BAYER

Real World Evidence

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Why should we care about any real world data versus clinical trial?

Effectiveness (Real-world data)

- Does it work under usual circumstances?
- Real world clinical practice
- Drug performance in the real world
- Flexible regimen with regular day to day clinic patient
- Low to high compliance
- External validity - medium to high

Efficacy (Clinical trial data)

- Does it work under ideal circumstances?
- Controlled clinical trial environment
- Geared to get FDA approval
- Fixed regimen with highly motivated patients
- Compliance usually high
- External validity - low to medium

Story Flow

Real World Evidence with Rivaroxaban

Dimensions of Real World Evidence Data for NOACs

Safety

- **Prospective study XANTUS** provides unique RWE in SPAF
  - Versus ROCKET AF: Complimentary in Baseline Characteristics and consistent in outcomes
  - Versus ARISTOTLE / RE-LY: Similar patient populations might lead to similar efficacy and safety outcomes

Efficacy

- **Retrospective Database Analysis REVISIT US** further confirms favorable efficacy and safety profile of Rivaroxaban vs Warfarin
- Rivaroxaban significantly reduced the combined endpoint of ischemic stroke and ICH vs warfarin

Adherence Persistence

- Rivaroxaban was associated with high persistence rates in Real World (exceeding warfarin or dabigatran)
- Patients treated with OD rivaroxaban demonstrated better adherence than those treated with BID regimens

Dosing

- Use of low-dose rivaroxaban in Real World is consistent with expectations from phase III - unlike Apixaban

You need to put all four Dimensions into Perspective to Judge on Real World Evidence Data

Effectiveness and Safety

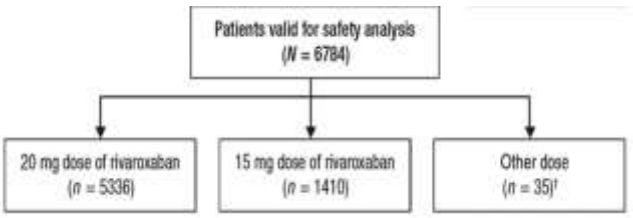
Real-world evidence data

European Heart Journal (2016) 37, 1145–1153
doi:10.1093/eurheartj/ehv466

FASTTRACK
ESC Clinical Registry

Atrial fibrillation

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation



Conclusion

XANTUS is the first large, international, prospective study describing the use of rivaroxaban for stroke prevention in a broad NVAF patient population. The rates of major bleeding and stroke with rivaroxaban were found to be low in routine clinical practice.

blood®
2014 124: 955-962
doi:10.1182/blood-2014-03-563577 originally published online May 23, 2014

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

n=1200

Key Points

- In a real-world setting, annualized bleeding rates of major rivaroxaban bleeding are lower than those reported for vitamin K antagonists.
- Treatment of major rivaroxaban bleeding is simple and rarely requires pro-coagulants; outcome at 90 days is better than that reported for vitamin K antagonists.

Quality and Outcomes

US Dod PMSS

Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27 467 Patients Taking Rivaroxaban

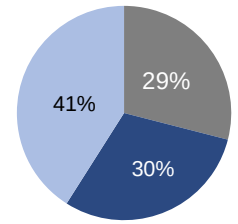
Conclusions: In this large observational study, the MB rate was generally consistent with the registration trial results, and fatal bleeds were rare.

U.S. Department of Defense (DoD)
PMSS (Post-Marketing Safety Surveillance)

Clin. Cardiol. 38, 2, 63–68 (2015)

Rivaroxaban tested in different populations in Randomized Clinical Trial and the Real World

XANTUS
Rivaroxaban[1]



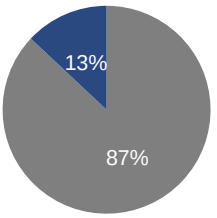
$CHADS_2$ score

≤1 2 3–6

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

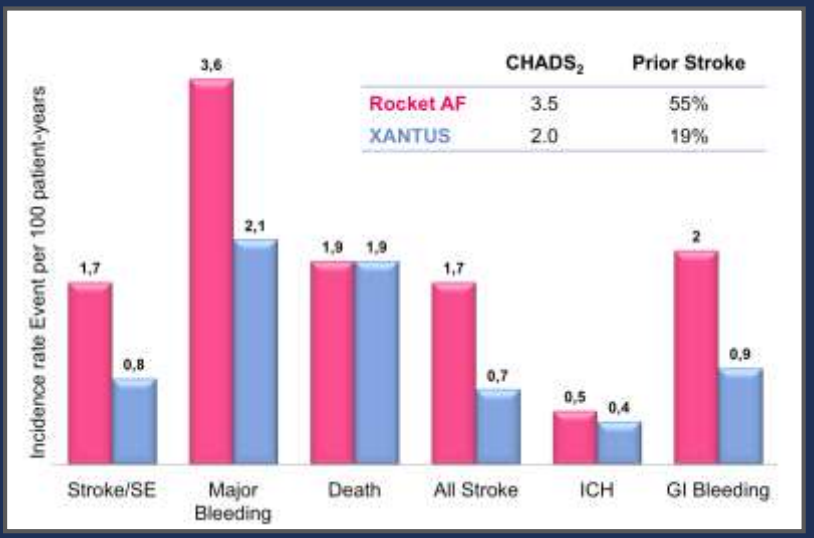
ROCKET AF
Rivaroxaban[2]



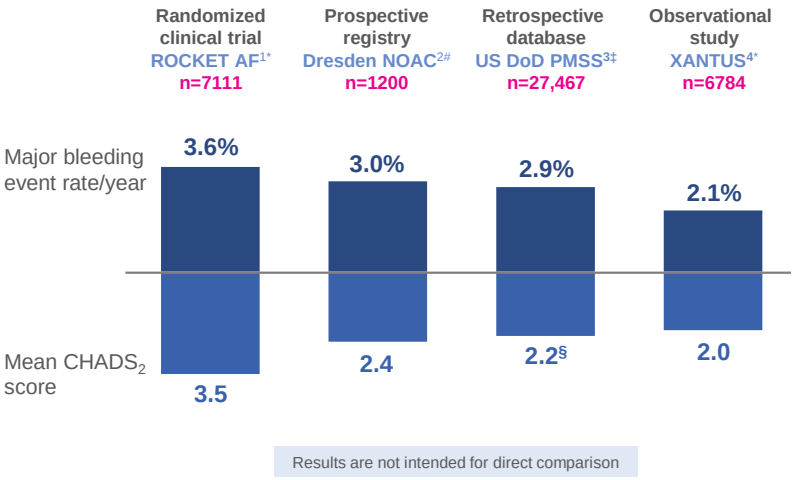
*Events per 100 patient-years; #includes prior stroke, SE or TIA

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

XANTUS vs ROCKET-AF



Safety Profile of Rivaroxaban Confirmed Through Real-World Evidence Regardless of Data Source

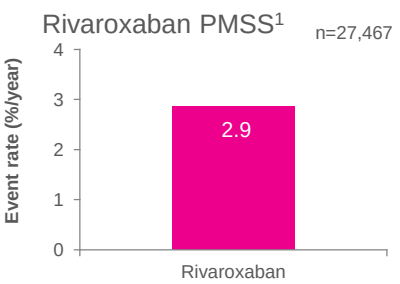


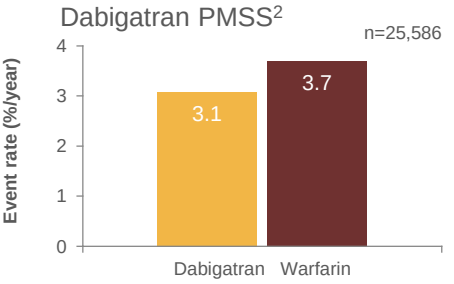
Results are not intended for direct comparison

*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;115(5):939-49;
3. Tamayo S *et al*, *Clin Cardiol* 2015;38:63–68; 4 Camm AJ *et al*, *Eur Heart J* 2016;37(4):1145-53;
5. Cunningham A *et al*, *Pharmacoepidemiol Drug Saf* 2011;20:560–566

Rivaroxaban, Dabigatran and Warfarin: Findings on Risk of Major Bleeding in Real World

Two retrospective analyses of U.S. Dod PMSS records[1,2]





	Rivaroxaban (%)
ICH	0.1
Fatal bleeding	<0.1
Major GI bleeding	1.5

	Dabigatran (%/year)	Warfarin (%/year)
ICH	0.27	0.56
Fatal bleeding	Not reported	Not reported
Major GI bleeding	2.54	2.37

Major bleeding was defined by the Cunningham algorithm in both studies[3]
1. Tamayo S et al. Clin Cardiol. 2015;38(2):63-68;
2. http://us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2014/11-17-14-us-department-defense-study-supports-favorable-benefit-risk-profile-pradaxa-dabigatran-etexilate-mesylate-reducing-stroke-risk-non-valvular-atrial-fibrillation.html;
3. Cunningham A et al. Pharmacoepidemiol Drug Saf. 2011;20(6):560-566.

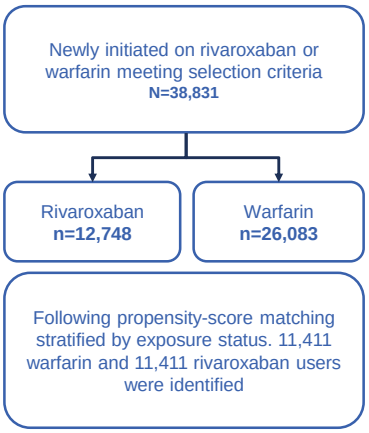
Background: Little data exists regarding the effectiveness and safety of rivaroxaban or apixaban versus warfarin in nonvalvular atrial fibrillation (NVAF) patients treated outside of clinical trials.

A retrospective study included adults, newly initiated on rivaroxaban, apixaban or warfarin for NVAF, with a baseline CHA_2DS_2-VASc score ≥2, and ≥180 days of continuous medical and prescription benefits.
Using Market Scan from January 2012 to October 2014.

Current Medical Research and Opinion
Volume 32, 2016 - Issue 12

REVISIT-US

REVISIT-US Baseline Characteristics Rivaroxaban vs Warfarin

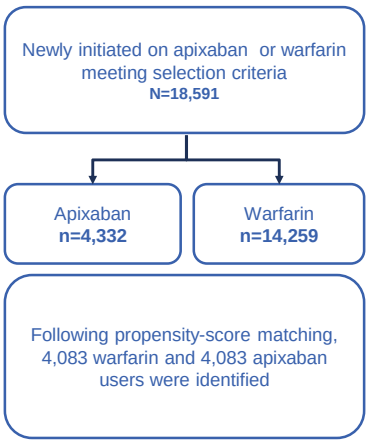


Characteristics of included patients (matched cohorts)		
Parameter	**Rivaroxaban (n=11,411) 7,715 PYs**	**Warfarin (n=11,411) 6,271 PYs**
Age in years, mean (SD)	70.70 (10.99)	70.72 (11.35)
Male, %	53.6	53.9
$CHADS_2$ Score, 180 day; mean (SD)	1.92 (1.08)	1.94 (1.08)
CHA_2DS_2-VASc Score, 180 day; mean (SD)	3.46 (1.37)	3.48 (1.35)
HASBLED Score, 180 day; mean (SD)	1.62 (0.69)	1.62 (0.71)
Reduced dose, %	17.3	NA

Coleman CI *et al, Curr Med Res Opin* 2016 Sep 15 [Epub ahead of print]; DOI:10.1080/03007995.2016.1237937

REVISIT-US

REVISIT-US Baseline Characteristics Apixaban vs Warfarin



Characteristics of included patients (matched cohorts)		
Parameter	**Apixaban (n=4,083) 2,125 PYs**	**Warfarin (n=4,083) 1,951 PYs**
Age in years, mean (SD)	71.15 (11.32)	71.00 (11.25)
Male, %	53.2	53.6
$CHADS_2$ Score, 180 day; mean (SD)	1.93 (1.07)	1.92 (1.07)
CHA_2DS_2-VASc Score, 180 day; mean (SD)	3.47 (1.38)	3.47 (1.35)
HASBLED Score, 180 day; mean (SD)	1.65 (0.69)	1.66 (0.72)
Reduced dose, %	15.5	NA

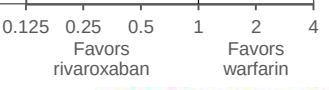
Coleman CI *et al, Curr Med Res Opin* 2016 Sep 15 [Epub ahead of print]; DOI:10.1080/03007995.2016.1237937

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

	Rivaroxaban Rate (%/year)	Warfarin Rate (%/year)	HR (95% CI) rivaroxaban vs. warfarin	HR (95% CI) rivaroxaban vs. warfarin
ICH	0.49	0.96	0.53 (0.35–0.79)*	
Ischemic stroke	0.54	0.83	0.71 (0.47–1.07)	
Combined	0.95	1.6	0.61 (0.45–0.82)*	



*p<0.05

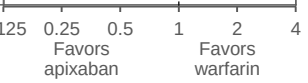
Coleman CI *et al, Curr Med Res Opin* 2016 Sep 15 [Epub ahead of print]; DOI:10.1080/03007995.2016.1237937

REVISIT-US

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

	Apixaban Rate (%/year)	Warfarin Rate (%/year)	HR (95% CI) apixaban vs. warfarin
ICH	0.38	0.97	0.38 (0.17–0.88)*
Ischemic stroke	0.56	0.51	1.13 (0.49–2.63)
Combined	0.89	1.44	0.63 (0.35–1.12)



*p<0.05

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://clinicaltrialresults.org/Slides/REVISIT_US_Slides.pptx

REVISIT-US

REVISIT-US Conclusion

Conclusions:

Rivaroxaban and apixaban were associated with less ICH than warfarin and both are likely associated with reductions in the combined endpoint.

Further investigation to validate the numerically higher rate of ischemic stroke with apixaban versus warfarin is required.

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Volume 32, 2016 - Issue 12

REVISIT-US

Summary: Effectiveness and Safety
Different Data Sources for RWE Data on NOACs

Prospective

XANTUS provides unique prospective RWE on Xarelto® in SPAF

XANTUS vs ROCKET AF

Major bleeding rate seem to depend on patient population ($CHADS_2$-Score)

XANTUS vs ARISTOTLE

Similar patient populations ($CHADS_2$-Score) have similar safety and efficacy outcomes

Conclusion: It is the rather the patient population that determines the outcome than the NOAC used

Retrospective

REVISIT US study also confirms the Rivaroxban results

Rivaroxaban was associated with less ICH than warfarin

Less ischemic strokes unlike Apixaban

Conclusion: Consistent results for rivaroxaban across different data sources

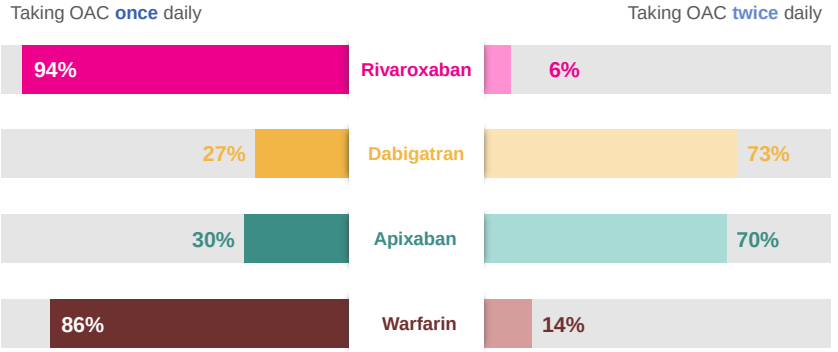
Adherence and Persistence

Real-world evidence data

One-Third of Twice-Daily Prescribed Medications Were Being Taken Once Daily

Therapy adherence

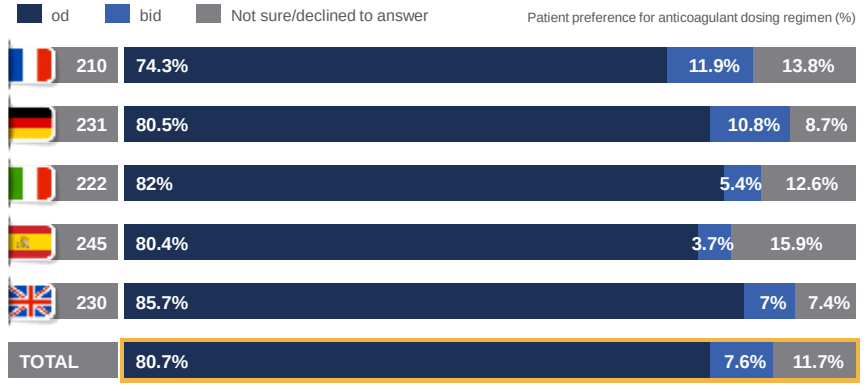
Self-reported patient survey (N=266)



Andrade JG *et al*, *Can J Cardiol* 2015;doi:0.1016/j.cjca.2015.09.023

AF Patients Strongly Prefer Once-Daily Dosing for Anticoagulation

European survey: 1507 patients with AF

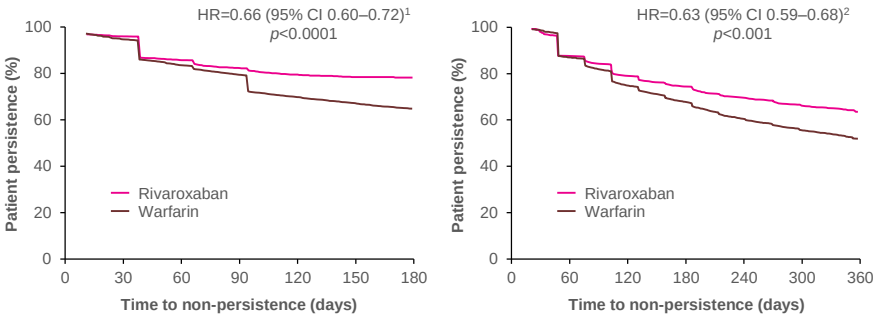


Overall, 81% preferred once-daily anticoagulation

Zamorano JL *et al*, presented at ESC 2012; Bakhai A *et al*, *BMC Cardiovasc Disord* 2013;13:108–117

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

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

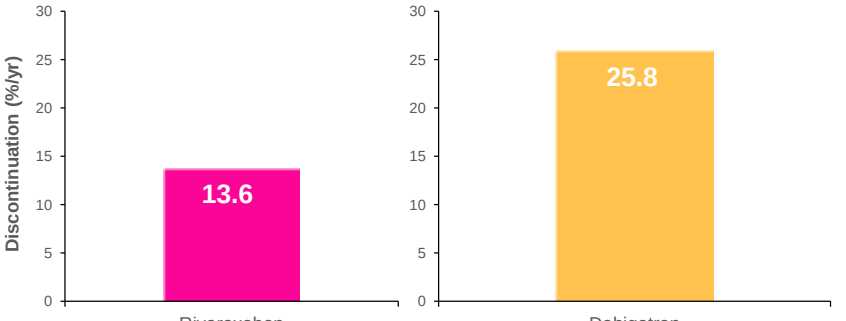


1. Laliberté F *et al*, *Curr Med Res Opin* 2014;30:1317–1325;
2. Nelson WW *et al*, *Curr Med Res Opin* 2014;30:2461–2469

Dresden NOAC Registry: In Real World AF Patients Stayed Longer on Rivaroxaban than on Dabigatran

Two analyses of the prospective Dresden NOAC registry

Treatment Discontinuation with Rivaroxaban and Dabigatran



Median follow-up: 544 days
1204 AF patients treated with rivaroxaban[1]

Not Intended for Direct Comparison

Median follow-up: 671 days
341 AF patients treated with dabigatran[2]

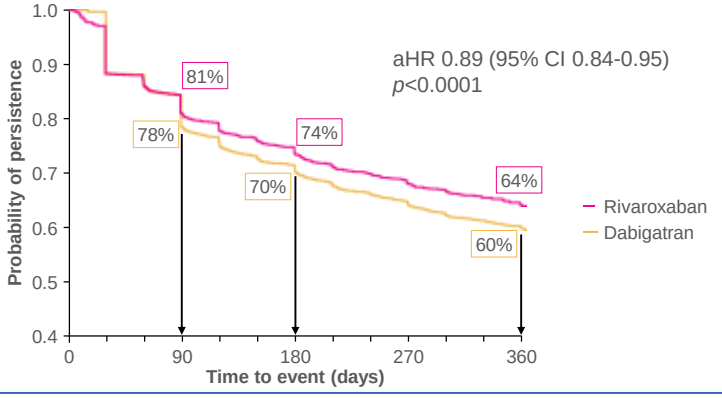
Treatment discontinuation with Rivaroxaban was lower than discontinuation with Dabigatran (two different analyses from the same registry)

1. Beyer-Westendorf J et al. Europace 2015;17(4):530-538; 2. Beyer-Westendorf J et al. Thromb Haemost. 2015;113(6):1247-1257

Higher Persistence with Rivaroxaban vs. Dabigatranin Patients with NVAF

Retrospective U.S. database analysis

- 7,259 Rivaroxaban patients were matched 1:1 with Dabigatran patients



Use of Rivaroxaban led to higher rates of persistence compared to Dabigatran among patients with AF

Nelson WW *et al. Curr Med Res Opin* 2015;doi: 10.1185/03007995.2015.1074064

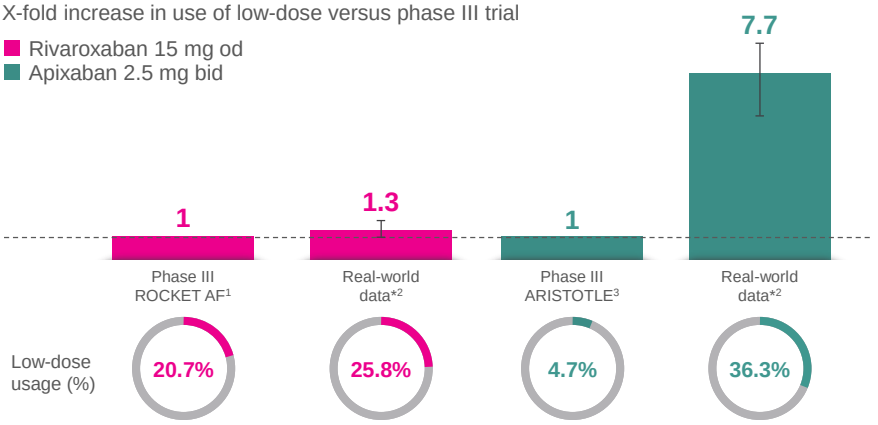
Not Intended for Direct Comparison

Dosing

Real-world evidence data

Rivaroxaban and Apixaban Low-Dose Usage in the Real World Versus Clinical Trials

Use of low-dose rivaroxaban consistent with expectations from phase III



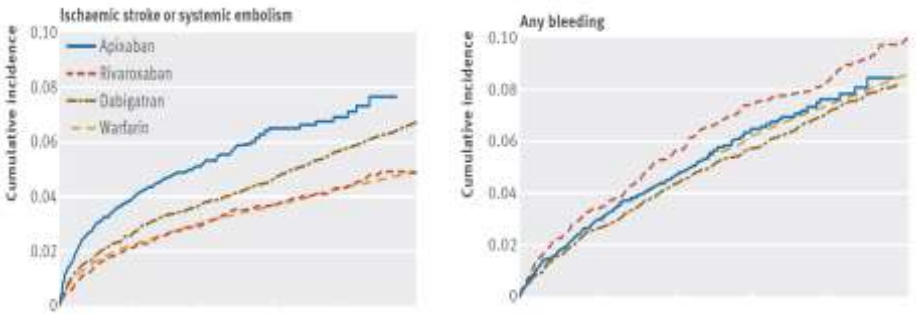
*Mean and range: data from the US, Germany, Canada and UK

1. Fox KA *et al*, *Eur Heart J* 2011;32:2387–2394; 2.IMS MIDAS. Q4 2014;
3. Granger GB *et al*, *N Engl J Med* 2011;365:981–992

Not Intended for Direct Comparison

Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

Peter Brønnum Nielsen,[1] Flemming Skjøth,[1,2] Mette Søgaard,[1,3] Jette Nordstrøm Kjældgaard,[1,3] Gregory Y H Lip,[1,4] Torben Bjerregaard Larsen[1,3]



BMJ 2017;356:j510

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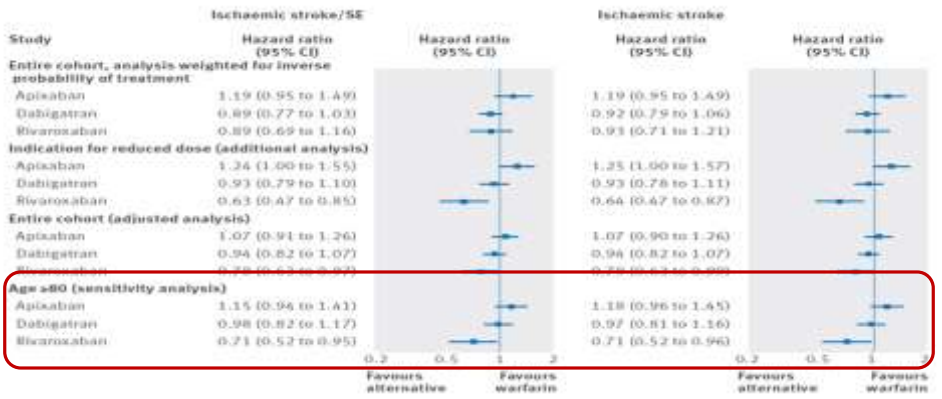

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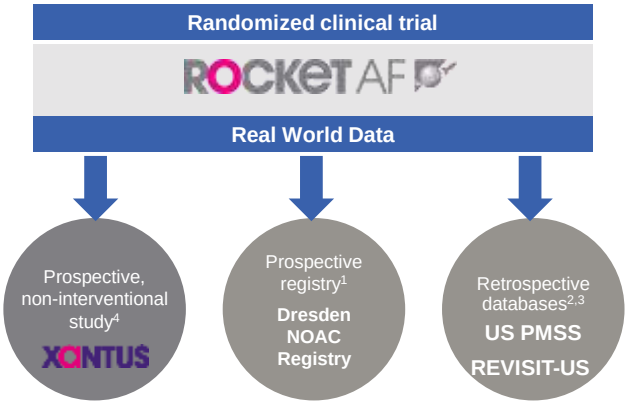
CONCLUSION

In this propensity weighted nationwide study of reduced dose non-vitamin K antagonist oral anticoagulant regimens, apixaban 2.5 mg twice a day was associated with a trend towards higher rates of ischaemic stroke/systemic embolism compared with warfarin, while rivaroxaban 15 mg once a day and dabigatran 110 mg twice a day showed a trend towards lower thromboembolic rates. The results were not significantly different. Rates of bleeding (the principal safety outcome) were significantly lower for dabigatran, but not significantly different for apixaban and rivaroxaban compared with warfarin.

BMJ 2017;356:j510

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* 2015;203:882–884; 4. Camm AJ *et al, Eur Heart J* 2015;doi:10.1093/eurheartj/ehv466

Conclusions

Registries and trials are complementary.

Randomized clinical trials determine the efficacy and safety of the Rivaroxaban compared with VKA.

Registries test how these drug work in the real world.

Some patients are overtreated and do not need anticoagulation (patients at very low risk for stroke).

Other patients at high risk for stroke do not receive the treatment they need.

Rivaroxaban provides a consistent and unique dataset covering the full patient risk spectrum

Unselected patients with AF in the real world

- 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 high persistence rates in Real World (exceeding warfarin or dabigatran)
- Adherence - Patients treated with OD rivaroxaban demonstrated better adherence than those treated with BID regimens
- Dosing - Use of low-dose rivaroxaban in Real World is consistent with expectations from phase III