SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
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Efficacia e sicurezza dei NAO nella prevenzione dell'ictus in pazienti con FANV: dai trials alla real life

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Piano della presentazione

1. Dimensione e rilevanza del problema:
   lo stroke cardioembolico da FA

2. La farmacoprofilassi: NOAC vs VKA

3. La farmacoprofilassi secondaria: NOAC vs VKA

4. Il problema dello stroke embolico criptogenetico

5. Problemi pratici nell'uso dei NAO

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Diagnosi eziopatogenetica clinico-strumentale dell'ictus ischemico: Classificazione TOAST

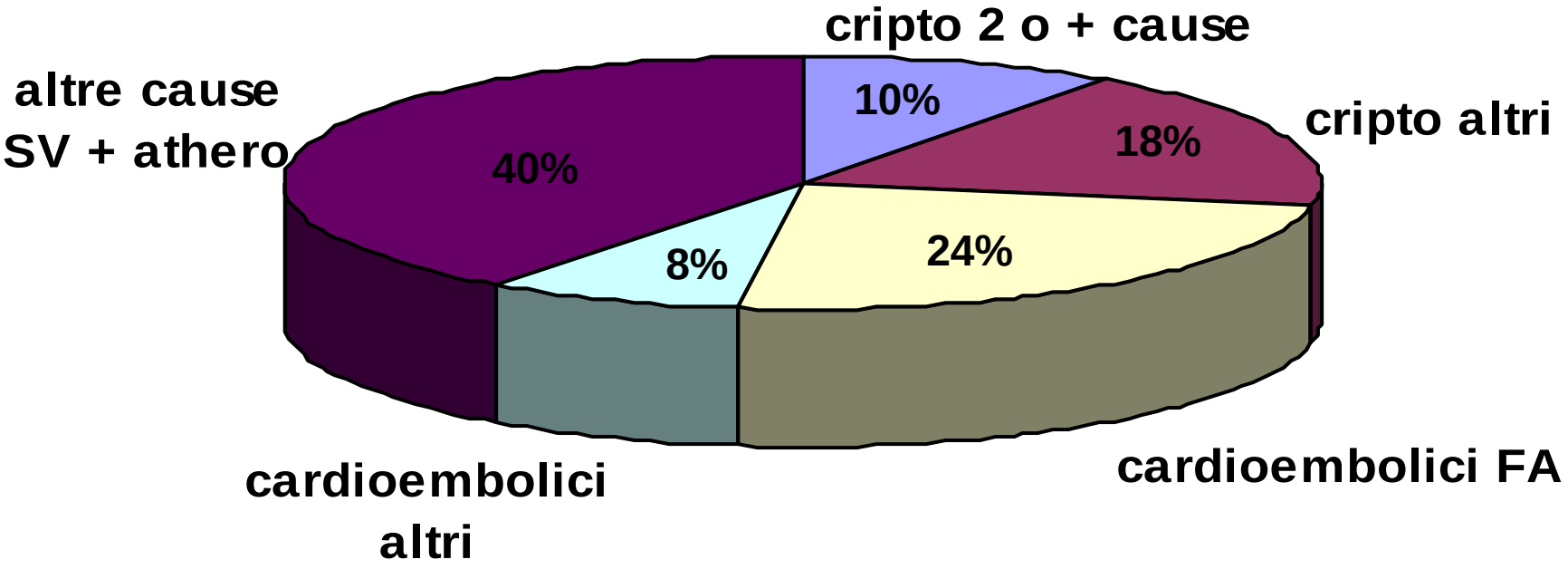
Classificazione su base fisiopatologica dei sottotipi dell'ictus ischemico	
	(criteri del TOAST, 1993)
Aterosclerosi dei vasi di grosso calibro	
Cardioembolia (possibile/probabile)	
Occlusione dei piccoli vasi	
Ictus da cause diverse	
Ictus da cause non determinate	a. identificazione di due o più cause b. valutazione negativa c. valutazione incompleta

Sottotipi di ictus ischemico e correlati clinico-strumentali					
Caratteristiche		aterosclerosi dei TSA	cardio-embolismo	lacunare	altri
Cliniche	disfunzione corticale o cerebellare	+	+	-	+/-
	sindrome lacunare	-	-	+	+/-
Neuroradiologiche	infarto corticale, cerebellare o subcorticale >1,5 cm	+	+	-	+/-
	infarto subcorticale o del tronco encefalico <1,5 cm	-	-	+/-	+/-
Indagini strumentali	stenosi della carotide interna extracranica	+	-	-	-
	sorgente cardioembolica	-	+	-	-
	altre anomalie	-	-	-	+

Registro stroke U.O. Neurologia (dal 2009)

1735 ictus ischemici
FA → 75% dei cardioembolici
Ictus cardioembolici → 89% in TAO alla dimissione

Note: tra gli ictus criptogenetici per presenza di 2 o più cause vi sono molti con cardioembolia probabile + altra causa probabile



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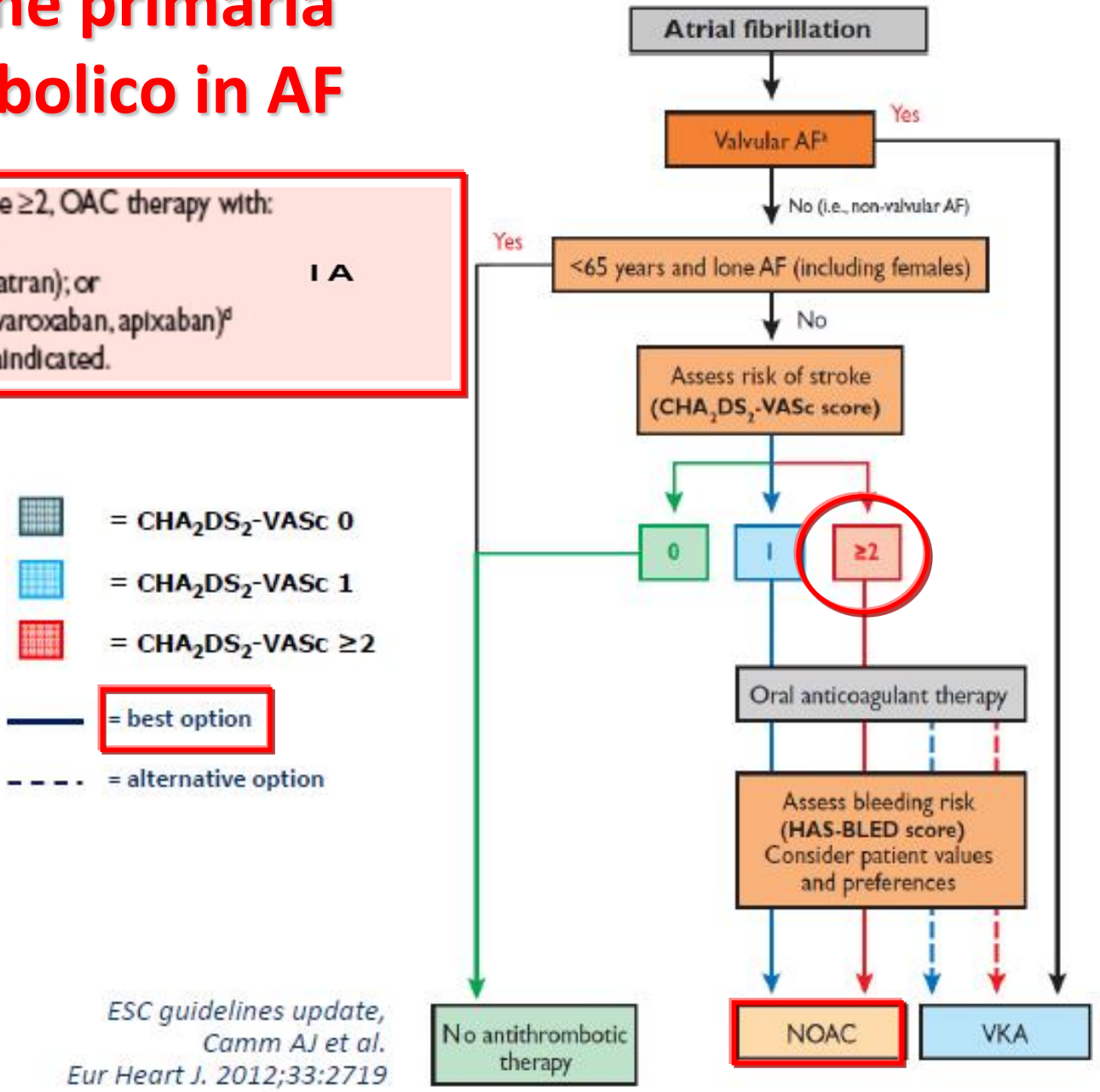
Prevenzione primaria rischio embolico in AF

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)[a]

… is recommended, unless contraindicated. **I A**



ESC guidelines update, Camm AJ et al. Eur Heart J. 2012;33:2719

Assessing Risk
CHA_2DS_2VASc

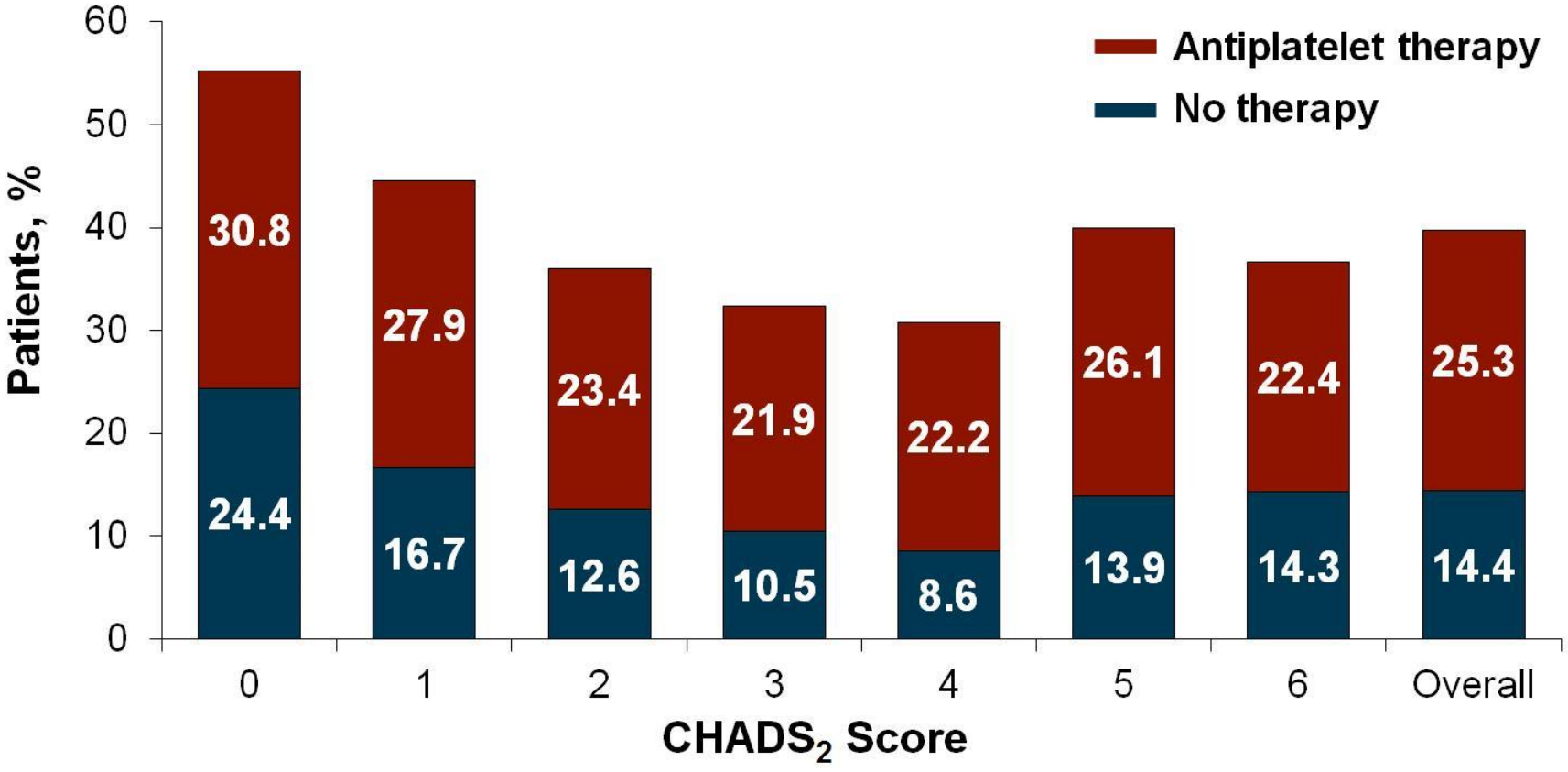
	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior stroke or TIA or thromboembolism	2
V	Vascular disease (eg, peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65-74 years	1
Sc	Sex category (ie, female sex)	1

CHA_2DS_2-VASc Score	Stroke Risk, %
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Lip GY, et al. *Chest*. 2010;137:263-72.[10]
Lip GY, et al. *Stroke*. 2010 Dec;41:2731-8.[32]

GARFIELD Registry

Patients receiving inadequate anticoagulation: data from December 2009 to October 2011



Kakkar AK, et al. *PLoS One* 2013;8:e63479.[9]

Limiti della terapia con VKA

La terapia con VKA presenta numerose limitazioni che ne rendono difficile l'utilizzo

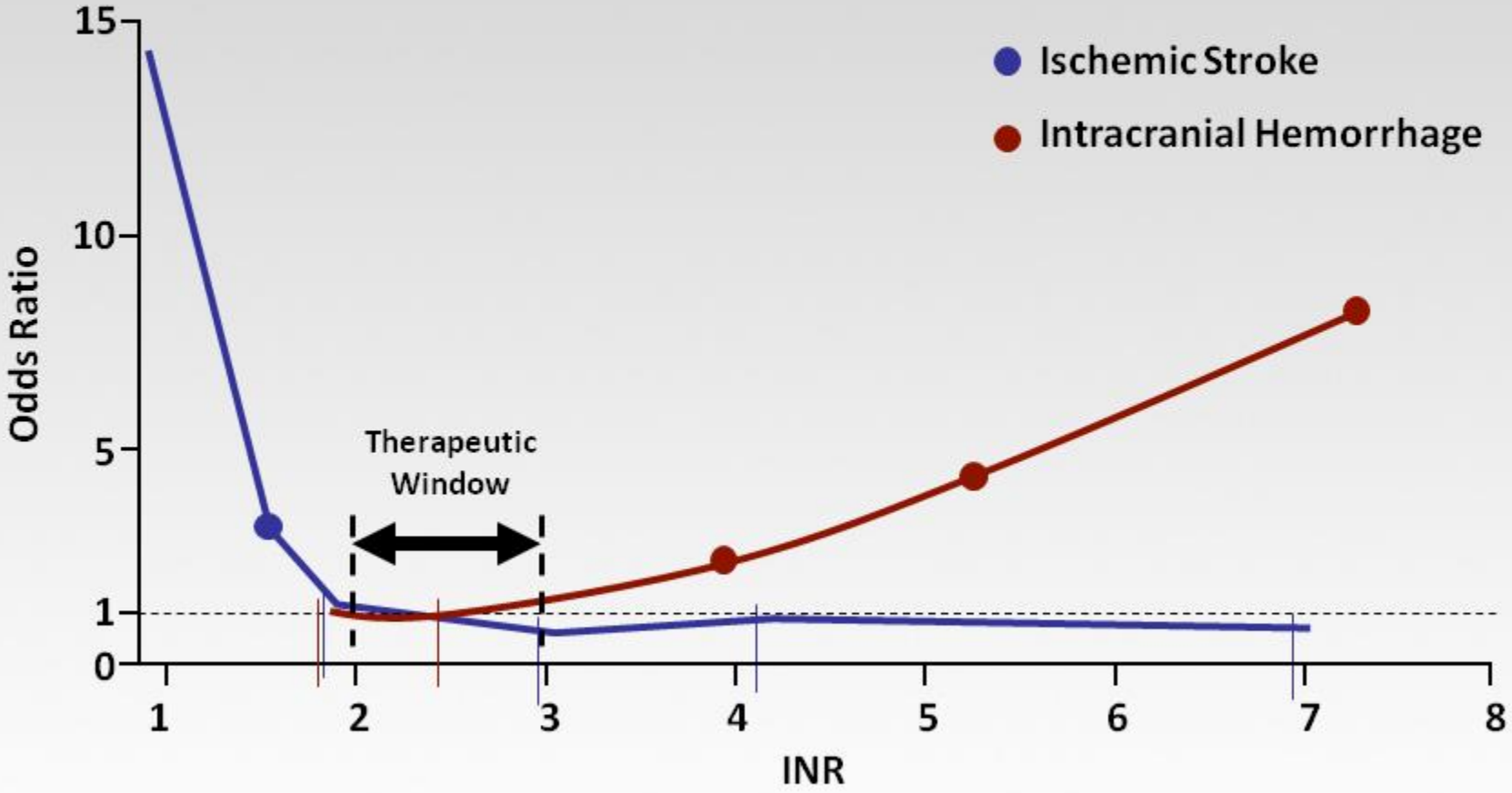
- Risposta Imprevedibile
- Ristretta finestra terapeutica (INR range 2-3)
- Monitoraggio periodico della coagulazione
- Frequenti aggiustamenti di dose
- Numerose interazioni con il cibo
- Numerose interzioni farmacologiche

Solo il 50% dei pazienti elegibili ricevono il Warfarin

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

INR 2-3 56%

Warfarin Has a Narrow Therapeutic Window: Relationship Between Clinical Events and INR



Hylek EM, et al. *Ann Intern Med.* 1994;120:897-902.
Hylek EM, et al. *N Engl J Med.* 1996;335:540-546.

Limiti superati con I NOAC

Risposta Imprevedibile

Ristretta finestra terapeutica (INR range 2-3)

Monitoraggio periodico della coagulazione

La terapia con i NOAC presenta numerosi vantaggi che rendono più sicuro l'utilizzo

Frequenti aggiustamenti di dose

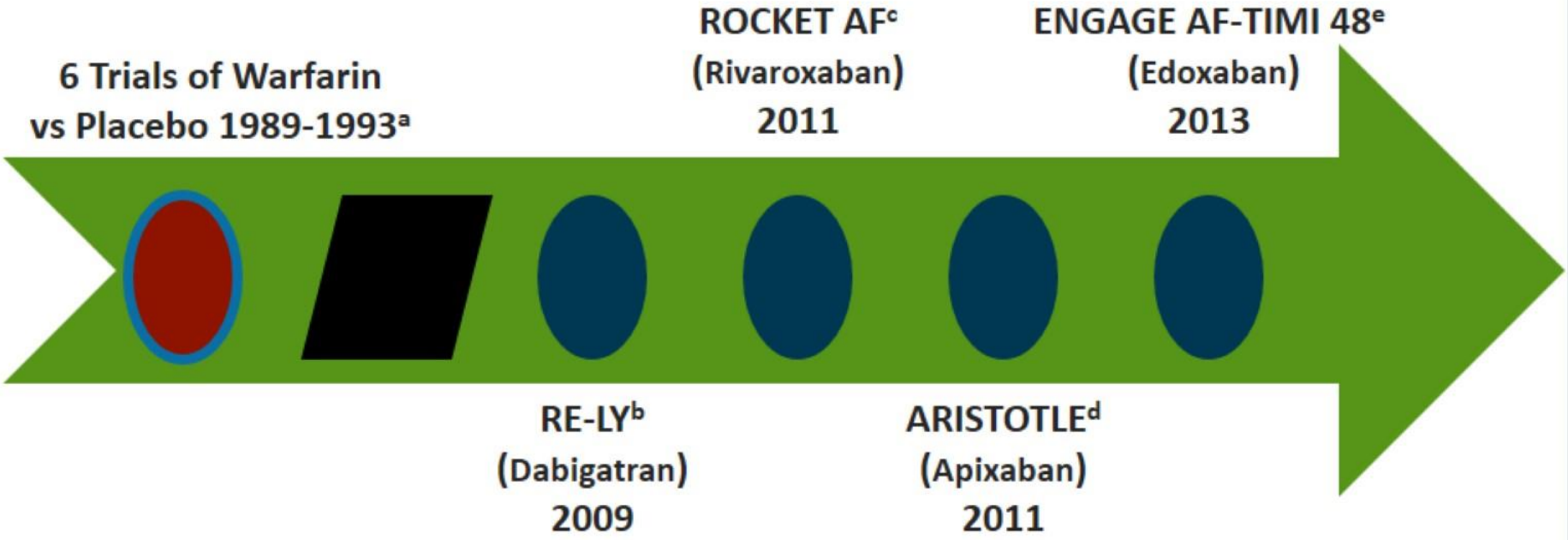
Numerose interazioni con il cibo

LIMITATE interazioni farmacologiche

Pivotal Warfarin-Controlled Trials Stroke Prevention in AF

Warfarin vs Placebo
2,900 Patients

NOACs vs Warfarin
71,683 Patients



a. Hart RG, et al. *Ann Intern Med* 2007;146:857-67[14]; b. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-51[15]; c. Patel MR, et al. *N Engl J Med*. 2011;365:883-91[16]; d. Granger CB, et al. *N Engl J Med*. 2011;365:981-92[17]; e. Giuliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[18]

Alternatives to Warfarin

	Apixaban	Rivaroxaban	Dabigatran
Target	Xa	Xa	Thrombin
Dosing interval	Twice daily	Once daily	Twice daily
Half-life	9-14 hours	5-9 hours Longer in elderly	8-17 hours
Renal metabolism	33%	25%	80%
Hepatic metabolism	67%	75%	20%

NOAC *vs.* warfarin: Study characteristics

	ARISTOTLE[1]	RE-LY[2]	ROCKET-AF[3]
Age	70 years (median)	71 years (mean)	73 years (median)
Men	65%	64%	60%
Type of AF*			
Persistent/permanent	84.7%	67.2%	81.0%
Paroxysmal	15.3%	32.8%	17.6%
Newly diagnosed	-	-	1.4%
$CHADS_2$ of patients, mean*	2.1	2.1	3.5
0 or 1	34.0%	31.9%	0%
2	35.8%	35.6%	13%
3-6	30.2%	32.5%	87%
Time in therapeutic range (TTR) in the warfarin group, mean % of the study period	62.2%	64%	55%
Patients with prior stroke or TIA	19.4%	20.2%	54.7%

**Data calculated for the overall study group*

1. Granger et al. NEJM 2011;365:981-92. 2. Connolly et al. NEJM 2009;361:1139-51. 3. Patel et al. NEJM 2011;365:883-91.

NOAC *vs.* warfarin: Inclusion criteria

ARISTOTLE[1]	RE-LY[2]	ROCKET-AF[3,4]
Documented NVAF or flutter with ≥1 of the following stroke risk factors:	**Documented NVAF with ≥1 of the following stroke risk factors:**	**Documented NVAF at moderate-to-high risk for stroke, i.e. $CHADS_2$≥2:***
• Previous **stroke**, **TIA or systemic embolism**	• Previous **stroke or TIA or systemic embolism**	• Prior **ischaemic stroke, TIA or systemic embolism** or
		• ≥2 or more of the following risk factors:
• **Age** ≥75 years	• **Age** ≥75 years, or • **Age** 65 to 74 years + **diabetes** on treatment, **hypertension** requiring treatment, or documented CAD	• **Age** ≥75 years
• Symptomatic **heart failure** within the previous 3 months, or **LVEF** ≤40%	• NYHA class ≥II **heart failure** symptoms within previous 6 months • **LVEF** <40%	• **Heart failure** or **LVEF** ≤35%
• **Diabetes** mellitus		• **Diabetes** (type 1 or type 2)
• **Hypertension** requiring treatment		• **Hypertension** (treated with antihypertensive agents within the previous 6 months or persistent SBP >140 or DBP >90 mmHg)

The proportion of patients with no previous ischaemic stroke/TIA/systemic embolism or no more than two risk factors was limited to 10%

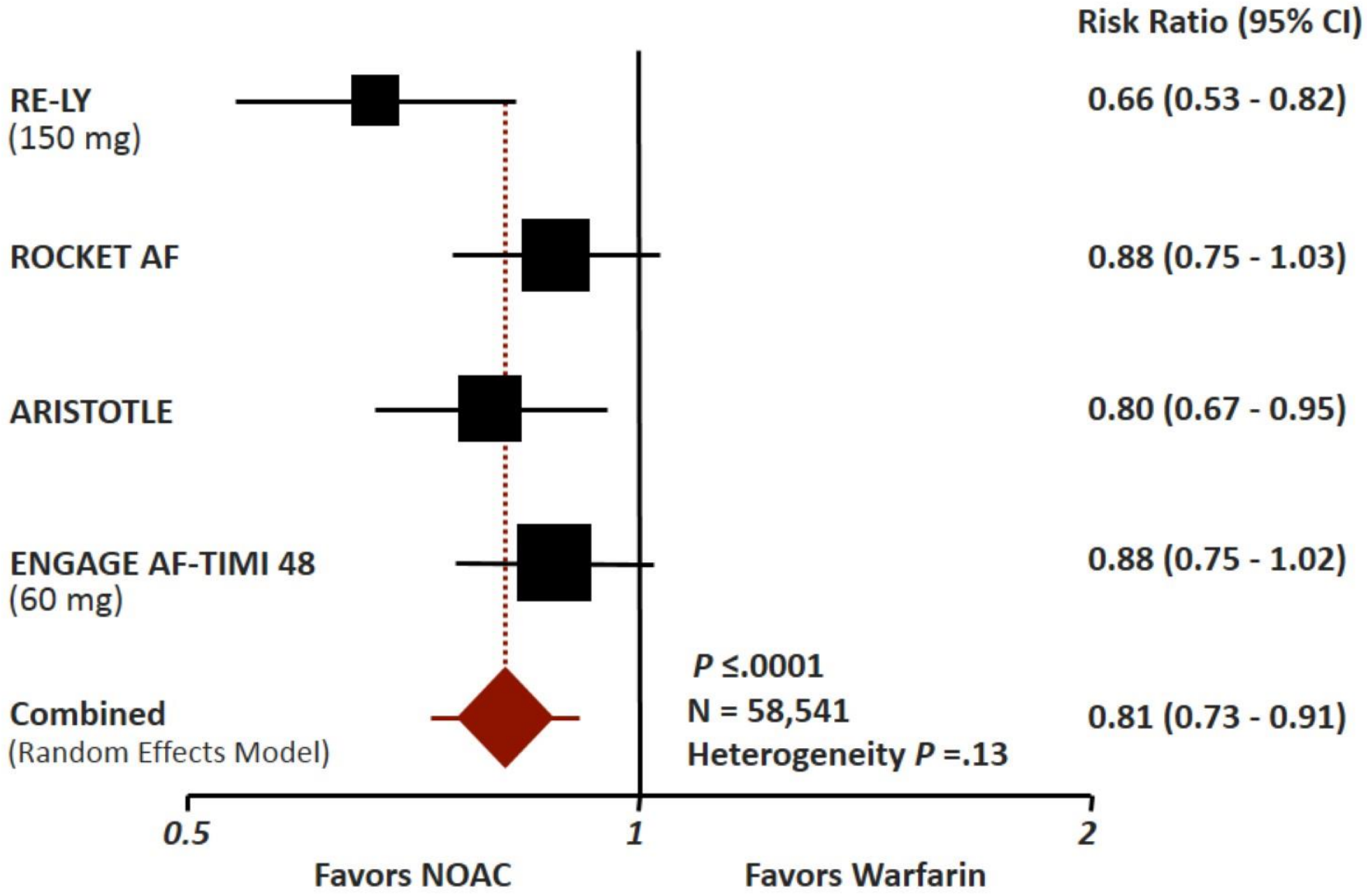
1. Granger et al. NEJM 2011;365:981-92. 2. Connolly et al. NEJM 2009;361:1139-51.
3. Patel et al. NEJM 2011;365:883-91. 4. Patel et al. NEJM 2011;365:883-91suppl app.

Main exclusion criteria in NOAC trials

RELY[1]	ROCKET[2,3]	ARISTOTLE[4]	AVERROES[5]
• Severe heart valve disorder	• Sigificant mitral stenosis,	• Moderate or severe mitral stenosis	• Presence of conditions other than AF for which the patient required long-term anticoagulation
• Stroke within 14 days or severe stroke within the previous 6 months	• Prosthetic heart valve	• Conditions other than AF requiring anticoagulation eg prosthetic heart valve	• Valvular disease requiring, surgery
• AF due to reversible cause	• Severe, disabling stroke within 3 months or any stroke within14 days	• Stroke within the previous 7 days	• AF due to reversible causes
• Plan to cure the AF by ablation or surgery	• TIA within 3 days	• AF due to reversible cause	• Serious bleeding event in the previous 6 months,
• A condition that increased the risk of haemorrhage	• AF due to reversible cause	• Planned ablation procedure	• A high risk of bleeding
• Active liver disease	• Planned cardioversion	• Increased bleeding risk	• Allergy to ASA
• **CrCL ≤30 mL/min**	• Active internal bleeding	• Need for ASA >65 mg/d or for ASA+clopidogrel,	• **CrCl <25 mL/min**
	• A condition that increased the risk of haemorrhage,	• **CrCl <25 mL/min**	• **Stroke within the previous 10 days**
	• **CrCl < 30 mL/min**		

1.Connolly SJ et al. N Eng J Med 2009;361:1139–1151
2.Patel MR et al. N Eng J Med 2011;365:883–891
3.ROCKET-AF investigators. Am Heart J 2010;159:340-347
4.Granger CB et al. N Eng J Med 2011;365:981–992
5. Connolly SJ et al. N Eng J Med 2011;364:806–817

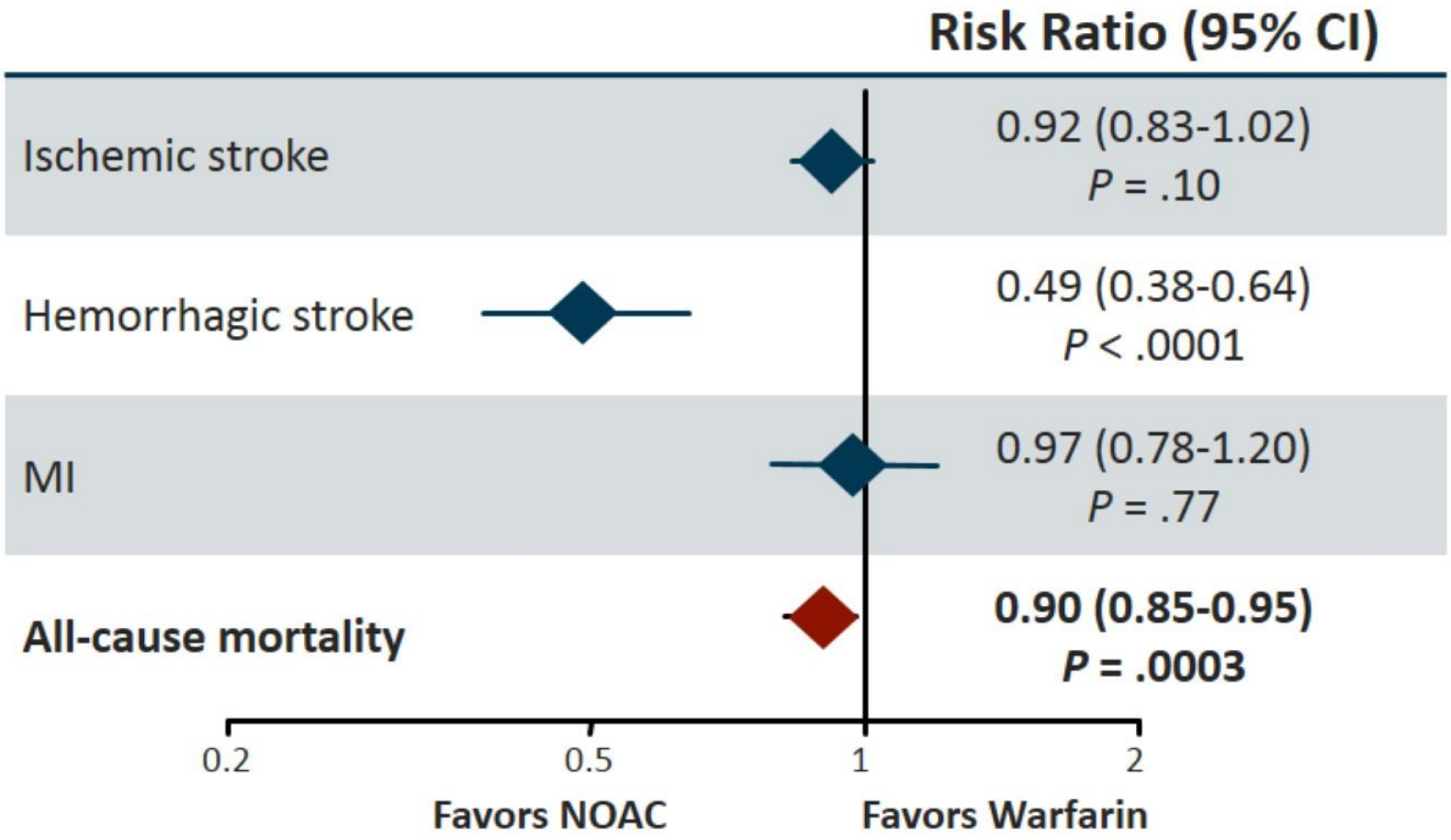
All NOACS: Stroke or SEE



Ruff CT, et al. *Lancet*. 2014;383:955-6.[19]

NOAC Meta-analysis

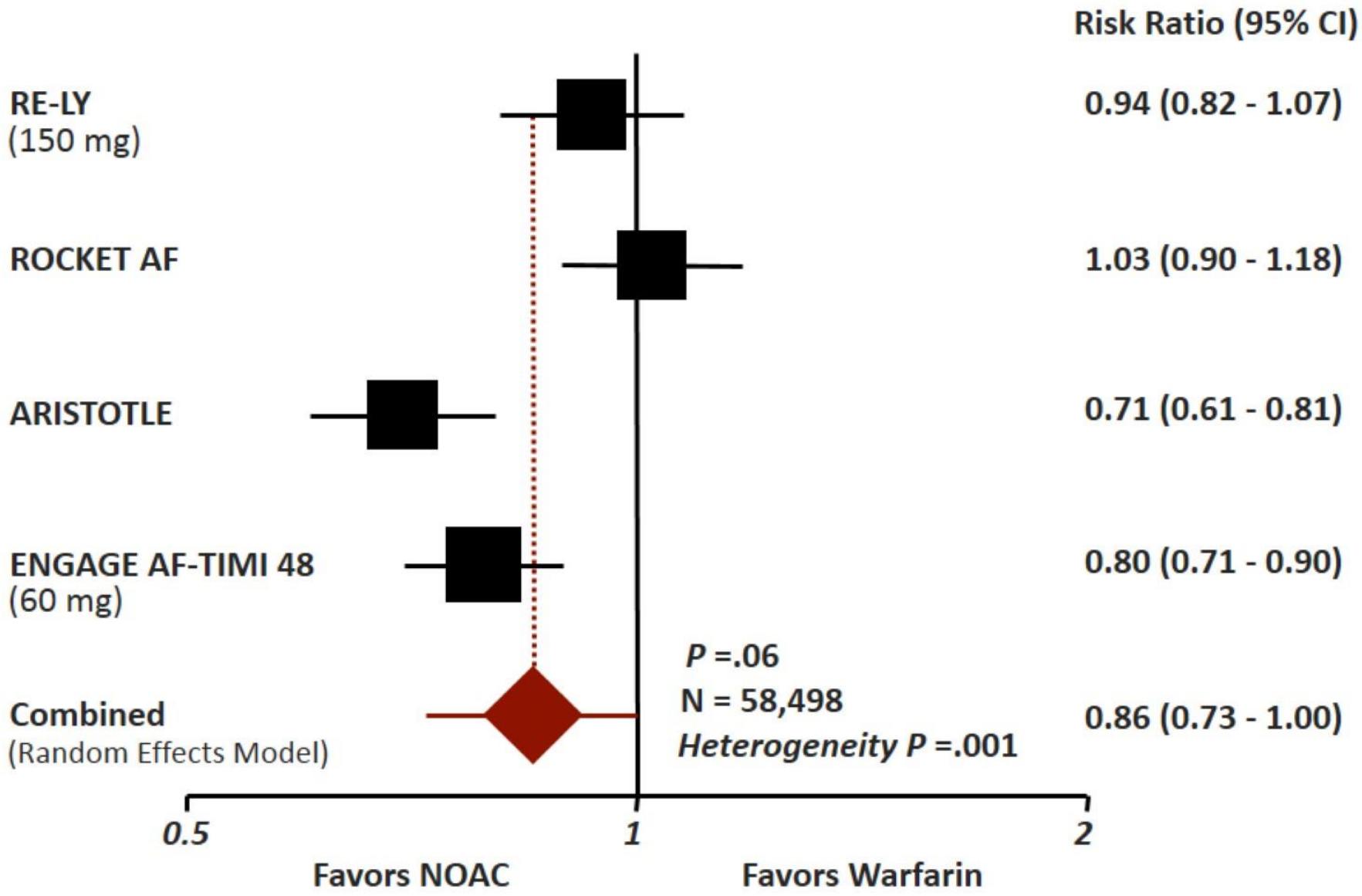
Secondary Efficacy Outcomes



Heterogeneity: *P* =NS for all outcomes

Ruff CT, et al. *Lancet* 2014;383:955-962[19]

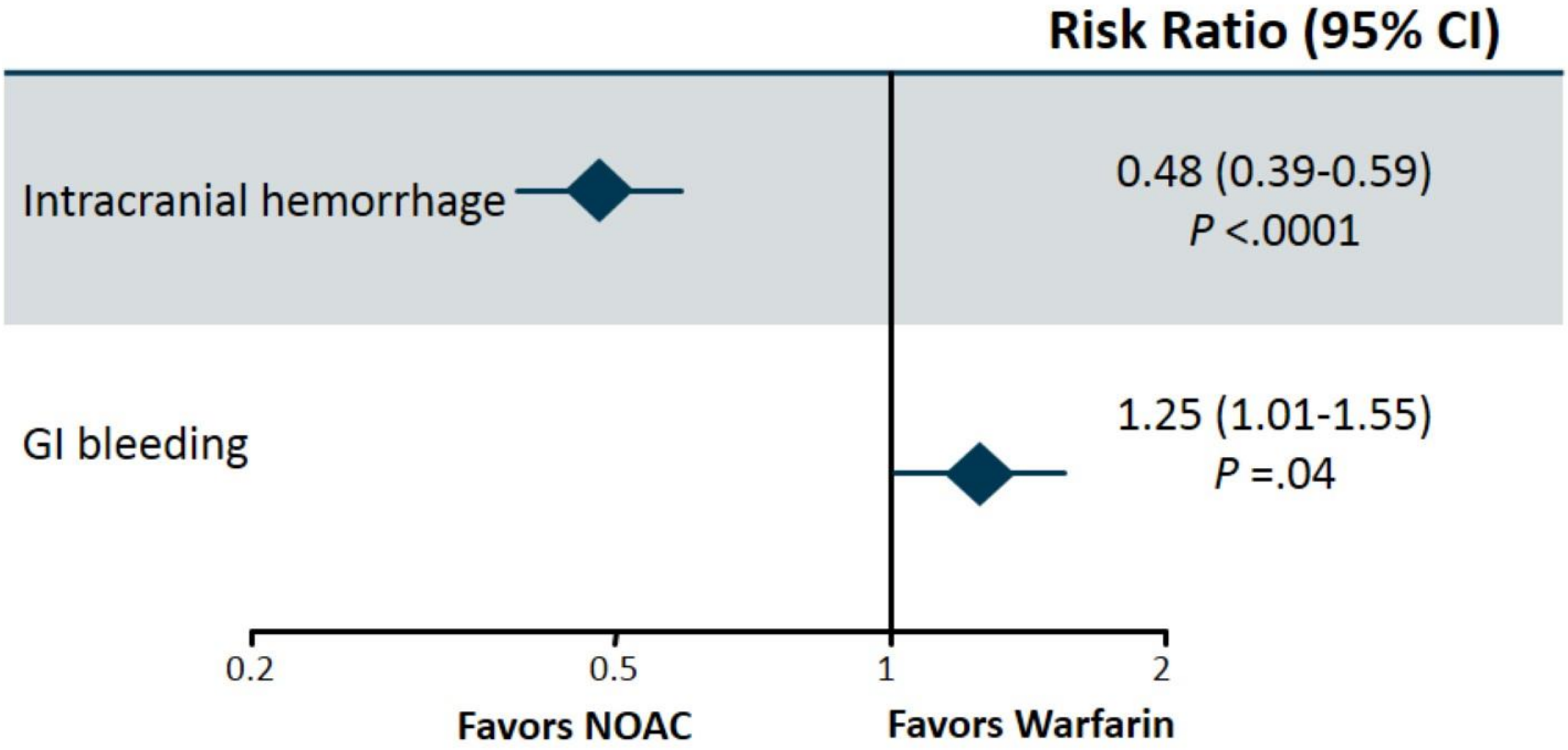
All NOACS: Major Bleeding



Ruff CT, et al. *Lancet*. 2014;383:955-6.[19]

NOAC Meta-analysis

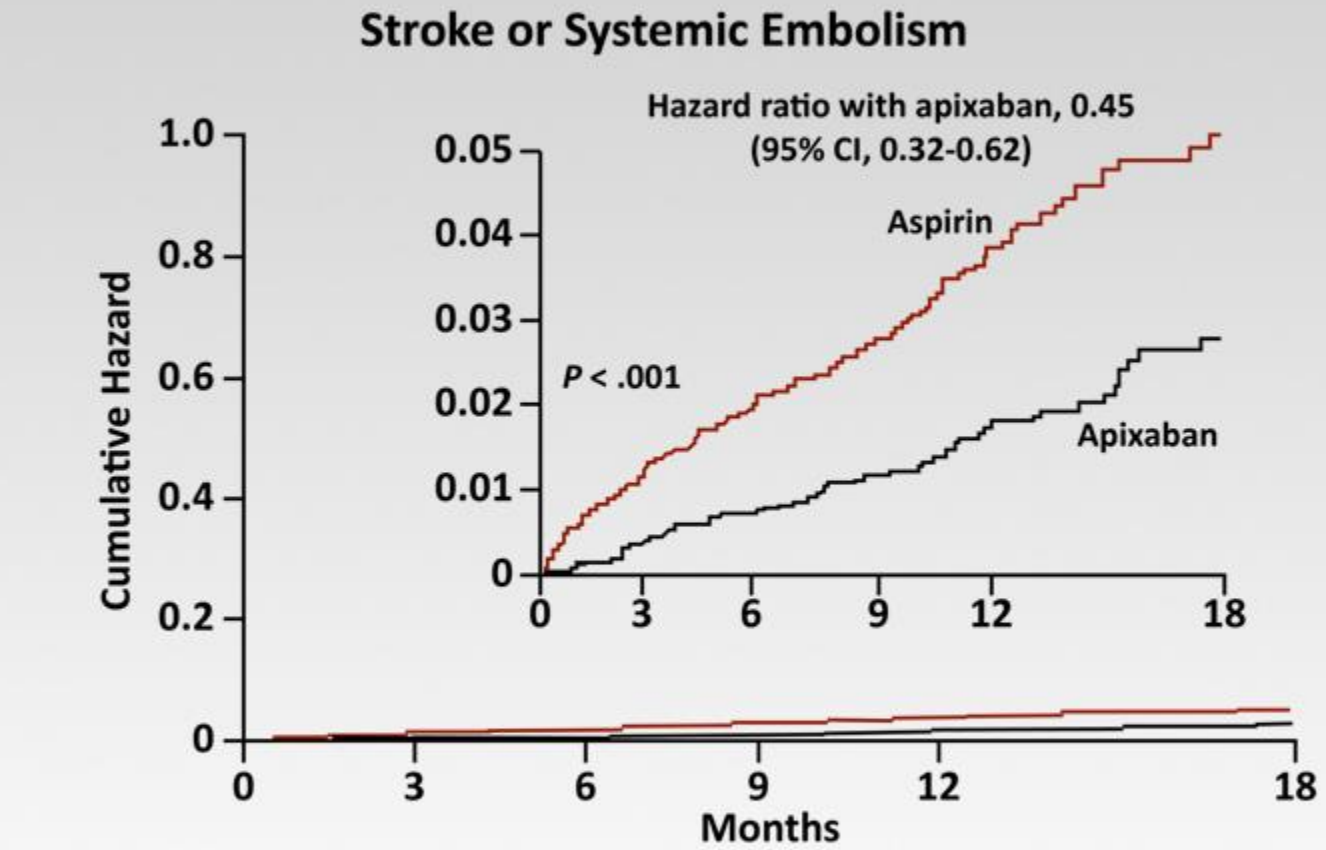
Secondary Safety Outcomes



Heterogeneity : ICH, *P* =.22; GI Bleeding, *P* =.009

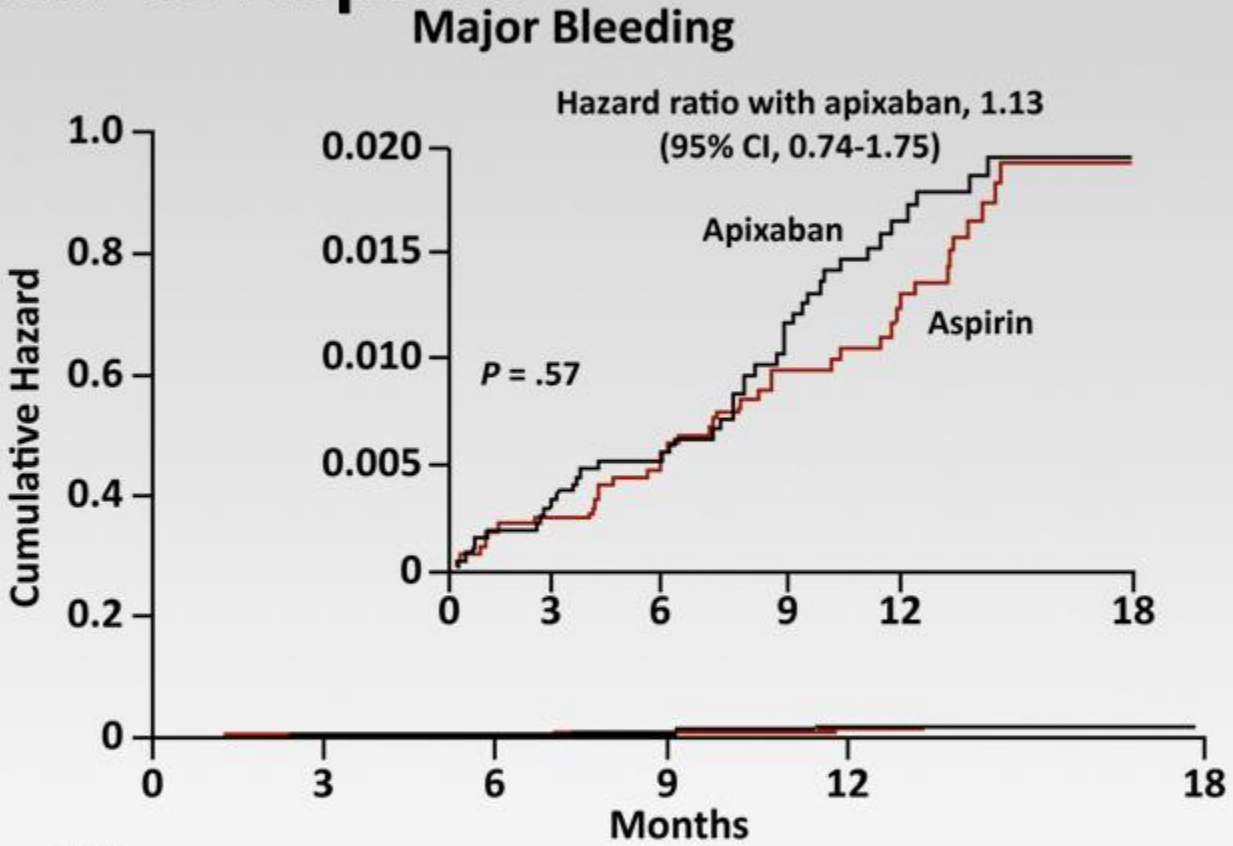
Ruff CT, et al. *Lancet* 2014;383:955-962[19]

AVERROES: Apixaban in Patients With AF



Connolly SJ, et al. *N Engl J Med.* 2011;364:806-817.

AVERROES: Risk for Major Bleeding With Apixaban vs Aspirin



Number at Risk						
Aspirin	2791	2738	2557	2140	1571	642
Apixaban	2808	2759	2566	2120	1521	622

At 2 years, the rates of permanent discontinuations were 17.9% per year with apixaban and 20.5% per year with aspirin (hazard ratio with apixaban, 0.88; 95% CI, 0.78-0.99; *P* = .03).

Connolly SJ, et al. *N Engl J Med.* 2011;364:806-817.

NOACs *vs.* warfarin

Table 2 Novel oral anticoagulants: a summary of main outcomes in their respective Phase 3 clinical trials

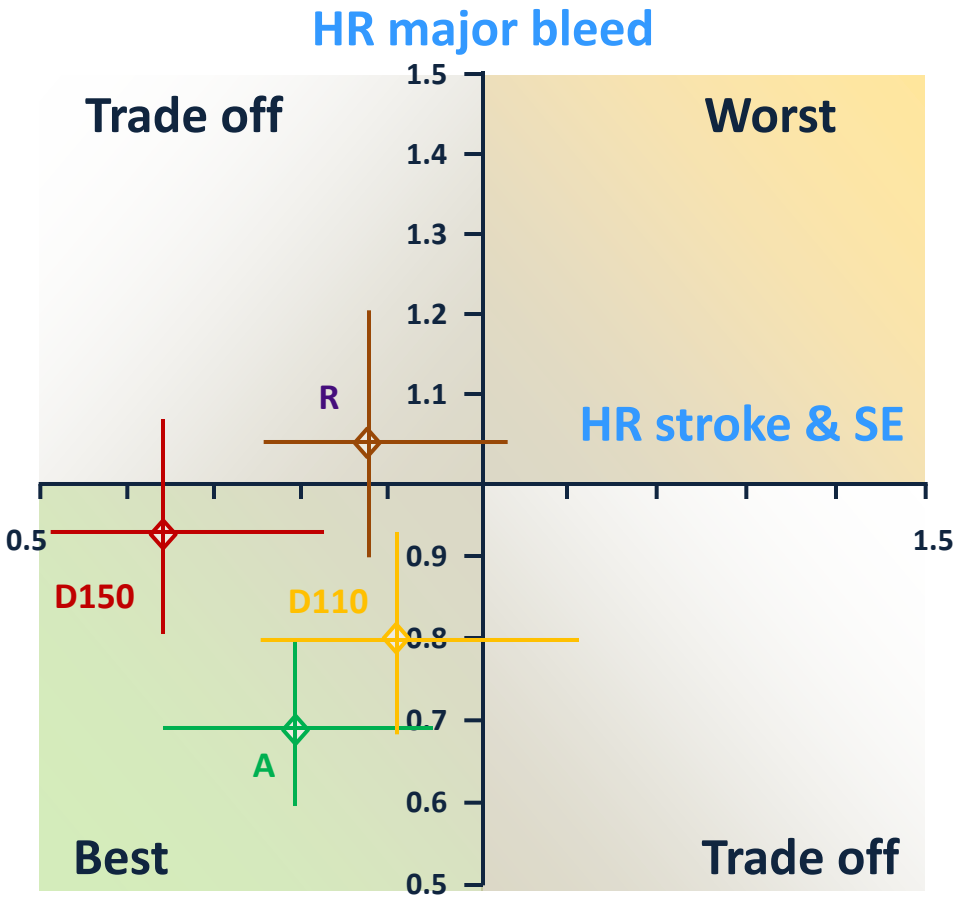
Effect on outcome event, vs. warfarin	D150	D110	Riva	Apix
Non-inferiority for stroke	√	√	√	√
Superiority for primary endpoint of stroke/SE	√			√
Reduction in hemorrhagic stroke	√	√	√	√
Reduction in ischemic stroke	√			
Reduction in mortality	(√)			√
Reduction in CV mortality	√			
Reduction in major bleeding		√		√
Reduction in major and minor bleeds	√	√		√
Increase in gastrointestinal major bleeds	√		√	
Increase in myocardial infarction	?	?		
Fewer treatment discontinuations				√

D150, dabigatran etexilate 150 mg b.i.d.; D110, dabigatran etexilate 110 mg b.i.d.; Riva, rivaroxaban; Api, apixaban. (√) indicates borderline significance.

G. Y. H. LIP J Thromb Haemost 2013; 11: 615–26.

NOACs vs. warfarin for stroke prevention in NVAF

- Hazard ratios (or for dabigatran risk reductions) and 95% confidence intervals in comparison with warfarin for
  - Primary efficacy outcome (horizontal lines)
  - Major bleeding (vertical lines)



These are not head-to-head comparisons between the NOACs

D150, dabigatran 150 mg bid; D110,dabigatran 110 mg bid; R, rivaroxaban 20 mg daily; A, apixaban 5 mg bid; bid, twice daily; HR, hazard ratio; NOACs, novel anticoagulants; SE, systemic embolism. Adapted from S. Schulman / *Thrombosis Research* 131, Suppl. 1 (2013) S63–S66.

Stroke prevention in patients with atrial fibrillation (1)

Recommendations	Class	Level
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A

European Heart Journal - doi:10.1093/eurheartj/ehw210

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Score CHA_2DS_2-VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

CHEST Original Research

THROMBOEMBOLISM

Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach

The Euro Heart Survey on Atrial Fibrillation

Gregory Y. H. Lip, MD; Robby Nieuwlaat, PhD; Ron Pisters, MD; Deirdre A. Lane, PhD; and Harry J. G. M. Crijns, MD

ESC Guidelines, Camm JA et al. Eur Heart J 2010; 31:2369

Reduction in stroke risk with OAC is greater for secondary prevention

Therapy comparison	Absolute reduction in stroke risk (% per year)	
	Primary prevention	Secondary prevention
VKA vs placebo	2.7 (NNT 32)	8.4 (NNT 12.5)
VKA vs ASA	0.7	7.0

Hart RG *et al*, 2007.

Prevenzione secondaria rischio embolico in AF

Raccomandazione 12.7 Grado A
Nell'ictus o TIA embolico associato a fibrillazione atriale non valvolare, la terapia anticoagulante orale è indicata mantenendo un INR tra 2 e 3.

LINEE GUIDA SPREAD

Nonvitamin-K-Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

George Ntaios, MD; Vasileios Papavasileiou, MD; Hans-Christoph Diener, MD; Konstantinos Makaritsis, MD; Patrik Michel, MD

Table. Characteristics of the Populations With Previous Stroke or Transient Ischemic Attack Included in the Meta-Analysis

	RE-LY	ROCKET AF	ARISTOTLE
Study population **14527 pts**	3623	7468	3436
Allocated to non-VKA/warfarin	2428/1195	3754/3714	1694/1742
Period in the therapeutic INR range (for patients allocated to warfarin)	63%	57.1%	65.0%
Duration of follow-up, median (IQR)	2.0 (1.14–2.86) y	676 (510–845) d	1.8 (1.4–2.3) y
Males, n (%)	2279 (62.9)	4538 (60.8)	2152 (62.6)
CHADS2 score, n (%)			
0–1	0 (0)	Not described	0 (0)
2	377 (10.4)	Not described	268 (8)
≥3	3246 (89.6)	Not described	3168 (92)

Effects of NOACs vs warfarin on efficacy outcomes:

stroke or systemic embolism;
stroke;
ischemic or unknown stroke;
disabling or fatal stroke

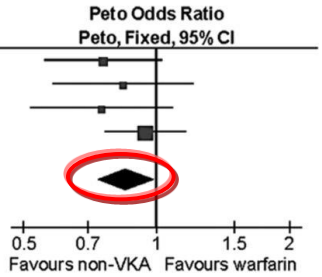
in patients with AF and previous stroke or TIA.

George Ntaios et al. Stroke. 2012;43:3298-3304

Stroke or systemic embolism

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	73	1694	98	1742	22.1%	0.76 [0.56, 1.03]
RELY 110	55	1195	65	1195	15.5%	0.84 [0.58, 1.21]
RELY 150	51	1233	65	1195	15.0%	0.75 [0.52, 1.09]
ROCKET-AF	179	3754	187	3714	47.4%	0.94 [0.77, 1.17]
Total (95% CI)		**7876**		**7846**	**100.0%**	**0.85 [0.74, 0.99]**
Total events	358		415			

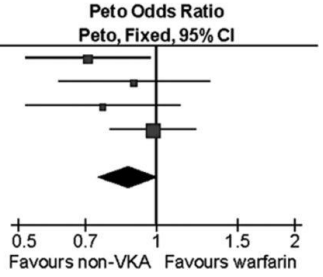
Heterogeneity: $\chi^2 = 1.93$, df = 3 ($P = 0.59$); $I^2 = 0\%$
Test for overall effect: Z = 2.15 ($P = 0.03$)



Stroke

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	67	1694	96	1742	22.5%	0.71 [0.52, 0.97]
RELY 110	53	1195	59	1195	15.5%	0.89 [0.61, 1.31]
RELY 150	47	1233	59	1195	14.7%	0.76 [0.52, 1.13]
ROCKET-AF	171	3754	172	3714	47.4%	0.98 [0.79, 1.22]
Total (95% CI)		**7876**		**7846**	**100.0%**	**0.87 [0.75, 1.01]**
Total events	338		386			

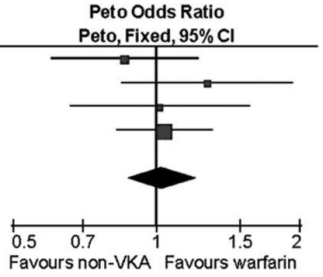
Heterogeneity: $\chi^2 = 3.29$, df = 3 ($P = 0.35$); $I^2 = 9\%$
Test for overall effect: Z = 1.87 ($P = 0.06$)



Ischemic or unknown stroke

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	57	1694	68	1742	21.0%	0.86 [0.60, 1.23]
RELY 110	52	1195	41	1195	15.6%	1.28 [0.84, 1.94]
RELY 150	43	1233	41	1195	14.1%	1.02 [0.66, 1.57]
ROCKET-AF	151	3754	144	3714	49.3%	1.04 [0.82, 1.31]
Total (95% CI)		**7876**		**7846**	**100.0%**	**1.03 [0.87, 1.21]**
Total events	303		294			

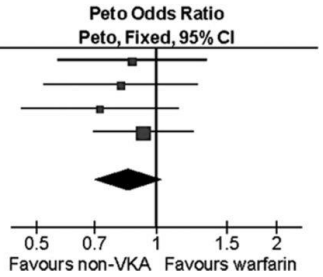
Heterogeneity: $\chi^2 = 2.07$, df = 3 ($P = 0.56$); $I^2 = 0\%$
Test for overall effect: Z = 0.33 ($P = 0.74$)



Disabling or fatal stroke

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	39	1694	46	1742	19.7%	0.87 [0.57, 1.34]
RELY 110	36	1195	44	1195	18.4%	0.81 [0.52, 1.27]
RELY 150	33	1233	44	1195	17.8%	0.72 [0.46, 1.13]
ROCKET-AF	92	3754	98	3714	44.1%	0.93 [0.69, 1.24]
Total (95% CI)		**7876**		**7846**	**100.0%**	**0.85 [0.71, 1.03]**
Total events	200		232			

Heterogeneity: $\chi^2 = 0.90$, df = 3 ($P = 0.83$); $I^2 = 0\%$
Test for overall effect: Z = 1.61 ($P = 0.11$)



American Heart Association.

Effects of NOACs vs warfarin on efficacy outcomes:

hemorrhagic stroke;
CV death;
death from any cause;
MI

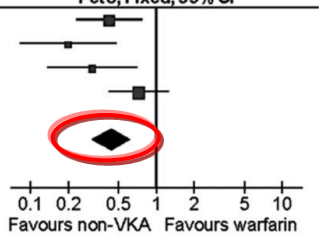
in patients with AF and previous stroke or TIA.

George Ntaios et al. Stroke. 2012;43:3298-3304

Hemorrhagic stroke

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	12	1694	31	1742	31.1%	0.42 [0.23, 0.77]
RELY 110	2	1195	18	1195	14.5%	0.20 [0.08, 0.48]
RELY 150	5	1233	18	1195	16.7%	0.31 [0.14, 0.70]
ROCKET-AF	22	3754	30	3714	37.8%	0.73 [0.42, 1.25]
Total (95% CI)		**7876**		**7846**	**100.0%**	**0.44 [0.32, 0.62]**
Total events	41		97			

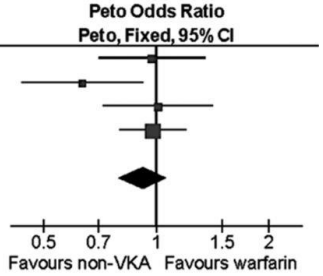
Heterogeneity: Chi² = 7.07, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 4.79 (P < 0.00001)



Cardiovascular death

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	72	1694	76	1742	18.8%	0.97 [0.70, 1.35]
RELY 110	45	1195	70	1195	14.6%	0.63 [0.44, 0.92]
RELY 150	73	1233	70	1195	17.9%	1.01 [0.72, 1.42]
ROCKET-AF	192	3754	194	3714	48.7%	0.98 [0.80, 1.20]
Total (95% CI)		**7876**		**7846**	**100.0%**	**0.92 [0.80, 1.06]**
Total events	382		410			

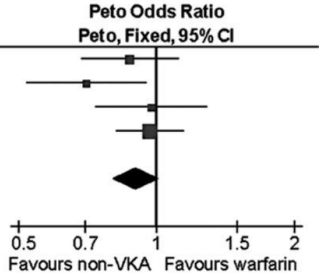
Heterogeneity: Chi² = 4.57, df = 3 (P = 0.21); I² = 34%
Test for overall effect: Z = 1.10 (P = 0.27)



Death from any cause

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	129	1694	150	1742	22.1%	0.88 [0.69, 1.12]
RELY 110	77	1195	107	1195	14.7%	0.70 [0.52, 0.95]
RELY 150	108	1233	107	1195	16.9%	0.98 [0.74, 1.29]
ROCKET-AF	288	3754	294	3714	46.3%	0.97 [0.82, 1.14]
Total (95% CI)		**7876**		**7846**	**100.0%**	**0.90 [0.81, 1.01]**
Total events	602		658			

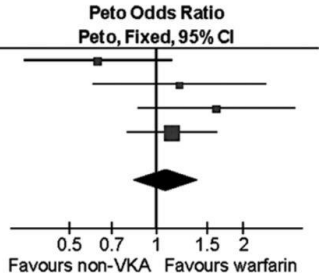
Heterogeneity: Chi² = 3.66, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 1.72 (P = 0.09)



Myocardial infarction

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	17	1694	28	1742	18.8%	0.63 [0.35, 1.13]
RELY 110	18	1195	15	1195	13.8%	1.20 [0.60, 2.39]
RELY 150	25	1233	15	1195	16.6%	1.61 [0.86, 3.01]
ROCKET-AF	65	3754	57	3714	50.8%	1.13 [0.79, 1.62]
Total (95% CI)		**7876**		**7846**	**100.0%**	**1.08 [0.84, 1.40]**
Total events	125		115			

Heterogeneity: Chi² = 5.01, df = 3 (P = 0.17); I² = 40%
Test for overall effect: Z = 0.61 (P = 0.54)



American Heart Association.

Effects of NOACs vs warfarin on safety outcomes:

major bleeding;
intracranial bleeding;
gastrointestinal bleeding

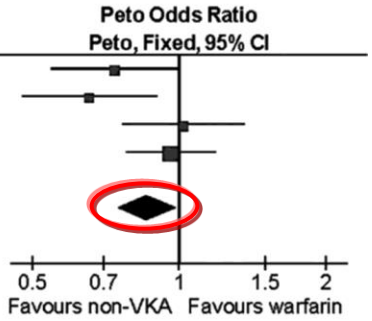
in patients with AF and previous stroke or TIA.

George Ntaios et al. Stroke. 2012;43:3298-3304

Major bleeding

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	77	1694	106	1742	20.4%	0.74 [0.55, 0.99]
RELY 110	65	1195	97	1195	17.8%	0.65 [0.48, 0.90]
RELY 150	102	1233	97	1195	21.5%	1.02 [0.76, 1.36]
ROCKET-AF	178	3754	183	3714	40.4%	0.96 [0.78, 1.19]
Total (95% CI)		**7876**		**7846**	**100.0%**	**0.86 [0.75, 0.99]**
Total events	422		483			

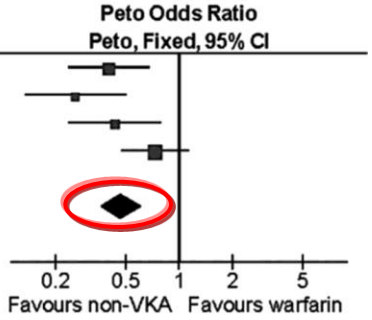
Heterogeneity: Chi² = 6.23, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 2.18 (P = 0.03)



Intracranial bleeding

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	15	1694	41	1742	26.0%	0.40 [0.24, 0.68]
RELY 110	6	1195	30	1195	16.7%	0.26 [0.13, 0.50]
RELY 150	13	1233	30	1195	19.9%	0.43 [0.24, 0.79]
ROCKET-AF	34	3754	46	3714	37.3%	0.73 [0.47, 1.13]
Total (95% CI)		**7876**		**7846**	**100.0%**	**0.47 [0.36, 0.62]**
Total events	68		147			

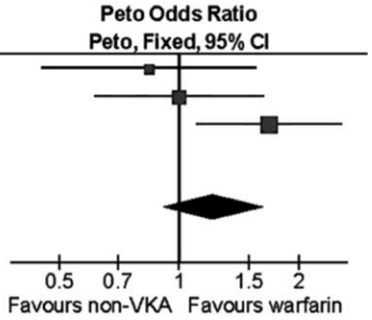
Heterogeneity: Chi² = 7.44, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 5.45 (P < 0.00001)



Gastrointestinal major bleeding

Study or Subgroup	Non-VKA Events	Non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	18	1694	22	1742	20.8%	0.84 [0.45, 1.57]
RELY 110	33	1195	33	1195	33.7%	1.00 [0.61, 1.63]
RELY 150	57	1233	33	1195	45.5%	1.68 [1.11, 2.57]
ROCKET-AF	0	0	0	0		Not estimable
Total (95% CI)		**4122**		**4132**	**100.0%**	**1.22 [0.92, 1.62]**
Total events	108		88			

Heterogeneity: Chi² = 4.26, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 1.39 (P = 0.17)



American Heart Association.

Nonvitamin-K-Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

George Ntaios, MD; Vasileios Papavasileiou, MD; Hans-Christoph Diener, MD; Konstantinos Makaritsis, MD; Patrik Michel, MD

Endpoint	RRR	ARR	NNT
Stroke/SE	14%	0,7%	134
Hemorrhagic stroke	57,9%	0,7%	139
Major bleeding	13%	0,8%	125
Intracranial bleeding	53,9%	1,0%	98

Conclusions—In the context of the significant limitations of combining the results of disparate trials of different agents, non-VKAs seem to be associated with a significant reduction in rates of stroke or systemic embolism, hemorrhagic stroke, and major bleeding when compared with warfarin in patients with previous stroke or transient ischemic attack. (***Stroke*.** **2012;43:3298-3304.**)

Secondary stroke prevention

Recommendations	Class	Level
Anticoagulation with heparin or LMWH immediately after an ischaemic stroke is not recommended in AF patients.	III (harm)	A
In patients who suffer a TIA or stroke while on anticoagulation, adherence to therapy should be assessed and optimized.	IIa	C
In patients who suffer a moderate-to-severe ischaemic stroke while on anticoagulation, anticoagulation should be interrupted for 3-12 days based on a multidisciplinary assessment of acute stroke and bleeding risk.	IIa	C
In AF patients who suffer a stroke, aspirin should be considered for prevention of secondary stroke until the initiation or resumption of oral anticoagulation.	IIa	B
Systemic thrombolysis with rtPA is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if aPTT is outside normal range).	III (harm)	C
NOACs are recommended in preference to VKAs or aspirin in AF patients with a previous stroke.	I	B
After TIA or stroke, combination therapy of OAC and an antiplatelet is not recommended.	III (harm)	B
After intracranial haemorrhage, oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled.	IIb	B

European Heart Journal - doi:10.1093/eurheartj/ehw210

Conclusioni 1

Warfarin-naive

- NAO preferibili a warfarin
  - Difficoltà di monitoraggio dell'INR
  - **Pregresso ictus ischemico**
  - **Pregressa emorragia intracranica**
  - In caso di giovane età
  - In caso candidato a cardioversione elettrica

Raviele A. G Ital Cardiol 2013

Conclusioni 2

Warfarin-experienced

- Switch ai NAO
  - Difficoltà logistiche nel monitoraggio dell'INR
  - Labilità dell'INR
  - Impiego giornaliero di basse dosi di W (8-10mg/set.)
  - Pregressa emorragia maggiore (esclusa gastrointestinale)
  - Qualità subottimale TAO (TTR <60%)
  - Impiego a lungo termine di farmaci interferenti con W e non con NAO
  - **Pregressa emorragia cerebrale in terapia con W con INR in range terapeutico**
  - **Pregresso ictus/TIA in corso di terapia con W con INR in range terapeutico**

Raviele A. G Ital Cardiol 2013

Piano della presentazione

1. Dimensione e rilevanza del problema:
   lo stroke cardioembolico da FA

2. La farmacoprofilassi: NOAC vs VKA

3. La farmacoprofilassi secondaria: NOAC vs VKA

4. **Il problema dello stroke embolico criptogenetico**

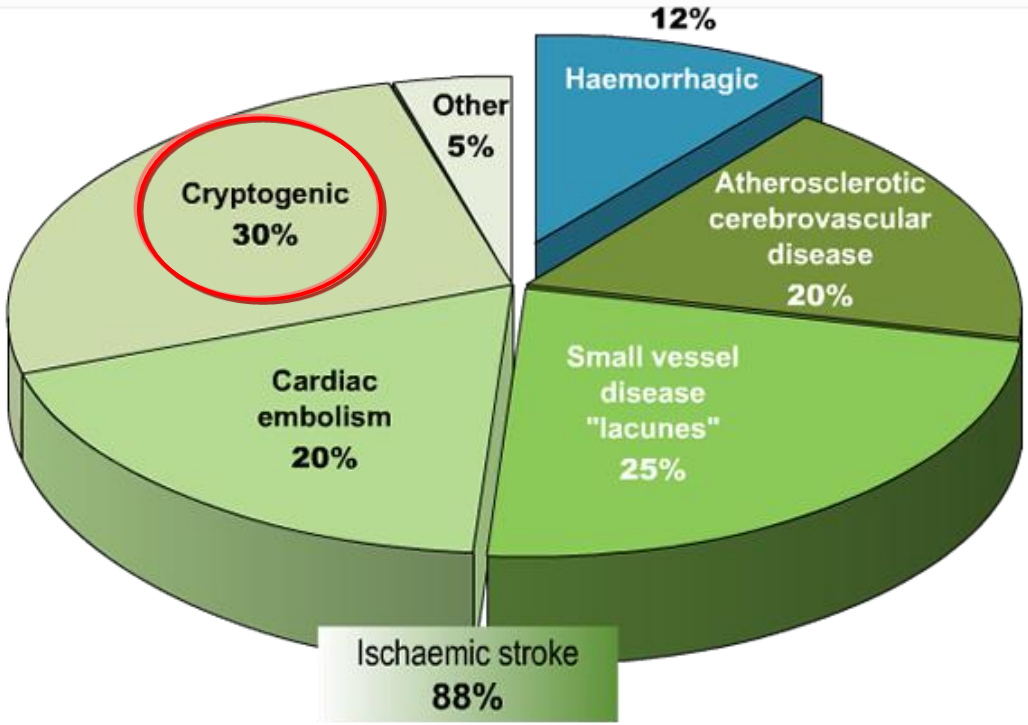
5. Problemi pratici nell'uso dei NAO

Classificazione su base fisiopatologica dei sottotipi dell'ictus ischemico

(criteri del TOAST, 1993)

- Aterosclerosi dei vasi di grosso calibro
- Cardioembolia (possibile/probabile)
- Occlusione dei piccoli vasi
- Ictus da cause diverse
- Ictus da cause non determinate

a. identificazione di due o più cause
b. valutazione negativa
c. valutazione incompleta



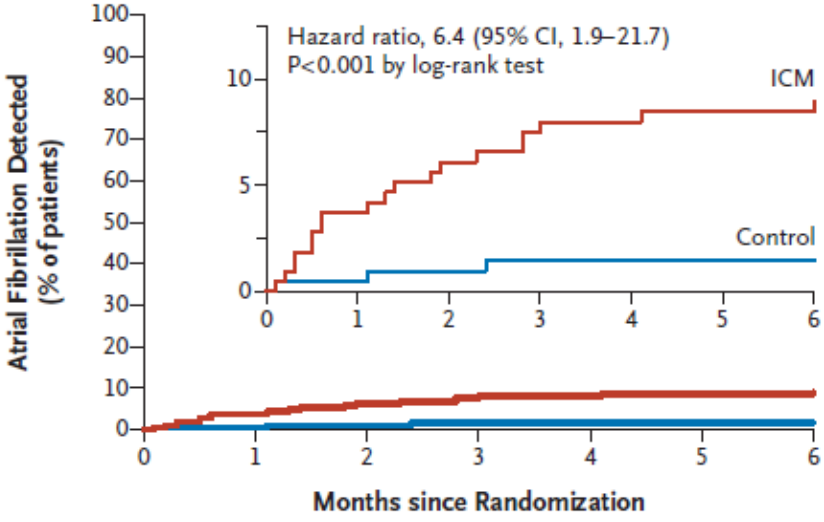
The NEW ENGLAND JOURNAL of MEDICINE

Cryptogenic Stroke and Underlying Atrial Fibrillation

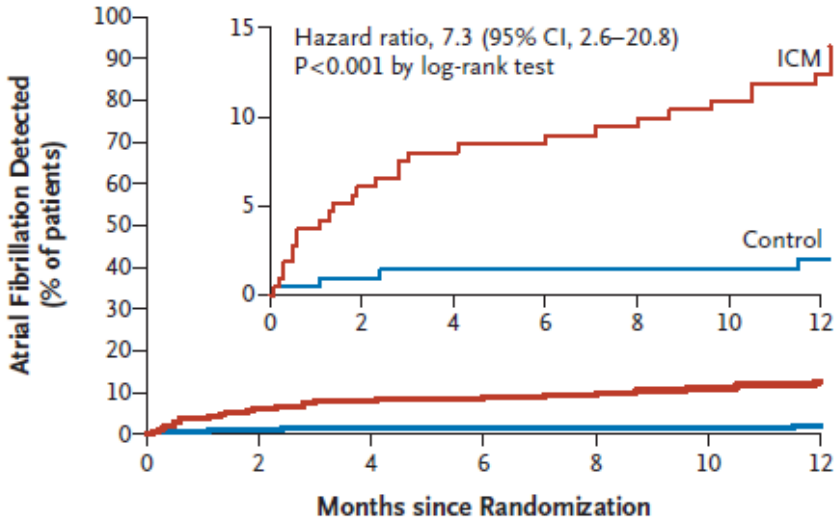
CRYSTAL AF Investigators

JUNE 26, 2014

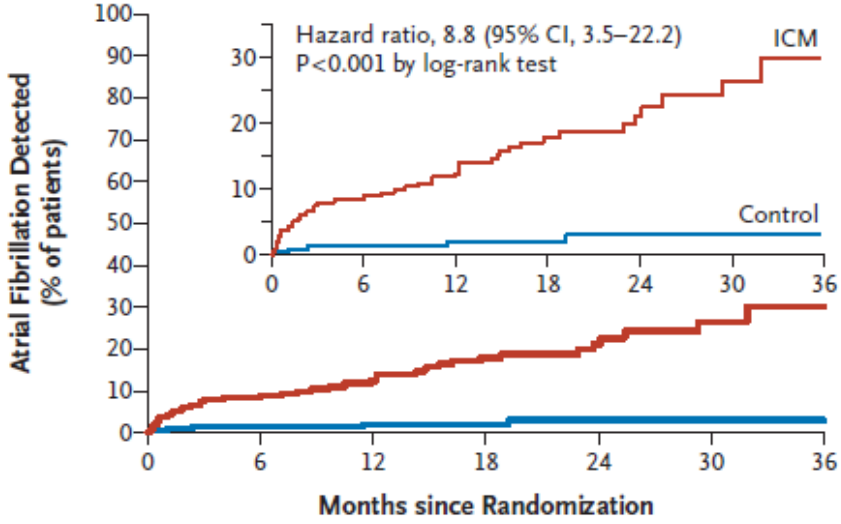
A Detection of Atrial Fibrillation by 6 Months



B Detection of Atrial Fibrillation by 12 Months



C Detection of Atrial Fibrillation by 36 Months



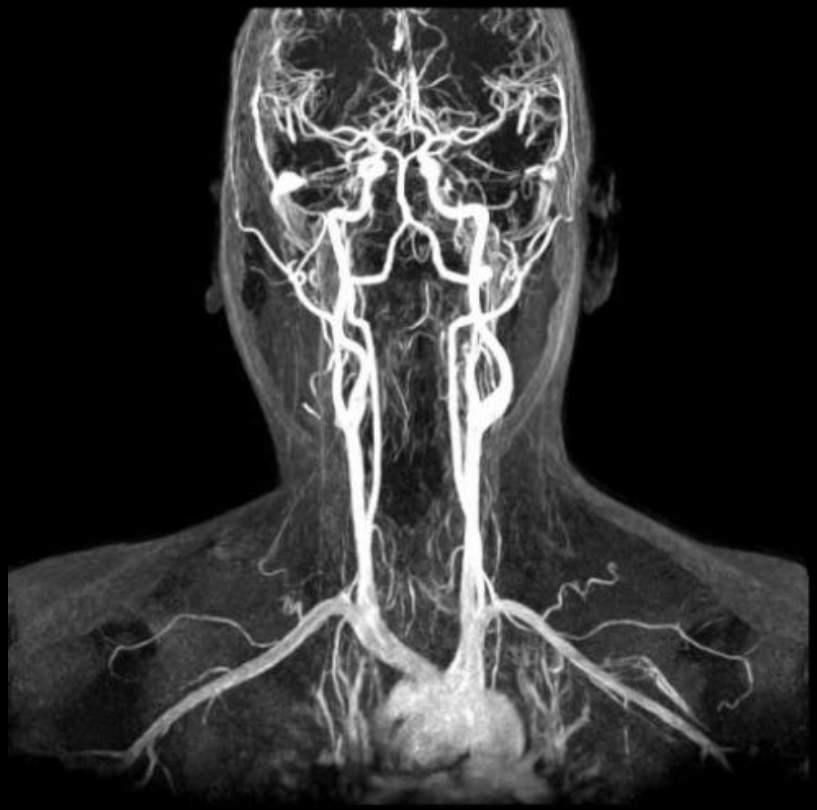
6 m → 1,4 vs 8,9%

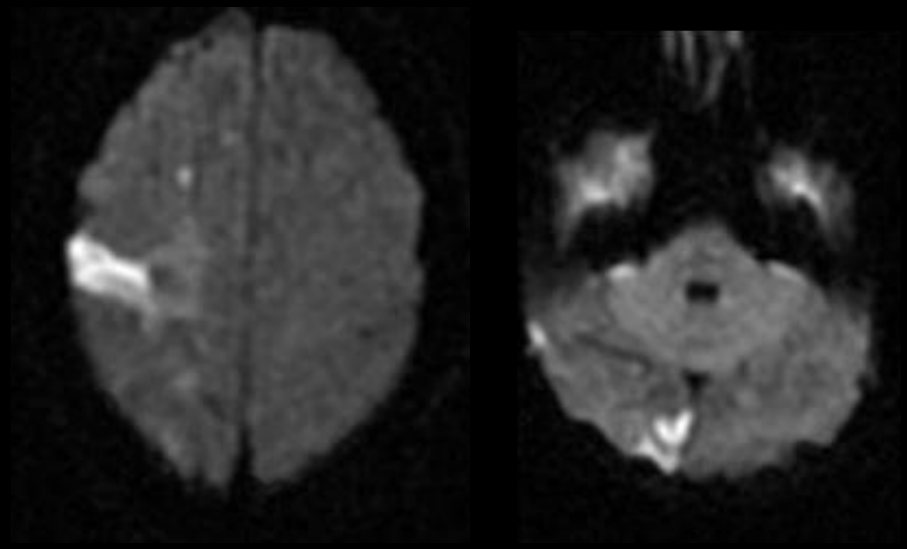
12 m → 2 vs 12,4%

36 m → 3 vs 30%

Stroke embolico criptogenetico:

E’ proprio necessario e costo-efficace insistere con i monitoraggi ECG prolungati alla ricerca della FA ?





Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

Lancet Neurol 2014; 13: 429–38

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

- Stroke detected by CT or MRI that is not lacunar†
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism‡
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.

Additional advanced diagnostic testing is unlikely to be a pragmatic solution for cryptogenic stroke because of the expense, additional diagnostic delays, and poor general availability…

…in terms of net clinical benefit that combines stroke and major haemorrhage (and particularly intracranial haemorrhage), NOACs seem likely to be of overall benefit in patients with ESUS.

Piano della presentazione

1. Dimensione e rilevanza del problema:
   lo stroke cardioembolico da FA

2. La farmacoprofilassi: NOAC vs VKA

3. La farmacoprofilassi secondaria: NOAC vs VKA

4. Il problema dello stroke embolico criptogenetico

5. **Problemi pratici nell'uso dei NAO**

Comparative PK/PD of NOACs

	Dabigatran[a]	Rivaroxaban[a,b]	Apixaban[a,c]	Edoxaban[d-f]
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to C_{max}	1.25-3	2-4	3-4	1-2
CYP metabolism, %	None	66	15	< 4
Bioavailability, %	6.5	80	50	62
Transporters	P-gp	P-gp	P-gp	P-gp
Protein binding, %	35	93	87	55
Half-life, hours	12-14	5-9	8-15	8-10
Renal clearance, %	80	35*	25	35

*An additional 33% is excreted unchanged in urine

a. Eriksson BI, et al. *Clin Pharmacokinet*. 2009;48:1-22[24]; b. Xarelto® PI 2011[25]; c. Eliquis® Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK. 2012[26]; d. Ruff CT, et al. *Hot Topics Cardiol.* 2009;18:7-14[27]; e. Matsushima N, et al. AAPS 2011. Poster T2632[28]; f. Ogata K, et al. *J Clin Pharmacol*. 2010;50:743-753.[29]

Table 5 Effect on NOAC plasma levels ('area under the curve, AUC') from drug–drug interactions and clinical factors and recommendations towards NOAC dosing

	Via	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (reduce dose by 50%)[a]	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[24]	+40%[SmPC]	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%)[a]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[SmPC]	No data yet	Up to +160%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	No data yet	+30–54%[26,27]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	−66%[34]	−54%[SmPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%[22–24]	No data yet	No effect	No effect[21,25]

NOAC Dose Reduction

RE-LY[a] Dabigatran	ROCKET AF[b] Rivaroxaban	ARISTOTLE[c] Apixaban	ENGAGE-AF[d] Edoxaban
• None – US Regulators • CrCl 15-30 mL/min: 75 mg BID • Age >80 years • CrCl 30-50 mL/min + P-gp inhibitor, dronedarone, or ketoconazole	• 20 → 15 mg QD for – CrCl <30-49 mL/min	• 5 → 2.5 mg BID for ANY TWO of – Age ≥80 years – Body weight ≤60 kg – Serum creatinine ≥1.5 mg/dL • US Regulators – Strong dual inhibitors of CYP3A4 and P-gp	• 60 → 30 mg QD or 30 → 15 mg QD for – CrCl 30-50 mL/min – Body weight ≤60 kg – Use of quinidine, verapamil, or dronedarone

BID = twice daily; QD = once daily; CrCl = creatinine clearance; P-gp = P-glycoprotein

a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151[15]; b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891[16]; c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[17]; d. Giuliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[18]

European Heart Journal
doi:10.1093/eurheartj/eht134

EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary†

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

Sospensione NAO in caso di interventi chirurgici programmati

Table 10 Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of 1 to 3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Ophthalmology
Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)
Interventions with low bleeding risk
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
Angiography
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with high bleeding risk
Complex left-sided ablation (pulmonary vein isolation; VT ablation)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy

European Heart Journal
doi:10.1093/eurheartj/eht134

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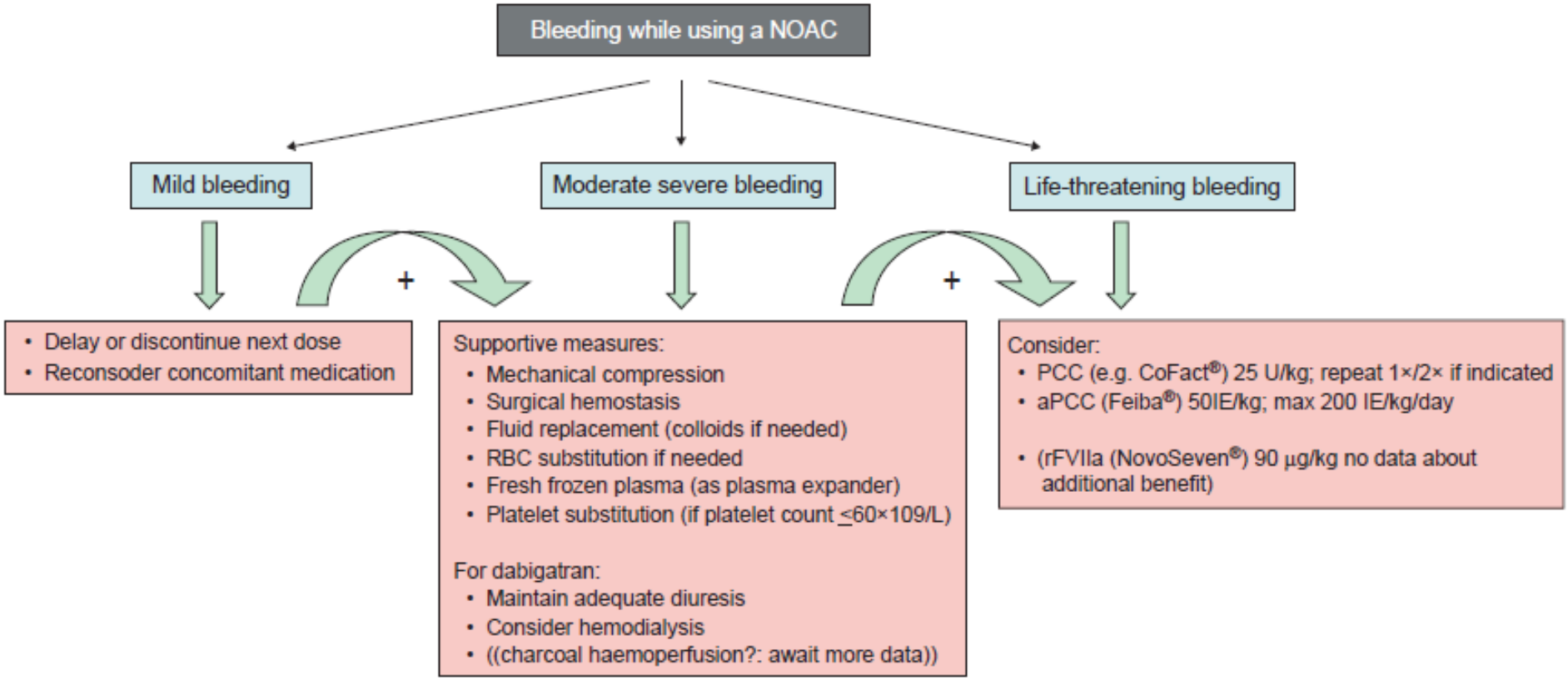
Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

Sospensione NAO in caso di interventi chirurgici programmati

Table 9 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

COMPLICANZE EMORRAGICHE



Pro: "Antidote for new anticoagulants" – Specific target of inhibition requires a specific target for neutralisation

Vanessa Roldán[1], Francisco Marín[2]

[1]Hematology and Medical Oncology Unit, Hospital Universitario Morales Meseguer, University of Murcia, Murcia, Spain; [2]Cardiology Unit, Hospital Universitario Virgen de la Arrixaca, University of Murcia, Murcia, Spain

Thromb Haemost 2012; doi:10.1160/TH12-06-0440

Contra: "Antidotes for novel anticoagulants?" – Do we really need them

Elise S. Eerenberg; Marcel Levi; Harry R. Buller

Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Thromb Haemost 2012; doi:10.1160/TH12-05-0298

Antidoto

Contro

- Emivita Breve
- Minor numero di complicanze emorragiche (Intracraniche!!!)
- Simile a EBPM/Fonda (antidoto?)

NOAC Antidotes in Clinical Trials

Andexanet[a] (PRT064445)	• Antidote for factor Xa inhibitors • Recombinant protein, targets and sequesters both direct and indirect Factor Xa inhibitors with high specificity
Aripazine[b] (PER977)	• Antidote for factor Xa inhibitors, DTIs, LMW heparins, and fondaparinux • Synthetic small molecule; reversal effect through direct binding to anticoagulant
Idarucizumab[c] (BI 655075)	• Antidote for DTIs • Fully humanized antibody fragment

DTI = direct thrombin inhibitor; LMW = low-molecular-weight

a. ClinicalTrials.gov[20]; b. Dolgin E. *Nat Med*. 2013;19:251[21]; c. ClinicalTrials.gov .[22]

NAO e ICH

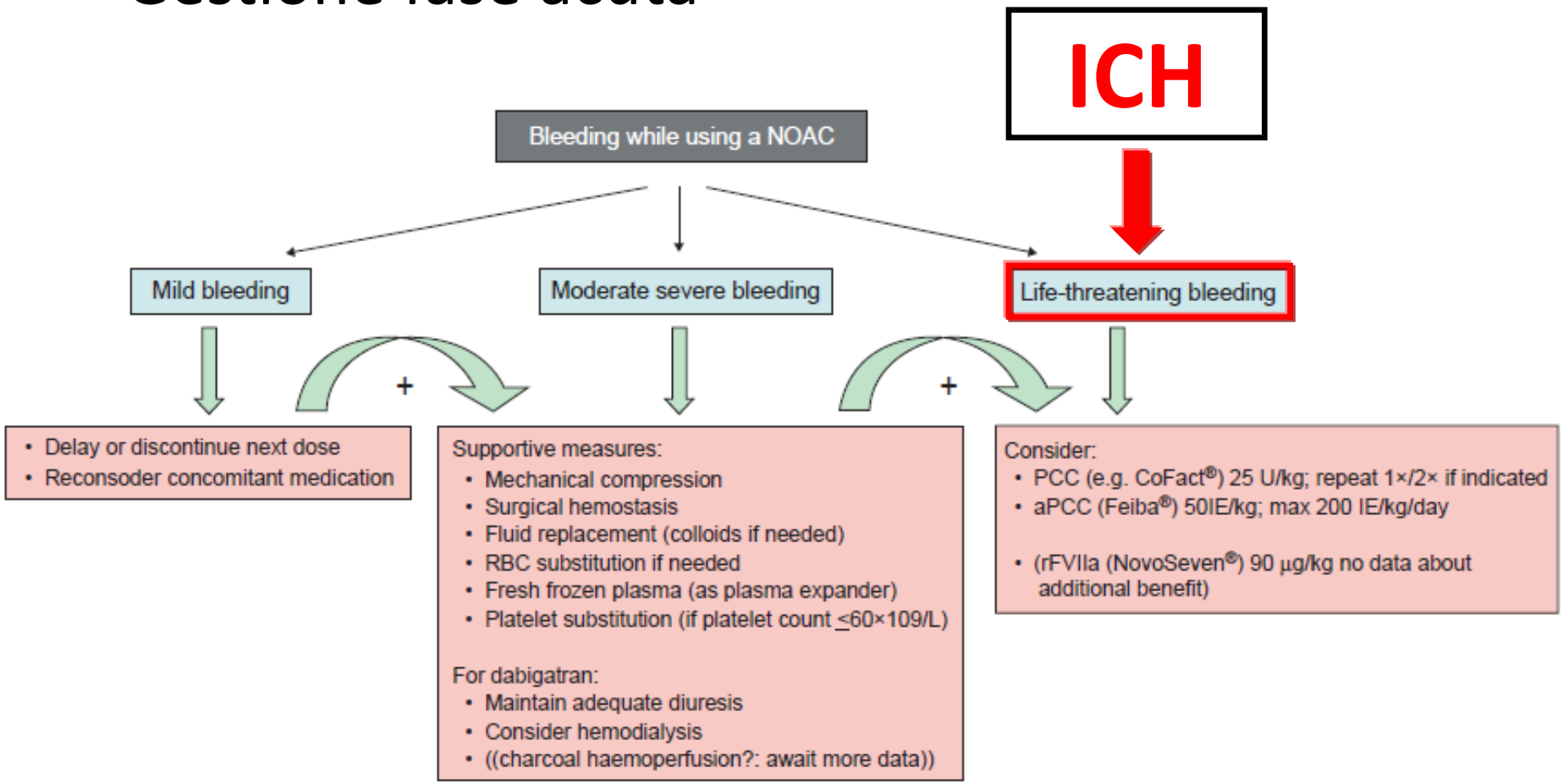
- Gestione fase acuta
- Gestione fase post acuta

NAO e AIS

- Gestione fase acuta
- Gestione fase post acuta

COMPLICANZE EMORRAGICHE

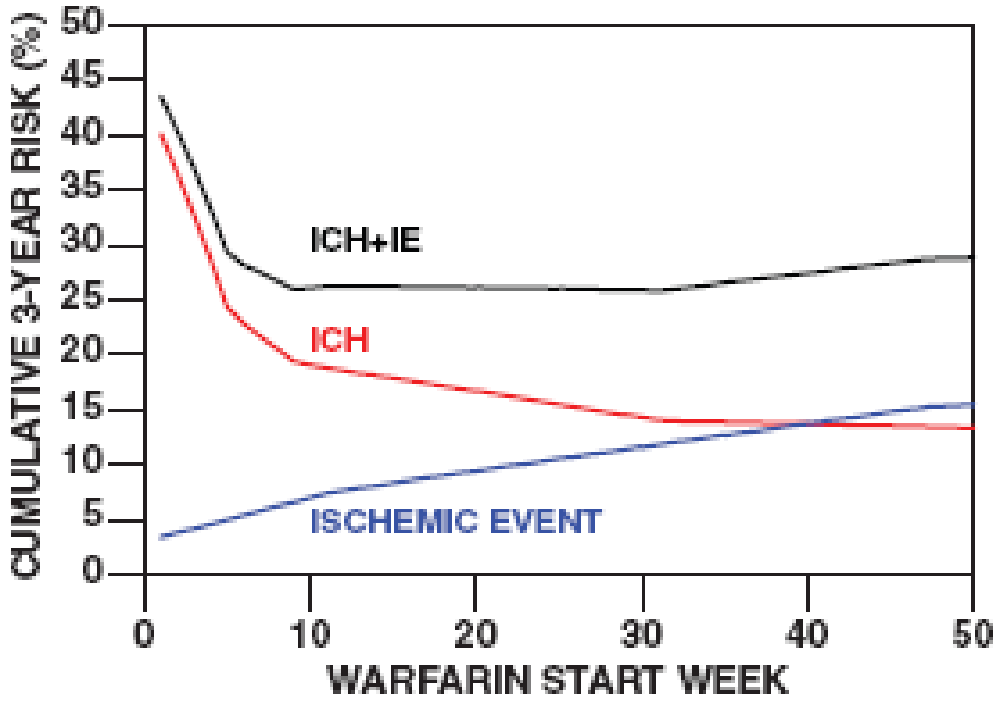
- Gestione fase acuta



Optimal Timing of Resumption of Warfarin After Intracranial Hemorrhage

Ammar Majeed, MD; Yang-Ki Kim, MD; Robin S. Roberts, PhD;
Margareta Holmström, MD, PhD; Sam Schulman, MD, PhD

Conclusion—The optimal timing for resumption of warfarin therapy appears to be between 10 and 30 weeks after warfarin-related intracranial hemorrhage. (*Stroke*. 2010;41:2860-2866.)



Raccomandazioni
ripresa TAO dopo ICH

SPREAD
Stroke Prevention And Educational Awareness Diffusion

Sintesi 12–14

Per la ripresa del trattamento anticoagulante in pazienti con pregressa emorragia cerebrale va tenuto conto che: A) il rischio emorragico è del 2,1%-3,7% annuo. B) la ripresa della terapia anticoagulante aumenta il rischio di sanguinamento cerebrale di cinque volte ma riduce il rischio di eventi ischemici del 90%.

- **Controindicazioni assolute alla ripresa della TAO**

  Emorragia lobare correlabile ad angiopatia amiloidea

- **Ripresa della terapia TAO dopo tre settimane**

  Nel paziente a rischio trombo embolico elevato per: CHA_2DS_2-VASc>$_2$ o $CHADS_2$ >3, protesi valvolare meccanica mitralica, trombosi delle camere cardiache, tromboembolismo venoso e arterioso <30 giorni.

- **Ripresa della terapia TAO dopo la trentesima settimana**

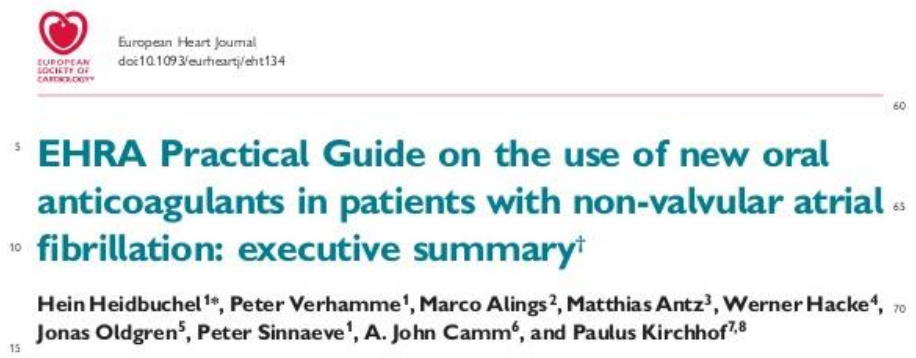
  Pazienti ad alto rischio emorragico per: microbleeds multiple alla RM-gradient ECHO, leucoaraiosi, emorragie lobari non correlabili ad angiopatia amiloidea

- **In tutti gli altri casi ripresa della terapia TAO tra la decima e la trentesima settimana**

*** GPP**

Il gruppo Spread ritiene che in casi particolari sia possibile riprendere la terapia con anticoagulanti orali prima della terza settimana.

Raccomandazioni
ripresa TAO dopo ICH



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- precedente emorragia intracranica → controindicazione all'uso di Warfarin e NAO secondo RCP
- è possibile riprendere **NAO dopo 10-14 gg** dall'ICH se alto rischio tromboembolico e basso rischio emorragico
- considerare la significativa RR ICH con NAO rispetto a Warfarin
- considerare prevenzione non farmacologica (ablazione o chiusura auricola).

Il PT RER

CARATTERISTICHE DEI PAZIENTI (Criteri di Elezione : almeno 1)

☐ **paziente già in trattamento con AVK** ☐ Time in Therapeutic Range (TTR*): ____ % o ☐ controlli in range** ____ %

- ☐ difficoltà logistico organizzative
- ☐ necessità di dosi di AVK < 8,25 mg/sett. per warfarin e di 6 mg/sett. per acenocumarolo
- ☐ pregressa emorragia maggiore in corso di INR sovraterapeutico
- ✓ pregressa emorragia intracranica

☐ **nuovo trattamento con anticoagulanti orali**

- ☐ paz. in FA trattati solo con ASA
- ☐ difficoltà logistico organizzative
- ☐ condizioni cliniche che rendono gravosa o non accettabile la terapia con AVK
- ☐ paz. ad alto rischio di interazioni farmacologiche con gli AVK
- ✓ pregressa emorragia intracranica
- ☐ FA di nuova diagnosi da sottoporre a cardioversione elettrica

Ripresa TAO dopo ICH

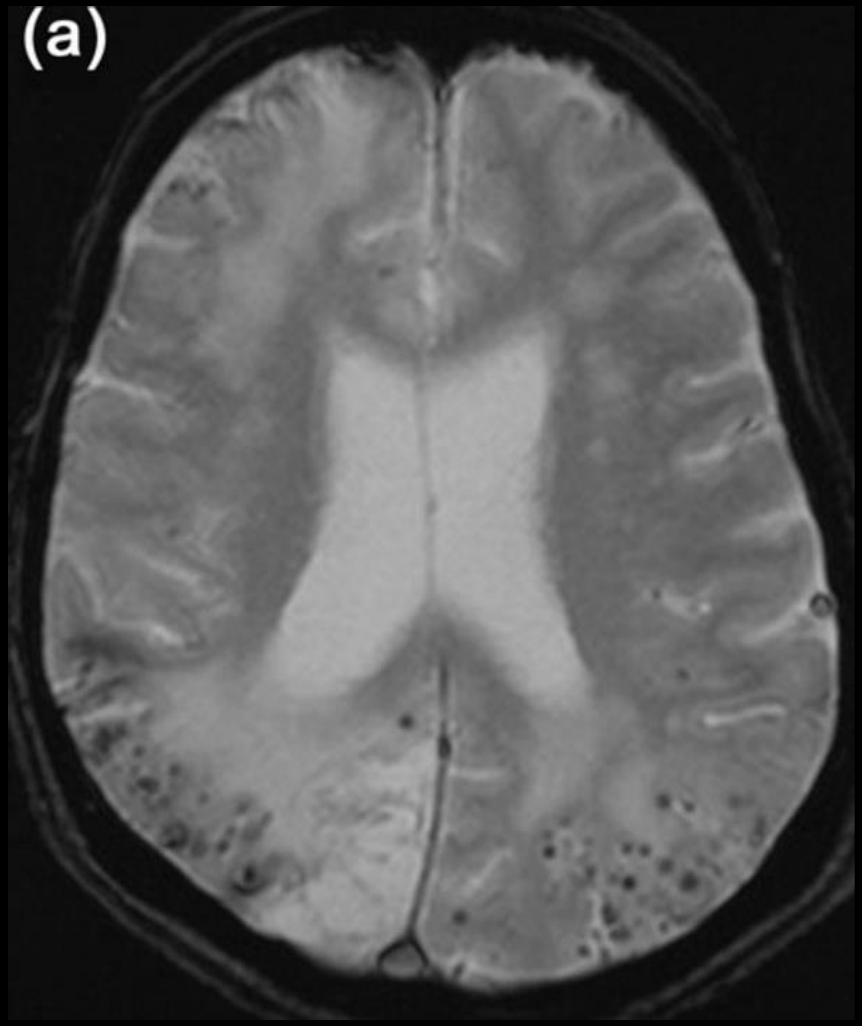
Anticipare (1-3 sett) se:

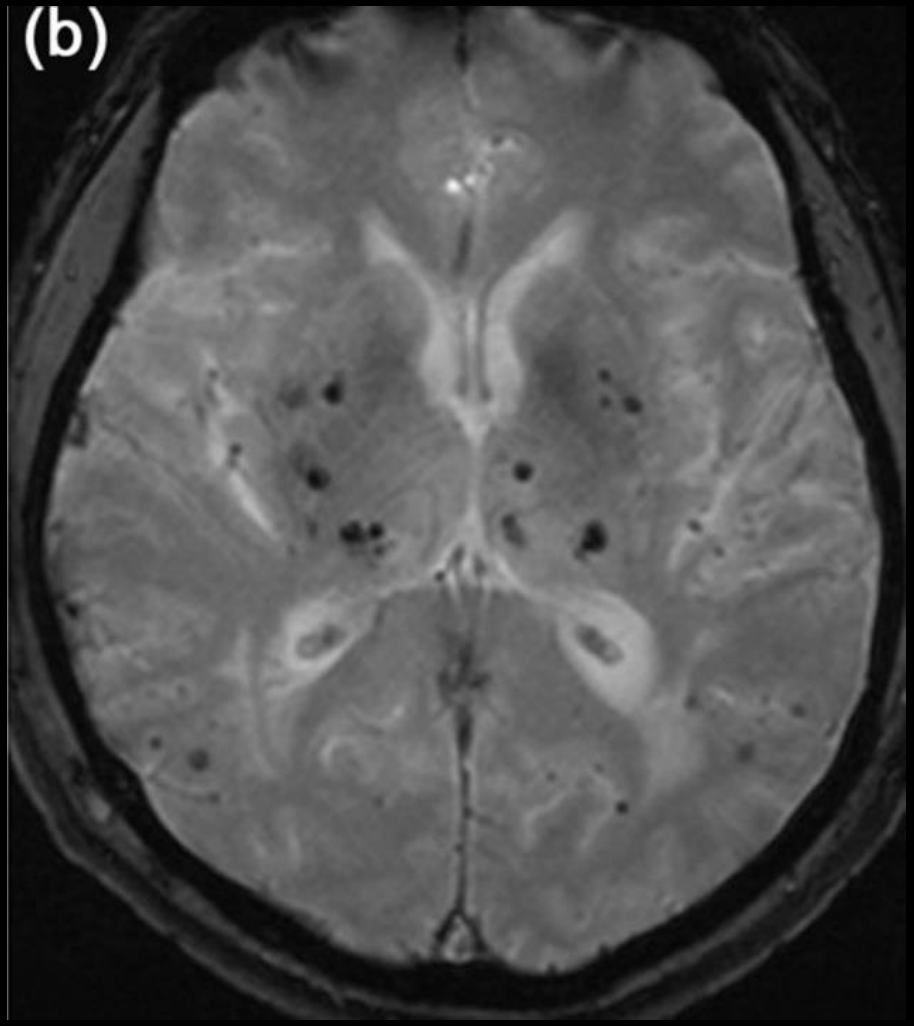
- CHA_2DS_2-VASc ≥ 2
- Protesi meccaniche
- Disfunzione Vsx
- Trombosi in Asx/Vsx
- Asx dilatato
- PA ben controllata
- PLTs nella norma

Ritardare (>30 sett) o cambiare strategia se:

- Emorragia lobare
- Diabete
- Microbleeds (GE-MRI)
- Leucoaraiosi
- PA di difficile controllo
- Piastrinopenia
- Abuso alcol

Lobar (a) and deep (b) microbleeds





NOAC e AIS

- Gestione **fase acuta**

Trombolisi ev possibile se:

- ultima assunzione nota e **> 24/48 h**

e

- **dTT** (Dabigatran) o **anti-Xa** (Rivaroxaban, Apixaban) normali

o, se non disponibili

- **aPTT** (Dabigatran) e **PT** (Rivaroxaban, Apixaban) normali

Se possibile, in presenza di occlusione di grossi vasi, preferire **rivascolarizzazione meccanica endovascolare**

Hans-Christoph Diener, Christian Foerch, Hanno Riess, Joachim Röther, Gerhard Schroth, Ralph Weber ***Lancet Neurol*** **2013; 12: 677–88**

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Recanalization Therapies in Acute Ischemic Stroke Patients: Impact of Prior Treatment with Novel Oral Anticoagulants on Bleeding Complications and Outcome - A Pilot Study

David J. Seiffge, Robbert-Jan Van Hooff, Christian H. Nolte, Yannick Béjot, Guillaume Turc, Benno Ikenberg, Eivind Berge, Malte Persike, Nelly Dequatre-Ponchelle, Daniel Strbian, Waltraud Pfeilschifter, Andrea Zini, Arnstein Tveiten, Halvor Næss, Patrik Michel, Roman Sztajzel, Andreas Luft, Henrik Gensicke, Christopher Traenka, Lisa Hert, Jan F. Scheitz, GianMarco De Marchis, Leo H. Bonati, Nils Peters, Andreas Charidimou, David J. Werring, Frederick Palm, Matthias Reinhard, Wolf-Dirk Niesen, Takehiko Nagao, Alessandro Pezzini, Valeria Caso, Paul Nederkoorn, Georg Kaegi, Alexander von Hessling, Visnja Padjen, Charlotte Cordonnier, Hebun Erdur, Philippe A. Lyrer, Raf Brouns, Thorsten Steiner, Turgut Tatlisumak and Stefan T. Engelter

Circulation. published online July 31, 2015:

NOAC e AIS

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- Gestione **fase post-acuta**
  Ripresa/avvio TAO dopo AIS

Considerare le dimensioni dell'area ischemica (regola 1-3-6-12)

Inclusione nei trials sui NAO dopo 7-14 giorni da AIS

Non necessario bridging EBPM – NAO

ASA non è un alternativa: se Warfarin controindicato, considerare Apixaban in quanto superiore ad ASA

Ripresa-avvio TAO dopo TIA/AIS

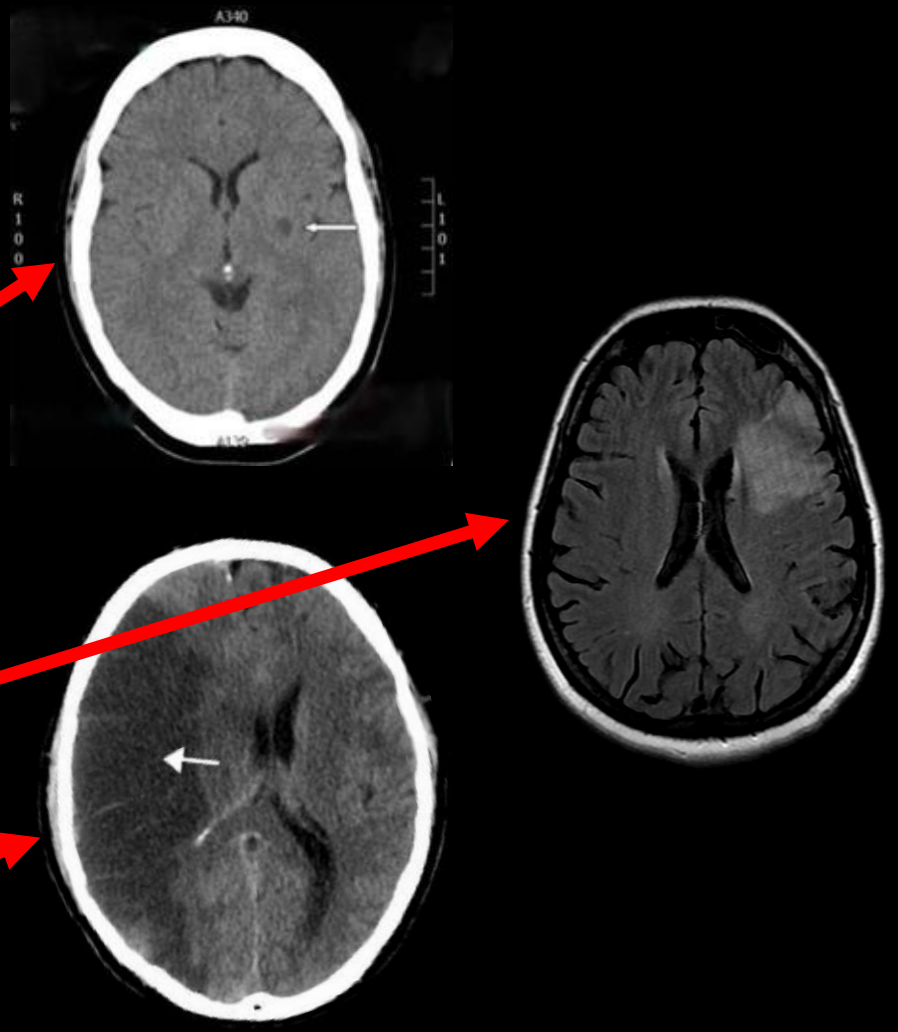
After days

1 → TIA

3 → Mild stroke

6 → Moderate stroke

12 → Severe stroke



Review

Management of acute stroke in patients taking novel oral anticoagulants

Graeme J. Hankey[1]*, Bo Norrving[2], Werner Hacke[3], and Thorsten Steiner[3,4]

International Journal of Stroke Vol 9, July 2014, 627–632

Ripresa-avvio TAO dopo AIS

Anticipare (1-3 gg) se:

- TIA o minor stroke
- CHA_2DS_2-VASc ≥ 2
- Alto rischio embolico (protesi meccaniche, disfunzione Vsx, trombosi Asx/Vsx, Asx dilatato)
- PA ben controllata
- PLTs nella norma
- Glicemia nella norma

Ritardare (2-3 sett) se:

- Major stroke
- Basso rischio embolico (lone AF)
- Microbleeds (GE-MRI)
- Leucoaraiosi
- PA di difficile controllo
- Diabete

Piano Terapeutico

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Piano Terapeutico

Età < 65 ☐ (Dabigatran, Rivaroxaban) ≥ 65 ☐ (Dabigatran, Rivaroxaban, Apixaban)

F.A. non valvolare ☐ F.A. permanente ☐ (Dabigatran, Rivaroxaban, Apixaban)
F.A. parossistica ☐ (Dabigatran, Apixaban)

Clearance Creatinina …….. (uso NAO non raccomandato se VFG < 30 ml/min)

Farmaco proposto: PRADAXA 110 mg ☐ PRADAXA 150 mg ☐
ELIQUIS 2,5 mg☐ ELIQUIS 5 mg☐
XARELTO 15 mg☐ XARELTO 20 mg ☐

Medico Proponente: Dr. Alessandro De Vito ☐ Dr. Cristiano Azzini ☐
Telefono : 0532 239189 e-mail: aledevito@hotmail.com – cristianoazzini@hotmail.com
U.O. Neurologia – Stroke Unit – Dipartimento Neuroscienze – Riabilitazione – AOU Ferrara
Data e firma……

MODALITA' PRESCRITTIVE AZOU FE

UUOO autorizzate secondo linee indirizzo RER

↓

medici propositori segnalati da direttore UO a direzione sanitaria

↓

Centro TAO

↓

PT e follow up pazienti


LO STROKE: TERAPIA INTERVENTISTICA E MODELLI ORGANIZZATIVI
CON IL PATROCINIO
COMUNE DI FERRARA
UNIVERSITÀ DEGLI STUDI DI FERRARA
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara
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2016
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Direttore: Dr.ssa Tugnoli Valeria

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