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Società Scientifica delle attività
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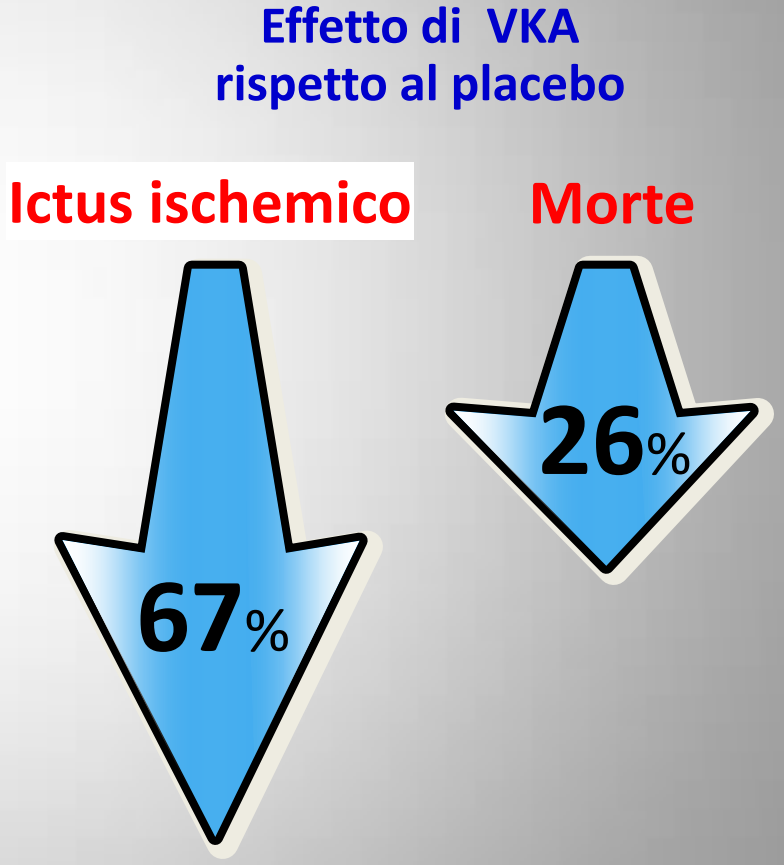
GESTIONE INTEGRATA DEL PAZIENTE
A RISCHIO CARDIOVASCOLARE:
ANTICOAGULAZIONE & DIABETE
SFIDE ED OPPORTUNITÀ

Sicurezza nella scelta di strategie terapeutiche in pazienti con FANV e gestione delle emergenze/urgenze

Antonio D'Onofrio MD, FAIAC, FANMCO, FESC
UOSD di Elettrofisiologia Studio e Terapia delle Aritmie
A.O.R.N. dei Colli Ospedale Monaldi
Napoli

L'ictus correlato a FA può essere prevenuto

- **Due terzi degli ictus** dovuti a FA possono essere **prevenuti** mediante un adeguato trattamento anticoagulante con un **antagonista della vitamina K (VKA) (INR 2,0–3,0)**[1]
- Una meta-analisi di 29 trials su 28.044 pazienti ha mostrato che warfarin con dosaggio ben controllato determina **una riduzione del tasso di ictus ischemico e di mortalità per tutte le cause** [1]
- I VKA sono associati a complicanze, quali un aumentato rischio di sanguinamento
  - Anticoagulazione con un VKA è consigliata per i pazienti con più di un fattore di rischio moderato [2]



1. Hart RG, et al. *Ann Intern Med* 2007;146:857-867. 2. Fuster V, et al. *J Am Coll Cardiol* 2006;48:854-906.

Limitazioni della terapia con AVK

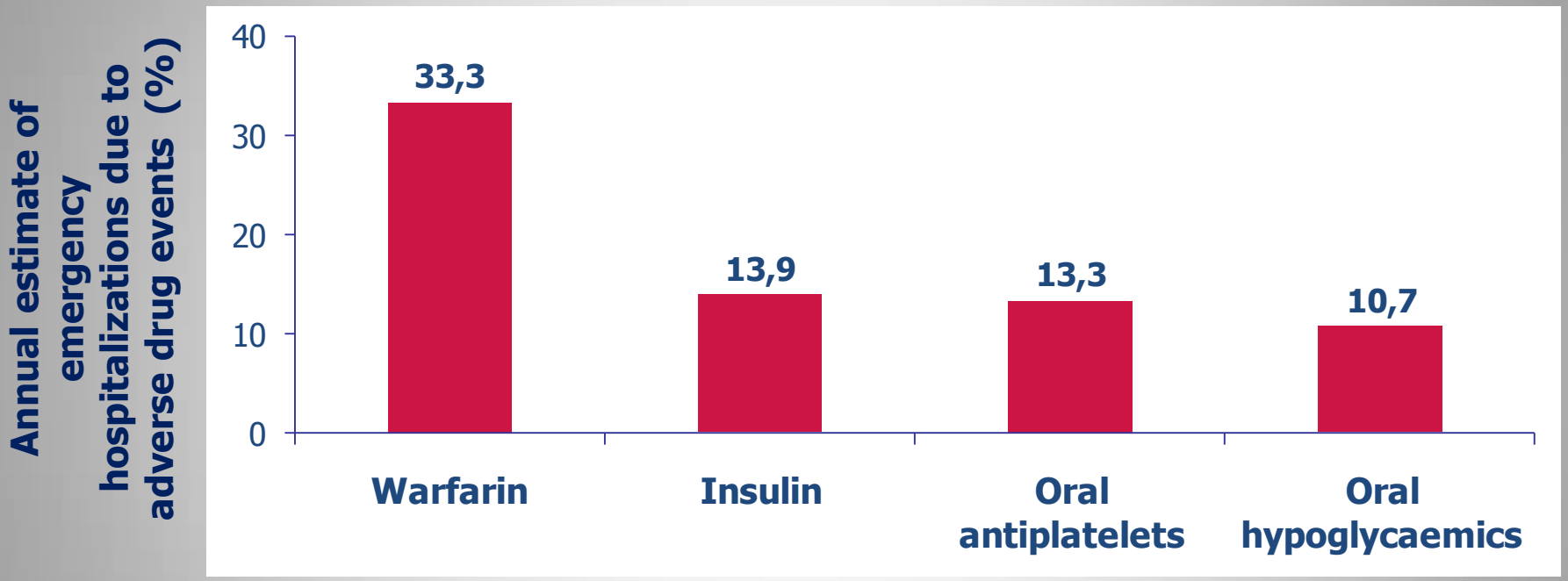
La terapia AVK presenta parecchie limitazioni che la rendono difficile da usare nella pratica clinica

- Risposta imprevedibile
- Finestra terapeutica Ristretta (range INR 2,0–3,0)
- Azione lenta insorgenza/cessazione
- Numerose interazioni con il cibo
- Numerose interazioni con i farmaci
- Farmaco-resistenza

Monitoraggio routinario della coagulazione → Frequenti aggiustamenti di dose

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

VKAs are implicated in large numbers of hospitalizations due to adverse drug events



63.3% of all warfarin-related hospitalizations were due to haemorrhage

Costs for warfarin-related haemorrhages estimated at hundreds of millions of dollars annually

Budnitz DS et al. *N Engl J Med* 2011;365:2002–12

Complicanze emorragiche da AVK

Emorragie intracraniche

3-10 ‰ incidenza annuale di emorragie intracraniche in pazienti con fibrillazione atriale trattati con AVK in studi clinici

Flaherty ML, Semin Neurol 2010; 30(5): 565-572

≈20% di tutte le emorragie intracraniche primarie sono associate a trattamento anticoagulante orale

Flaherty ML, Semin Neurol 2010; 30(5): 565-572

50%-90% delle emorragie intracraniche si verificano con AVK in range INR tra 2 e 3

Bechtel et al. International Journal of Emergency Medicine 2011, 4:40

46%-68% mortalità associata ad emorragie intracraniche in pazienti trattati con anticoagulanti orali

Hart RG et al. Stroke. 1995; 26: 1471-1477

AVK: antagonista della vitamina K

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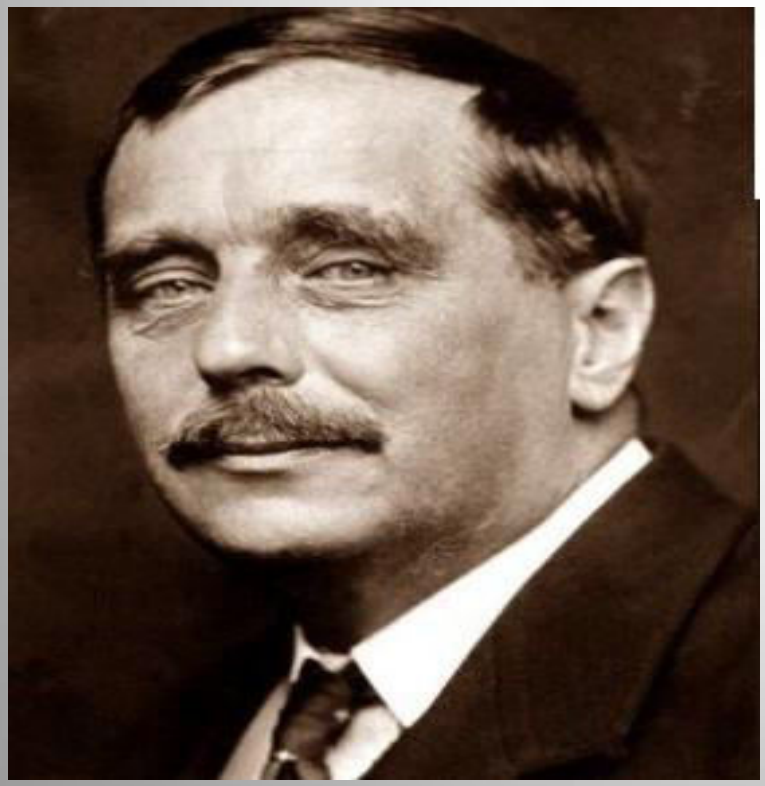
GESTIONE INTEGRATA DEL PAZIENTE A RISCHIO CARDIOVASCOLARE: ANTICOAGULAZIONE & DIABETE SFIDE ED OPPORTUNITÀ



Ogni progresso è
dovuto agli scontenti.
Le persone contente
non desiderano
alcun cambiamento.
H. G. Wells

Comparison of Phase 3 SPAF Trials for NOACs: A Robust Trial Base

CARD Confederazione Associazioni Regionali di Distretto
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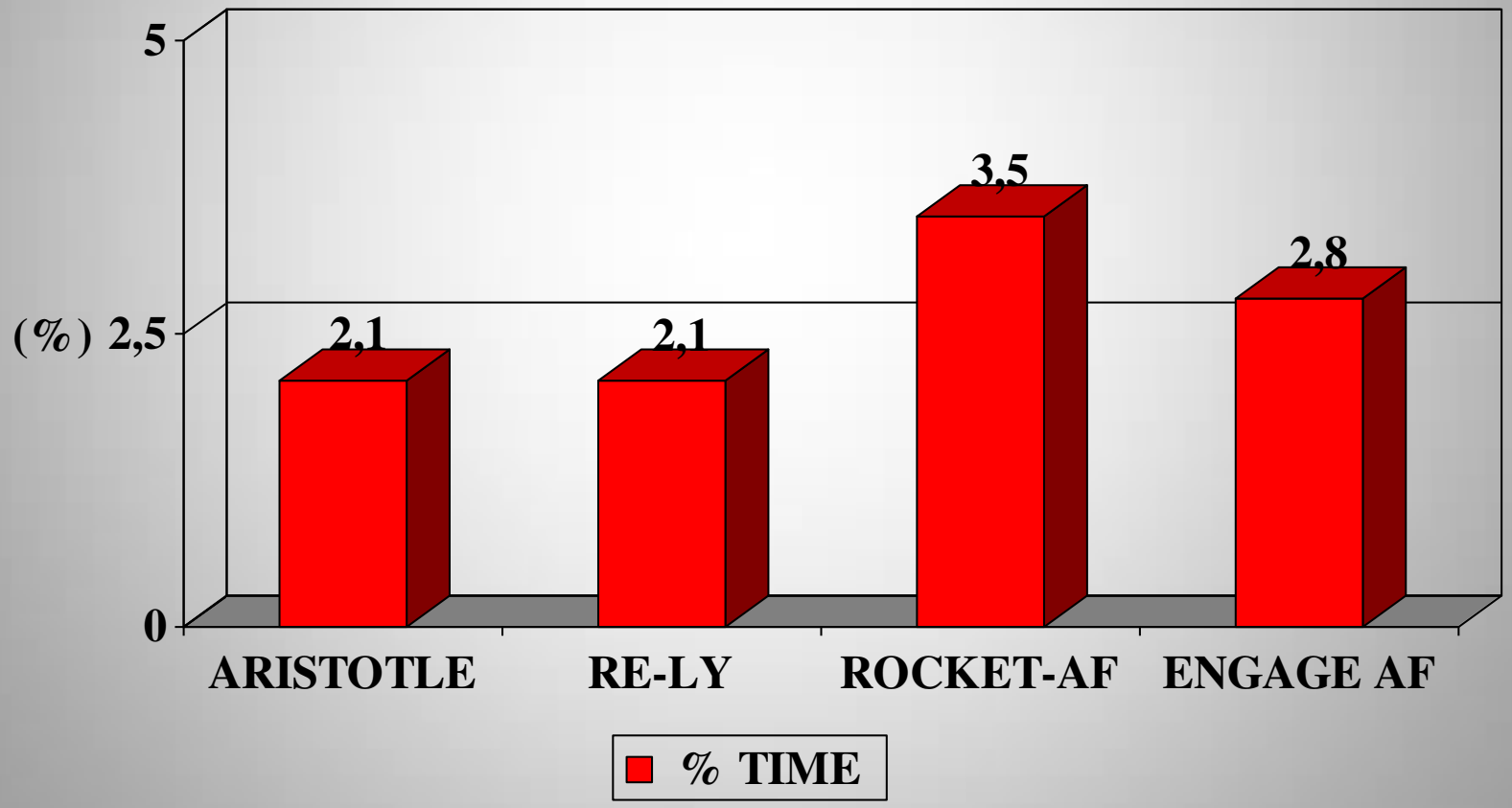
GESTIONE INTEGRATA DEL PAZIENTE A RISCHIO CARDIOVASCOLARE: ANTICOAGULAZIONE & DIABETE SFIDE ED OPPORTUNITÀ

Novel Anticoagulants

FIIa Inhibitor	Fxa Inhibitor		
Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Open Label	Double Blind	Double Blind	Double Blind
Two Doses	Two Doses	Two Doses	Two Doses
Twice Daily	Once Daily	Twice Daily	Once Daily
RE-LY	**ROCKET-AF**	**ARISTOTLE**	**ENGAGE AF**
N Engl J Med 2009; 361:1139-1151	N Engl J Med 2011; 365:883-891	N Engl J Med 2011; 365:981-92.	N Engl J Med 2013; 369:2093-2104

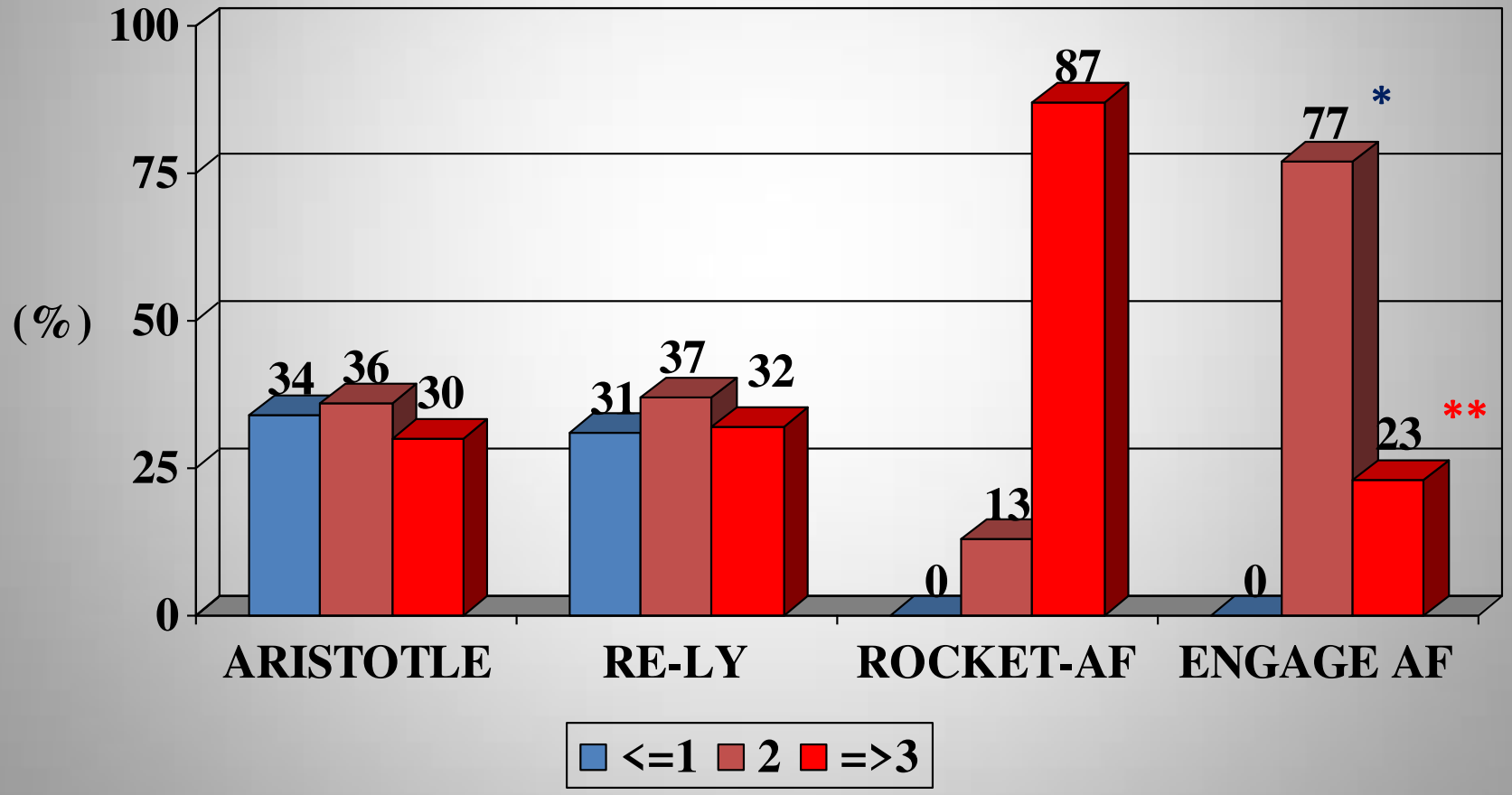
Patients characteristics in the four trials with NOACs

Mean CHADS2 score



Patients characteristics in the four trials with NOACs

CHADS2 score in the four trials

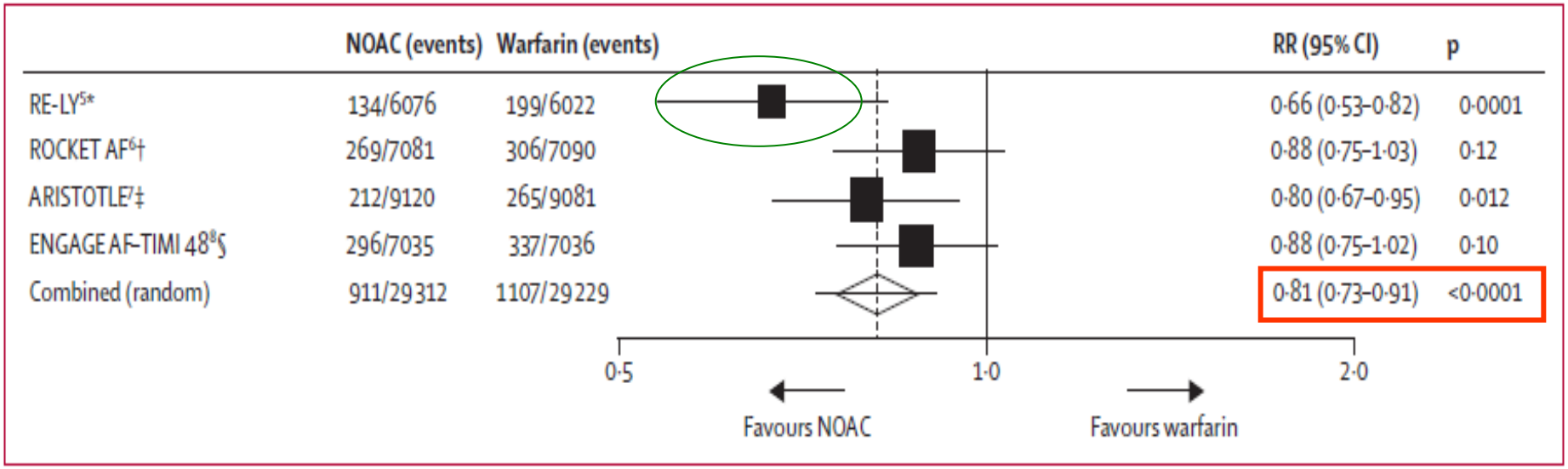


* CHADS2 score <=3; ** CHADS2 score >3

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

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

Effects on stroke or systemic emboli



www.thelancet.com Vol 383 March 15, 2014

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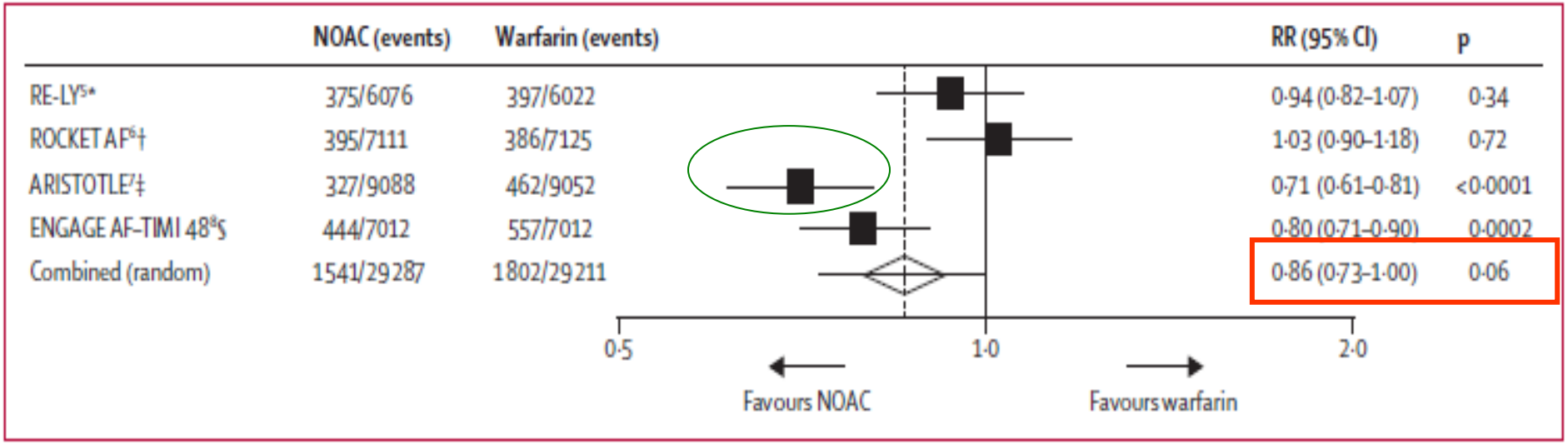
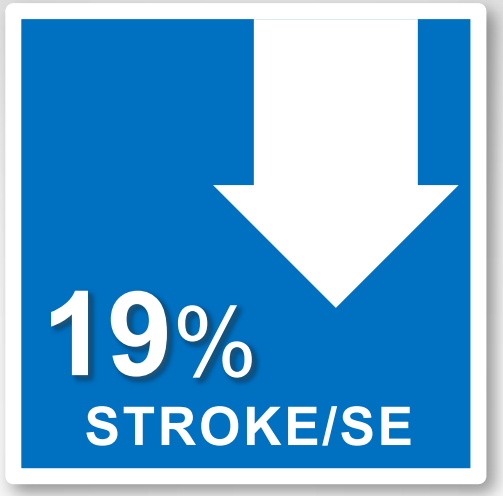
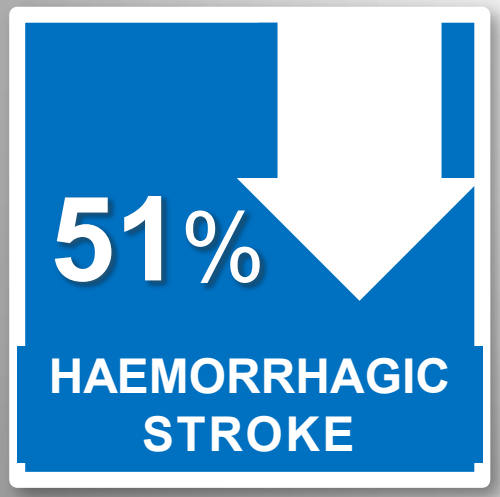
Major bleeding

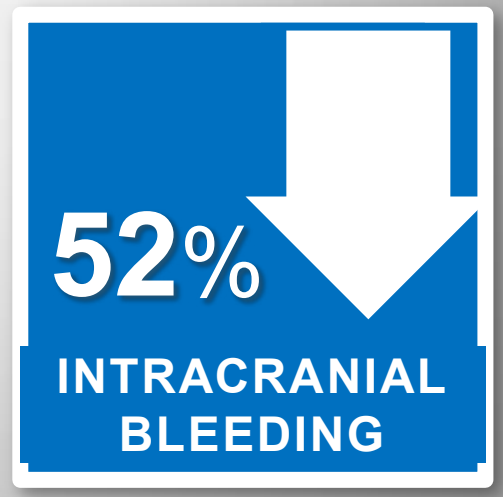


www.thelancet.com Vol 383 March 15, 2014

NOAC innovation means improved outcomes on key stroke endpoints vs VKA therapies







Meta-analysis of data from RE-LY®, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48

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

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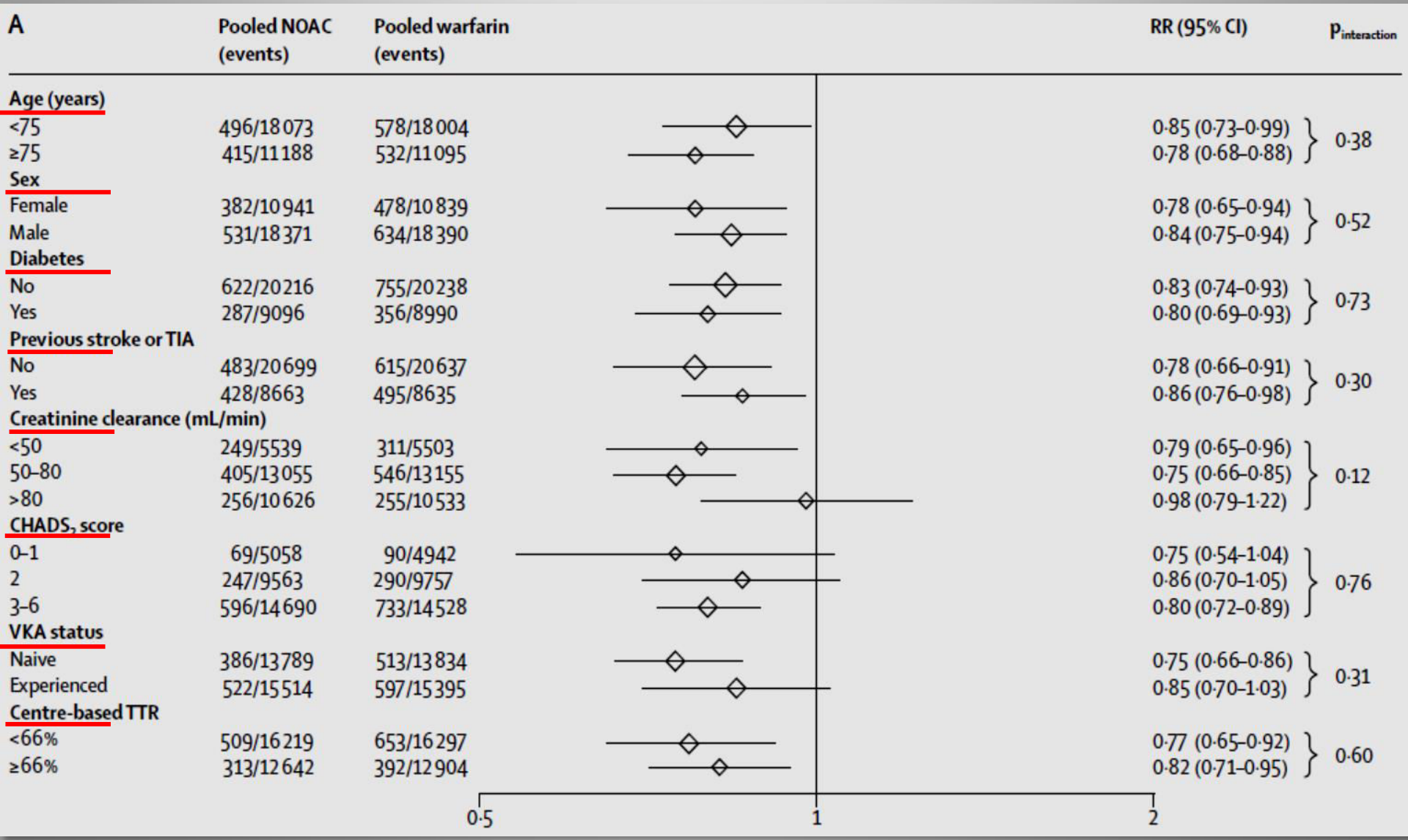
	Risk Ratio (95% CI)	*P*	*P* Heterogeneity
ICH	0.48 (0.39-0.59)	< .0001	.22
GI bleeding	1.25 (1.01-1.55)	.043	.009

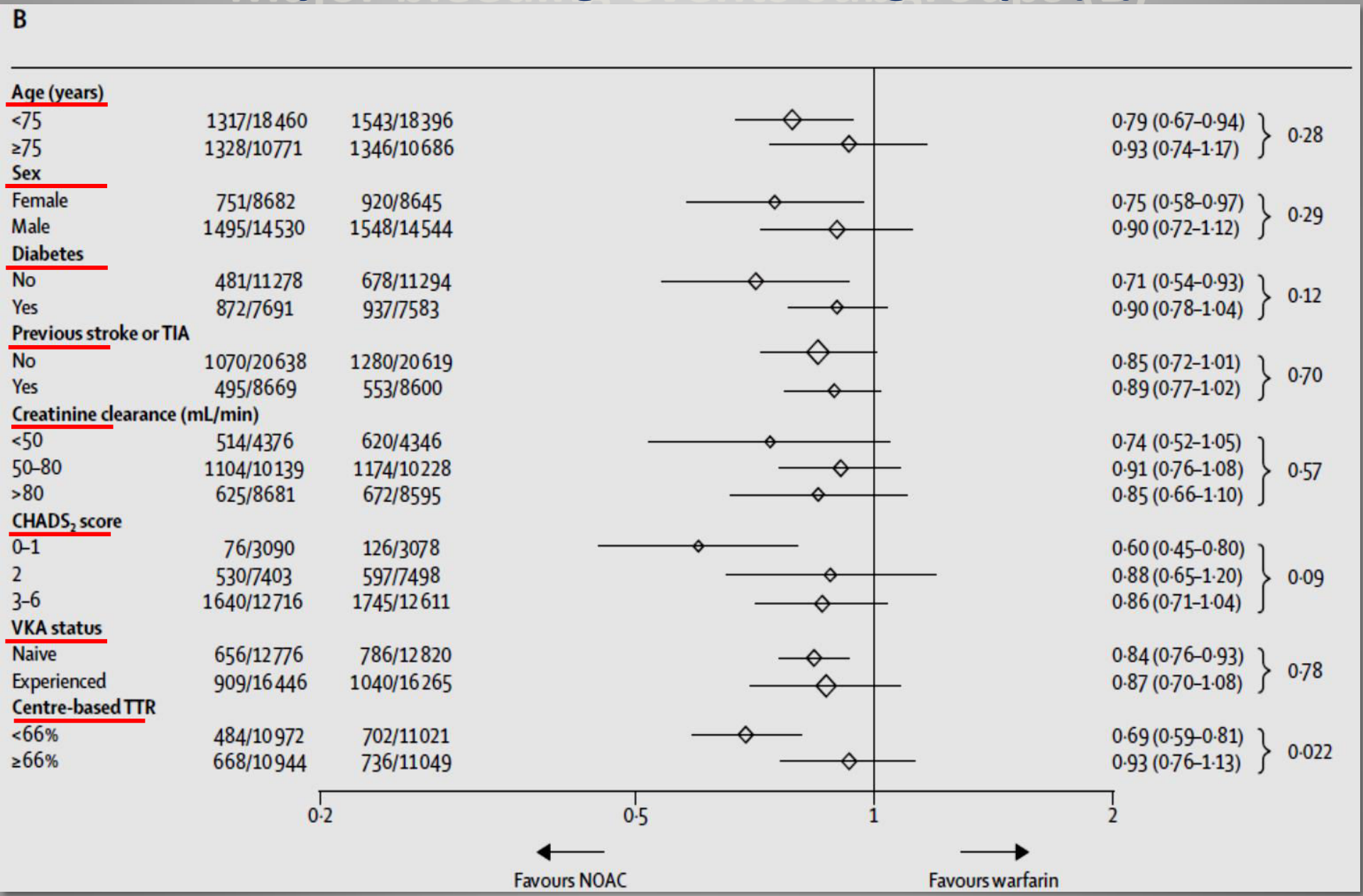
Ruff C, et al. *Lancet.* 2014;383:955-962.

Stroke or Sistemic embolic events (A)



Ruff *et al. Lancet* 2014;383:955-62

Major bleeding events subgroups (B)



Ruff *et al. Lancet* 2014;383:955-62

Effects of **Dabigatran** according to age in atrial fibrillation

Dabigatran: la sicurezza sia nel paziente giovane che nell'anziano

DABI 150 mg

ORIGINAL RESEARCH ARTICLE

Effects of dabigatran according to age in atrial fibrillation

Mandy N Lauw,[1] John W Eikelboom,[1] Michiel Coppens,[1] Lars Wallentin,[2] Salim Yusuf,[1] Michael Ezekowitz,[3,4] Jonas Oldgren,[2] Juliet Nakamya,[1] Jia Wang,[1] Stuart Connolly[1]

STROKE o EMBOLISMO SISTEMICO

<75 aa	75-79 aa	80-84 aa	>84 aa
-37%	-35%	-33%	-30%

EMORRAGIA INTRACRANICA

<75 aa	75-79 aa	80-84 aa	>84 aa
-57%	-77%	-45%	-39%

Heart Online First, published on February 17, 2017 as 10.1136/heartjnl-2016-310358

Effects of **Dabigatran** according to age in atrial fibrillation

Dabigatran: la sicurezza sia nel paziente giovane che nell'anziano

The Elderly Patients

DABI 110 mg

STROKE o EMBOLISMO SISTEMICO

<75 aa	80-84 aa	>84 aa
-7%	-25%	-48%

EMORRAGIA INTRACRANICA

<75 aa	75-79 aa	80-84 aa	>84 aa
-78%	-49%	-70%	-87%

Heart Online First, published on February 17, 2017 as 10.1136/heartjnl-2016-310358

Diabetes Mellitus

International Journal of Cardiology 196 (2015) 127–131

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/ijcard

Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: Results from the RE-LY trial☆

Michela Brambatti [a,b,*], Harald Darius [c], Jonas Oldgren [d], Andreas Clemens [e,f], Herbert H. Noack [e], Martina Brueckmann [e,g], Salim Yusuf [a], Lars Wallentin [d], Michael D. Ezekowitz [h], Stuart J. Connolly [a], Jeff S. Healey [a]

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[b] Clinica di Cardiologia, Universita' Politecnica delle Marche, Ancona, Italy
[c] Vivantes Klinikum Neukölln, Berlin, Germany
[d] Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden
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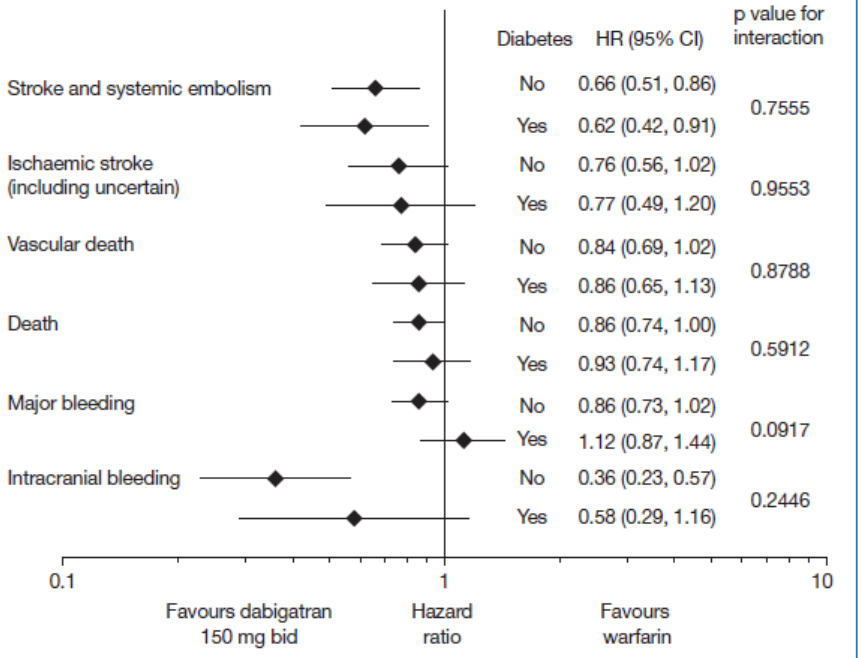
[f] Center for Thrombosis and Hemostasis, University Medical Center, Mainz, Germany
[g] Faculty of Medicine Mannheim of the University of Heidelberg, Germany
[h] Lankenau Institute for Medical Research, Wynnewood, PA

4221 Pazienti diabetici
Trattati

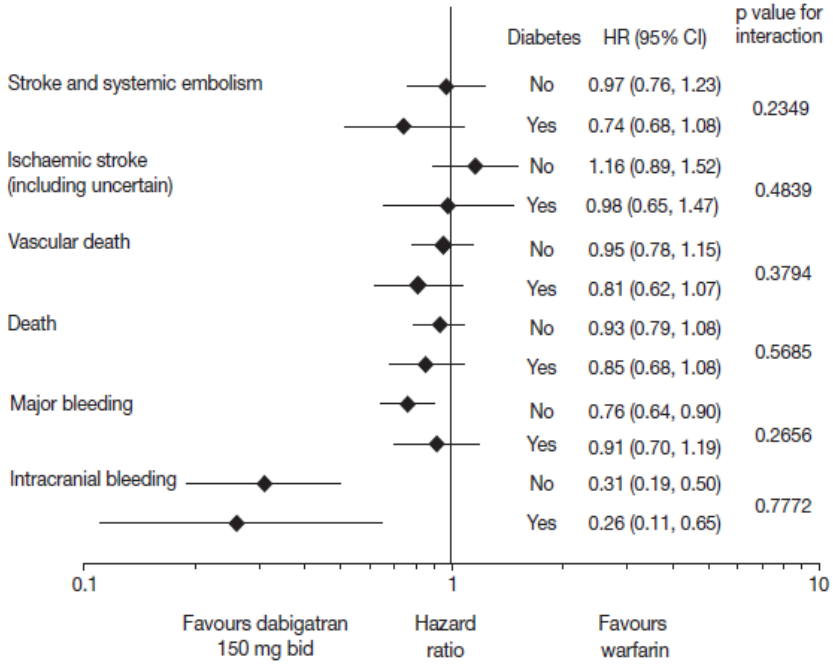
Dabigatran la sicurezza anche nel paziente diabetico

Figure 2: Hazard ratios (95% CI) for efficacy and safety outcomes for dabigatran 150 mg bid versus warfarin in patients with or without diabetes



CI, confidence interval; HR, hazard ratio.

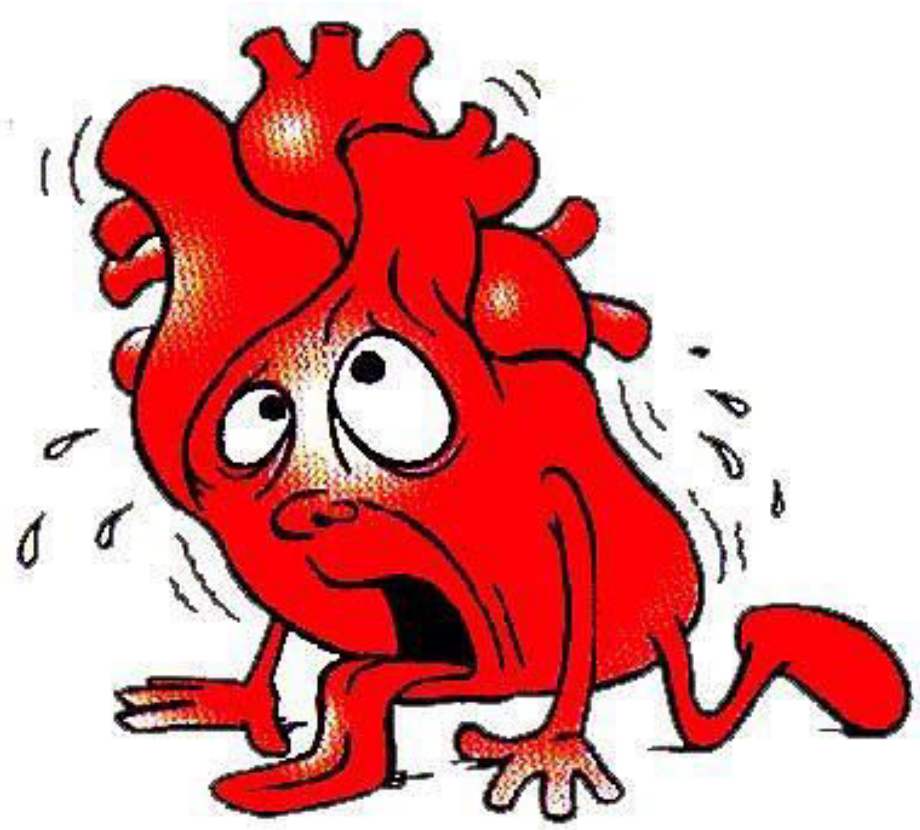
Figure 3: Hazard ratios (95% CI) for efficacy and safety outcomes for dabigatran 110 mg bid versus warfarin in patients with or without diabetes



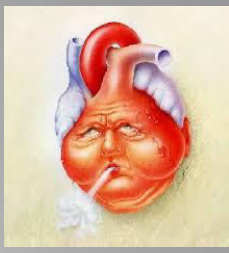
CI, confidence interval; HR, hazard ratio.

Int J Cardiol. 2015 Oct 1;196:127-31. doi: 10.1016/j.ijcard.2015.05.141. Epub 2015 May 28

Symptomatic heart failure subgroup analysis



Symptomatic heart failure subgroup analysis: rationale



- Heart failure and AF frequently co-exist
  - AF predicts poor prognosis in heart failure
  - Heart failure is a risk factor for stroke in patients with AF

- **In RE-LY®, 4904 patients had symptomatic heart failure at baseline**

- Subanalysis conducted to investigate:
  - Effects of dabigatran vs. warfarin on efficacy and safety outcomes in these patients
  - Impact of symptomatic heart failure on outcomes

Ferreira J et al. Circulation 2011;124: A10956

Symptomatic heart failure subgroup analysis: safety outcomes

Dabigatran la sicurezza anche nel paziente con insufficenza cardiaca

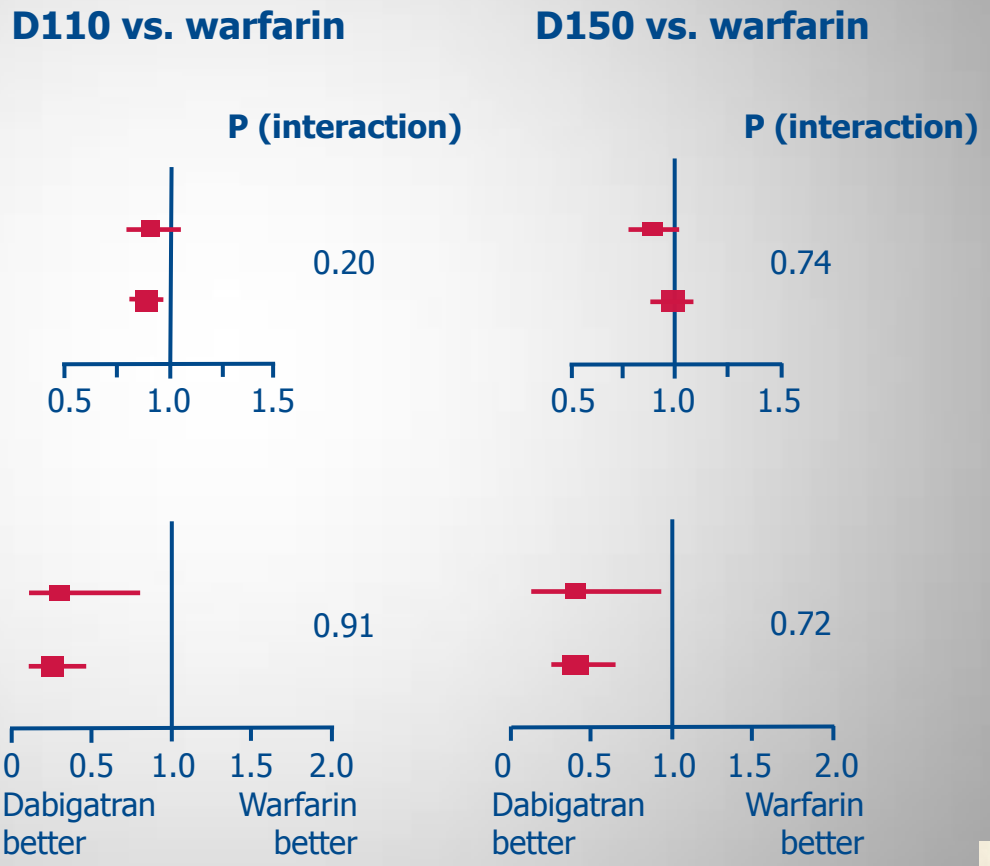
- **Benefits of dabigatran vs. warfarin not significantly affected by sHF status**

Major bleeding

	Rate (% per year)		
	D110	D150	W
With sHF	3.26	3.10	3.90
Without sHF	2.73	3.39	3.45

Intracranial bleeding

With sHF	0.22	0.26	0.65
Without sHF	0.23	0.34	0.80



E 110 = dabigatran 110 mg twice daily; DE 150 = dabigatran 150 mg twice daily;
sHF = symptomatic heart failure; W = warfarin

Ferreira J et al. Circulation 2011;124:A10956; data presented at AHA 2011

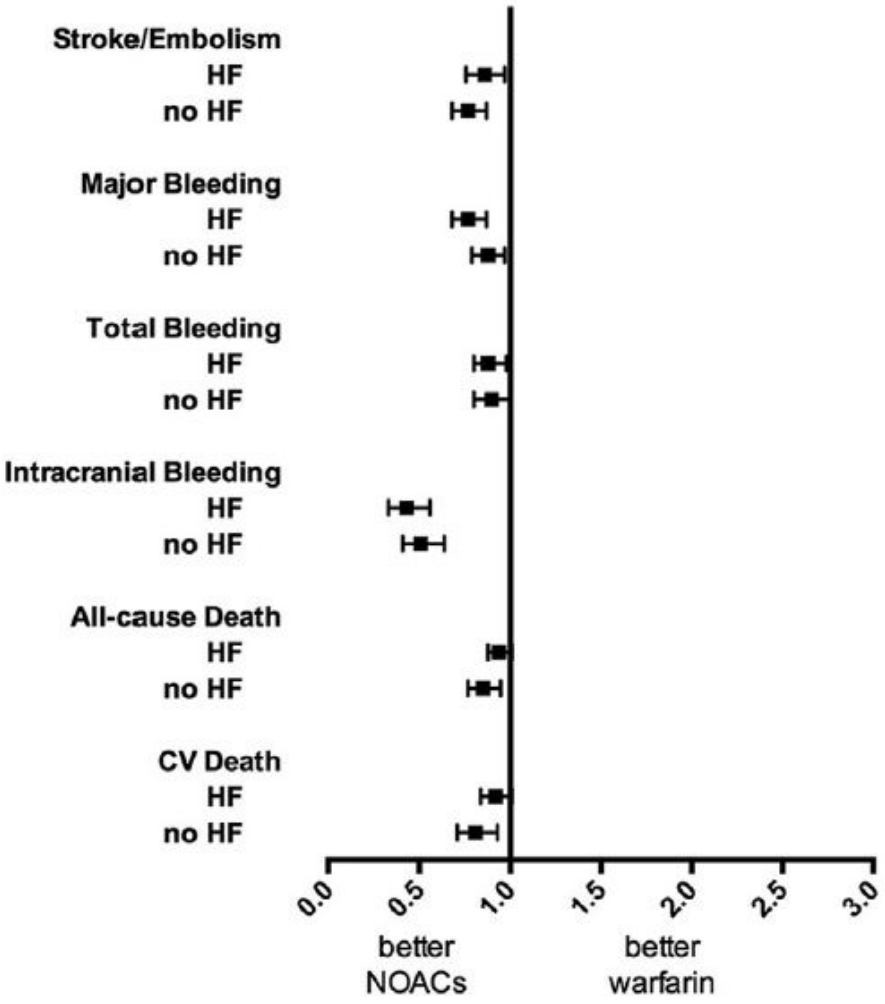
Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure

A Meta-Analysis

Gianluigi Savarese, MD,[a,b] Robert P. Giugliano, MD, SM,[c] Giuseppe M.C. Rosano, MD, PhD,[d] John McMurray, MD,[e] Giulia Magnani, MD,[c] Gerasimos Filippatos, MD, PhD,[f] Santo Dellegrottaglie, MD, PhD,[g,h] Lars H. Lund, MD, PhD,[b] Bruno Trimarco, MD, PhD,[a] Pasquale Perrone-Filardi, MD, PhD[a]

JACC Heart Fail 2016 Nov;4(11):870-880

Effects of NOAC in HF Versus No HF Subgroups



Outcome	ER NOACs	ER Warfarin	RR (95% CI)	p for interaction
Stroke/Embolism				
HF	1.60	1.87	0.86 (0.76, 0.97)	0.23
no HF	1.45	1.88	0.77 (0.68, 0.87)	
Major Bleeding				
HF	2.35	3.06	0.77 (0.68, 0.87)	0.09
no HF	2.83	3.22	0.88 (0.79, 0.97)	
Total Bleeding				
HF	11.11	12.50	0.88 (0.80, 0.98)	0.99
no HF	14.66	16.57	0.90 (0.80, 1.00)	
Intracranial Bleeding				
HF	0.27	0.63	0.43 (0.33, 0.56)	0.32
no HF	0.41	0.80	0.51 (0.41, 0.64)	
All-cause Death				
HF	5.05	5.37	0.94 (0.88, 1.01)	0.13
no HF	2.94	3.45	0.85 (0.77, 0.95)	
CV Death				
HF	3.47	3.77	0.92 (0.84, 1.01)	0.11
no HF	1.64	2.03	0.81 (0.71, 0.93)	

Savarese G. et al. JACC Heart Fail 2016 Nov;4(11):870-880

European Review for Medical and Pharmacological Sciences 2015; 19: 3961-3967

Efficacy and safety of dabigatran in a "real-life" population at high thromboembolic and hemorrhagic risk: data from MonaldiCare registry

V. RUSSO, V. BIANCHI[1], C. CAVALLARO[1], F. VECCHIONE[1], S. DE VIVO[1], L. SANTANGELO, B. SARUBBI, P. CALABRÒ, G. NIGRO, A. D'ONOFRIO[1]

Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples, Monaldi Hospital, Naples, Italy
[1]Department of Cardiology, Monaldi Hospital, AORN Ospedali dei Colli, Naples, Italy

Caratteristiche cliniche dei pazienti MonaldiCare rispetto ai pazienti MEDICARE e RE-LY

Characteristics, %	Medicare*		MonaldiCare		RE-LY®		
	Dabigatran* (n=67 207)	Warfarin (n=67 207)	Dab 150 (n=1075)	Dab 110 (n=1033)	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (6015)	Warfarin (n=6022)
Mean age	***59% > 75***	*59% > 75*	**64,9**	**74.0**	**71.5**	**71.4**	71.6
Male sex	**49**	48	**56,7**	**49.4**	**63.2**	**64.3**	63.3
$CHADS_2$ score ≥ 3	**31**	32			**33**		32
CHA_2DS_2VASC ≥ 3			**94,3**	**73.4**	**77,7**		
HAS-BLED ≥ 3			**59,7**	**87,4**			
Hypertension	**87**	87	**92.9**	**97.4**	**78.9**	**78.8**	78.9
Prior MI	**2**	2	**15.5**	**26.8**	**17**	**16.8**	16
Diabetes	**33**	34	**14.2**	**16.0**	**23.1**	**23.4**	23.4
Heart failure	**18**	18	**16.8**	**24.7**	**31.8**	**32.2**	31.9
Prior stroke	**3**	4	**30.9**	**19.6**	**20.3**	**19.9**	20.8
Prior TIA	**7**	7					
Prior VKA			**84.5**	**81.8**	**50.2**	**50.1**	51.4
Antiplatelets	**17**	17	**44.6**		**38.7**	**40.0**	40.6

*16% of Medicare patients received dabigatran 75 mg BID

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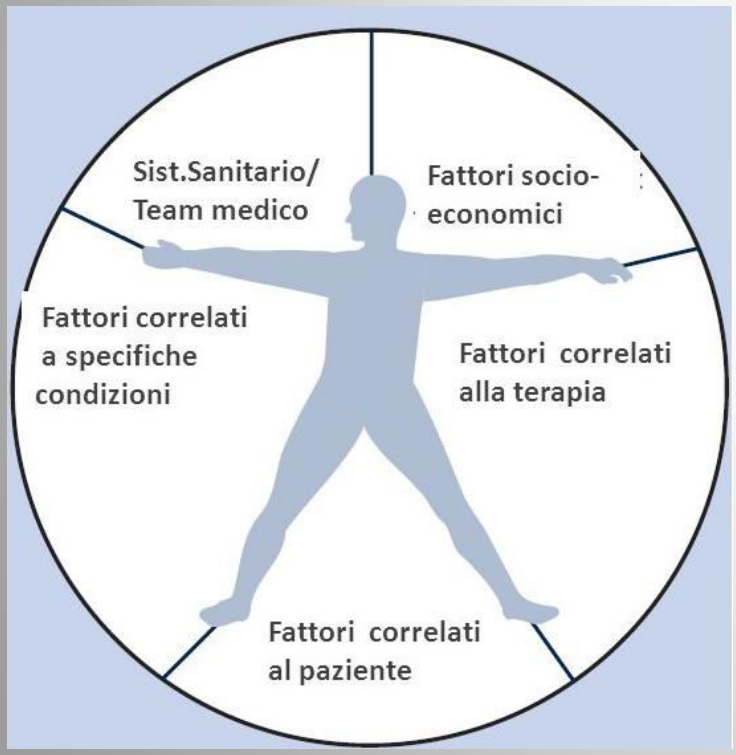
[1]Department of Cardiology, Monaldi Hospital, AORN Ospedali dei Colli, Naples, Italy

Outcome: *Aderenza e Compliance alla terapia*



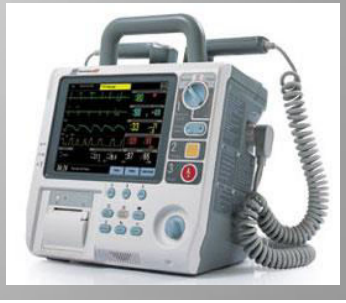
- *Solo il 6% dei pazienti ha occasionalmente dimenticato una assunzione del farmaco*
- *Tutti i pazienti in trattamento hanno affermato di preferire la nuova terapia perché non necessitava di controllo periodico dell'INR e non obbligava a restrizioni dietetiche.*

MonaldiCare: *120 Cardioversioni Elettriche*

	DAB 110		DAB 150	
	n	%	n	%
CVE performed	23	19	97	81
TEE	23	100	31	31,9

Tutti i pazienti hanno assunto DAB per almeno 3 settimane prima della CVE e 4 settimane dopo

Il 34% dei pazienti ha effettuato TEE: *NESSUN TROMBO RILEVATO*



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Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples, Monaldi Hospital, Naples, Italy
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MonaldiCare registry showed a **safety profile of both dosages** of dabigatran regarding major of fatal bleeding in a "real life" single center italian **population at high thromboembolic and hemorrhagic risk.**

Letter to the Editor

Transesophageal echocardiography in patients with persistent atrial fibrillation undergoing electrical cardioversion on new oral anticoagulants: A multi center registry ☆

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Clinical characteristics of study population (n = 219 patients).

Variable	Mean ± SD or %
Mean age (years)	67 ± 9.9
Sex (male/female)	156/63
Heart disease (%)	86
Hypertension (%)	83
Coronary artery disease (%)	26
Valvulopathy	13
Dilated cardiomyopathy	4
Diabetes (%)	17
Previous stroke (%)	4
Mean CHA_2DS_2-VASc score	2.37 ± 1.44

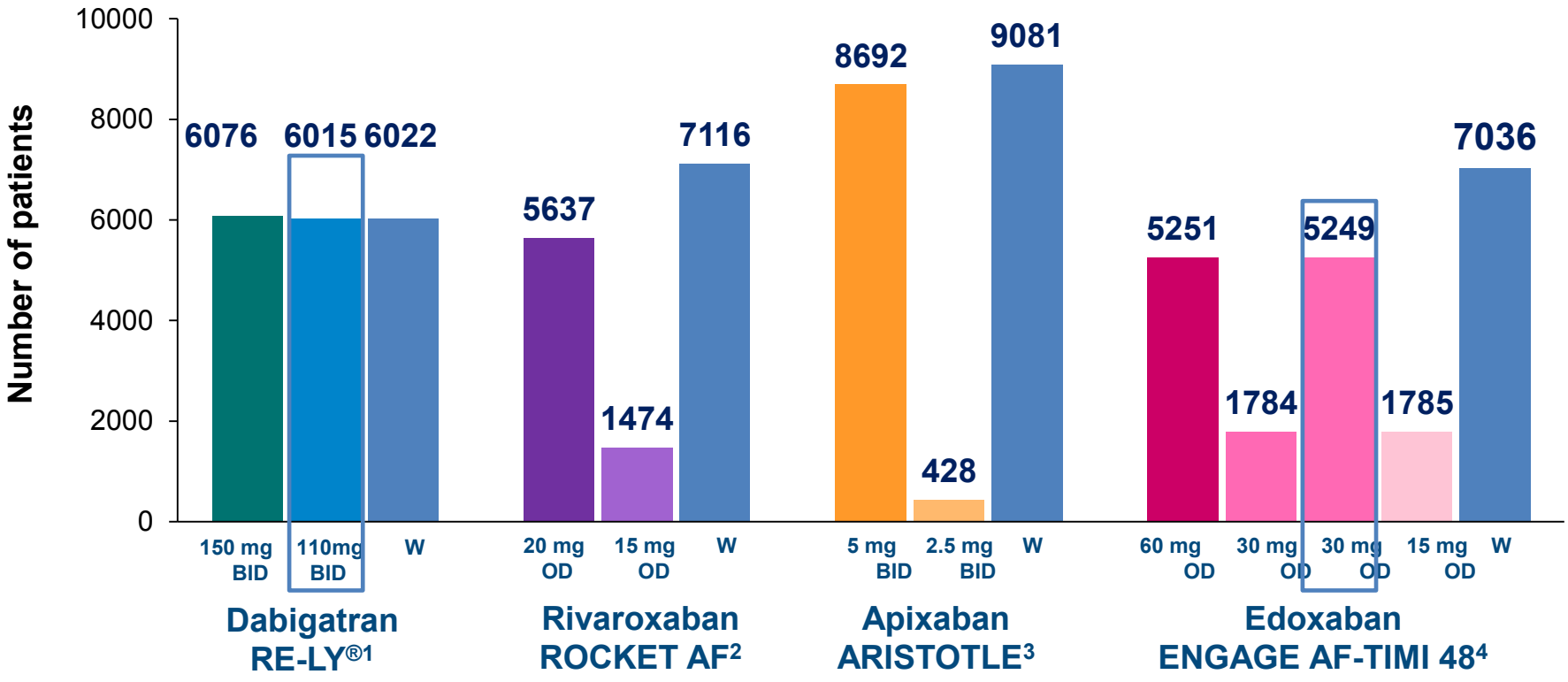
The incidence of atrial thrombus in patients assuming NOACs before electrical cardioversion is reasonably low *(1.3%)* and similar to the incidence observed with VKA treatment *(0.8-1.8%).*

86 pazienti dabigatran (39%)
73 pazienti apixaban (33%)
61 pazienti rivaroxaban (28%)

International Journal of CARDIOLOGY

DOACs e utilizzo appropriato dei bassi dosaggi

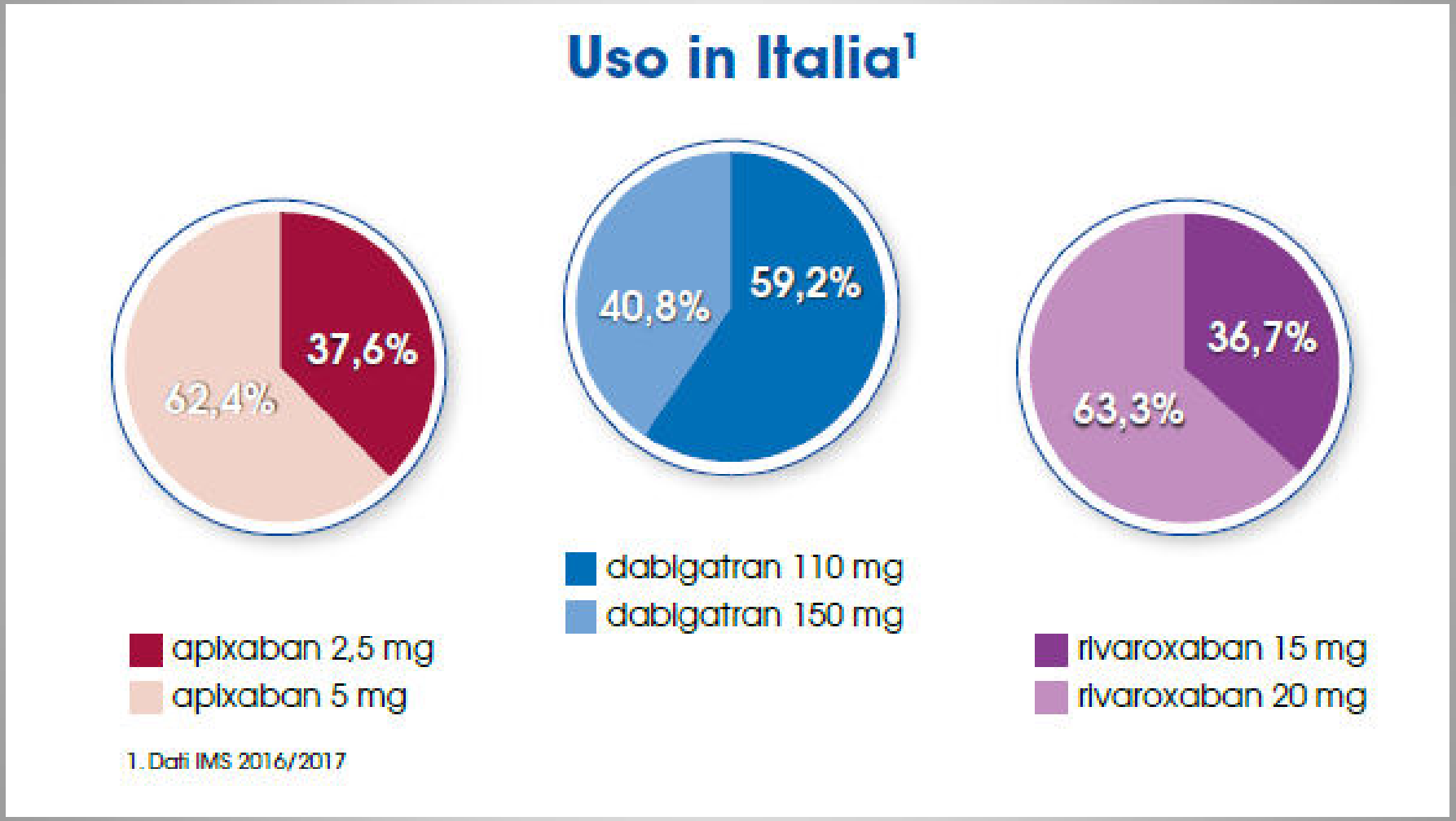
In RE-LY®, both dabigatran doses were compared with warfarin in an adequately powered number of patients



Dose adjustments for rivaroxaban and apixaban were tested in a limited prespecified population

1. Connolly et al. N Engl J Med 2009; 2. Fox et al. Eur Heart J 2011; 3. Granger et al. N Engl J Med 2011; 4. Giugliano et al. N Engl J Med 2013

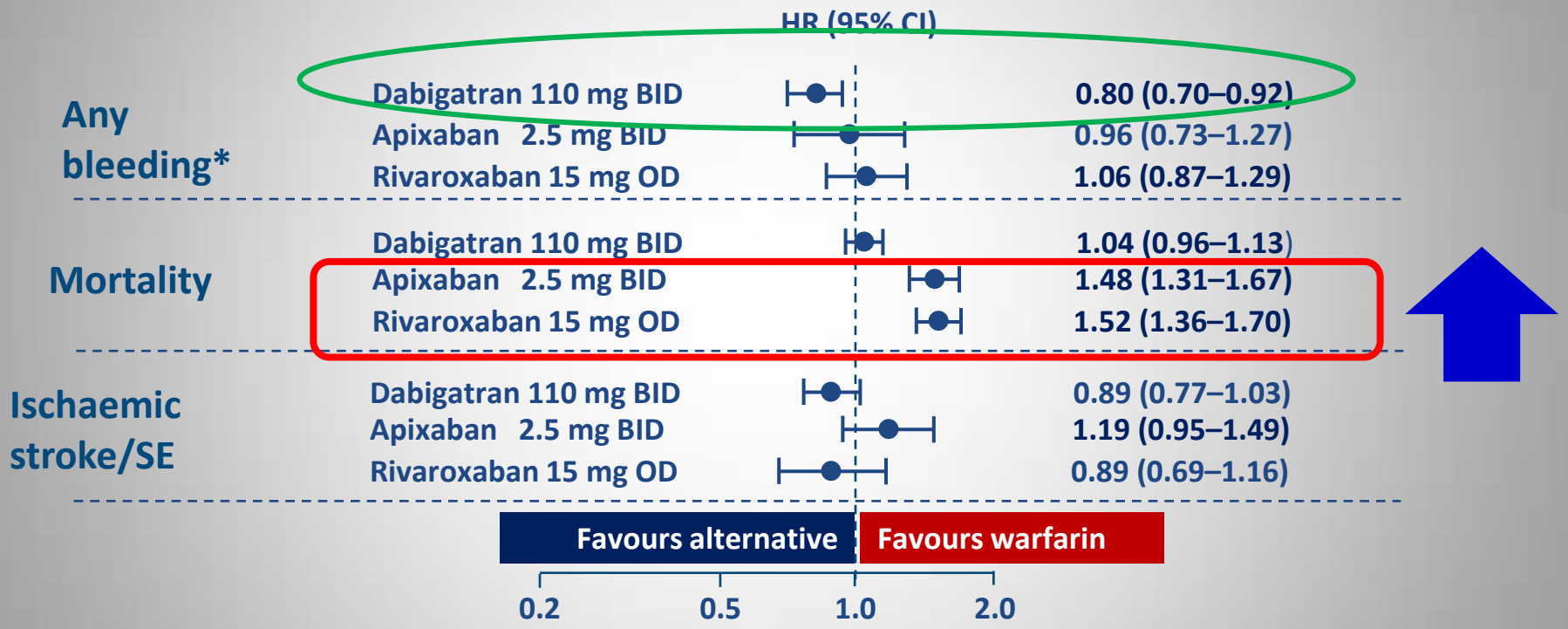
Utilizzo nella pratica clinica italiana dei dosaggi ridotti dei DOACs



Effectiveness and Safety of Reduced Dose NOAC and Warfarin in AF

Independent

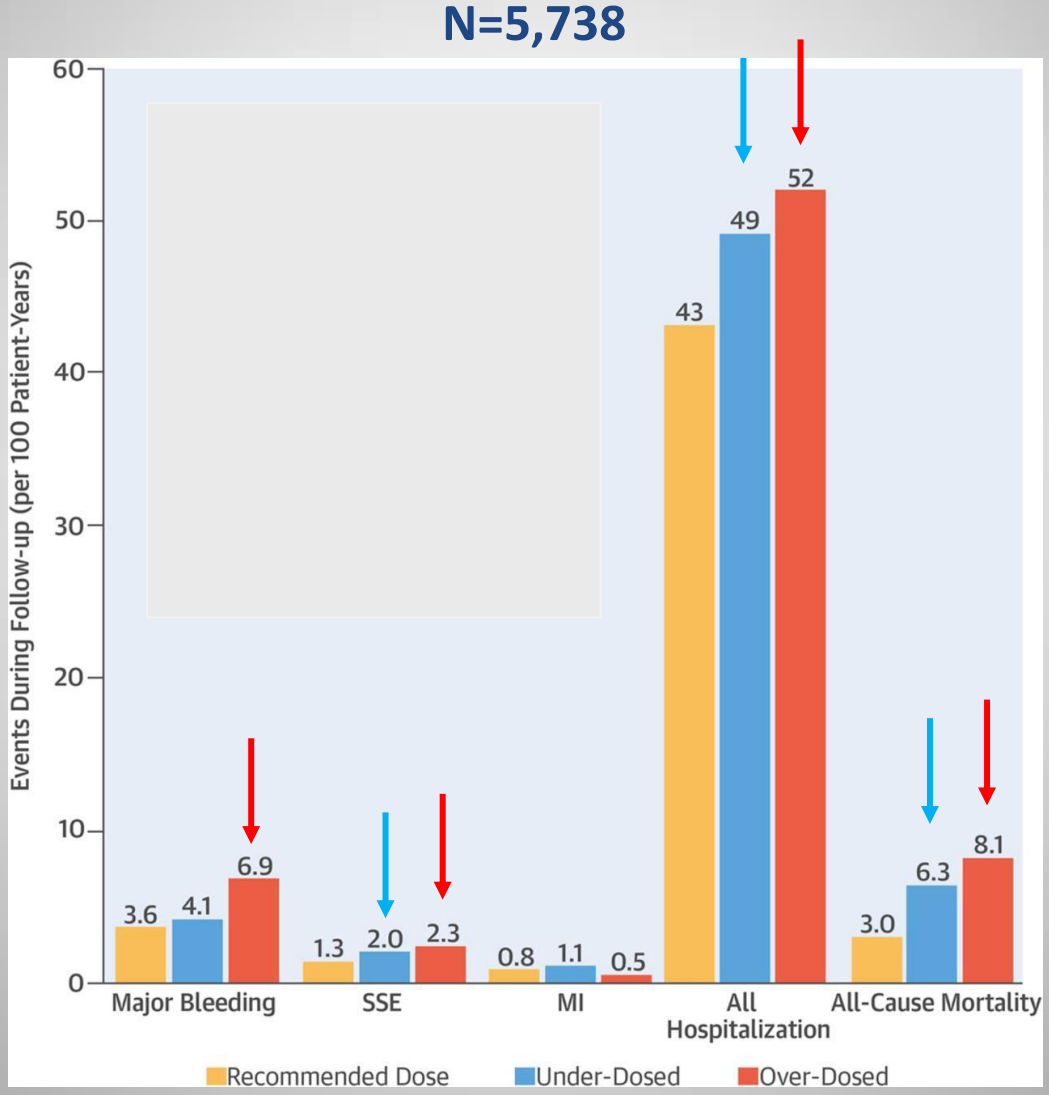
Safety and Effectiveness at one-year follow-up
Reduced NOAC doses



- *Haemorrhagic stroke, major gastrointestinal bleeding; SE, systemic embolism; Propensity-weighted cohort study of three nationwide Danish registries of OAC-naïve patients with AF, safety outcomes at one year follow-up; dabigatran 110 mg BID, n=8875; apixaban 2.5 mg BID, n=4400; rivaroxaban 15 mg OD, n=3476; warfarin, n=38 893

Nielsen PB, et al . BMJ 2017;356:j510

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Outcome



The ORBIT-AF II Registry - J Am Coll Cardiol, December 2016

What is the rationale for a specific reversal agent?

Reversal agents for NOACs may encourage appropriate stroke prevention in patients with AF

Cardiac Safety Research Consortium

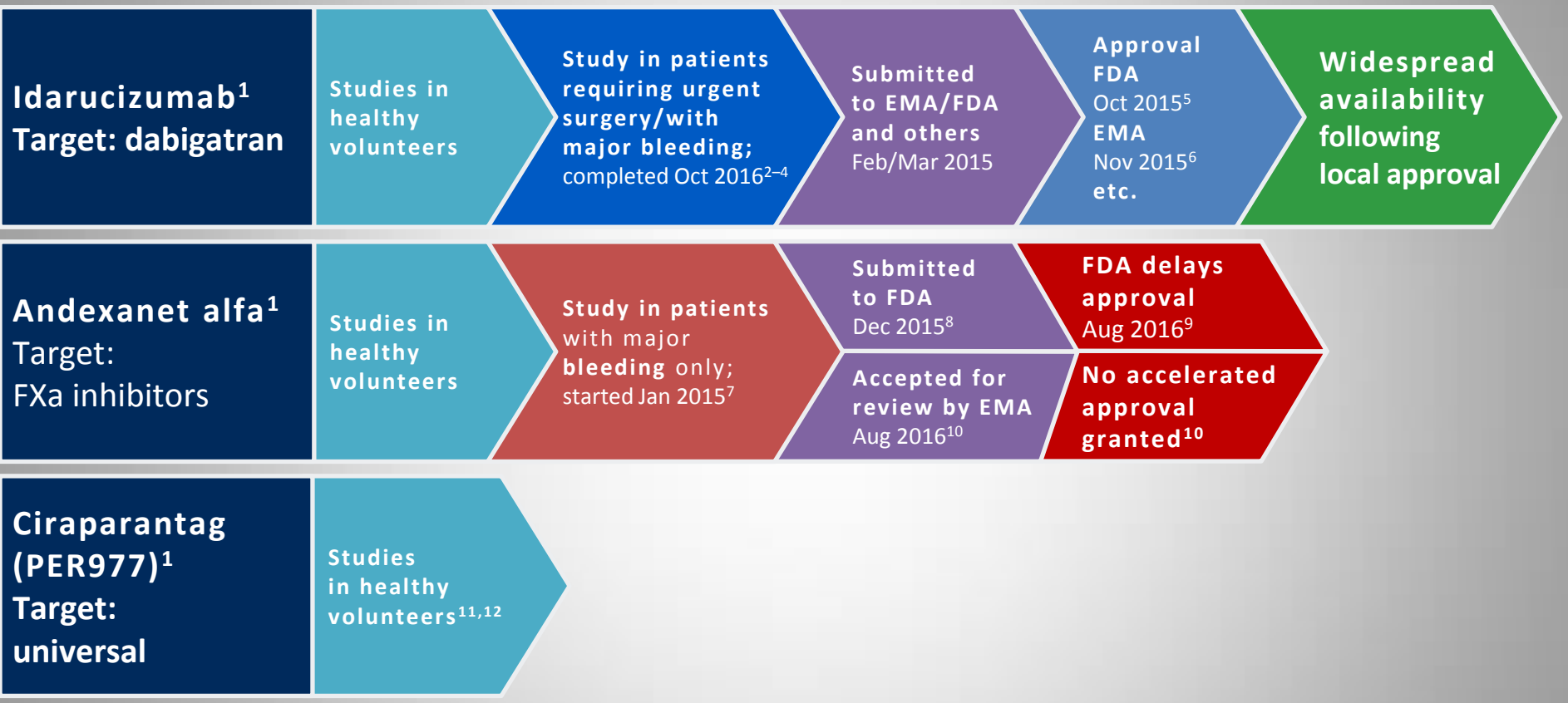
U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

'The availability of specific reversal agents for the NOACs would improve the confidence of clinicians and patients in these new agents and encourage an increase in appropriate stroke preventive therapy for patients with NVAF'[1]

In addition, reversal agents would be beneficial in rare emergency situations to manage patients who require urgent surgery or interventions and to treat those with life-threatening bleeds[1]

1. Sarich TC et al. Am Heart J 2015 (Anticoagulant-Induced Bleeding and Reversal Agents Think Tank co-sponsored by the Cardiac Safety Research Consortium and the FDA on 22 April 2014)

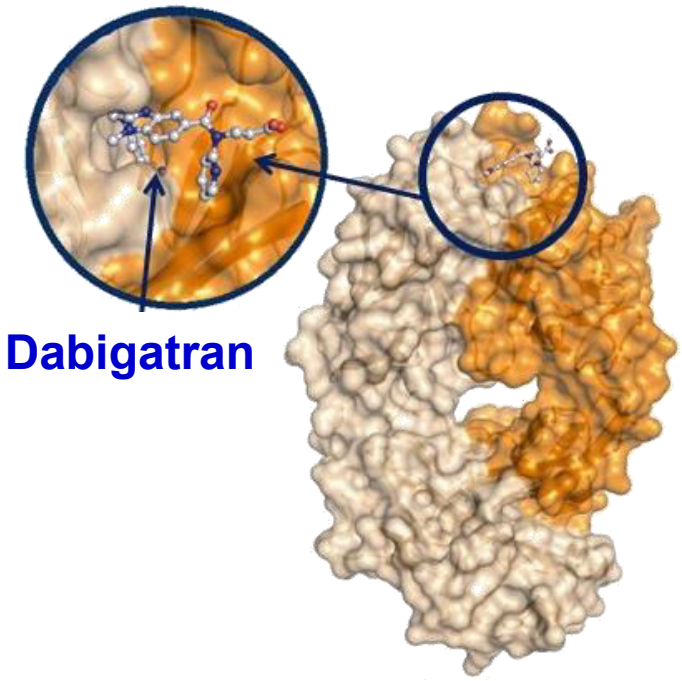
Idarucizumab is the only approved and widely available NOAC reversal agent



1. Greinacher A et al. Thromb Haemost 2015; 2. Pollack C et al. N Engl J Med 2017; 3. Pollack C et al. Thromb Haemost 2015; 4. Boehringer Ingelheim, data on file; 5. US FDA 2015 press release, 16 October 2015; 6. European Commission Community Register of Medicinal Products for Human Use 2015; 7. ClinicalTrials.gov Identifier: NCT02329327; 8. Portola Pharmaceuticals press release, 18 Dec 2015; 9. Portola Pharmaceuticals press release, 17 August 2016; 10. Portola Pharmaceuticals press release, 19 August 2016; 11. Ansell JE et al. N Engl J Med 2014; 12. Ansell JE et al. Thromb Res 2016

Idarucizumab was designed as a specific reversal agent for the anticoagulant activity of dabigatran

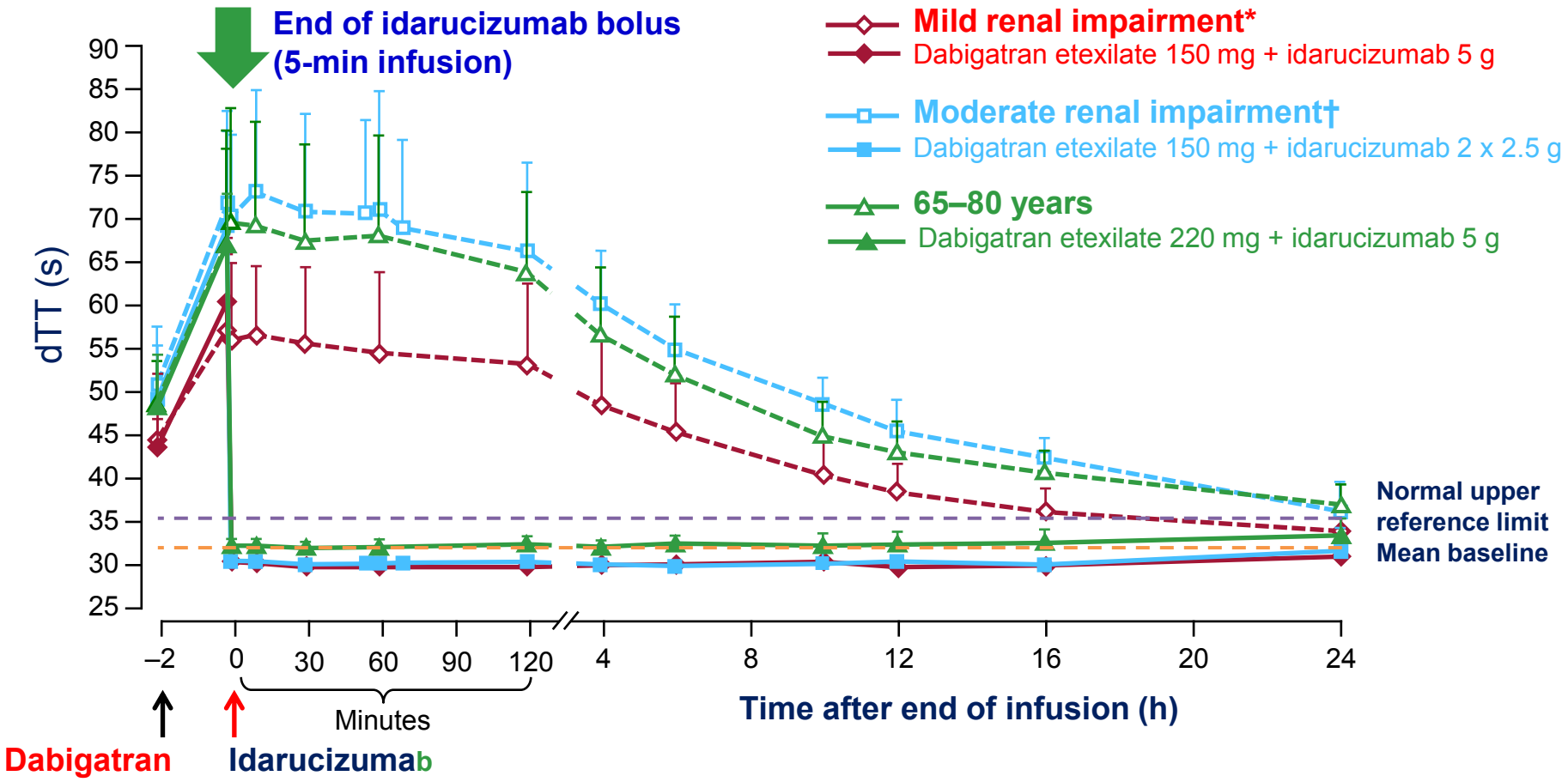
- Humanized antibody fragment (Fab)
- Specific to dabigatran
- Binding affinity for dabigatran ~350× higher than dabigatran to thrombin, resulting in essentially irreversible binding
- No endogenous targets



- Ready to use solutions for IV administration
- Immediate onset of action
- No intrinsic procoagulant or anticoagulant activity
- Idarucizumab–dabigatran complex is eliminated quickly (within a few hours)

Adapted from Schiele F et al. Blood 2013; Eikelboom J et al. Circulation 2015; Praxbind® EU SPC, 2015; Schmohl M et al. Thromb Haemost 2016

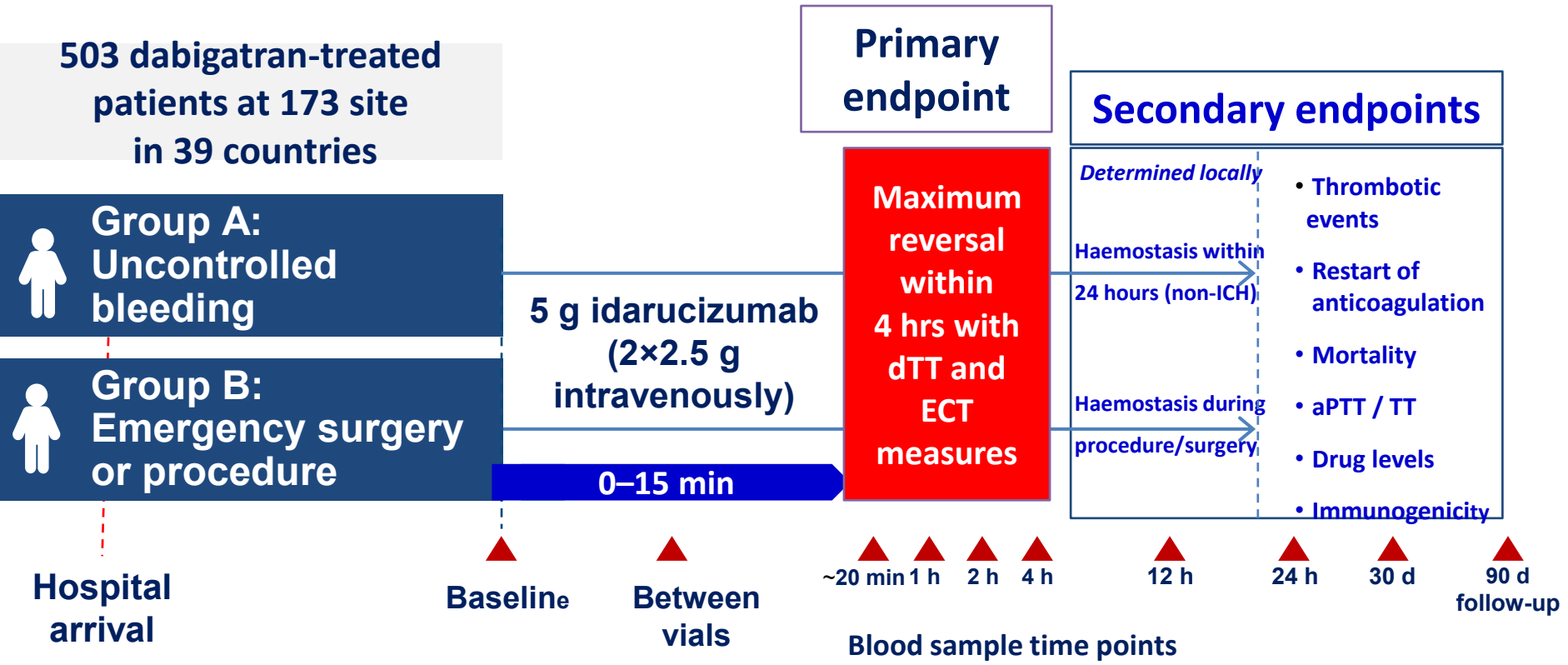
Idarucizumab shows **immediate, complete, and sustained** reversal in healthy elderly subjects and those with mild or moderate renal impairment



- *CrCl ≥60–<90 mL/min; †CrCl ≥30–<60 mL/min; dTT, diluted thrombin time
- Glund S et al. Clin Pharmacokinet 2016

RE-VERSE AD

a multicentre, open-label, single-arm Phase III trial



- aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; TT, thrombin time;
- Pollack C et al. N Eng J Med 2017; Pollack C et al. Thromb Haemost 2015

RE-VERSE AD: on average, enrolled patients were elderly with moderate renal impairment

Characteristic	Group A (n=301)	Group B (n=202)	Total (N=503)
Age (yrs)*	79 (24–96)	77 (21–96)	78 (21–96)
Male sex, n (%)	172 (57.1)	102 (50.5)	274 (54.5)
Creatinine clearance (mL/min)*	50.8 (6.1–216.9)	56.0 (7.9–198.7)	52.6 (6.1–216.9)
Comorbidities, n (%)			
Congestive heart failure	117 (38.9)	65 (32.2)	182 (36.2)
Diabetes	95 (31.6)	57 (28.2)	152 (30.2)
Coronary artery disease	110 (36.5)	68 (33.7)	178 (35.4)
Prior stroke / TIA	73 (24.3) / 27 (9.0)	36 (17.8) / 20 (9.9)	109 (21.7) / 47 (9.3)
Dabigatran, n (%)			
Atrial fibrillation indication	288 (95.7)	190 (94.1)	478 (95.0)
Daily dose 150 mg BID	94 (31.2)	57 (28.2)	151 (30.0)
110 mg BID	185 (61.5)	126 (62.4)	311 (61.8)
75 mg BID	16 (5.3)	8 (4.0)	24 (4.8)
Patient-reported time since last dose (hrs)*	14.6 (1.5, 90.4)	18.0 (2.6, 105.8)	15.6 (1.5, 105.8)
Elevated dTT at baseline, n (%)	244 (81.1)	152 (75.2)	396 (78.7)
Elevated dTT or ECT at baseline, n (%)	276 (91.7)	185 (91.6)	461 (91.7)

- *Shown as median (range); TIA, transient ischaemic attack

Pollack C et al. N Engl J Med 2017

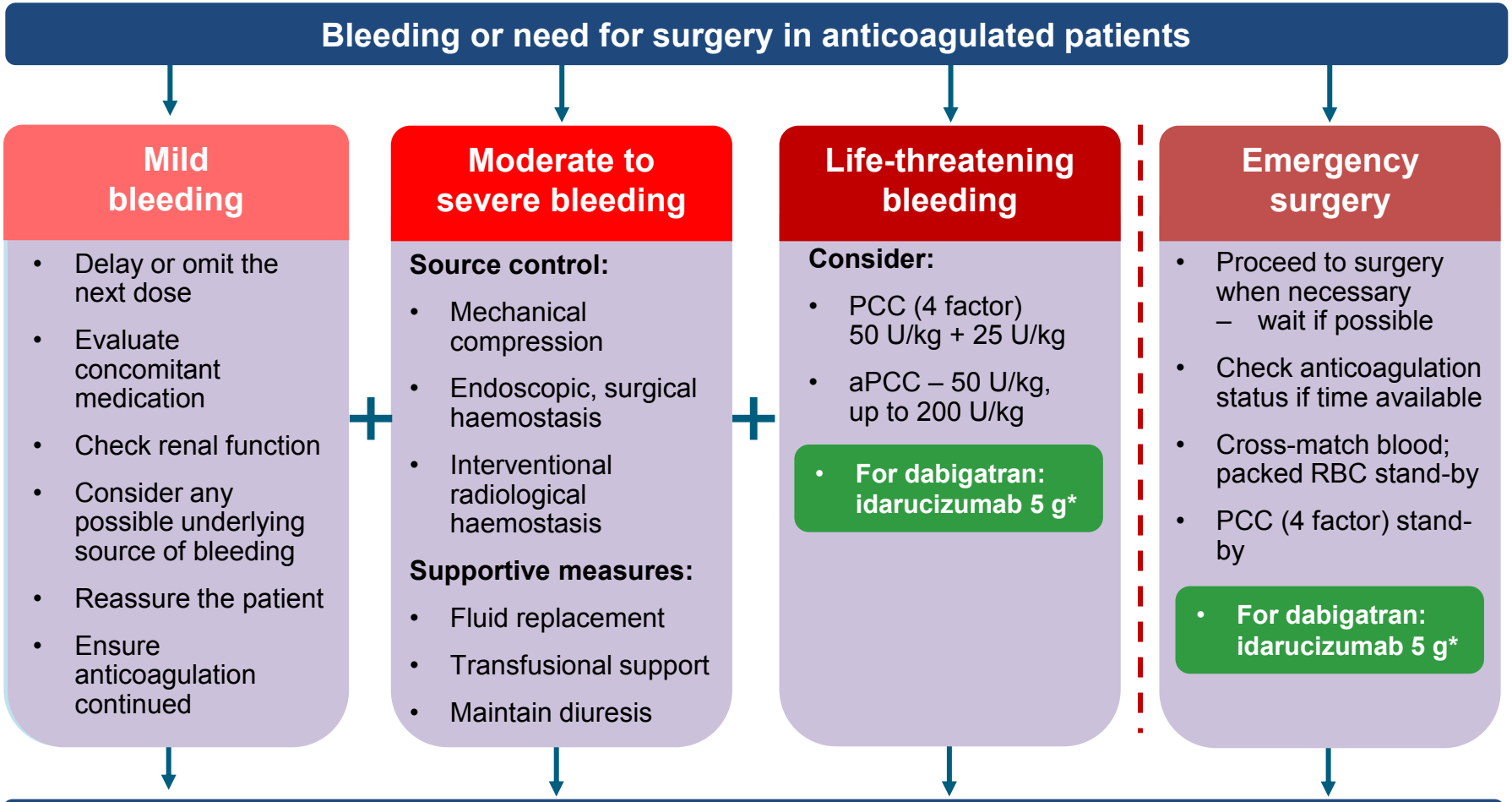
RE-VERSE AD: key results in a cohort of multi-morbid elderly patients presenting with life-threatening emergencies

1. 5 g of idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran anticoagulation
2. Median time to cessation of assessable extracranial bleeding in Group A was 2.5 hours after reversal
3. Median time to surgery after reversal was 1.6 hours, with 'normal' intraoperative haemostasis in 93% of Group B patients
4. No safety concerns identified to date

Pollack C et al. N Engl J Med 2017

How can idarucizumab improve the management of emergency situations?

Idarucizumab is recommended to reverse dabigatran anticoagulation in patients requiring emergency surgery or with life-threatening bleeding



- Idarucizumab is the preferred treatment to reverse dabigatran; PCC, prothrombin complex concentrate; RBC, red blood cell; Anticoagulation Education Task Force White Paper: Ageno W et al. Thromb Haemost 2016

Conclusions

1. Dabigatran has a favourable safety profile shown in clinical trials and confirmed in real-world studies
2. Dabigatran is the only NOAC with a specific reversal agent
3. Idarucizumab provides immediate, complete, and sustained reversal of dabigatran's anticoagulant effect; there are no contraindications
4. Idarucizumab provides an additional option in the emergency management of dabigatran-treated patients taking the NOAC effect out of the equation

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GESTIONE INTEGRATA DEL PAZIENTE
A RISCHIO CARDIOVASCOLARE:
ANTICOAGULAZIONE & DIABETE
SFIDE ED OPPORTUNITÀ

Sicurezza nella scelta di strategie terapeutiche in pazienti con FANV e gestione delle emergenze/urgenze

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