QUIN ES EL MILLOR NACO?: Revisió dels estudis pivotals!!

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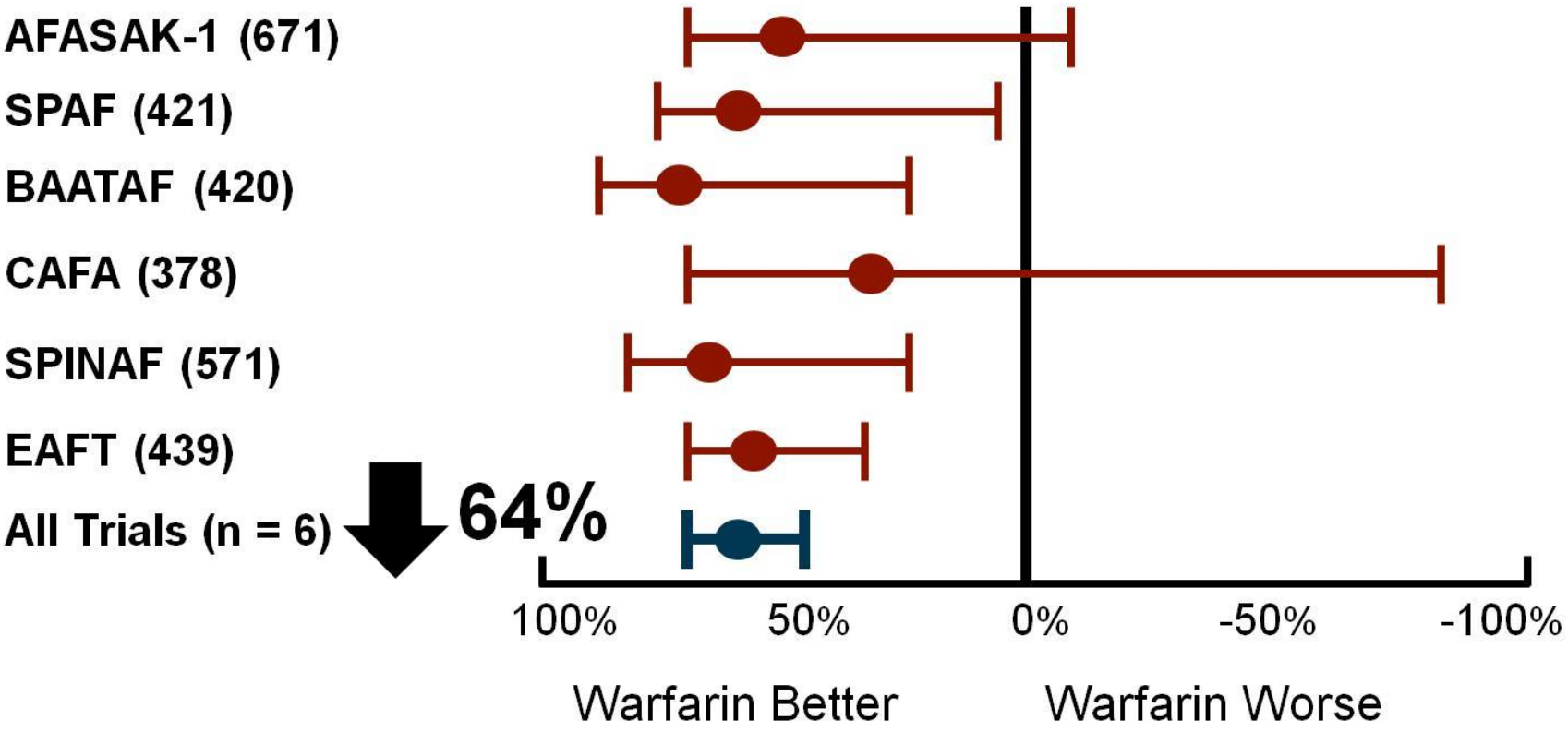
Per un digestoleg

- Quin es el que fa menys sangrat GI?

Stroke Prevention in AF Warfarin vs Placebo



Hart RG, et al. *Ann Intern Med.* 2007;146:857-867.[29]

Pivotal Warfarin-Controlled Trials Stroke Prevention in AF

Warfarin vs Placebo
2,900 Patients

NOACs vs Warfarin
71,683 Patients

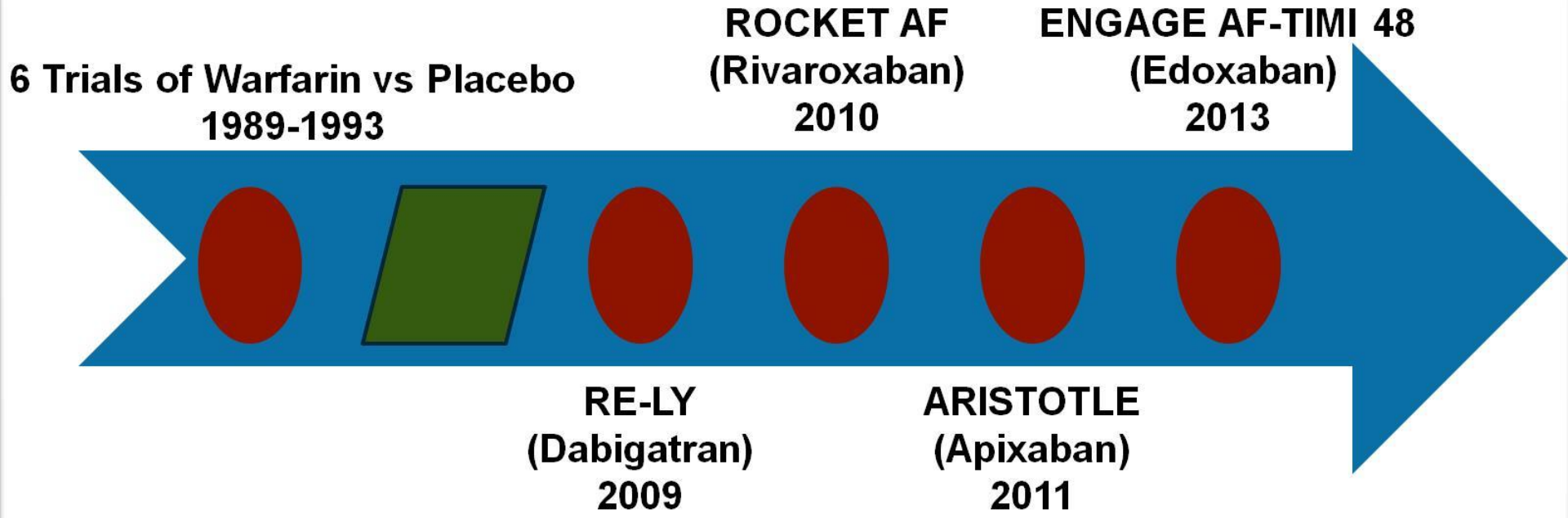


Table 1 Main pharmacokinetics and pharmacodynamics of the novel oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban [11, 19–21, 27, 31, 64]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct free and fibrin-bound thrombin inhibitor. Prevention of thrombin-mediated cleavage of fibrinogen to fibrin monomers and activation of factors V, VIII, XI, and XIII	Reversible inhibitor of factor Xa in both the intrinsic and extrinsic coagulation pathway. Inhibition of thrombin-mediated platelet activation and conversion of fibrinogen to fibrin		
Distribution volume (L)	50–70	50	21	107
Time to C_{max} (h)	1–2 (delayed by food)	2–4	1–3	1–2
Metabolism	Hepatic. Dabigatran etexilate (prodrug) is hydrolyzed to dabigatran (active compound) by plasma and hepatic esterases. Less than 10 % is converted to an active acylglucuronide by hepatic glucuronidation	Hepatic via CYP3A4-dependent and -independent pathways (including CYP2J2)	Hepatic mainly via CYP3A4/5 and partially via CYP1A2, 2C8, 2C9, 2C19, and 2J2 to inactive metabolites	Minimally metabolized via CYP3A4 (<4 %)
Cytochrome P450 metabolism (%)	None	66	15	<4
Bioavailability (%)	6–7	80	66	62
Transporters	P-gp	P-gp/BCRP	P-gp	P-gp
Protein binding (%)	35	>90	87	55
Half-life (h)	12–14. Prolonged in elderly and subjects with renal impairment (>24 h)	5–13	8–15	10–14
Renal elimination (%)	80	66[a]	25	50
Linear PK	Yes	Up to 15 mg daily	Yes	Yes

BCRP breast cancer resistance protein, C_{max} maximum concentration, *P-gp* P-glycoprotein, *PK* pharmacokinetics

[a] Half of the 66 % is excreted unchanged in the urine

Implicaciones clínicas

- En pacientes con alteración de la función renal dabigatran se ha de evitar
- En pacientes que estén tomando drogas que se metabolicen por el Cit p 450, el uso de dabigatran o edoxaban pueden ser ventajoso.

NOAC SPAF Trials

	RE-LY[a]	ROCKET AF[b]	ARISTOTLE[c]	ENGAGE AF[d]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
# Randomized	18,113	14,266	18,201	21,105
Dose (mg)	150, 110	20	5	60, 30
Frequency	Twice Daily	Once Daily	Twice Daily	Once Daily
Dose Adjustment, %	No	20 → 15	5 → 2.5	60 → 30 30 → 15
At Baseline	0	21	5	25
After Randomization	No	No	No	>9
Target INR (Warfarin)	2.0-3.0	2.0-3.0	2.0-3.0	2.0-3.0
Design	PROBE*	2x blind	2x blind	2x blind

*PROBE = prospective, randomized, open-label, blinded end point evaluation

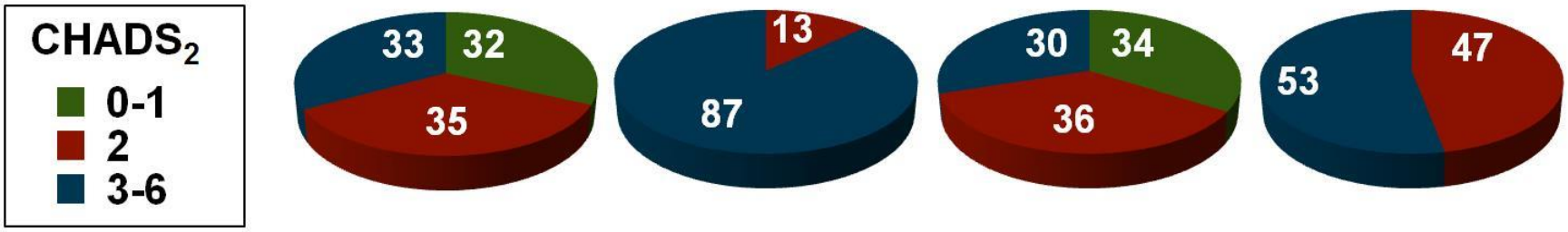
a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151.[14]
b. Patel MR, et al. *N Engl J Med.* 2011;365:883-891.[15]
c. Granger CB, et al. *N Engl J Med.* 2011;365:981-992.[16]
d. Giugliano RP, et al. *N Engl J Med.* 2013;369:2093-2104.[17]

Table 2 Major differences in entry criteria in the four novel oral anticoagulant trials

	RE-LY [36, 55]	ROCKET-AF [39, 65]	ARISTOTLE [40]	ENGAGE AF-TIMI 48 [42, 43]
INCLUSION CRITERIA				
Rhythm	Atrial fibrillation	Atrial fibrillation	Atrial fibrillation or flutter	Atrial fibrillation
$CHADS_2$ score	≥1	≥2	≥1	≥2
EXCLUSION CRITERIA				
Aspirin dose	Not specified	>100 mg/day excluded	>165 mg/day excluded	Recommended dose <100 mg/day, but higher doses permitted
DAPT (aspirin and thienopyridine)	Patients on DAPT were allowed in the study	Aspirin in combination with thienopyridines within 5 days	Patients on DAPT were excluded	Patients on DAPT were excluded
Stroke or TIA	Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days	Stroke within 14 days or TIA within 3 days before randomization	Stroke within 7 days before randomization	Stroke within 30 days before randomization
Renal function	CrCl ≤30 mL/min	CrCl <30 mL/min	Serum Cr >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Liver disease	• Persistent ALT, AST, AP >2 × ULN • Active hepatitis A, B, or C • Transaminase elevation with ximelagatran	• Known liver disease • AST >3 × ULN	• ALT or AST >2 × ULN • TBili ≥1.5 ULN	• ALT or AST >2 × ULN • TBili ≥1.5 ULN
GI bleeding	GI bleeding within the past year; symptomatic or endoscopically documented gastroduodenal ulcer disease in the prior 30 days	Clinically significant GI bleeding in the prior 6 months	Not specified[a]	Gastrointestinal bleeding or active ulcer within the previous year

Baseline Characteristics

	RE-LY[a] (Dabigatran)	ROCKET-AF[b] (Rivaroxaban)	ARISTOTLE[c] (Apixaban)	ENGAGE AF[d] (Edoxaban)
# Randomized	18,113	14,264	18,201	21,105
Age, years	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	35	38
Paroxysmal AF, %	32	18	15	25
VKA naïve, %	50	38	43	41
Aspirin use,%	40	36	31	29



a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.[14]
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c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992.[16]
d. Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[17]

Implicaciones clinicas

- La evidencia en pacientes con CHADS mas altos es mayor en el caso del Rivaroxaban y el edoxaban. Sin embargo en pacientes de bajo riesgo es nula con rivaroxaban y escasa con edoxaban.
- En pacientes con doble antiagregación solo dabigatran puede ofrecer datos
- Pacientes con función renal por debajo de 25-30 de aclaramiento no tenemos datos.
- En pacientes con fluter solo apixaban ofrece datos.

Trial Metrics

	RE-LY[a] (Dabigatran)	ROCKET AF[b] (Rivaroxaban)	ARISTOTLE[c] (Apixaban)	ENGAGE AF[d] (Edoxaban)
Median Follow-up, y	2.0	1.9	1.8	2.8
Median TTR	66	58	66	68
Lost to Follow-up, N	20	32	90	1

*TTR, time in therapeutic range

a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151.[14]
b. Patel MR, et al. *N Engl J Med.* 2011;365:883-891.[15]
c. Granger CB, et al. *N Engl J Med.* 2011;365:981-992.[16]
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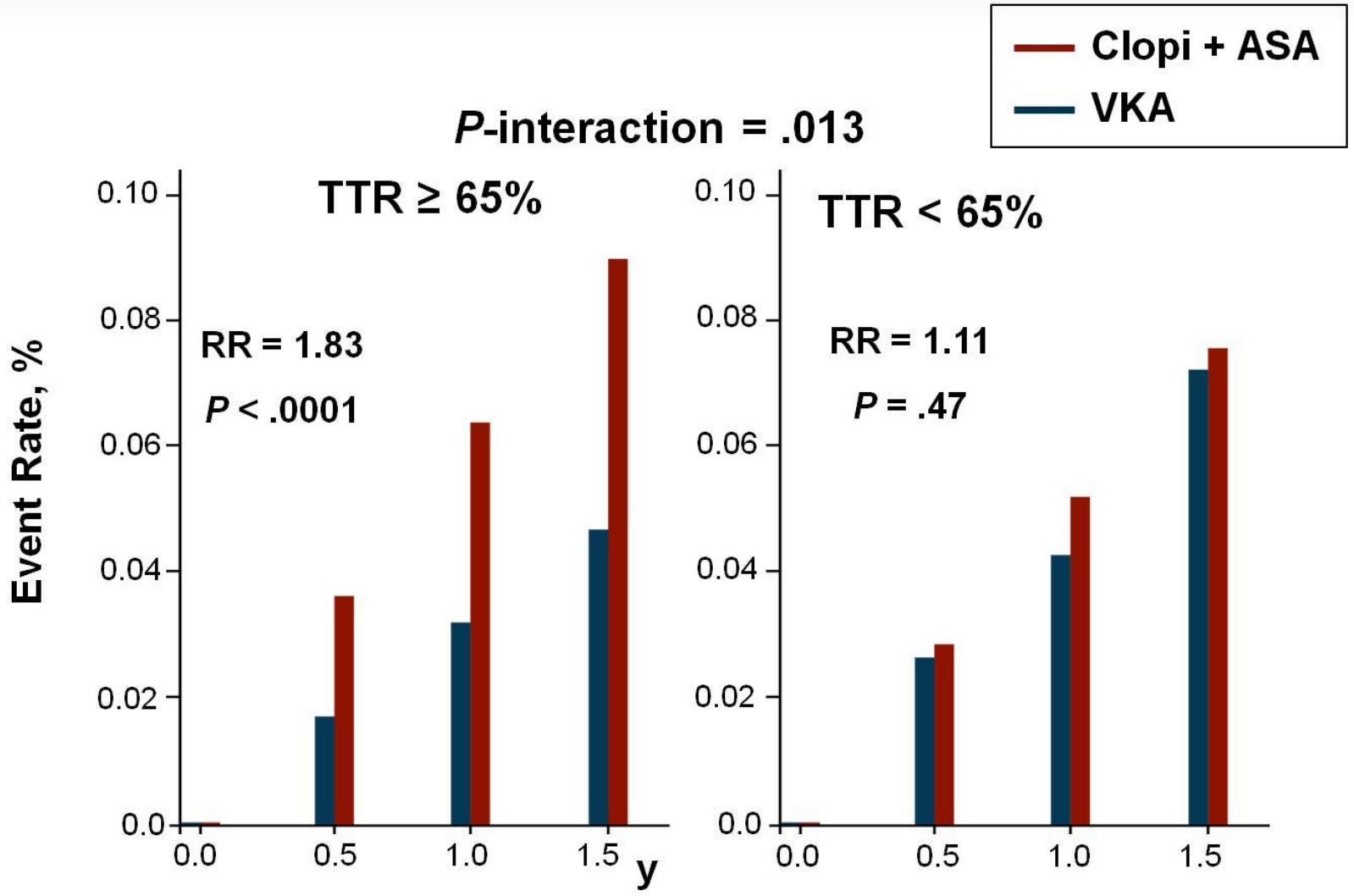
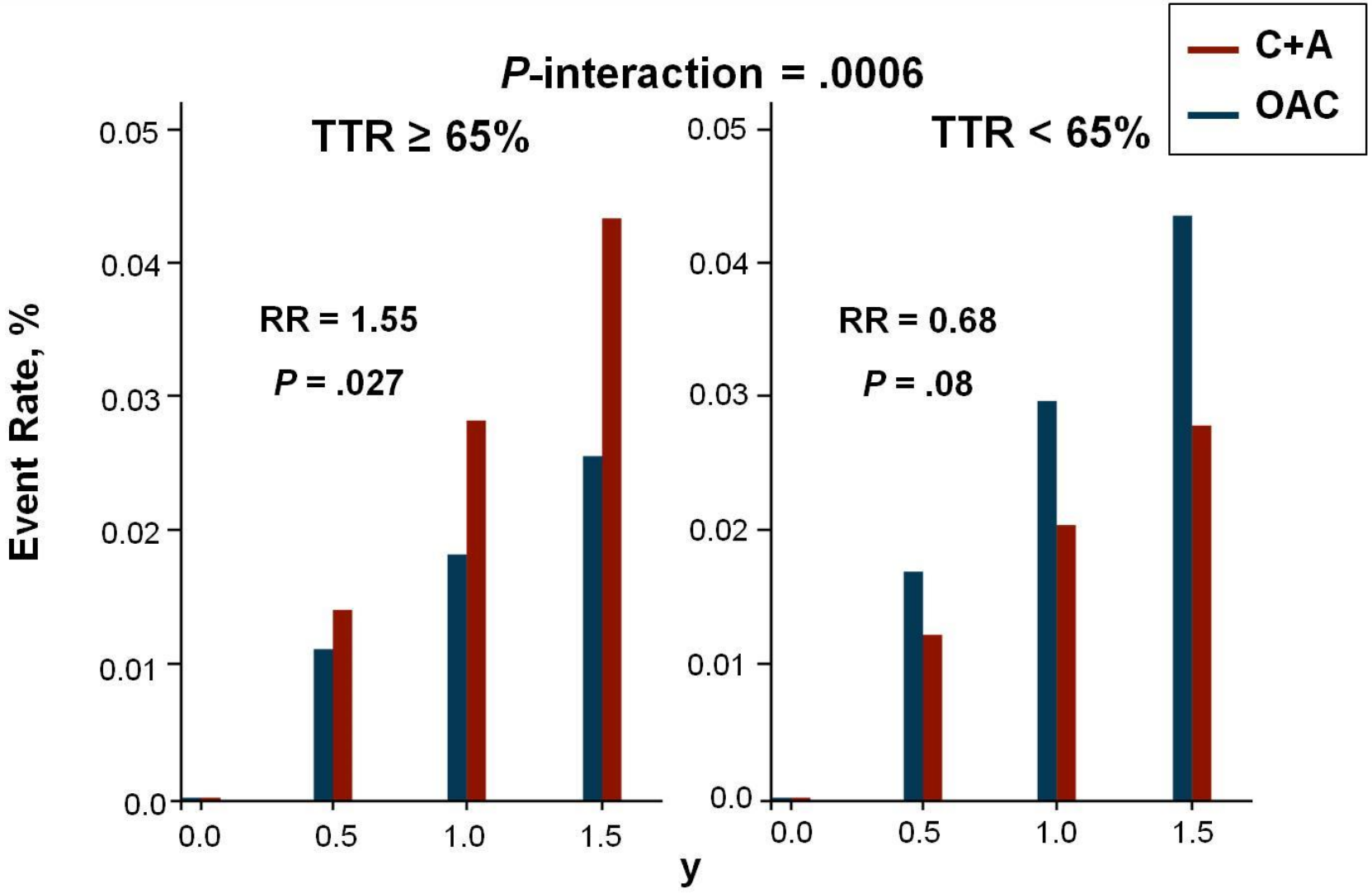
ACTIVE-W
Stroke or SEE



Connolly SJ, et al. *Circulation.* 2008;118:2029-2037.[31]

ACTIVE-W
Major Bleeding

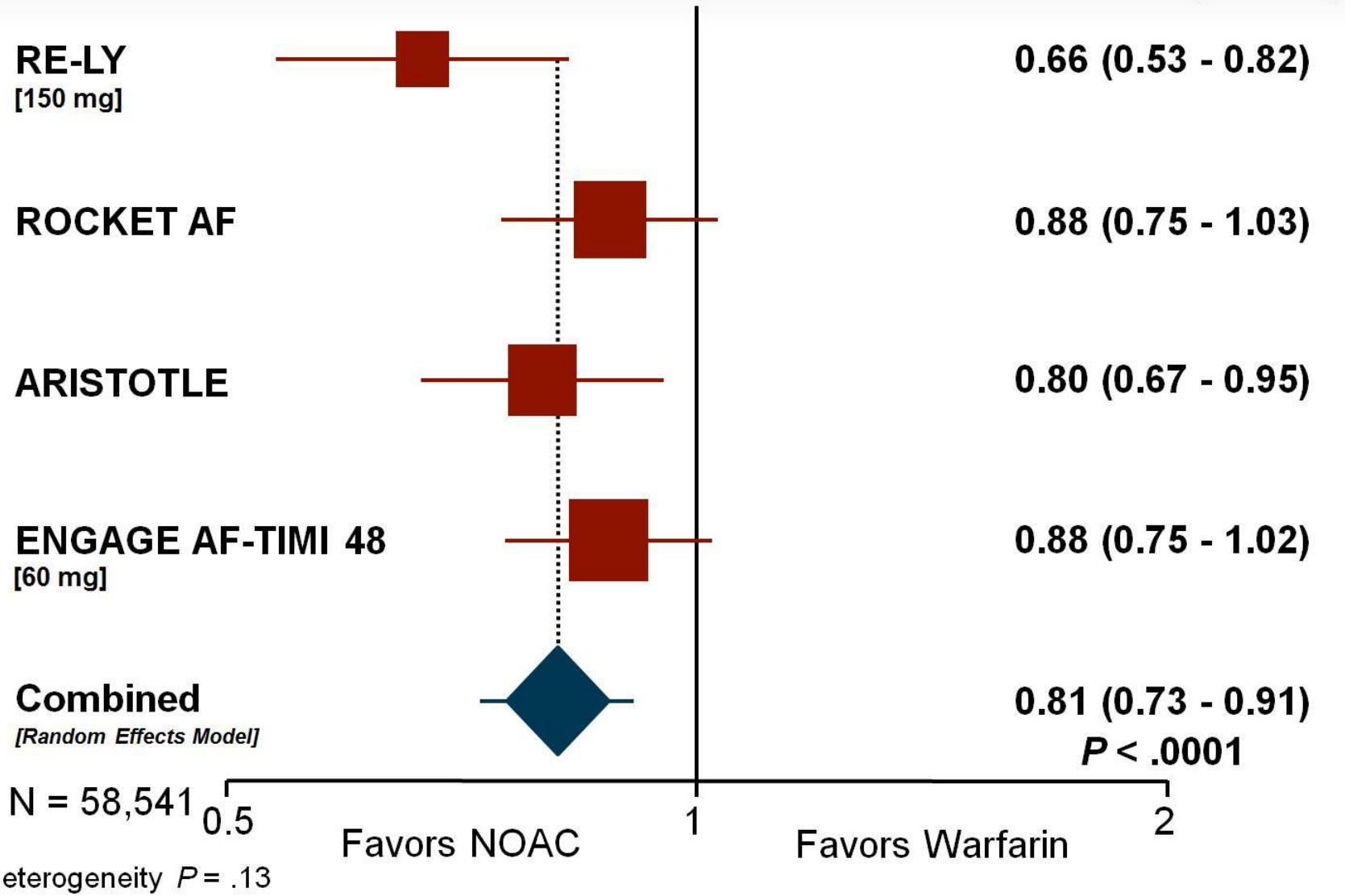


Connolly SJ, et al. *Circulation* 2008;118:2029-2037.[31]

TTR Consideraciones

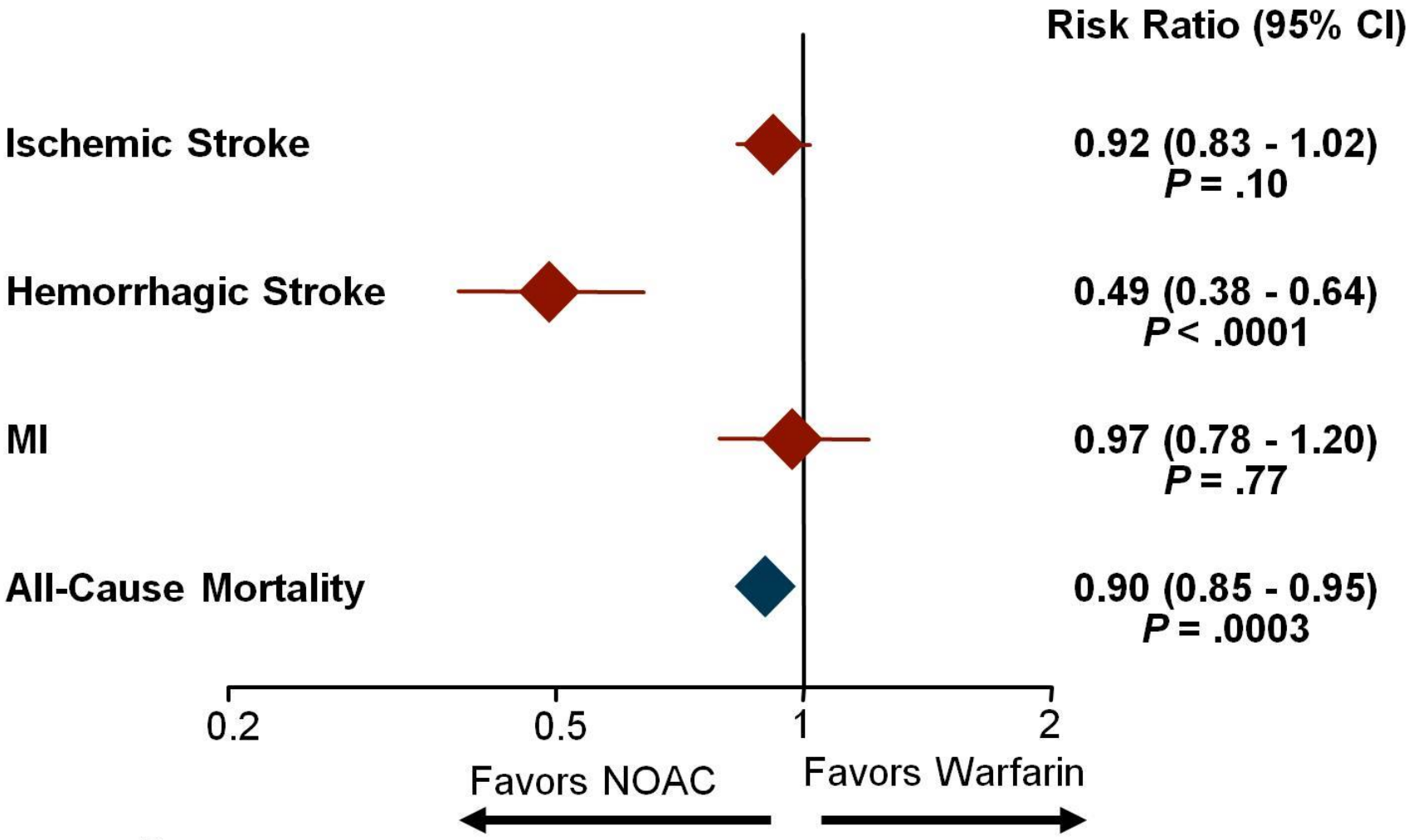
- En el RELY conocer que tomaban warfarina pudo contribuir a un mejor TTR.
- TTR del ROCKET aunque bajo (mas beneficio esperado del NACO) se acerca a la realidad de los registros clínicos. El TTR del ENGAGE es el más alto y supondría un peor resultado para el NACO.
- En el objetivo primario no se observaron diferencias en cuanto a la eficacia de los NACOS frente a warfarina a pesar del TTR.
- Sin embargo en las hemorragias mayores no hubo diferencias en el beneficio del NACO en el ARISTOTLE y en el ENGAGE a pesar de diferentes TTR. Pero el efecto beneficioso del fármaco se diluyo en el RELY y en el ROCKET cuando el TTR era bajo.

All NOACs
Stroke or SEE



Ruff CT, et al. *Lancet*. 2013;Early Online Publication.[30]

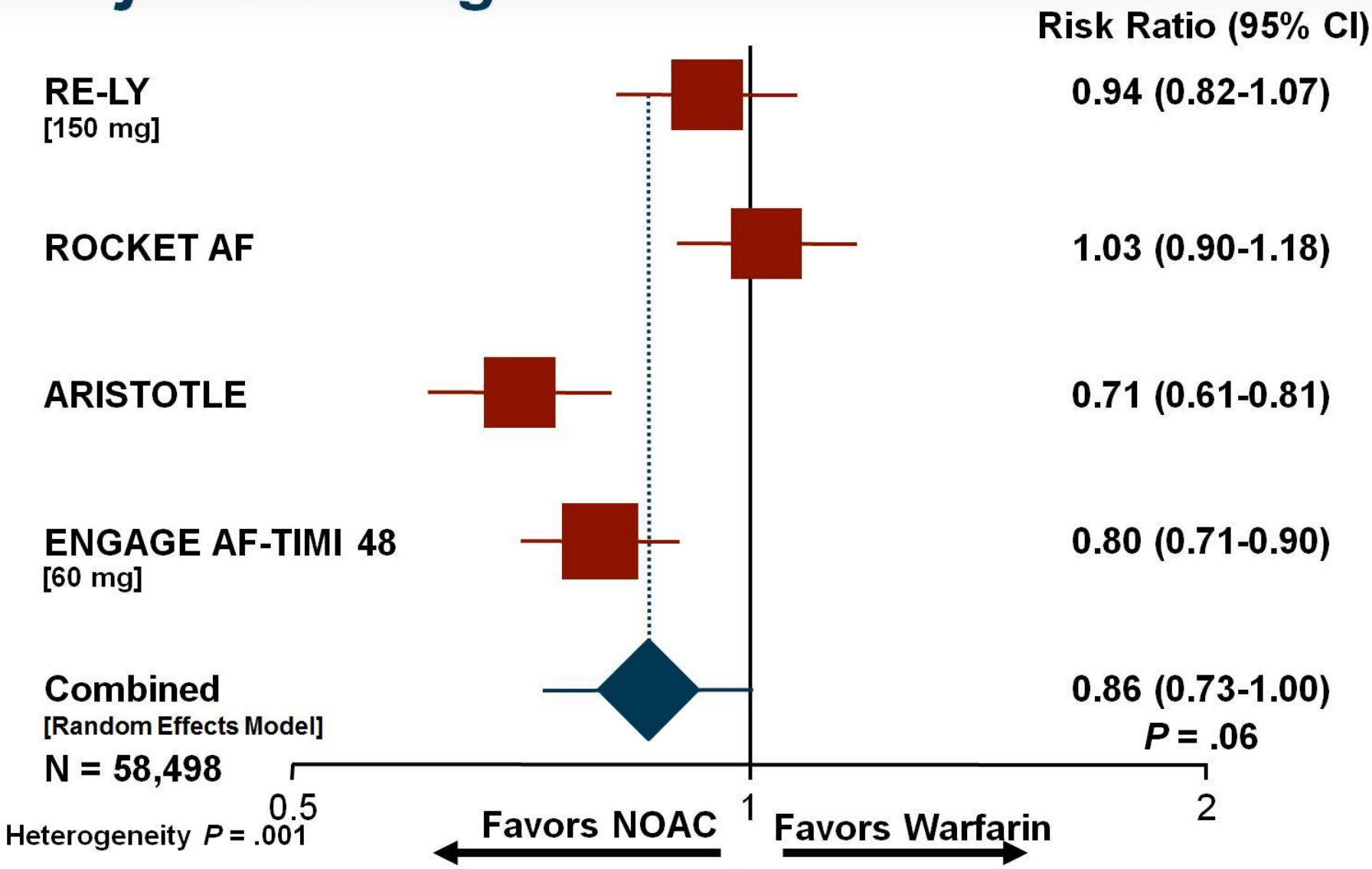
Secondary Efficacy Outcomes



Heterogeneity P = NS for all outcomes

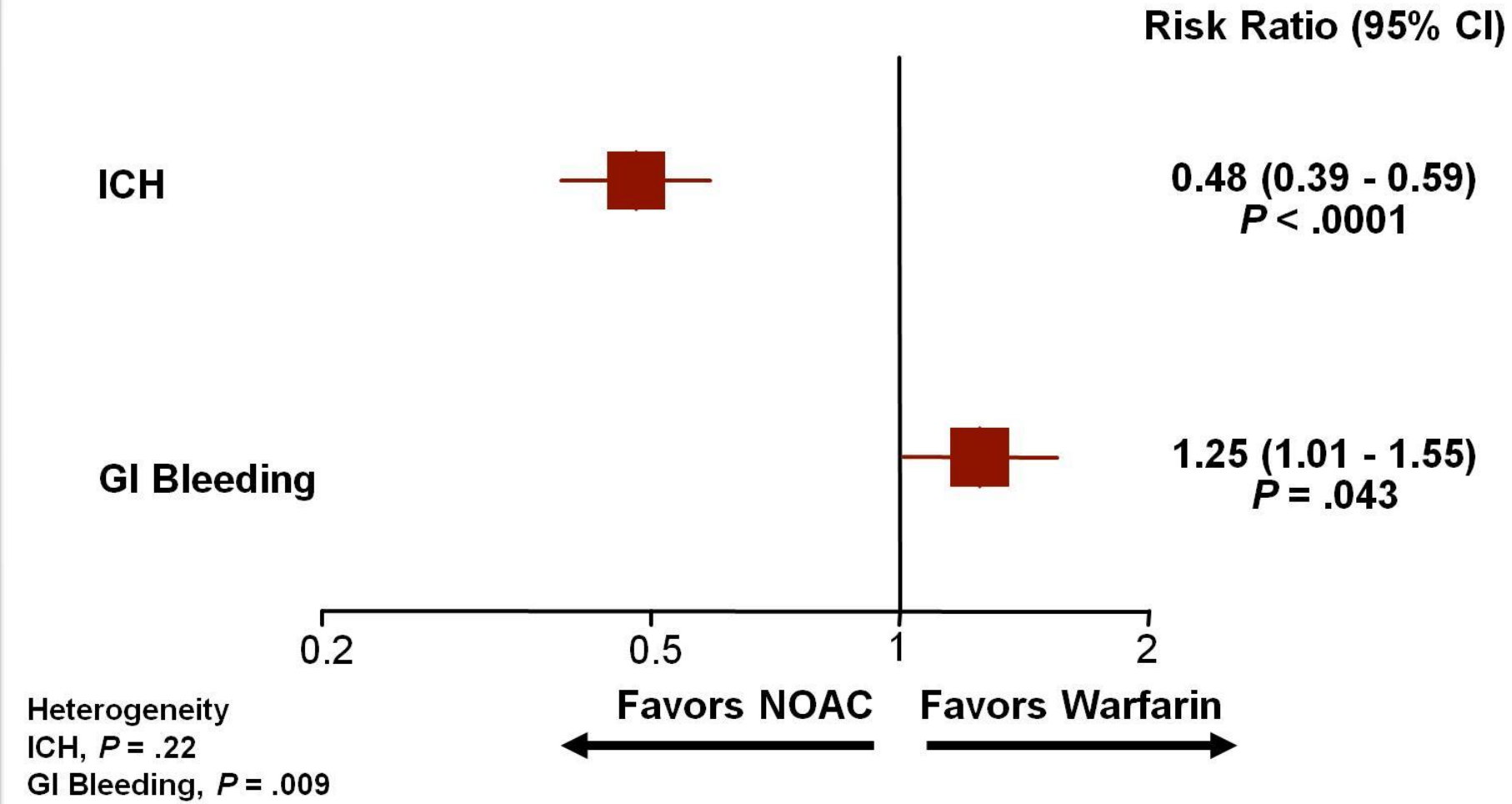
Ruff CT, et al. *Lancet*. 2013;Early Online Publication.[30]

All NOACs
Major Bleeding



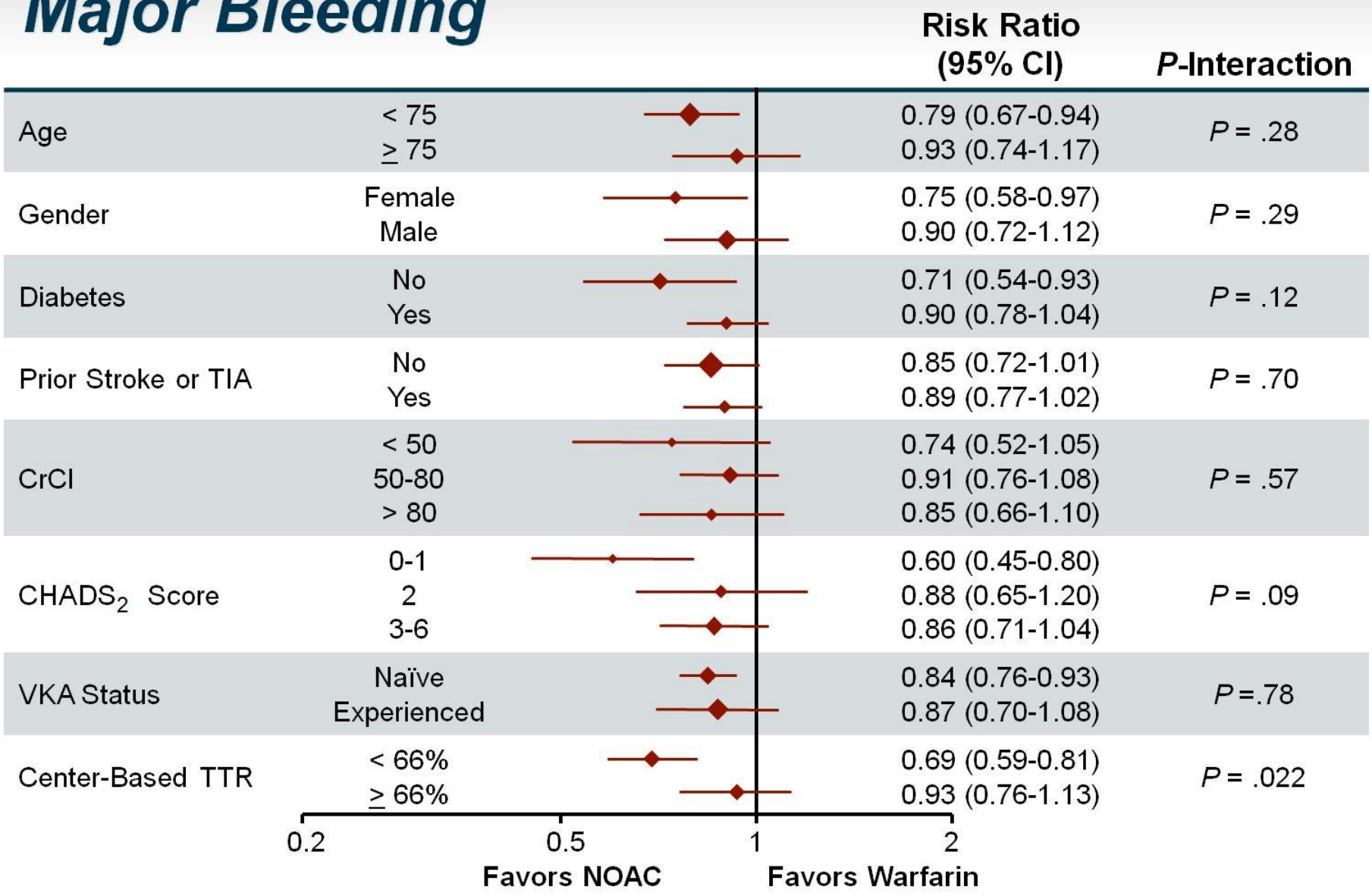
Ruff CT, et al. *Lancet*. 2013;Early Online Publication.[30]

Secondary Safety Outcomes



Ruff CT, et al. *Lancet*. 2013;Early Online Publication.[30]

Subgroups
Major Bleeding



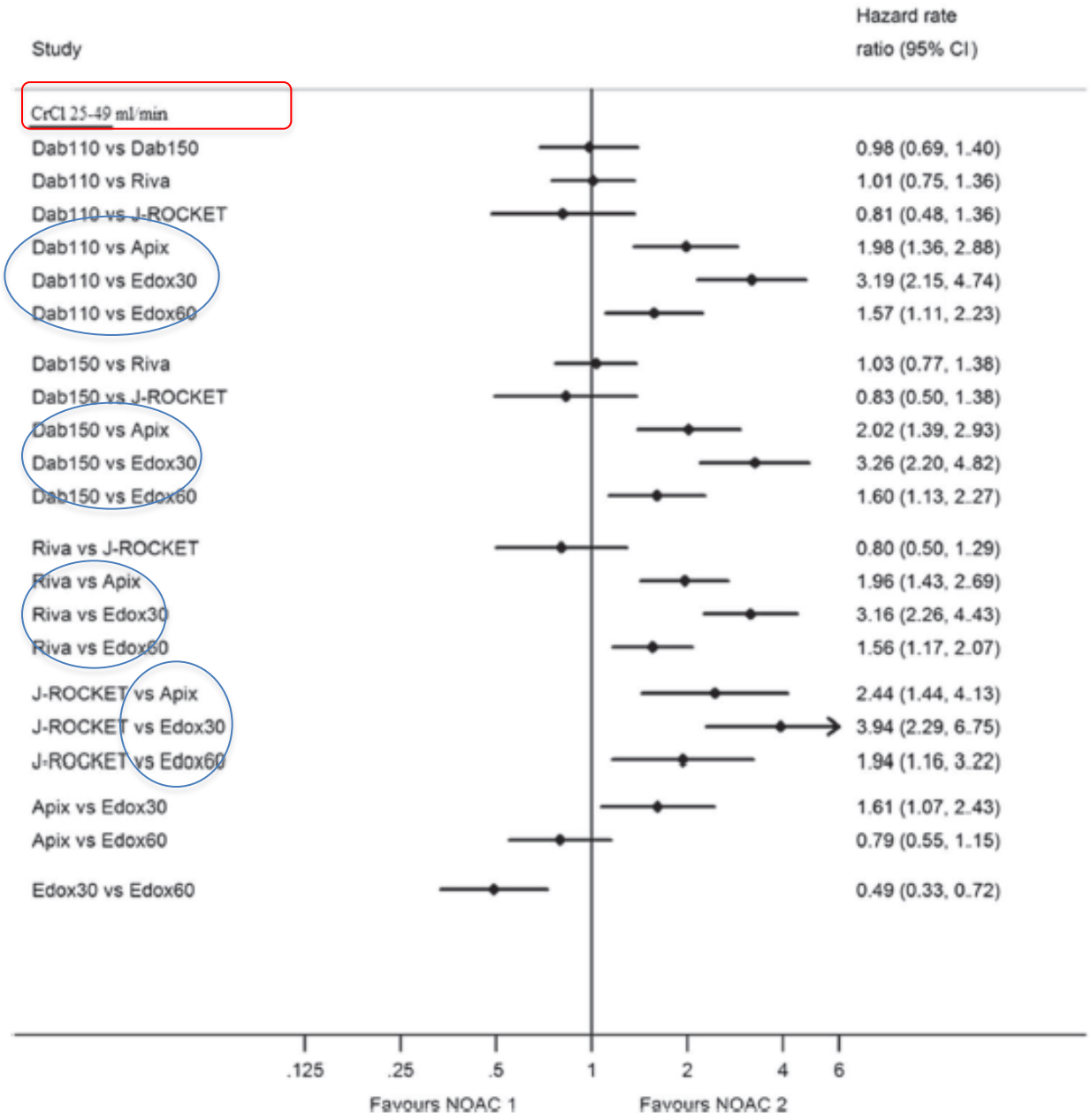
Ruff CT, et al. *Lancet*. 2013;Early Online Publication.[30]

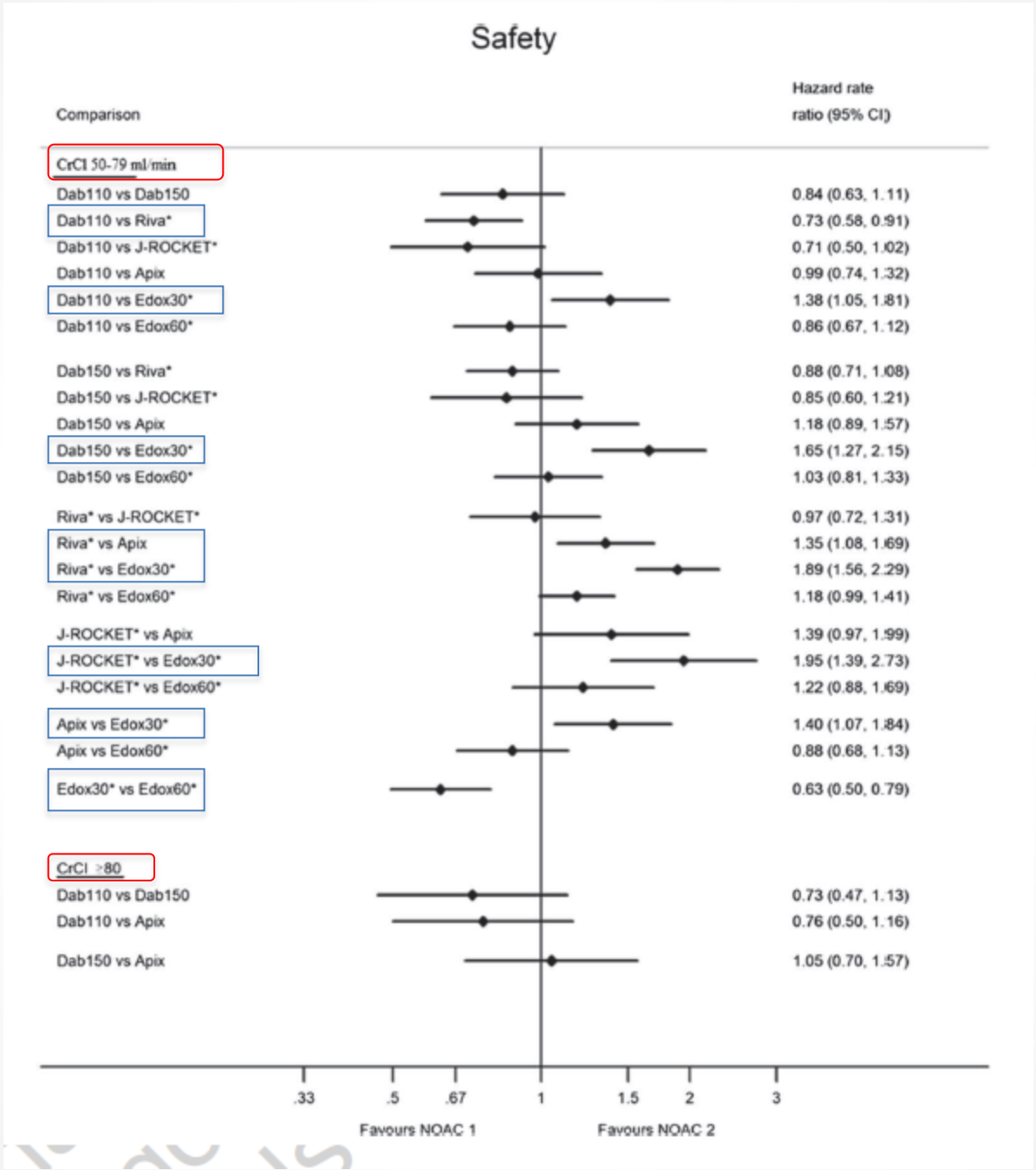
Renal function and non-vitamin K oral anticoagulants in comparison with warfarin on safety and efficacy outcomes in atrial fibrillation patients: a systemic review and meta-regression analysis

Clin Res Cardiol 2014

	Moderate renal impairment (95 % CI)	Mild renal impairment (95 % CI)	Non renal impairment (95 % CI)
Safety			
Dabigatran 110 [39]	0.99[b] (0.77–1.28)	0.76 (0.62–0.94)	0.61[c] (0.44–0.84)
Dabigatran 150 [39]	1.01[b] (0.79–1.30)	0.91 (0.75–1.11)	0.84[c] (0.62–1.13)
Rivaroxaban [40]	0.98[b] (0.84–1.14)	NR	1.04[d] (0.96–1.13)
J-ROCKET [41]	1.22[b] (0.78–1.91)	NR	1.07[d] (0.80–1.43)
Apixaban [30]	0.50[a] (0.38–0.66)	0.77 (0.65–0.94)	0.80[d] (0.61–1.04)
Edoxaban 30 [9]	0.31[b] (0.23–0.42)[e]	NR	0.55[d] (0.46–0.65)[f]
Edoxaban 60 [9]	0.63[b] (0.50–0.81)[e]	NR	0.88[d] (0.76–1.03)[f]
Efficacy			
Dabigatran 110 [39]	0.85[b] (0.59–1.24)	0.93 (0.70–1.23)	0.84[d] (0.54–1.32)
Dabigatran 150 [39]	0.56[b] (0.37–0.85)	0.68 (0.50–0.92)	0.67[d] (0.42–1.09)
Rivaroxaban [40]	0.84[b] (0.57—1.23)	NR	0.78[d] (0.63–0.98)
J-ROCKET [41]	0.82[b] (0.25–2.69)	NR	0.36[d] (0.14–0.93)
Apixaban [30]	0.79[a] (0.55–1.14)	0.74 (0.56–0.97)	0.88[c] (0.64–1.22)
Edoxaban 30 [9]	1.17[b] (0.92–1.45)[e]	NR	1.10[d] (0.92–1.32)[f]
Edoxaban 60 [9]	0.86[b] (0.68–1.15)[e]	NR	0.87[d] (0.82–1.05)[f]

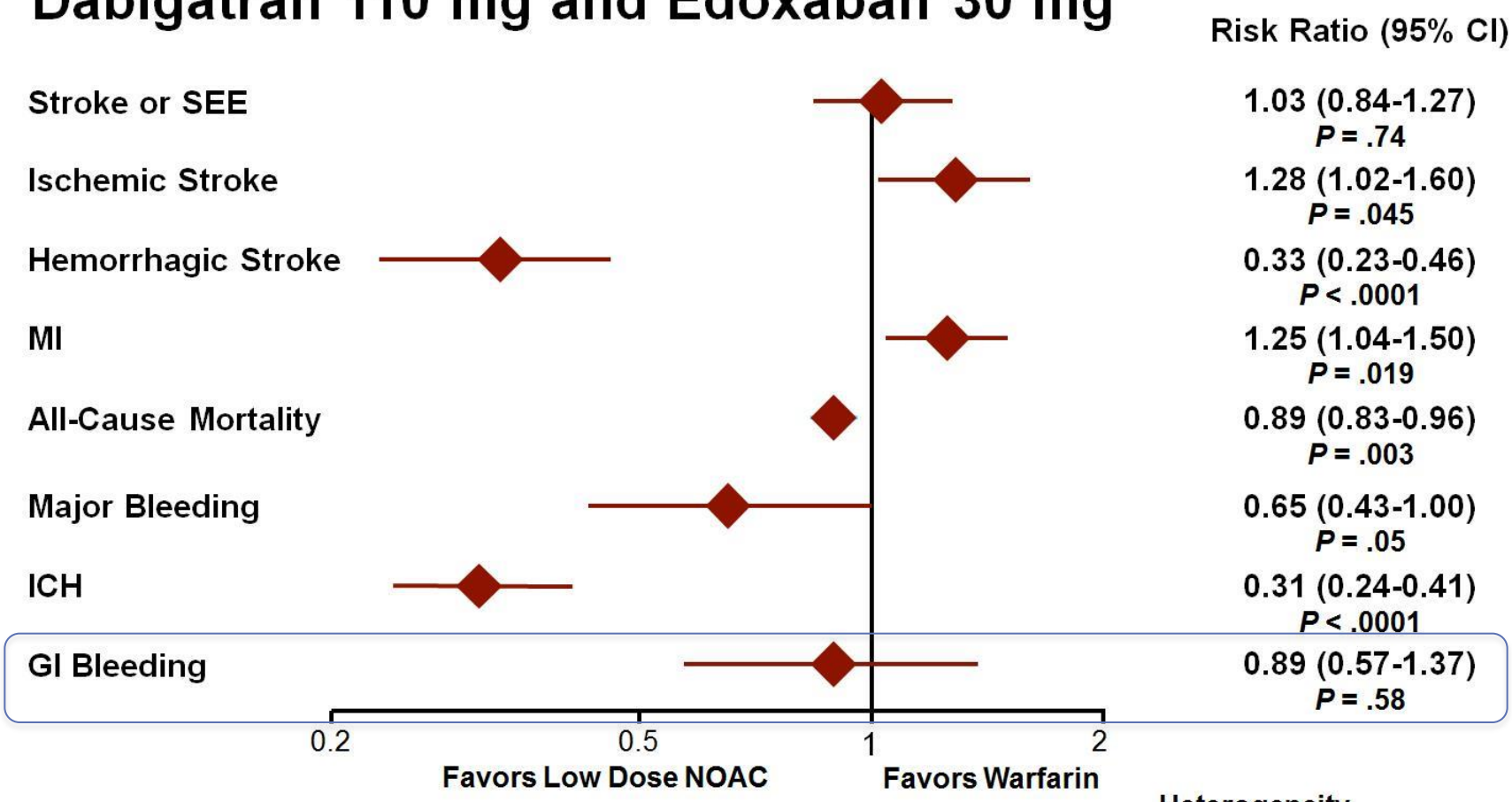
Safety


Study
Hazard rate ratio (95% CI)
CrCl 25-49 ml/min
Dab110 vs Dab150
0.98 (0.69, 1.40)
Dab110 vs Riva
1.01 (0.75, 1.36)
Dab110 vs J-ROCKET
0.81 (0.48, 1.36)
Dab110 vs Apix
1.98 (1.36, 2.88)
Dab110 vs Edox30
3.19 (2.15, 4.74)
Dab110 vs Edox60
1.57 (1.11, 2.23)
Dab150 vs Riva
1.03 (0.77, 1.38)
Dab150 vs J-ROCKET
0.83 (0.50, 1.38)
Dab150 vs Apix
2.02 (1.39, 2.93)
Dab150 vs Edox30
3.26 (2.20, 4.82)
Dab150 vs Edox60
1.60 (1.13, 2.27)
Riva vs J-ROCKET
0.80 (0.50, 1.29)
Riva vs Apix
1.96 (1.43, 2.69)
Riva vs Edox30
3.16 (2.26, 4.43)
Riva vs Edox60
1.56 (1.17, 2.07)
J-ROCKET vs Apix
2.44 (1.44, 4.13)
J-ROCKET vs Edox30
3.94 (2.29, 6.75)
J-ROCKET vs Edox60
1.94 (1.16, 3.22)
Apix vs Edox30
1.61 (1.07, 2.43)
Apix vs Edox60
0.79 (0.55, 1.15)
Edox30 vs Edox60
0.49 (0.33, 0.72)
.125
.25
.5
1
2
4
6
Favours NOAC 1
Favours NOAC 2


Safety
Comparison
Hazard rate ratio (95% CI)
CrCl 50-79 ml/min
Dab110 vs Dab150
0.84 (0.63, 1.11)
Dab110 vs Riva*
0.73 (0.58, 0.91)
Dab110 vs J-ROCKET*
0.71 (0.50, 1.02)
Dab110 vs Apix
0.99 (0.74, 1.32)
Dab110 vs Edox30*
1.38 (1.05, 1.81)
Dab110 vs Edox60*
0.86 (0.67, 1.12)
Dab150 vs Riva*
0.88 (0.71, 1.08)
Dab150 vs J-ROCKET*
0.85 (0.60, 1.21)
Dab150 vs Apix
1.18 (0.89, 1.57)
Dab150 vs Edox30*
1.65 (1.27, 2.15)
Dab150 vs Edox60*
1.03 (0.81, 1.33)
Riva* vs J-ROCKET*
0.97 (0.72, 1.31)
Riva* vs Apix
1.35 (1.08, 1.69)
Riva* vs Edox30*
1.89 (1.56, 2.29)
Riva* vs Edox60*
1.18 (0.99, 1.41)
J-ROCKET* vs Apix
1.39 (0.97, 1.99)
J-ROCKET* vs Edox30*
1.95 (1.39, 2.73)
J-ROCKET* vs Edox60*
1.22 (0.88, 1.69)
Apix vs Edox30*
1.40 (1.07, 1.84)
Apix vs Edox60*
0.88 (0.68, 1.13)
Edox30* vs Edox60*
0.63 (0.50, 0.79)
CrCl >80
Dab110 vs Dab150
0.73 (0.47, 1.13)
Dab110 vs Apix
0.76 (0.50, 1.16)
Dab150 vs Apix
1.05 (0.70, 1.57)
.33
.5
.67
1
1.5
2
3
Favours NOAC 1
Favours NOAC 2

Low Dose Regimens
Efficacy and Safety Outcomes

Dabigatran 110 mg and Edoxaban 30 mg



N = 26,107

Heterogeneity
P = NS for outcomes except:
Major Bleeding, *P* = < .001
GI Bleeding, *P* = .01

Ruff CT, et al. *Lancet*. 2013;Early Online Publication.[30]

ENGAGE

Table 3. Safety and Net Clinical End Points.*

Outcome	Warfarin (N=7012)		High-Dose Edoxaban (N=7012)		High-Dose Edoxaban vs. Warfarin		Low-Dose Edoxaban (N=7002)		Low-Dose Edoxaban vs. Warfarin	
					Hazard Ratio (95% CI)	P Value			Hazard Ratio (95% CI)	P Value
	no. of patients with event	*% of patients/yr*	*no. of patients with event*	*% of patients/yr*			*no. of patients with event*	*% of patients/yr*		
Major bleeding	524	3.43	418	2.75	0.80 (0.71–0.91)	<0.001	254	1.61	0.47 (0.41–0.55)	<0.001
Fatal	59	0.38	32	0.21	0.55 (0.36–0.84)	0.006	21	0.13	0.35 (0.21–0.57)	<0.001
Bleeding into a critical organ or area	211	1.36	108	0.70	0.51 (0.41–0.65)	<0.001	69	0.44	0.32 (0.24–0.42)	<0.001
Overt bleeding with blood loss of ≥2 g/dl	327	2.13	317	2.08	0.98 (0.84–1.14)	0.78	187	1.19	0.56 (0.47–0.67)	<0.001
Any intracranial bleeding	132	0.85	61	0.39	0.47 (0.34–0.63)	<0.001	41	0.26	0.30 (0.21–0.43)	<0.001
Fatal intracranial bleeding	42	0.27	24	0.15	0.58 (0.35–0.95)	0.03	12	0.08	0.28 (0.15–0.53)	<0.001
Gastrointestinal bleeding	190	1.23	232	1.51	1.23 (1.02–1.50)	0.03	129	0.82	0.67 (0.53–0.83)	<0.001
Upper gastrointestinal tract	111	0.71	140	0.91	1.27 (0.99–1.63)	0.06	88	0.56	0.78 (0.59–1.03)	0.08
Lower gastrointestinal tract	81	0.52	96	0.62	1.20 (0.89–1.61)	0.23	44	0.28	0.54 (0.37–0.77)	<0.001
Bleeding in other location	211	1.37	131	0.85	0.62 (0.50–0.78)	<0.001	87	0.55	0.40 (0.31–0.52)	<0.001
Bleeding during transition to open-label oral anticoagulation therapy										
Day 1–14	6	—	4	—	—	—	5	—	—	—
Day 15–30	5	—	6	—	—	—	13	—	—	—
Life-threatening bleeding	122	0.78	62	0.40	0.51 (0.38–0.70)	<0.001	40	0.25	0.32 (0.23–0.46)	<0.001
Clinically relevant nonmajor bleeding	1396	10.15	1214	8.67	0.86 (0.79–0.93)	<0.001	969	6.60	0.66 (0.60–0.71)	<0.001
Minor bleeding	714	4.89	604	4.12	0.84 (0.76–0.94)	0.002	533	3.52	0.72 (0.65–0.81)	<0.001
Major or clinically relevant nonmajor bleeding	1761	13.02	1528	11.10	0.86 (0.80–0.92)	<0.001	1161	7.97	0.62 (0.57–0.67)	<0.001
Any overt bleeding	2114	16.40	1865	14.15	0.87 (0.82–0.92)	<0.001	1499	10.68	0.66 (0.62–0.71)	<0.001
Net clinical outcome†										
Primary	1462	8.11	1323	7.26	0.89 (0.83–0.96)	0.003	1248	6.79	0.83 (0.77–0.90)	<0.001
Secondary	987	5.23	883	4.64	0.88 (0.81–0.97)	0.008	837	4.38	0.83 (0.76–0.91)	<0.001
Tertiary	1123	6.02	999	5.30	0.88 (0.81–0.96)	0.003	1010	5.37	0.89 (0.82–0.97)	0.007

ARISTOTLE

Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

RELY

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

MEDICARE Graham, Circ 2014
Dabigatran 150mg/12h

	No. events		Incidence rate per 1000 person-years		Adjusted hazard ratio (95% CI)	P-value
	Dabigatran	Warfarin	Dabigatran	Warfarin		
Primary outcomes						
Ischemic stroke	205	270	11.3	13.9	0.80 (0.67-0.96)	0.02
Major hemorrhage	777	851	42.7	43.9	0.97 (0.88-1.07)	0.50
Gastrointestinal	623	513	34.2	26.5	1.28 (1.14-1.44)	< 0.001
Intracranial	60	186	3.3	9.6	0.34 (0.26-0.46)	< 0.001
Intracerebral	44	142	2.4	7.3	0.33 (0.24-0.47)	< 0.001
Acute myocardial infarction	285	327	15.7	16.9	0.92 (0.78-1.08)	0.29
Secondary outcomes						
All hospitalized bleeds	1079	1139	59.3	58.8	1.00 (0.92-1.09)	0.97
Mortality*	603	744	32.6	37.8	0.86 (0.77-0.96)	0.006

* For 1,064 deaths not preceded by a primary study outcome, the adjusted hazard ratio (95% CI) was 0.89 (0.79-1.00), p=0.051, while for 283 deaths occurring within 30 days after a primary outcome, the adjusted hazard ratio (95% CI) was 0.77 (0.61-0.98), p=0.03.

because of lower rates of hemorrhagic stroke and other intracranial bleeding. In contrast, bleeding from gastrointestinal sites, including upper, lower, and rectal sites, occurred more frequently in the rivaroxaban group, as did bleeding that led to a drop in the hemoglobin level or bleeding that required transfusion. Even though patients in our trial were at increased risk for bleeding events, rates of major bleeding were similar to those in other recent studies involving patients with atrial fibrillation.[4,15,22,23]

Gastrointestinal Bleeding in Patients With Atrial Fibrillation Treated With Rivaroxaban or Warfarin

ROCKET AF Trial

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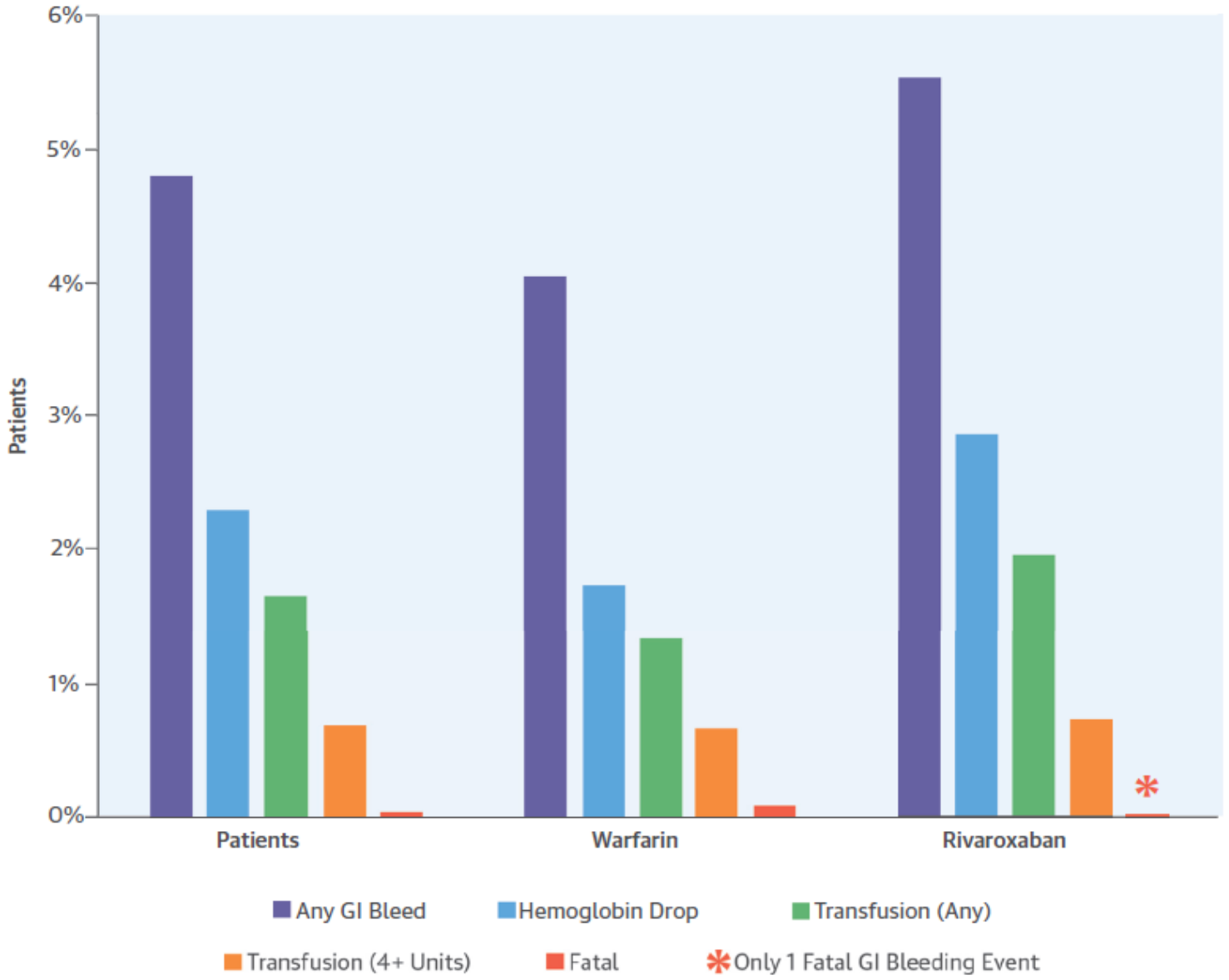
TABLE 3 Overall Rates of GI Bleeding by Treatment Arm

Outcomes	Rivaroxaban (n = 7,111) Events/100 Patient-Years (Total Events)	Warfarin (n = 7,125) Events 100/Patient-Years (Total Events)	Rivaroxaban vs. Warfarin Adjusted HR (95% CI)*	p Value
Major or NMCR bleeding	3.61 (394)	2.60 (290)	1.42 (1.22–1.66)	<0.0001
Major bleeding	2.00 (221)	1.24 (140)	1.66 (1.34–2.05)	<0.0001
Hemoglobin drop ≥2 g/dl	1.84 (204)	1.11 (125)	1.69 (1.35–2.12)	<0.0001
Transfusion	1.27 (141)	0.85 (96)	1.56 (1.20–2.02)	0.0010
Transfusion ≥4 U	0.47 (52)	0.41 (47)	1.19 (0.80–1.77)	0.39
Fatal	0.01 (1)	0.04 (5)	0.21 (0.02–1.76)	0.15
NMCR	1.75 (193)	1.39 (156)	1.28 (1.43–1.59)	0.023

*Hazard ratios (HRs) and p values are from Cox proportional hazards models that include randomized treatment and all identified predictors of major or nonmajor clinical bleeding (NMCR) GI bleeding (Table 5).

CI = confidence interval; other abbreviation as in Table 1.

CENTRAL ILLUSTRATION **GI Bleeding in ROCKET AF Trial: Histogram of the Distribution of GI Bleeding Stratified by Treatment Arm**



Sherwood, M.W. et al. J Am Coll Cardiol. 2015; 66(21):2271–81.

XANTUS

Major bleeding	128 (1.9)	2.1 (1.8–2.5)
Fatal	12 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	43 (0.6)	0.7 (0.5–0.9)
Intracranial haemorrhage	26 (0.4)	0.4 (0.3–0.6)
Intraparenchymal	6 (0.1)	
Subarachnoid	5 (0.1)	
Intraventricular	6 (0.1)	
Subdural haematoma	6 (0.1)	
Epidural haematoma	1 (<0.05)	
Haemorrhagic transformation of ischaemic stroke	3 (<0.05)	
Missing	2 (<0.05)	
Mucosal bleeding[a]	60 (0.9)	1.0 (0.7–1.3)
Gastrointestinal	52 (0.8)	0.9 (0.6–1.1)
Haemoglobin decrease ≥2 g/dL[b]	52 (0.8)	0.9 (0.6–1.1)
Transfusion of ≥2 units of packed red blood cells or whole blood[b]	53 (0.8)	0.9 (0.6–1.1)
Non-major bleeding events	878 (12.9)	15.4 (14.4–16.5)

Conclusions

- NOACs significantly reduce stroke (↓19%)
  - Primarily driven by reduction in hemorrhagic stroke (↓51%)
- NOACs significantly reduce mortality (↓10%)
- Trend toward less bleeding
  - Substantial reduction in ICH (↓52%)
  - Increased GI bleeding (↑25%)
- The relative efficacy and safety of NOACs consistent across a wide spectrum of AF patients
  - Even less bleeding when INR not as well controlled
- Low-dose NOAC regimens reduce mortality and have a very favorable bleeding profile but more ischemic events *
- Differences in agents, patients, and trials may not be accounted for
  - Heterogeneity major bleeding and GI bleeding

Más conclusiones

- No pudiendo decir que NACO es mejor que otro, deberiamos plantear, en aras a la seguridad, la indicación por perfiles de pacientes.
- Nuevos estudios en marcha nos darán las respuestas que necesitamos.

"Pointers*" Towards which NOAC to Choose

Specific patient characteristics

High risk of bleeding, e.g. HAS-BLED ≥ 3; very old	Consider agent / dose with the lowest incidence of bleeding	Dabi 110, Edox 30, Apix
High risk of ischemic stroke, low bleeding risk	Consider agent / dose with the best reduction of ischemic stroke	Dabi 150
Previous stroke (secondary prevention)	Consider best investigated agent or greatest reduction of 2^0 stroke	Riva, Apix, Edox
CAD, previous MI or high-risk for ACS/MI	Consider agent with a positive effect in ACS	Riva?
Renal impairment	Consider agent least dependent on renal function	Apix, Edox 30 Riva 15
Concomitant CYP inhib.	Consider agents with no/little metabolism via CYP system	Dabi, Edox
Patient preference	Consider once daily formulation	Riva, Edox

Adapted from Savelieva I , Camm AJ. Clin Cardiol 2014;37:32-47 and Gonzalez-Quesada CJ , Giugliano RP. Am J Cardiovascular Drugs 2014;14:111-127

All of these "pointers" are debatable

¿Cual es la alternativa?