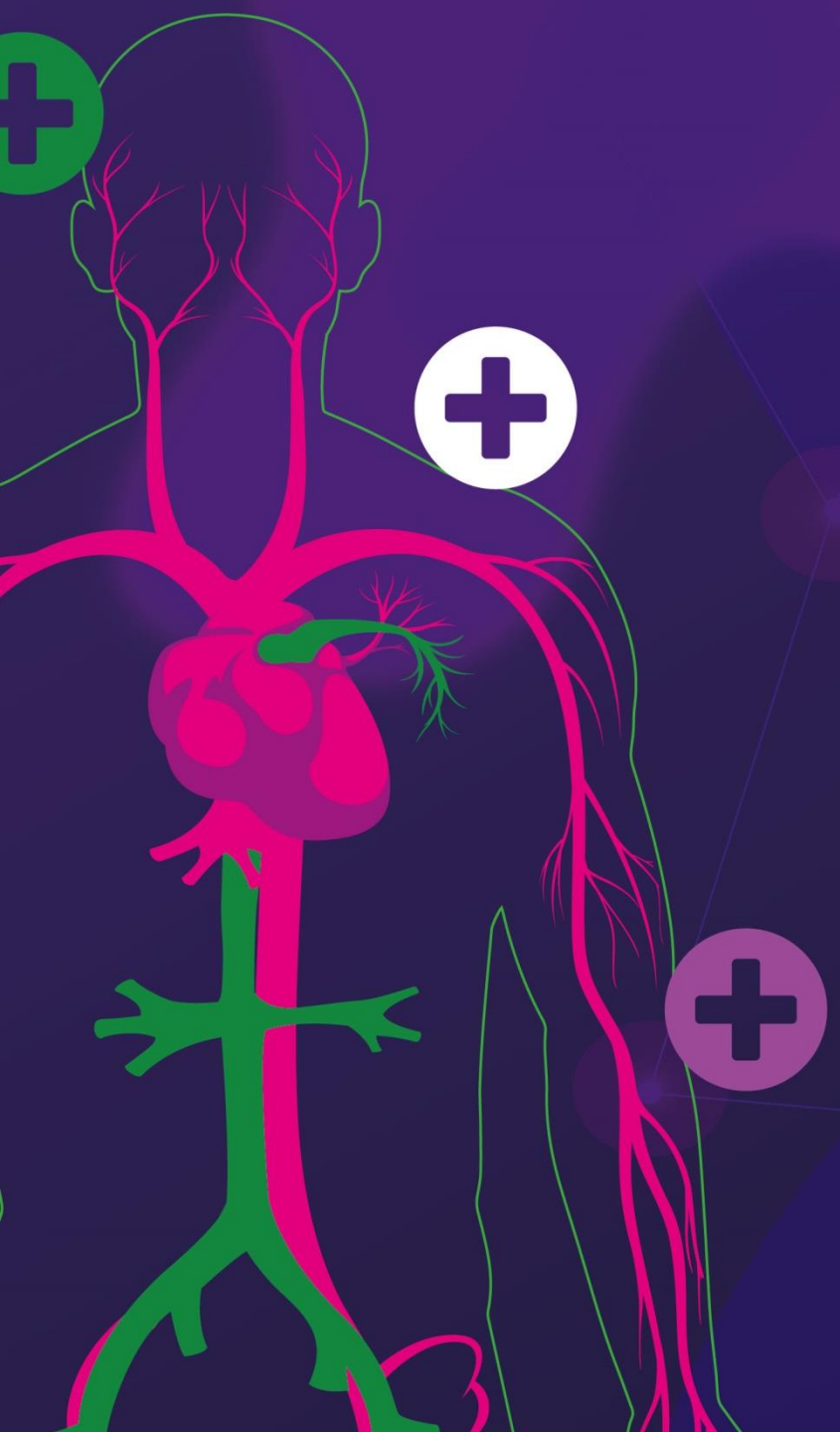


24.25.26
MAGGIO 2019
SORRENTO
HILTON SORRENTO PALACE
Via Sant'Antonio, 13

DOAC 4.0:
IL PAZIENTE AL CENTRO E NUOVI PARADIGMI

DOAC, evidenze di efficacia e sicurezza nel mondo reale

Dott. Leopoldo Pagliani MD Ph.D

Responsabile Centro FA e Tromboembolismo

Ospedale Riabilitativo di Alta Specializzazione di Motta di Livenza (TV)

Direttore U.O. Riabilitazione Cardio-Polmonare

Ospedale Codivilla-Putti di Cortina D'ampezzo

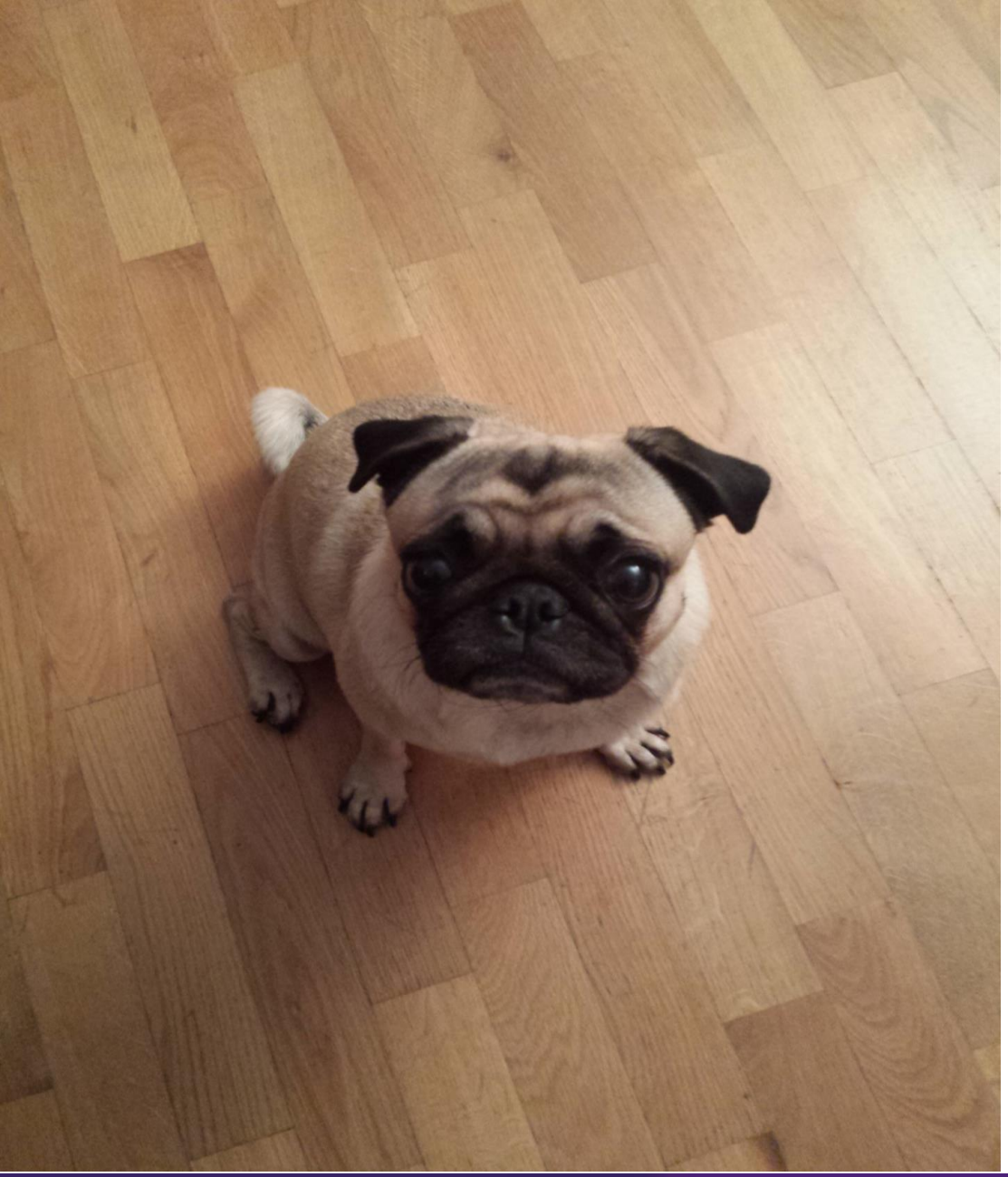
Dr. Pagliani Leopoldo
Disclosure Statement

Affiliation/Financial Interest:

Grant/Research Support: Astra-Zeneca, Pfizer, BMS, Philips Ultrasound, Esaote, Bayer, Medtronic

Consultant: Boehringer Ingelheim, Bayer, Daiichi-Sankyo, Pfizer, Esaote, Servier, Sanofi, Amgen

Speaker's Bureau: Bayer, Servier, Malesci, Lusofarmaco, Astra-Zeneca, Pfizer, Sanofi, Novartis



We know human attention is dwindling

12 seconds

The average human attention span in

2000

Source: Statistic brain

Qual è la principale ragione per la quale preferire un DOAC al warfarin ?

1. Riduzione di stroke ed embolia sistemica
2. Riduzione di sanguinamenti maggiori
3. Riduzione di emorragia intracranica
4. Riduzione di mortalità
5. Comodità gestionale per il paziente

Codice 0003

La lunga marcia della terapia anticoagulante nella fibrillazione atriale

1989-1993

2010

2013

6 Trials of Warfarin vs Placebo[a]

ROCKET[c] (Rivaroxaban)

ENGAGE AF TIMI 48[e] (Edoxaban)

RE-LY[b] (Dabigatran)

ARISTOTLE[d] (Apixaban)

2009

2011

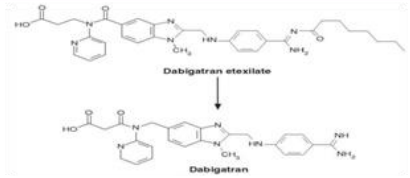
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steeri

ABSTRACT



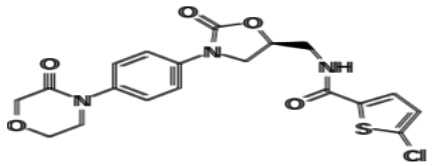
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

ABSTRACT



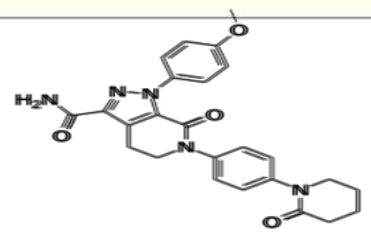
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

ABSTRACT

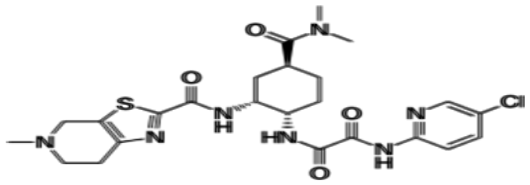


ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

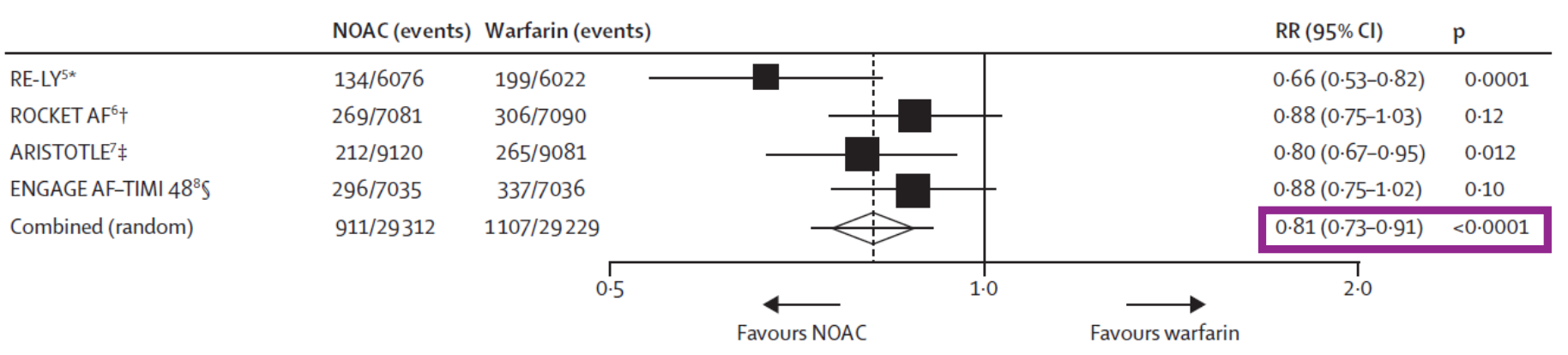
Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

ABSTRACT

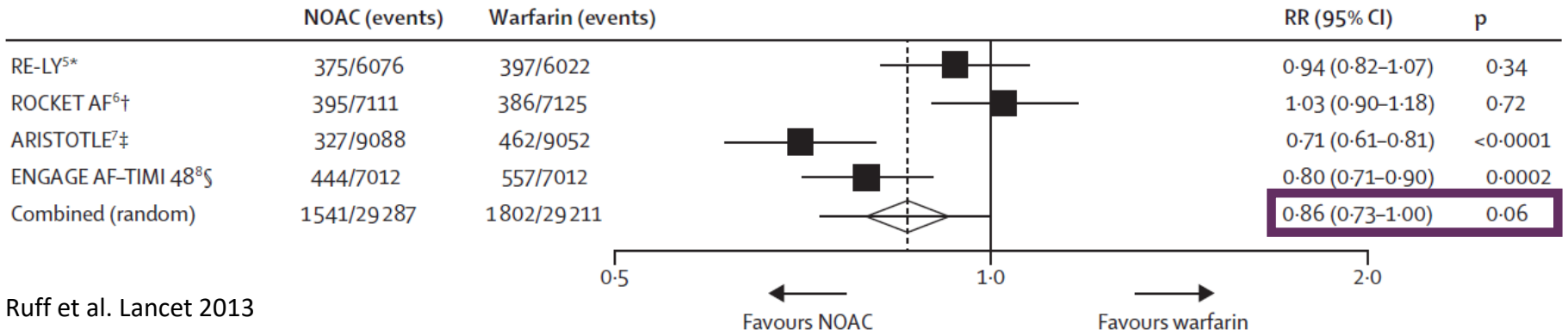


Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Stroke or SE



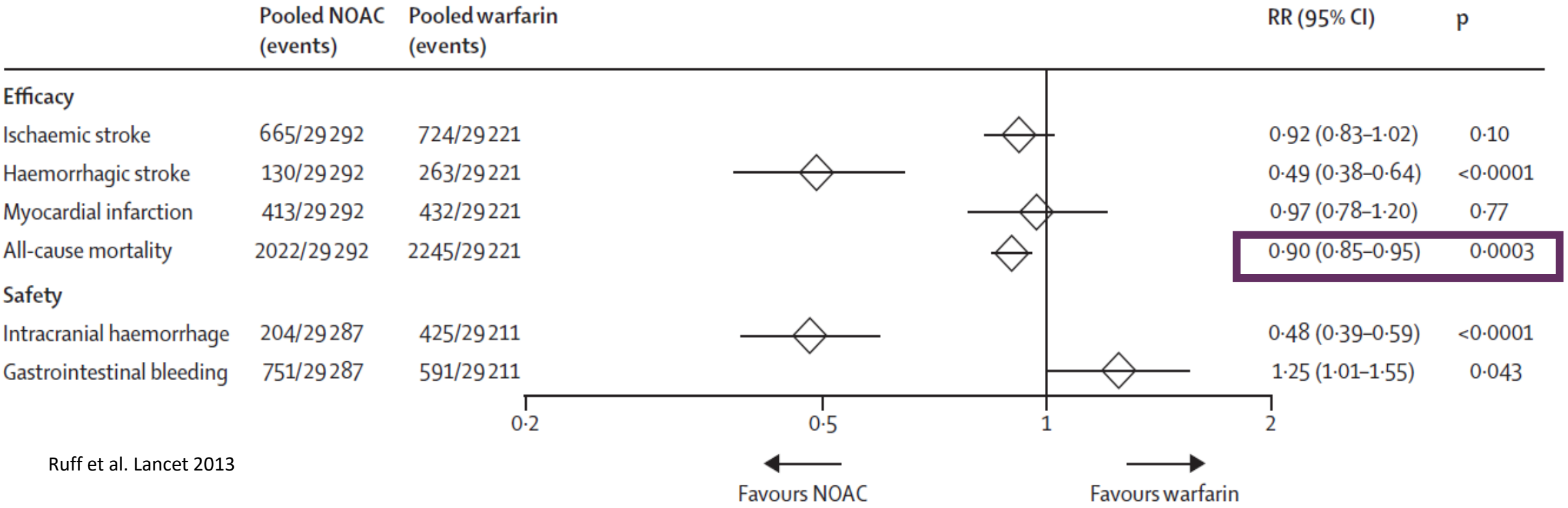
Major Bleeding



Ruff et al. Lancet 2013

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Other endpoints

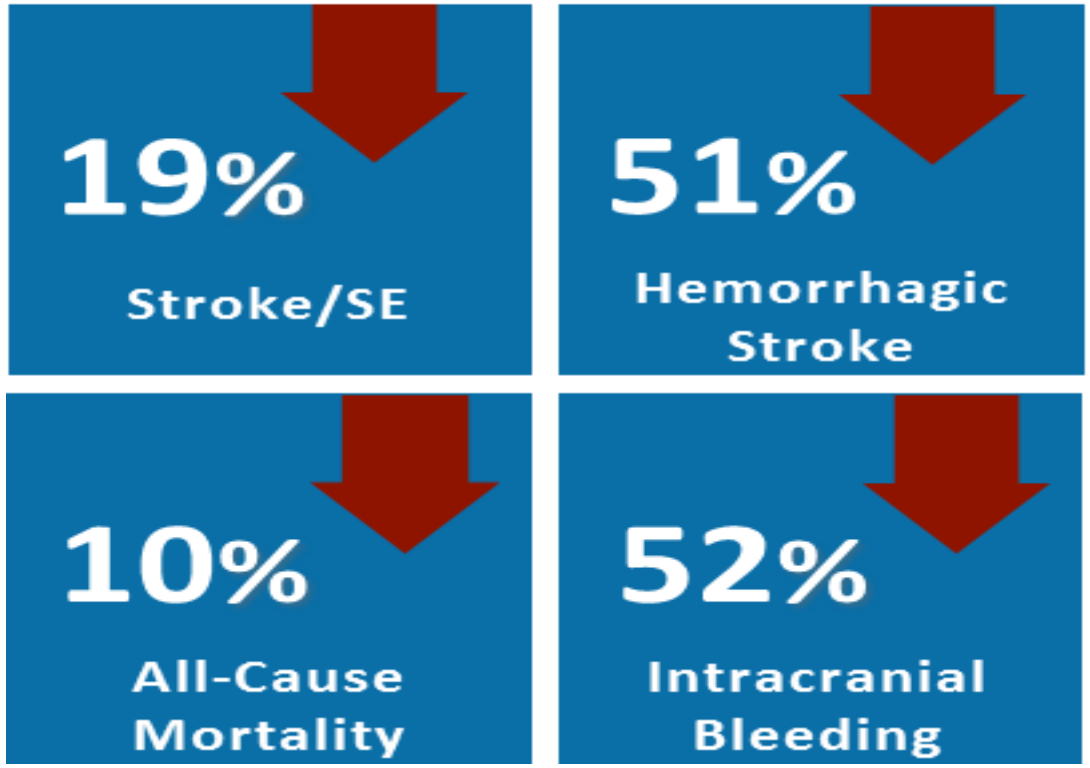


Ruff et al. Lancet 2013

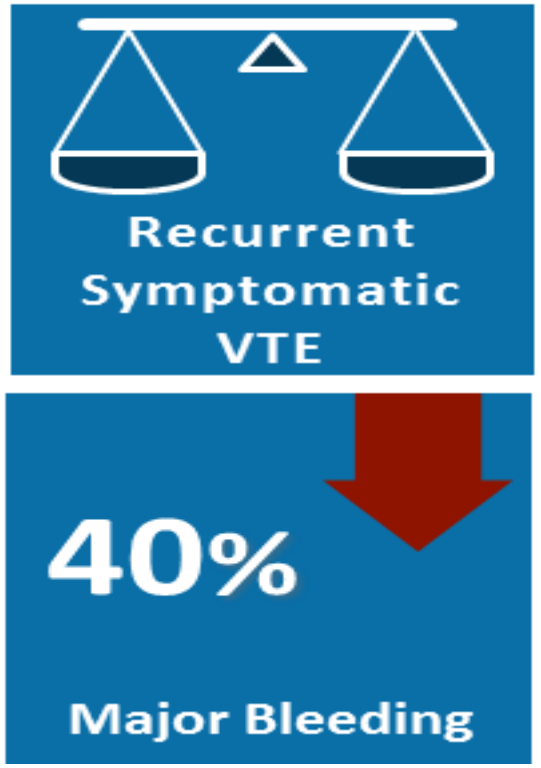
NOACs Vs VKAS: Efficacy and Safety profiles in clinical trials

a) Ruff C et al., Lancet 2014; 383: 955–62
b) Hirschl M., Kundi M., Vasa 2014; 43:353-364

Stroke prevention in AF[a]



DVT/PE treatment[b]



2016 ESC Guidelines

	Class	LOE
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 VKA	I	A

Kirchhof P, et al. *Eur Heart J.* 2016;37:2893-2962.

Differences Between the Four NOACs RCTs that Impact the Robustness of Cross-study

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
Dose reduction	No dose reduction–patients randomized between two doses of dabigatran (110 or 150 mg bid)	At randomization: Rivaroxaban 15mg od for patients with CrCl 30–49 mL/min	At randomization: apixaban 2.5 mg bid for patients with ≥2 of the following criteria: • Age ≥80 years • Body weight ≤60 kg • Serum creatinine level ≥1.5 mg/dL	Throughout the study period: edoxaban 30 mg od for patients with ≥1 of the following criteria: • CrCl 30–50 mL/min • Body weight ≤60 kg • Concomitant use of verapamil or quinidine
Patients taking reduced NOAC dose	50.0%	20.7%	4.7%	25.3%
EOS transition period[a]	No defined EOS transition period Events after the end of the study not reported Selected patients were eligible to remain on dabigatran as part of a long-term, open-label extension study (RELY-ABLE)	30-day EOS transition period Increased NOAC event rates during this period likely caused by the slow onset of VKA therapy	30-day EOS transition period (3-day supply of apixaban or placebo) Increased NOAC event rates during this period likely caused by the slow onset of VKA therapy	30-day EOS bridging/ transition period (edoxaban half-dose or placebo) No increase in NOAC event rates
Definition of NVAF	Patients with a history of heart valve disorders were excluded	Patients with AF and valvular disease (defined as mitral stenosis or prosthetic valve) were excluded	Patients with moderate or severe mitral stenosis were excluded	Patients with moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve were excluded

Camm AJ, et al. Europace 2018;20:1-11

Differences between the Four NOACs RCTs that Impact the Robustness of Cross-study

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
Major bleeding	Reduction in the Hb level of ≥2 g/dL, transfusion of ≥2 units of blood or packed red cells, or symptomatic bleeding in a critical area or organ, or bleeding that leads to death	Clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site, fall in Hb concentration ≥2 g/dL, transfusion of ≥2 units of whole blood or packed red blood cells, or permanent disability	ISTH: Clinically overt bleeding accompanied by a decrease in the Hb level of ≥2 g/dL over 24 h or transfusion of ≥2 units of packed red cells, occurring at a critical site, or resulting in death	ISTH with minor modifications for Hb decrease and blood transfusion requirements. Clinically overt bleeding event that met ≥1 of the following: fatal bleeding, symptomatic bleeding in a critical site, clinically overt bleeding event that causes a fall in Hb level of ≥2.0 g/dL, adjusted for transfusions. Each unit of packed red blood cell or whole blood is counted as a 1.0 g/dL decrease in Hb
CRNM bleeding	Not recorded	**Overt bleeding not meeting criteria for major bleeding but requiring medical intervention, unscheduled contact with a physician, temporary interruption of study drug, pain, or impairment of daily activities**	**Clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician guided medical or surgical treatment, or a change in antithrombotic therapy**	**Clinically overt bleeding event that required medical attention**

Camm AJ, et al. Europace 2018;20:1-11

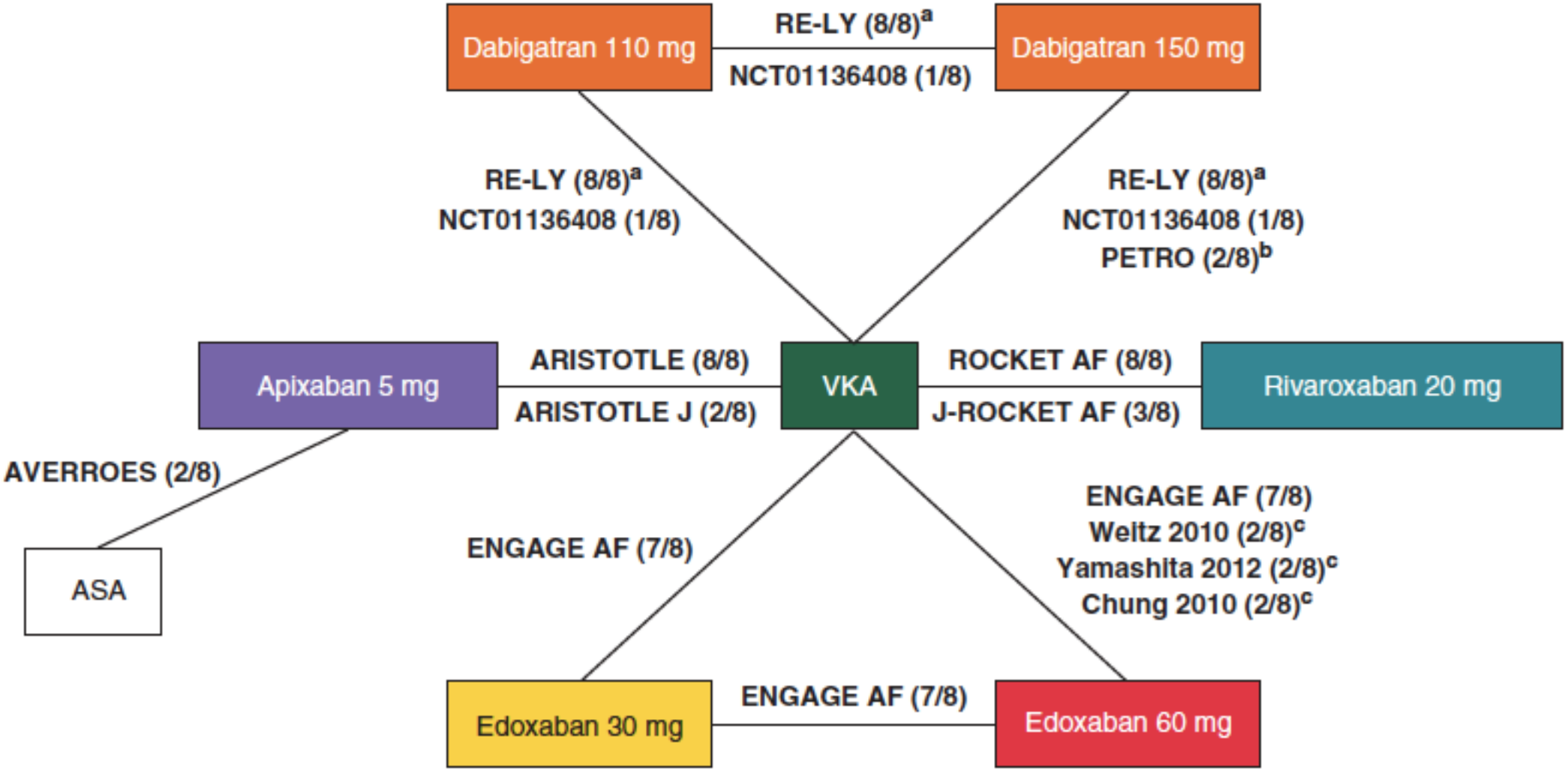
TAKE HOME MESSAGE I

- **Methodological differences**, with regard to study design, **patient populations**, and **outcomes definitions** clearly exist across the four phase III RCTs of NOACs for stroke prevention in patients with NVAF

- Without taking these key issues into consideration, **direct comparison** of summary results across the trials is potentially **misleading**

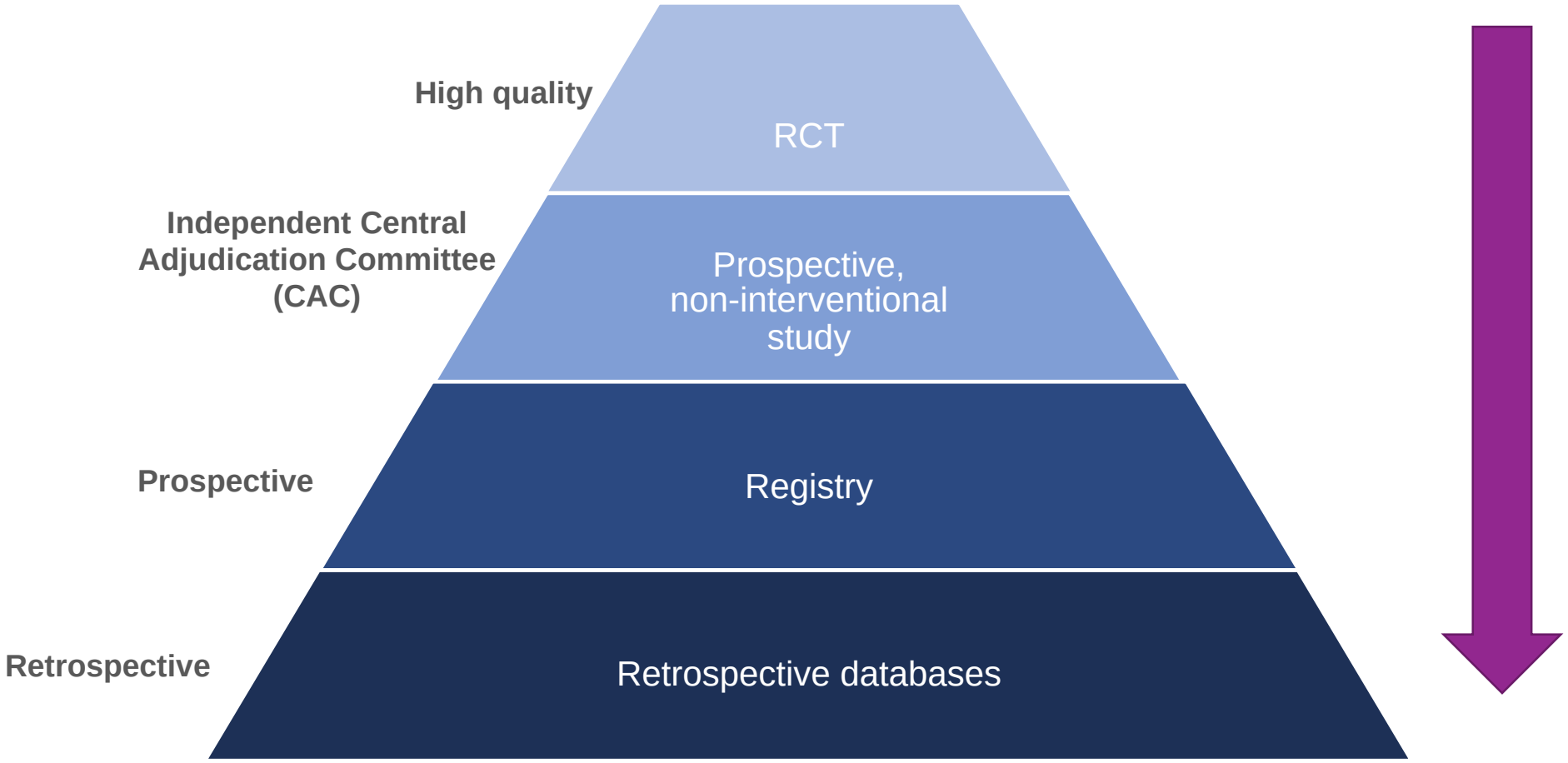
- Although pooled analyses may be superficially attractive, they do not obviate the need to study individual trial characteristics to interpret reported benefits and hazards in the respective trials.

Camm AJ, et al. Europace 2018;20:1-11



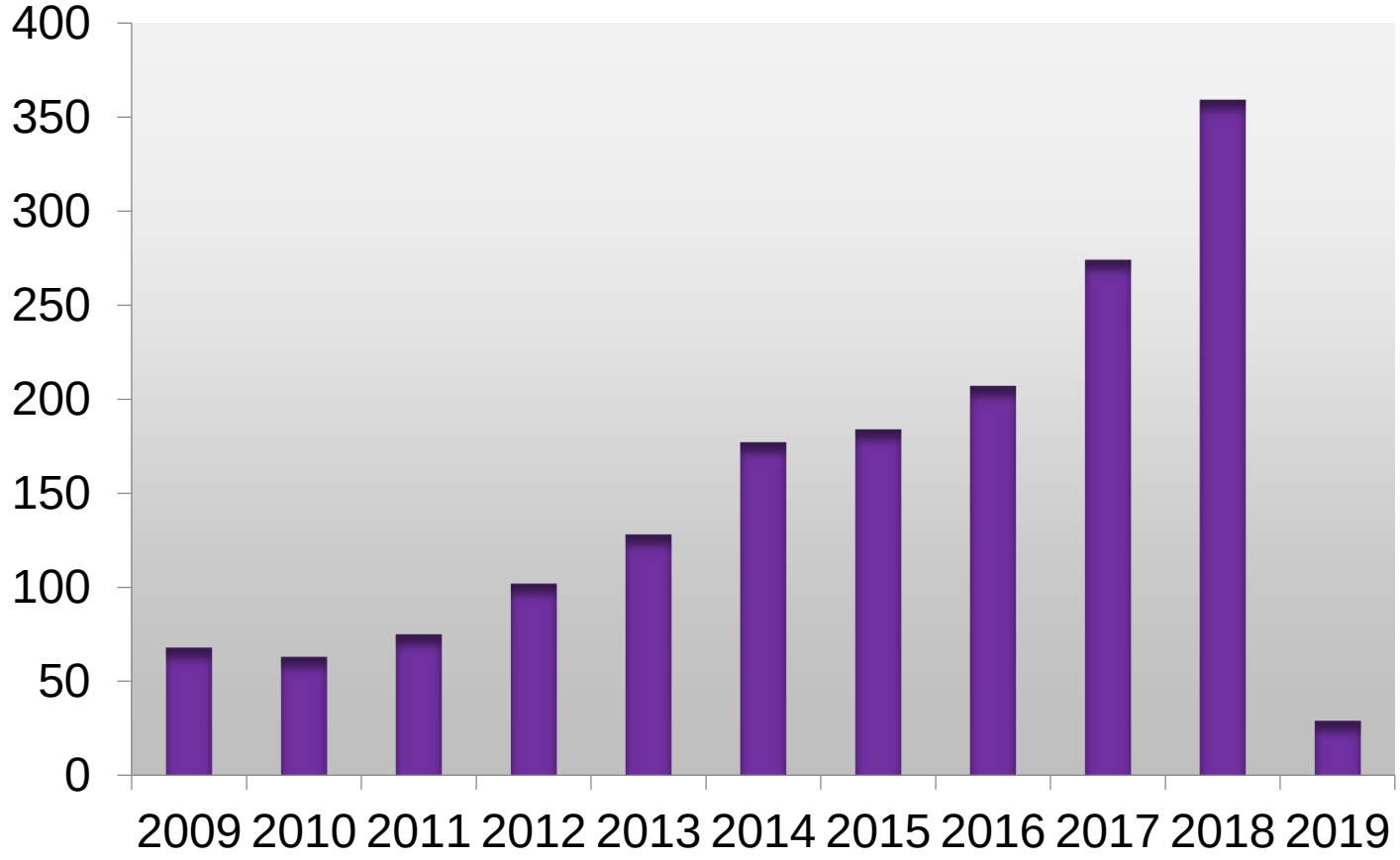
Camm AJ, et al. Europace 2018;20:1-11

Evidence classification



Real life AND Atrial Fibrillation

PubMed search March 2019



Cosa è la RWE?

A cosa ci serve se abbiamo gli RCTs?

Ma davvero ci servono gli RCTs?

RCT, randomized controlled trial; RWE, real world evidence

Limiti degli RCTs

1. Molto costosi (tempo e denaro)
2. Condotti su popolazioni di soggetti selezionati, in settings protetti
3. Dimensioni ***relativamente*** ridotte
4. Durate del follow-up ***relativamente*** brevi
5. Effetto trial

Efficacy vs effectiveness

Gli RCTs sono studi di ***efficacy*** (valutazione della efficacia di un intervento in condizioni pre-specificate)

Gli studi di RWE sono studi di ***effectiveness*** (valutazione della efficacia nelle normali condizioni di uso)

RCT ⟹ efficacy

- Numero definito di pazienti
- Campione selezionato
- Condizioni controllate
- Monitoraggio intensivo
- Condotto in centri specializzati

RWE ⟹ effectiveness

- Numero elevato di pazienti
- Campione non selezionato
- Soggetti con polipatologie
- Compliance non sempre adeguata
- Aperto a tutte le istituzioni

ISPOR-ISPE Special Task force on RWE in Health Care Decision Making Value in Health 2017

Efficacy vs effectiveness

Studio di efficacy PORCHE 911

	Manuale	PDK
Prezzo	da EUR 55.237,00 IVA inclusa	
Potenza (DIN)	220 kW (300 CV) a 6.500 giri/min	
Accelerazione 0-100 km/h	5,1 s	
Velocità massima	275 km/h	
Ciclo combinato l/100 km	7,4	
Emissioni di CO2 a g/km	168	
Altezza	1.295 mm	
Larghezza	1.801 mm	
Lunghezza	4.379 mm	
Passo	2.475 mm	

Su pista/strada perfettamente asfaltata
Guidata da piloti professionisti
....

Efficacy vs effectiveness

Studio di effectiveness
PORCHE 911

PORSCHE

Dopo la fase registrativa, è indispensabile continuare a studiare il profilo rischio-beneficio dei farmaci

- Cartelle cliniche elettroniche
- Registri di patologia
- Registri di monitoraggio dei farmaci
- Database amministrativi
- Database di vendita
- Registri assicurativi
- Dati derivati da app o devices di salute

Traversa G. Istituto Superiore di Sanità – R&P 2016

Le fonti del RWD: quali criticità?

È importante conoscere la qualità della fonte dei dati per decidere se uno specifico data-set può essere usato per rispondere ad un determinato quesito scientifico e di ricerca

Con quale finalità è stato costruito il database?
Come entrano i pazienti nel database?
Perché i pazienti lasciano il database?
Cosa viene registrato/non registrato?

Rivaroxaban: Broad spectrum of evidence from RCTs to RWE

PROSPECTIVE Non-interventional Ph IV study

- Prospective safety data collection
- Prespecified protocol
- End points definition
- Adjudication events committee
- Source data verification visit

XANTUS[3,4]
(XAPASS)[6]
XALIA[7]

PROSPECTIVE Registry

Dresden
NOAC Registry[8]

RETROSPECTIVE Database

- Huge population
- Often data are collected not for research purpose
- Data verification/ quality issues
- Incomplete data
- Coding issues

US PMSS[9]

Phase III Study

The unique option to **compare** drugs/strategies

- **ROCKET AF[1]**
- **EINSTEIN Phase III Program[2]**

1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Prins *et al*. Thrombosis Journal 2013 11:21; 3. Camm AJ et al. Eur Heart J 2016;37:1145-53 4. Kirchhof, P. et al. J Am Coll Cardiol. 2018;72(2):141–53.; 6. Ogawa et al. J Arrhythm.2018 Apr; 34(2):167-175; 7. Ageno *et al*. Lancet Haematol 2016;3: e12–21; 8. Hecker J *et al*, Thromb Haemost 2016;115:939-49; 9. Tamayo S et al, *Clin Cardiol* 2015;38:63–68.

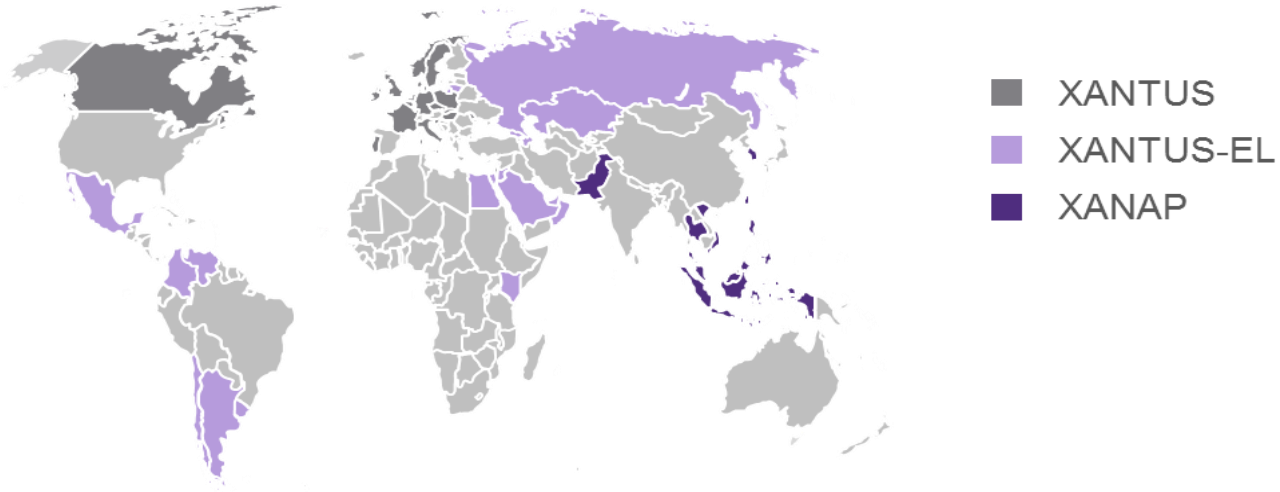
XANTUS Program: >11,000 Patients Receiving Rivaroxaban Globally

- XANTUS pooled is the largest pre-planned, prospective, observational analysis of a single NOAC, rivaroxaban, used for stroke prevention in patients with AF
  - The analysis uses combined data from three multicentre non-interventional studies enrolling >11,000 patients from 47 countries worldwide

XANTUS
Europe, Israel and Canada

XANTUS-EL
Middle East, Eastern Europe, Africa and Latin America

XANAP
Asia Pacific

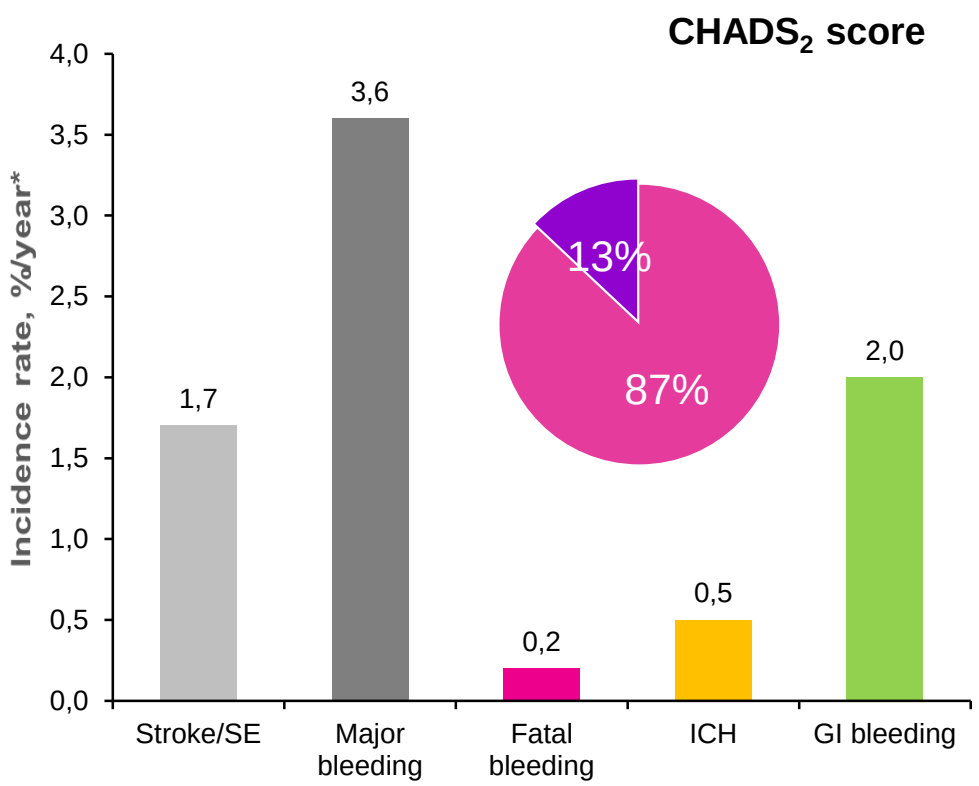


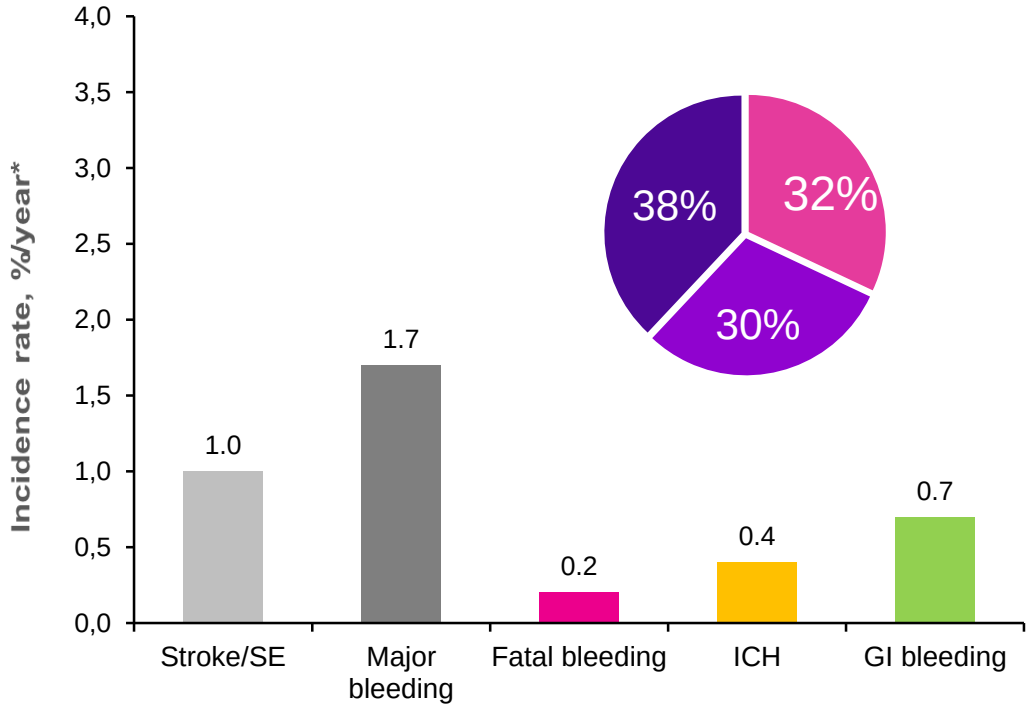
Kravinof P. et al. J Am Coll Cardiol. 2015;72(2):141-53.

Incidence of events strictly linked to patient profile

ROCKET AF[1] — 3,5 CHADS$_2$ score | 55% Precedent stroke#

XANTUS Pooled[2] — 2,0 CHADS score | 21% Precedent stroke#



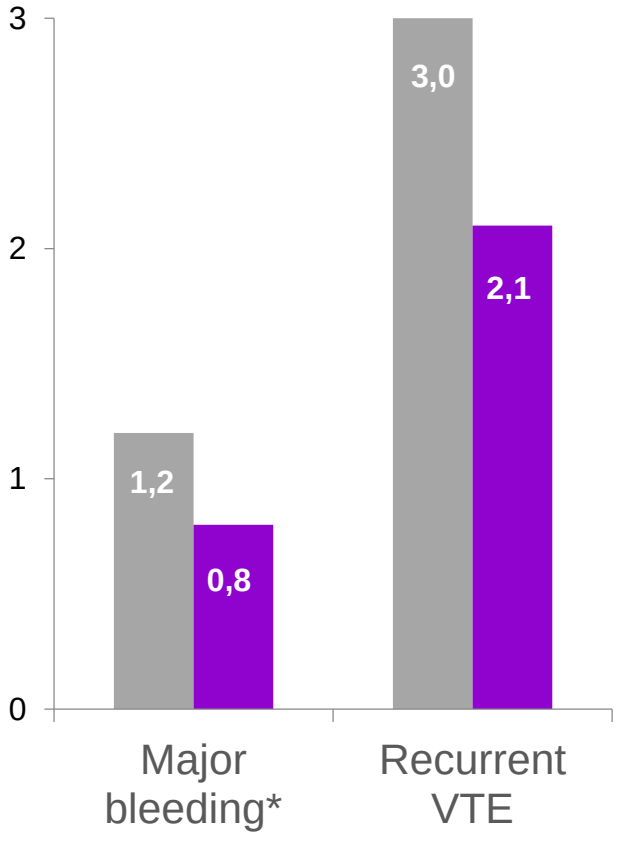


1. Patel MR *et al, N Engl J Med* 2011;365:883–891;
2. Kirchhof, P. et al. J Am Coll Cardiol. 2018;72(2):141–53

EINSTEIN DVT[1] and XALIA[2]: Consistency of efficacy and safety

VTE

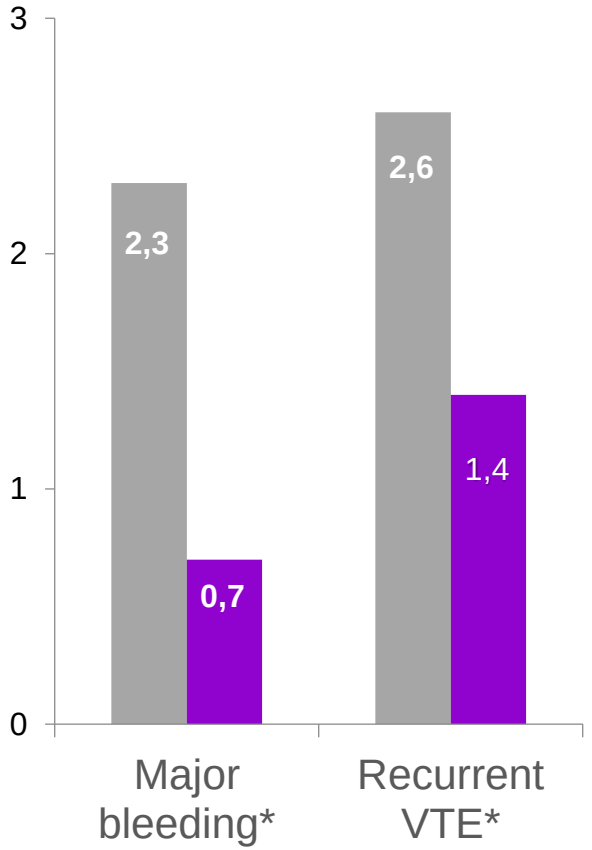
EINSTEIN DVT



Patients Characteristic		
55.8	Age§(years)	57.3†
57.4%	Male	54.5%
19.4%	Previous VTE	24.1%
6.8%	Baseline active cancer	5.6%
6.2%	Known thrombophilia	6.0%

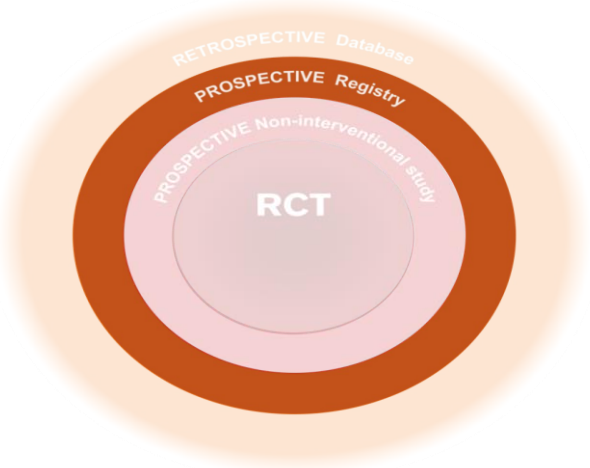
Standard of therapy
Rivaroxaban

XALIA

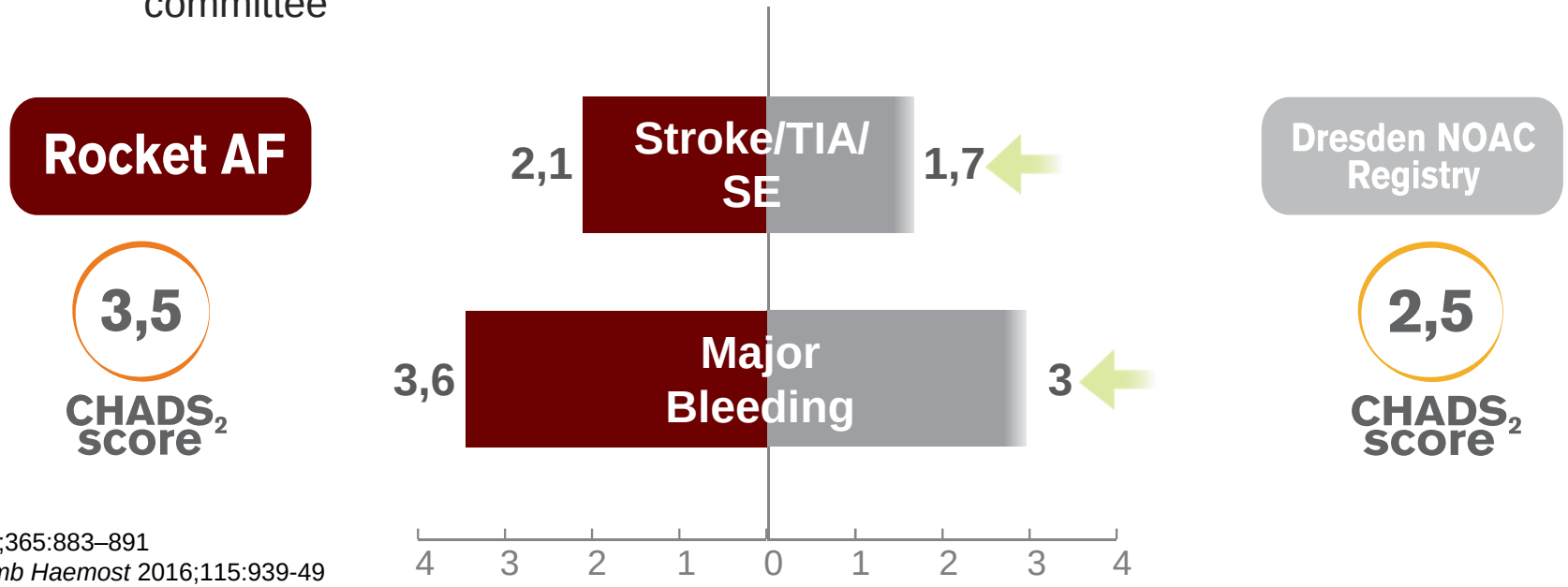


#ITT analysis; *Safety population (patients taking ≥1 dose of study drug); §mean †ASH, USA, December 2015, A894The EINSTEIN Investigators, *N Engl J Med* 2010;363:2499–2510;
[2] Ageno W *et al, Lancet Haematol* 2016;3(1):e12–e21

Dresden NOAC Registry Consistent Effectiveness and Safety of Rivaroxaban for AF



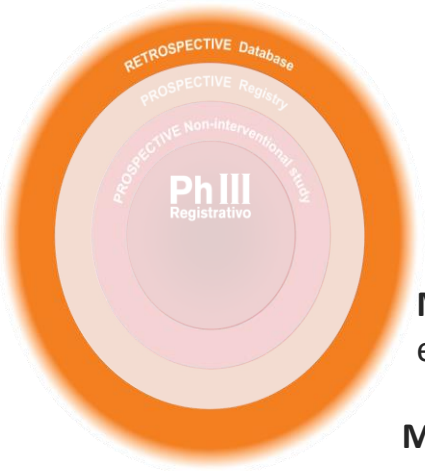
- **Objective**: to assess effectiveness and safety of rivaroxaban in SPAF
- **Design**: large, prospective registry in the administrative district of Dresden.
  - All suspected outcome events are reviewed by a central adjudication committee

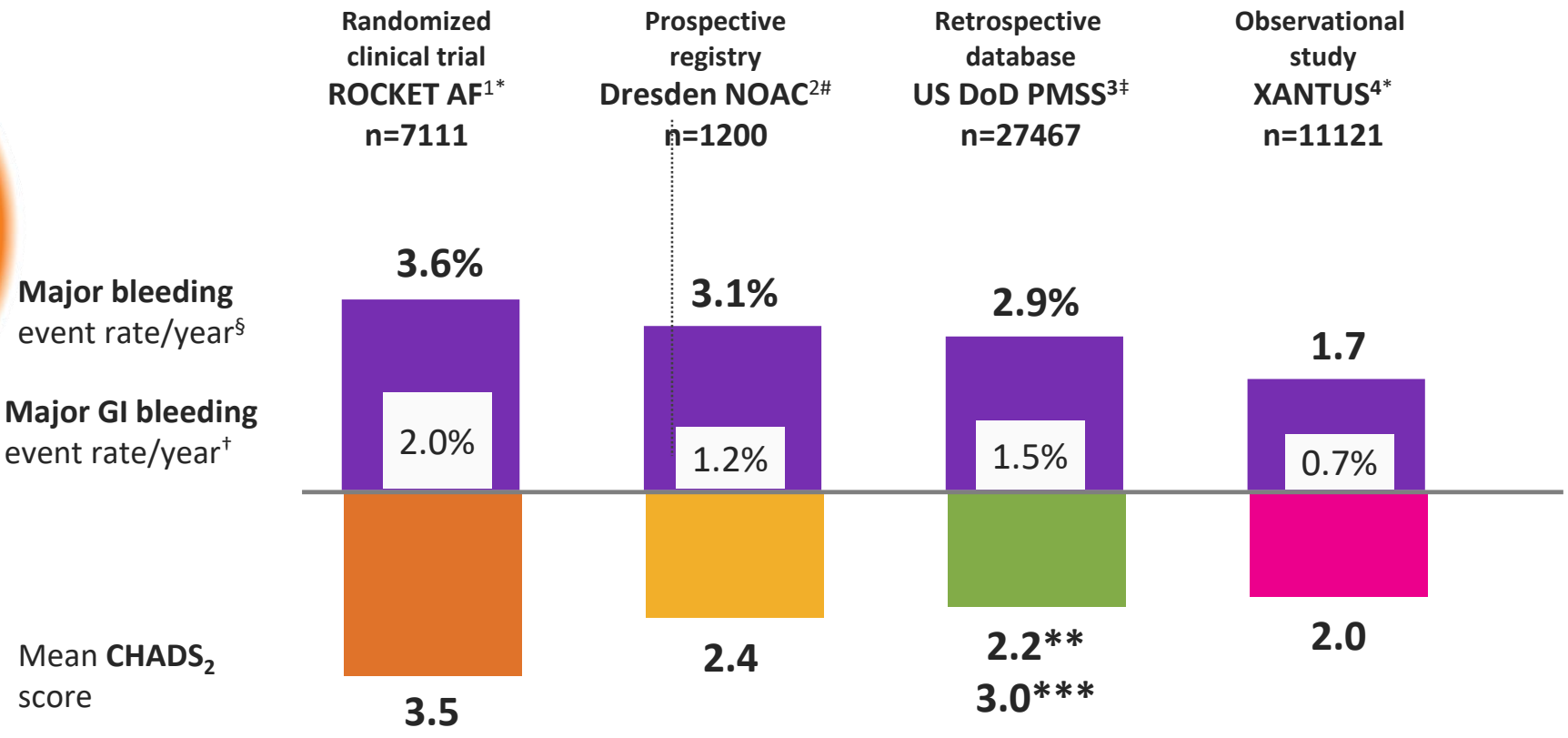


1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891
2. Adapted from Hecker J *et al*, *Thromb Haemost* 2016;115:939-49

Major bleeding events during rivaroxaban therapy occurred **LESS FREQUENTLY** than in the ROCKET AF trial.

Safety Profile of Rivaroxaban Confirmed Through Real-World Evidence Regardless of Data Source[6]



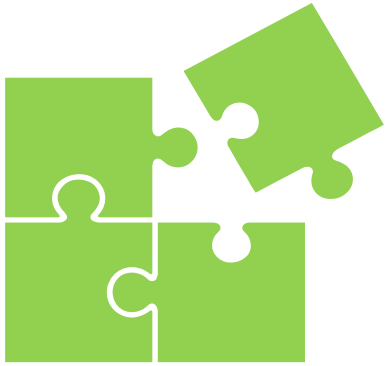


- US DoD PMSS
- U.S. Department of Defense Pharmacovigilance

*Major bleeding definition according to ISTH; #modified ISTH definition (additionally included surgical revision from bleeding);
‡major bleeding defined by the Cunningham algorithm[5];
§ Warfarin MB 3,4% †Warfarin MB-GI 1,24

1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Hecker J *et al*, *Thromb Haemost* 2016 Jan 21;115(5)]; 3. Tamayo S *et al*, *Clin Cardiol* 2015;38:63–68; 4 ; Camm AJ et al, Eur Heart J 2016;37(4):1145-53 5. Cunningham A *et al*, *Pharmacoepidemiol Drug Saf* 2011;20:560–566 6. Modified from Beyer-Westendorf J et al Thromb Hemost 2016:116:S13-S23

TAKE HOME MESSAGE II



- Real-world evidence studies have the potential to **complement** findings from RCTs and provide valuable information about how **a drug performs in the real-world** setting across an unselected patient population with a broader range of co-morbidities than those examined in phase III studies with caution

- **Rivaroxaban and other** provides a **consistent dataset** covering the full patient-risk spectrum

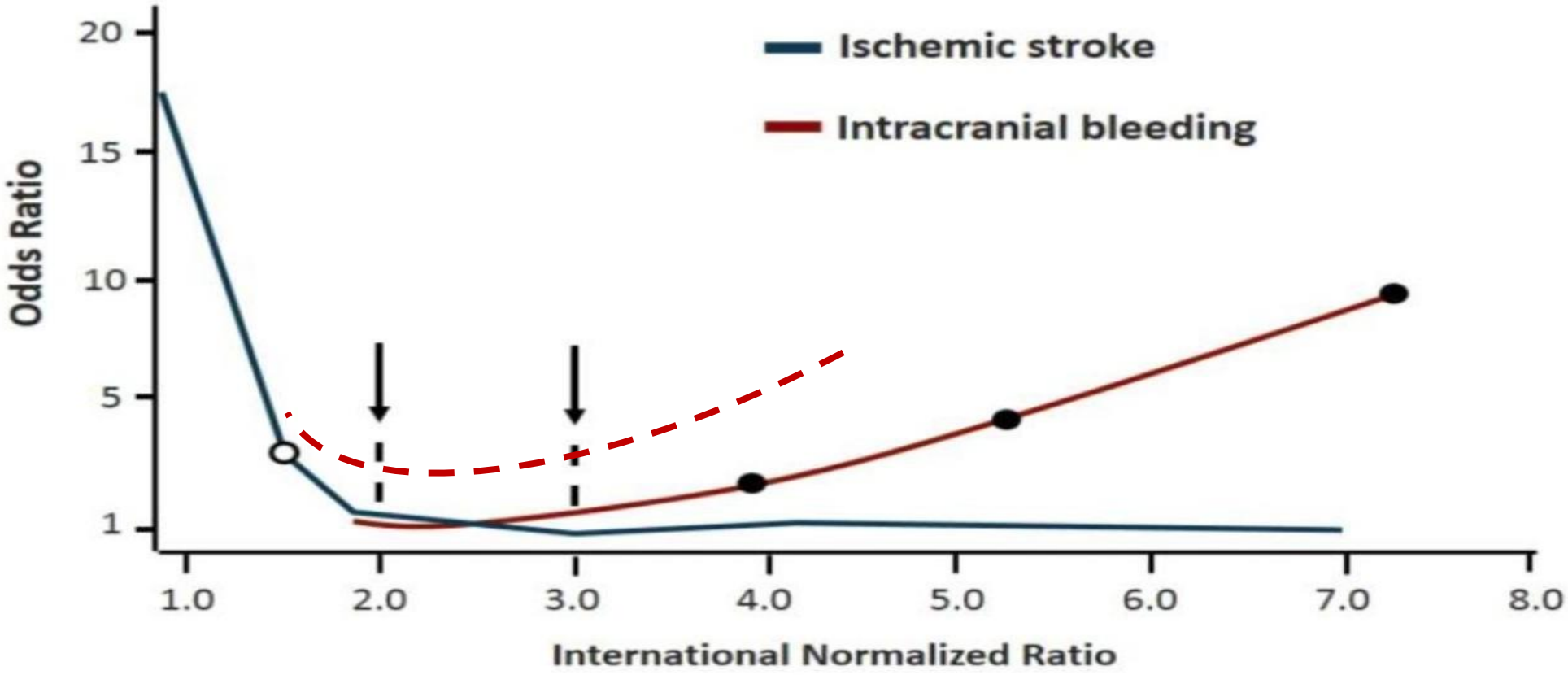
- As for the phase III RCTs, differences between studies can make comparisons potentially misleading or even invalid. **Any comparative meta-analyses based on real-world studies should be avoided** or treated with caution

Come si comporterebbe nei riguardi di un paziente con aderenza subottimale ai farmaci anticoagulanti?

1. Lo invierei ad un centro TAO/NAO
2. Sceglierei Warfarin in modo di controllare l'INR
3. DOAC, ma monodose o bidose non fanno grande differenza, dipende dalla scelta del paziente
4. La monodose è meglio perché aumenta l'aderenza
5. La bi-dose è meglio perché è sicura

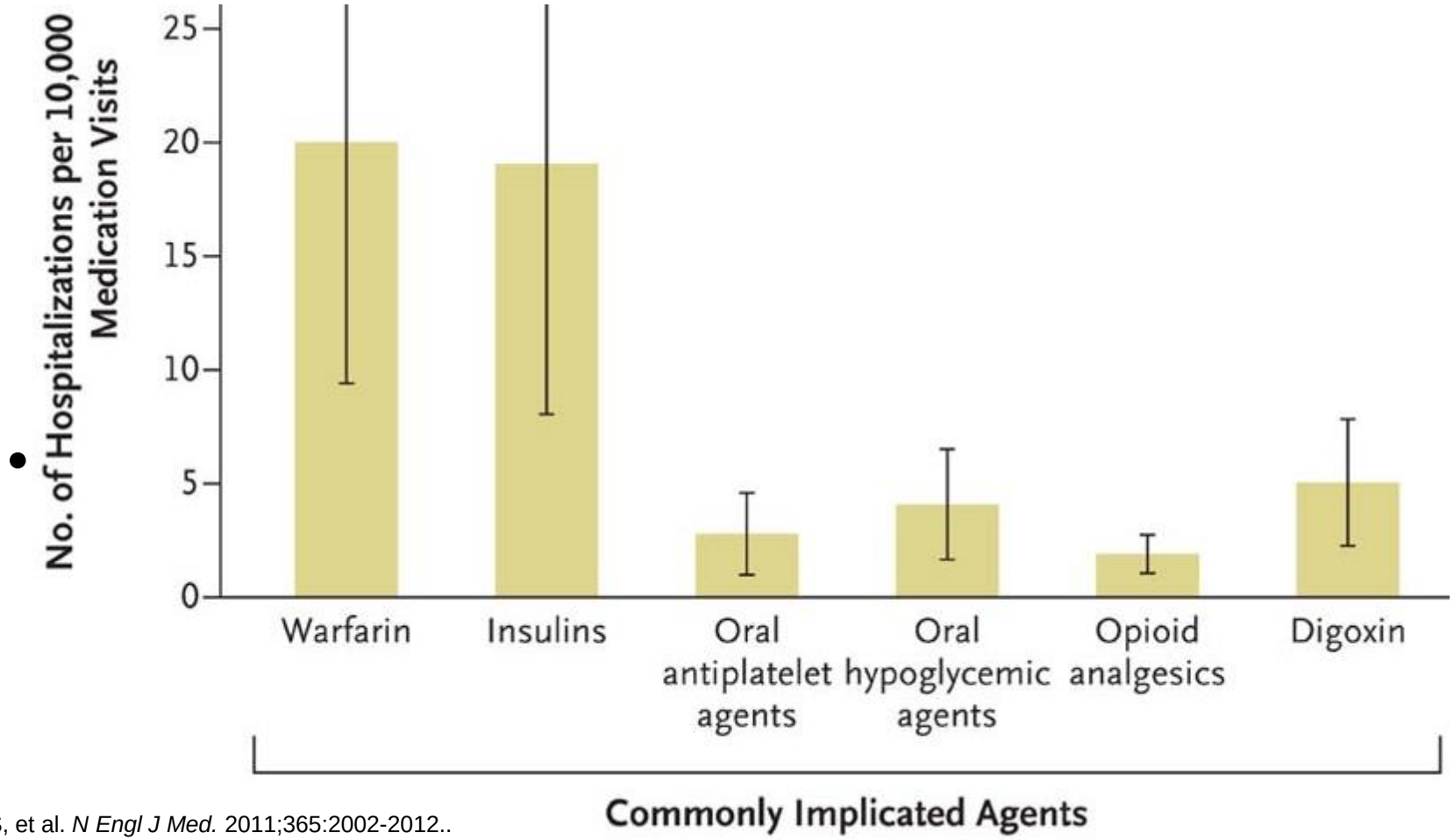
Codice 0003

Sicurezza…warfarin???



Fang MC et Al., Ann Intern Med 2004

Emergency Hospitalizations for Adverse Drug Events in Older US Adults (2016–2018)



Adapted from: Budnitz DS, et al. *N Engl J Med.* 2011;365:2002-2012..

Analisi dei dati relativi alle reazione avverse da farmaci rilevate dalla Rete Nazionale di Farmacovigilanza (ADR)

G.ITAL.CARDIOL. | Volume 19 | Suppl. 1 al n.10 |2018

Alcuni Database amministrativi di qualità

RWE

RegioneLombardia

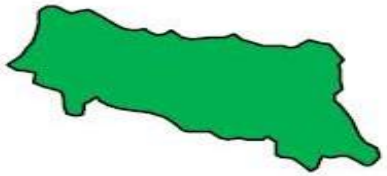
10.0M

REGIONE AUTONOMA
FRIULI VENEZIA GIULIA

1.2M

Regione Emilia-Romagna

4.4M



Regione Toscana
Diritti Valori Innovazione Sostenibilità

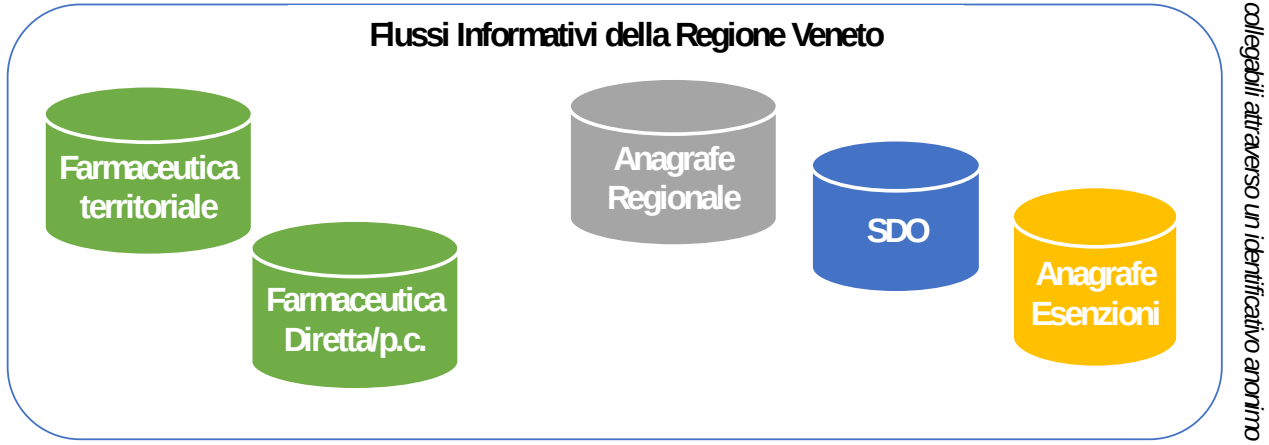
3.7M

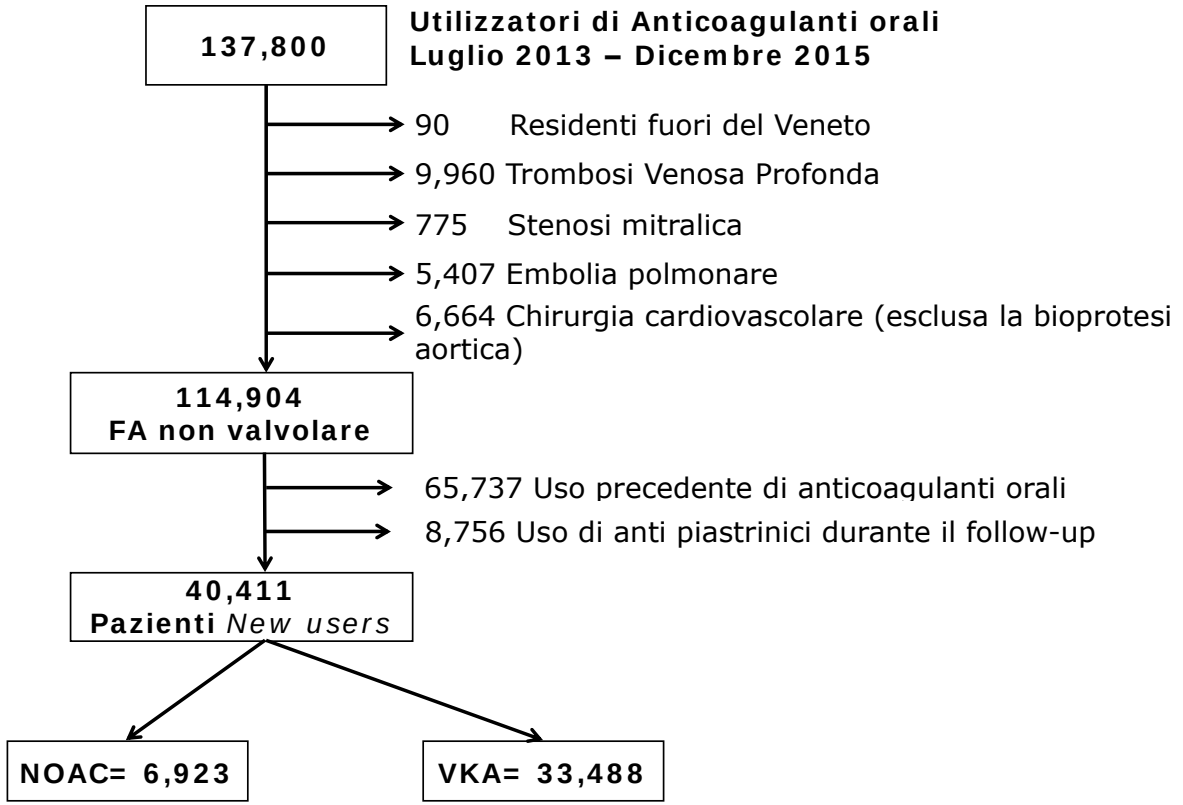
REGIONE DEL VENETO

4.9M

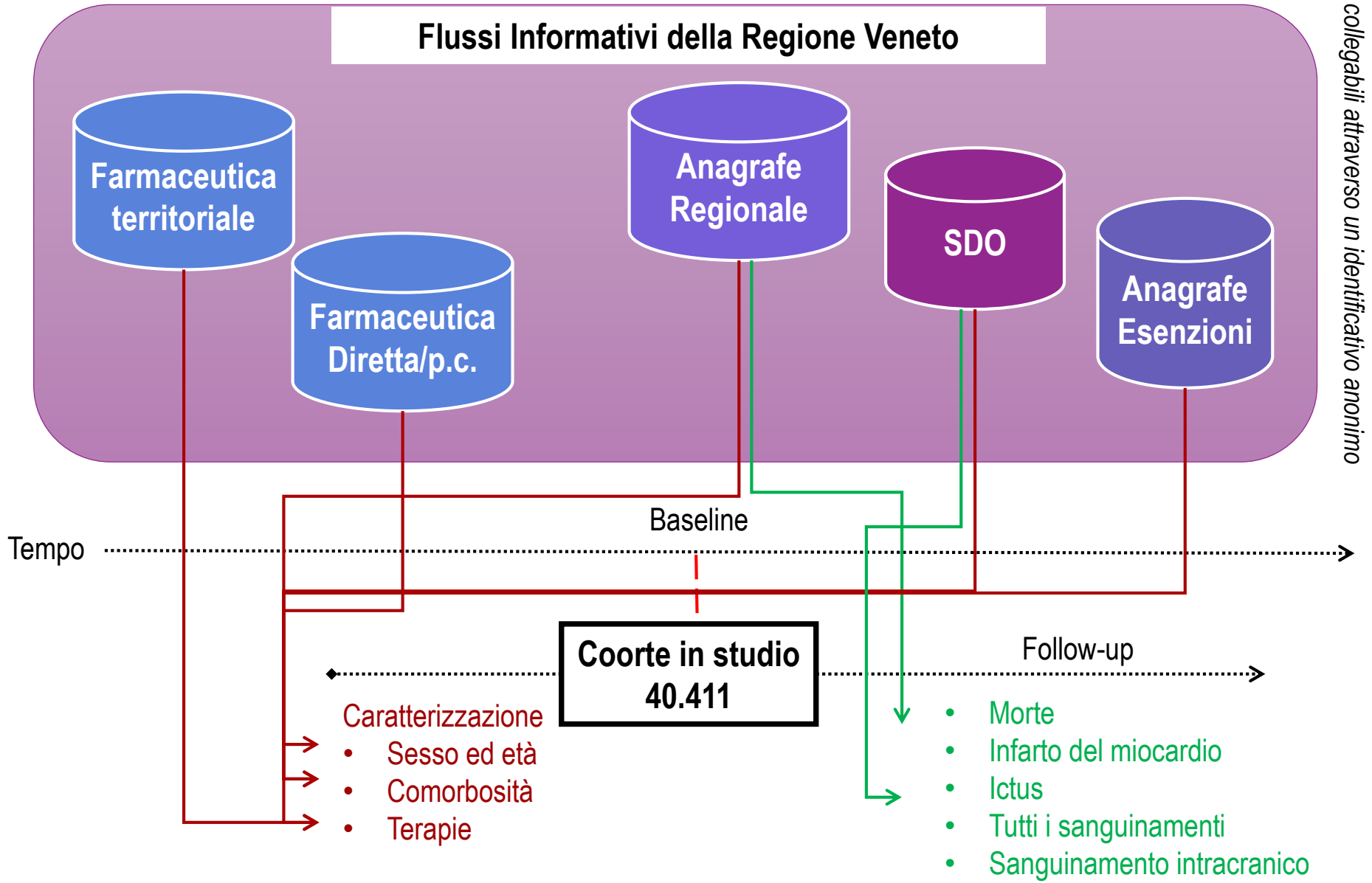
Anticoagulazione nella FANV: Registro Veneto

Ricadute della commercializzazione dei nuovi anticoagulanti orali sullo stato di salute della popolazione con fibrillazione atriale non valvolare nella Regione Veneto

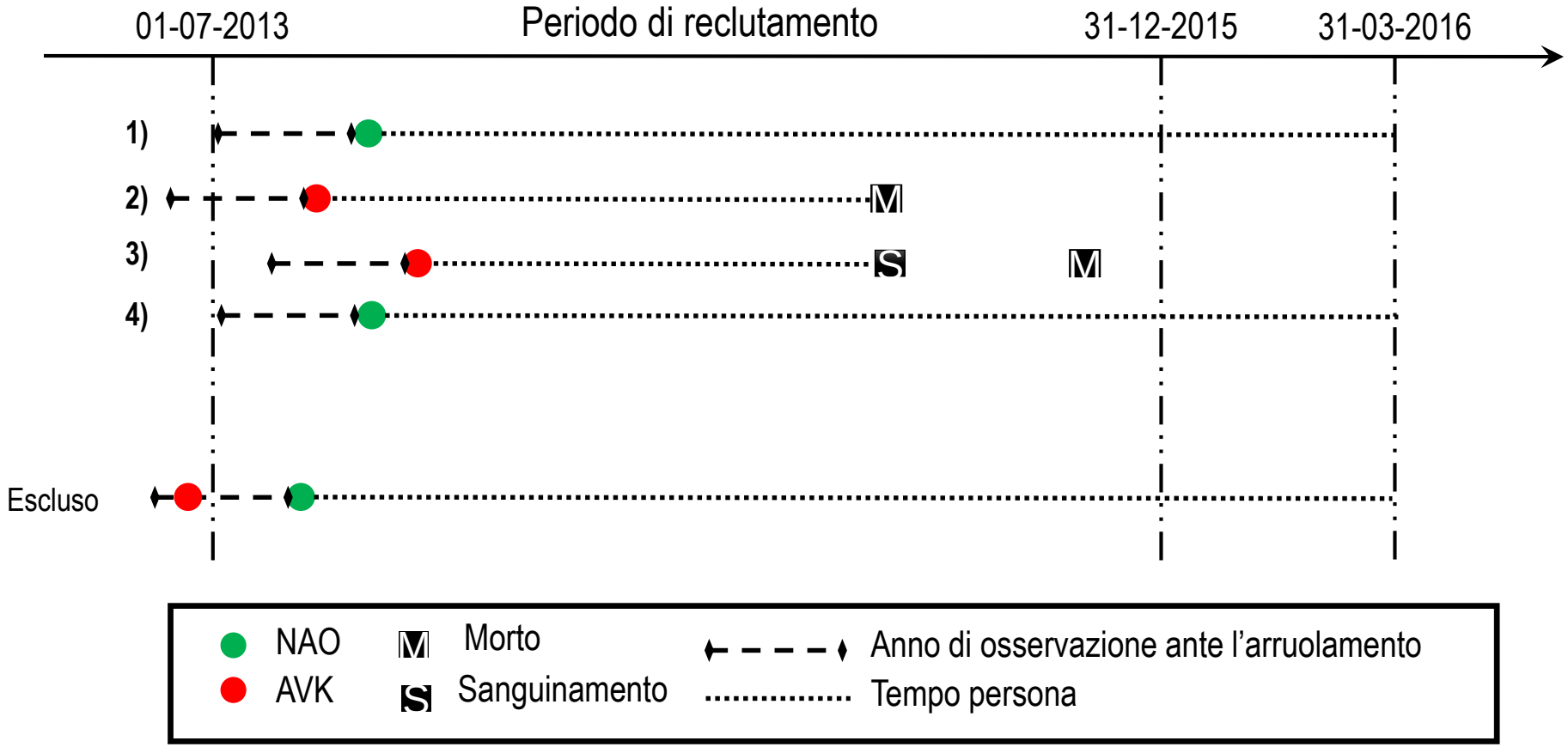




Denas et al. International Journal of Cardiology 249 (2017) 198–203


Flussi Informativi della Regione Veneto
Farmaceutica territoriale
Farmaceutica Diretta/p.c.
Anagrafe Regionale
SDO
Anagrafe Esenzioni
collegabili attraverso un identificativo anonimo
Tempo
Baseline
Coorte in studio 40.411
Follow-up
Caratterizzazione
• Sesso ed età
• Comorbosità
• Terapie
• Morte
• Infarto del miocardio
• Ictus
• Tutti i sanguinamenti
• Sanguinamento intracranico

ANALISI PER INTENZIONI DI TRATTAMENTO (ITT)



Denas et al. International Journal of Cardiology 249 (2017) 198–203

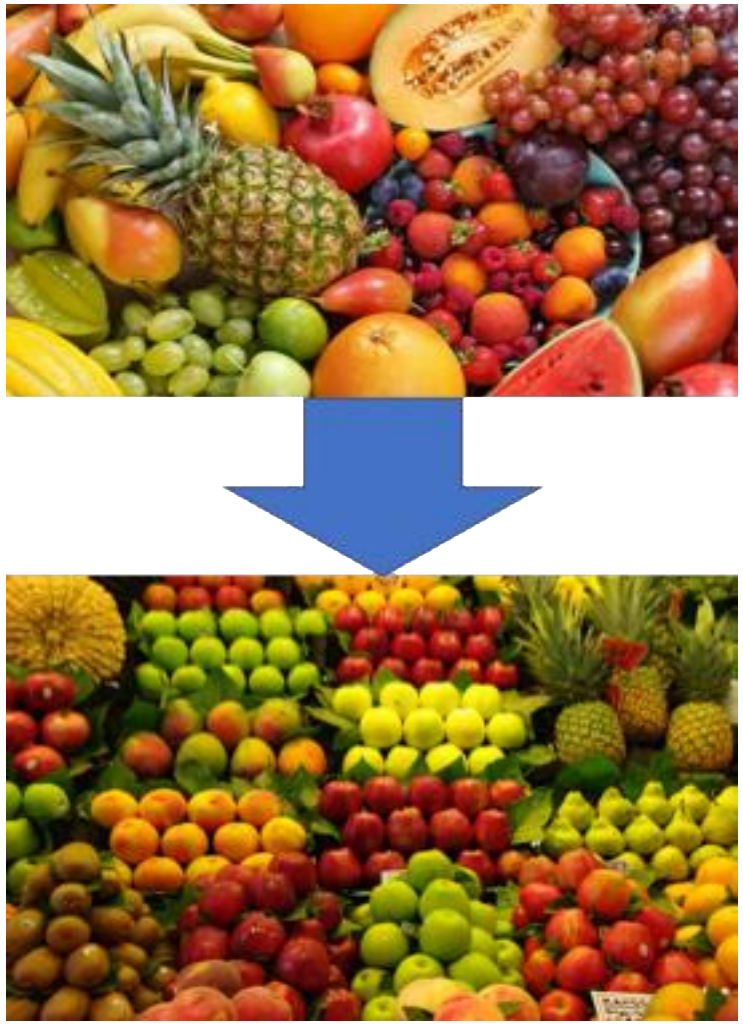
Confronto tra i due gruppi: Propensity score

Definizione intuitiva

- Il PS è una un tecnica che permette ridurre una serie di covariante in un unico indice sintetico (la probabilità di trattamento)

Perché usare il propensity score rispetto alla modellistica classica?

- Gestisce meglio le situazioni con numerosi confondenti e/o eventi rari inoltre permette di rendere esplicito il grado di sovrapposizione dei due gruppi (anche nei domini)



Baseline demographics and clinical characteristics of study subjects treated with NOACs or VKAs (propensity score 1:1 match).

	All study subjects			Propensity score-matched		
	NOAC (n = 6923)	VKA (n = 33,488)	P value	NOAC (n = 6740)	VKA (n = 6740)	P value
Subjects no.	6923	33,488		6740	6740	
Gender						
Male	47.3%	52.2%	<0.001	47.9%	48.2%	0.809
Female	52.7%	47.8%		52.1%	51.8%	
Age: mean (SE)	75.3 (0.14)	74.3 (0.06)	<0.001	75.2	75.1	0.491
Age groups						
<65 yrs	14.8%	15.8%	<0.001	15.1%	15.1%	0.987
65–74 yrs	24.5%	26.8%		24.7%	24.6%	
75–84 yrs	39.3%	41.0%		39.5%	39.5%	
85 + yrs	21.3%	16.4%		20.7%	20.8%	
Risk scores at baseline						
CHA_2DS_2VASc mean (SD)	3.23 (1.45)	3.05 (1.42)	<0.001	3.20 (1.45)	3.19 (1.45)	0.7
HAS-BED mean (SD)	2.36 (1.10)	2.19 (1.03)	<0.001	2.33 (1.09)	2.32 (1.09)	0.12
Comorbidities						
Congestive heart failure	9.8%	11.5%	<0.001	9.9%	10.1%	0.646
Hypertension	73.0%	73.1%	0.812	72.8%	72.3%	0.512
Stroke/TIA/thromboembolism	22.5%	9.9%	<0.001	20.5%	20.1%	0.492
Myocardial infarction	2.2%	2.3%	0.808	2.2%	2.3%	0.485
Peripheral artery disease	1.4%	1.8%	0.046	1.5%	1.4%	0.512
Diabetes	16.2%	17.6%	<0.001	16.1%	16.6%	0.456
Cancer	9.4%	9.5%	0.652	9.4%	9.5%	0.791
Chronic renal disease	2.5%	4.3%	<0.001	2.6%	2.7%	0.591
Chronic liver disease	1.4%	1.3%	0.390	1.4%	1.3%	0.501
History of bleeding	3.5%	2.1%	<0.001	3.1%	3.1%	0.961

Denas et al. International Journal of Cardiology 249 (2017) 198–203

Anticoagulazione nella Regione Veneto

- I pazienti sono mantenuti dentro il range terapeutico per la maggior parte del tempo **(TTR = 69%)**

- Esiste **vantaggio** clinico dei **NAO** in un contesto di **gestione ottimale della terapia** con **AVK** ?

OAC treatment efficacy

mTTR 64%

RELY®
Study of stroke prevention in atrial fibrillation

mTTR 55%

ROCKET AF

mTTR 62%

ARISTOTLE

mTTR 65%

Engage AF
TIMI 48

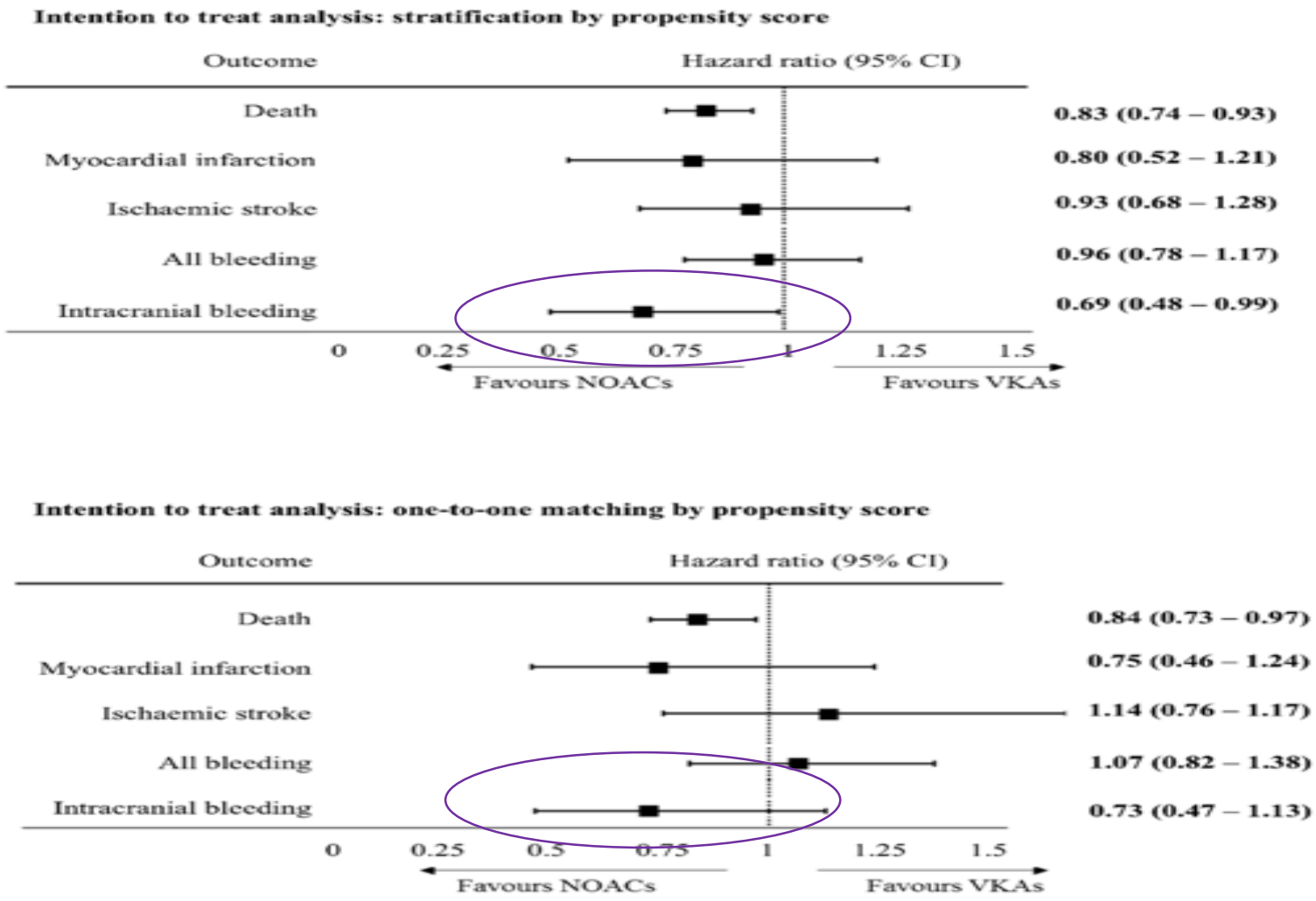
Efficacia

Despite the higher risk for ischaemic stroke in the NOACs group (higher CHA_2DS_2VASc score), we found equal crude effectiveness of NOACs versus VKAs

	NOACs Mean CHA2DS2VASc = 3.2			VKAs Mean CHA2DS2VASc = 3.0		
	n	patient-years	Rate per 100 patient-years	n	patient-years	Rate per 100 patient-years
Intention to treat						
Ischemic Stroke	53	7645.2	0.7	282	47428.2	0.6
Major bleeding	124	7645.2	1.6	778	47428.2	1.6
As treated						
Ischemic Stroke	39	6178.3	0.6	110	20611.0	0.5
Major bleeding	97	6178.3	1.5	416	20611.0	2.0

Denas et al. International Journal of Cardiology 249 (2017) 198–203

Safety of NOACs maintained even with propensity score



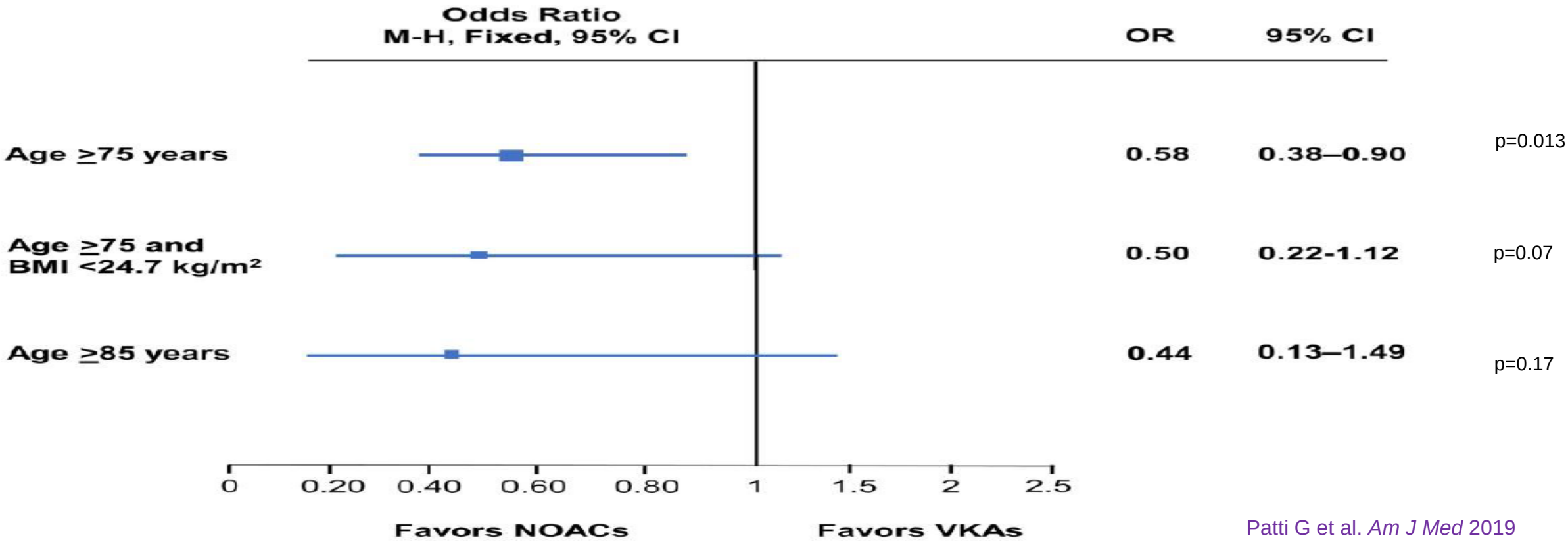
Denas et al. International Journal of Cardiology 249 (2017) 198–203

Net Clinical Benefit of Non-Vitamin K Antagonist Versus Vitamin K Antagonist Anticoagulants in Elderly Patients With Atrial Fibrillation

Patti G et al. *Am J Med* 2019 Jan 18 doi: 10.1016/j.amjmed.2018.12.036

The clinical benefit of NOACs was maintained in Elderly patients with low BMI and in **Very Elderly** patients

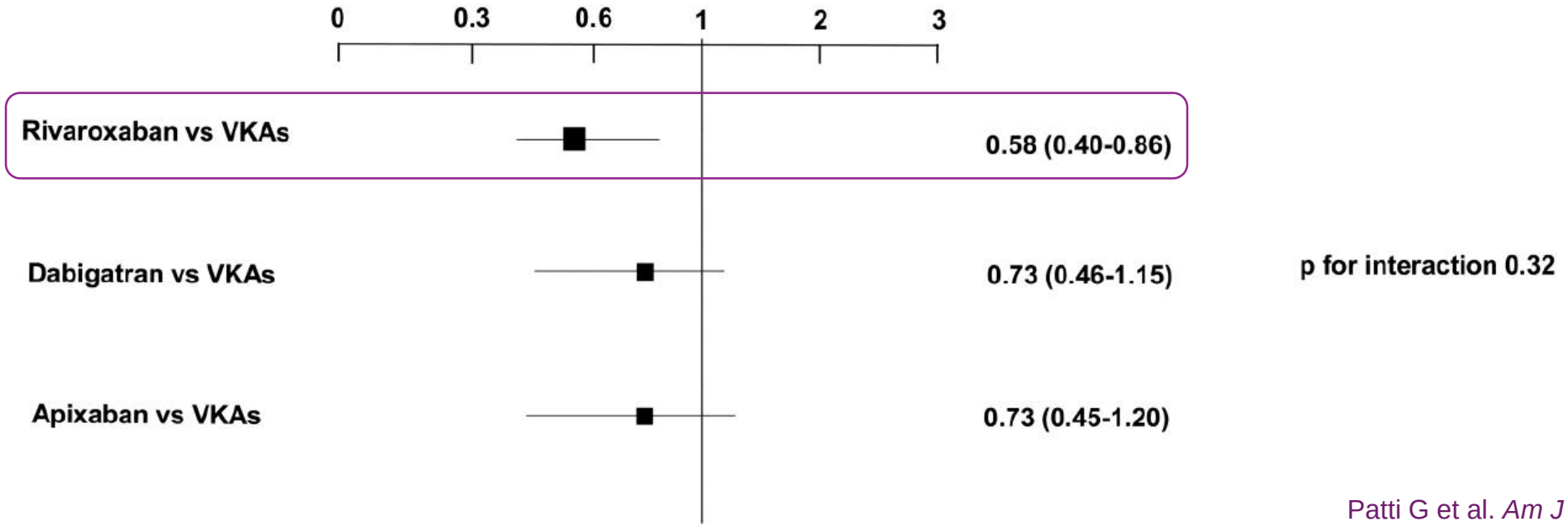
Adjusted odds ratios (OR) for major bleeding with NOACs versus VKAs in elderly patients (aged ≥75 years; n=3825), elderly patients with BMI <24.7 kg/m² (n=1103) and very elderly patients (aged ≥85 years; n=658)



Patti G et al. *Am J Med* 2019

Exploratory analysis on the net composite endpoint with **different NOACs** vs VKAs

Adjusted odds ratios (OR) for the net composite endpoint of the different NOACs versus VKAs



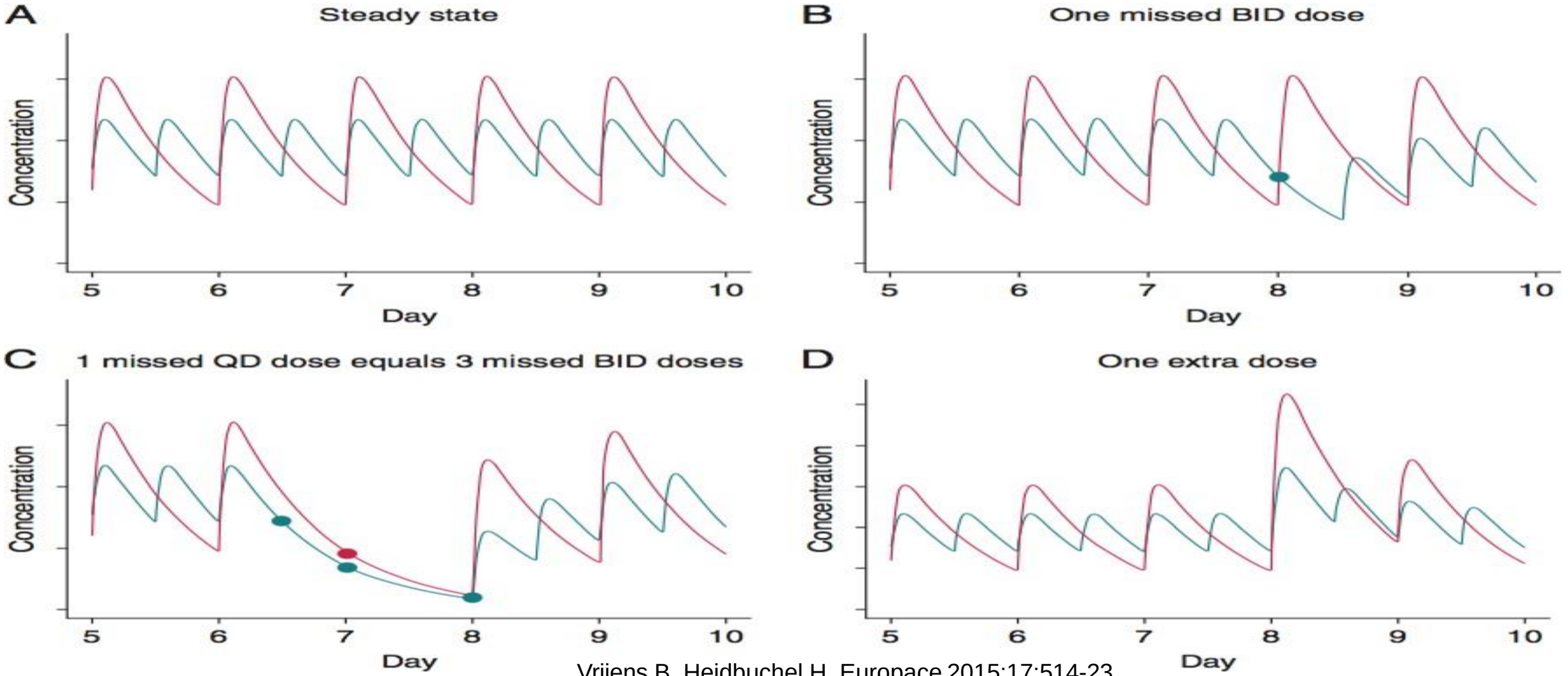
Patti G et al. *Am J Med* 2019

Rivaroxaban use was associated with a 42% lower incidence of the net composite endpoint including major bleeding and ischemic cardiovascular events *vs* VKAs

TAKE HOME MESSAGE III

- I dati *real world* sono uno strumento importante per rispondere a domande cliniche critiche non risolte dagli RCT a causa di rigorosi criteri di selezione
- Il registro di dati *real world* della Regione Veneto ha dimostrato che i NAO mantengono il loro profilo di sicurezza rispetto gli AVK gestiti in modo ottimale
- Rispetto ai VKA, l'uso di NOAC è associato a un beneficio clinico netto migliore nei pazienti anziani (età ≥75 anni) con fibrillazione atriale
- L'uso di Rivaroxaban è stato associato ad un'incidenza inferiore del 42% dell'endpoint composito netto, inclusi sanguinamento maggiore ed eventi cardiovascolari ischemici vs VKAs

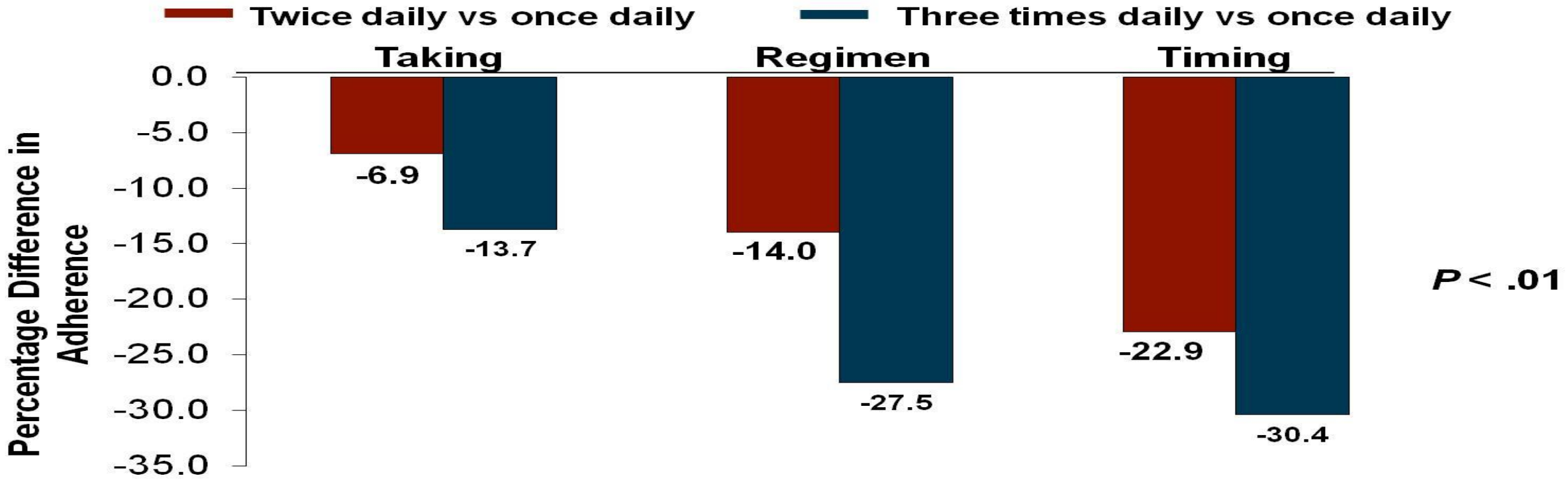
Il problema dell'aderenza con la mono e la bi somministrazione



Vrijens B, Heidbuchel H. Europace 2015;17:514-23

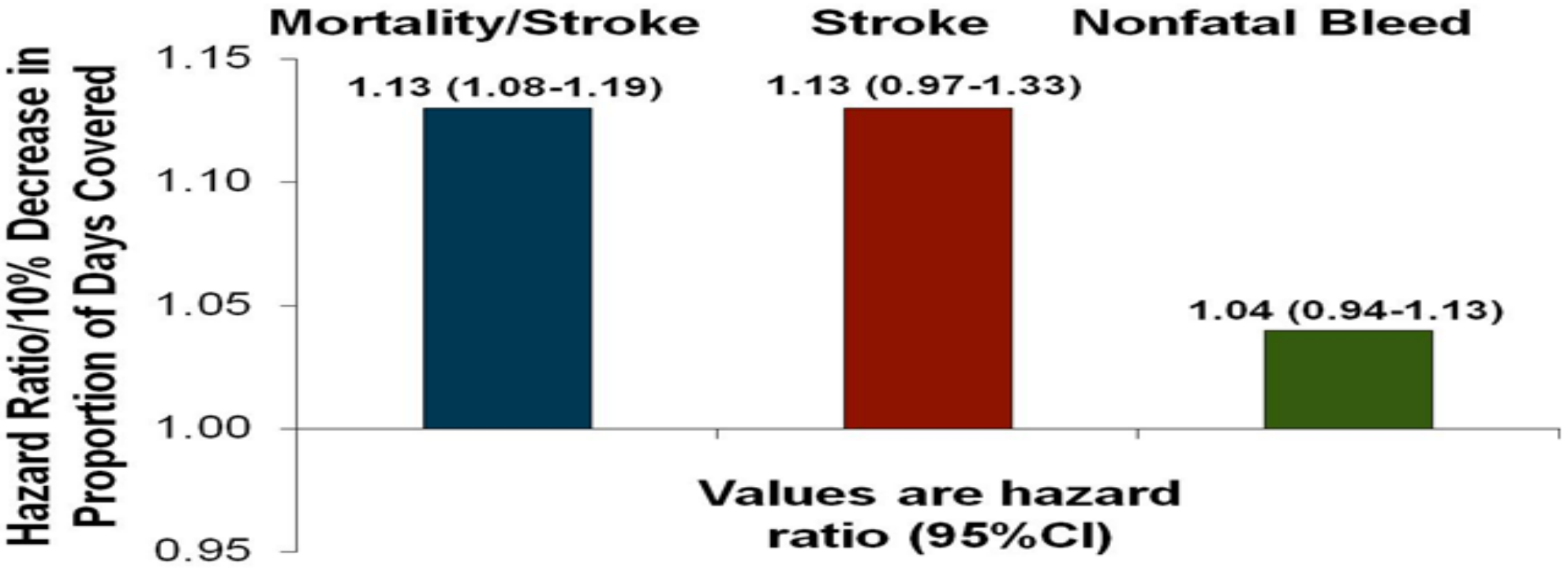
Chronic Cardiovascular Medication Adherence

Meta-analysis demonstrated decreased adherence with twice-daily and thrice-daily vs once-daily regimens with 3 definitions of adherence used



Coleman CI, et al. *Curr Med Res Opin*. 2012;28:669-680.[19]

Nonadherence to a NOAC is Associate to Worse Outcomes

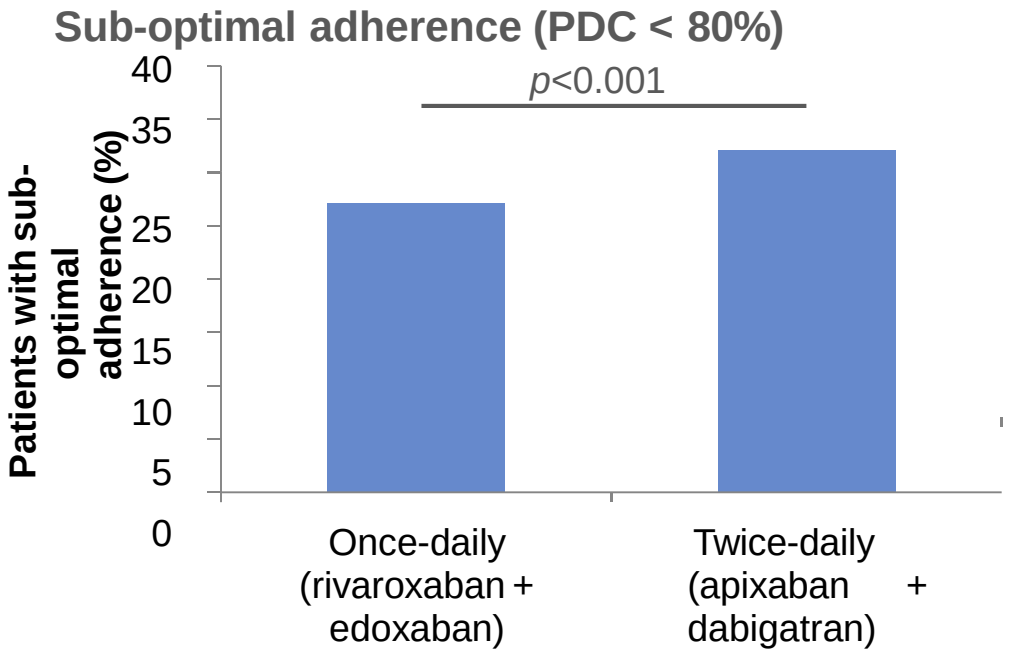


5376 veterans with nonvalvular atrial fibrillation (71.3 ± 9.7 years; 98.3% were men; mean $CHADS_2$ score was 2.4 ± 1.2; median follow-up was 244 days, initiated on dabigatran from October 2010 to September 2012).

Shore S, *Am Heart J* 2014;167:810-817.

Adherence on Once-Daily NOACs is Greater Than on Twice-Daily NOACs

- Retrospective database analysis: adherence and outcomes in matched patient cohorts on once-daily or twice-daily NOACs



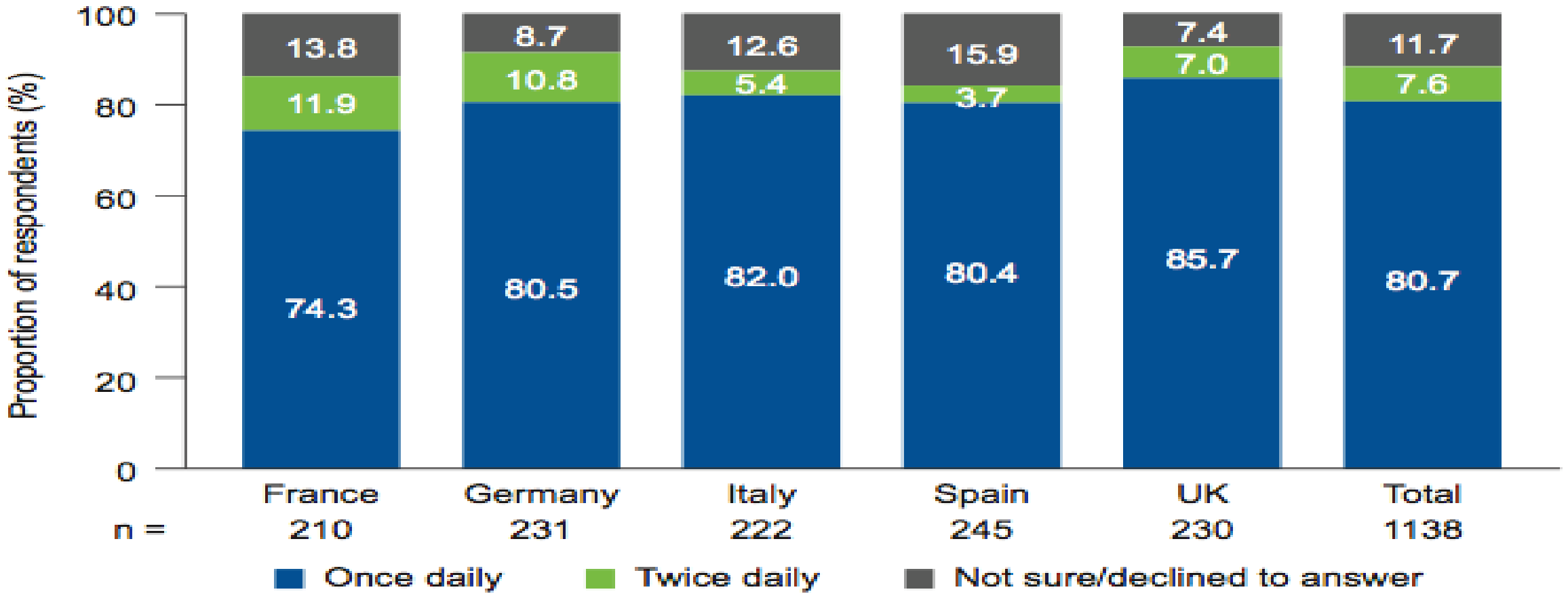
Patients with sub-optimal adherence had **50% increase in risk of ischaemic stroke**, irrespective of dosing regimen
(HR for OD: 1.47; HR for BID; 1.50)

In sub-optimal adherers, no stroke advantage seen with BID regimen

PDC: Proportion of days covered

Alberts MJ et al, Int J Cardiol 2016;215:11

Patient preferences for chronic treatment for stroke prevention: results from the EUropean Patient Survey in Atrial Fibrillation (EUPS-AF)

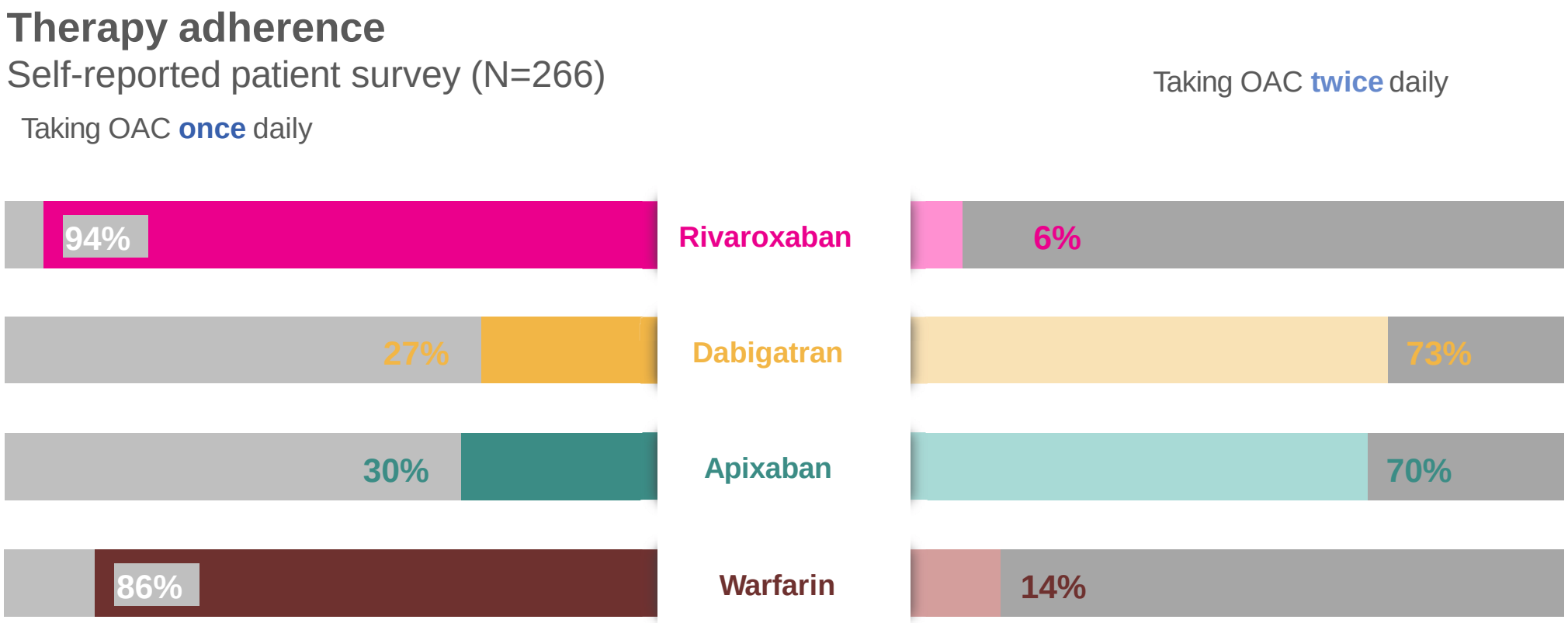


Zamorano JL et al; ESC 2012

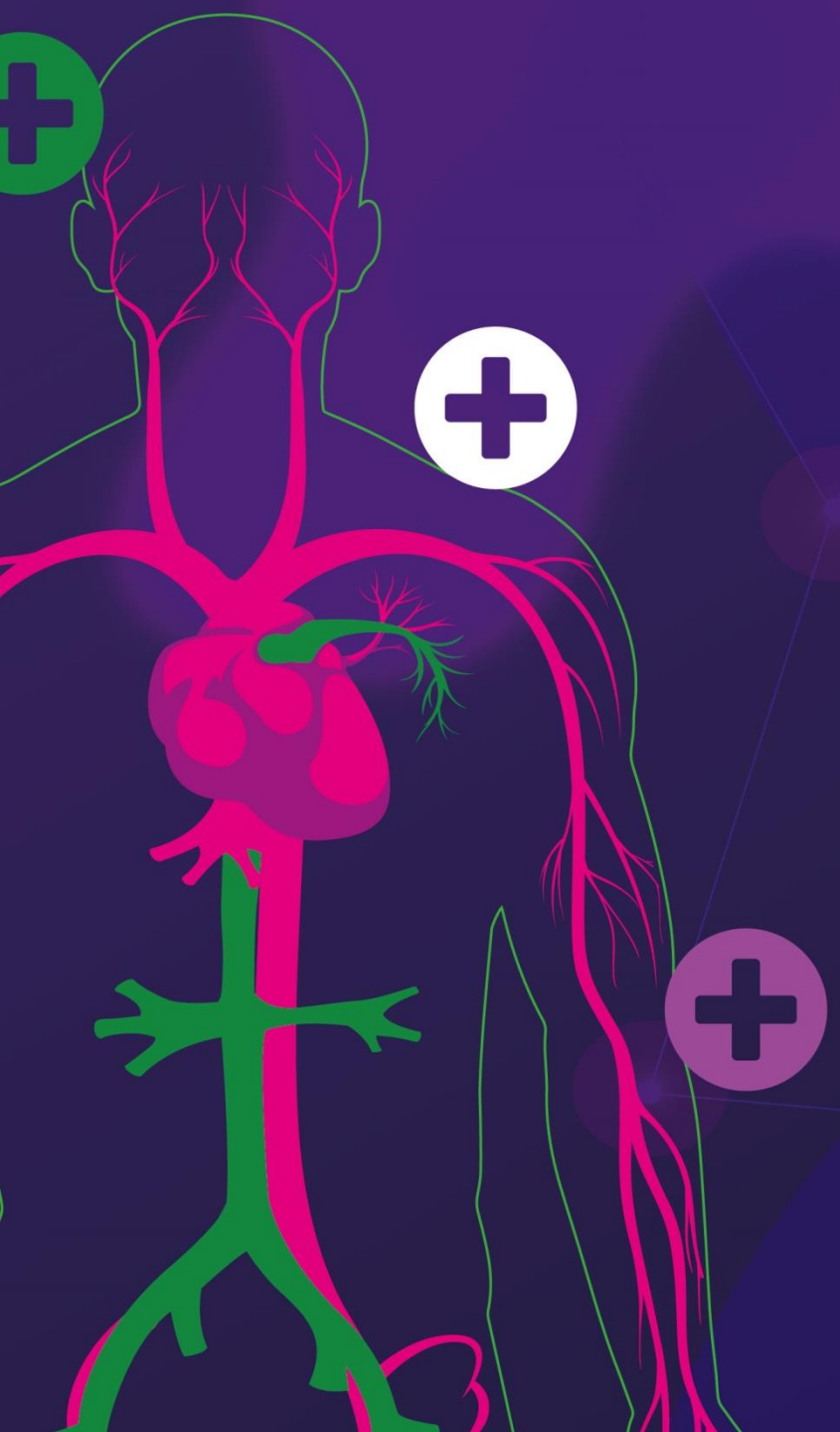
One-Third of Twice-Daily Prescribed Medications Were Being Taken Once Daily

Therapy adherence

Self-reported patient survey (N=266)



Andrade JG et al, Can J Cardiol 2015;doi:0.1016/j.cjca.2015.09.023



24.25.26
MAGGIO 2019
SORRENTO
HILTON SORRENTO PALACE
Via Sant'Antonio, 13

DOAC 4.0:
IL PAZIENTE AL CENTRO E NUOVI PARADIGMI