Advances in Cardiac Diseases and Great Innovations in Cardiology

Stroke Prevention in AF

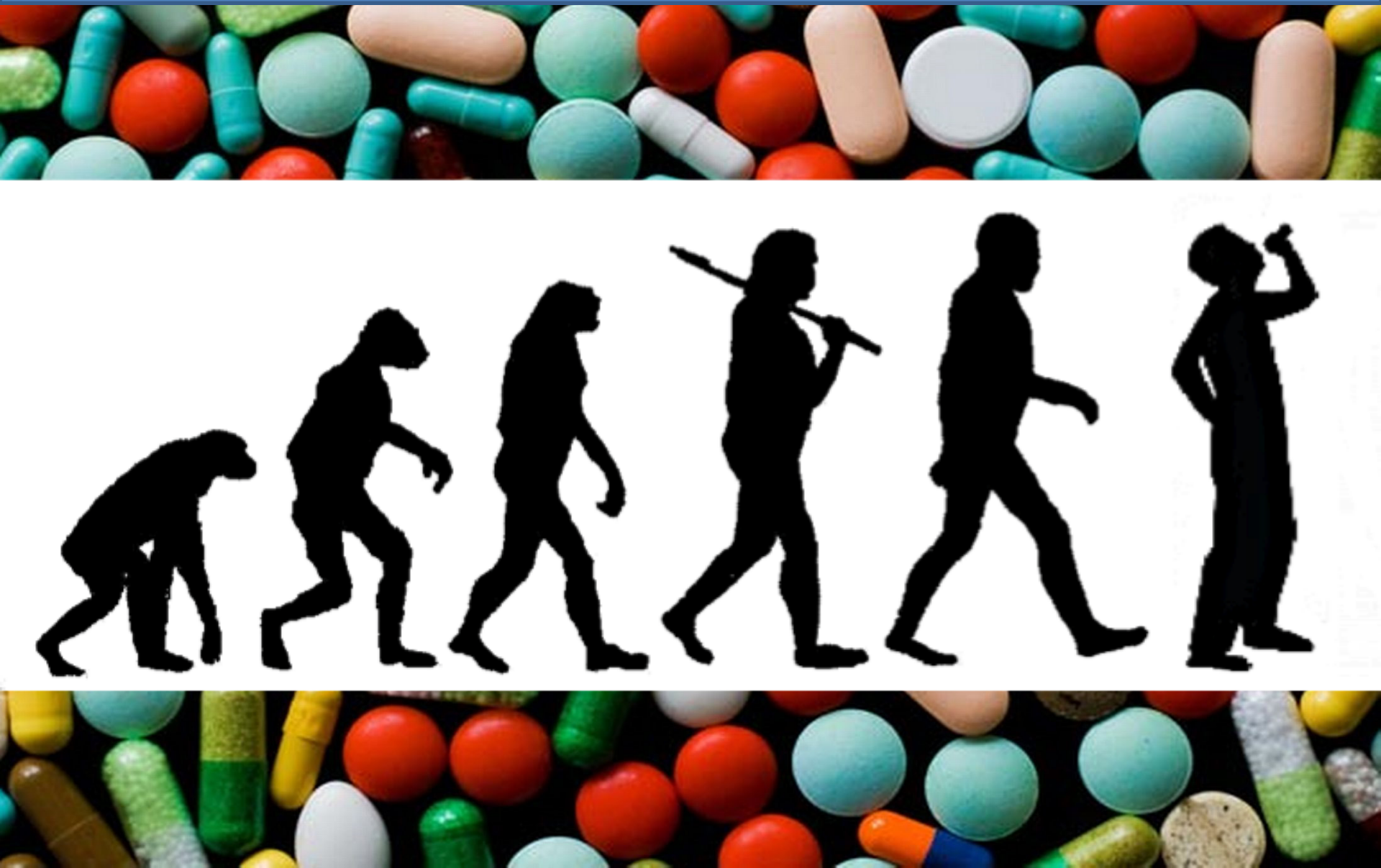
Torino, Centro Congressi Unione Industriale
13-15 Ottobre 2016

Rivaroxaban

Leonardo De Luca, MD, PhD, FACC, FESC, FSCAI

Division of Cardiology
Interventional Cardiology Unit
San Giovanni Evangelista Hospital
Tivoli (Rome), Italy
leo.deluca@libero.it

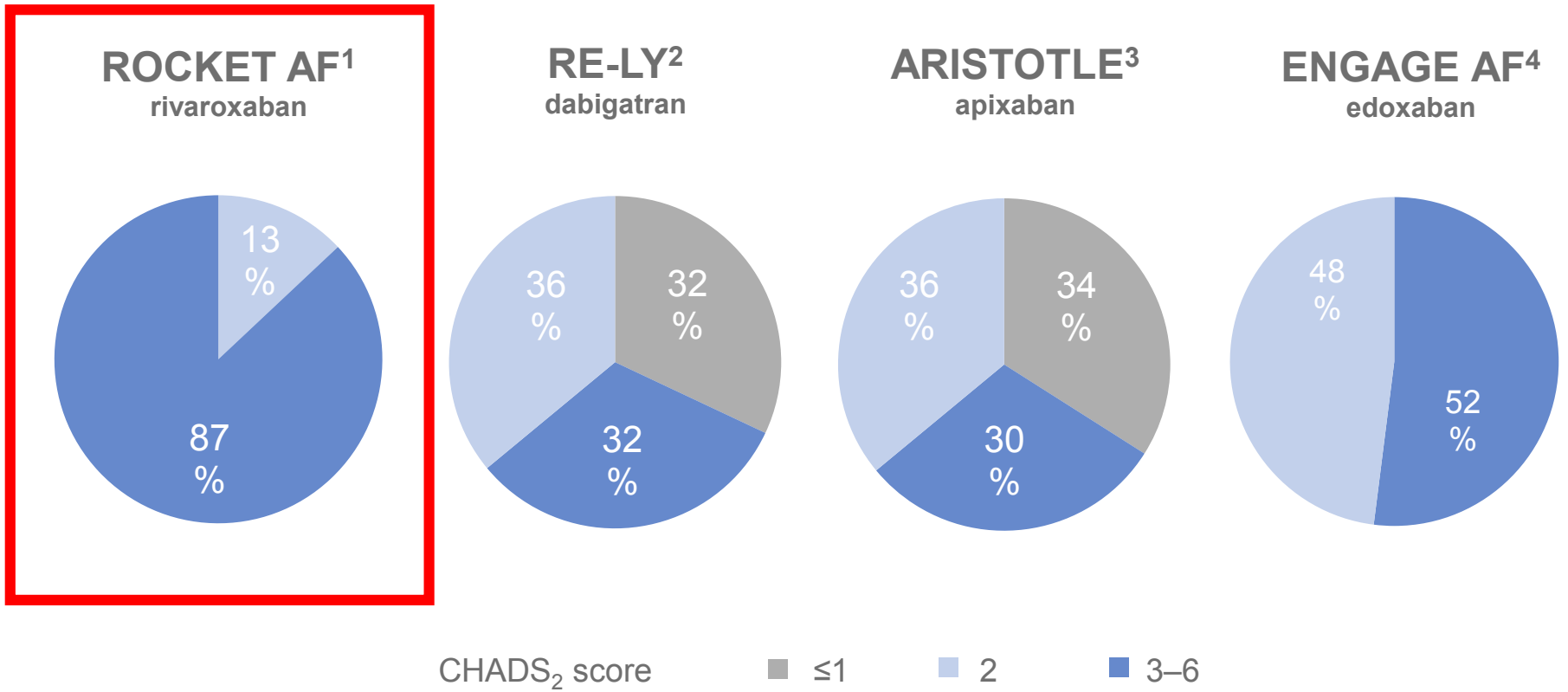
Adaptation is the Key of Evolution



Adaptation is the Key of Evolution

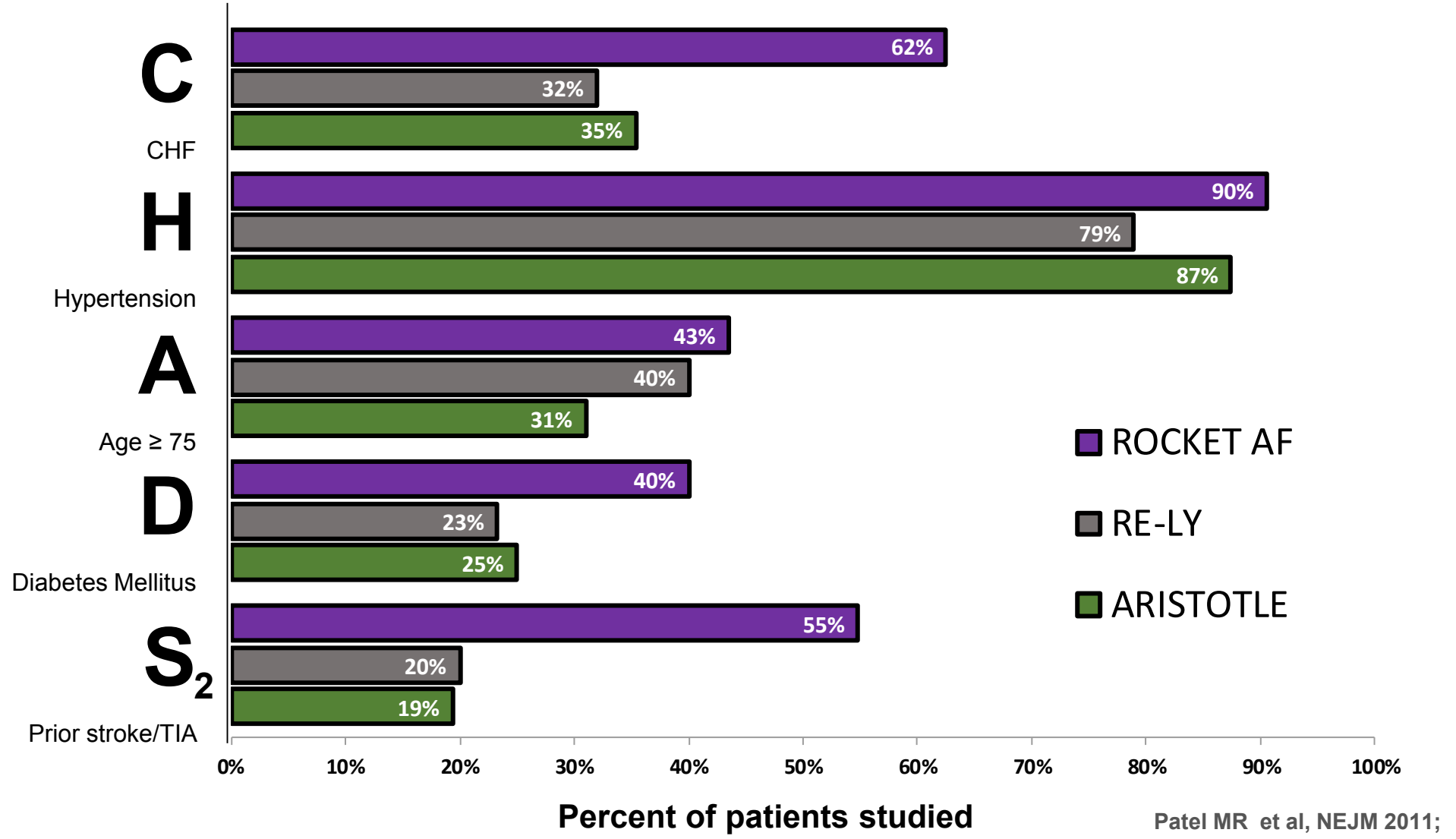
Stroke Risk of AF Patients in Phase III Trials

$CHADS_2$-Score patient distribution



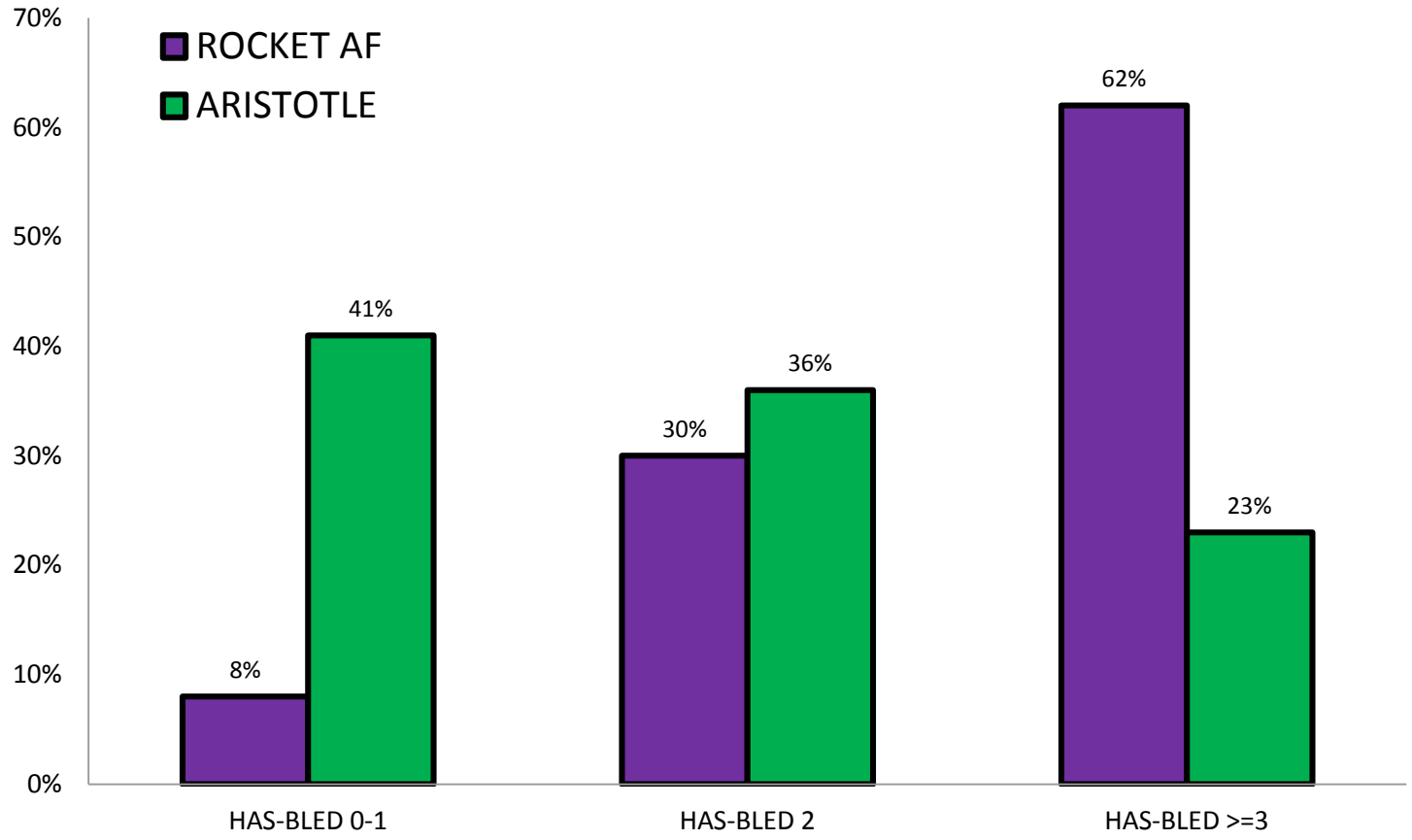
1. Patel MR et al. N Engl J Med. 2011;365(10):883-891; 2. Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151;
3. Granger CB et al. N Engl J Med. 2011;365(11):981-992; 4. Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104

Comorbidities in Phase III RCTs on NOACs



Patel MR et al, NEJM 2011;
Connolly SJ, et al. N Engl J Med. 2009
Granger C et al, N Eng J Med; 2011

Bleeding Risk in ROCKET AF and ARISTOTELE

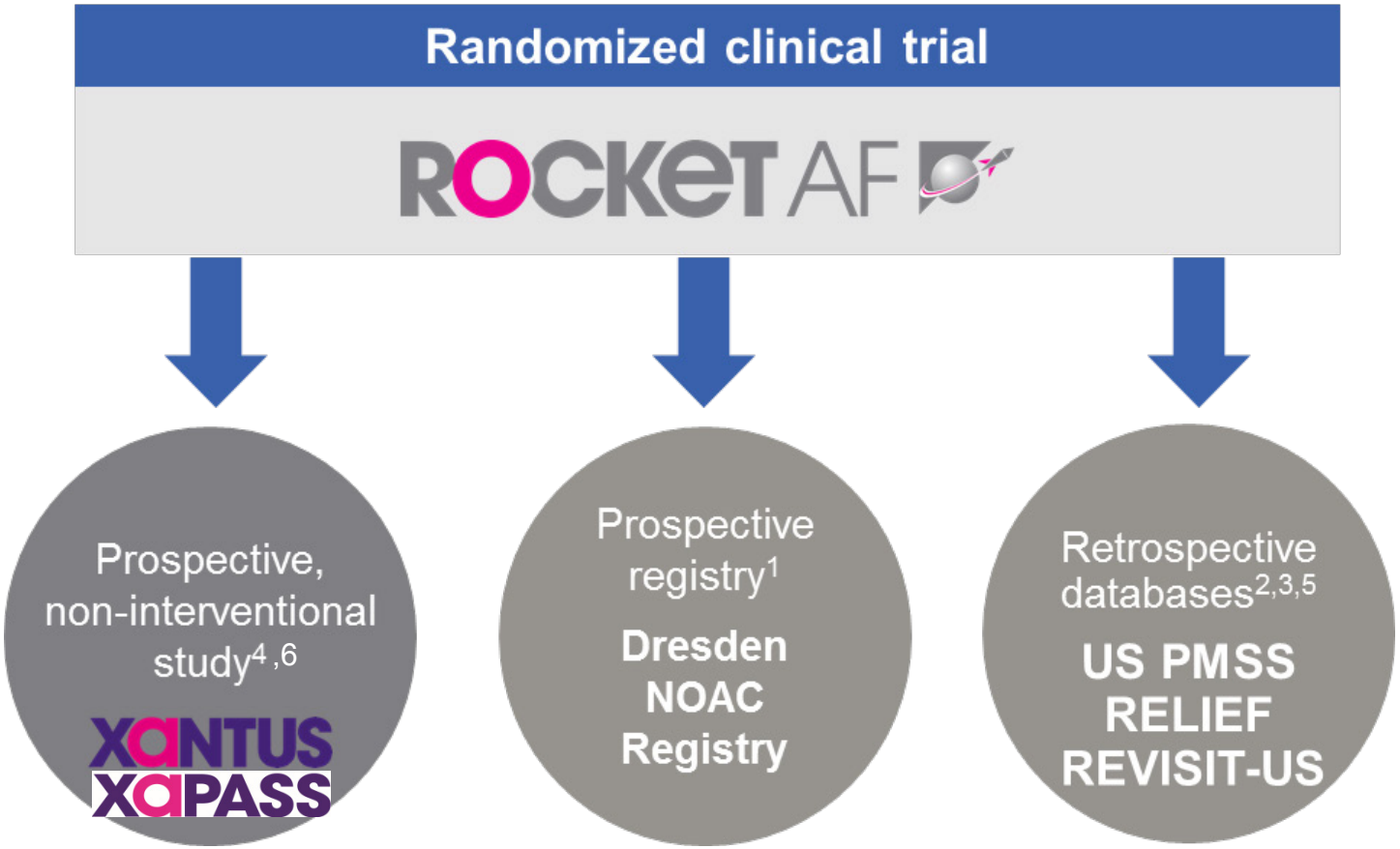


Jones WS, et al. Eur Heart J 2013
Lopes RD, et al. Lancet 2012

Sources and Reliability of Data

Pivotal Trial	Prospective Observational Study	Registry	Database
Highest quality	Endpoint definition Blinded Adjudication Committee?	Endpoint definition?	Recognized by HA? Independent? Endpoint adjudication and definition?

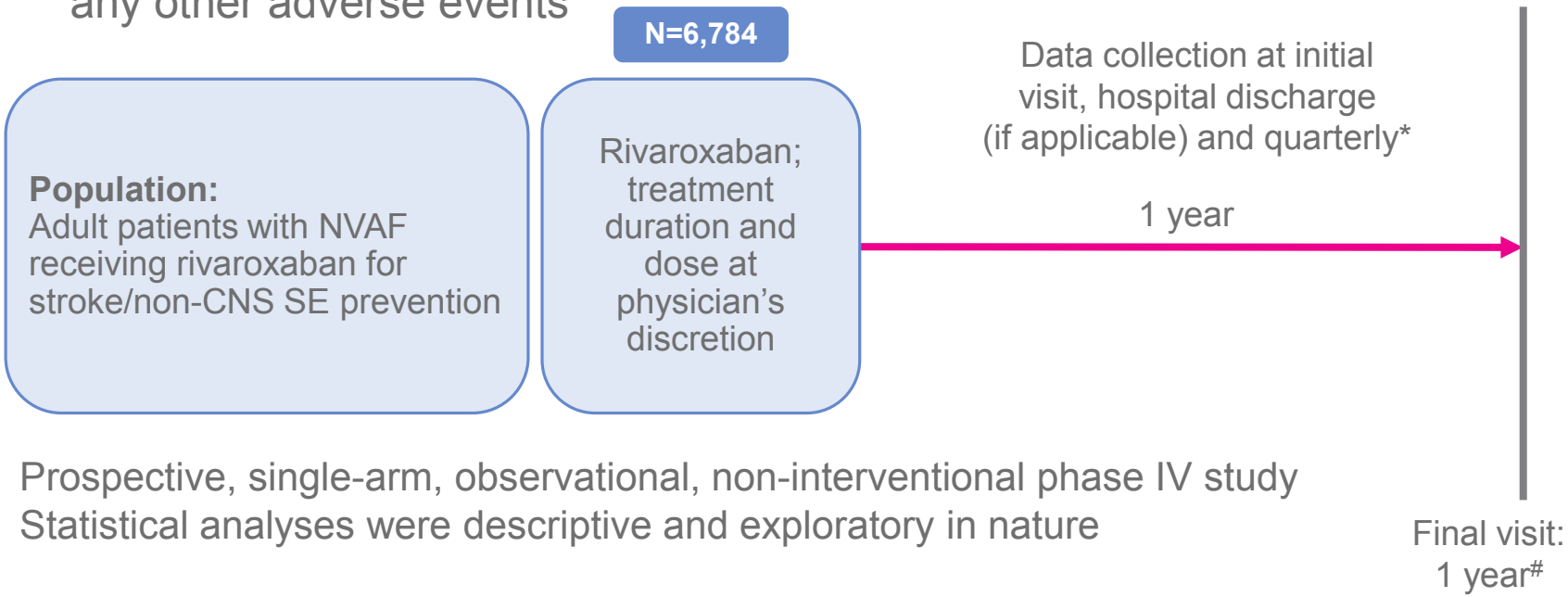
Rivaroxaban Provides a Consistent and Unique Dataset Covering the Full Patient-Risk Spectrum



1.Beyer-Westendorf J *et al*, *Blood* 2014;124;955–962; 2. Tamayo S *et al*, *Clin Cardiol* 2015;38:63–68; 3. Coleman C *et al, Int J Card Med* 2016;203:882–884; 4. Camm AJ *et al*, *Eur Heart J* 2016;37(4):1145-53; 5. Coleman CI *et al, Curr Med Res Opin* 2016 Sep 15 ; 6.Ogawa et al., J Stroke Cerebrovasc Dis, 2014;23:2520-6

XANTUS:
Study Objective and Design

- To collect real world data on adverse events in patients with NVAF treated with rivaroxaban to determine the safety profile of rivaroxaban across the broad range of patient risk profiles encountered in routine clinical practice
  - Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events

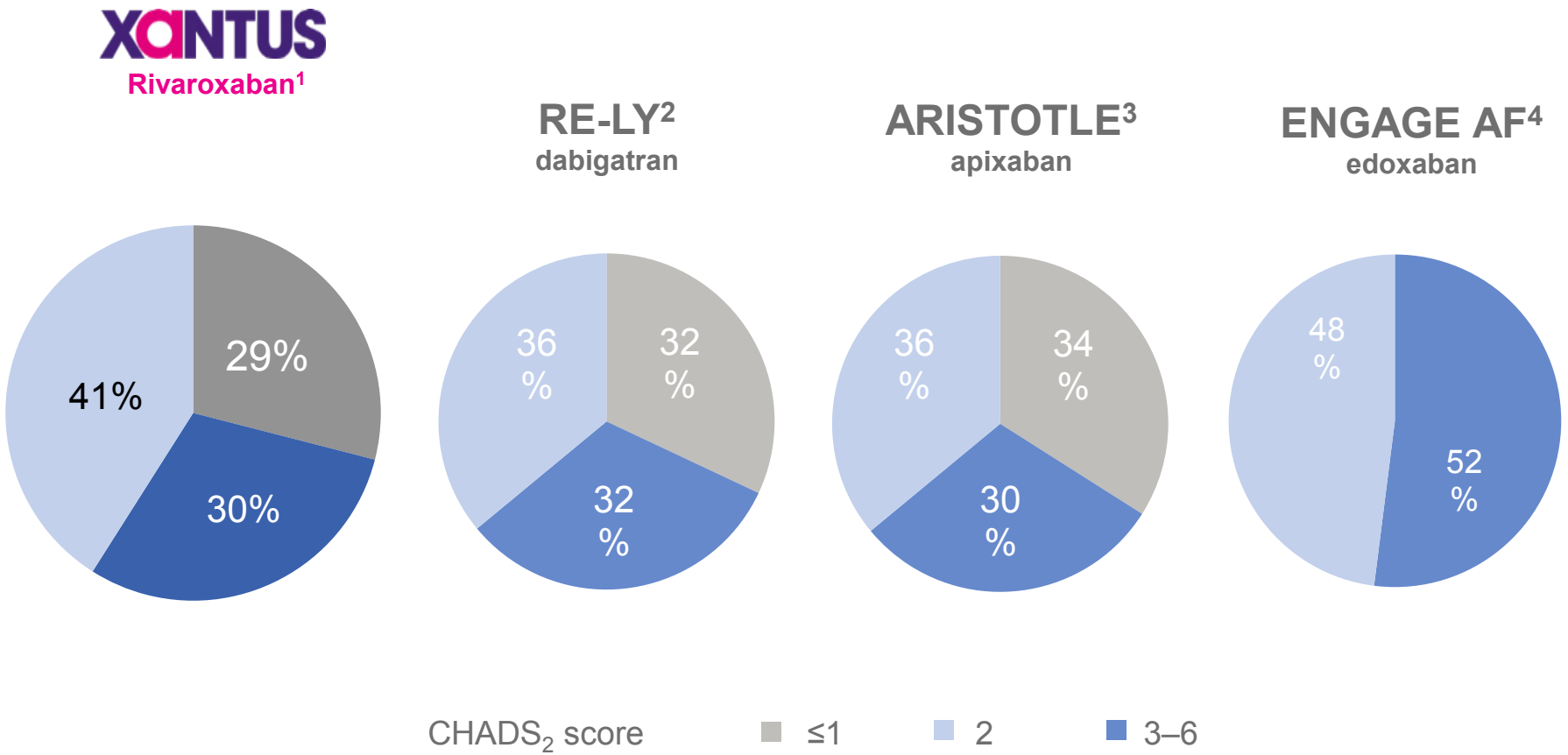


Prospective, single-arm, observational, non-interventional phase IV study
Statistical analyses were descriptive and exploratory in nature

*Exact referral dates for follow-up visits not defined (every 3 months recommended); #for rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose. Observational design means no interference with clinical practice was allowed

1. Camm AJ *et al*, *Vasc Health Risk Manag* 2014;10:425–434; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

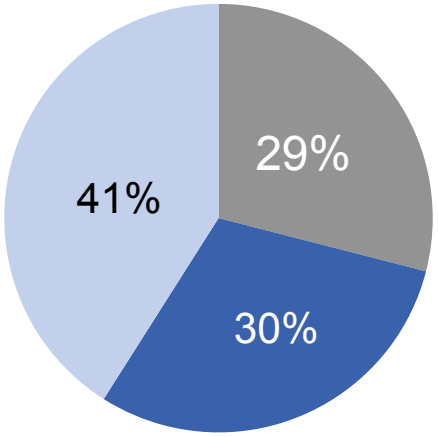
Stroke Risk of AF Patients in XANTUS and Some Phase III Trials



1. Camm AJ et al, Eur Heart J 2016;37:1145; 2. Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151;
3. Granger CB et al. N Engl J Med. 2011;365(11):981-992; 4. Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104

Rivaroxaban Tested in Different Populations in Randomized Clinical Trial and the Real World

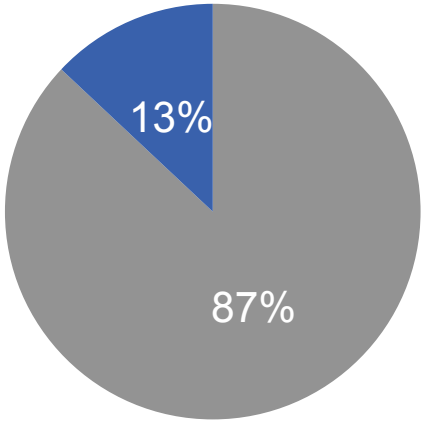
XANTUS
Rivaroxaban[1]



XANTUS[1]	Baseline	ROCKET AF[2]
2.0	$CHADS_2$	3.5
41%	0–1	0%
30%	2	13%
29%	≥3	87%
19%	Heart failure	63%
75%	Hypertension	91%
37%	Age >75 years	44%
20%	Diabetes	40%
19%	Prior stroke#	55%
10%	Prior MI	17%

Results are not intended for direct comparison

ROCKET AF
Rivaroxaban[2]



$CHADS_2$ score ≤1 2 3–6

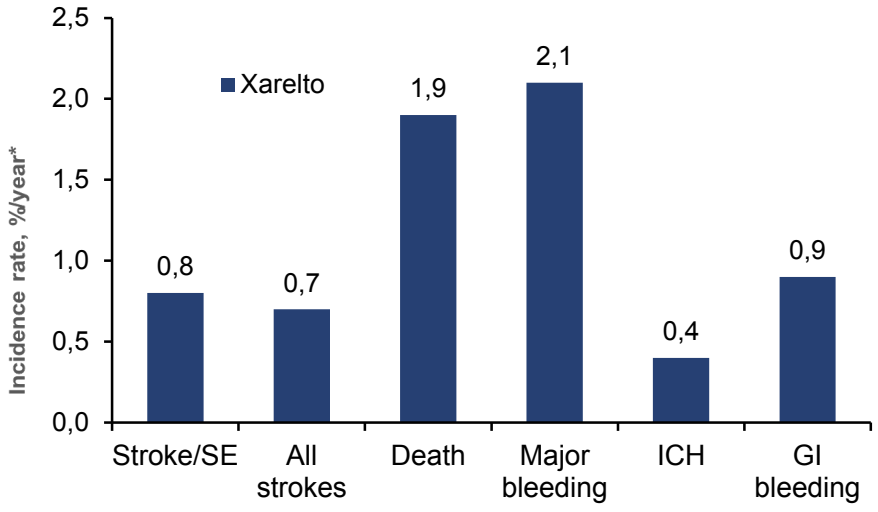
*Events per 100 patient-years; #includes prior stroke, SE or TIA

Adapted from: 1.Camm AJ *et al*, *Eur Heart J* 2016;37(4):1145-53; 2. Patel MR *et al*, *N Engl J Med* 2011;365:883–891

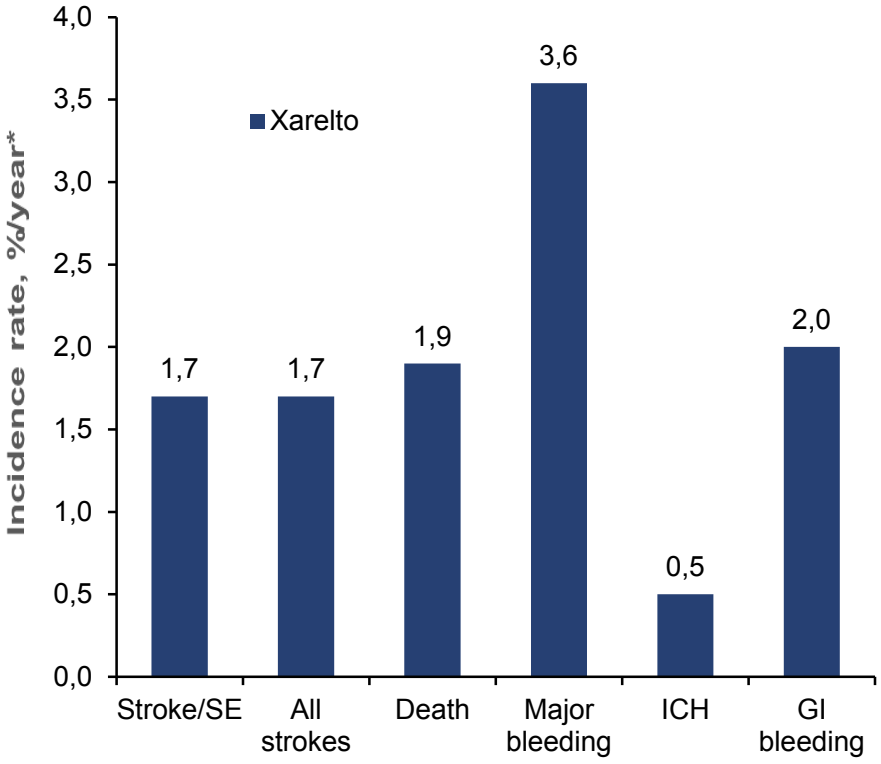
Comparison of Main Outcomes: XANTUS versus ROCKET AF

	$CHADS_2$	Prior stroke#
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%

XANTUS



ROCKET AF



#Includes prior stroke, SE or TIA;

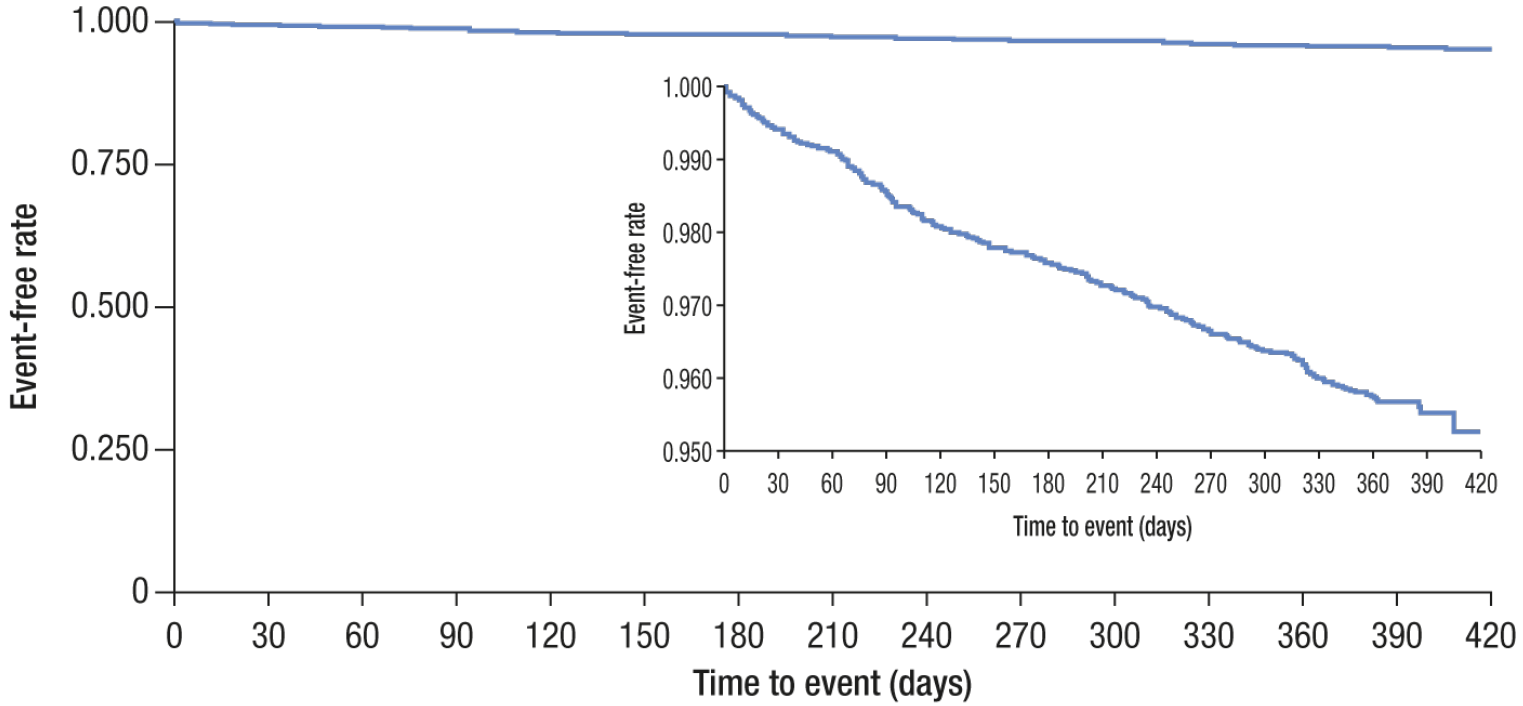
*Events per 100 patient-years

1. Patel MR et al, N Engl J Med 2011;365:883;
2. Camm AJ et al, Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466

Event-Free Rate for Treatment-Emergent Primary Outcomes

XANTUS

- In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding or stroke/SE



- Persistence with rivaroxaban in XANTUS was 80% at 1 year
- 8.8% of pts had at least one interruption of rivaroxaban therapy, which was most commonly because of a need for surgery, or because of bleeding or another AE

Camm AJ et al, Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466

Management of Major Bleeding

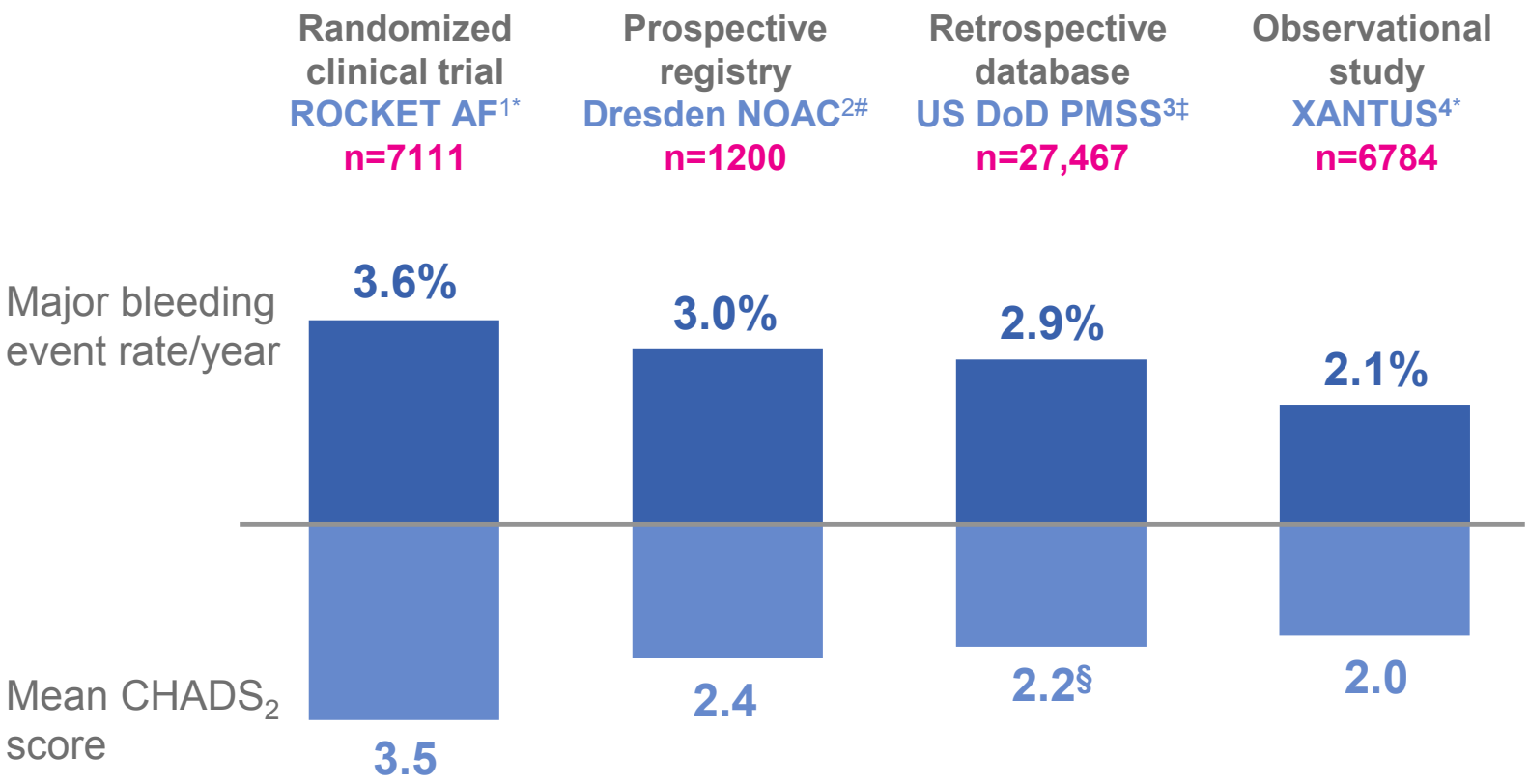
XANTUS

- Major bleeding was mostly treated using conservative methods[1]
  - 0.8% of patients (n=53) received transfusions of ≥2 units of packed RBCs or whole blood
- Throughout the study use of non-specific reversal agents – such as prothrombin complex concentrate (PCC) - was low[1]
  - Use of PCC documented in two patients
  - Use of tranexamic acid documented in three patients
  - Use of etamsylate documented in one patient
- These findings are in line with outcomes from ROCKET AF [2] and the Dresden NOAC Registry[3]

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466;
2. Piccini JP *et al, Eur Heart J* 2014; 35(28):1873-80;
3. Beyer-Westendorf J *et al, Blood* 2014; 124(6):955-62

Major Bleeding Rates with Rivaroxaban: Low and Consistent in RCT and Real Life Setting

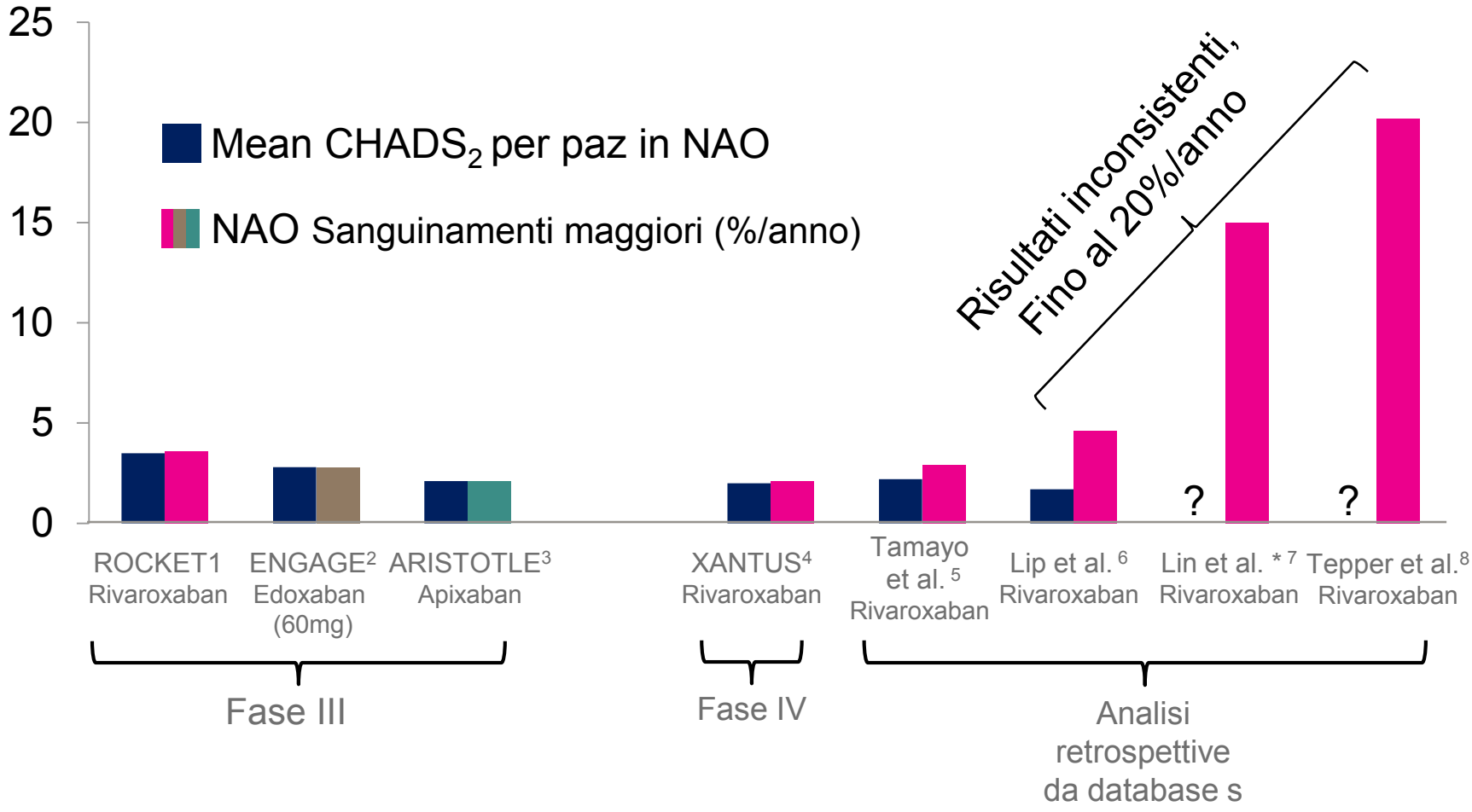
Data on more than **54.000** rivaroxaban treated patients



*Major bleeding definition according to ISTH; #modified ISTH definition (additionally included surgical revision from bleeding);
‡major bleeding defined by the Cunningham algorithm[5]; §No major bleeding cohort (representative of >98% of the patient population)

1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Hecker J *et al*, *Thromb Haemost* 2016 Jan 21;115(5) [Epub ahead of print];
3. Tamayo S *et al*, *Clin Cardiol* 2015;38:63–68; 4 Camm AJ *et al*, *Eur Heart J* 2015;doi:10.1093/eurheartj/ehv466;
5. Cunningham A *et al*, *Pharmacoepidemiol Drug Saf* 2011;20:560–566

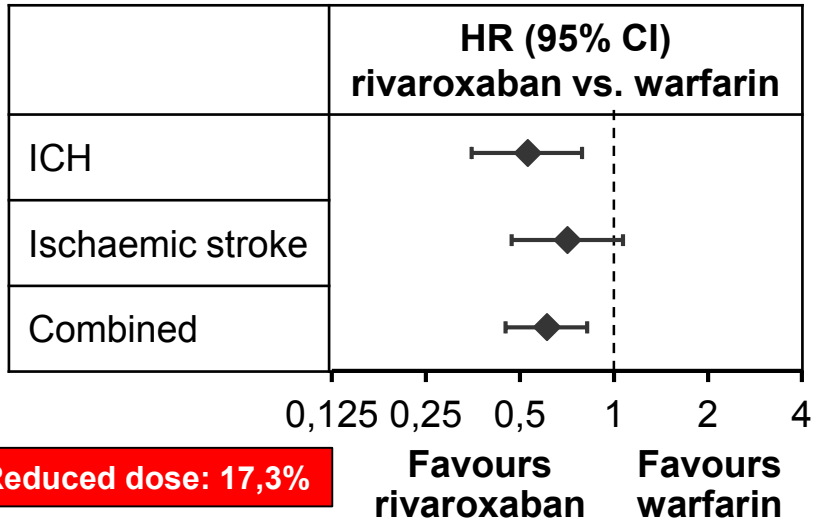
Incosistenza relativa all'incidenza di sanguinamenti maggiori dai claim database

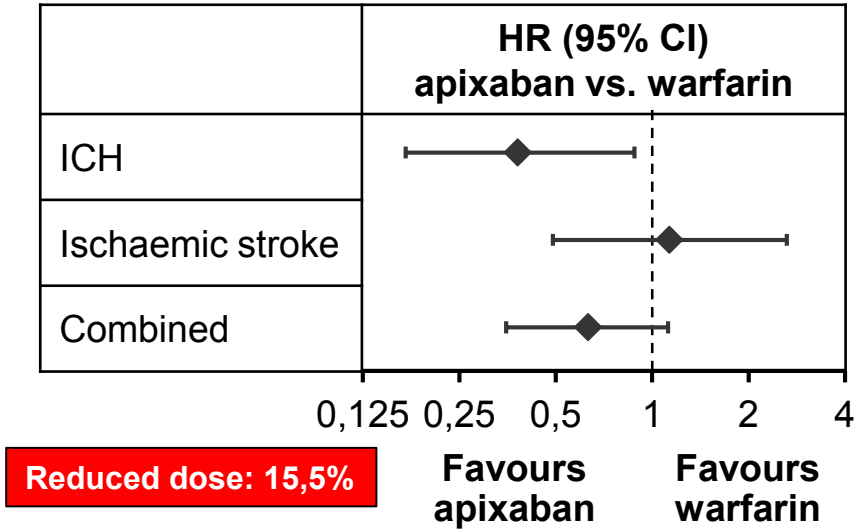


* Defined as any recorded bleeding at critical sites

Adapted from 1. Patel MR et al. *N Engl J Med* 2011; 365(10):883–891; 2. Giugliano R.P. *N Engl J Med* 2013; 3. Granger C.B. *N Engl J Med* 2011; 4. Camm et al Eur Heart J 2015; 5. Tamayo et al. *Clin Cardiol* 2015; 6. Lip G.Y.H. *Eur Heart J* 2015 (36) (Abstract supplement); 7. Lin l. *Eur Heart J* 2015 (36) (Abstract supplement); 8 Tepper P. Eur Heart J 2015 (36) (Abstract supplement-. abstract n.1975)

REVISIT-US:
Rivaroxaban vs warfarin and apixaban vs warfarin





	HR (95% CI) rivaroxaban vs. warfarin
ICH	0.53 (0.35–0.79)*
Ischaemic stroke	0.71 (0.47–1.07)
Combined	0.61 (0.45–0.82)*

	HR (95% CI) apixaban vs. warfarin
ICH	0.38 (0.17–0.88)*
Ischaemic stroke	1.13 (0.49–2.63)
Combined	0.63 (0.35–1.12)

*$p<0.05$ vs warfarin

Coleman CI *et al, Curr Med Res Opin* 2016 Sep 15

REVISIT-US

Adaptation is the Key of Evolution

NOACs
Dose Reduction

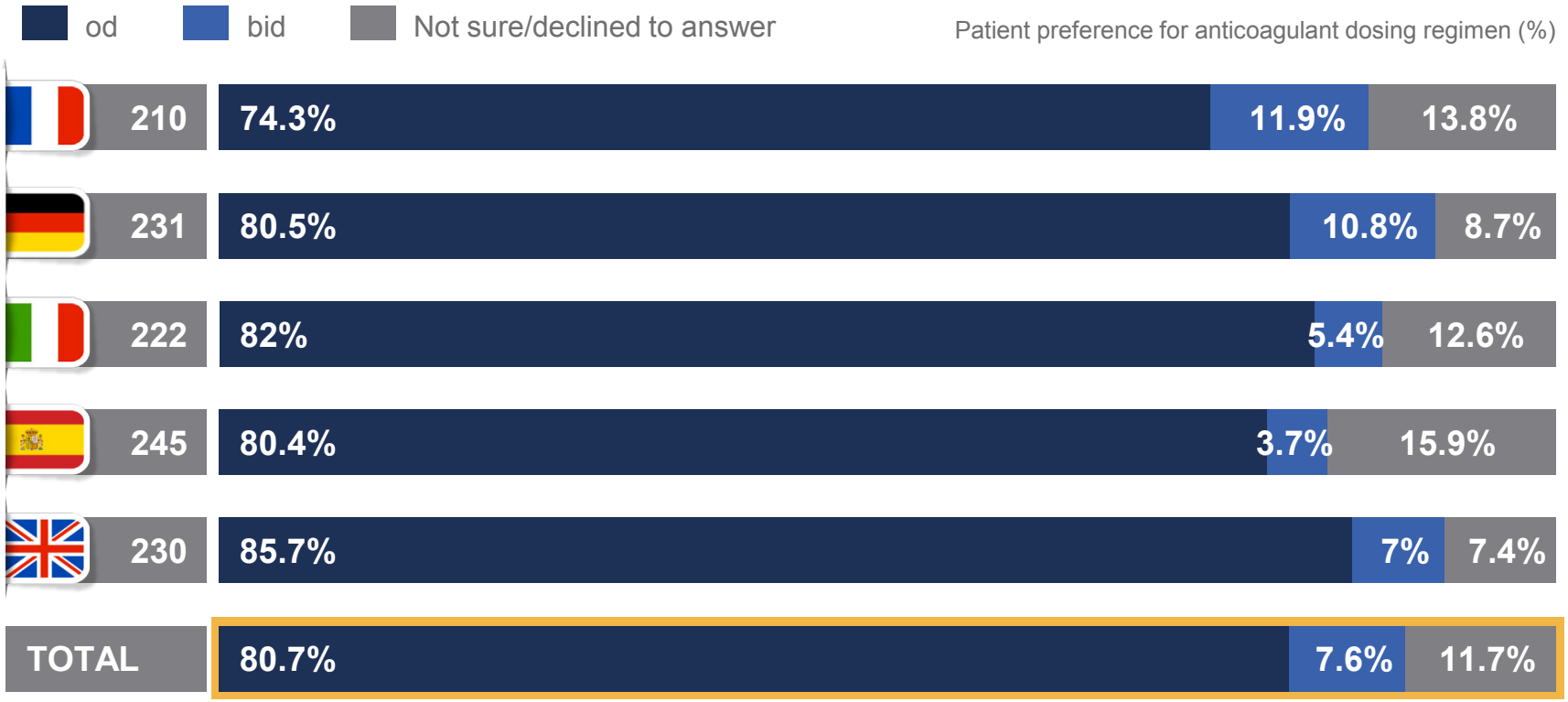
RE-LY[a] Dabigatran	ROCKET AF[b] Rivaroxaban	ARISTOTLE[c] Apixaban	ENGAGE-AF[d] Edoxaban
• None – US Regulators • CrCl 15-30 mL/min: 75 mg BID • Age > 80 years • CrCl 30-50 mL/min + P-gp inhibitor, dronedarone, or ketoconazole	• 20 → 15 mg OD for – Creatinine clearance < 30-49 mL/min	• 5 → 2.5 mg BID for ANY TWO of –Age ≥ 80 years –Body weight ≤ 60 kg –Serum creatinine ≥ 15 mg/dL • US Regulators – Strong dual inhibitors of CYP3A4 and P-gp	• 60 → 30 mg OD or 30 → 15 mg OD for – Creatinine clearance 30-50 mL/min – Body weight ≤ 60 kg – Use of quinidine, verapamil, or dronedarone

BID = twice daily; OD = once daily

a. Connoly SJ, et al. N Engl J Med 2009;361:1139; b. Patel MR, et al. N Engl J Med 2011;365:883;
c. Granger CB, et al. N Engl J Med 2011;365:981; d. Giuliano RP, et al. N Engl J Med 2013;369:2093

AF Patients Strongly Prefer Once-Daily Dosing for Anticoagulation

European survey: 1507 patients with AF

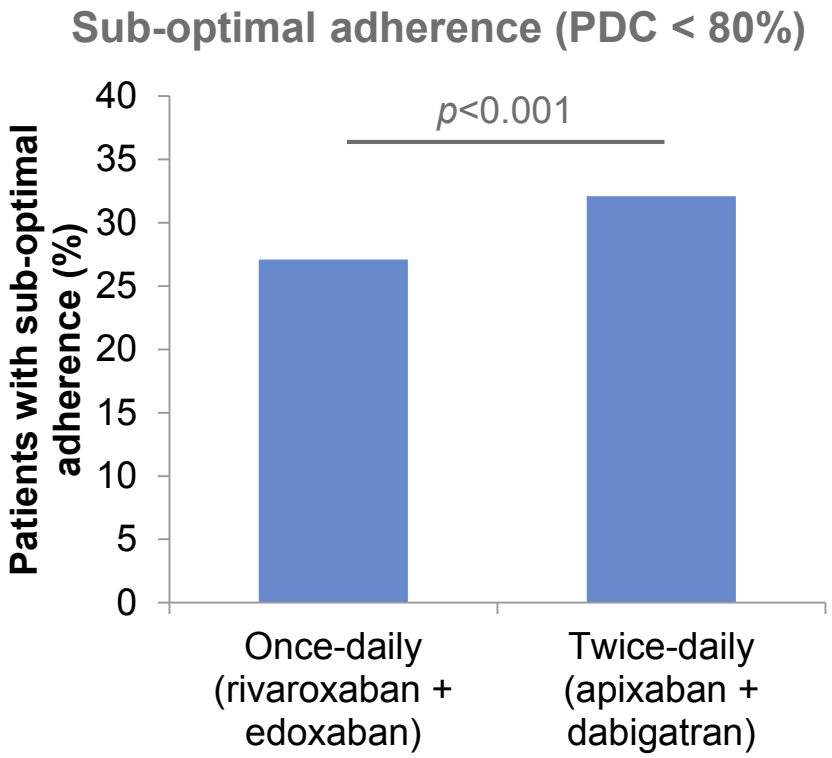


Overall, 81% preferred once-daily anticoagulation

Zamorano JL et al, presented at ESC 2012; Bakhai A et al, BMC Cardiovasc Disord 2013;13:108

Adherence on Once-Daily NOACs is Greater Than on Twice-Daily NOACs

- Retrospective database analysis: adherence and outcomes in matched patient cohorts on once-daily or twice-daily NOACs



Patients with sub-optimal adherence had **50% increase in risk of ischaemic stroke**, irrespective of dosing regimen (HR for OD: 1.47; HR for BID; 1.50)

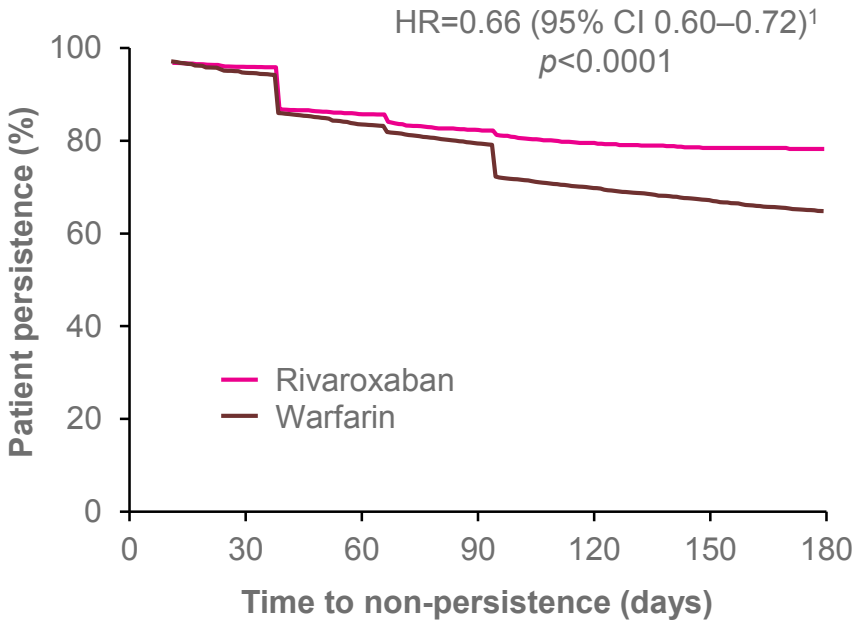
In sub-optimal adherers, no stroke advantage seen with BID regimen

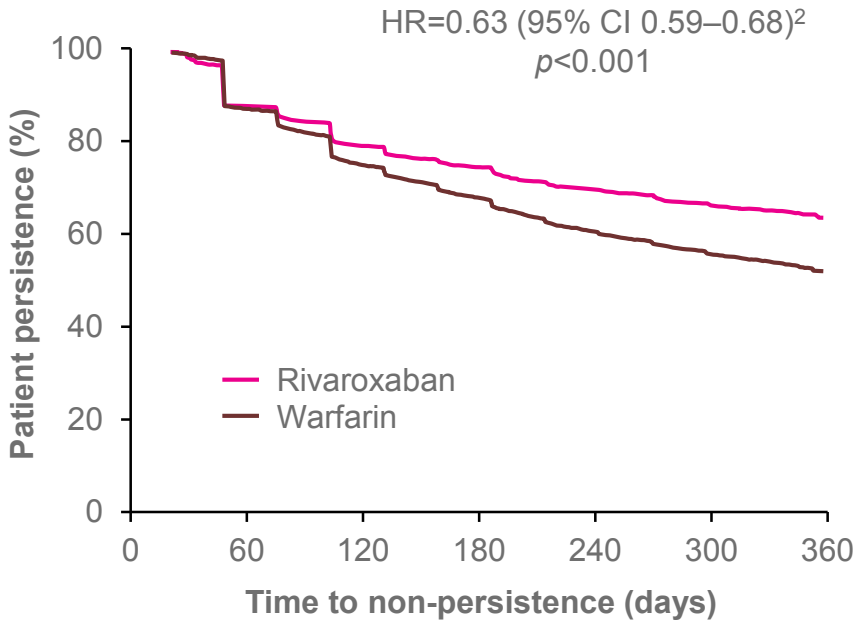
PDC: Proportion of days covered

Alberts MJ et al, Int J Cardiol 2016;215:11

Patients Stayed Longer on Rivaroxaban than on Warfarin in Real-World Studies

34–37% lower risk of non-persistence with rivaroxaban versus warfarin[1,2]





1. Laliberté F et al, Curr Med Res Opin 2014;30:1317;
2. Nelson WW et al, Curr Med Res Opin 2014;30:2461

Summary

- Efficacy - Effectiveness of rivaroxaban across RWE datasets was consistent with efficacy outcomes reported in ROCKET AF
- Safety - Rates of major bleeding in RWE datasets with rivaroxaban were lower than those reported for VKAs and consistent with findings from ROCKET AF
- Persistence - Rivaroxaban was associated with higher persistence rates in Real World compared to warfarin
- Dosing - Use of low-dose rivaroxaban in Real World is consistent with expectations from phase III