CENTRI EMOSTASI E TROMBOSI, SPECIALISTI OSPEDALIERI E MEDICINA DEL TERRITORIO NELLA GESTIONE DELLE MALATTIE EMORRAGICHE E TROMBOEMBOLICHE

Emorragie e trombosi in corso di trattamento anticoagulante

Cremona, 10 marzo 2017

Francesco Marongiu

University of Cagliari,
Cagliari, Italy

Internal Medicine and
Haemostasis and Thrombosis Unit

DOAC versus Warfarin in the RCT

AF

Anticoagulant	Major Bleeding %/yr	Stroke or systemic embolism %/yr
Dabi… 150 mg	3.11	1.11
	2.71	1.53
	3.36	1.69
	3.60	2.10
	3.40	2.40
Api… 5 mg	2.13	1.27
Warfarin	3.09	1.60
Edoxaban 60 mg	2.75	1.25
Edoxaban 30 mg	1.61	1.25
Warfarin	3.43	1.77

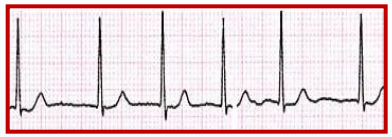
Major Bleeding
Warfarin: >3 %/y
DOAC: 2.13-3.11 %/y

NOA and Atrial Fibrillation

Anticoagulant	ICH	GI Bleeding
Dabigatran 150 mg	0.10	1.51
Dabigatran 110 mg	0.12	1.12
Warfarin	0.38	1.02
Rivaroxaban 20 mg	0.50	2.00
Warfarin 2.0-3.0 INR	0.70	1.24
Apixaban 5 mg	0.24	0.76
Warfarin	0.47	0.86
Edoxaban 60 mg	0.26	1.51
Edoxaban 30 mg	0.16	0.82
Warfarin	0.47	1.23

Am J Med 2016 Aug 29. pii: S0002-9343(16)30652-0

%/year



FA

Sono non inferiori, superiori o inferiori a seconda del dosaggio

Ictus ischemico		
Anticoagulante	**HR e IC 95 %**	**p**
Dabigatran 110 mg	**1.11, 0.88-1.39**	**0.35**
Dabigatran 150 mg	**0.76, 0.59-0.97**	**0.03**
Rivaroxaban 20 mg	**0.99, 0.82-1.20**	**0.91**
Apixaban 5 mg	**0.92, 0.74-1.13**	**0.42**
Edoxaban 60 mg	**1.00, 0.83-1.19**	**0.97**
Edoxaban 30 mg	**1.41, 1.19-1.67**	**<0.001**

Solo il Dabigatran 150 è superiore al Warfarin.
Edoxaban 30 mg è inferiore al Warfarin.
Dabigatran 110 non è non inferiore al Warfarin.
Gli altri sono non inferiori al Warfarin.

Outcomes in a Warfarin-Treated Population With Atrial Fibrillation

Outcomes	Warfarin (n=34851) and AF
Any thromboembolism	2.12 % (1.99-2.24)
Arterial	1.54 % (1.44-1
Venous	0.12 % (0.09

2,0 % ~

Outcomes	Warfarin (n=34851) a
Any major bleeding	2.04 % (1.92-2.16)
Intracranial	0.41 % (0.35-0.46)
GI tract	0.67 % (0.60-0.74)

JAMA Cardiol. 2016;1(2):172-180.

Outcomes in a Warfarin-Treated Population With Atrial Fibrillation

1.6 % ~

	Warfarin TTR ≥ 70 n=22185	Warfarin TTR <70 % n=19428
Major bleeding	1.61, 1.49-1.73 %	3.81, 3.51- 4.11 %
Intracranial	0.34, 0.28-0.39 %	0.72, 0.59-0.85 %
GI bleeding	0.56, 0.49-0.63 %	1.26, 1.09-1.43 %

An optimal management of the therapy induces a low bleeding risk

JAMA Cardiol. 2016;1(2):172-180.

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

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

La tecnica del *propensity* score permette di creare gruppi di pazienti con simile probabilità di ricevere un trattamento.

Il *propensity* score rappresenta la metodologia statistica più utilizzata per ridurre i *bias* nel confronto tra gruppi negli studi osservazionali: creare un ottimale bilanciamento tra trattamenti

Covariate usate per il Propensity score:
età, sesso, ictus ischemico, TIA, ipertensione, diabete, cancro, aspirina, β-bloccanti, FANS, statine, CHA_2DS_2-VASc e HAS-BLED

BMJ 2016;353:i3189

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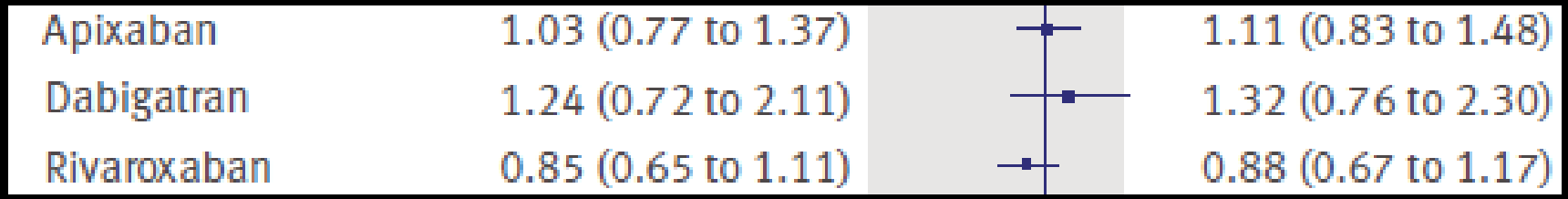
61 678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants.

When the analysis was restricted to systemic embolism and stroke and to ischaemic stroke, NOACs were not significantly different from warfarin.

HR and 95 % CI



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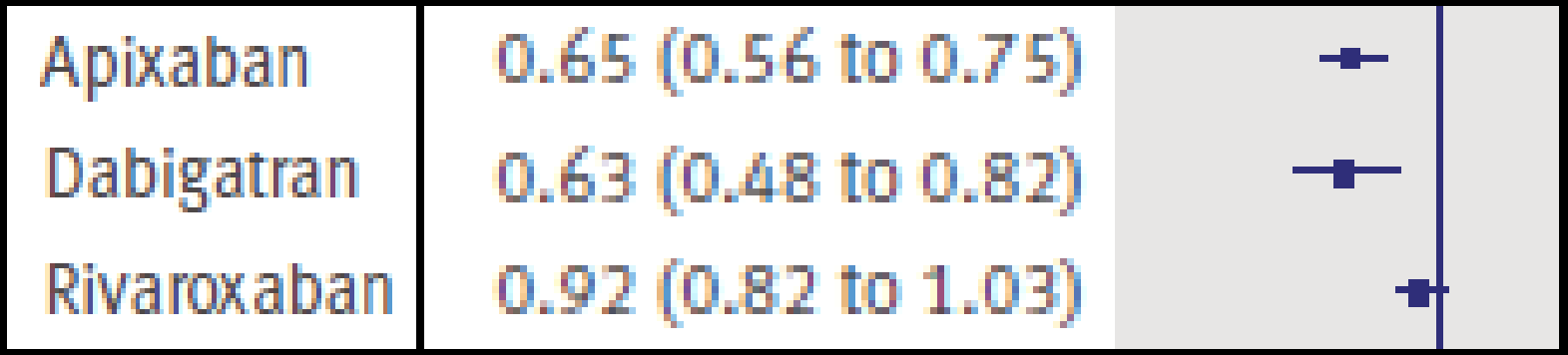
Annual risk of death:
significantly lower with Apixaban (5.2%), Dabigatran (2.7%),
compared with warfarin (8.5%)
but not with rivaroxaban (7.7%)

HR and 95 % CI



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2.4-5.3 %
~

Any bleeding:

nd dabigatran (2.4%) was significantly lower
5.0%).
varoxaban (5.3%) had comparable annual bleeding rates

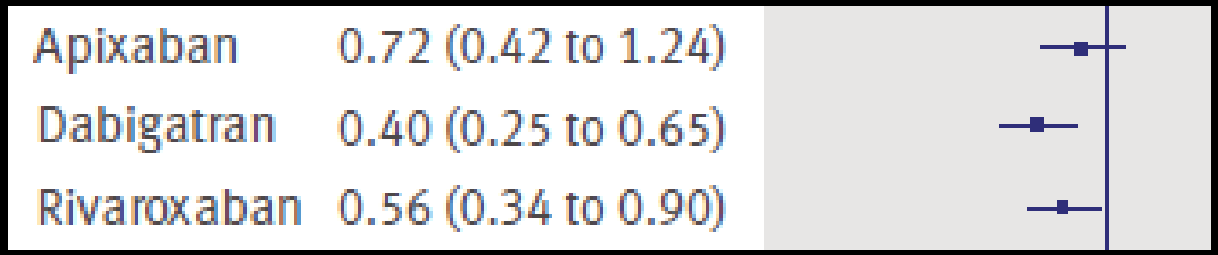
HR and 95 % CI

Commento
Warfarin 5 %:
percentuale altissima se la TAO è ben condotta

BMJ 2016;353:i3189

Intracranial bleeding

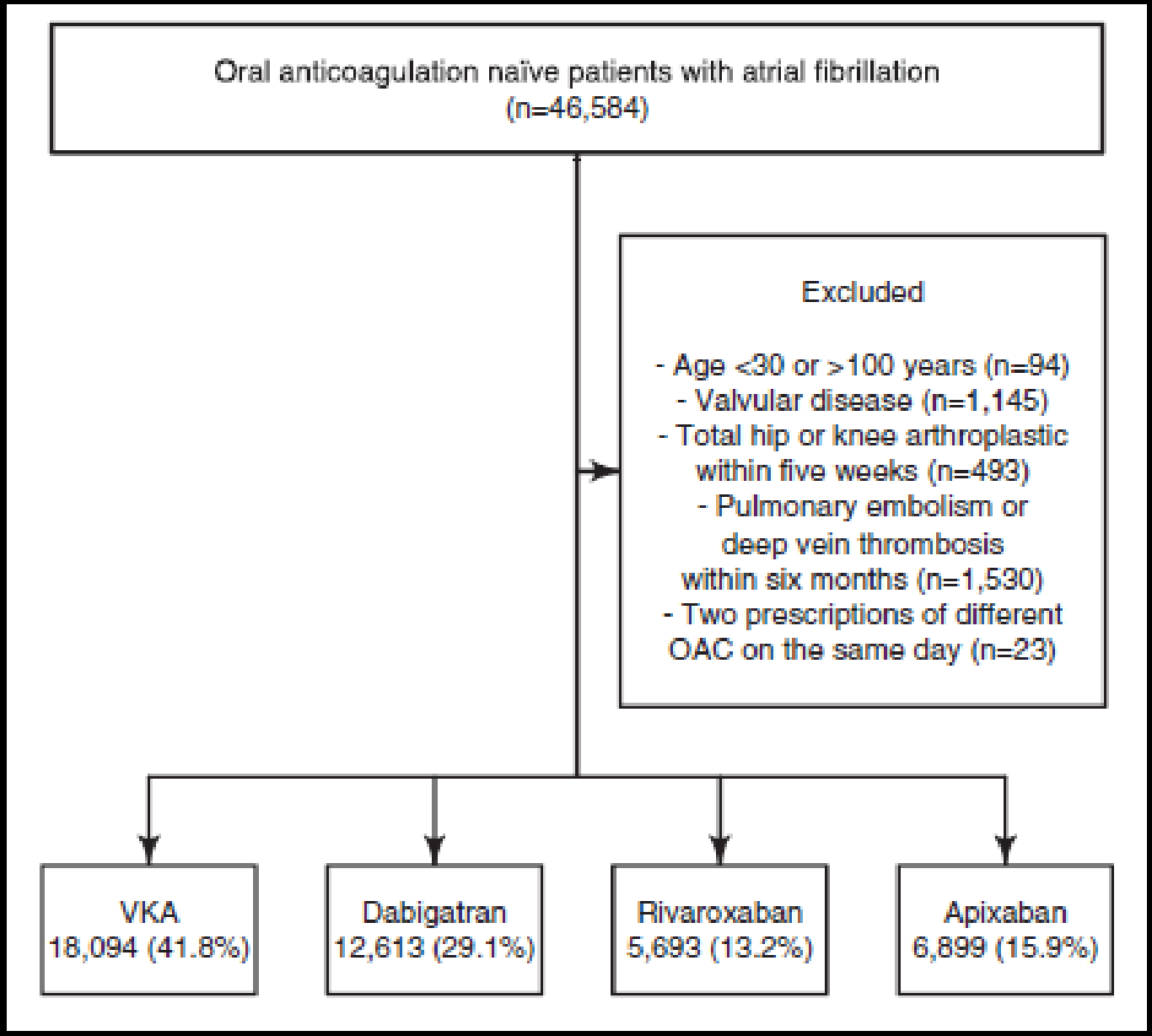
NOA:
percentuali maggiori rispetto ai Trials



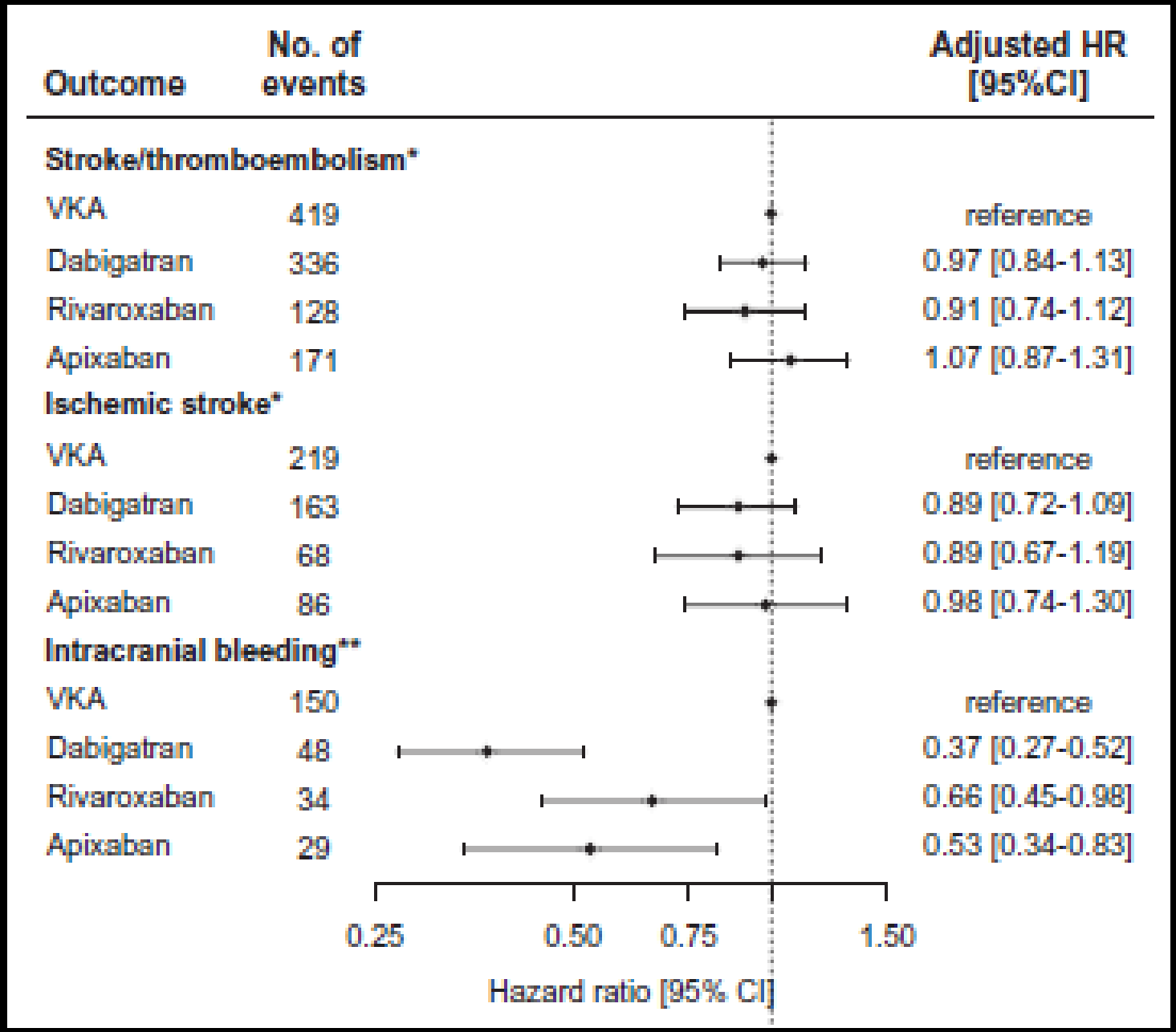
Warfarin 0.6 % year

Warfarin
(Trials):
0.38 - 0.70 %

BMJ 2016;353:i3189



European Heart Journal (2016) **0**, 1–9



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Good clinical results in warfarin-treated patients managed in italian anticoagulation clinics (the ISCOAT 2016 study). Comparison with the ISCOAT study published 20 years ago

Palareti G et al. 2016 (Manuscript submitted)

Patients n.	**5707**
Males n (%)	**3029 (53)**
Age mean (range) y	**73.0 (19.0)**
Age n (%) <70	**2069 (36.2)**
≥70	**3638 (63.8)**
>80	**1605 (28.1)**
Indication for anticoagulation n (%)	
Venous Thromboembolism	**1593 (28.0)**
Atrial fibrillation	**3516 (61.6)**
Heart-valve prosthesis	**219 (3.5)**
Biological	**115 (53.8)**
Mechanical	**101 (46.2)**
Heart-valve disease	**32 (0.56)**
Other	**347 (6.08)**

Quality of anticoagulation control	
median (IQR) percent time spent in relation to the therapeutic range (2.0-3.0 INR)	
Below	**21.0 (12.0-33.0)**
Within (TTR)	**66.0 (53.0-77.0)**
Above	**9.0(3.0-16.0)**
median (IQR) TTR in patients according the indication for treatment	**67.0 (54.0-77.0)**
AF	**65.0 (50.0-76.0)**
VTE	**51.0 (33.0-68.0)**
Other	
TTR in relation to age median (IQR)	
≤ 80 y	**65.0 (50.0-76.0)**
> 80	**66.0 (54.0-76.5)**

Events n. (rate % annually)	Bleeding complications	Thrombotic complications
Major events	123 (1.38)	47 (0.53)
Fatal	10 (0.11)	4 (0.04)
	Intracranial 38 (0.43; 7 fatal)	Stroke 12 (0.13; 4 fatal)
	Digestive 29 (0.32.6; 3 fatal)	TIA 12
	Haematuria 7	AMI 9 (0.10)
	Haemarthrosis 3	Recurrent VTE 7
	Other 45	SVT 5
		Arterial embolism 2
Sex		
Males	71 (1.48)	22 (0.46)
Females	52 (1.24)	25 (0.60)
Age		
<70	30 (1.0)	17 (0.58)
≥70	93 (1.55)	30 (0.50)
RR	1.50 (1.0-2.4) p=0.04	

Good clinical results in warfarin-treated patients managed in italian anticoagulation clinics (the ISCOAT 2016 study). Comparison with the ISCOAT study published 20 years ago

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	ISCOAT 2016 5007 paz	ISCOAT 1996 2745 paz
Major bleeding n. (% annually) [fatal]	123 (1.38)	28 (1.39)
Fatal	10 (0.11)	5 (0.25)
ICH	38 (0.43) [7]	9 (0.45) [5]
Gastrointestinal	29 (0.32) [3]	7 (0.35) [/]
Other	56 (45.5) [/]	12 (0.60) [/]
Major + NMCRB events occurring during the first 90 days of treatment n/N (%)	78/267 (29.2)	62/153 (40.5)

Anticoagulant	Major Bleeding	ICH
Dabigatran 150 mg	3.11	0.10
Dabigatran 110 mg	2.71	0.12
Warfarin	3.36	0.38
Rivaroxaban 20 mg	3.60	0.50
Warfarin 2.0-3.0 INR	3.40	0.70
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Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment

Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation

Daniela Poli, MD; Emilia Antonucci, MD; Sophie Testa, MD; Alberto Tosetto, MD; Walter Ageno, MD; Gualtiero Palareti, MD; for the Italian Federation of Anticoagulation Clinics (FCSA)

4093 pazienti (80-100 anni)
di cui 3015 (73.7 % con FA)

Fibrillazione Atriale
Sanguinamento maggiore
1.73 % anni/paz

Sanguinamento cerebrale
0.55 % anni/paz

Circulation 2011;124:824-29

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Major bleeding n. (% annually) [fatal]	123 (1.38)	28 (1.39)
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START–Register

SURVEY ON ANTICOAGULATED PATIENTS – REGISTER

Registro computerizzato per la raccolta dei dati di pazienti trattati cronicamente con anticoagulanti

FCSA-START Study: bleeding and thrombotic events in an italian prospective cohort of patients treated with DOAC

Antonucci E, Migliaccio L, Marongiu F, Pengo V, Poli D, Testa S, Tripodi A, Guazzaloca G , Moia M, Palareti G on behalf of the FCSA-START-Register participating centers

XXIV Congresso Nazionale
Abano 9-12- Novembre 2016

Characteristic of patients in relation to indication

	AF	VTE
Number	1196	691
Median Age, y (IQR)	76.5 (71,82)	60 (46,73)
Males (%)	54.9	58.0
Type of DOACs Apixaban Dabigatran Rivaroxaban	 35.5% 36.4% 28.1%	 4.7% 6.3% 89.0%
CrCl 30-60 ml/min^2 CrCl ≤30 ml/min^2	36% 1.4%	16% 0.5%
Patients Shifted from VKA	47.7%	31%
Low Dose DOACS	42.4%	36.5 %

START–Register
SURVEY ON ANTICOAGULATED PATIENTS – REGISTER
Registro computerizzato per la raccolta dei dati di pazienti trattati cronicamente con anticoagulanti

DOAC patients Follow-up

Bleeding and thrombotic events

	AF	VTE
Follow up (pt-yrs)	1350	523
Major bleeding rate: x100 pt yrs	30 (2.2)	3 (0.57)
Cerebral Gastrointestinal Other	6 14 10	- 2 1
Fatal	3 (0.22)	
NMCRB Rate: x100 pty rs	21 (1.5)	5 (0.95)
Thromboembolic events Rate: x100 pt yrs	11 (0.8)	10 (1.9)

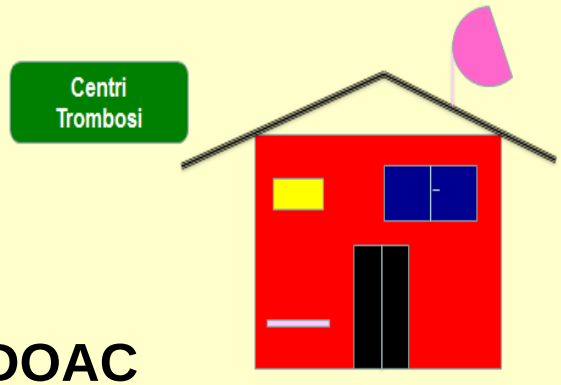
	RELY	START Dab	ARISTOTLE	START Apix
Age yrs	71.5±8.8	74±8.3	70 (63.76)	77 (72,83)
Male Sex (%)	64.3	64	64.5	51
$CHADS_2$ m ±SD	2.2±1.1	2.0±1.18	2.1±1.1	2.29±1.6
M Bleed	3.11	2.0	2.13	1.5
Cerebral	0.32	0.34	0.33	0.74
CRNMB	NA	1.03	4.07	0.74

Comparison with clinical trials

Comparison with clinical trials and real life data

	ROCKET	START Riva	XANTUS	Tamayo Medi Care	Dresda Registry
Age yrs	73 (65,78)	75 (69,80)	71.5±10	71.5±10	74±14
Male Sex (%)	60.3	64	59	55	51
$CHADS_2$ m±SD	3.48±0.94	2.4±1.3	2.1±1.2	2.6±1.2	NA
M Bleed	3.6	3.2	2.1	2.86	3.4
Cerebral	0.5	0.3	0.4	NA	NA
CRNMB	11.8	0.54	12.9	NA	19.7

Conclusioni



1 In generale i DOAC non sono superiori agli AVK se questi sono seguiti bene.

2 Le emorragie cerebrali sono inferiori con i DOAC ma questa differenza sfuma se gli AVK sono ben gestiti.

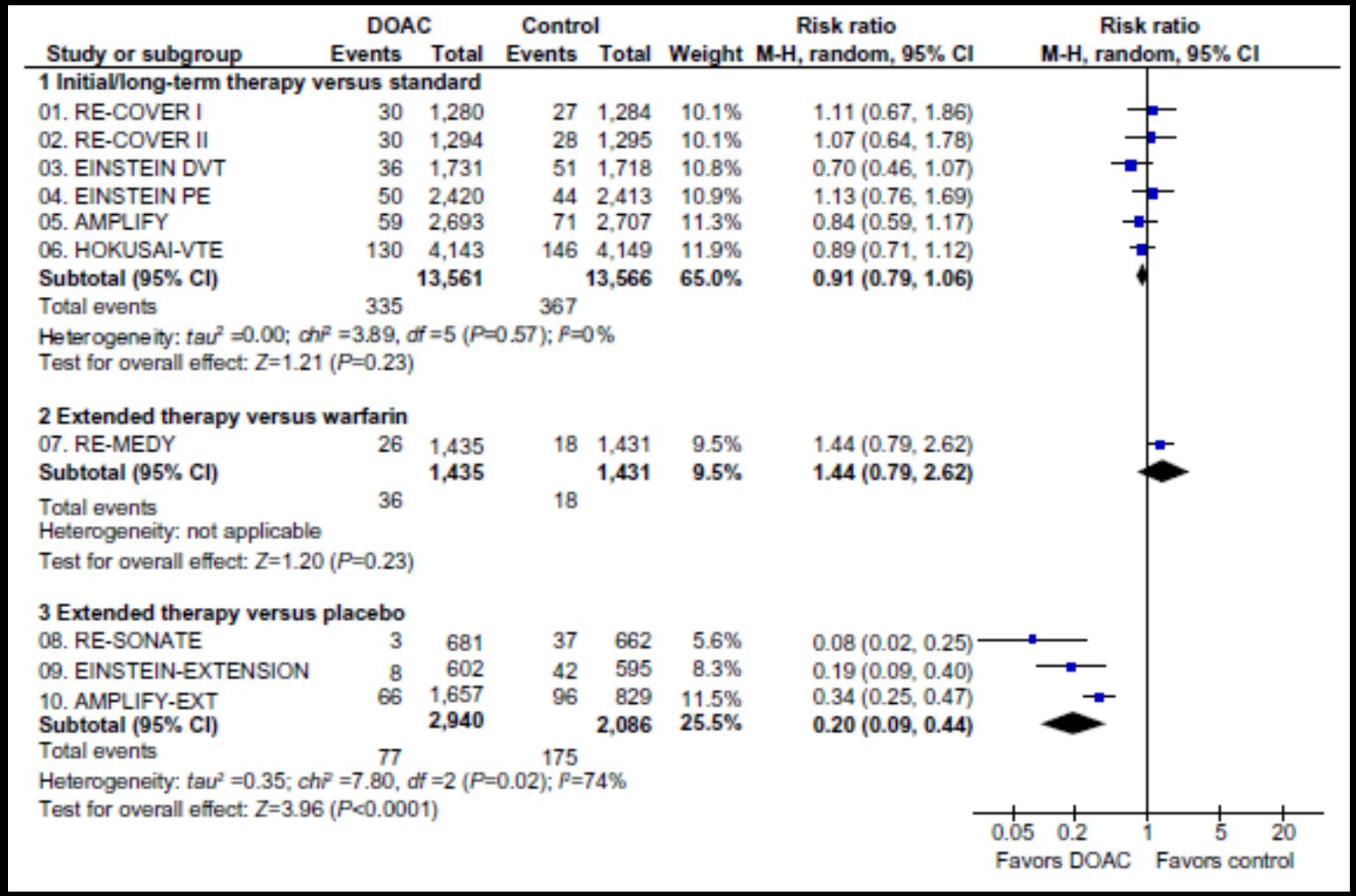
3 I risultati dello *START Register* indicano che sia i DOAC sia gli AVK possono far scendere le percentuali del rischio emorragico intorno al 2% o a meno dell'1.5 % se i pazienti sono regolarmente seguiti presso i Centri Trombosi (FCSA).

4 I DOAC comunque possono essere considerati la prima scelta, soprattutto nel TEV.

5 I Centri FCSA devono proseguire la loro attività considerando sia i DOAC sia gli AVK, seguendo i pazienti con un regolare *follow-up.*

Recurrent VTE

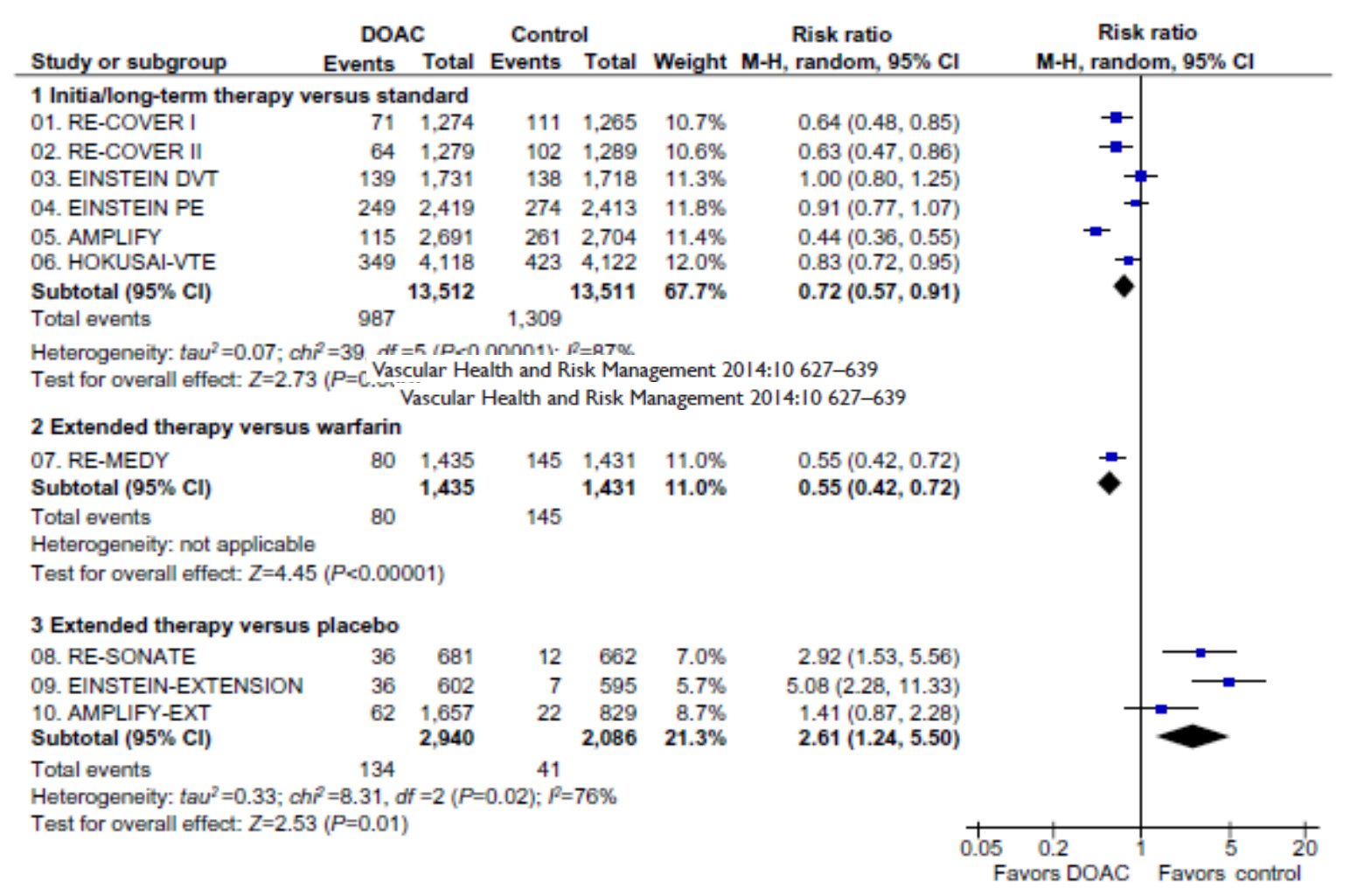
Direct oral anticoagulants in the treatment of venous thromboembolism, with a focus on patients with pulmonary embolism: an evidence-based review



Vascular Health and Risk Management 2014:10 627–639

Major Bleeding

Direct oral anticoagulants in the treatment of venous thromboembolism, with a focus on patients with pulmonary embolism: an evidence-based review



Study or subgroup	DOAC Events	DOAC Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1 Initia/long-term therapy versus standard						
01. RE-COVER I	71	1,274	111	1,265	10.7%	0.64 (0.48, 0.85)
02. RE-COVER II	64	1,279	102	1,289	10.6%	0.63 (0.47, 0.86)
03. EINSTEIN DVT	139	1,731	138	1,718	11.3%	1.00 (0.80, 1.25)
04. EINSTEIN PE	249	2,419	274	2,413	11.8%	0.91 (0.77, 1.07)
05. AMPLIFY	115	2,691	261	2,704	11.4%	0.44 (0.36, 0.55)
06. HOKUSAI-VTE	349	4,118	423	4,122	12.0%	0.83 (0.72, 0.95)
Subtotal (95% CI)		**13,512**		**13,511**	**67.7%**	**0.72 (0.57, 0.91)**
Total events	987		1,309			
Heterogeneity: tau^2=0.07; chi^2=39, df=5 (P<0.00001); I^2=87%						
Test for overall effect: Z=2.73 (P=0.0[illegible]						
2 Extended therapy versus warfarin						
07. RE-MEDY	80	1,435	145	1,431	11.0%	0.55 (0.42, 0.72)
Subtotal (95% CI)		**1,435**		**1,431**	**11.0%**	**0.55 (0.42, 0.72)**
Total events	80		145			
Heterogeneity: not applicable						
Test for overall effect: Z=4.45 (P<0.00001)						
3 Extended therapy versus placebo						
08. RE-SONATE	36	681	12	662	7.0%	2.92 (1.53, 5.56)
09. EINSTEIN-EXTENSION	36	602	7	595	5.7%	5.08 (2.28, 11.33)
10. AMPLIFY-EXT	62	1,657	22	829	8.7%	1.41 (0.87, 2.28)
Subtotal (95% CI)		**2,940**		**2,086**	**21.3%**	**2.61 (1.24, 5.50)**
Total events	134		41			
Heterogeneity: tau^2=0.33; chi^2=8.31, df=2 (P=0.02); I^2=76%						
Test for overall effect: Z=2.53 (P=0.01)						

Vascular Health and Risk Management 2014:10 627–639

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