Dose Plus 2 Days) According to Center Quartiles Time Below/Above Range (Imputed)



Treatment Comparisons for the Ischemic Stroke (Adjudicated by CEC) (up to Last Dose Plus 2 Days) According to Center Quartile Time Below Range (INR<2) (Imputed)

	Rivaroxaban		Warfarin	
Center TTR	N= 7061 n/J	Event Rate (100 pt-yr)	N= 7082 n/J	Event Rate (100 pt-yr)
0.0-17.6%	27/1667	0.97	32/1807	1.05
17.6-24.9%	38/1725	1.37	36/1762	1.26
24.9-34.1%	46/1740	1.70	48/1775	1.71
34.2-100%	38/1759	1.44	44/1736	1.7

Treatment by Quartile p-value : 0.886



ROCKET AF Trial

n=number of subjects with event ; J=number of subjects in subgroup

Anticoagulant Use Excluding VKA After Last Dose of Study Drug Completers Safety Population

	Rivaroxaban N=4591 n (%)	Warfarin N=4657 n (%)
Number of Subjects Who Used Other Anticoagulants Excluding VKA After Last Dose of Study Drug	117 (2.55)	89 (1.91)
Start Date Relative to Last Day of Study Drug		
Before Last Dose	21 (0.46)	21 (0.45)
0- 2 Days After Last Dose	40 (0.87)	39 (0.84)
3- 7 Days After Last Dose	24 (0.52)	8 (0.17)
8-14 Days After Last Dose	9 (0.20)	3 (0.06)
15-21 Days After Last Dose	6 (0.13)	5 (0.11)
22-30 Days After Last Dose	14 (0.30)	9 (0.19)
>30 Days or Never After Last Dose	4477 (97.52)	4572 (98.17)

Deaths by Primary Cause
ITT/Regardless of Treatment Exposure

	Rivaroxaban N=7081 n (%)	Warfarin N=7090 n (%)
Total subjects who died	621 (8.77)	667 (9.41)
Vascular	398 (5.62)	421 (5.94)
Non-Vascular	160 (2.26)	167 (2.36)
Unknown	63 (0.89)	79 (1.11)

Time to First Occurrence of Secondary Efficacy Endpoint ITT/Regardless of Treatment Exposure

Endpoint	Rivaroxaban N=7081 n (rate)	Warfarin N=7090 n (rate)	Rivaroxaban vs. Warfarin HR (95% CI)	p-value
Secondary Efficacy Endpoint 1	612 (4.59)	638 (4.79)	0.96 (0.86,1.07)	0.442
Secondary Efficacy Endpoint 2	701 (5.29)	741 (5.61)	0.94 (0.85,1.05)	0.266
Myocardial Infarction	132 (0.98)	148 (1.10)	0.89 (0.71,1.13)	0.337
All Cause Mortality	621 (4.58)	667 (4.92)	0.93 (0.84,1.04)	0.204
Vascular Death	398 (2.94)	421 (3.11)	0.95 (0.82,1.08)	0.426
Non-vascular Death	160 (1.18)	167 (1.23)	0.96 (0.77,1.19)	0.704
Unknown Death	63 (0.46)	79 (0.58)	0.80 (0.57,1.11)	0.182

rate = number of events per 100 patient-years
ROCKET AF Trial

Secondary Efficacy Endpoints - North America

ITT/Regardless of Treatment Exposure

Endpoints	Rivaroxaban N= 1339 n (rate)	Warfarin N= 1342 n (rate)	Rivaroxaban vs. Warfarin HR (95% CI)
Secondary Efficacy Endpoint 1	117 (4.31)	110 (4.01)	1.08 (0.83, 1.40)
Secondary Efficacy Endpoint 2	141 (5.25)	137 (5.06)	1.04 (0.82, 1.31)
Myocardial Infarction	41 (1.51)	36 (1.31)	1.15 (0.74, 1.80)
All Cause Mortality	149 (5.43)	155 (5.56)	0.98 (0.78, 1.23)
Vascular Death	80 (2.91)	78 (2.80)	1.04 (0.76, 1.43)
Non-vascular Death	54 (1.97)	52 (1.86)	1.06 (0.72, 1.55)
Unknown Death	15 (0.55)	25 (0.90)	0.61 (0.32, 1.16)

n=number of subjects with events , rate = number of events per 100 patient-years

ROCKET AF trial

Time to First Occurrence of Secondary Efficacy Endpoint
US Only
ITT/Up To Site Notification

Endpoints	Rivaroxaban N = 965		Warfarin N=966		Rivaroxaban vs. Warfarin
	n	rate	n	rate	HR (95% CI)
Secondary Efficacy Endpoint 1	78	4.08	80	4.14	0.99 (0.72,1.35)
Secondary Efficacy Endpoint 2	97	5.12	105	5.52	0.93 (0.70,1.22)
Myocardial Infarction	30	1.57	29	1.5	1.05 (0.63,1.74)
All Cause Mortality	104	5.38	107	5.43	0.99 (0.76,1.30)
Vascular Death	52	2.69	53	2.69	1.00 (0.68,1.47)
Non-vascular Death	40	2.07	38	1.93	1.07 (0.69,1.68)
Unknown Death	12	0.62	16	0.81	0.77 (0.36,1.62)

ROCKET AF Trial
Rate = number of events per 100 patient-years

Hazard Ratio with Additional Events Added in the Rivaroxaban Group (Primary Efficacy, ITT/SN)

	Rivaroxaban (N=7081) n (Rate/100ptyr)			Warfarin (N=7090) n (Rate/100ptyr)			
	Observed Follow-up Period	Missing Follow-up Period (Hypothetical)	Combined†	Observed Follow-up Period	Missing Follow-up Period (Hypothetical)	Combined†	Hazard Ratio ‡ (95% CI)
Observed	269 (2.2)	N/A	269 (2.2)	306 (2.4)	N/A	306 (2.4)	0.88 (0.75, 1.04)
Scenario 1	269 (2.2)	77 (15.2)	346 (2.8)	306 (2.4)	0 (0.0)	306 (2.4)	1.16 (1.00, 1.36)
Scenario 2	269 (2.2)	87 (17.2)	356 (2.8)	306 (2.4)	10 (2.3)	316 (2.4)	1.16 (1.00, 1.35)

Scenario 1: No event would occur during the missing follow-up period in the warfarin group.
Scenario 2: Event rate in the missing follow-up period in the warfarin group would be similar to the event rate observed in the actual follow-up period.
† Combined event rate = the total number of observed and imputed events/the sum of observed and missing follow-up time .
‡ Based on the least favorable time allocation and the most favorable time allocation for imputed events.

EF-798

Primary Efficacy Endpoint Without Hemorrhagic Stroke Safety Last Dose Plus 2 Days (Stroke)

Endpoint	Rivaroxaban N=7061 n (rate)	Warfarin N=7082 n (rate)	Rivaroxaban vs. Warfarin HR (95% CI)	p-value
Primary Hemorrhagic Stoke	29 (0.26)	50 (0.44)	0.59(0.37, 0.93)	0.024*
Primary Efficacy End Point Excluding Hemorrhagic Stroke	160 (1.44)	193 (1.71)	0.84 (0.68, 1.04)	0.106

rate = number of events per 100 patient-years

Note: * Statistically significant at nominal 0.05 (two-sided)

ROCKET AF Trial

Major Bleeding without Hemorrhagic Stroke

Endpoint	Rivaroxaban N=7111 n	Rivaroxaban Event Rate (100 pt-yr)	Warfarin N=7125 n	Warfarin Event Rate (100 pt-yr)	Rivaroxaban vs. Warfarin HR (95% CI)	p-value
Major Bleeding excluding IHI & IHV	357	3.25	327	2.93	1.11(0.96, 1.29)	0.172

ROCKET AF trial
INI=intraparenchymal
IHV=intraventricular

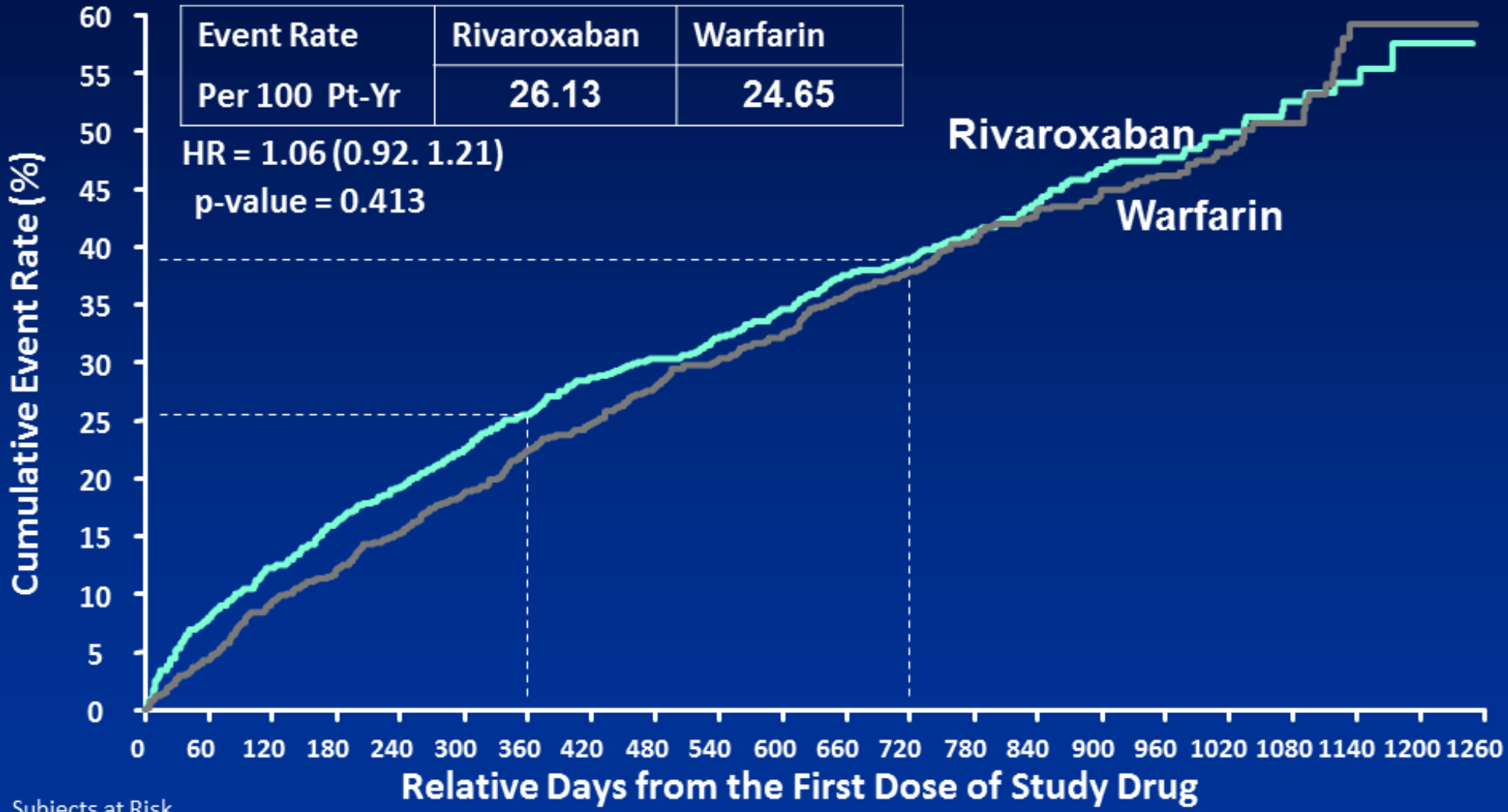
Percent Time On-Treatment

	Rivaroxaban N=7131	Warfarin N=7133
On-Treatment Patient Years (Mean)	11240.39 (1.57)	11375.81 (1.59)
Total Follow Up Patient Years (Mean)	13600.07 (1.90)	13596.16 (1.90)
Percentage	82.6%	83.7%

ROCKET AF Trial

Time from First to Last Study Drug for Early Study Medication Discontinuation-US Only

Safety Population



No. Subjects at Risk

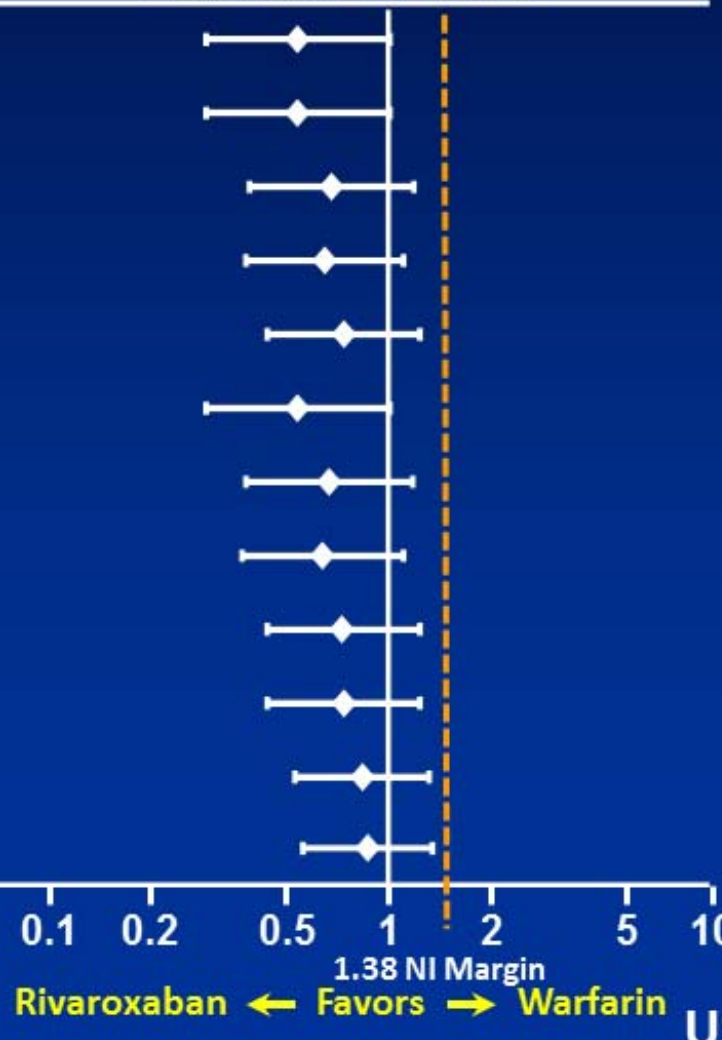
Rivaroxaban	962	888	845	808	778	748	717	676	613	563	508	435	392	334	276	227	176	121	72	38	13	1
Warfarin	964	923	874	852	818	785	750	717	633	588	533	453	400	332	280	232	192	135	85	33	11	1

ROCKET AF trial

EF-942

Primary Efficacy Endpoint
US Only
All Populations/Multiple Observation Periods

	Rivaroxaban		Warfarin	
	n/N	Event Rate (100 Pt-yr)	n/N	Event Rate (100 Pt-yr)
Per Protocol, On Treatment	15/950	0.95	29/956	1.76
Per Protocol, On treatment (Restrictive Definition)	15/950	0.95	29/956	1.76
Per Protocol, Last Dose Plus 7 Days	20/950	1.26	31/956	1.87
Per Protocol, Last Dose Plus 14 Days	21/950	1.31	34/956	2.03
Per Protocol, Last Dose Plus 30 Days	24/950	1.46	34/956	1.99
Safety, On Treatment	15/962	0.94	29/964	1.75
Safety, Last Dose Plus 7 Days	20/962	1.24	31/964	1.86
Safety, Last Dose Plus 14 Days	21/962	1.29	34/964	2.02
Safety, Last Dose Plus 30 Days	24/962	1.44	34/964	1.97
ITT – Follow-Up Visit	25/965	1.48	35/966	2.00
ITT – Site Notification	34/965	1.78	41/966	2.12
ITT – Regardless of Treatment Exposure	36/965	1.81	42/966	2.09



US-002

Time to First Occurrence of Primary Efficacy Endpoint
US Only
ITT/Up To Site Notification

Endpoints	Rivaroxaban N = 965 n	Rivaroxaban N = 965 rate	Warfarin N = 966 n	Warfarin N = 966 rate	Rivaroxaban vs. Warfarin HR (95% CI)
Primary Efficacy Endpoint	34	1.78	41	2.12	0.84 (0.53,1.32)
Total Strokes	29	1.51	35	1.8	0.84 (0.51,1.38)
Primary Hemorrhagic	6	0.31	9	0.46	0.68 (0.24,1.91)
Primary Ischemic	21	1.09	24	1.23	0.89 (0.49,1.59)
Unknown	2	0.1	2	0.1	1.02 (0.14,7.22)
Non-CNS Systemic Embolism	7	0.36	6	0.31	1.18 (0.40,3.52)

ROCKET AF Trial
Rate = number of events per 100 patient-years

Time to First Occurrence of Primary Efficacy Endpoint US Only

Safety/On Treatment

Endpoints	Rivaroxaban N= 962 n (rate)	Warfarin N=964 n (rate)	Rivaroxaban vs. Warfarin HR (95% CI)
Primary Efficacy Endpoint	15 (0.94)	29 (1.75)	0.54 (0.29, 1.01)
Total Strokes	14 (0.88)	24 (1.45)	0.61 (0.32, 1.18)
Primary Hemorrhagic	6 (0.38)	8 (0.48)	0.79 (0.27, 2.28)
Primary Ischemic	8 (0.50)	16 (0.96)	0.52 (0.22, 1.22)
Unknown	0 (0.00)	0 (0.00)	
Non-CNS Systemic Embolism	1 (0.06)	5 (0.30)	0.21 (0.02, 1.77)

n=number of subjects with events; rate = number of events per 100 patient-years
ROCKET AF trial

US-043

Switching from Warfarin to Rivaroxaban
Absolute INR Values at Trough Concentrations

Time	n	Warfarin / rivaroxaban	n	Warfarin / placebo	n	Rivaroxaban alone
		Warfarin		Warfarin		
Baseline	28	1.035 (0.93 – 1.34)	28	1.040 (0.92 – 1.21)		
		Warfarin / rivaroxaban		**Warfarin / placebo**		**Rivaroxaban alone**
Day 0 Trough	27	**2.230** (1.92 – 2.55)	26	**2.285** (1.90 – 2.70)	28	1.015 (0.87 – 1.20)
Day 1 Trough	27	**1.850** (1.53 – 2.31)	28	**1.675** (1.34 – 2.13)	28	1.055 (0.91 – 1.32)
Day 2 Trough	28	**1.420** (1.19 – 2.04)	28	**1.290** (1.08 – 1.67)	28	1.060 (0.94 – 1.39)
Day 3 Trough	28	**1.175** (1.01 – 1.48)	28	**1.120** (1.01 – 1.33)	28	1.060 (0.93 – 1.46)
Day 4 Trough	28	**1.135** (0.93 – 1.41)	28	**1.075** (0.87 – 1.19)	28	1.040 (0.93 – 1.49)
Day 5 Trough	28	**1.060** (0.91 – 1.28)	27	**1.030** (0.90 – 1.17)	28	1.010 (0.88 – 1.30)
Day 6 Trough	28	**1.025** (0.90 – 1.22)	28	**1.030** (0.90 – 1.19)	28	0.995 (0.89 – 1.29)
Final exam.		**1.020** (0.86 – 1.25)		**0.995** (0.85 – 1.17)	28	1.005 (0.87 – 1.30)

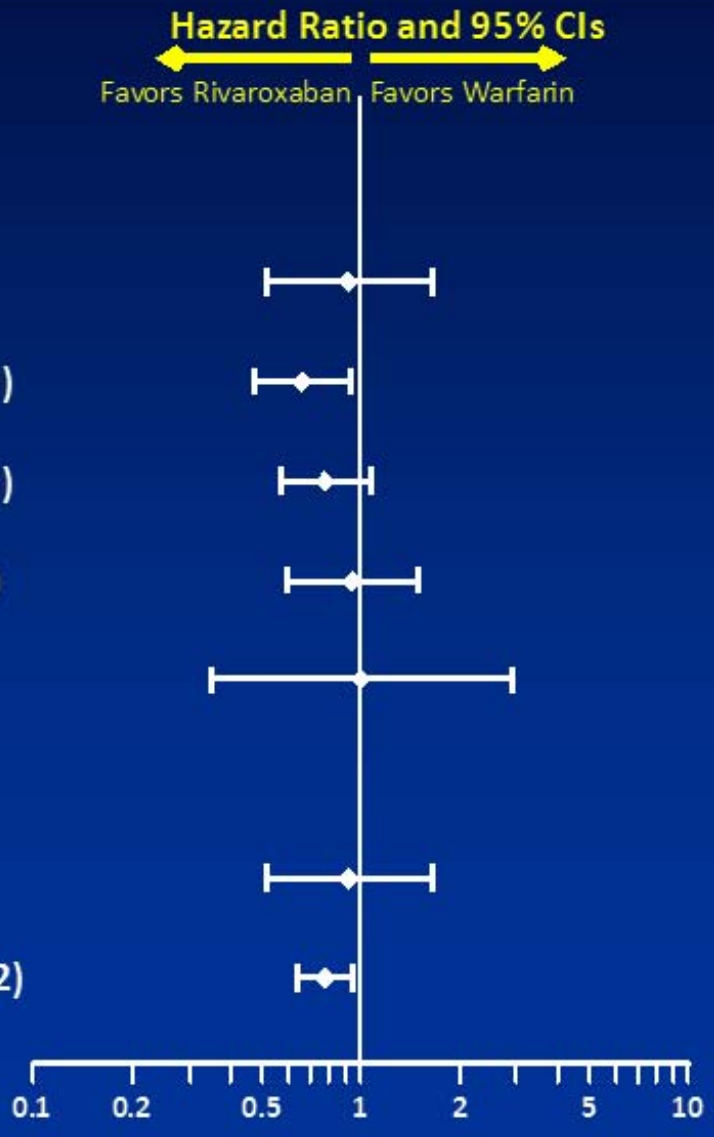
Similar absolute INR values when assessed at Trough

Phase 1 Clinical Trial 10849: Switching from Warfarin to rivaroxaban

CP-003

Primary Efficacy Endpoint by Subgroup: $CHADS_2$
Safety/On Treatment

	Rivaroxaban N=7061 n/J (Rate)	Warfarin N=7082 n/J (Rate)
CHADS2 (1)		
2	21/922 (1.2)	24/931 (1.3)
3	56/3025 (1.19)	87/3131 (1.79)
4	71/2073 (2.24)	88/1988 (2.88)
5	35/918 (2.57)	36/875 (2.71)
6	6/122 (3.66)	8/155 (3.87)
CHADS2 (2)		
Moderate: 2	21/922 (1.2)	24/931 (1.3)
High: >=3	168/6138 (1.79)	219/6149 (2.32)



ROCKET AF trial

EF-558