

Management of multimorbid patients with non-valvular atrial fibrillation

Cairo, February 27th, 2018

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Germany

Greetings from Munich



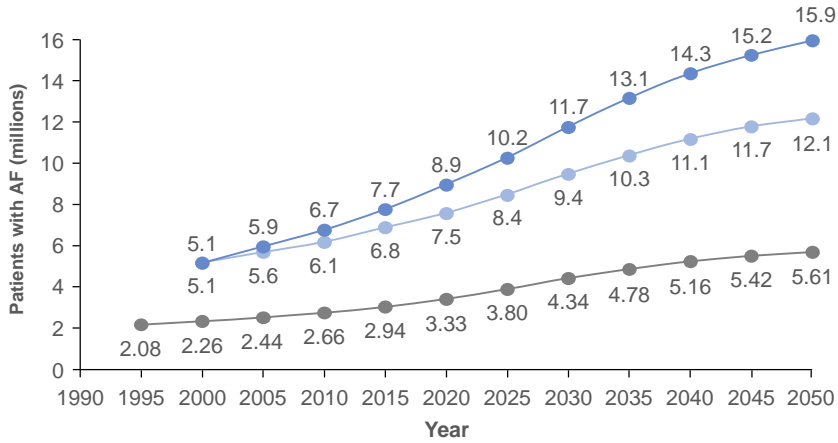
Disclosure

- ◆ Scientific Advisory Board member for Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Sanofi
- ◆ Received honoraria from Aspen, Bayer Healthcare, Bristol-Myers Squibb, Daiichi-Sankyo and Pfizer

Agenda

- ◆ Some thoughts about
 - Prevalence of AF
 - Burden of stroke in AF patients
 - Trial evidence of NOACs for stroke prevention
 - Real world evidence of NOACs in patients with AF
 - Challenge of NOACs in multimorbid patients

AF Is Common and Its Prevalence World-Wide is Anticipated to Increase

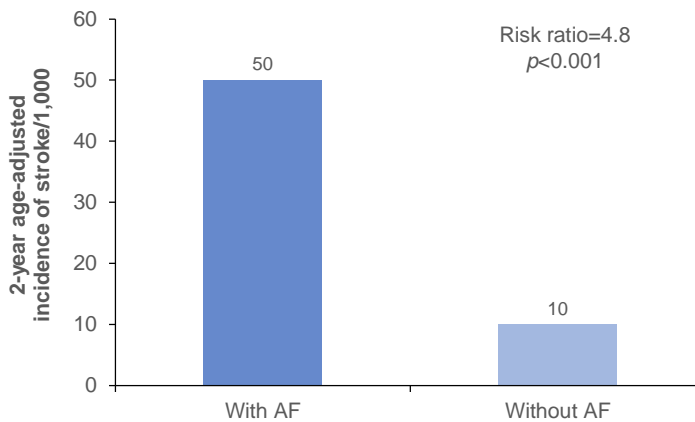


- Olmsted County data, 2006¹ (assuming a continued increase in AF incidence)
- Olmsted County data, 2006¹ (assuming no further increase in AF incidence)
- ATRIA study data, 2000²

1. Miyasaka Y et al. Circulation 2006;114(2):119-125; 2. Go AS et al. JAMA 2001;285(18):2370-2375

Patients With AF Have an Approximately Fivefold Increased Risk of Ischaemic Stroke

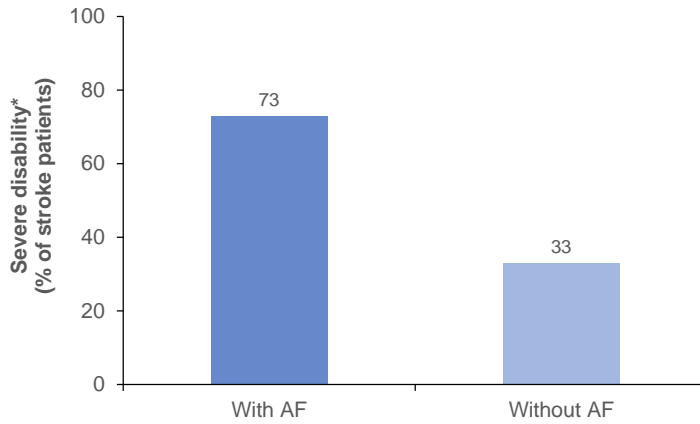
Framingham Heart Study (n=5,070)



Wolf PA et al. Stroke 1991;22(8):983-988

Stroke in Patients With AF Is More Severe Than in Those Without AF

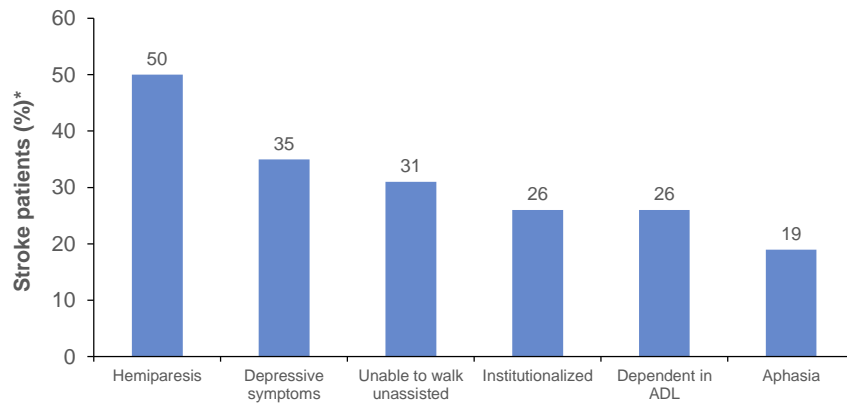
Framingham Heart Study (n=5,070)



*Severe disability was defined as a score of ≤ 40 in the modified BI of activities of daily living

Lin HJ et al. Stroke 1996;27(10):1760-1764

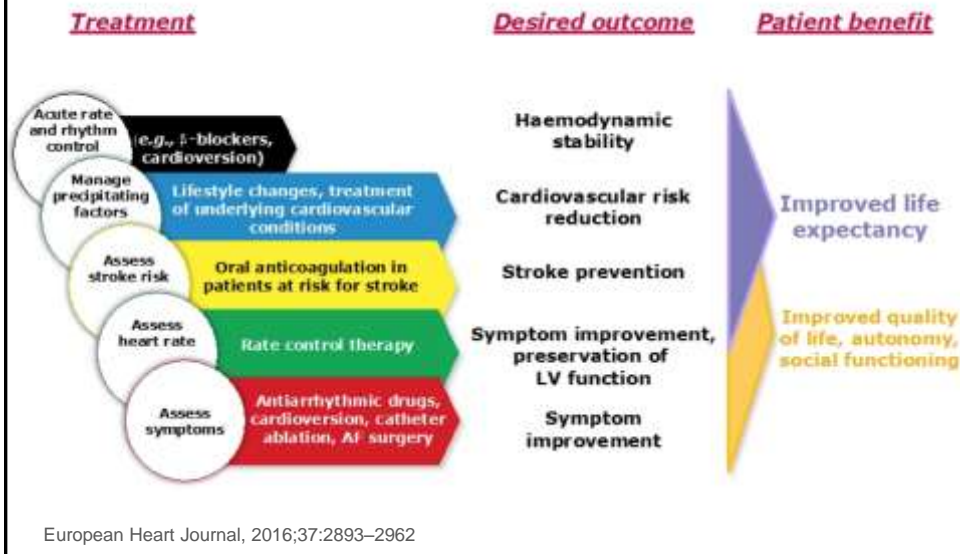
Ischaemic Stroke Survivors Experience Significant and Persistent Disability



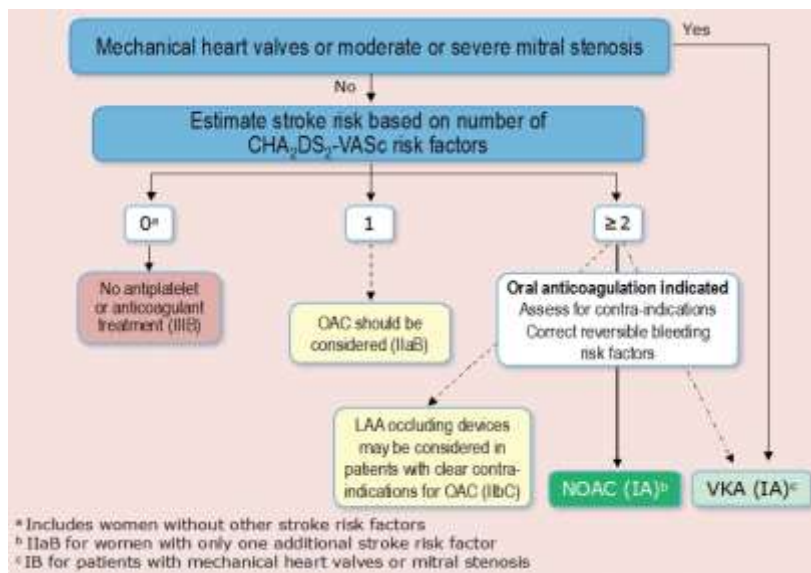
*6 months after stroke. Patients included in the study were n=108; ADL, activities of daily living

Kelly-Hayes M et al. J Stroke Cerebrovasc Dis. 2003;12(3):119-126

Five domains of integrated AF management

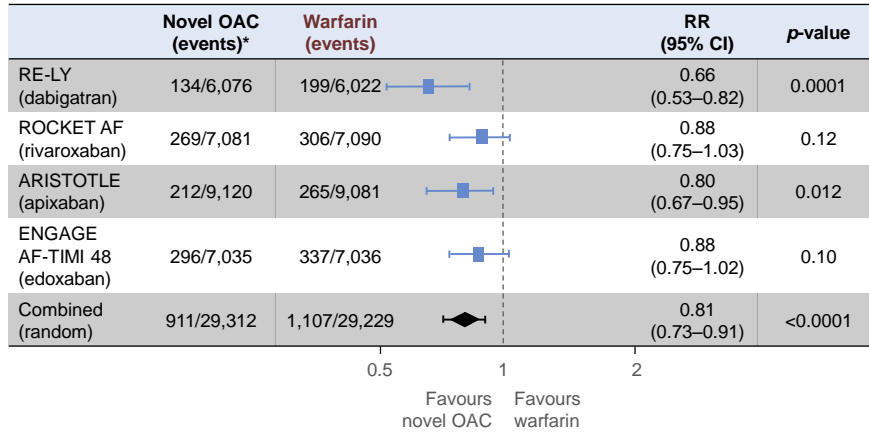


Stroke prevention in AF



Comparing Phase III Trials: Results are Consistent for Reduction in Stroke/SE

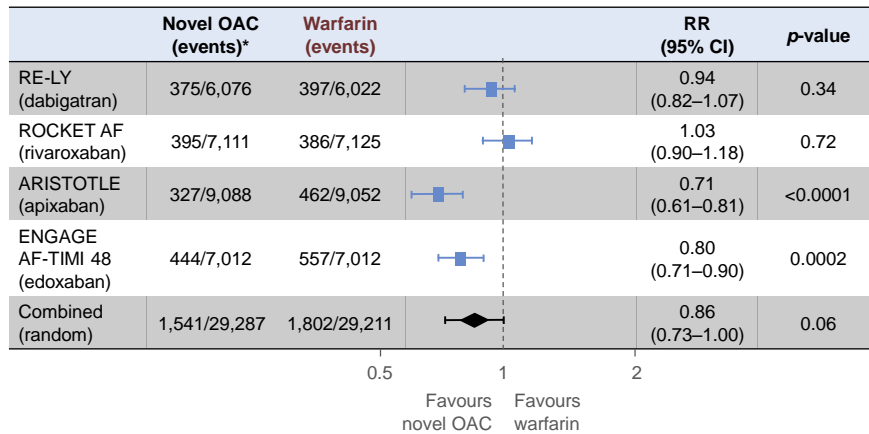
Meta-analysis of four phase III trials: Stroke/SE



Heterogeneity: I²=47%; p=0.13
 Different risk profiles
 *Novel OAC doses as follows: Dabigatran 150 mg BID, Rivaroxaban 20 mg OD, Apixaban 5 mg BID, Edoxaban 60 mg OD
 Ruff CT et al. Lancet. 2014;383(9921):955-962

Comparing Phase III Trials: Results are Consistent for Major Bleeding

Meta-analysis of four phase III trials: Major bleeding



Heterogeneity: I²=83%; p=0.001
 Different risk profiles
 *Novel OAC doses as follows: Dabigatran 150 mg BID, Rivaroxaban 20 mg OD, Apixaban 5 mg BID, Edoxaban 60 mg OD
 Ruff CT et al. Lancet. 2014;383(9921):955-962

Comparing Phase III Trials: There are Differences in Patient Characteristics....

	ROCKET AF ¹ (n=14,264)	ARISTOTLE ² (n=18,201)	ENGAGE AF ³ (n=21,105)	RE-LY ^{4,5} (n=18,113)
Mean CHADS₂-Score	3.5	2.1	2.8	2.1
C CHF	62%	35%	57%	32%
H Hypertension	91%	87%	94%	79%
A Age ≥75 years	43%	31%	40%	40%
D Diabetes mellitus	40%	25%	36%	23%
S ₂ Prior stroke or TIA	55%	19%	28%	20%
Moderate renal impairment	21%	15%	19%	19%
Specific dose studied prospectively	✓	✗	✗	✗

AF Patients studied in ROCKET AF had higher risk of stroke than patients in other phase III trials with novel OACs.

1. Patel MR et al. N Engl J Med. 2011;365(10):883-891; 2. Granger CB et al. N Engl J Med. 2011;365(11):981-992; 3. Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104; 4. Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151; 5. Eikelboom JW et al. Circulation 2011;123(21):2363-2372

Summary: Meta-Analyses of Novel OAC Trials vs. Warfarin

- ◆ In meta-analyses of all four novel OACs studied in phase III trials for stroke/SE prevention in patients with AF vs. warfarin, novel OACs had a favorable risk-benefit profile¹
- ◆ Novel OACs reduced stroke vs. warfarin^{1,2}
 - 51% reduction in haemorrhagic stroke¹
- ◆ There were substantial reductions in ICH (-52%) but increased GI bleeding (+25%) vs. warfarin¹
- ◆ The relative efficacy and safety of novel OACs was consistent across a wide spectrum of AF patients¹
- ◆ Due to differences in study design, patient populations, endpoint definitions direct comparisons between different phase III trials cannot be made

1. Ruff CT et al. Lancet. 2014;383(9921):955-962; 2. Hankey G. Lancet Neurol. 2014;13(2):178-194

Real-world Evidence on Stroke prevention In patients with aTtrial Fibrillation in the United States

Craig I. Coleman, Matthias Antz, Edgar Simard, Thomas Evers, Kevin Bowrin, Hendrik Bonnemeier, Riccardo Cappato

Coleman CI et al. Real-world Evidence on Stroke prevention In patients with aTtrial Fibrillation in the United States (REVISIT-US) [Presentation at ECAS 2016] Available at: http://clinicaltrialsresults.org/Slides/REVISIT_US_Slides.pptx

reVISIT-US

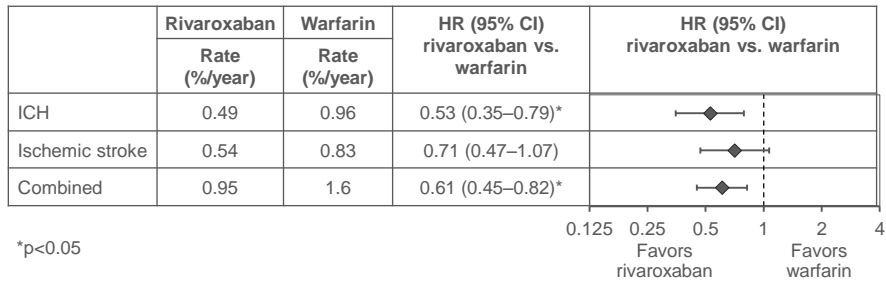
Objective

- ◆ To assess the real-world effectiveness and safety of newly-initiated rivaroxaban or apixaban compared to warfarin in NVAf patients

reVISIT-US

REVISIT US - Significant Reduction in the Combined Endpoint for Rivaroxaban vs warfarin

- ◆ Rivaroxaban was associated vs warfarin with a
 - Significant 47% reduction in ICH
 - Non-significant 29% decrease in ischemic stroke
 - Significant 39% reduction in the combined endpoint of ICH and ischemic stroke

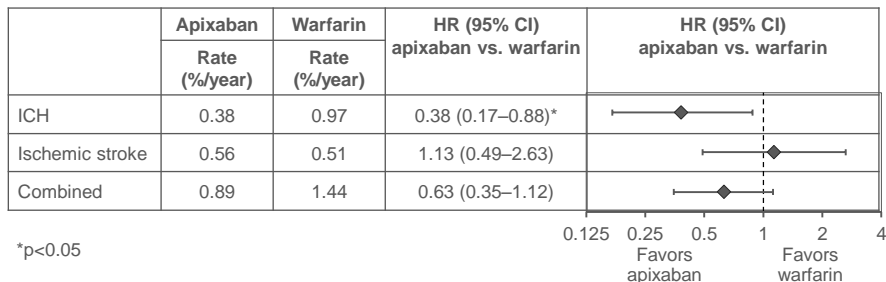


Coleman CI et al. Real-world Evidence on Stroke prevention In patients with aTrial Fibrillation in the United States (REVISIT-US) [Presentation at ECAS 2016] Available at: http://clinicaltrialsresults.org/Slides/REVISIT_US_Slides.pptx



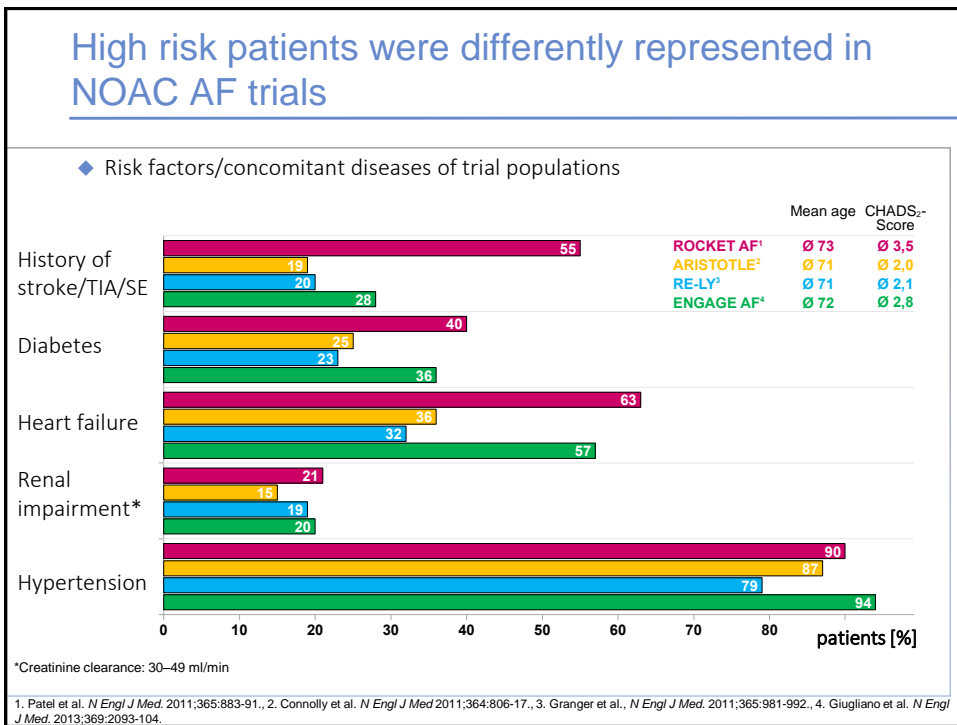
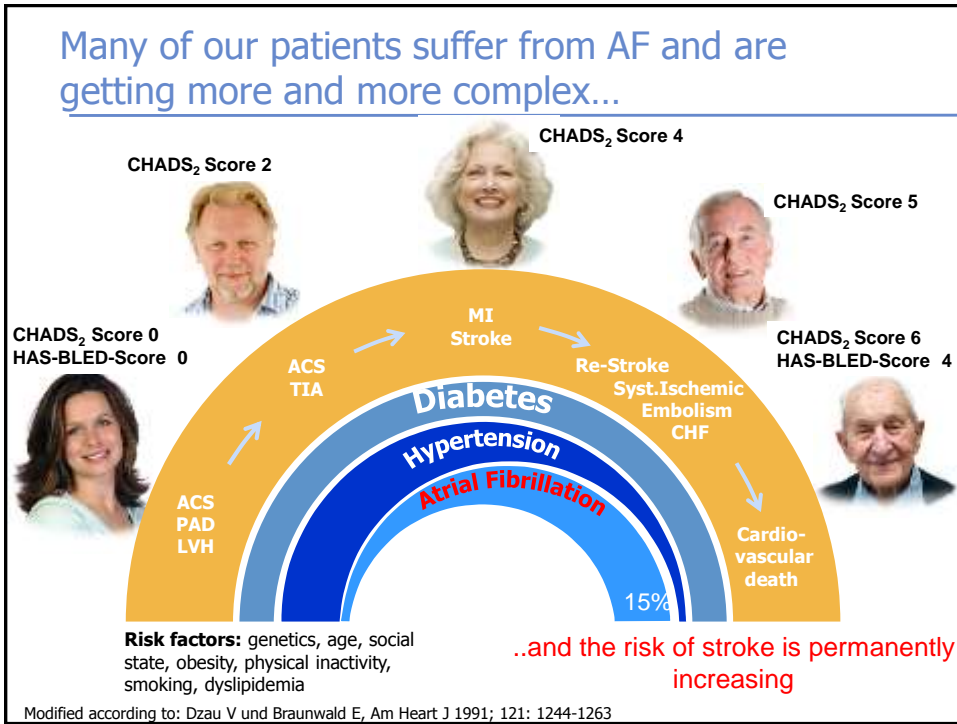
REVISIT US – No Significant Reduction in the Combined Endpoint for Apixaban vs warfarin

- ◆ Apixaban was associated vs warfarin with a
 - Significant 62% reduction in ICH vs. warfarin
 - Non-significant 13% increase in ischemic stroke vs. warfarin
 - Non-significant 37% reduction in the combined endpoint of ICH and ischemic stroke vs. warfarin

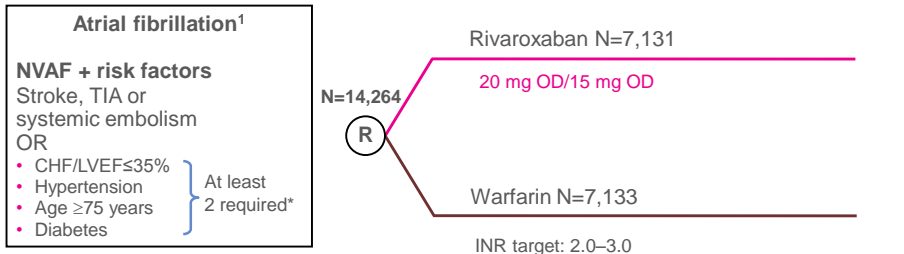


Coleman CI et al. Real-world Evidence on Stroke prevention In patients with aTrial Fibrillation in the United States (REVISIT-US) [Presentation at ECAS 2016] Available at: http://clinicaltrialsresults.org/Slides/REVISIT_US_Slides.pptx





ROCKET AF Prospectively Tested a Reduced Dose in AF Patients With Renal Impairment

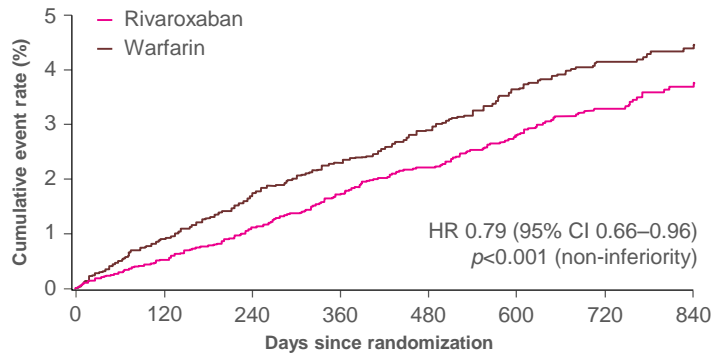


- ◆ AF patients with moderate renal impairment (CrCl 30-49 ml/min) received a reduced dose of rivaroxaban 15 mg OD (21%)^{1,2}
- ◆ Primary efficacy endpoint: stroke or non-CNS systemic embolism
- ◆ Primary safety endpoint: major or NMCR bleeding

*Enrolment of patients without prior stroke, TIA or systemic embolism and only two factors capped at 10%. LVEF, left ventricular ejection fraction; NVAF, non-valvular atrial fibrillation
 1. Patel MR et al. N Engl J Med. 2011;365(10):883-891; 2. Fox KA et al. Eur Heart J. 2011;32(19):2387-2394

ROCKET AF: Effective Stroke Prevention in Patients With Non-Valvular AF vs. Warfarin (PPP)

Primary efficacy endpoint: Stroke/SE

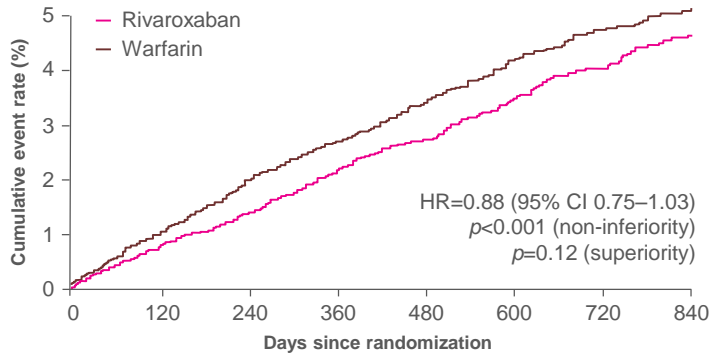


Number of subjects at risk								
Rivaroxaban	6,958	6,211	5,786	5,468	4,406	3,407	2,472	1,496
Warfarin	7,004	6,327	5,911	5,542	4,461	3,478	2,539	1,538

PPP=Per-protocol population on-treatment=all ITT patients without major predefined protocol violations.
 Patel MR et al. N Engl J Med. 2011;365(10):883891

ROCKET AF: Effective Stroke Prevention in Patients With Non-Valvular AF vs. Warfarin (ITT)

Primary efficacy endpoint: Stroke/SE



Number of subjects at risk

Rivaroxaban	7,081	6,879	6,683	6,470	5,264	4,105	2,951	1,785
Warfarin	7,090	6,871	6,656	6,440	5,225	4,087	2,944	1,783

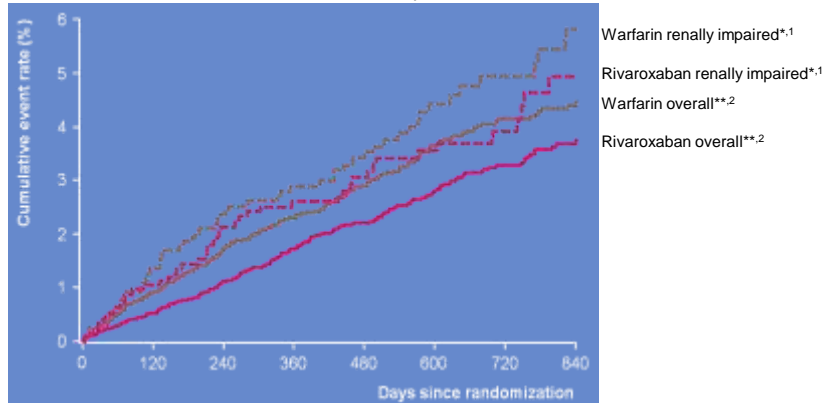
ITT population = intention-to-treat population = all patients randomized

Patel MR et al. N Engl J Med. 2011;365(10):883-891

Some learnings from subgroup analyses of ROCKET-AF for “real life”

ROCKET AF Subanalysis moderate renal impairment

Primary endpoint: Stroke or SE in patients with CrCl 30–49 mL/min vs. all ROCKET AF patients



Per-protocol on-treatment population

* among patients with CrCl 30–49 mL/min; HR 0.84 (95% CI: 0.57–1.23)
 ** HR 0.79 (95% CI: 0.66–0.96), p<0.001 (non-inferiority)

¹ Fox KA et al. Eur Heart J 2011;32(19): 2387–2394; ² Patel MR et al. N Engl J Med 2011; 365 (10): 883–891

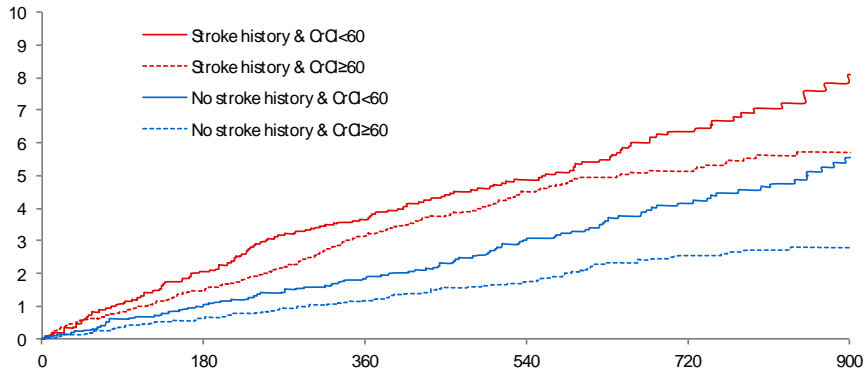


Predictors of Stroke or Systemic Embolism in ROCKET AF

	LR Chi-Square	HR	95% CI	P-value
Prior stroke or TIA	40.77	1.83	1.51–2.20	<0.0001
CrCl (per 10 mL/min decrease)	26.38	1.12	1.07–1.16	<0.0001
Diastolic BP (per 10 mm Hg increase)	6.56	1.12	1.03–1.22	0.0104
Paroxysmal AF	5.00	0.77	0.61–0.98	0.0254
Vascular disease	4.74	1.24	1.03–1.51	0.0296
Heart rate (per 10 bpm increase)	4.05	1.06	1.00–1.12	0.0441
Female sex	3.42	1.18	0.99–1.40	0.0644
Diabetes	1.83	1.13	0.946–1.357	0.1756
Hypertension	1.43	1.20	0.884–1.629	0.2317
Age (per 10 year increase)	0.84	1.06	0.939–1.188	0.3603
Heart failure	0.59	0.93	0.785–1.111	0.4424

Piccini JP. Circulation. 2013; 127: 224–232

CKD & Incident Stroke in ROCKET AF



Piccini JP. *Circulation*. 2013; 127: 224-232

Circulation. 2016;134:37-47. DOI: 10.1161/CIRCULATIONAHA.116.021890

ORIGINAL RESEARCH ARTICLE

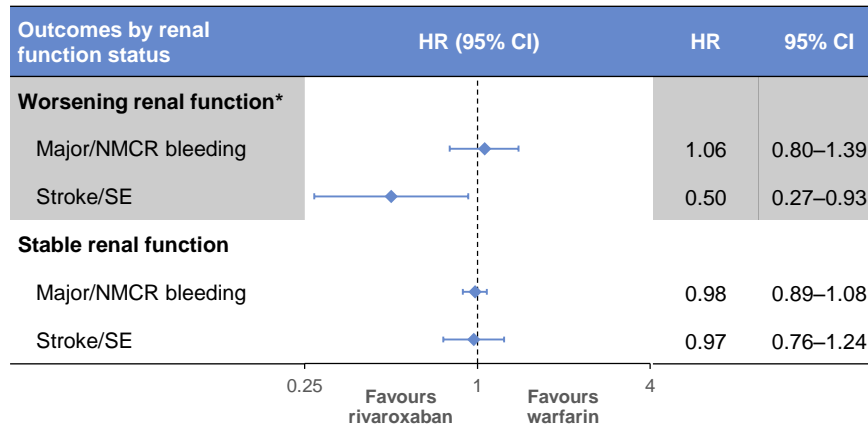
On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin

Insights From ROCKET AF

Christopher B. Fordyce, MD, MHS, MSc, Anne S. Hellkamp, MD, Yehya Lakkajyana, PhD, Samuel M. Lindsley, MD, Jonathan P. Piccini, MD, MHS, Richard C. Becker, MD, Scott D. Berkowitz, MD, Graeter Boothard, MD, Keith A. Fox, MD, Kenneth W. Mahaffey, MD, Christopher C. Nessel, MD, Daniel E. Singer, MD, Manish R. Patel, MD; on behalf of the comité directivo y los investigadores del estudio ROCKET AF

ROCKET AF: Significantly lower rates of stroke/SE for rivaroxaban versus warfarin in patients with worsening renal function

Patients with >20% decrease in creatinine clearance during study (worsening renal function) and those without (stable renal function)



*Worsening renal function = a decrease of >20% from screening CrCl measurement at any time point during the study
 Fordyce C et al. *Circulation* 2016;134:37-47

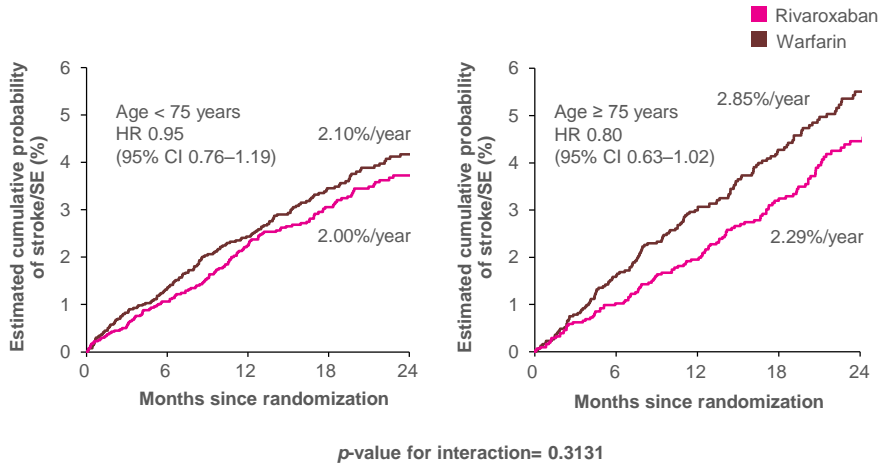
ROCKET AF in worsening renal function patients conclusions:

- ◆ Among patients with on-treatment WRF, rivaroxaban was associated with lower rates of the primary end point of stroke and systemic embolism compared with warfarin without an increase in the composite bleeding endpoint.¹
- ◆ Patients treated with rivaroxaban also presented less decline in renal impairment than warfarin.¹
- ◆ These data suggest that rivaroxaban may be a better choice of anticoagulant for patients with AF who experience on-treatment worsening renal function¹.

1. Fordyce CB et al. *Circulation*, 2016; 134: 37-47

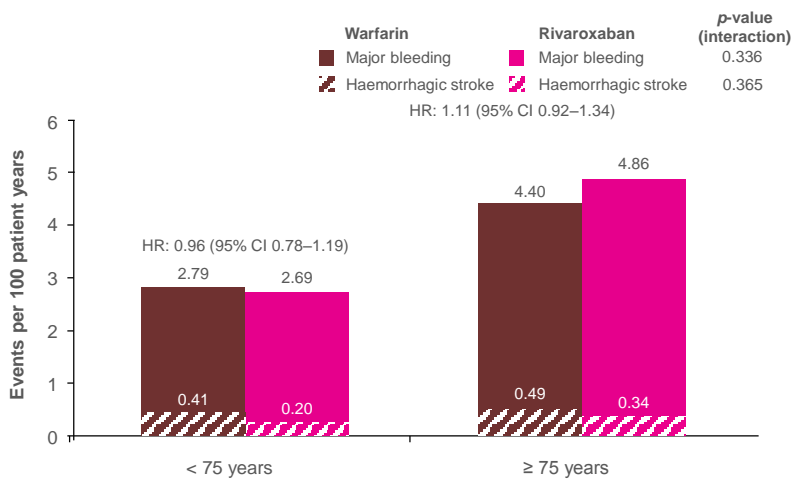
ROCKET AF Subanalysis elderly patients – Results

Primary efficacy endpoint: Stroke and SE



ITT population
Halperin JL *et al. Circulation.* 2014;130:138-146

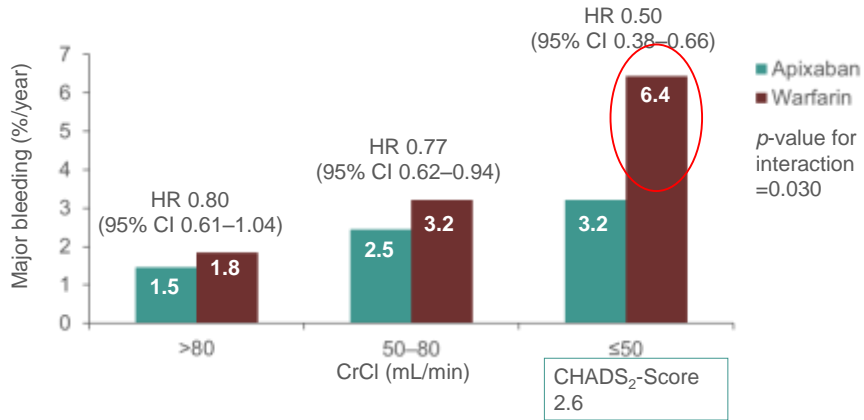
ROCKET AF Subanalysis elderly patients – Results



The overall relative effects of rivaroxaban vs. warfarin were consistent among elderly and younger patients for both efficacy and safety

Halperin JL *et al. Circulation.* 2014;130:138-146

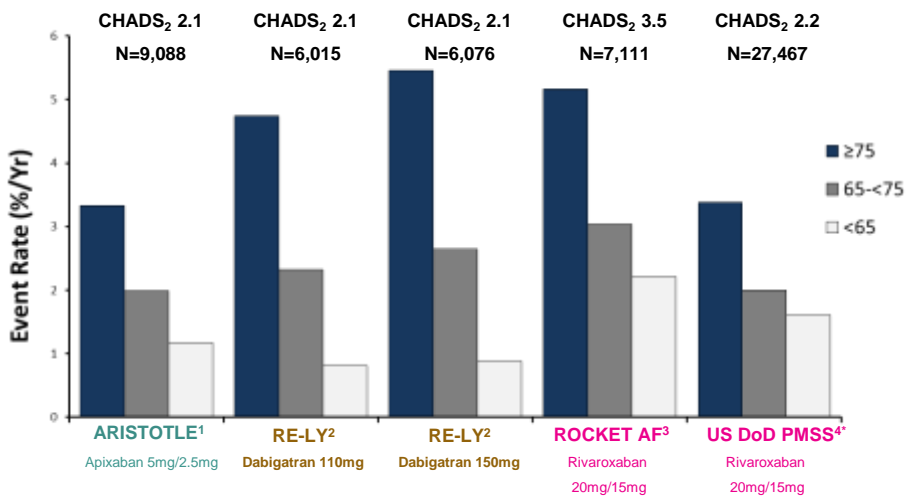
ARISTOTLE: Major Bleeding According to Renal Function



Differences in major bleeding are driven by increased bleeding in warfarin patients with CrCl ≤50 mL/min

Hohnloser SH et al. *Eur Heart J.* 2012;33(22):2821-2830.

Major Bleeding Rates by Age, in NOAC Arms of Phase III Trials and Real World Studies



* ≥75 and <65 age categories represent 75-84 and 55-64 in Rivaroxaban Real World Data; In RE-LY and ROCKET AF, the age categories are <65, 65-75, and >75.
 1. Eliquis © PM, 2014; 2. Pradaxa PM, 2014; 3. Xarelto © PM 2014; 4. Tamayo S et al. *Clin Cardiol.* 2015; 38(2):63-68

Conclusions

- ◆ High Risk for stroke also high risk for bleeding (CHA₂DS₂-VASc – HAS-BLED)
- ◆ Age and renal function are particular risk drivers
- ◆ Patients at highest risk have most to gain from a NOAC
- ◆ Pay attention to dosing and evidence of effect for a dose
- ◆ Multimorbid and renally impaired AF patients –
 - **Not a challenge, but a chance for NOACs!**