I NAO nella prevenzione del cardioembolismo nella fibrillazione atriale

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OSPEDALE GUGLIELMO DA SALICETO
PIACENZA

Il *sottoscritto Imberti Davide*

dichiara

di aver avuto negli ultimi due anni rapporti di consulenza con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *ALFA WASSERMANN*
- *BAYER*
- *BOHERINGER INGELHEIM*
- *DAIICHI-SANKYO*
- *ITALFARMACO*
- *KEDRION*
- *PFIZER*
- *SANOFI AVENTIS*

Features of novel oral anticoagulants

	Dabigatran[1]	Rivaroxaban[1,2]	Apixaban[1,3]	Edoxaban[4-6]
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to Cmax	1.25-3	2-4	3-4	1-2
CYP metabolism	None	32%	Yes	Minimal (<4%)
Bioavailability	6%	80%	60%	62%
Transporters	P-gp	P-gp/BCRP	P-gp/ BCRP	P-gp
Protein binding	35%	93%	87%	50%
Half-life	14-17 h	7-11 h	8-15 h	8-10 h
Renal elimination	80%	33%	25%	50%

BCRP, breast cancer resistance protein
CYP, cytochrome P450; P-gp, P-glycoprotein
NR, not reported

1. Eriksson et al. Clin Pharmacokinet 2009;48:1-22; 2. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2011; 3. ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK; 4. Ruff et al. Hot Topics in Cardiology 2009;18:1-32; 5. Matsushima et al. Am Assoc Pharm Sci 2011; abstract; 6. Ogata et al. J Clin Pharmacol 2010;50:743-53

NOAC AF studies

	RE-LY[1]	ROCKET-AF[2]	ARISTOTLE[3]	ENGAGE AF[4]
Drug	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
N	18,113	14,264	18,201	21,105
Dose (mg)	150, 110	20	5	60, 30
Frequency	BID	QD	BID	QD
Initial dose adjustment	No	20→15 mg	5→2.5 mg	60→30 mg 30→15 mg
Dose adjustment at baseline, %	0	21	5	25
Dose adjustment after randomization	No	No	No	Yes (7%)
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
Follow up (years)	2.0	1.9	1.8	2.8

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

1. Connolly et al. N Engl J Med 2009;361:1139–1151; 2. Patel et al. N Engl J Med 2011;365:883–891
3. Granger et al. N Engl J Med 2011;365:981–992; 4. Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Dose adjustment for patient characteristics in NOAC studies

RE-LY[1]	ROCKET-AF[2]	ARISTOTLE[3]	ENGAGE-AF[4]
• None	• 20→15 mg QD 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	• 60→30 mg QD or 30→15 mg QD for: – Creatinine clearance 30–50 mL/min – body weight ≤60 kg – Use of quinidine, verapamil or dronedarone

BID=twice daily; QD=once daily

1. Connolly et al. New Engl j Med 2009;361:1139–1151
2. Patel et al. N Engl J Med 2011;365:883–891
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La terapia con i NAO nei pazienti con FA non-valvolare

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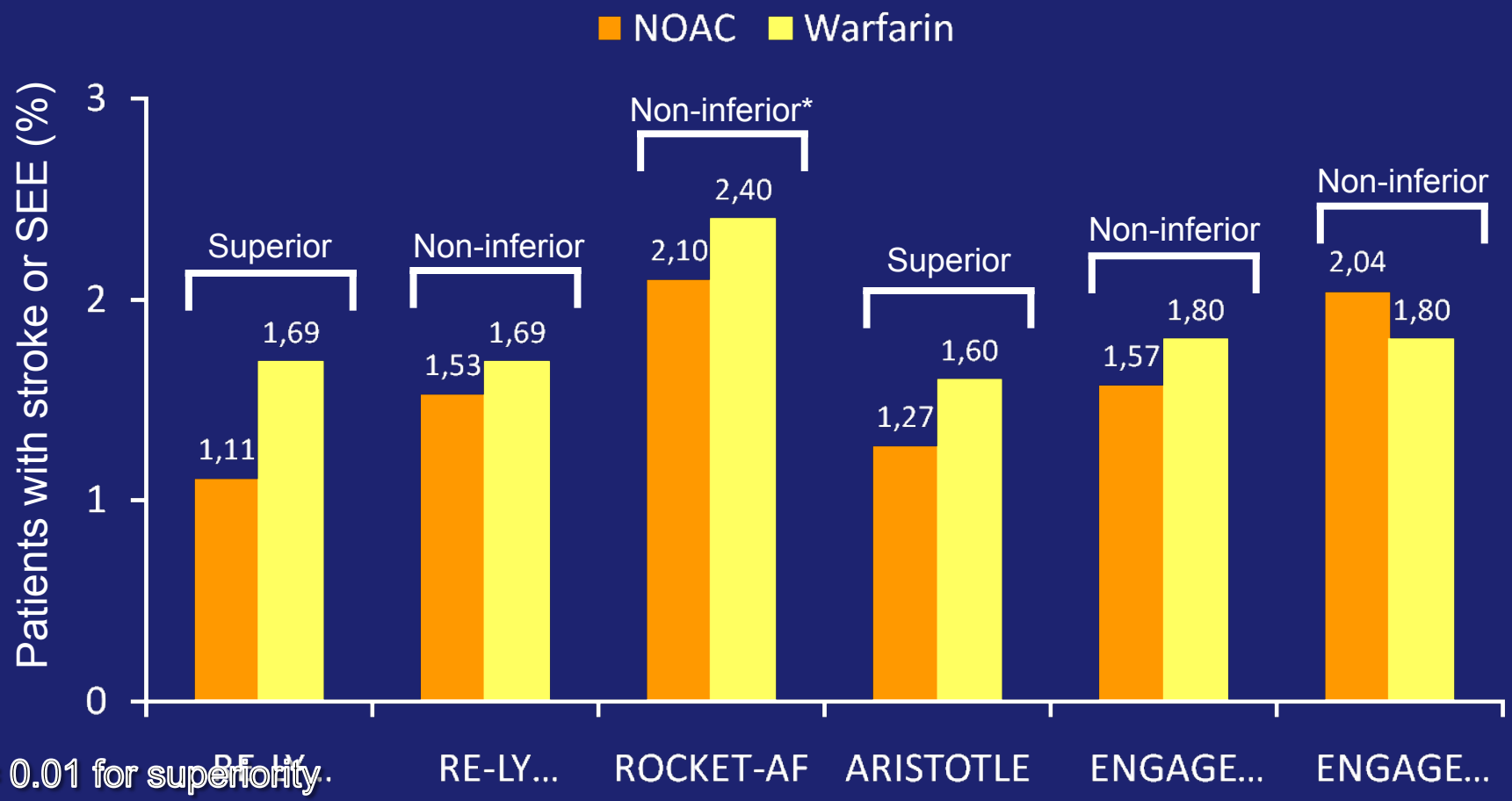
Phase III AF trials: ITT efficacy



p = 0.01 for superiority

1. Connolly et al. N Engl J Med 2009;361:1139–1151; 2. Patel et al. N Engl J Med 2011;365:883–891
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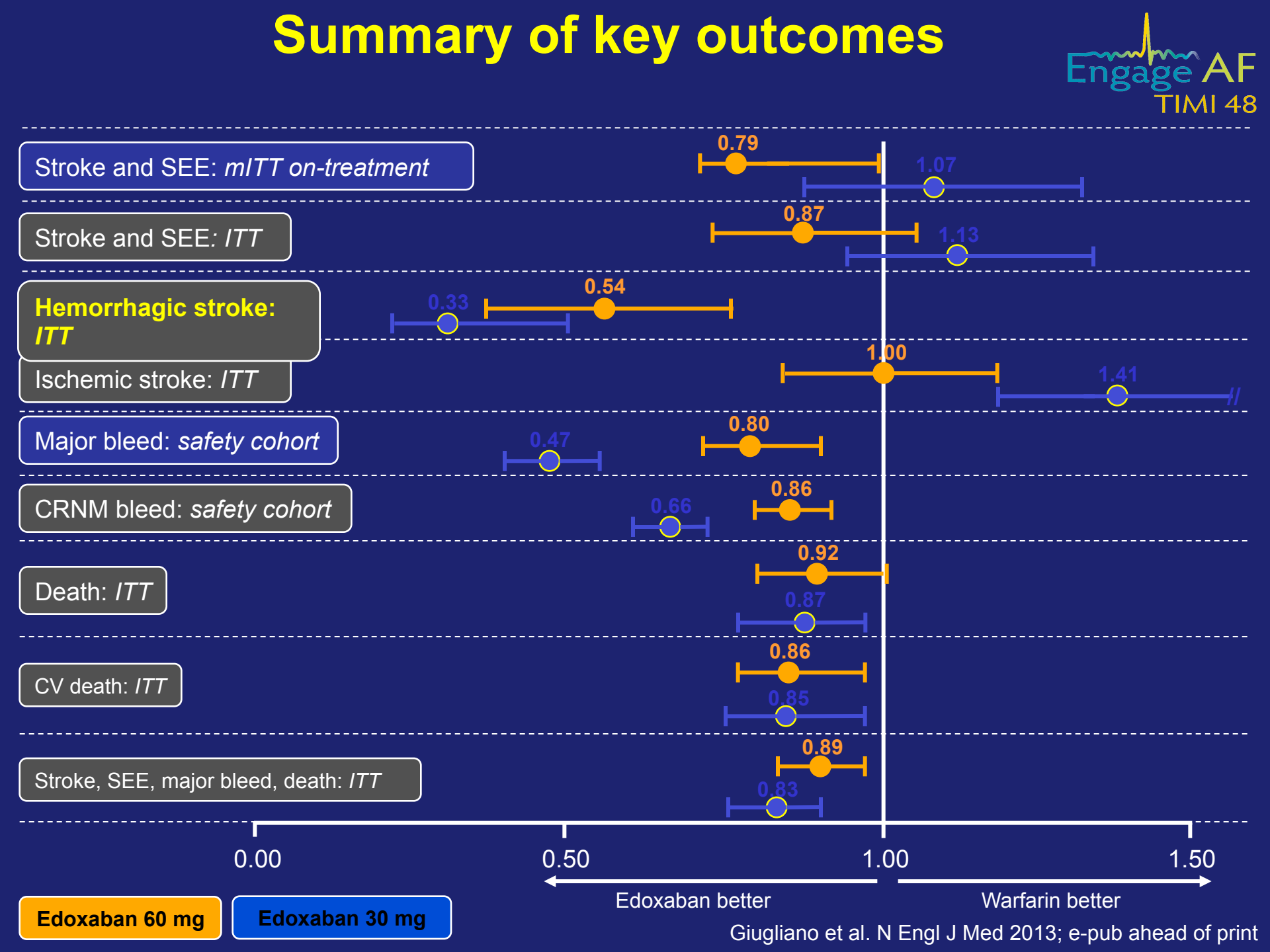
Hemorrhagic Stroke

		HR	ITT P-value
RELY			
Dabigatran 110 mg	0.12% / yr	0.31	<0.001
Dabigatran 150 mg	0.10% / yr	0.26	<0.001
Warfarin	0.38% / yr		
ROCKET			
Rivaroxaban 20 mg	0.26% / yr	0.59	0.012*
Warfarin	0.44% / yr		
ARISTOTLE			
Apixaban 5 mg	0.24% / yr	0.51	<0.001
Warfarin	0.47% / yr		

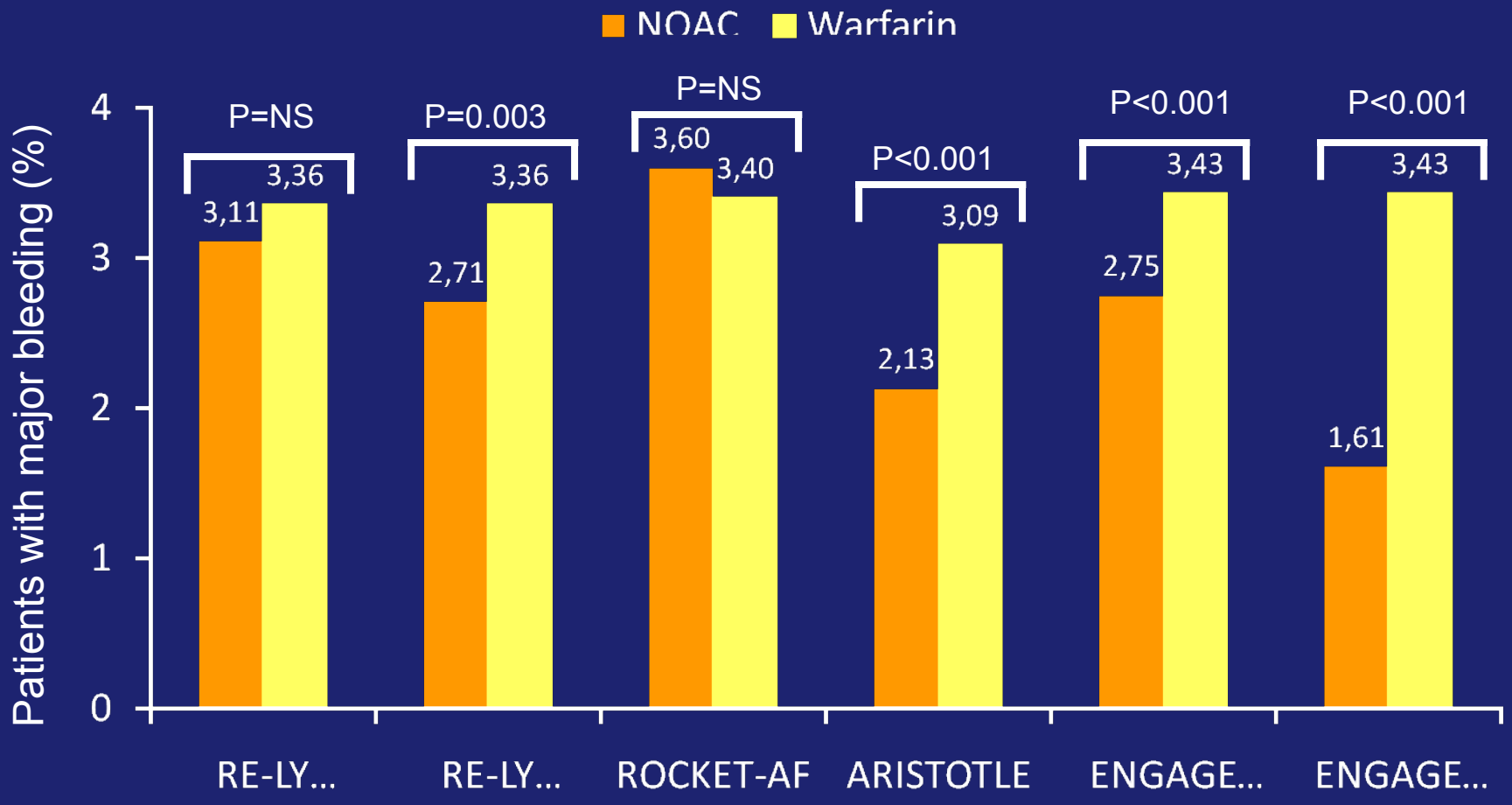
*In an on treatment analysis in Rocket AF Hemorrhagic Stoke rates were 0.26% / yr for rivaroxaban and 0.44% / yr for warfarin, p=0.024. No on treatment analysis is available from RE-LY.

Summary of key outcomes



Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Phase III AF trials: major bleeding



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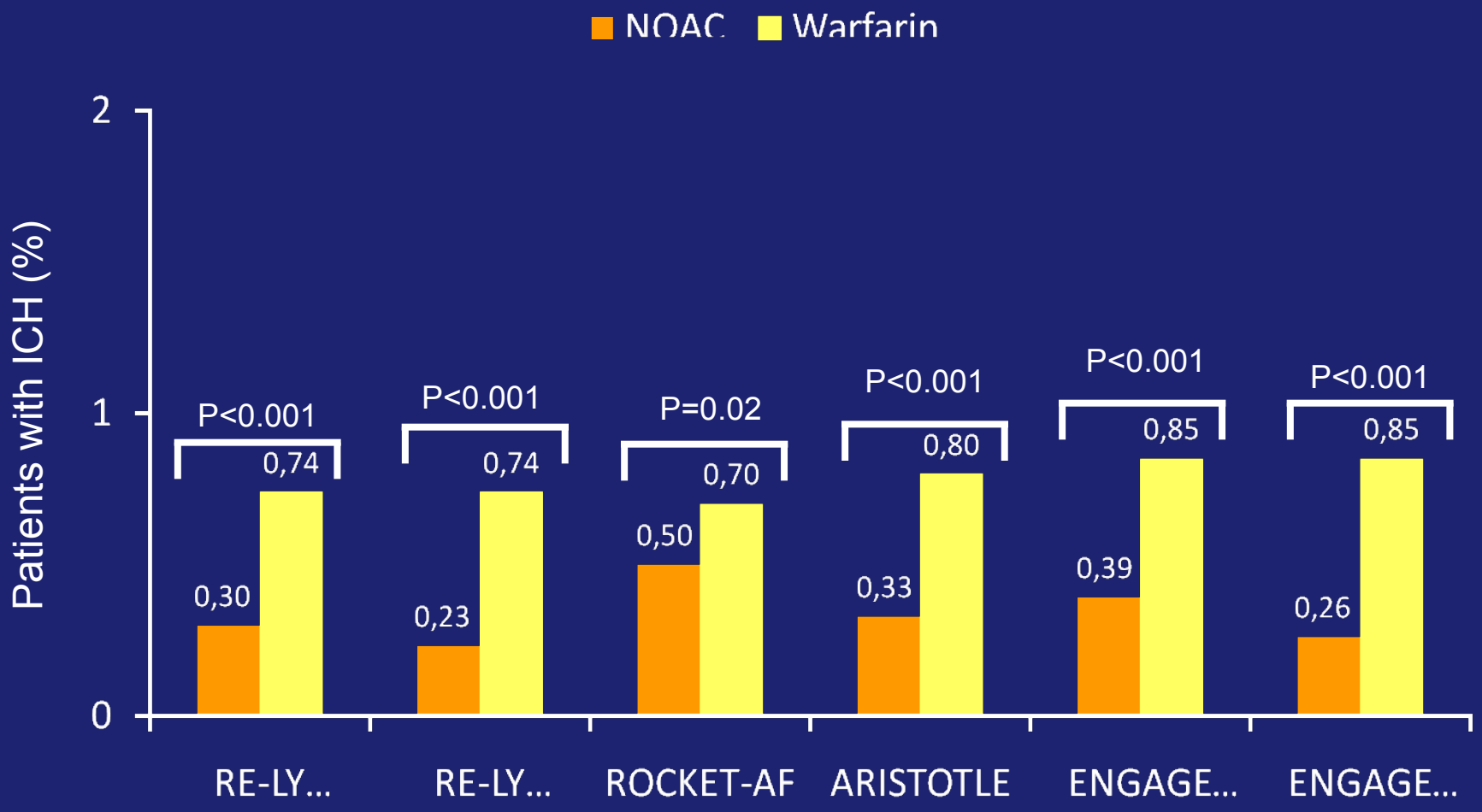
Phase III AF trials: intracranial hemorrhage



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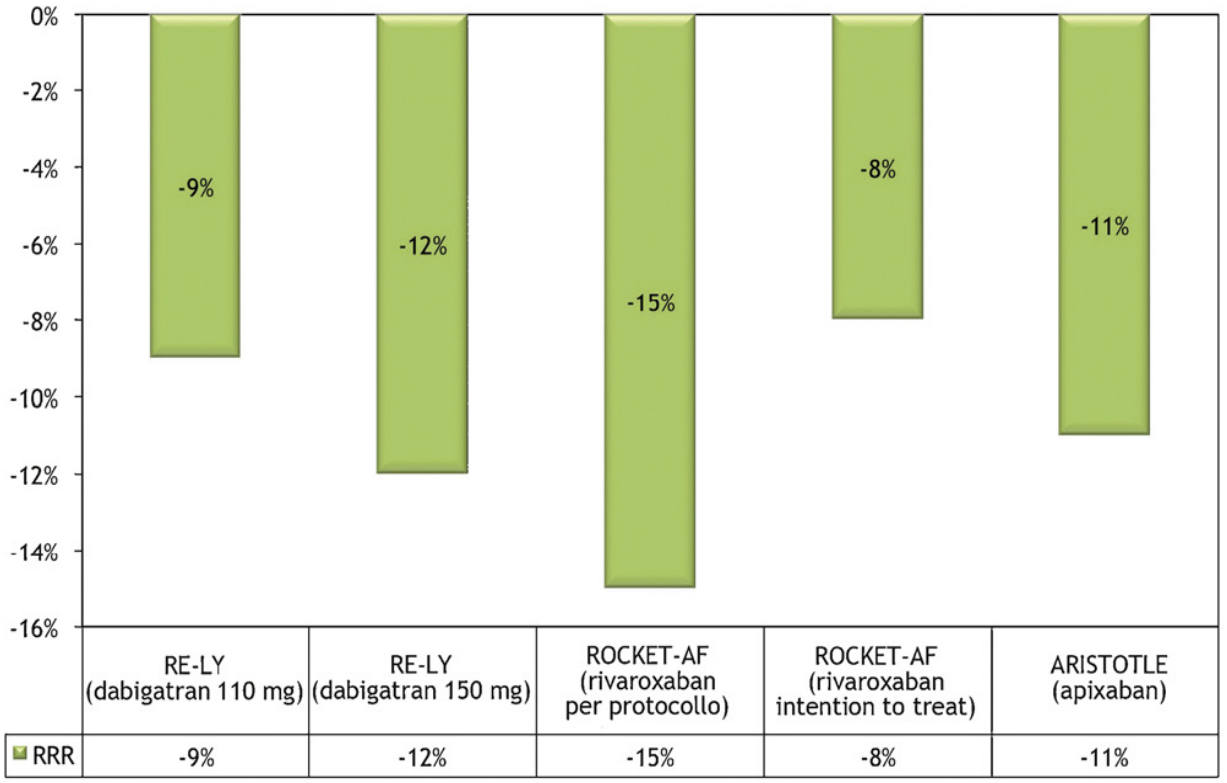
RRR della mortalità per tutte le cause rispetto al warfarin



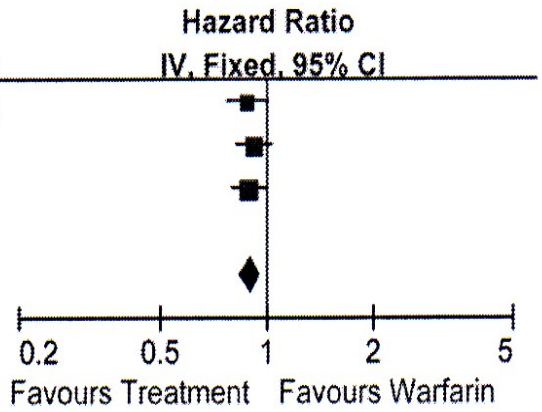
Masotti, Internal J Med, 2012

Survival benefit of new anticoagulants compared witf warfarin in patients with AF: a meta-analysis

A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
RELY	-0.128	0.067	26.6%	0.88 [0.77, 1.00]	2009
ROCKET AF	-0.083	0.058	35.4%	0.92 [0.82, 1.03]	2011
ARISTOTLE	-0.117	0.056	38.0%	0.89 [0.80, 0.99]	2011
Total (95% CI)			**100.0%**	**0.90 [0.84, 0.96]**	

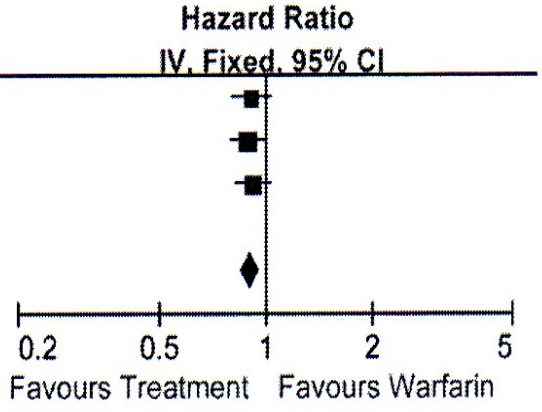
Heterogeneity: Chi² = 0.30, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)



B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
RELY (2)	-0.094	0.064	28.4%	0.91 [0.80, 1.03]	2009
ARISTOTLE	-0.117	0.056	37.1%	0.89 [0.80, 0.99]	2011
ROCKET AF	-0.083	0.058	34.6%	0.92 [0.82, 1.03]	2011
Total (95% CI)			**100.0%**	**0.91 [0.85, 0.97]**	

Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)



Liu, Int J Cardiol, 2012

Key secondary outcomes

Engage AF TIMI 48

Outcome	Warfarin (n=7,036)		Edoxaban 60 mg (n=7,035)		Edoxaban 60 mg versus warfarin		Edoxaban 30 mg (n=7,034)		Edoxaban 30 mg versus warfarin	
	n	%/yr	n	%/yr	HR (95% CI)	P	n	%/yr	HR (95% CI)	P
Stroke, SEE, CV death	831	4.43	728	3.85	0.87 (0.78–0.96)	0.005	796	4.23	0.95 (0.86–1.05)	0.32
MACE	926	4.98	827	4.41	0.88 (0.81–0.97)	0.01	913	4.90	0.98 (0.90–1.08)	0.69
Stroke, SEE or death	1046	5.57	949	5.01	0.90 (0.82–0.98)	0.02	985	5.23	0.94 (0.86–1.02)	0.13
Death or ICH	926	4.88	817	4.27	0.87 (0.79–0.96)	0.004	773	4.03	0.82 (0.75–0.90)	<0.001
Death or disabling stroke	878	4.61	812	4.24	0.92 (0.83–1.01)	0.08	794	4.15	0.90 (0.81–0.99)	0.02
All-cause mortality	**839**	**4.35**	**773**	**3.99**	**0.92 (0.83–1.01)**	**0.08**	**737**	**3.80**	**0.87 (0.79–0.96)**	**0.006**
CV death	611	3.17	530	2.74	0.86 (0.77–0.97)	0.013	527	2.71	0.85 (0.76–0.96)	0.008
Myocardial infarction	141	0.75	133	0.70	0.94 (0.74–1.19)	0.600	169	0.89	1.19 (0.95–1.49)	0.13

Data are from the ITT cohort during the overall study period with 95% CI and P values for superiority

CI=confidence intervals; CV=cardiovascular; ICH=intracranial hemorrhage; ITT=Intent-To-Treat
MACE=major adverse cardiac event (composite of MI, stroke, SEE and CV death)
MI=myocardial infarction; SEE=systemic embolic event

Giugliano et al. N Engl J Med 2013; e-pub ahead of print

“Class effects”

- All four novel anticoagulants are non-inferior to warfarin in reducing the risk of stroke and systemic embolization

- All four novel anticoagulants are associated with a reduction of haemorrhagic stroke

- All four agents reduce the risk of bleeding (fatal and in critical organ for Rivaroxaban, major for Apixaban and Edoxaban, major at 110 mg for Dabigatran,) and intracranial hemorrhage

- The directionality and magnitude of the mortality reduction is consistent and approximates a RRR of 10% / year

New OACs vs Warfarin: Summary

Effect on outcome event	D150	D110	Riva	Apx
Non inferiority stroke	√	√	√	√
↓ hemorragic stroke	√	√	√	√
↓ ischemic stroke	√			
↓ mortality	(√)			√
↓ major bleeding		√		√
↑ GI bleeding	√		√	
↑ MI	(√)	(√)		
↓ CV mortality	√			

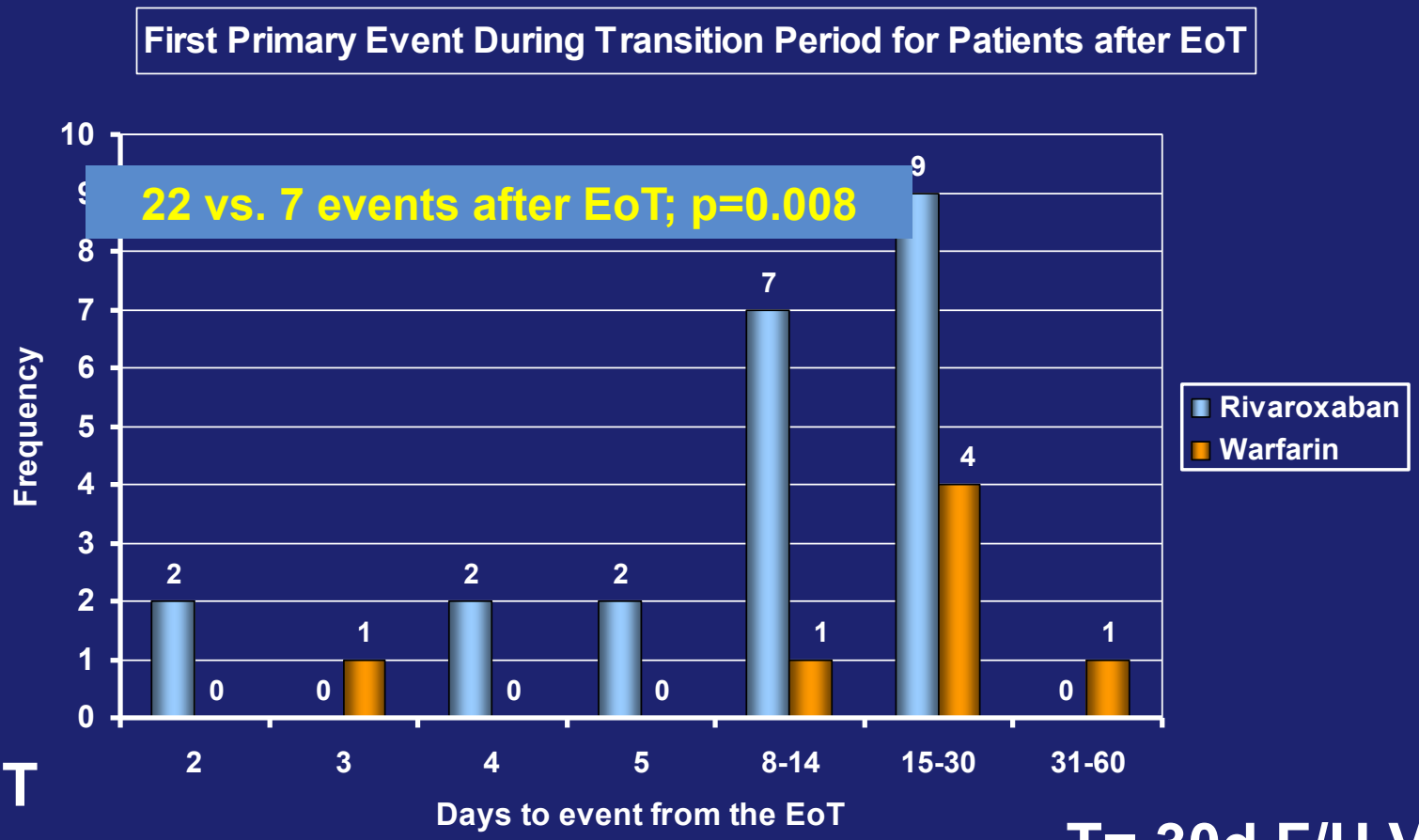
New OACs vs Warfarin: Summary

Effect on outcome event	E30	E60
Non inferiority stroke	√	√
↓ Hemorragic stroke	√	√
↓ ischemic stroke		
↓ mortality	√	(√)
↓ major bleeding	√	√
↑ GI bleeding		√
↑ MI		
↓ CV mortality	√	√

NOACS
Post end-of-treatment events

- Discontinuation of study anticoagulants and transition to non-study anticoagulants is associated with excess thrombeomblic events, particularly in blinded trials
- Impact greatest for rivaroxaban because ROCKET-AF included higher risk patients who had higher discontinuation and stroke rates

Differential Event Rates & TTR INR for the 60d Transition after EoT to F/U



T=EoT

R

T= 30d F/U Visit

Median time to TTR INR 13d / 365 d x avg. annual risk 8.5% x 7131 = 21.6

W

Median time to TTR INR 3 / 365 d x avg. annual risk 8.5% x 7133 = 4.98

Stroke or Systemic Embolism

Patients Who Completed Treatment

	Apixaban		Warfarin	
Days After Last Dose	**n/N**	**% / yr**	**n/N**	**% / yr**
1 – 30	**21 / 6791**	**4.02**	**5 / 6569**	**0.99**
1 – 2	1 / 6791	2.69	1 / 6569	2.78
3 – 7	4 / 6787	4.31	0 / 6566	0
8 – 14	5 / 6780	3.85	1 / 6559	0.80
15 – 30	11 / 6771	4.18	3 / 6548	1.18

Impact on discontinuation on results of blinded NOACS trials

TRIAL	CHADS 2 Score (median)	% of events after discontinuation	Superiority result
ROCKET-AF	3.5	25%	Negated
ARISTOTLE	2.1	16%	Unaffectd

Primary efficacy outcome

Outcome	Warfarin (n=7,036)		Edoxaban 60 mg (n=7,035)		Edoxaban 60 mg versus warfarin		Edoxaban 30 mg (n=7,034)		Edoxaban 30 mg versus warfarin	
	n	%/yr	n	%/yr	HR (95% CI)	P	n	%/yr	HR (95% CI)	P
Stroke or SEE										
mITT, on-treatment	232	1.50	182	1.18	0.79 (0.63–0.99)$^{\Delta}$	<0.001*	253	1.61	1.07 (0.87–1.31)$^{\Delta}$	0.005*
ITT	337	1.80	296	1.57	0.87 (0.73–1.04)$^{\Delta}$	0.08	383	2.04	1.13 (0.96–1.34)$^{\Delta}$	0.10
Post-study 30-days transition	**7**	-	**7**	-	-	-	**7**	-	-	-
Stroke	317	1.69	281	1.49	0.88 (0.75–1.03)	0.11	360	1.91	1.13 (0.97–1.31)	0.12
Hemorrhagic	90	0.47	49	0.26	0.54 (0.38–0.77)	<0.001	30	0.16	0.33 (0.22–0.50)	<0.001
Ischemic	235	1.25	236	1.25	1.00 (0.83–1.19)	0.97	333	1.77	1.41 (1.19–1.67)	<0.001$^{\#}$
Non-disabling, nonfatal	190	1.01	154	0.81	0.80 (0.65–0.99)	0.044	214	1.13	1.12 (0.92–1.36)	0.26
Disabling or fatal	135	0.71	132	0.69	0.97 (0.76–1.23)	0.81	152	0.80	1.11 (0.89–1.40)	0.36
Fatal	86	0.45	80	0.42	0.92 (0.68–1.25)	0.61	73	0.38	0.84 (0.61–1.15)	0.27
SEE	23	0.12	15	0.08	0.65 (0.34–1.24)	0.19	29	0.15	1.24 (0.72–2.15)	0.43

Giugliano et al. N Engl J Med 2013; e-pub ahead of print

La terapia con i NAO nei pazienti con FA non-valvolare

- "Class effect"
- Evidenze delle letteratura: le analisi per sottogruppi
- Cosa dicono le Linee Guida

Common misconception about patients eligibility for use of NOACS

- Elderly
- Moderate renal impairment

NOACS in the elderly

TRIAL	> 75 ys	Results
RE-LY	7,258	Consistent efficacy, ICH Increased ECH
ROCKET-AF	6,229	Consistent efficacy, ICH Increased ECH
ARISTOTLE	5,678	Consistent efficacy, Consistent safety

Hart, Can J Cardiol, 2013

NOACS in patients with moderate renal impairment

TRIAL	eGFR 30-50 ml/min	Results
RE-LY	3,505	Consistent results
ROCKET-AF	2,950	Consistent results
ARISTOTLE	3,017	Less bleeding in moderate CKD

Hart, Can J Cardiol, 2013

La terapia con i NAO nei pazienti con FA non-valvolare

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Recommendations	Class	Level
In patients with a CHA2DS2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban …. is recommended, unless contraindicated.	I	A
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A

[d] = pending EMA/FDA approval – prescribing information is awaited

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

Anticoagulation - NOACs

Recommendations for prevention of thromboembolism in non-valvular AF - NOACs		
Recommendations	**Class**	**Level**
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)d … is recommended.	I	B
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)d … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

Anticoagulation - NOACs

- In the absence of head-to-head trials, **it is inappropriate to be definitive on which of the NOACs is best**, given the heterogeneity of the different trials.

- **There is insufficient evidence to recommend one NOAC over another**, although some patient characteristics, drug compliance and tolerability, and cost may be important considerations in the choice of agent.

Le raccomandazioni dell'AIAC

Nei pazienti ***warfarin-naïve*** i nuovi anticoagulanti orali sono da preferire al warfarin in presenza di:

- difficoltà logistiche nell'effettuare il monitoraggio della TAO,
- pregresso ictus ischemico,
- pregressa emorragia intracranica,
- giovane età,
- paziente candidato a cardioversione elettrica

Linee Guida sulla FA, G Ital Cardiol , 2013

Le raccomandazioni dell'AIAC

Nei pazienti ***warfarin-experienced*** è proponibile lo *switch* ai nuovi anticoagulanti orali in caso di:

- difficoltà logistiche nell'effettuare il monitoraggio della TAO/ labilità dell'INR

- impiego giornaliero di basse dosi di warfarin (8-10 mg/ settimana)

- pregressa emorragia maggiore (escluse le emorragie gastrointestinali)

Linee Guida sulla FA, G Ital Cardiol, 2013

Le raccomandazioni dell'AIAC

Nei pazienti ***warfarin-experienced*** è proponibile lo *switch* ai nuovi anticoagulanti orali in caso di:

- qualità subottimale della TAO (tempo trascorso all'interno del range terapeutico <60%)
- impiego a lungo termine di farmaci interferenti con il warfarin e non interferenti con i nuovi anticoagulanti orali
- pregressa emorragia cerebrale in corso di terapia con warfarin con INR in range terapeutico
- pregresso ictus/TIA in corso di terapia con warfarin con INR in range terapeutico.

Linee Guida sulla FA, G Ital Cardiol, 2013