Evidences for real-life use in fragile patients: Renal failure and cancer

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Approval number: L.IT.MA.11.2016.1839

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Stroke prevention in AF patients

Treatment of venous thromboembolism

Clinical Frailty Scale

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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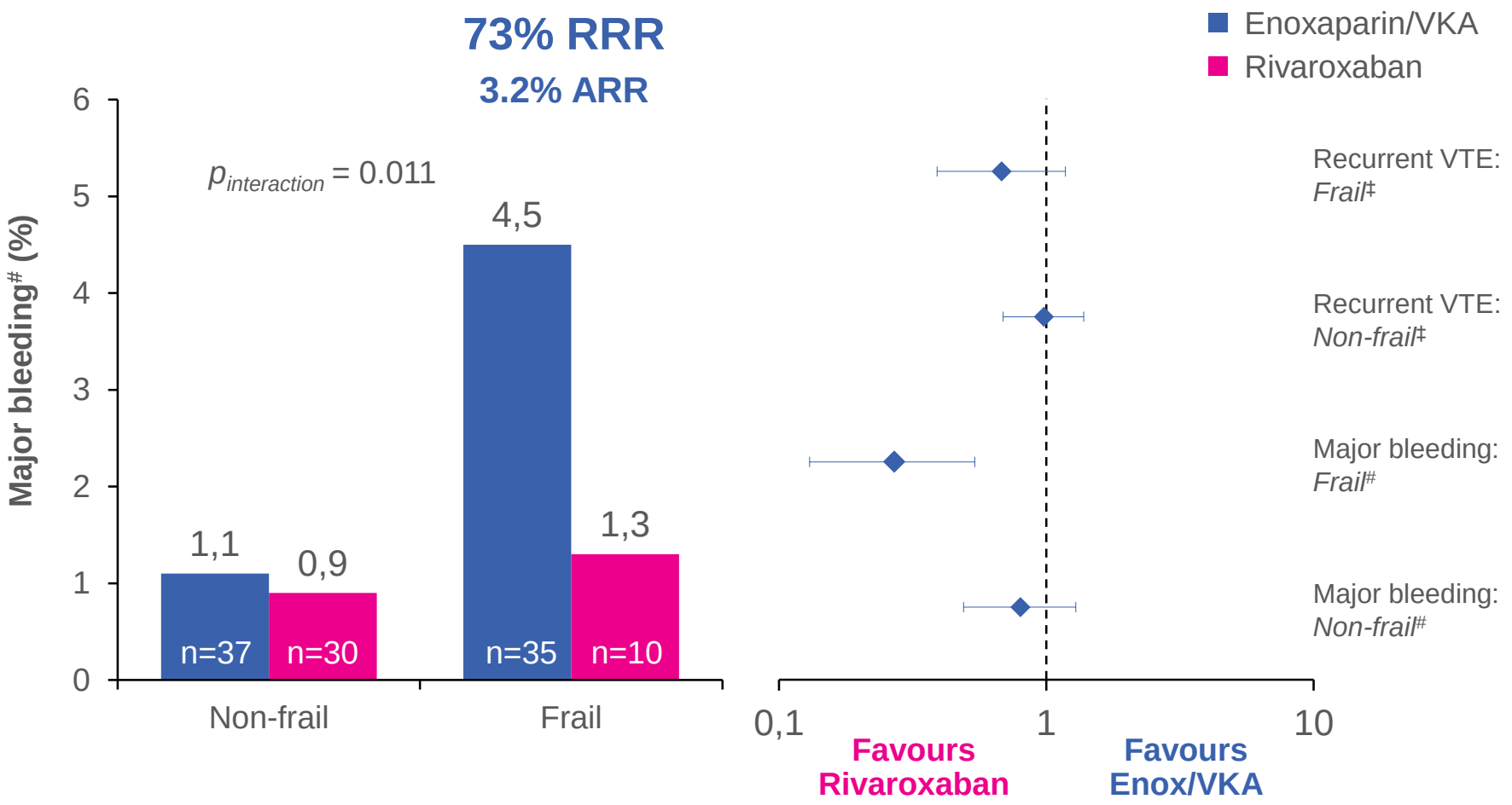
Rivaroxaban for the Treatment of Frail VTE patients

***One or more of: >75 years old, CrCl <50 ml/min, low body weight (≤50 kg)**



Prins MH *et al, Thromb J* 2013;11:21

Use in fragile patients: Cancer

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NOACs in cancer-associated VTE

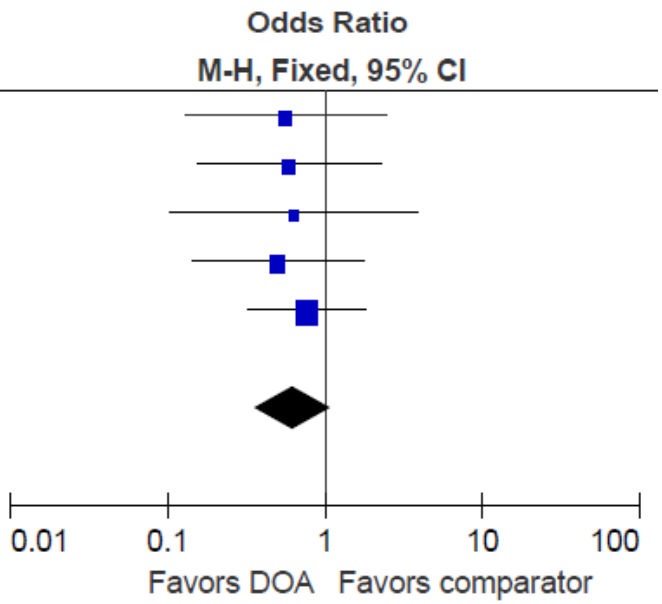
6 studies: 1132 patients with cancer at baseline

Recurrent VTE

	DOA		Comparator			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]
EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]
EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]
HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]
RECOVER I & II 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]
Total (95% CI)		**595**		**537**	**100.0%**	**0.63 [0.37, 1.10]**
Total events	23		32			

Heterogeneity: Chi² = 0.36, df = 4 (P = 0.99); I² = 0%

Test for overall effect: Z = 1.62 (P = 0.10)



Vedovati et al. *CHEST 2015*

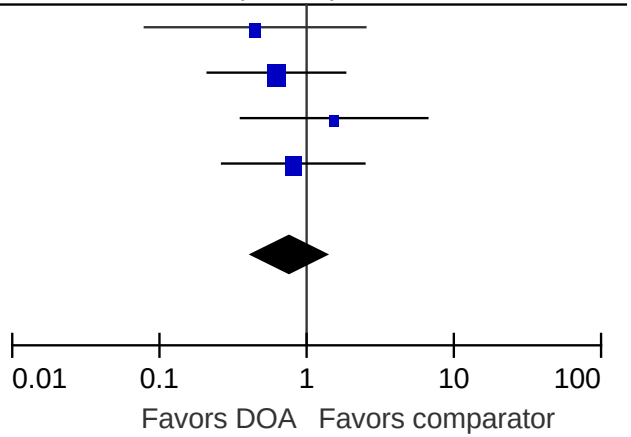
DOACs for cancer-associated VTE: meta-analysis

Major Bleeding

	DOA		Comparator			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
AMPLIFY 2013	2	87	4	80	18.2%	0.45 [0.08, 2.51]
EINSTEIN DVT & PE 2013	6	232	8	196	37.7%	0.62 [0.21, 1.83]
HOKUSAI 2013	5	109	3	99	13.4%	1.54 [0.36, 6.61]
RECOVER I & II 2013	6	159	7	152	30.7%	0.81 [0.27, 2.47]
Total (95% CI)		**587**		**527**	**100.0%**	**0.77 [0.41, 1.44]**
Total events	19		22			

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.70); I² = 0%

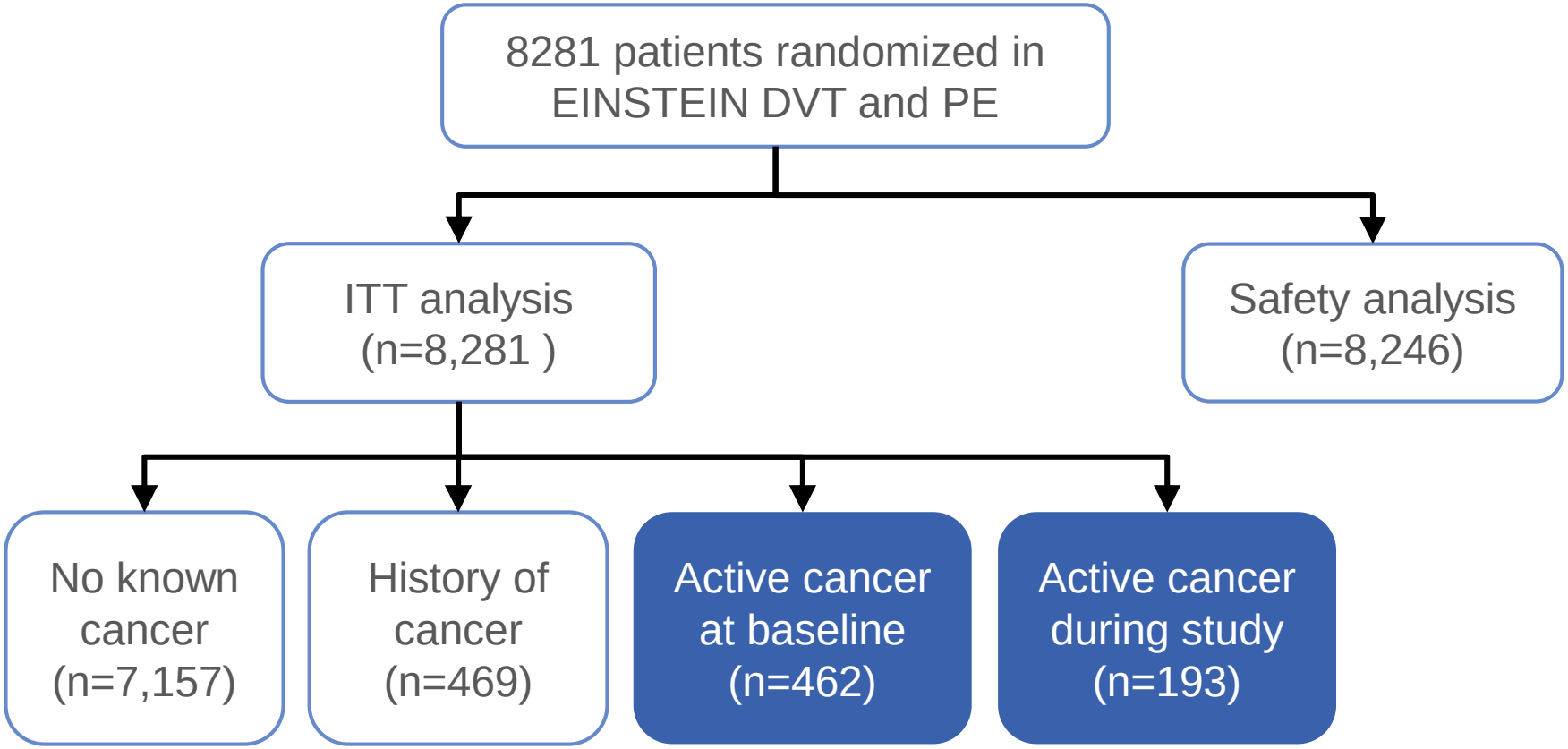
Test for overall effect: Z = 0.81 (P = 0.42)



3.2% vs 4.2%

Vedovati et al. *CHEST 2015*

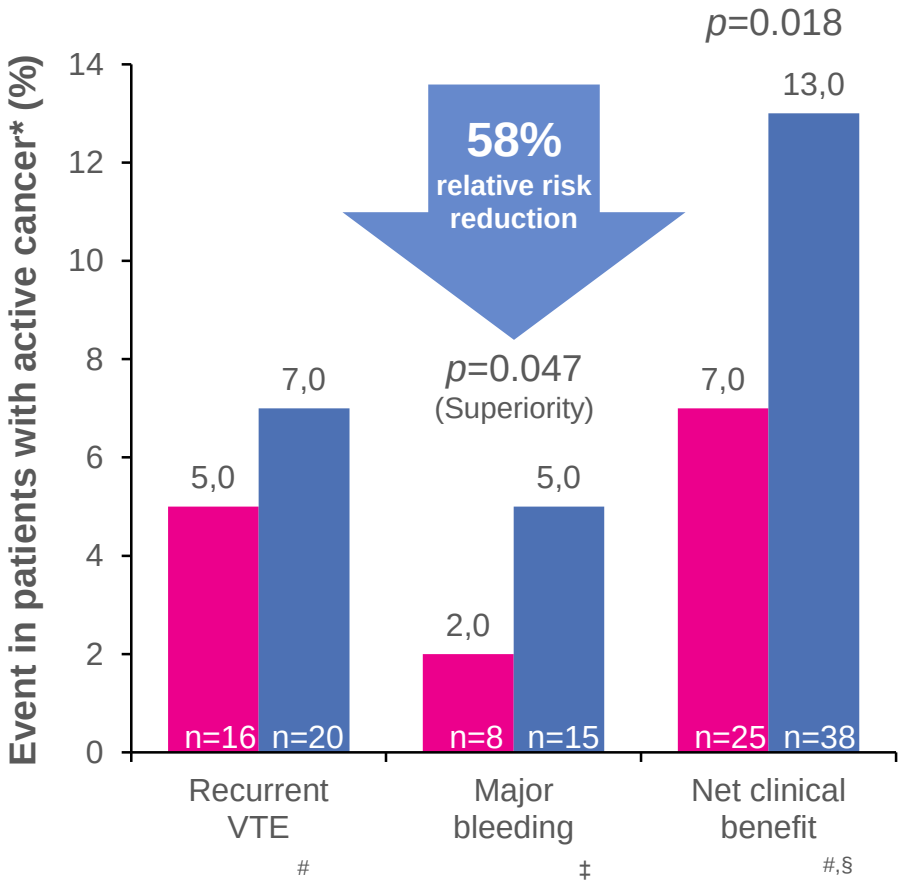
EINSTEIN DVT/PE : Pooled Cancer Subanalysis

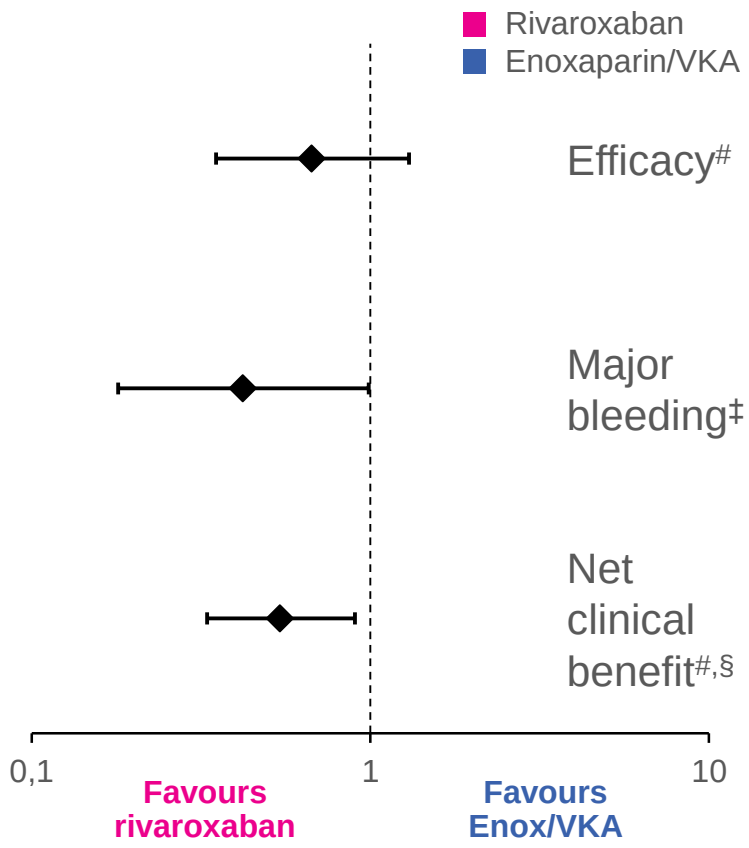


Prins M *et al. Lancet Haematol* 2014;1:e37–e46

EINSTEIN DVT/PE Pooled Analysis: Patients with Active Cancer

655 patients with active cancer at baseline or during the study period





§composite of recurrent VTE and major bleeding.

Modifed from: Prins MH *et al*. *Lancet Haematol* 2014;1:e37–e46

Recurrent Venous Thromboembolism Across Subgroups

	Rivaroxaban		Standard anticoagulation		HR (95% CI)
	n/N	(%)	n/N	(%)	
All patients	36/2505	(1.4)	47/2010	(2.3)	
Age					
<60 years	17/1286	(1.3)	16/785	(2.0)	
≥60 years	19/1219	(1.6)	31/1225	(2.5)	
Weight					
≤70 kg	8/522	(1.5)	13/495	(2.6)	
>70–<90 kg	8/843	(0.9)	18/663	(2.7)	
≥90 kg	11/599	(1.8)	12/482	(2.5)	
Active cancer at baseline					
Yes	5/144	(3.5)	14/338	(4.1)	
No	31/2361	(1.3)	33/1672	(2.0)	
First available CrCl					
<50 ml/min*	1/98	(1.0)	3/194	(1.5)	
≥50–<80 ml/min	6/410	(1.5)	11/366	(3.0)	
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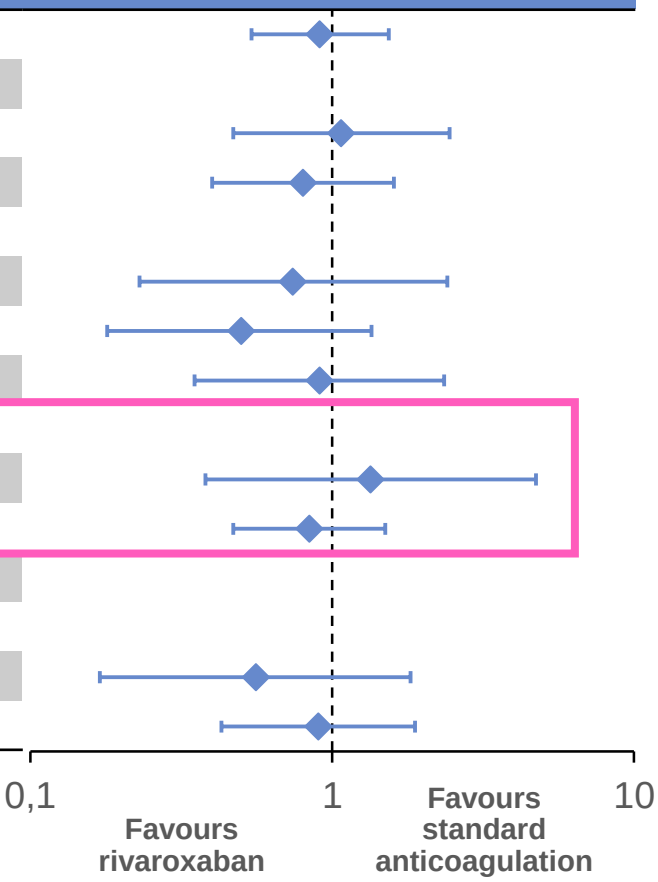

Note: some demographic parameters have data missing;
* HR not calculated because of too few events
Propensity score-adjusted population

Ageno W *et al, Lancet Haematol* 2016;3(1):e12–21

XALIA

Treatment-Emergent **Major Bleeding** Across Subgroups

	Rivaroxaban		Standard anticoagulation		HR (95% CI)
	n/N	(%)	n/N	(%)	
All patients	19/2505	(0.8)	43/2010	(2.1)	
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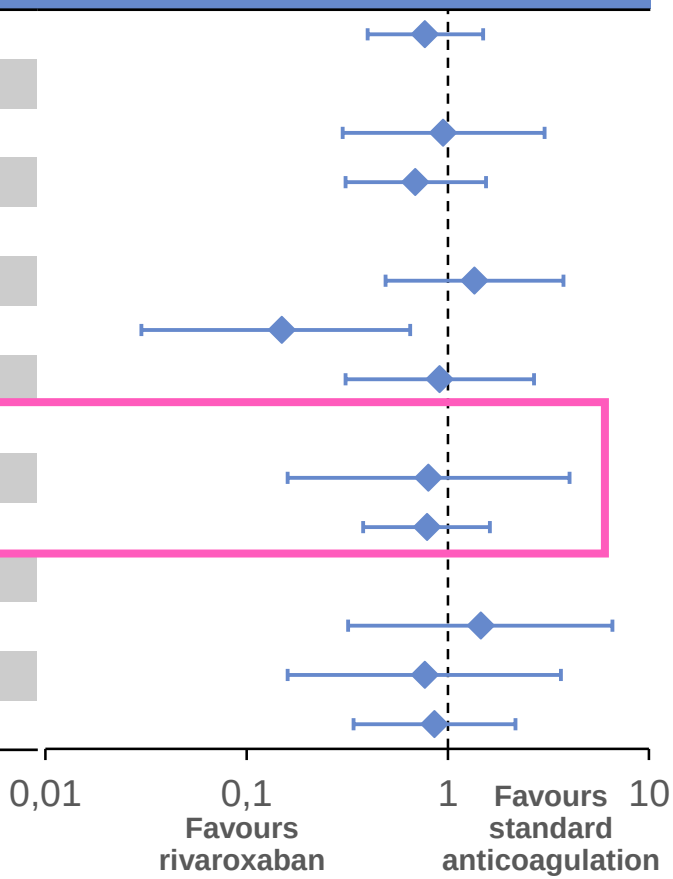

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Ageno W *et al, Lancet Haematol* 2016;3(1):e12–21

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“Real World” rivaroxaban for cancer-associated VTE

mean follow-up of 1.36 0.5 years

Variable	Cancer (n = 118)	No Cancer (n = 178)	*P*-Value
VTE recurrence, n (%)	4 (3.3)*	5 (2.8)	.53
DVT, n	3	4	1.0000
PE, n	1	1	1.0000
Major bleed, n (%)	3 (2.5)	0	.06
NMCRB, n (%)	4 (3.4)	1 (0.6)	.08
Major and NMCRB, n (%)	7 (5.9)	1 (0.6)	.008
Minor bleed, n (%)	3 (2.5)	3 (1.7)	.69
Death, n (%)	37 (31)	0	<.0001

D.M.Bott-Kitslaar 2016 Am J of Med

CALLISTO: Addressing Evidence Gaps in CAT

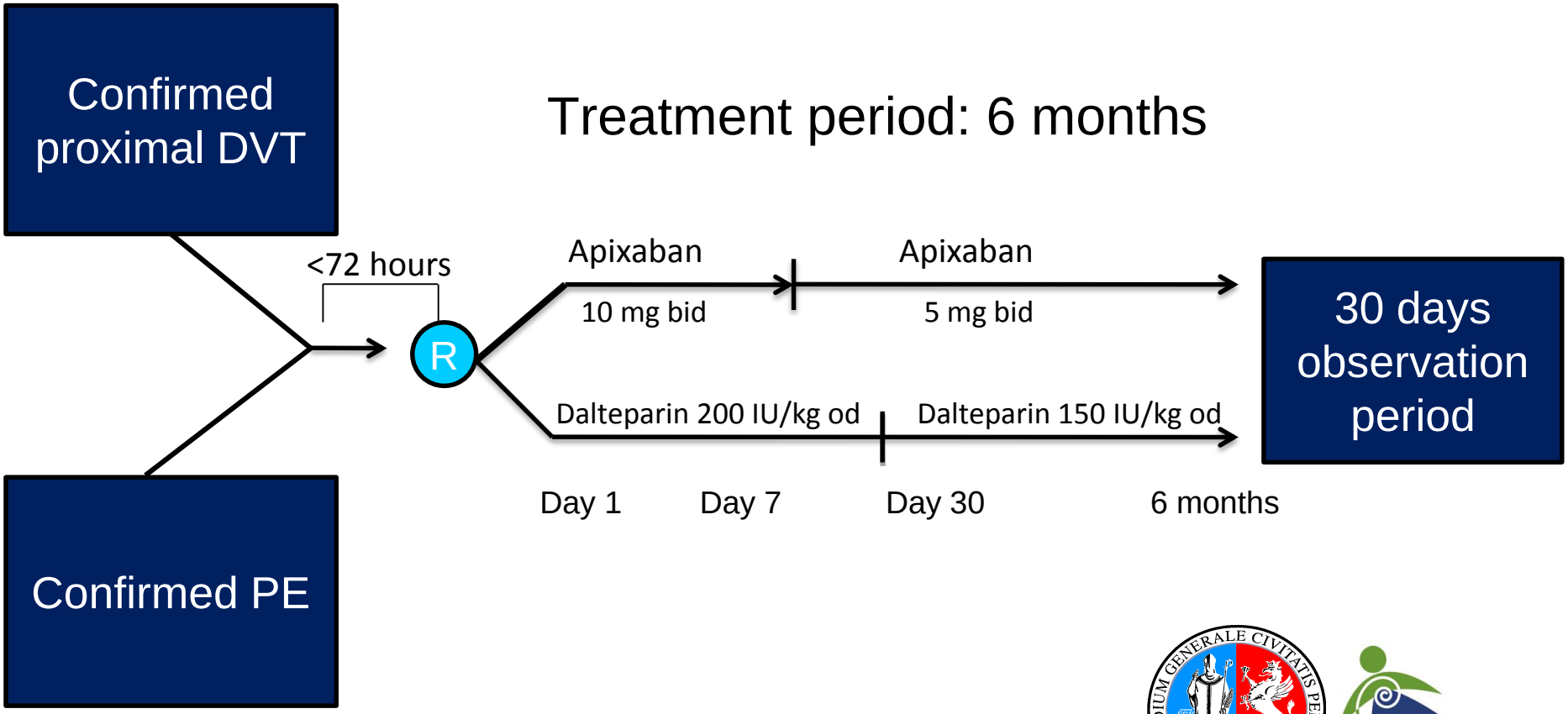
Data gaps	Currently Ongoing
Effectiveness and safety of rivaroxaban for the prevention and treatment of CAT	CASSINI, select-d, CONKO-011, QAI
Treatment satisfaction, treatment persistence and quality of life in cancer patients receiving rivaroxaban	select-d, COSIMO, CONKO-011
Effectiveness and safety of rivaroxaban for extended treatment (>6 months) of CAT	
Drug–drug interactions between rivaroxaban and commonly used cancer therapies	
Dosing in patients with chemotherapy-induced side effects	COSIMO
How to?	
Manage temporary interruptions of rivaroxaban for invasive procedures	COSIMO
Provide continuous anticoagulation for patients with chemotherapy-induced side effects	COSIMO

PD, pharmacodynamics; PK, pharmacokinetics; QAI, Quality Improvement Initiative/Clinical Pathway; VTEp, VTE prevention; VTEx, VTE treatment

CALLISTO

Caravaggio: Study design

Randomized, open-label, PROBE, non inferiority study



REAL-LIFE USE OF NOACs IN PATIENTS WITH CANCER ASSOCIATED VENOUS THROMBOEMBOLISM: DATA FROM A PROSPECTIVE COHORT

Maria Cristina Vedovati

University of Perugia

Venerdì 11
Ore 10,00
Sala Plenaria

Use in fragile patients: Renal failure

Stroke prevention in AF patients

Treatment of venous thromboembolism

Pharmacological Characteristics of the NOACs

	Xabans			DTI
	Rivaroxaban[3]	Apixaban[2]	Edoxaban[4]	Dabigatran[1]
Target	Factor Xa			Thrombin
Prodrug	No	No	No	Yes
Oral bioavailability	80–100%*	50%	62%	6.5%
Renal clearance of absorbed active drug	**~33%**	**~27%**	**~55–60%**	**>80%**
T_{max} (h)	2–4	3–4	1–2	2–6[#]
Half-life (h)	5–13	12	10–14	12–14
Fixed dosing (AF indication)	od	bid	od	bid

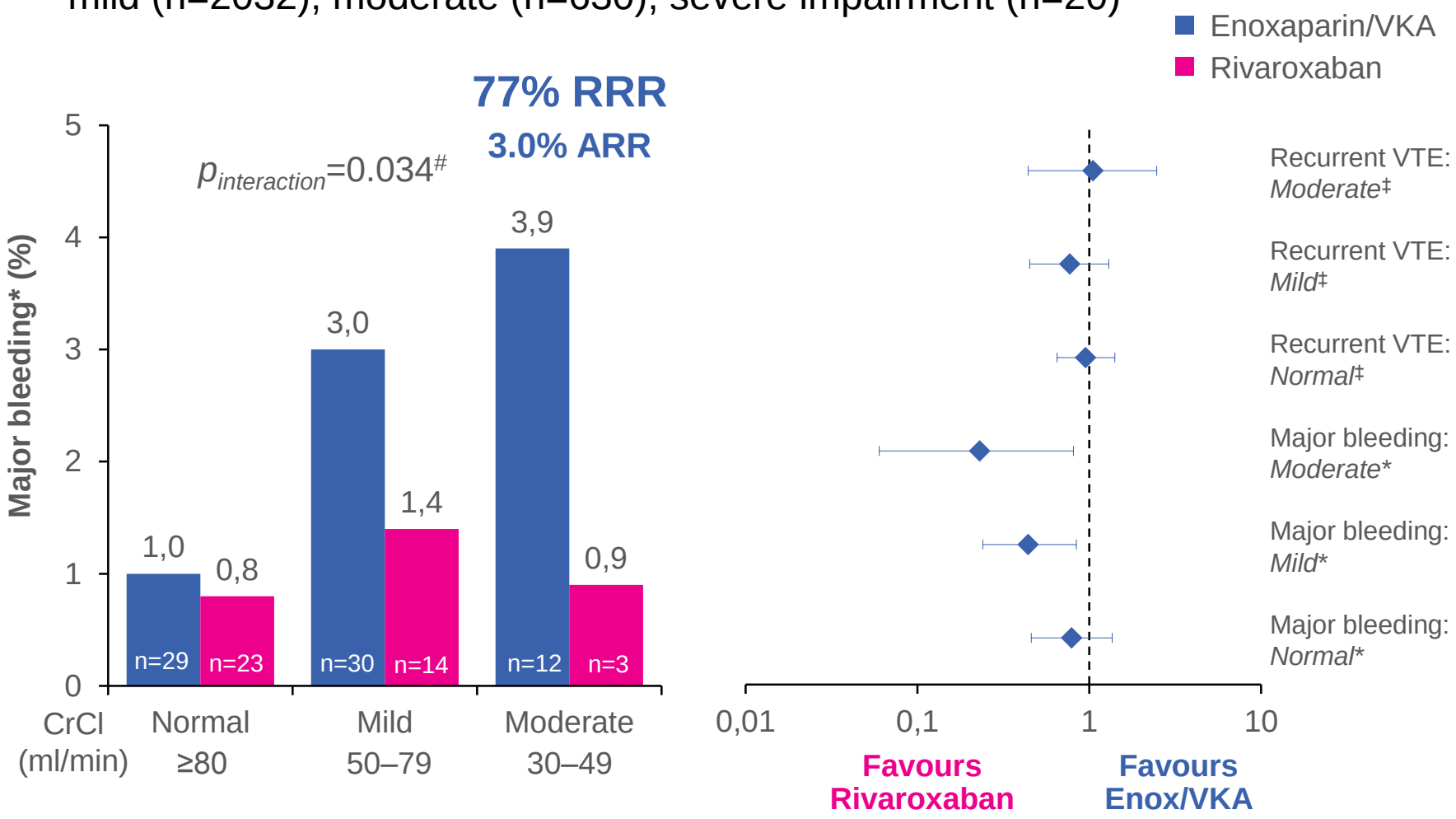
*15–20 mg to be taken with food; [#]Postoperative period;

1. Dabigatran SmPC; 2. Apixaban SmPC; 3. Rivaroxaban SmPC; 4. Edoxaban SmPC

VTE Treatment in Patients with Renal Impairment

normal function (n=5549);

mild (n=2032); moderate (n=630); severe impairment (n=20)



Bauersachs RM *et al, Thromb J* 2014;12:25

Xalia:
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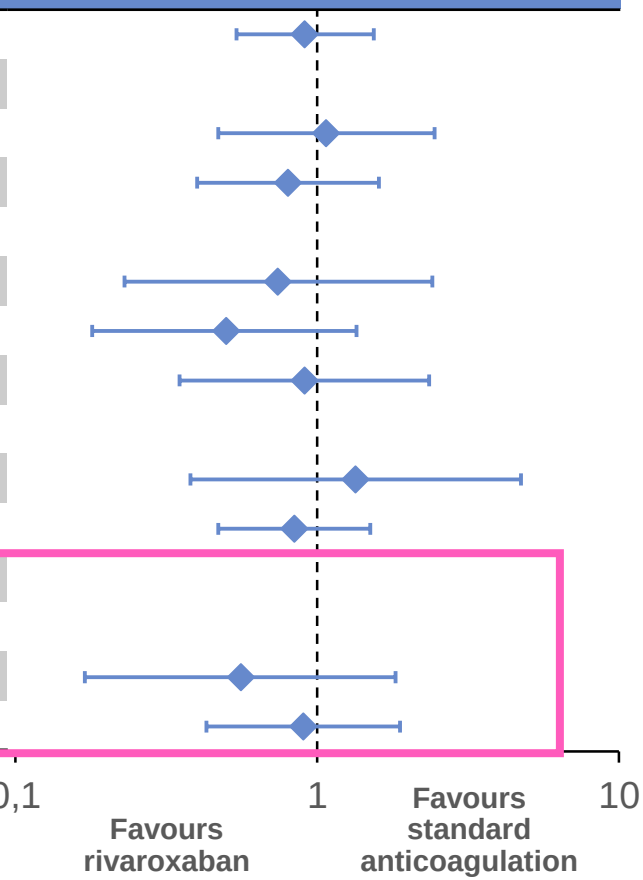

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XALIA

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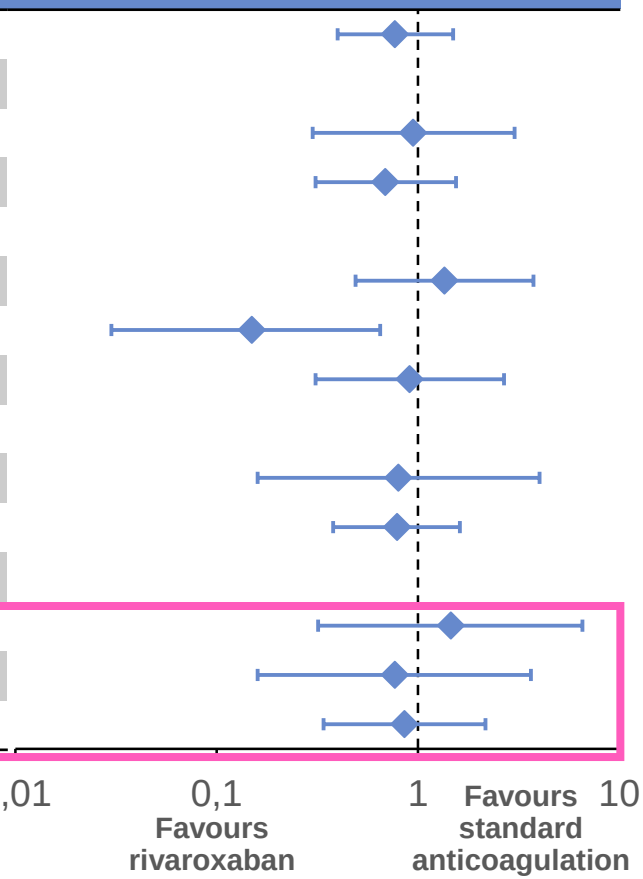


Note: some demographic parameters have data missing
Propensity score-adjusted population

Ageno W *et al, Lancet Haematol* 2016;3(1):e12–21

XALIA

Moderate Renal Impairment in Phase III AF Trials

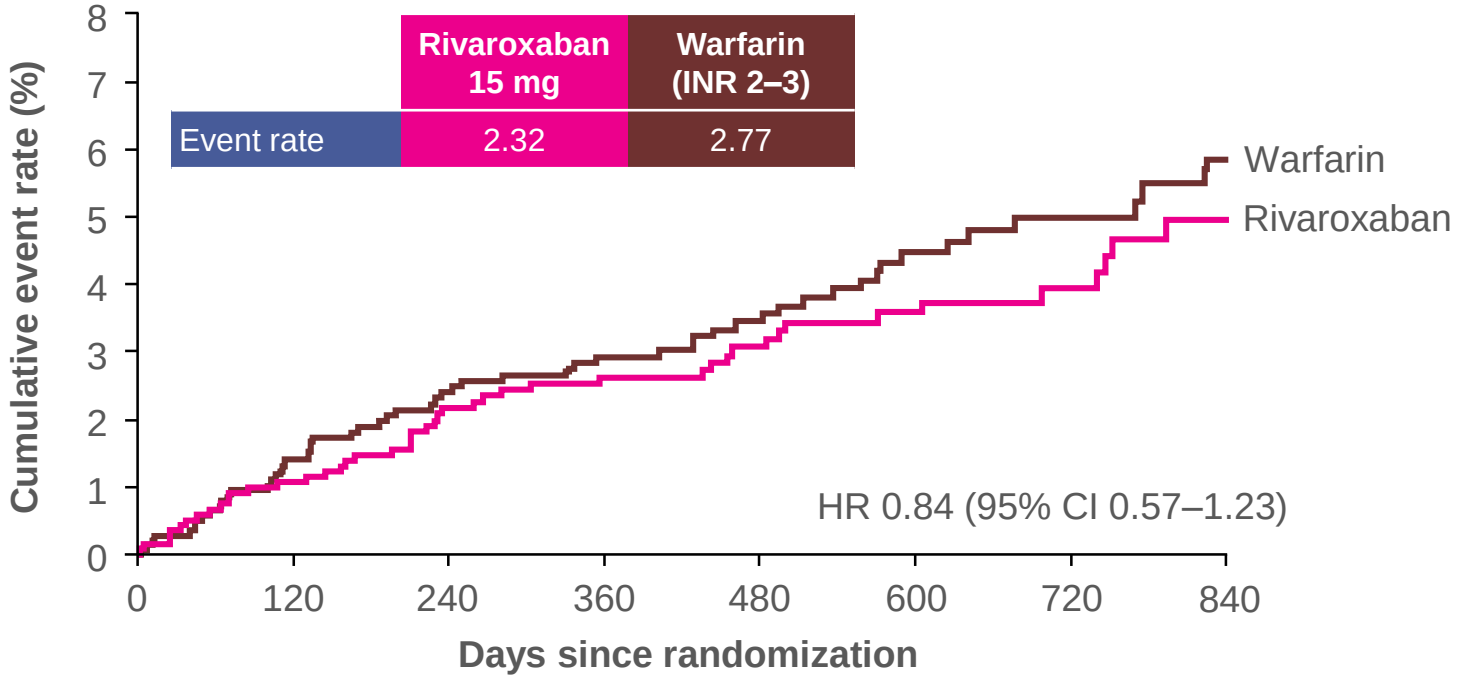
	ROCKET AF[1] (n=14,264)	ARISTOTLE[2-4] (n=18,201)	ENGAGE AF[5,6] (n=21,105)	RE-LY[7,8] (n=18,113)
Specific renal dose studied to support safety	✓	✗	✗	✗
Proportion of patients with moderate renal impairment	21%*	15%†	19%‡	20%§
Number of patients studied with **low dose**	15 mg OD: 1474	2.5 mg BD: 428	30 mg BD#: 1784	110 mg BD: 6015
Number of patients studied with **low dose** with moderate renal impairment	1474	149¶	1379#	1196
Number of patients studied with low dose with moderate renal impairment – as a proportion of all patients studied with the NOAC	20.7%	1.6%	19.6%#	9.9%

*CrCl 30-49 ml/min; †CrCl >30-50 ml/min; ‡CrCl ≤50 ml/min; ¶Scr ≥ 1.5 mg/dL ; §eGFR ,<50 ml/min
Data given for dose adjusted arm of 'High-Dose' (60/30) group as 'Low-Dose' (30/15) regimen not approved

1. Fox KAA *et al*, *Eur Heart J* 2011;32:2387–2394; 2. Granger GB *et al*, *N Engl J Med* 2011;365:981–992;
3. Hohnloser SH *et al*, *Eur Heart J* 2012;33:2821–2830; 4. FDA. Clinical Review of apixaban NDA 202155, p 213
5. Giugliano RP *et al*, *N Engl J Med* 2013;369:2093–2104; 6. Bohula EA *et al*, *Circulation* 2015;132: A17169;
7. Connolly SJ *et al*, *N Engl J Med* 2009;361:1139–1151; 8. Hijazi Z et al. Circulation 2014;129:961–70

ROCKET AF
Subanalysis moderate renal impairment: efficacy

Stroke or SE in patients with CrCl 30–49 ml/min
(Per protocol on treatment)

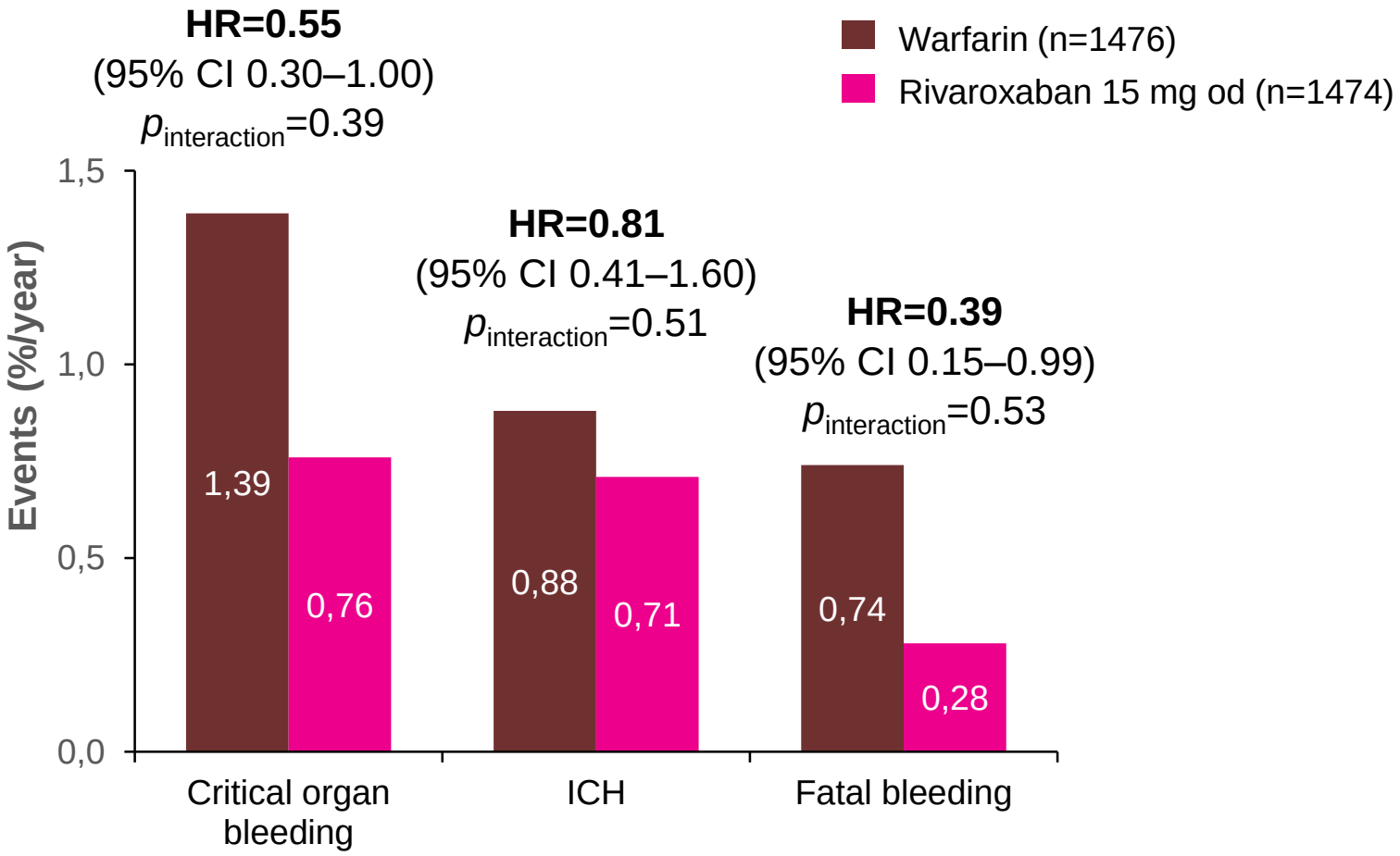


No. at Risk								
Rivaroxaban	1,434	1,226	1,103	1,027	806	621	442	275
Warfarin	1,439	1,261	1,140	1,052	832	656	455	272

Per-protocol on-treatment population
Fox KA *et al. Eur Heart J* 2011;32(19): 2387–2394

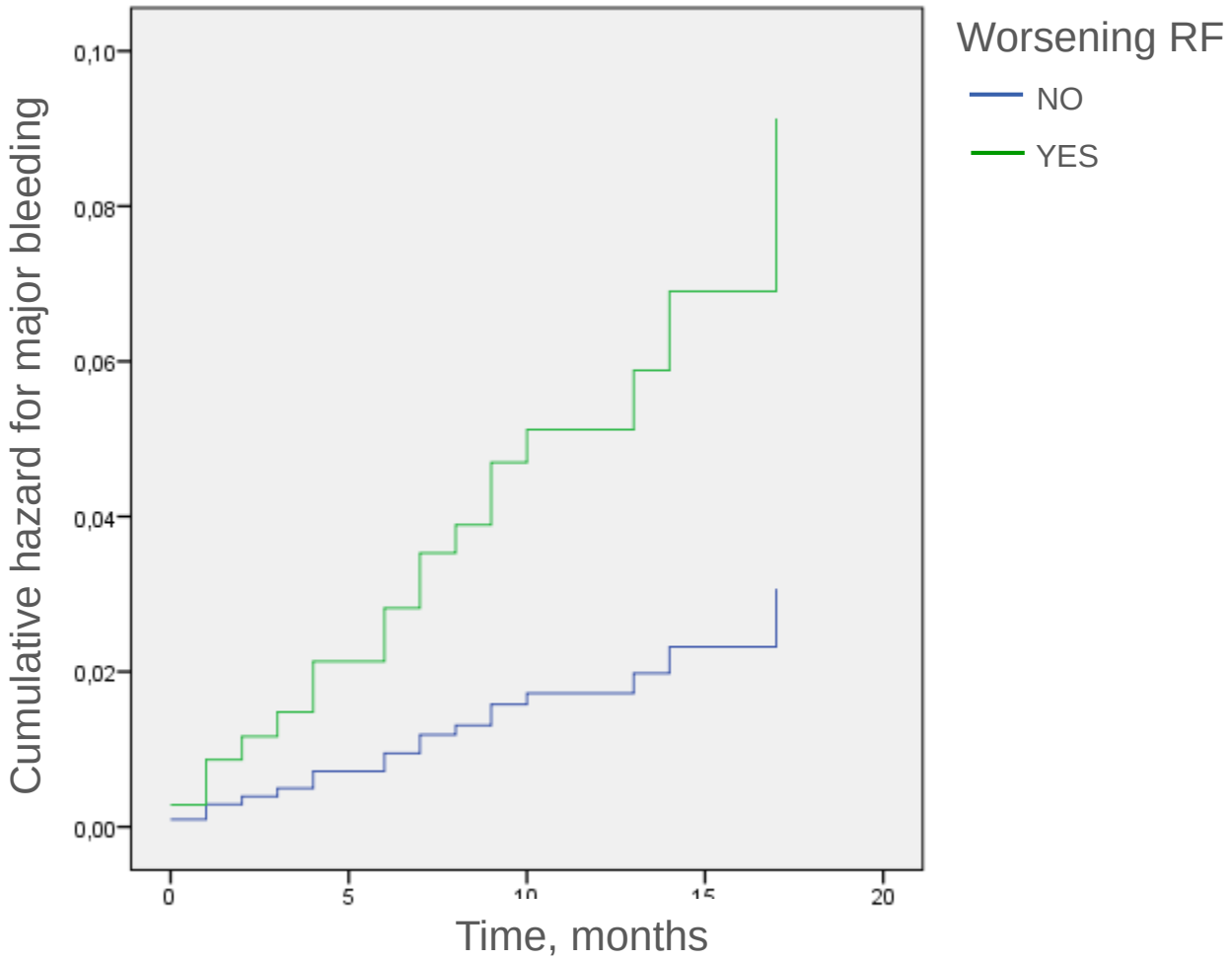
ROCKET AF
Subanalysis Moderate Renal Impairment: safety

Relevant safety endpoints in patients with CrCl 30–49 ml/min
(Safety on treatment population)



Fox KAA *et al*, *Eur Heart J* 2011;32:2387–2394

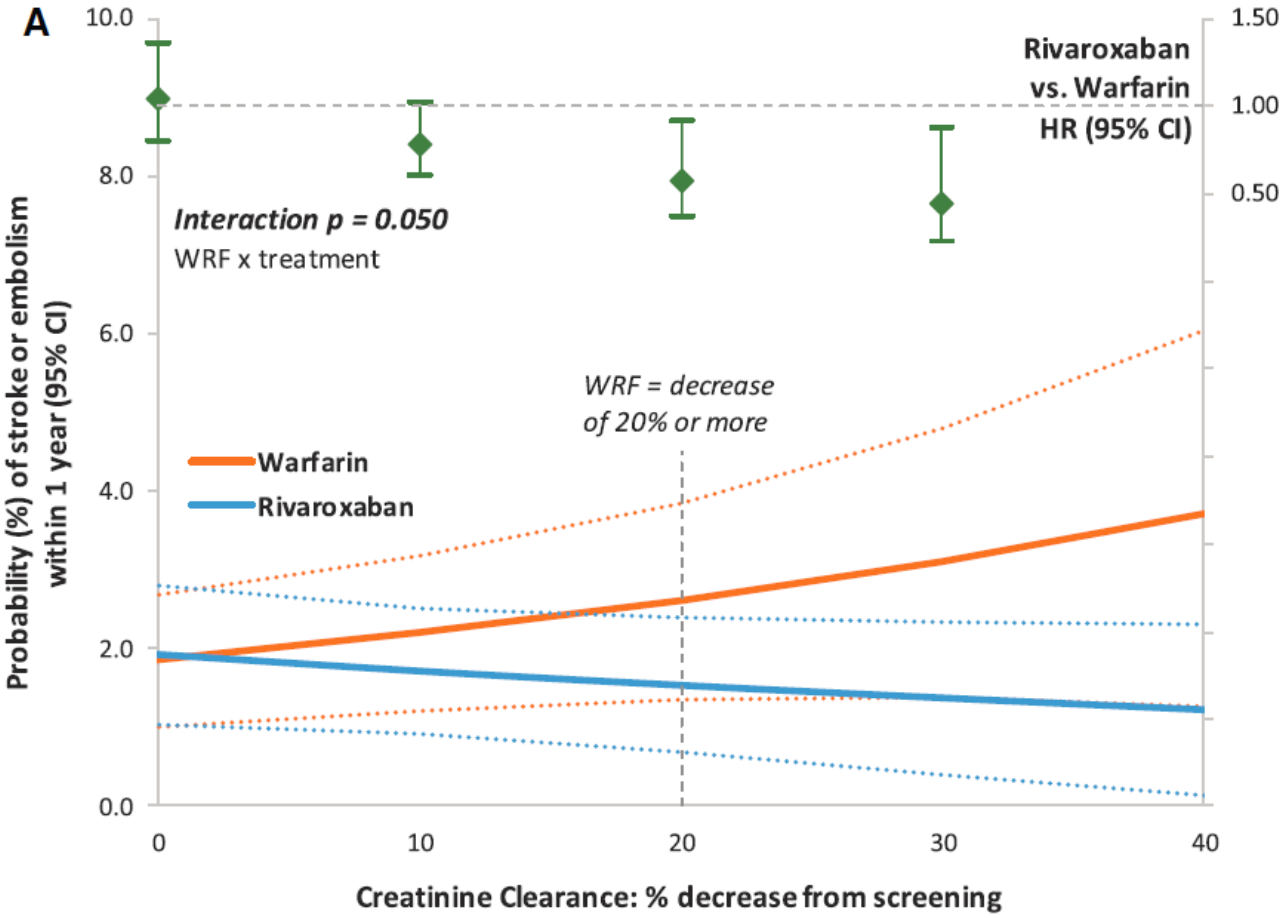
Worsening Renal Function and MB with NOACs in AF



Becattini et al., submitted

ROCKET AF stroke or SE With Worsening Renal Function

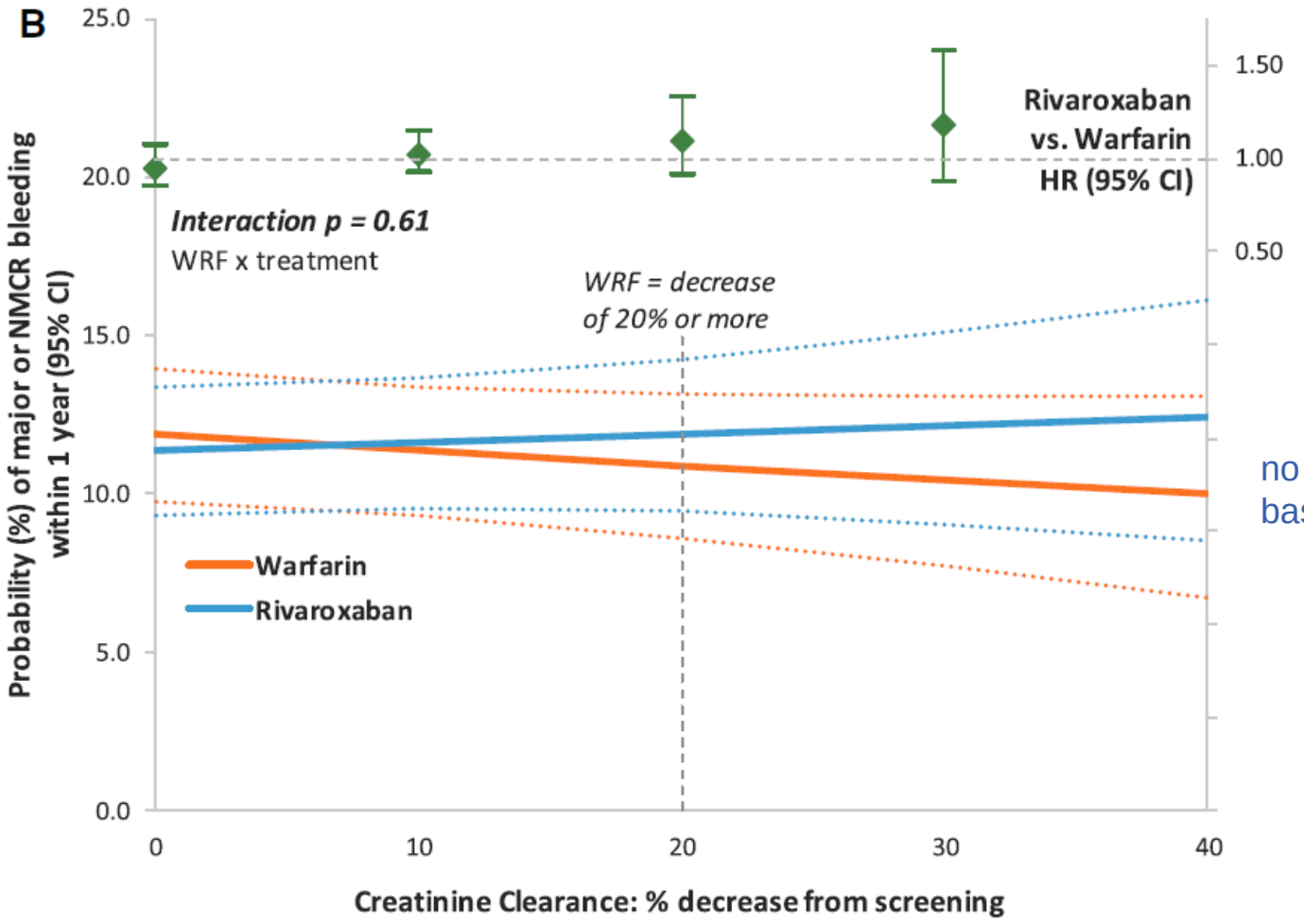
3320 (26.3%) had WRF
Rivaroxaban = 1632 (20 mg, 41%; 15 mg, 10%)



In Rocket AF trial
no dose adjustments after baseline for changing CrCl

Fordyce, *Circulation July 2016*.116.021890

ROCKET AF: CRB With Worsening Renal Function



In Rocket AF trial
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Fordyce, *Circulation July 2016*.116.021890

Evidences for real-life use in fragile patients: Renal failure and cancer

Fragile patients have an increased risk of thromboembolic events and bleeding complications

The efficacy of NOACs and in particular of rivaroxaban is confirmed in subgroups of fragile patients without safety concerns

Evidences for real-life use in fragile patients: Renal failure and cancer

Cecilia Becattini

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