“Gestione integrata del paziente a rischio cardiovascolare: Anticoagulazione & Diabete sfide ed opportunità”

Napoli – 27 ottobre 2017

I Sessione: Gestione del paziente a rischio cardiovascolare con FANV

Criteri di scelta terapeutica nei pazienti con FANV, opportunità terapeutiche e dati di RWE.

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CARD
Confederazione Associazioni Regionali di Distretto
Società Scientifica delle attività Sociosanitarie Territoriali

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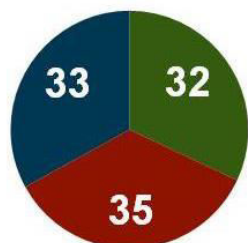
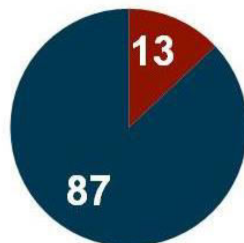
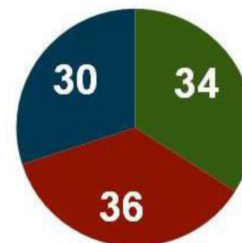
Baseline Characteristics

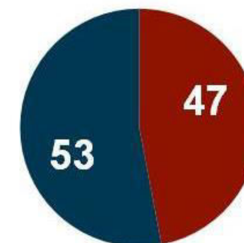
	RE-LY[a] (Dabigatran)	ROCKET-AF[b] (Rivaroxaban)	ARISTOTLE[c] (Apixaban)	ENGAGE AF[d] (Edoxaban)
Randomized, N	18,113	14,264	18,201	21,105
Age, y	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	35	38
Paroxysmal AF, %	32	18	15	25
VKA naive, %	50	38	43	41
Aspirin use,%	40	36	31	29

CHADS$_2$



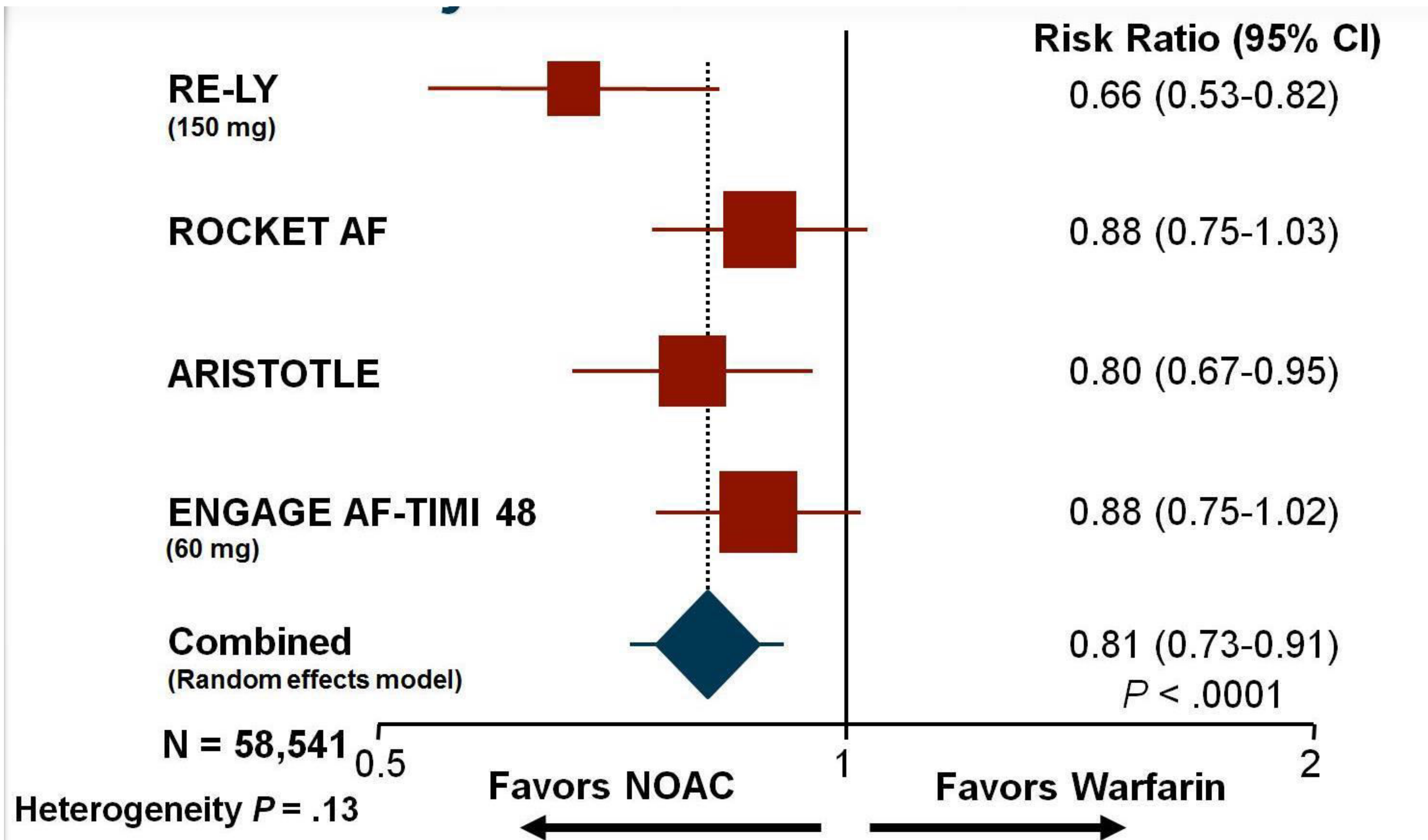






a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151[3]; b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891[4]; c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[5];d. Giuliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[6]

NOACs: Stroke or Systemic Embolic Events



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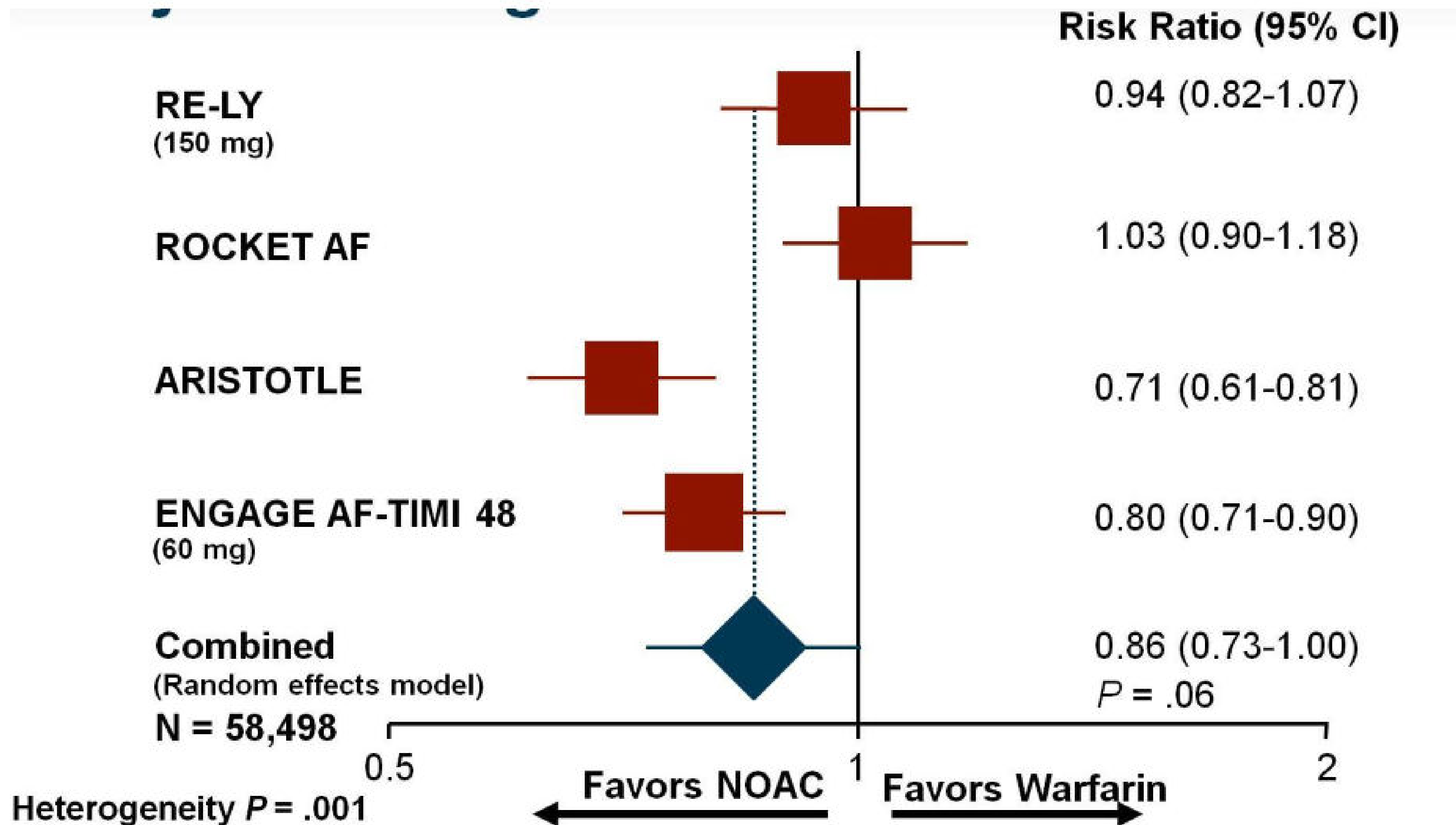
NOACs: Major Bleedin

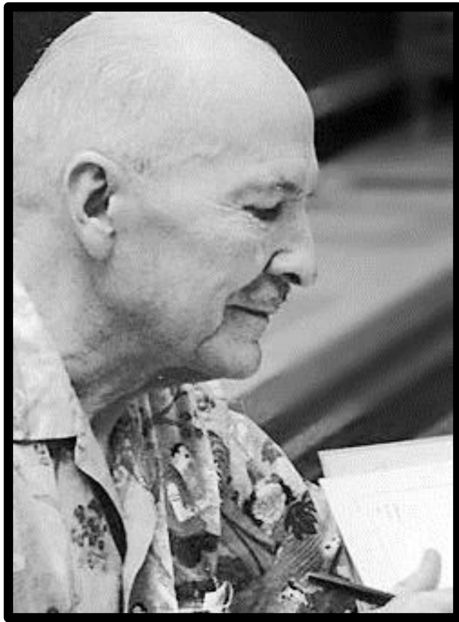


Reproduced from Ruff CT, et al. *Lancet*. 2014;383:955-962. ©2014, with permission from Elsevier.[15]

Safety outcomes of NOACs vs. warfarin: Data from RE-LY, ROCKET AF and ARISTOTLE

	Dabigatran 150mg BID	Dabigatran 110mg BID	Rivaroxaban 20mg OD	Apixaban 5mg BID
Major bleeds	=	↓	=	↓
ICH	↓	↓	↓	↓
Life-threatening bleeds	↓	↓	NA	↓
Major GI bleeds	↑	=	↑	=
Total bleeds	↓	↓	=*	↓

NA=not available; * Includes major and nonmajor clinically relevant bleeding events only
Based on an indirect comparison, where dabigatran , rivaroxaban and apixaban were all compared against the reference drug warfarin (target INR 2-3). Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6 ; Patel MR et al. N Engl J Med 2011;365:883–91 ; Granger CB et al. N Engl J Med 2011;365:981–92



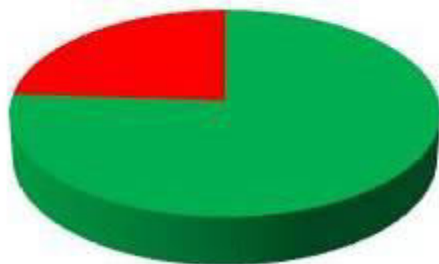
Robert Anson Heinlein

Se qualcosa non può essere espresso in numeri non è scienza: è opinione.

I pazienti del 'mondo reale' sono sovrapponibii a quelli arruolati nei mega-trials sui NOACs ?

Su 100 pazienti consecutivi con FA presenti nel *UK General Practice Research Databaseed eleggibili alla terapia anticoagulante (CHADS2≥1; n=71.493), quanti soddisfano i criteri di inclusione nei mega-trials?*

DABIGATRAN
RE-LY

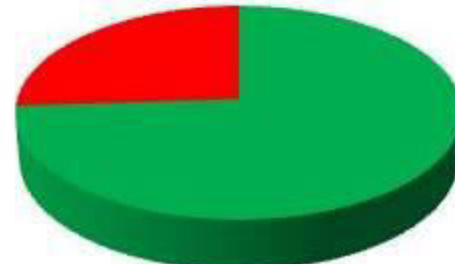


76%
Eligibile

RIVAROXABAN
ROCKET-AF

56%
Eligibile

APIXABAN
ARISTOTLE

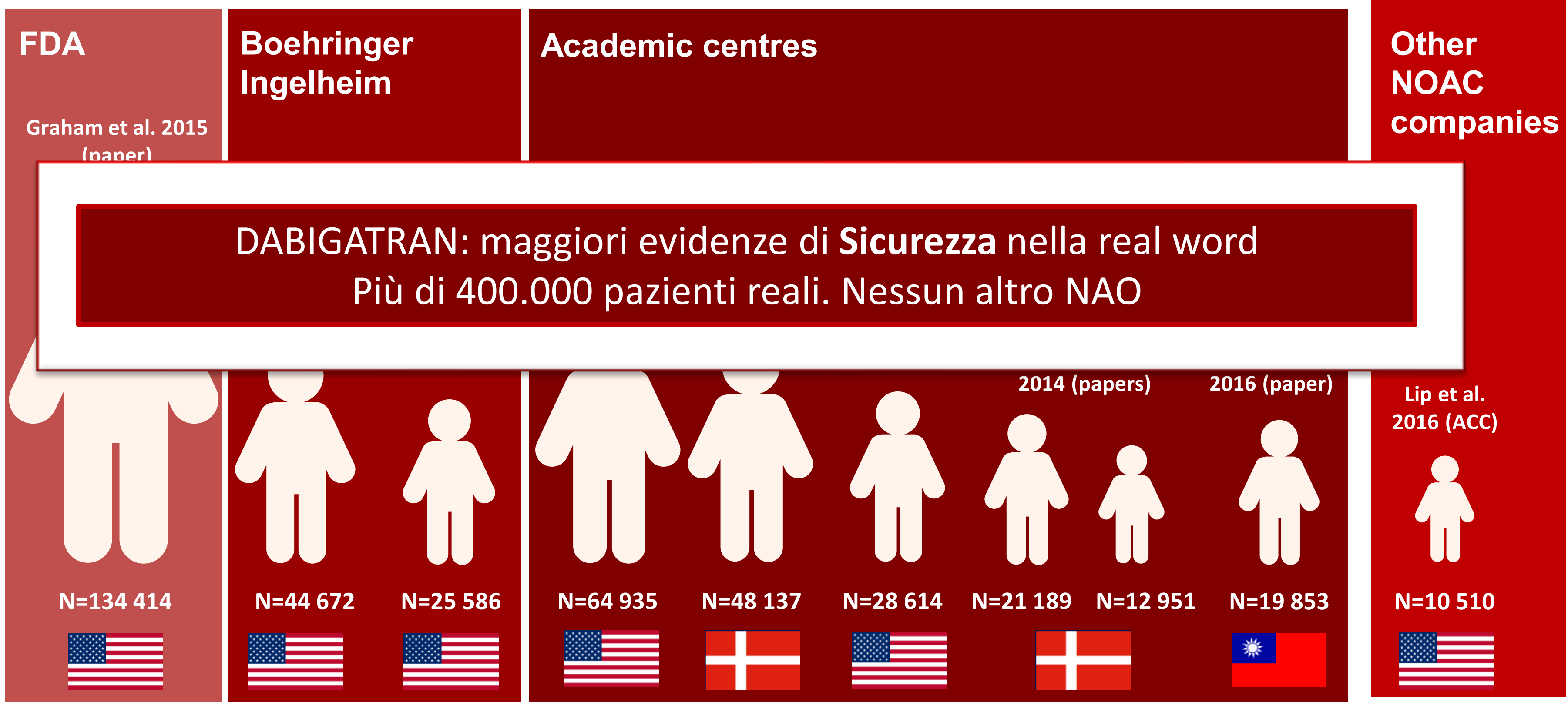


72%
Eligibile

***Criteri più selettivi, popolazione con CHADS2 medio più elevato**

Lee et al. BMJ Open 2012;2:e001768. doi:10.1136/bmjopen-2012-001768

Real-world studies, sponsored by various groups, confirm the favourable safety profile of dabigatran vs warfarin

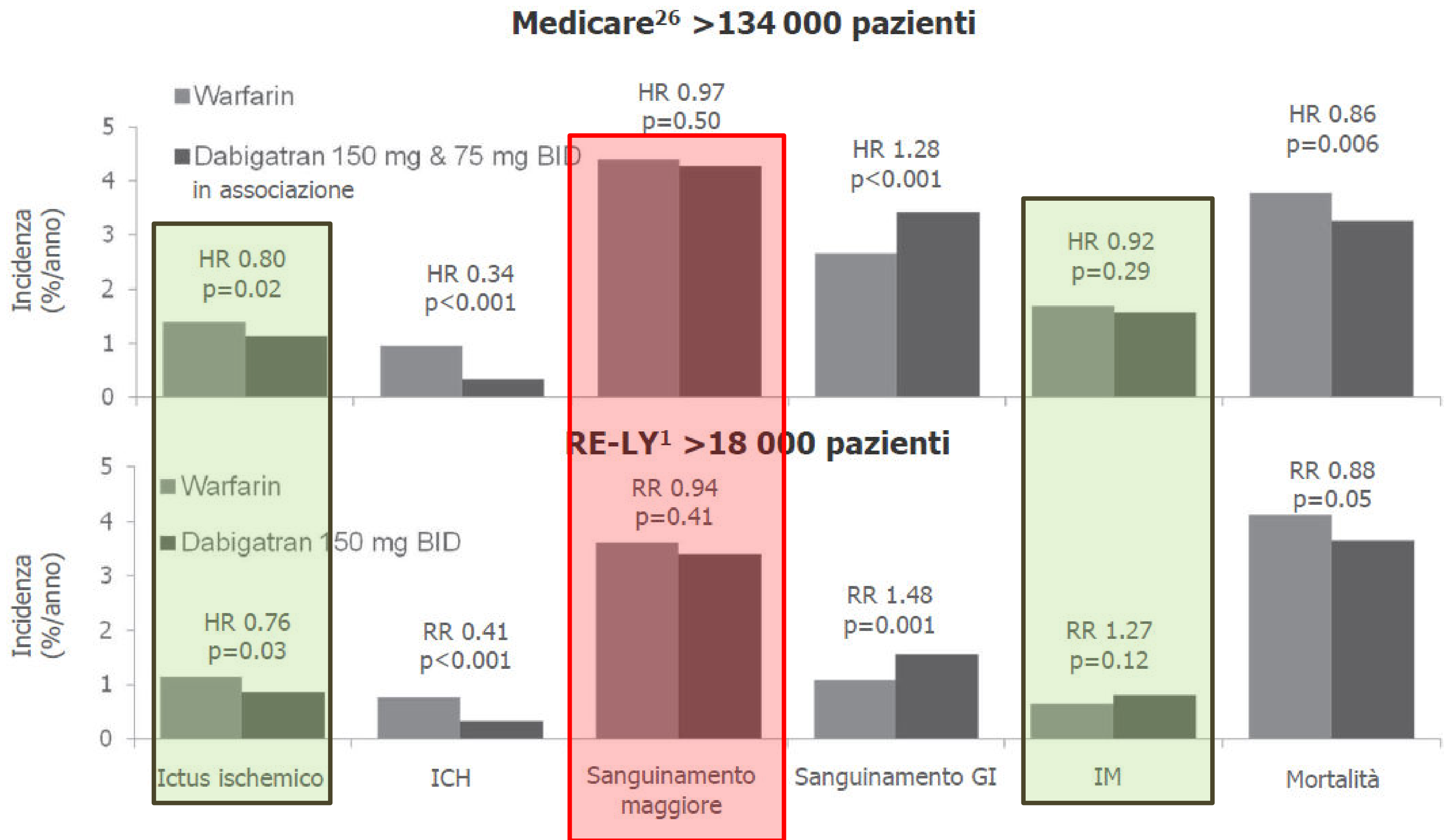


Example studies comparing dabigatran with warfarin. N relates to number of patients in the dabigatran vs warfarin comparison.
References in slide notes

Dati di real world dei nuovi anticoagulanti orali.
DABIGATRAN

Registro	Pazienti con fibrillazione atriale	Follow-up (mesi)	Risultati vs warfarin
Registro Mini-Sentinel	>10 000 pazienti naïve alla terapia anticoagulante orale	12	↓ Rischio di emorragia intracranica ↓ Rischio di sanguinamenti gastrointestinali
Registro danese	>4000 pazienti naïve alla terapia anticoagulante orale	12	= Rischio di ictus ischemico = Rischio di sanguinamenti maggiori ↓ Rischio di emorragia intracranica, infarto miocardico e mortalità
Registro danese	>61 000 pazienti naïve alla terapia anticoagulante orale	22	= Rischio di ictus ischemico ed embolie sistemiche ↓ Rischio di sanguinamenti maggiori ↓ Rischio di mortalità
Registro Medicare	>67 000 pazienti naïve alla terapia anticoagulante orale	26	↓ Rischio di ictus ischemico, embolie sistemiche, emorragia intracranica e mortalità = Rischio di sanguinamenti maggiori ed infarto miocardico ↑ Rischio di sanguinamenti gastrointestinali con dabigatran 150 mg bid
Registro MonaldiCare	>2000 pazienti naïve alla terapia anticoagulante orale	6	Bassissimo rischio di sanguinamenti maggiori con entrambi i dosaggi di dabigatran

Profilo di rischio/beneficio di dabigatran nella fibrillazione atriale nel mondo reale nord-americano.



Graham DJ, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation 2015;131:157-64.*

Dati di real world dei nuovi anticoagulanti orali.
RIVAROXABAN

Registro	Pazienti con fibrillazione atriale	Follow-up (mesi)	Risultati vs warfarin
Registro Dresda	>2700 pazienti *naïve alla terapia anticoagulante orale*	16	↓ Rischio di ictus, attacco ischemico transitorio ed embolie sistemiche ↓ Rischio di sanguinamenti maggiori
Studio XANTUS	>6000 pazienti (50% *naïve alla terapia* anticoagulante orale)	12	↓ Rischio di ictus, attacco ischemico transitorio, embolie sistemiche, emorragia intracranica e mortalità = Rischio di sanguinamenti maggiori ↓ Rischio di sanguinamenti fatali
Studio RELIEF	>1000 pazienti *naïve alla terapia anticoagulante orale*	12	↓ Rischio di ictus, attacco ischemico transitorio, infarto miocardico ed emorragia intracranica
Studio REVISIT-US	>30 000 pazienti *naïve alla terapia anticoagulante orale*	33	↓ Rischio di ictus ischemico/emorragia intracranica (endpoint combinato)

European Heart Journal Advance Access published September 1, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv466

FASTTRACK
ESC Clinical Registry

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

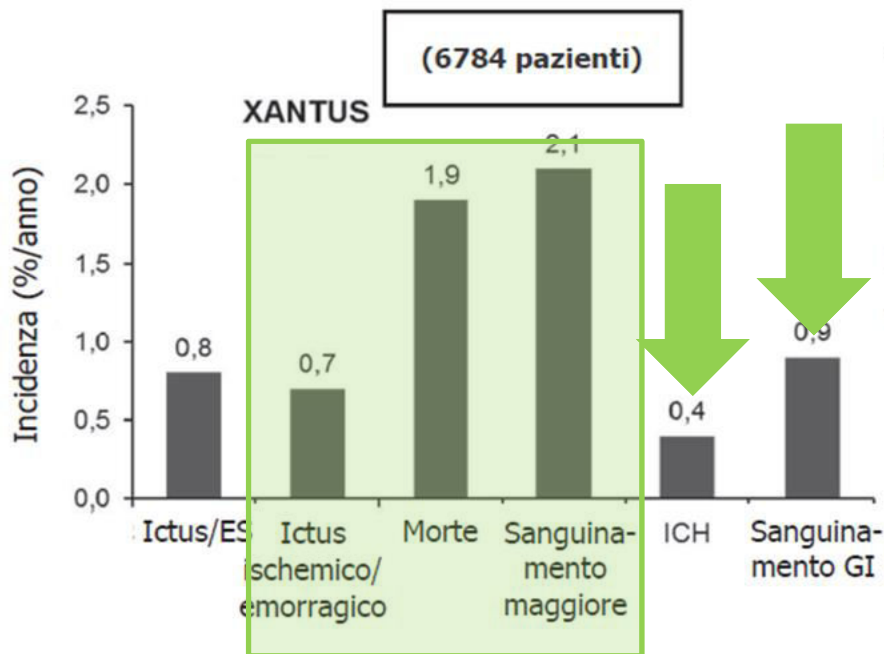
% della popolazione nel Trial

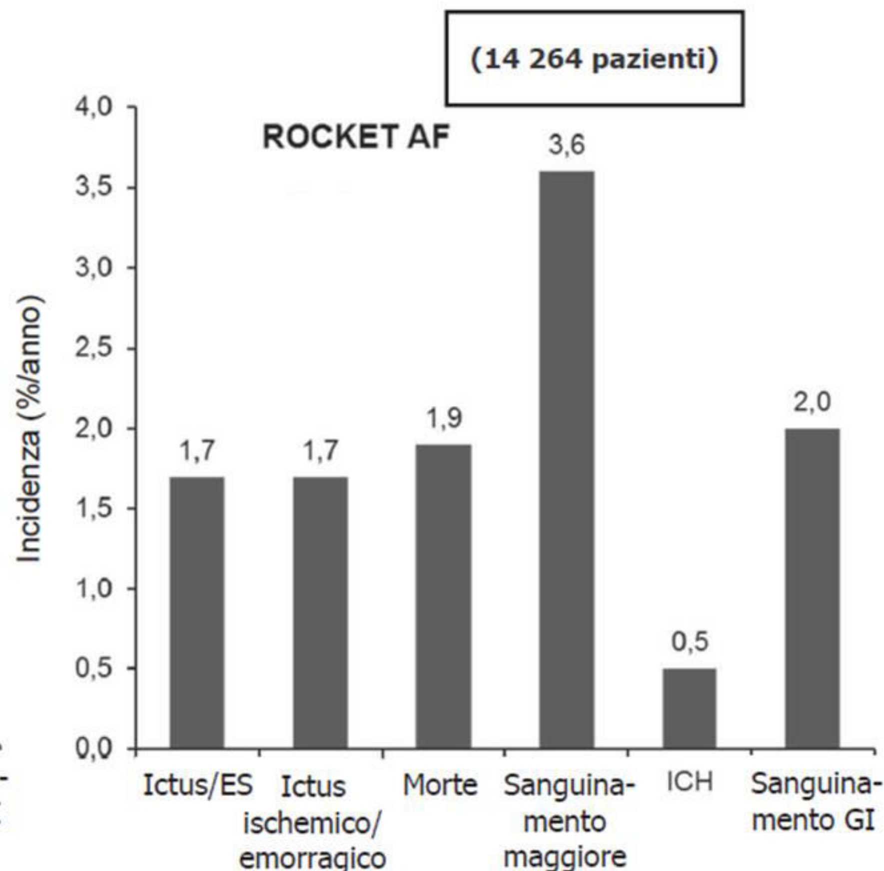
	CHADS$_2$ 0	CHADS$_2$ 1	CHADS$_2$ 2	CHADS$_2$ 3	CHADS$_2$ 4	CHADS$_2$ 5	CHADS$_2$ 6
ROCKET AF	0	0	13	43,6	28,7	12,7	2
XANTUS	10,4	30,4	30	16,4	9,1	3,3	0,5

XANTUS

Profilo di rischio/beneficio di rivaroxaban nella fibrillazione atriale nel mondo reale.

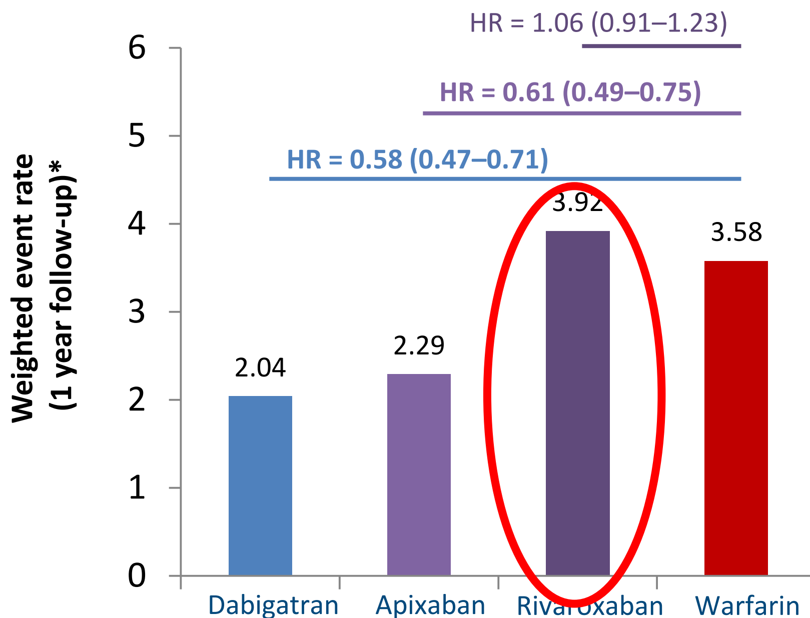
	$CHADS_2$	Prior Stroke
Rocket AF	3.5	55%
XANTUS	2.0	19%

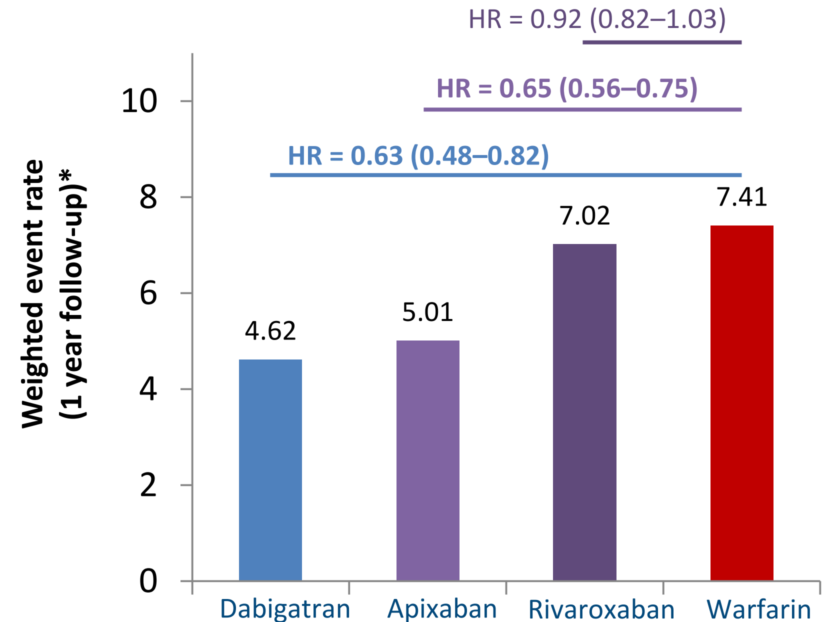




Camm AJ, Amarenco P, Haas S, et al.; XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016;37:1145-53.

Comparative effectiveness and safety of NOACS and warfarin in patients with AF: propensity weighted nationwide cohort study - *Larsen et al. BMJ 2016;353:i3189*





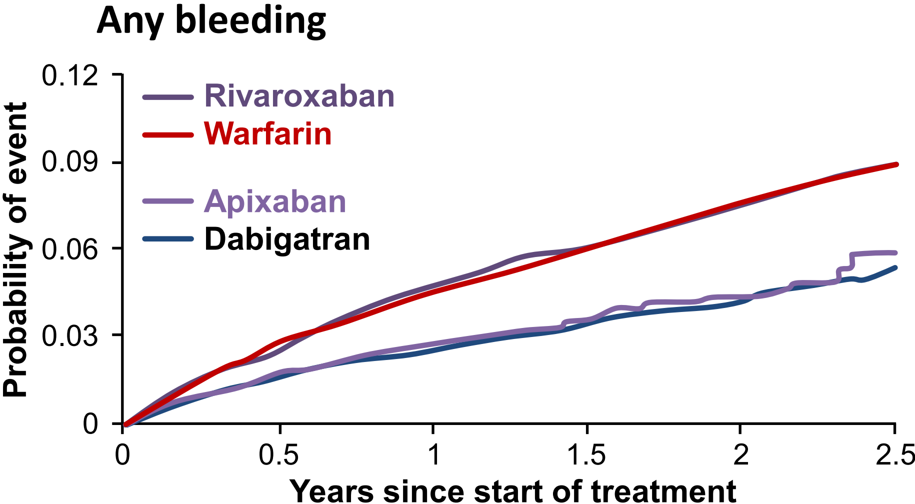
Dabigatran and apixaban were associated with a statistically significantly lower risk of any bleeding, major bleeding, and death compared with rivaroxaban or warfarin

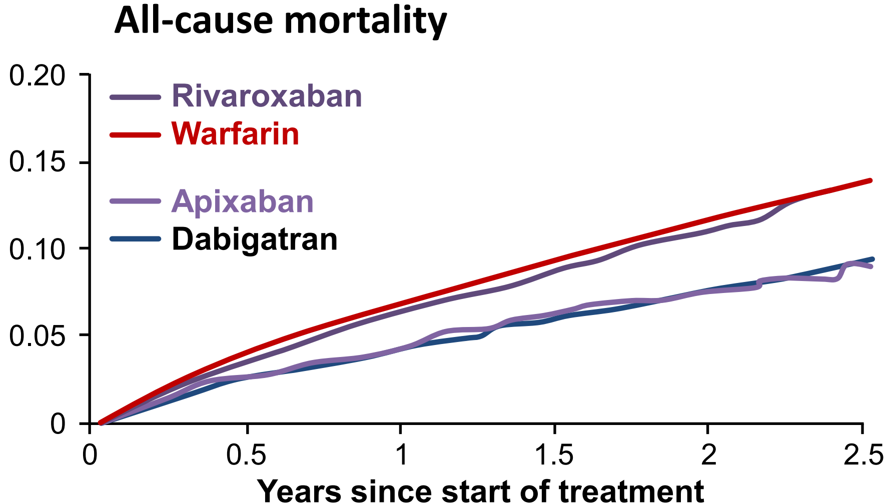
Only standard doses of NOACs were compared in this study. *Inverse probability of treatment weighted and expressed as population average treatment rates per 100 years. Adjusted HR (95% CI), bold values indicate statistical significance. Limitations: ITT analysis; limited variables for adjustment; limited follow-up; patients included prior to availability of apixaban. Larsen TB et al. BMJ 2016

Analysis of Danish registry data supports the safety profile of dabigatran being comparable to apixaban and more favourable than rivaroxaban

Kaplan–Meier analysis

Weighted failure curves (ITT only)





Patients initiating treatment with dabigatran or apixaban experienced a significantly lower risk of bleeding or death than those initiating treatment with warfarin or rivaroxaban

Only standard doses of NOACs were compared in this study. *Any bleed is a combination of major and clinically relevant non-major bleeding. Limitations: ITT analysis; limited variables for adjustment; limited follow-up for some patients; patients included prior to availability of apixaban. Larsen TB et al. BMJ 2016

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]

Design

Observational nationwide cohort study.

What is already known on this topic

The use of non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) has been increasing since their introduction

Based on data from clinical practice, however, limited evidence exists on effectiveness and safety of NOACs compared with warfarin

What this st udy adds

No significant difference in risk of ischaemic stroke was evident between NOACs and warfarin

Rivaroxaban was associated with a lower risk of ischaemic stroke or systemic embolism than warfarin, but with comparable major bleeding rates.

Dabigatran and apixaban had non-significant hazard ratios compared with warfarin for ischaemic stroke or systemic embolism, whereas major bleeding rates were significantly lower with reference to warfarin

Dati di real world dei nuovi anticoagulanti orali.
APIXABAN

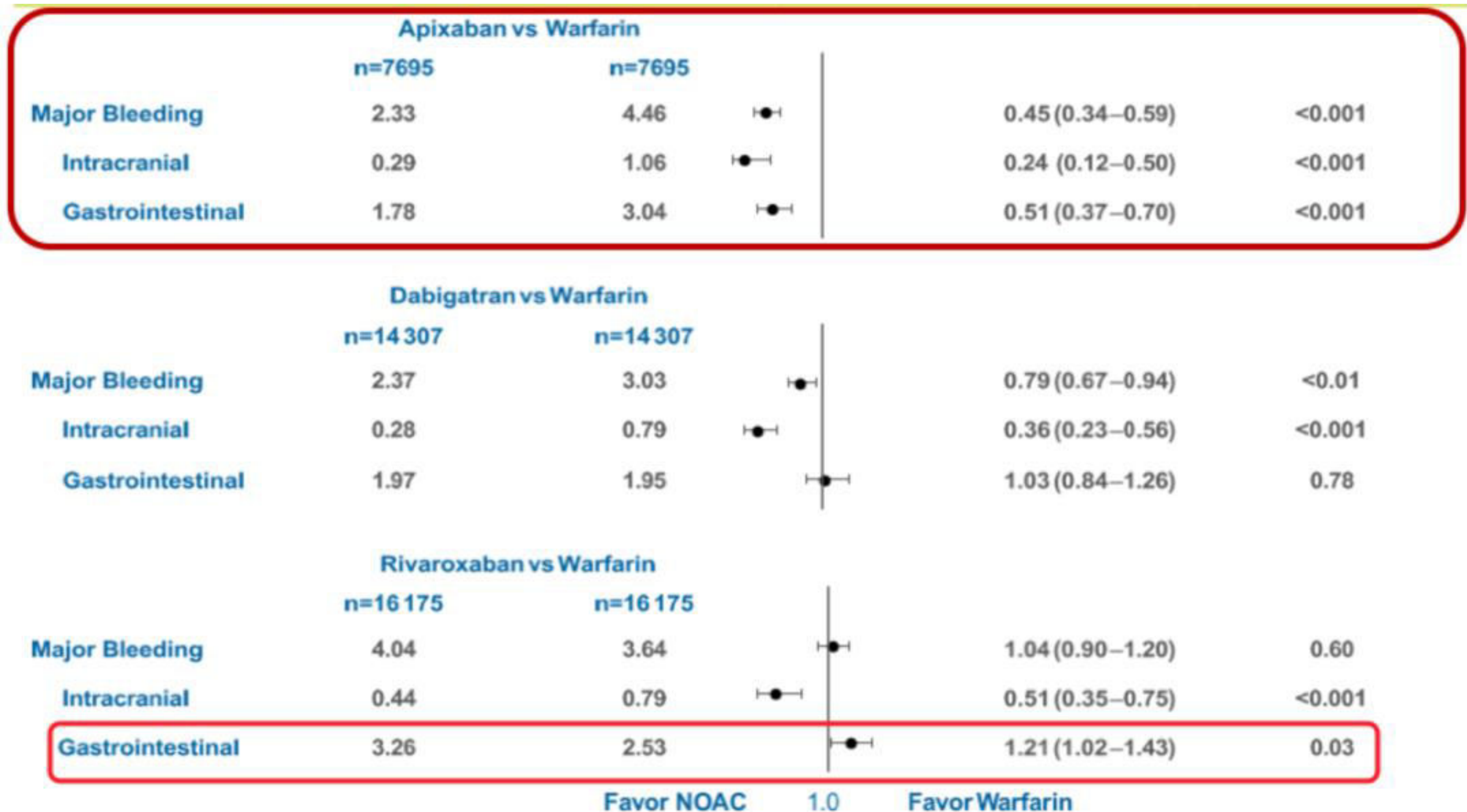
Registro	Pazienti con fibrillazione atriale	Follow-up (mesi)	Risultati vs warfarin
Registro Medicare	>15 000 pazienti *naïve alla terapia anticoagulante orale*	56	↓ Rischio di ictus ed embolie sistemiche ↓ Rischio di sanguinamenti maggiori ↓ Rischio di sanguinamenti gastrointestinali

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, Noseworthy PA

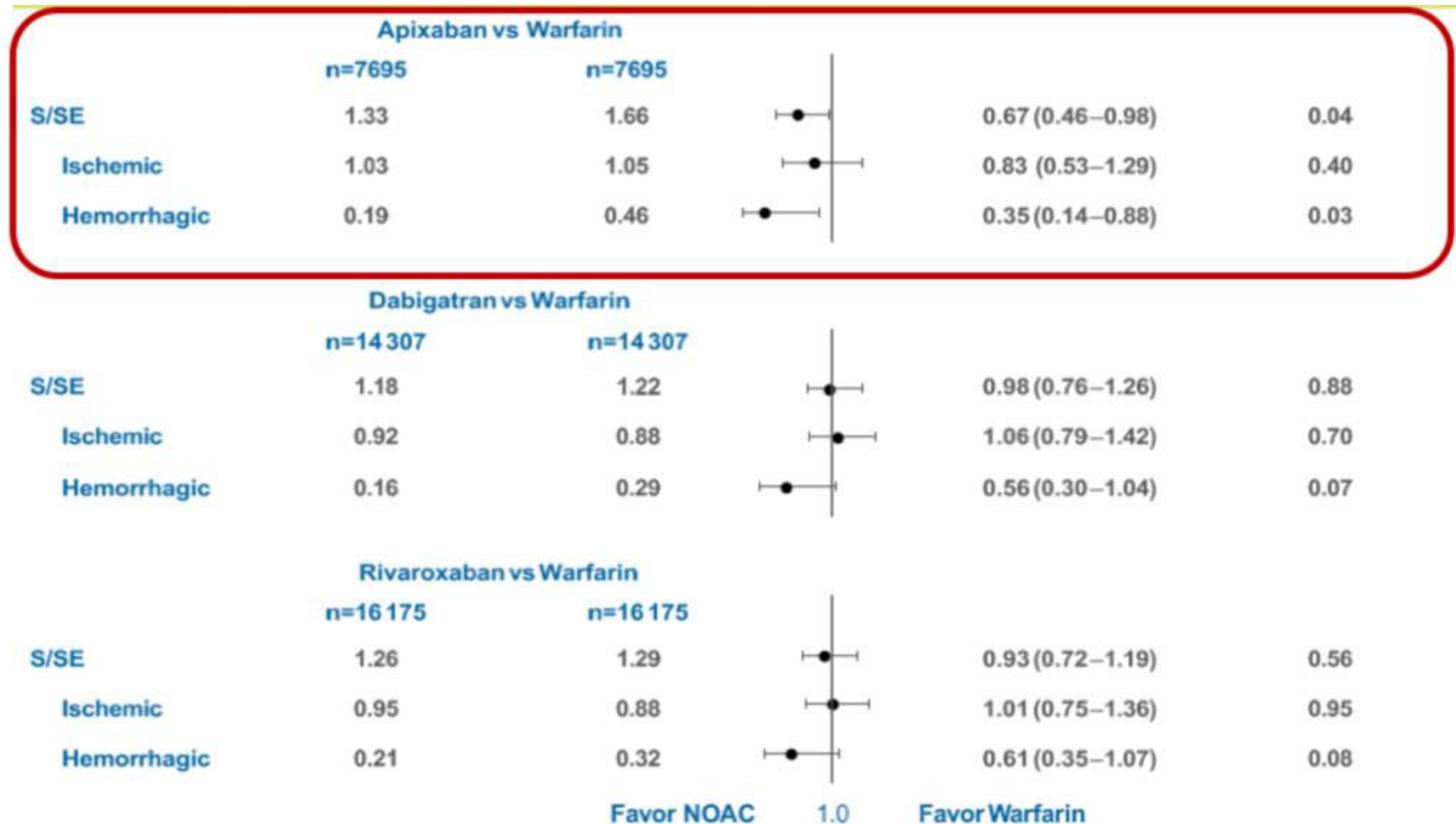
Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular AF. J Am Heart Assoc 2016;5:e003725.

Dati di real world dei nuovi anticoagulanti orali.
APIXABAN



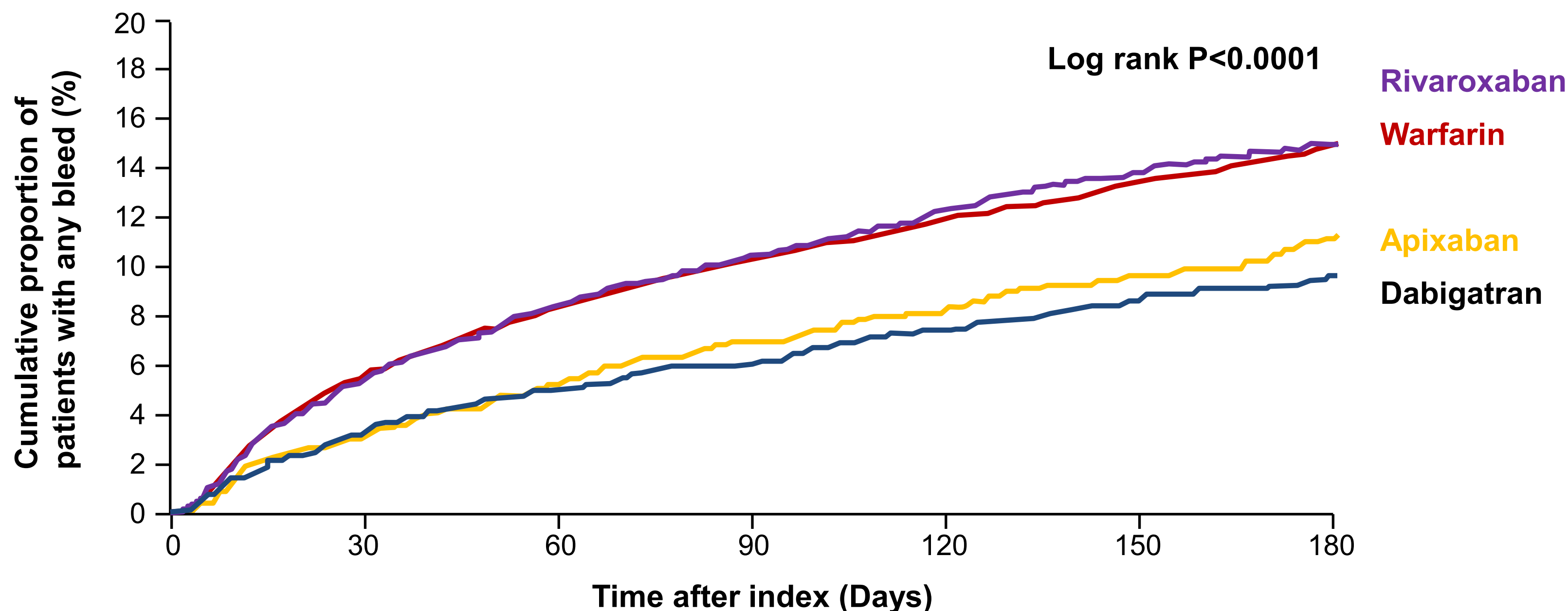
Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular AF. J Am Heart Assoc 2016;5:e003725.

Dati di real world dei nuovi anticoagulanti orali.
APIXABAN



Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular AF. J Am Heart Assoc 2016;5:e003725.

Real-world bleeding risk among non-valvular atrial fibrillation (NVAF) patients prescribed apixaban, dabigatran, rivaroxaban and warfarin: analysis of electronic health records - *Lin et al. ESC 2015; Abstr P6215*



Patients initiating treatment with dabigatran or apixaban experienced a significantly lower risk of bleeding than those initiating treatment with warfarin

*Any bleed is a combination of major and clinically relevant non-major bleeding. Limitations: abstract only; may include switchers from other OACs; limited variables for adjustment; moderate sample size; only 6 months of follow-up; treatment discontinuations not taken into account

Conclusioni 1

- La prima scelta riguarda l'*opportunità di anticoagulare.*

- La seconda scelta riguarda il farmaco, ricordando che *non dovrebbe esserci più posto per l'ASA*.

- Gli anticoagulanti orali diretti *offrono vantaggi* per i pazienti che iniziano la terapia.

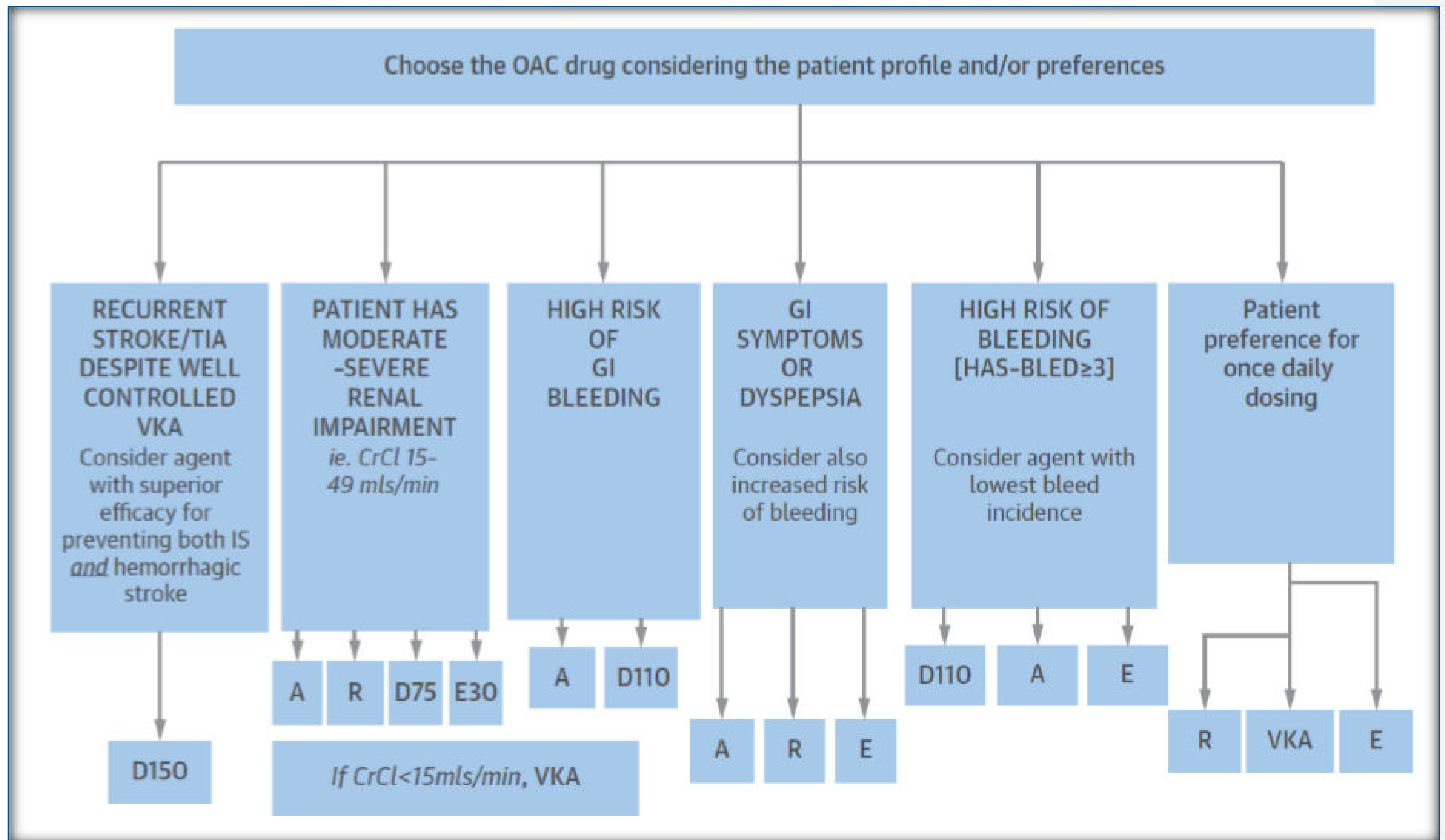
- Esiste probabilmente il farmaco (e il dosaggio) *giusto per il singolo paziente*, ma dobbiamo imparare di più.

Conclusioni

• A tutt'oggi, i risultati dei mega-trials randomizzati con i NAO stanno trovando una *sostanziale conferma* nella 'vita reale'.
• Abbiamo enorme bisogno di 'Registri' ben pianificati e condotti sull'impiego dei *NAO nella vita reale*.
• *Attenzione all'interpretazione del 'confronti indiretti'* tra i NAO negli studi di 'vita reale'.
• Sarebbe utile uno studio *randomizzato 'testa a testa'* tra NAO differenti.

Gli spunti che possiamo trarre ???

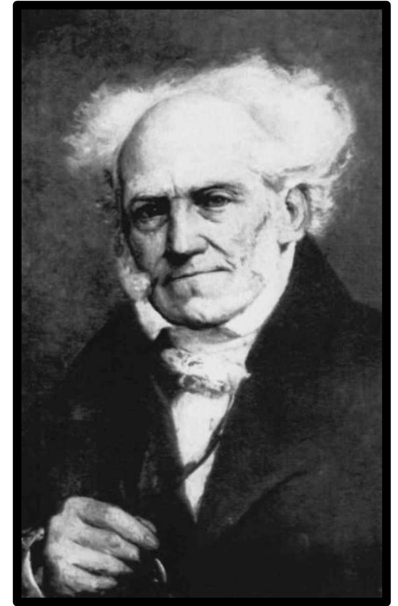
Quale NAO per quale paziente?



A= Apixaban, D=dabigatran, E= edoxaban, R=rivaroxaban

Jacc 2015

Arthur Schopenauer



Ogni verità passa attraverso tre fasi: prima viene ridicolizzata; poi è violentemente contestata; infine viene accettata come ovvia.