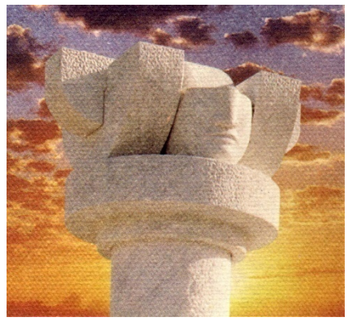
I NAO in emergenza-urgenza

Francesco Cipollone



Clinica Geriatrica
Centro di Eccellenza Europeo
e di Riferimento Regionale per
l'Aterosclerosi, l'Ipertensione Arteriosa
e le Dislipidemie

Università "G. d'Annunzio" Chieti

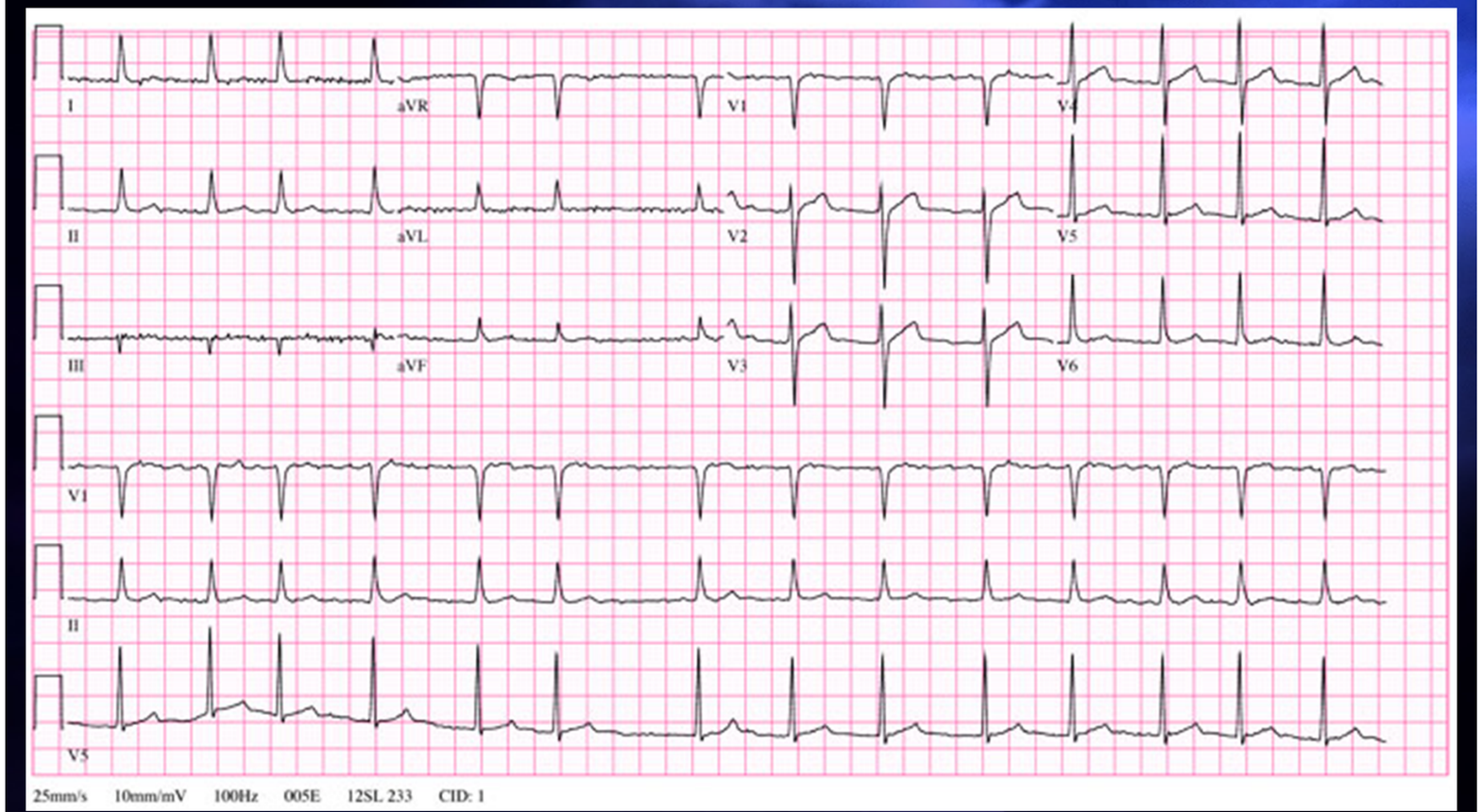
NAO: indications

- FA
- DVT/PE

NAO: indications

- **FA**
- **DVT/PE**

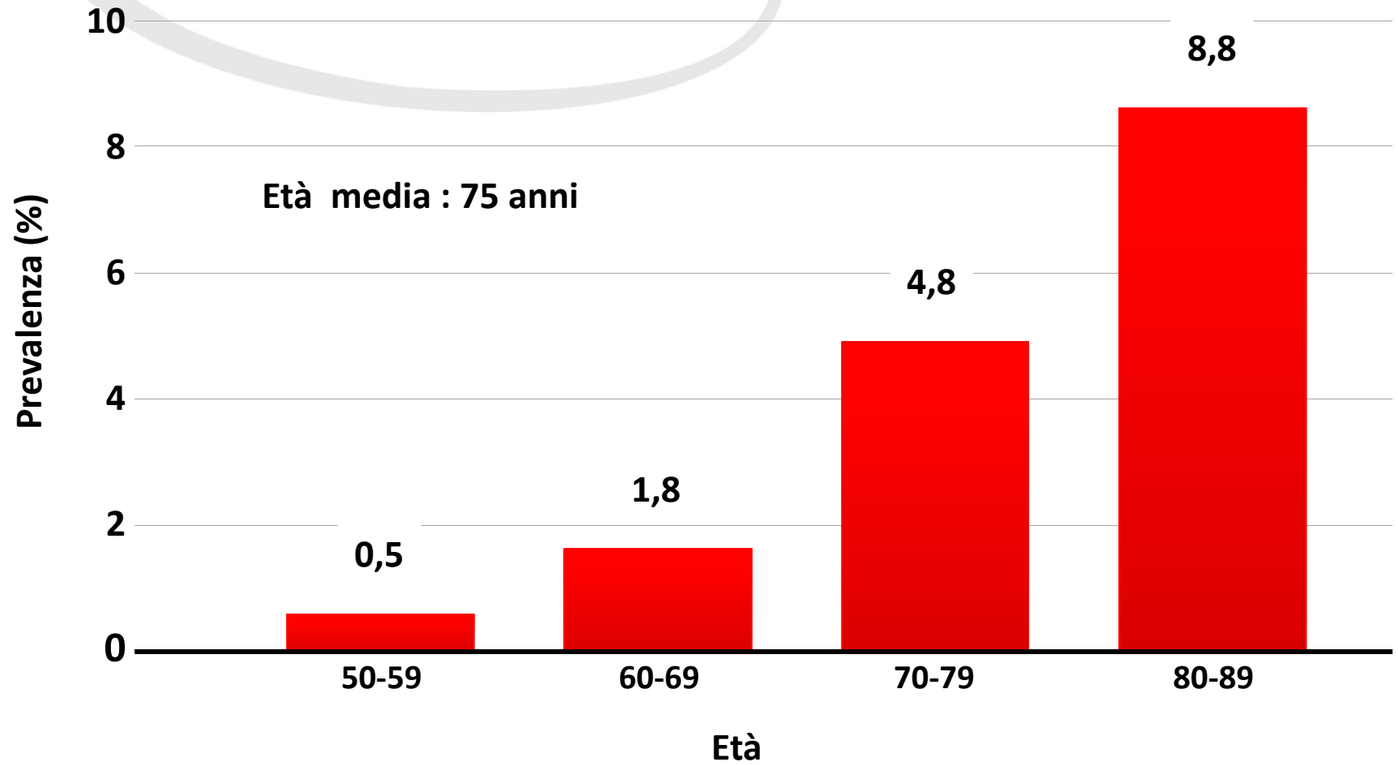
Atrial Fibrillation



Key message

- **FA: aritmia estremamente frequente (in Italia da 600.000 a 1.200.000 persone affette + 120.000 nuovi casi ogni anno)**

Prevalenza di Fibrillazione Atriale nella popolazione generale in base all'età



Wolf PA et al. Stroke 1991; 22: 983-988

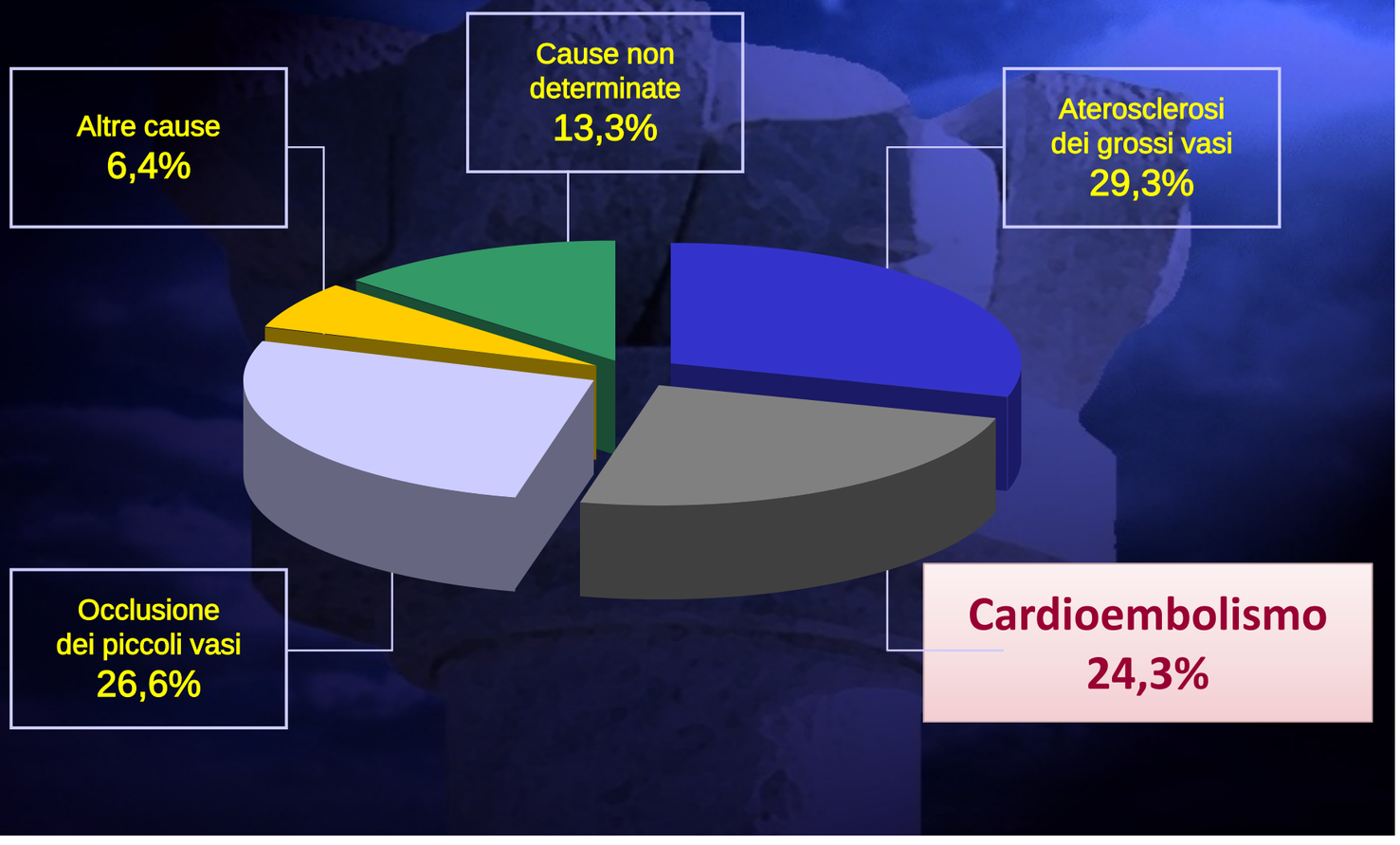
Fibrillazione Atriale: eventi tromboembolici

Incidenza annuale in pazienti con FA

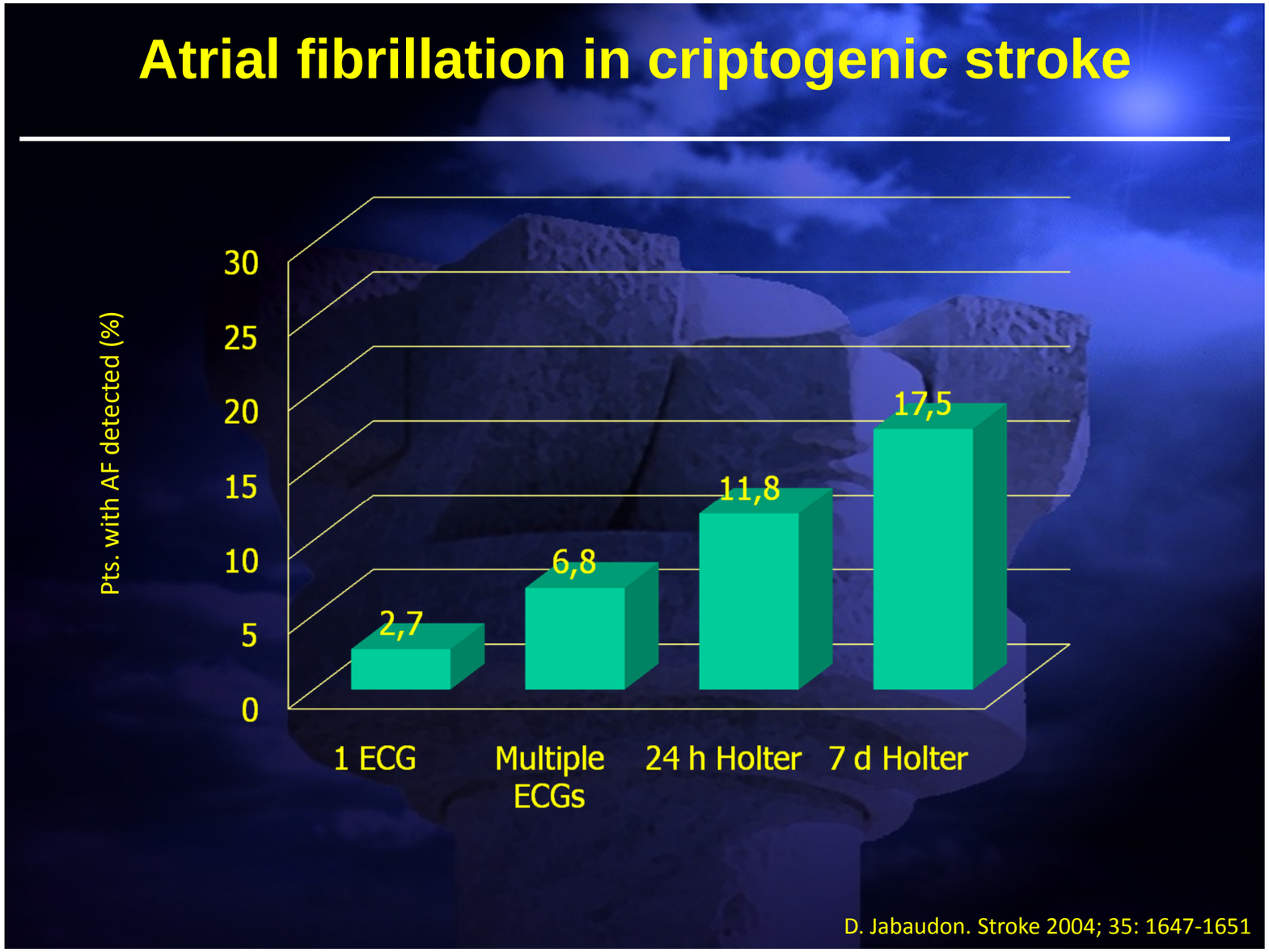
FA	→	**4,5%**
Controlli	→	**0,2% - 1,4%**

The SPAF Investigators. AIM 1992; 116: 1 – 5

L’ictus è una complicanza frequente della FA: I dati italiani



Atrial fibrillation in criptogenic stroke

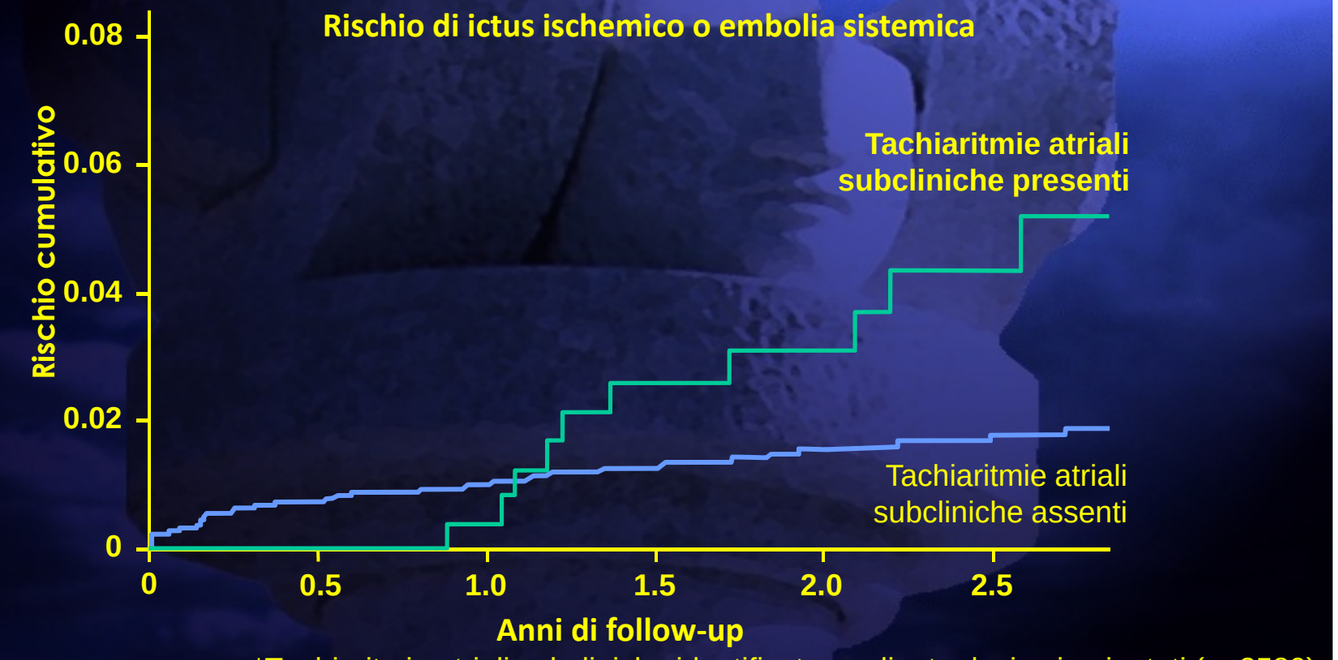


D. Jabaudon. Stroke 2004; 35: 1647-1651

Il rischio di Ictus in pazienti con FA subclinica

L'FA subclinica è associata a un rischio 2,5 volte maggiore di ictus ischemico o embolia sistemica

- 4,2% vs 1,7% senza aritmia (P=0,007)

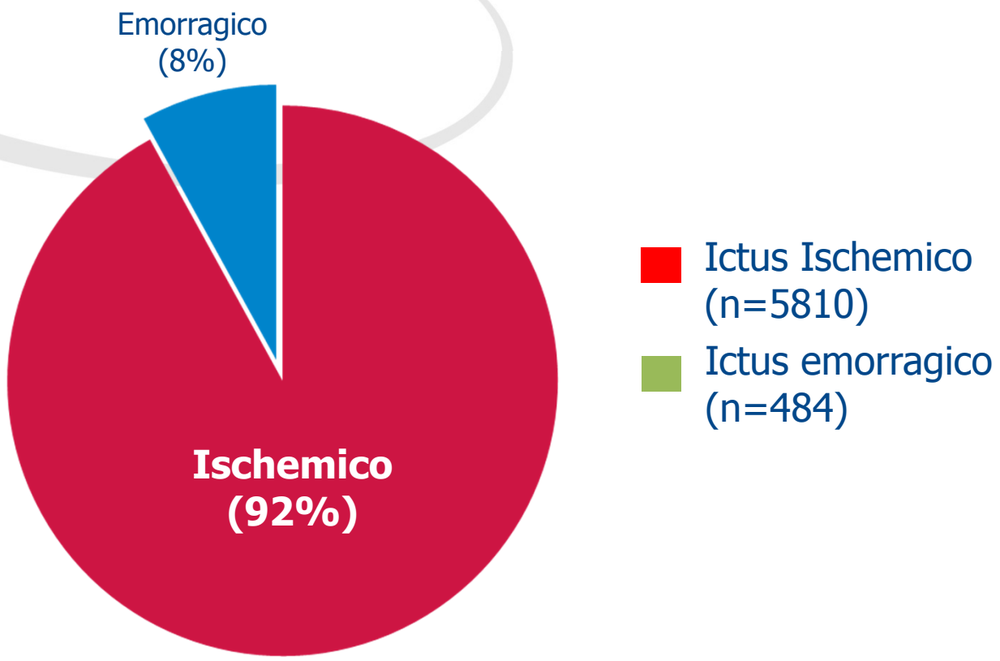


*Tachiaritmie atriali subcliniche identificate mediante device impiantati (n=2580)

Healey JS et al. N Engl J Med 2012;366:120–9

Strategie Terapeutiche

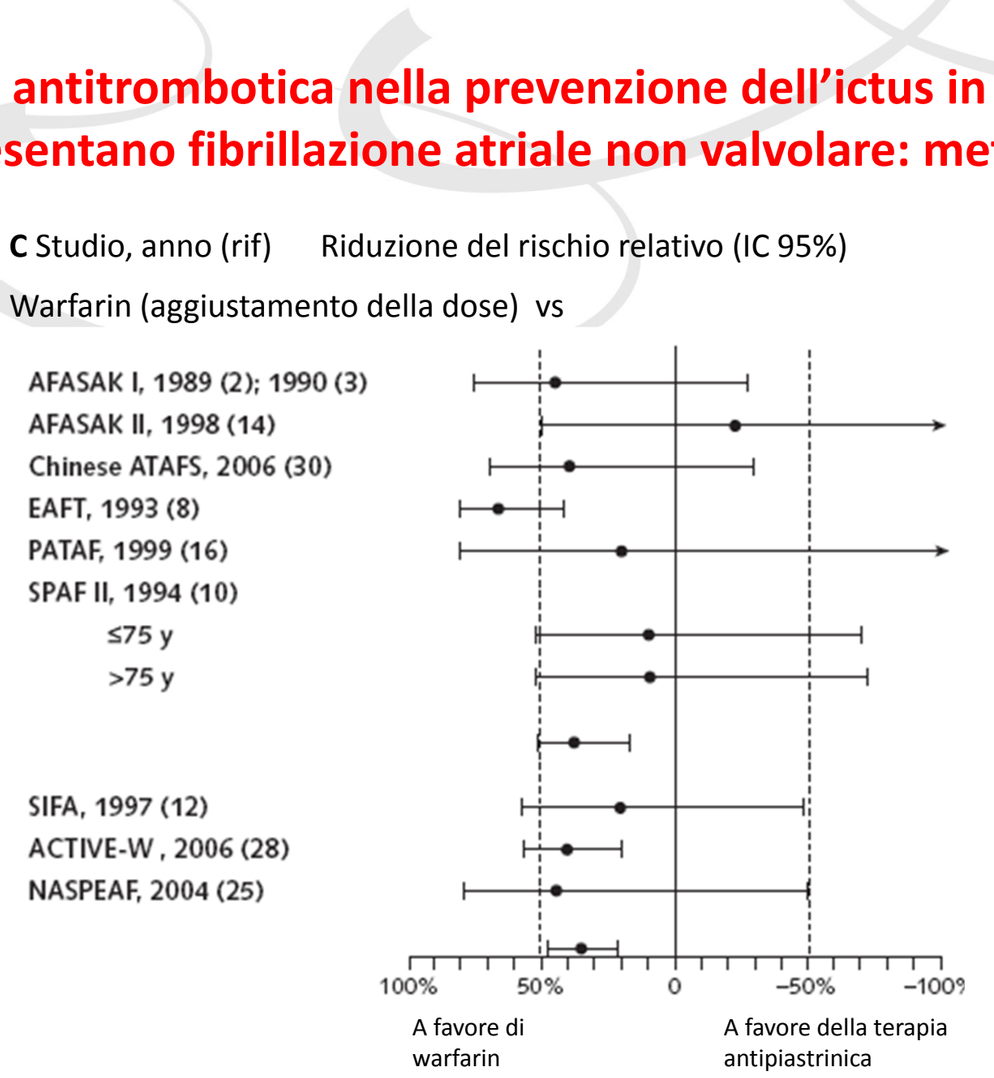
La maggior parte degli ictus associati a fibrillazione atriale sono ischemici



Coorte di 39484 pazienti (inclusi 6294 pazienti con FA) ospedalizzati per ictus -Danish National Indicator Project-

Andersen KK et al. Stroke 2009;40:2068–72

Terapia antitrombotica nella prevenzione dell'ictus in pazienti che presentano fibrillazione atriale non valvolare: meta-analisi



Hart RG Ann Intern Med 2007;146:857–867.

Warfarin vs Aspirina nella FA

	Tasso ictus con ASA	Tasso ictus con warfarin	Riduzione RR	NNT
Ictus o TIA pregresso	10,0%/anno	4,0%/anno	60%	17
Prevenzione primaria	2,7%/anno	1,5%/anno	44%	83
Età < 75 anni	3,4%/anno	1,3%/anno	62%	48
Età 75 anni	5,9%/anno	3,7%/anno	37%	45

Hart RG. Pract Neurol 2003;3:260-267

ACTIVE W

Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events–Warfarin arm (ACTIVE W) trial

(Studio su clopidogrel nella fibrillazione atriale con Irbesartan per la prevenzione di eventi vascolari- braccio Warfarin)

La terapia con warfarin è risultata superiore all'associazione clopidogrel/aspirina (riduzione del RR 40%; 95% IC 18–56), nessuna differenza negli eventi emorragici

ACTIVE Investigators. Lancet 2006;367:1903–1912

Cosa dicono le linee guida?

Stratificazione del Rischio di ictus sulla base dello score $CHADS_2$-VASc

Fattori di Rischio		Score
C	Congestive HF (Scompenso cardiaco)	1
H	Hypertension (Ipertensione)	1
A	Age ≥75 yrs (Età)	1
D	Diabetes mellitus (Diabete)	1
S_2	Stroke or TIA (Ictus o TIA pregresso)	2
V	Vascular disease (pregresso IM, PAD, placca aortica)	1
A	Age 65-74 yrs	1
Sc	Sex category (genere femminile)	1

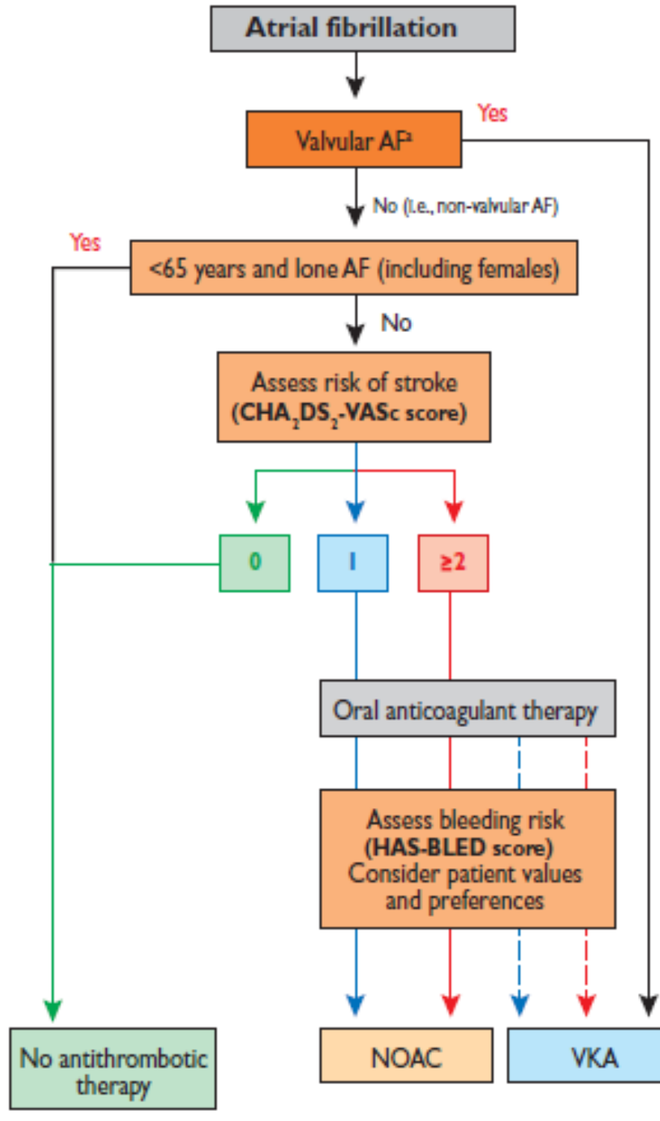
Tot 9

NB: Le linee guida pongono la FA parossistica allo stesso livello di rischio della FA permanente

European Heart Journal doi:10.1093/eurheartj/ehq278

Choice of anticoagulant

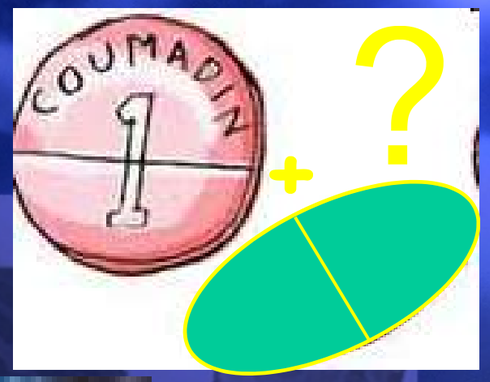
•Valvular AF includes rheumatic valvular disease and prosthetic valves

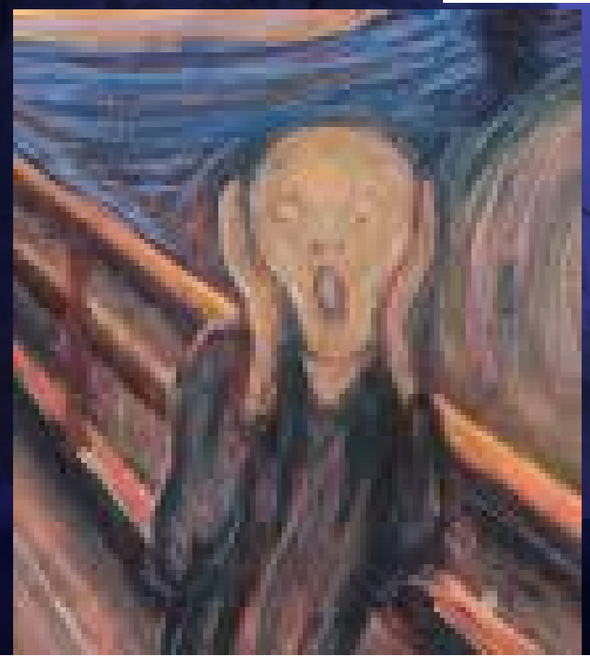


Colour CHA_2DS_2-VASc: green = 0, blue = 1, red ≥2; line: solid = best option; dashed = alternative option

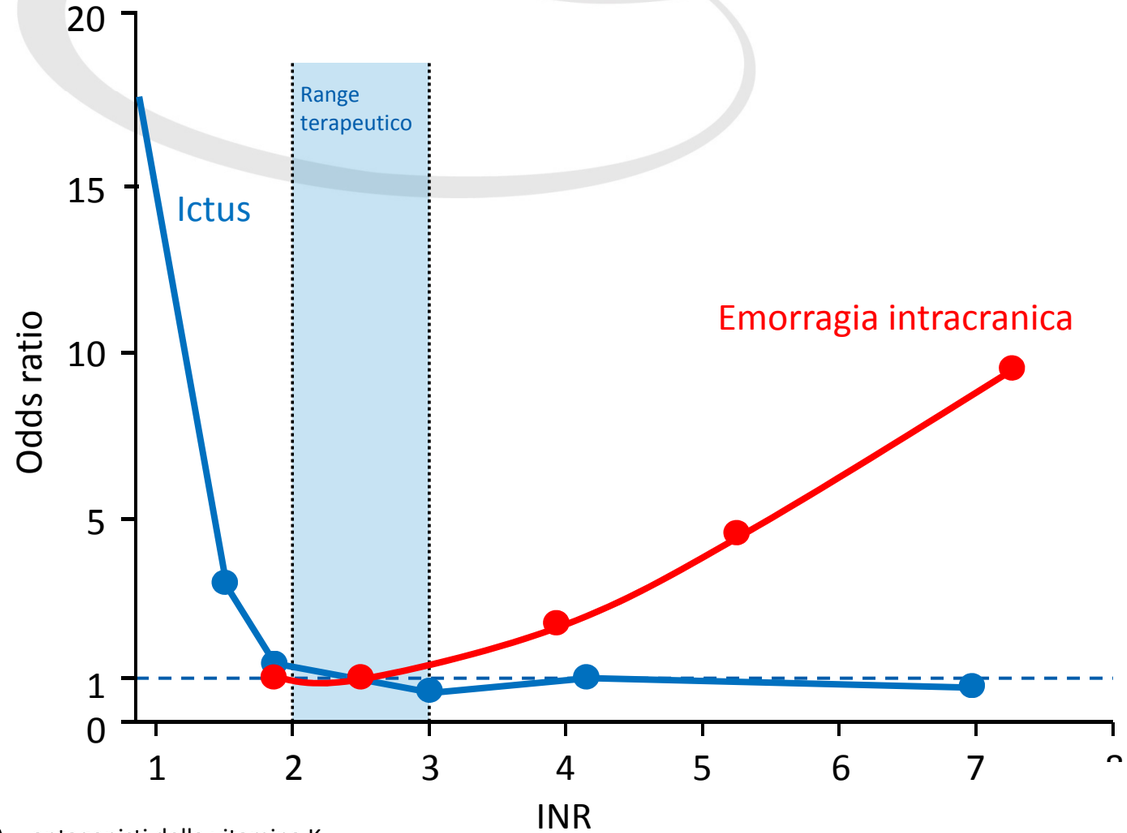
Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

LA DIFFICILE GESTIONE DEL FARMACO





I VKA hanno una finestra terapeutica ristretta



VKA = antagonisti della vitamina K

ACC/AHA/ESC guidelines: Fuster V et al. Circulation 2006;114:e257–354
& Eur Heart J 2006;27:1979–2030

Interazioni farmacologiche e alimentari associate ad aumento della potenza dei VKA

Farmaco/alimento	Esempi
Analgesici	Paracetamolo, propossifene, salicilati
Antiaritmici	Amiodarone, propafenone, chinidina
Antibiotici	Ciprofloxacina, eritromicina, metronidazolo
Antimicotici	Fluconazolo, itraconazolo, miconazolo
Beta-bloccanti	Propranololo
Anti-H_2/PPI	Cimetidina, omeprazolo
Farmaci ipolipemizzanti	Lovastatina, atorvastatina
Prodotti a base di erbe/integratori alimentari	Vitamina E, aglio, artiglio del diavolo
Varie	Alcool (se epatopatia concomitante)

PPI = inibitori della pompa protonica; VKA = antagonisti della vitamina K

Holbrook AM et al. Arch Intern Med 2005;165:1095–106;
du Breuil AL & Umland EM. Am Fam Physician 2007;75:1031–42

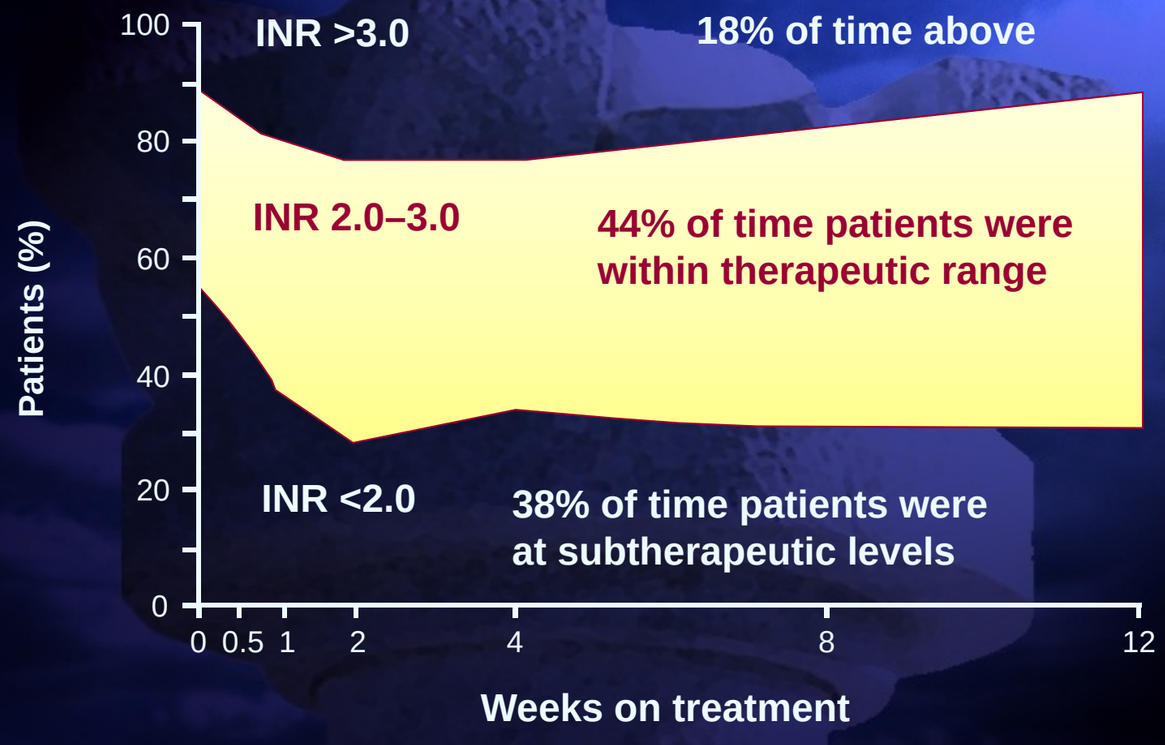
Interazioni farmacologiche e alimentari associate a ridotta potenza dei VKA

Farmaco/alimento	Esempi
Antibiotici	Dicloxacillina, nafcillina, rifampicina
Antimicotici	Griseofulvina
Immunosoppressori	Azatioprina, ciclosporina
Farmaci ipolipemizzanti	Colestiramina
Prodotti a base di erbe/integratori alimentari	Coenzima Q10, ginseng, erba di San Giovanni
Alimenti	Té verde, avocado (in grandi quantità), alimenti ad alto contenuto di vitamina K, fra cui broccoli e spinaci
Varie	Carbamazepina, sucralfato, trazodone

VKA = antagonisti della vitamina K

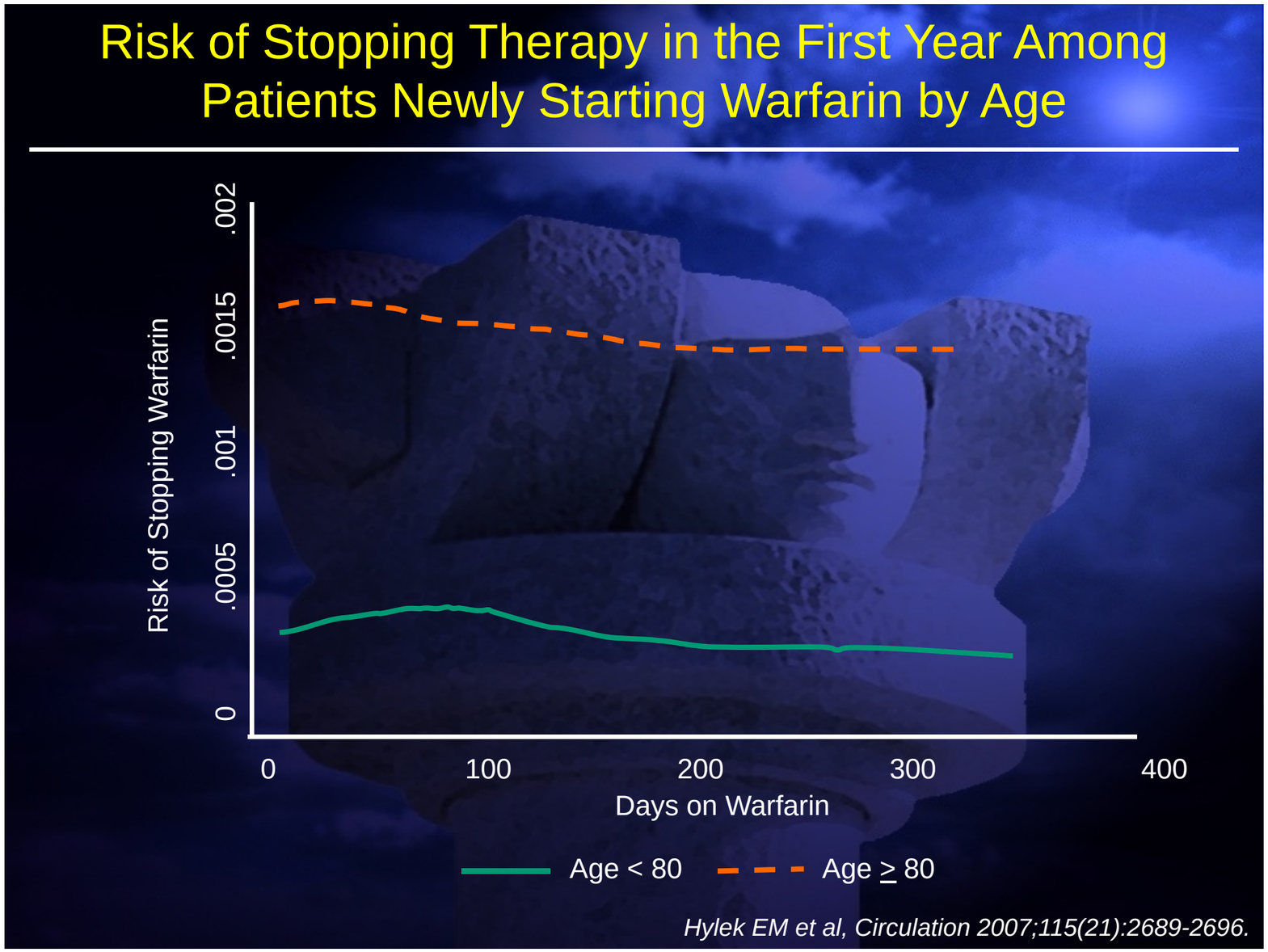
Holbrook AM et al. Arch Intern Med 2005;165:1095–106;
du Breuil AL & Umland EM. Am Fam Physician 2007;75:1031–42

Warfarin is difficult to monitor even in the trial setting (SPORTIF II Trial)



Petersen P et al. *J Am Coll Cardiol* 2003;41:1445-51

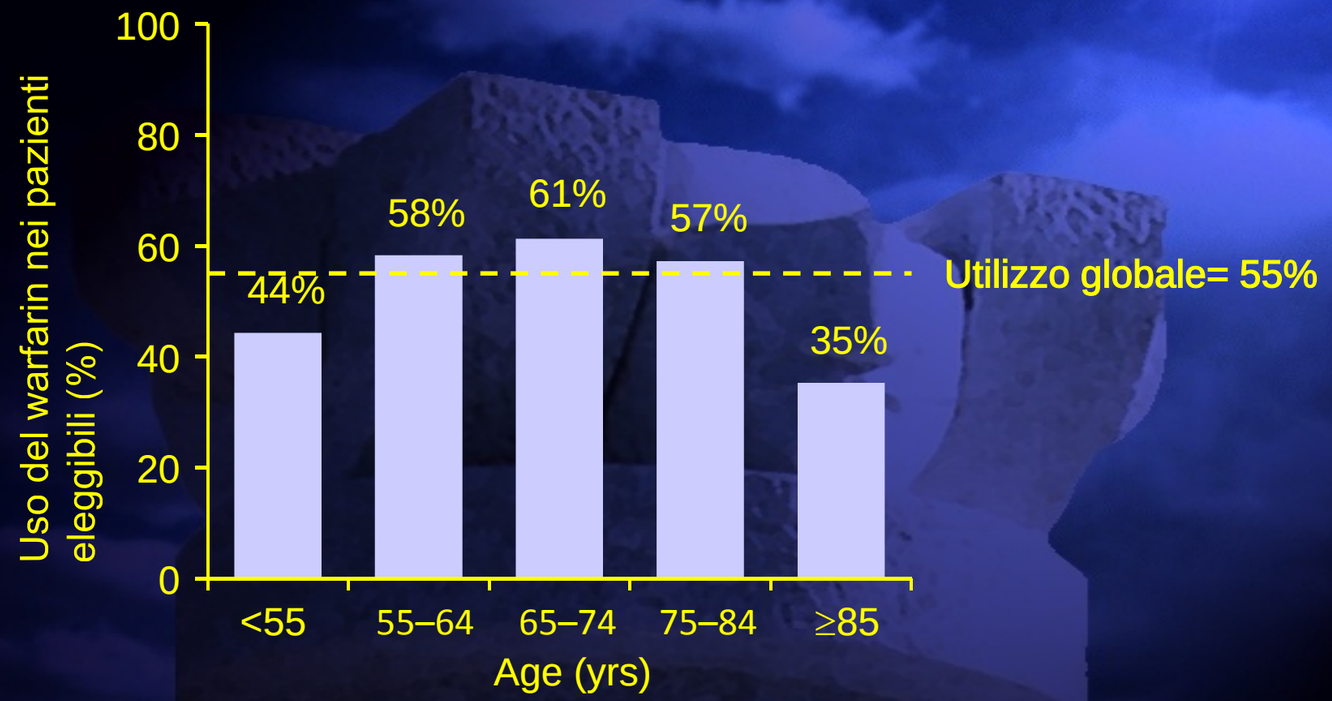
Risk of Stopping Therapy in the First Year Among Patients Newly Starting Warfarin by Age



Hylek EM et al, Circulation 2007;115(21):2689-2696.


consequences…

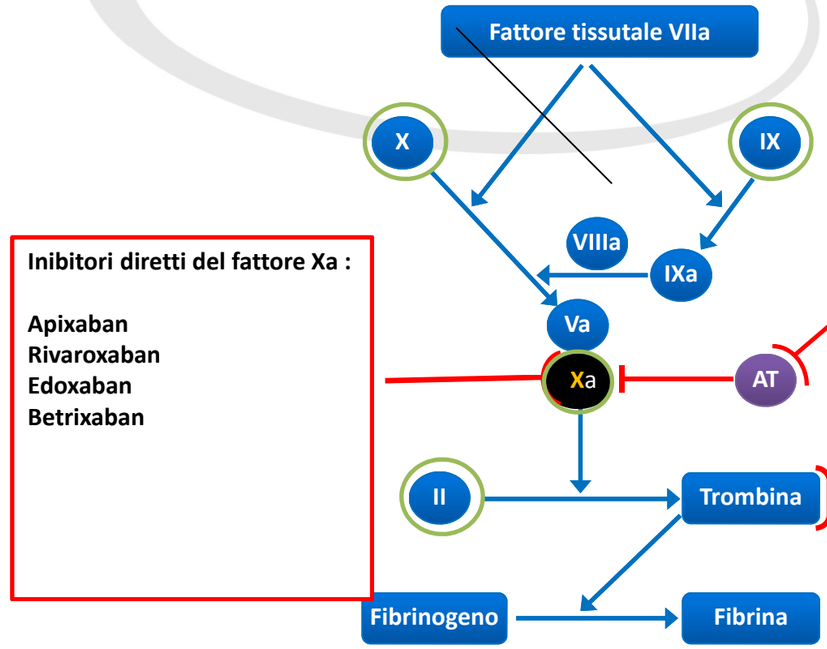
Warfarin è utilizzato solo in metà dei pazienti con FA



Il warfarin è sotto-utilizzato soprattutto nei pazienti anziani che sono quelli a più alto rischio di ictus

Go A et al. Ann Intern Med 1999;131:927

Bersagli dei nuovi antitrombotici nella cascata della coagulazione



Antagonisti della vitamina K:

Tecarfarin (Fase II completata)[2]

Inibitori diretti del fattore Xa :

Apixaban
Rivaroxaban
Edoxaban
Betrixaban

Inibitori indiretti del fattore Xa:

Idraparinux (terminata Fase III)[3]
Idrabiotaparinux (sospeso nel 2009)[4]

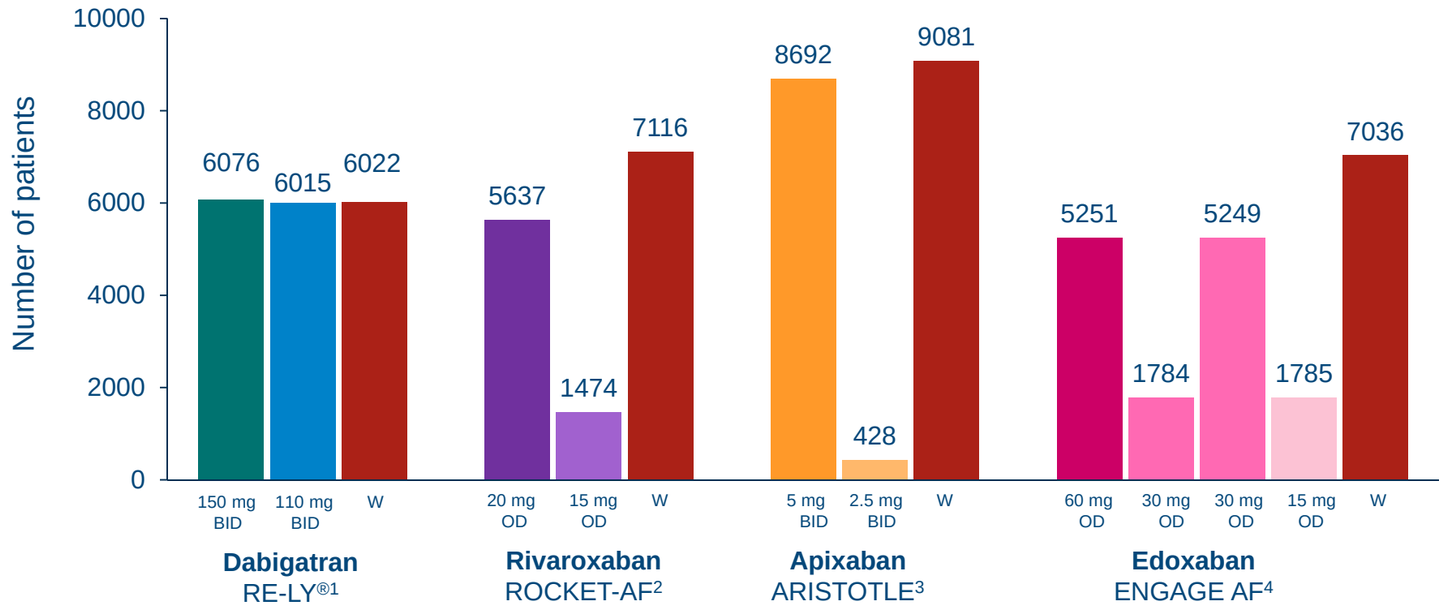
Inibitori diretti della trombina:

Dabigatran etexilato
Ximelagatran (sospeso nel 2006)[11,12]
AZD0837 (completata Fase II)[13]

antitrombina

1. Adattato da Turpie AG. Eur Heart J 2008;29:155–65; 2. Ellis DJ et al. Circulation 2009;22:120:1029–35; 3. Bousser MG et al. Lancet 2008;371:315–21; 4. NCT00580216; available at www.ClinicalTrials.gov; accessed Sept 09; 5. Lopes RD et al. Am Heart 2010;159:331–9; 6. Eikelboom JW et al. Am Heart J 2010;159:348–53; 7. ROCKET-AF Study Investigators. Am Heart J 2010;159:340–47; 8. NCT00781391; available at www.ClinicalTrials.gov; accessed Sept 09; 9. NCT00742859; available at www.ClinicalTrials.gov; accessed Sept 09; 10. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 11. Olsson SB et al. Lancet 2003;362:1691–8; 12. Albers GW et al. JAMA 2005;293:690–8; 13. Lip GY et al. Eur Heart J 2009;30:2897–907

Four pivotal studies including over 71 000 patients have compared NOACs with warfarin for stroke prevention in AF



W, warfarin

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

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

Stroke or systemic embolism

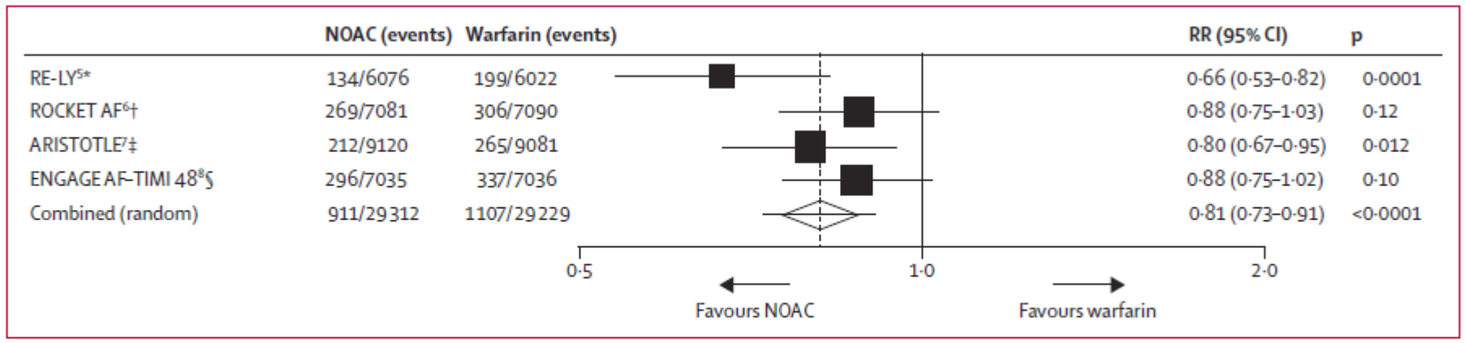
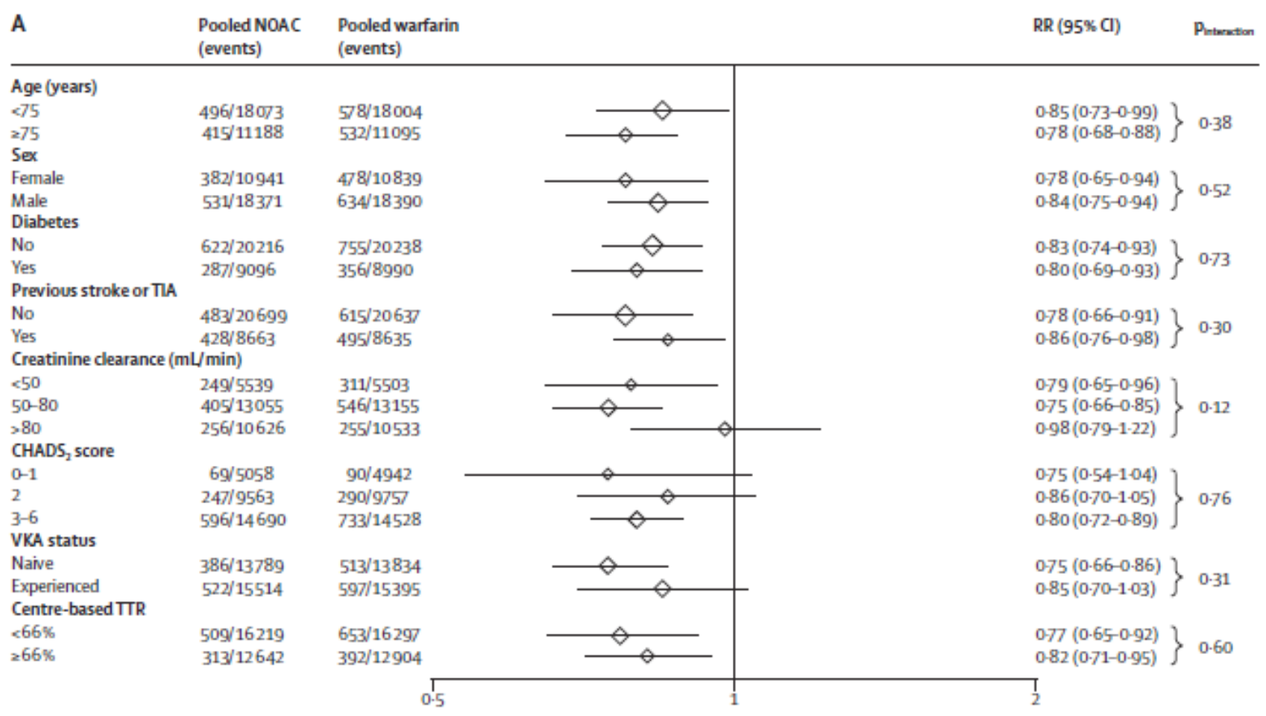


***Figure 1*: Stroke or systemic embolic events**
Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Allocation to a new oral anticoagulant significantly reduced the composite of stroke or systemic embolic events by **19%** compared with warfarin.

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



The benefit of NOACs compared with warfarin in reducing stroke or systemic embolic events was consistent across all subgroups examined:

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

Secondary efficacy and safety outcomes

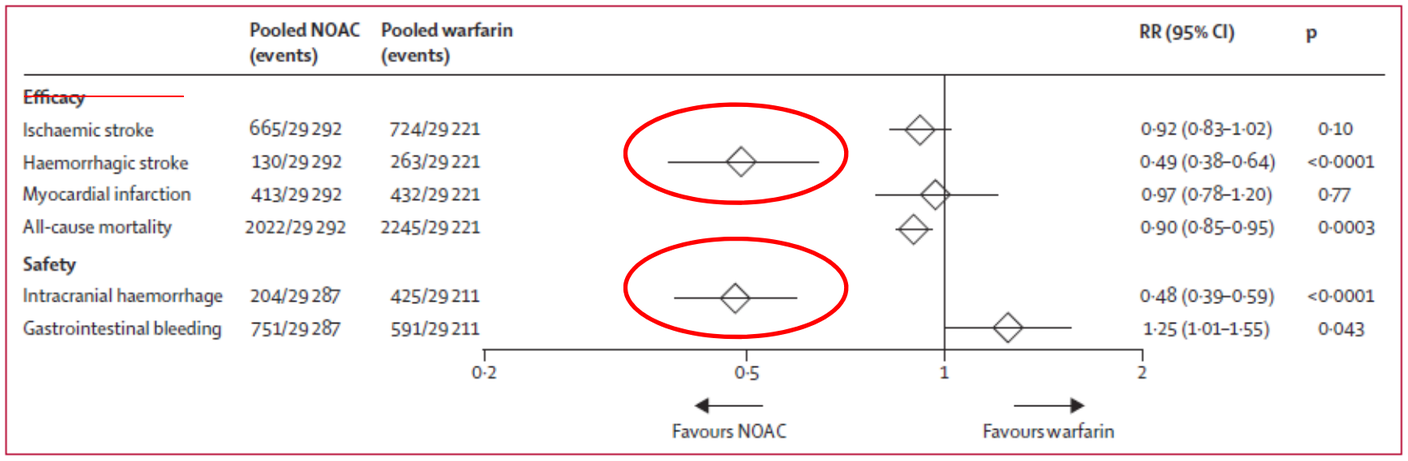
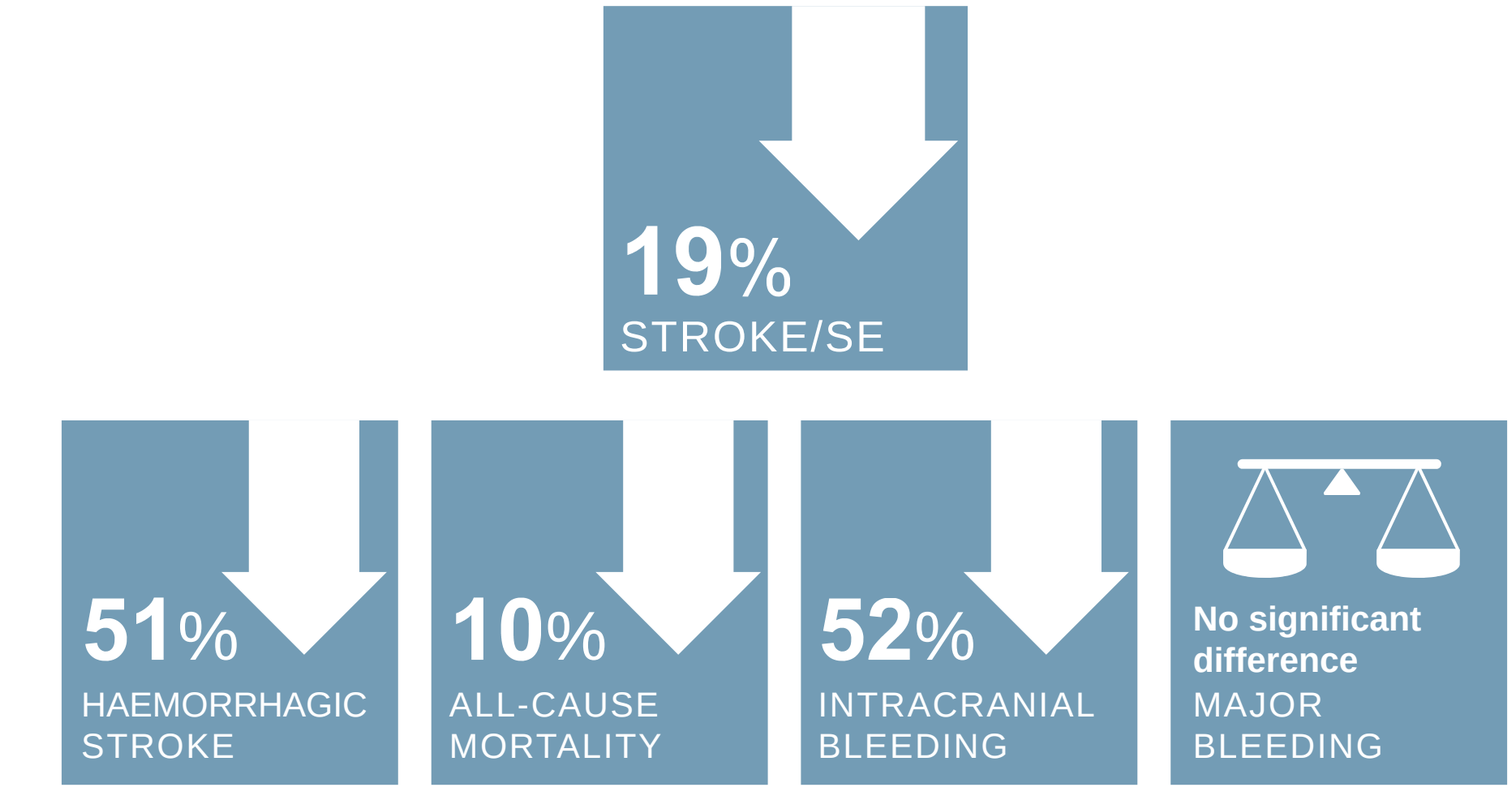


***Figure 2*: Secondary efficacy and safety outcomes**
Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

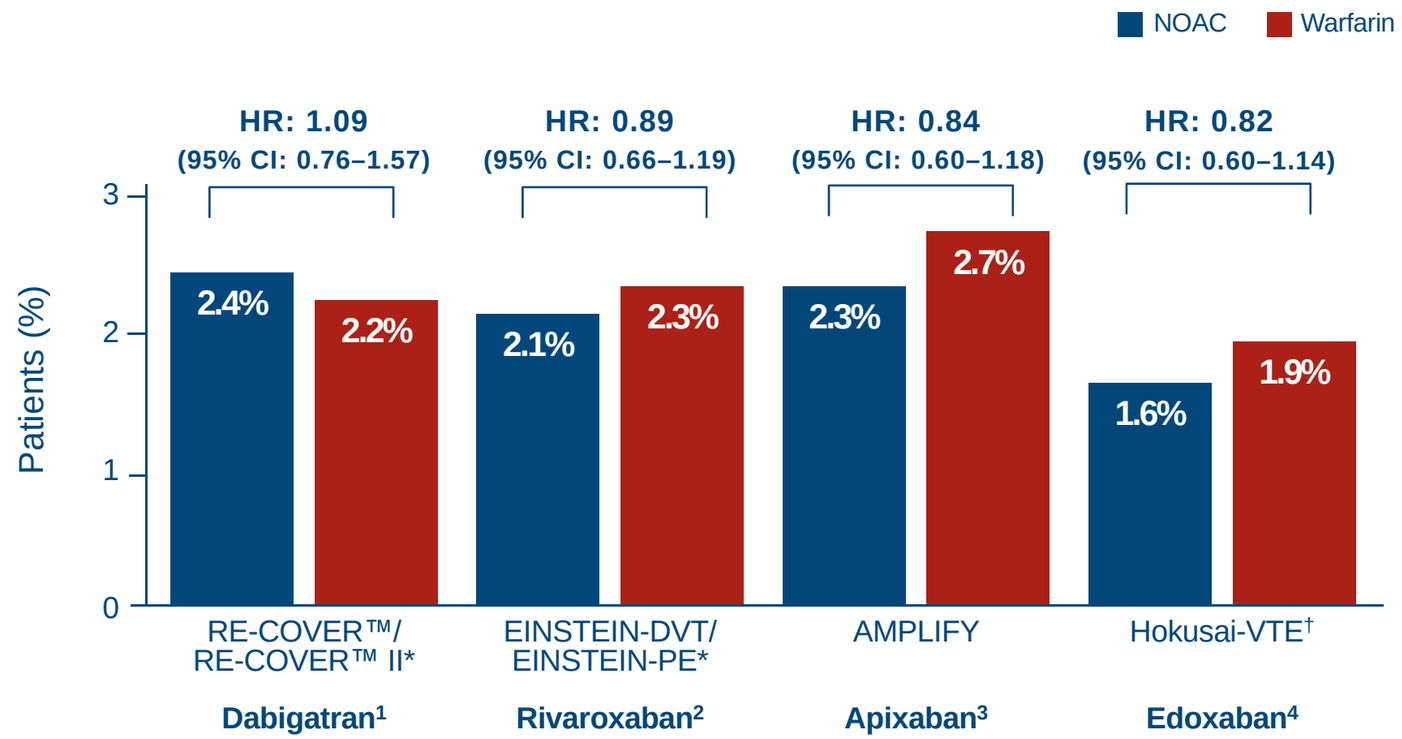


Meta-analysis of data from RE-LY®, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48
Ruff et al. Lancet 2013

NAO: indications

- FA
- **DVT/PE**

Acute treatment: all NOACs non-inferior to warfarin for prevention of recurrent DVT/PE in their Phase III trials

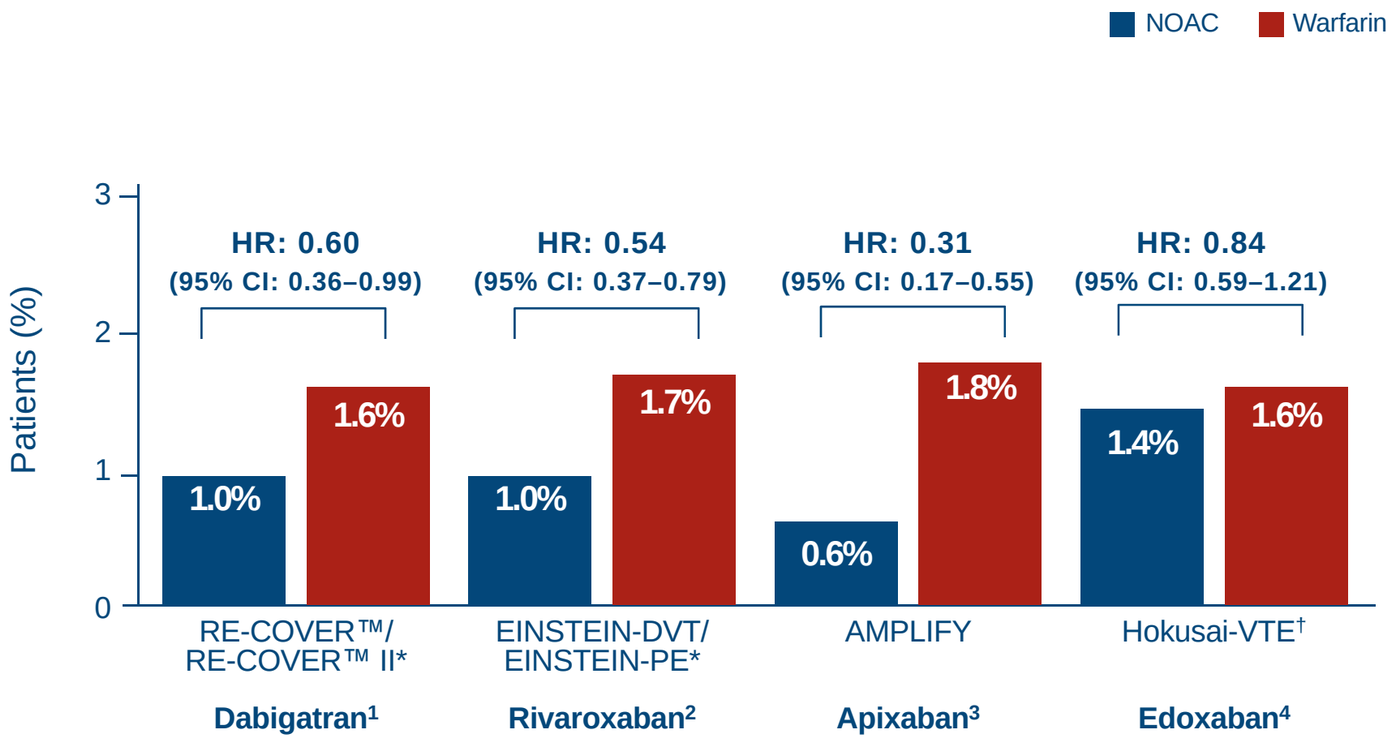


Head-to-head studies do not exist, comparisons between studies and drugs may not be made.
For illustrative purposes only

*Pooled analysis; †On treatment

1. Schulman et al. Circulation 2014; **2.** Prins et al. Thromb J 2013; **3.** Agnelli et al. N Engl J Med 2013;
4. Hokusai-VTE Investigators et al. N Engl J Med 2013

Acute treatment: all NOACs associated with less major bleeding versus warfarin in their Phase III trials



Head-to-head studies do not exist, comparisons between studies and drugs may not be made.
For illustrative purposes only

*Pooled analysis; †On treatment

1. Schulman et al. Circulation 2014; **2.** Prins et al. Thromb J 2013; **3.** Agnelli et al. N Engl J Med 2013;
4. Hokusai-VTE Investigators et al. N Engl J Med 2013

Is a NOAC a treatment option in this patient? What do the guidelines say?


ESC GUIDELINES

European Heart Journal
doi:10.1093/eurheartj/ehu283

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

Authors/Task Force Members: Stavros Konstantinides* (Chairperson) (Germany/Greece), Adam Torbicki* (Co-chairperson) (Poland), Giancarlo Agnelli (Italy), Nicolas Danchin (France), David Fitzmaurice (UK), Nazzareno Galiè (Italy), J. Simon R. Gibbs (UK), Menno Huisman (The Netherlands), Marc Humbert† (France), Nils Kucher (Switzerland), Irene Lang (Austria), Mareike Lankeit (Germany), John Lekakis (Greece), Christoph Maack (Germany), Eckhard Mayer (Germany), Nicolas Meneveau (France), Arnaud Perrier (Switzerland), Piotr Pruszczyk (Poland), Lars H. Rasmussen (Denmark), Thomas H. Schindler (USA), Pavel Svitil (Czech Republic), Anton Vonk Noordegraaf (The Netherlands), Jose Luis Zamorano (Spain), Maurizio Zompatori (Italy)

ESC Committee for Practice Guidelines (CPG): Jose Luis Zamorano (Chairperson) (Spain), Stephan Achenbach (Germany), Helmut Baumgartner (Germany), Jeroen J. Bax (Netherlands), Hector Bueno (Spain), Veronica Dean (France), Christi Deaton (UK), Çetin Erol (Turkey), Robert Fagard (Belgium), Roberto Ferrari (Italy), David Hasdai (Israel), Arno Hoes (Netherlands), Paulus Kirchhof (Germany/UK), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Patrizio Lancellotti (Belgium), Ales Linhart (Czech Republic), Petros Nihoyannopoulos (UK), Massimo F. P

PE without shock or hypotension (intermediate or low risk)

As an alternative to VKA treatment:

dabigatran is recommended following acute-phase parenteral anticoagulation

edoxaban* is recommended following acute-phase parenteral anticoagulation

As an alternative to combination of parenteral anticoagulation with VKA:

rivaroxaban is recommended

apixaban is recommended

*Was not approved for this indication at the time of publication of the guidelines

Konstantinides et al. Eur Heart J 2014

Eminence-based medicine

or

Evidence-based medicine?

Eminence-based medicine

Per i NOACs non esiste antidoto, per il warfarin si (vitamina K).

Evidence-based medicine

- **Fino all'Ottobre 2015, l'unico anticoagulante che aveva un vero antidoto (solfato di protamina) era l'eparina sodica.**

- **La vitamina K <u>NON</u> è un antidoto per il warfarin.**

- **I NOACs hanno una emivita di 12-14 ore circa, il warfarin di 120 ore.**

- **Sono ora disponibili antidoti per i NOACs.**

NOAC reversal agents are in development

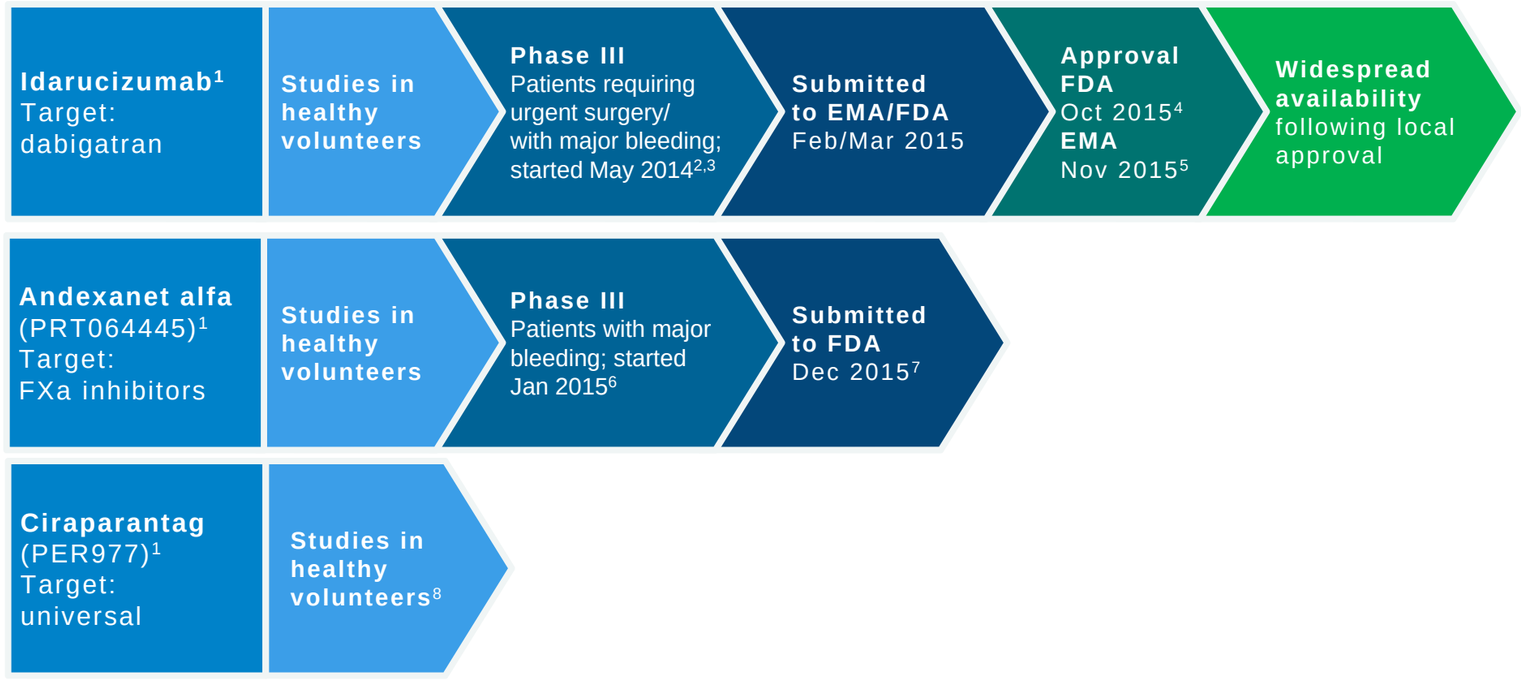
NOAC reversal agent	Target	Mechanism of action
Idarucizumab[1]	Dabigatran	Humanized Fab: specifically binds dabigatran with high affinity[2]
Andexanet alfa (PRT064445)[1]	FXa inhibitors	Recombinant modified FXa: competitive affinity for direct FXa inhibitors[3]
Ciraparantag (PER977)[1]	Universal	Synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin)[4]

Idarucizumab is not approved in all countries. Please check your local prescribing information for details. Andexanet alfa and ciraparantag are investigational compounds and are not approved in any country. This information is presented for medical education purposes only

FXa, activated Factor X

1. Greinacher et al. Thromb Haemost 2015; **2.** Schiele et al. Blood 2013; **3.** Lu et al. Nat Med 2013;
4. Ansell et al. N Engl J Med 2014

NOAC reversal agents: stages of development



Idarucizumab is not approved in all countries. Please check your local prescribing information for details.
Andexanet alfa and ciraparantag are investigational compounds and are not approved in any country.
This information is presented for medical education purposes only

1. Adapted from Greinacher et al. Thromb Haemost 2015; **2.** Clinicaltrials.gov: NCT02104947; **3.** Pollack et al. Thromb Haemost 2015; **4.** US FDA press release 16 Oct 2015; **5.** European Commission Community Register of Medicinal Products for Human Use 20 November 2015; **6.** ClinicalTrials.gov Identifier: NCT02329327; **7.** ClinicalTrials.gov Identifier: NCT02207257

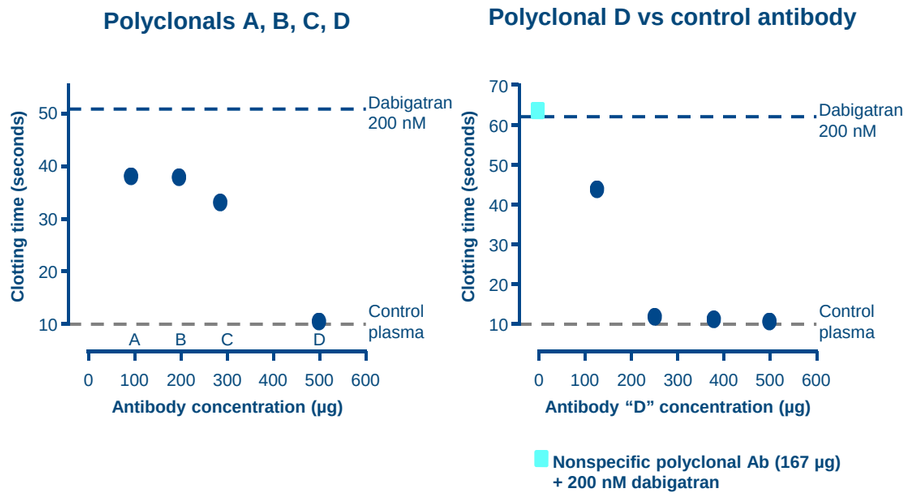
How it all started

- American Society Hematology (ASH), San Francisco, 2008
- Poster with data about reversing anticoagulation with a specific antidote

‘The ability to turn the anticoagulation effect on and off as required could provide further benefit for patients in need of intervention while on anticoagulation’

Proof of concept (2009): reversal of dabigatran anticoagulant activity

- Four polyclonal rabbit antibodies to dabigatran were available
- All four neutralized the anticoagulant effect of dabigatran in human plasma using clotting assay
- Inhibition was concentration-dependent and specific



2014 onwards

RE-VERSE AD™

Study of reversal effects of idarucizumab in patients on active dabigatran

2008 onwards

PROOF OF CONCEPT

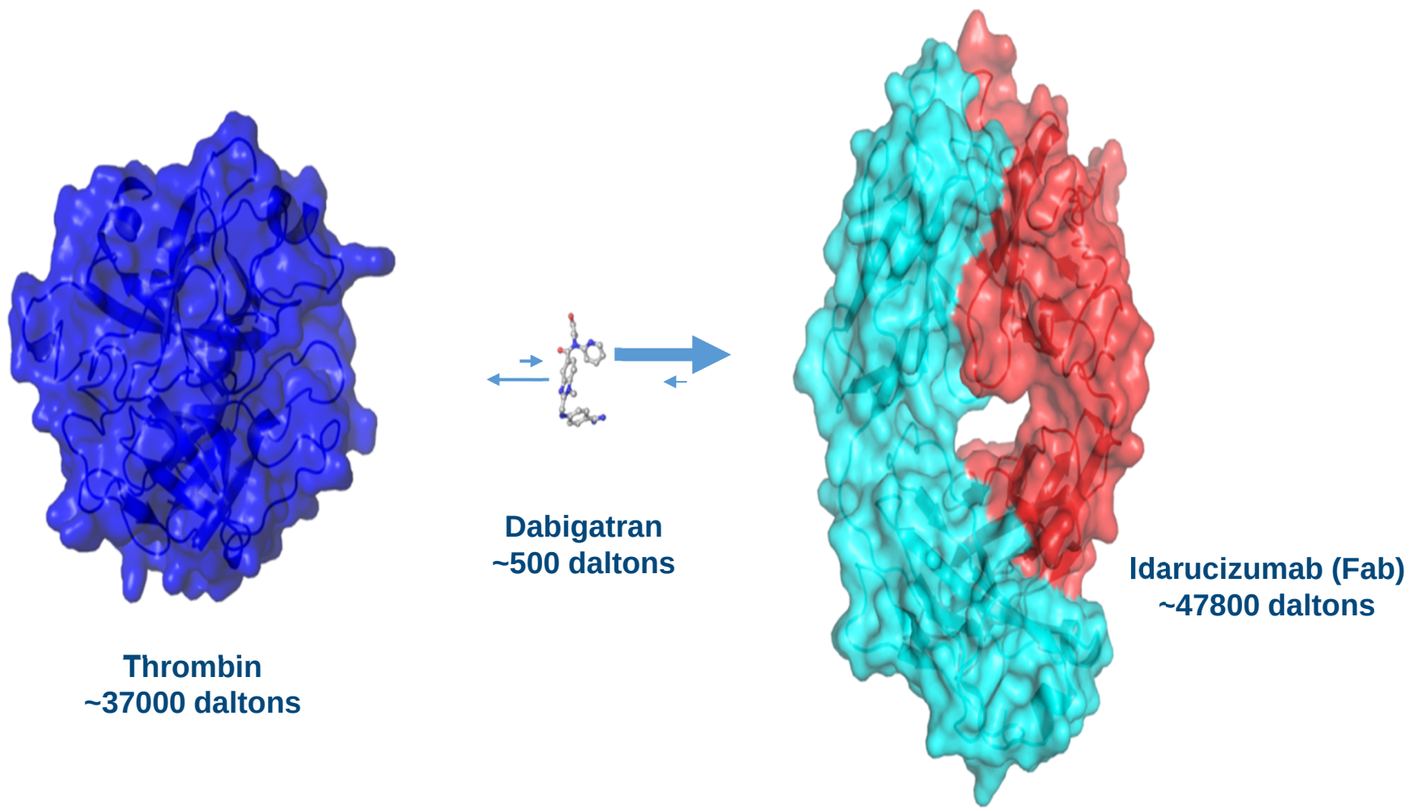
2015/2016

REGULATORY APPROVAL

2009 onwards

PRECLINICAL AND PHASE I TESTING

Relative size and affinity of dabigatran, idarucizumab, and thrombin



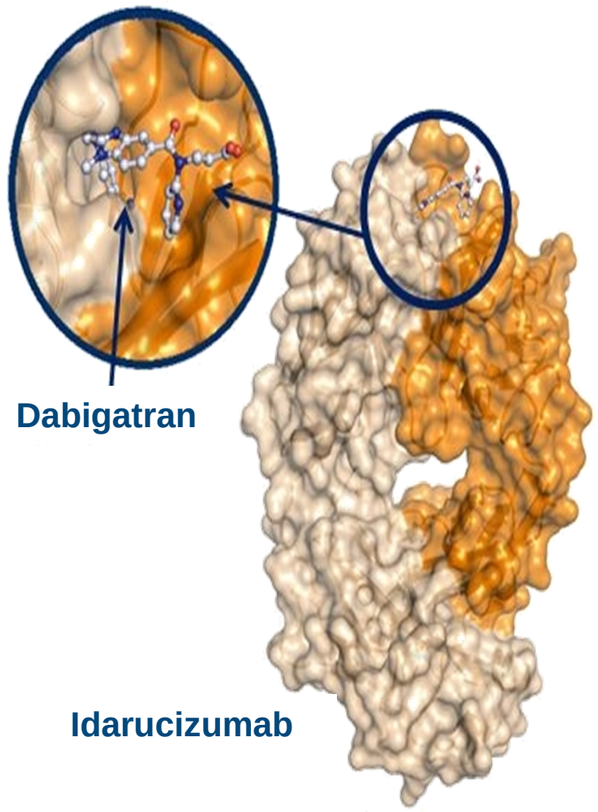
Thrombin
~37000 daltons

Dabigatran
~500 daltons

Idarucizumab (Fab)
~47800 daltons

Pollack et al. Thromb Haemost 2015

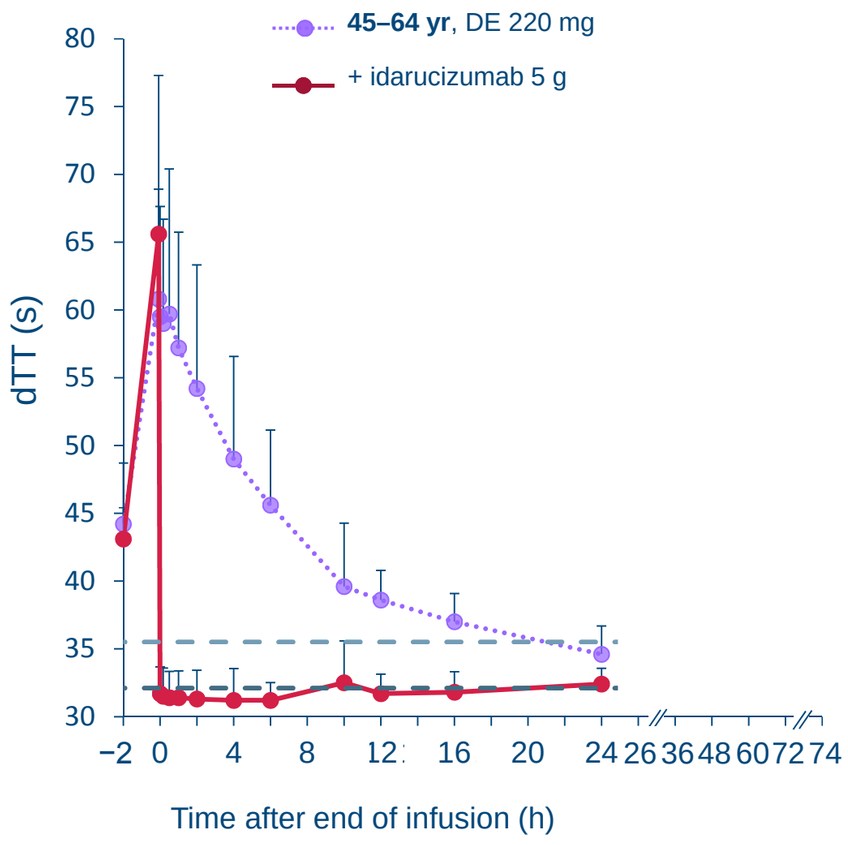
Idarucizumab was designed as a specific reversal agent for the anticoagulant activity of dabigatran



- Humanized Fab fragment
- Binding affinity for dabigatran **~350× higher** than dabigatran to thrombin
- IV administration, immediate onset of action
- Short half-life
- No intrinsic procoagulant or anticoagulant activity expected

Schiele et al. Blood 2013; Praxbind®: EU SPC, 2016

Immediate onset of action: few minutes after idarucizumab administration



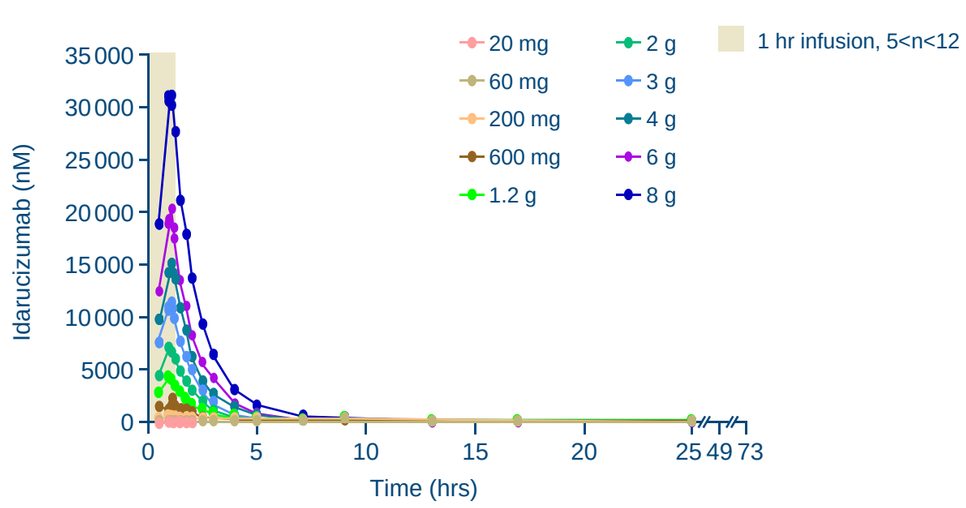
Middle-aged subjects (45–64 yrs) received 5 g idarucizumab or placebo

N=6–8/group, mean ± SE

Glund et al. Blood 2014

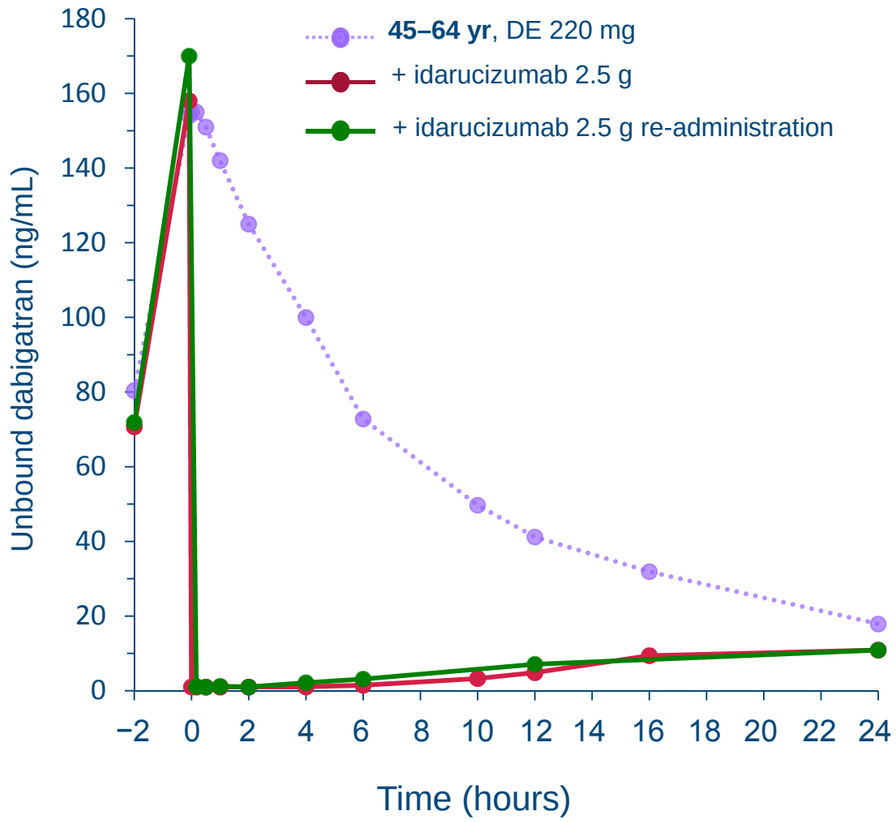
Short half-life: Idarucizumab plasma concentrations in healthy volunteers

- Low volume of distribution
- Short half-life: initial $t_{1/2}$ ~45 min; terminal $t_{1/2}$ 4.5–9 hours
- Within 6 hours 90% of dose had cleared



Glund et al. Thromb Haemost 2015

No immunogenic activity: re-dosing of idarucizumab ~2 months after first dose: unbound dabigatran



Idarucizumab (2.5 g) was re-administered 2 months after first administration

Re-administration was safe and well tolerated

Re-administration resulted in similar efficacy vs first dose

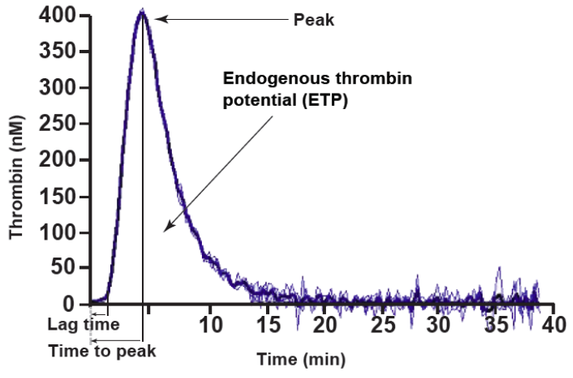
N=6/group, gmean

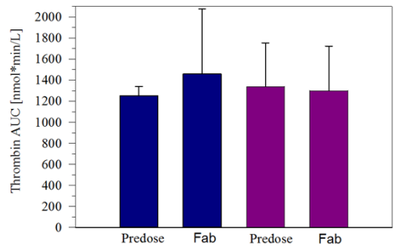
Glund et al. Blood 2014

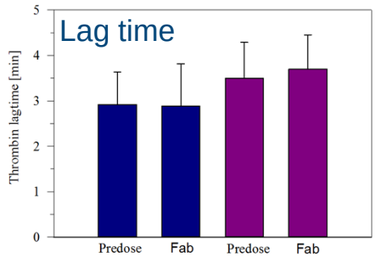
No procoagulant effects: idarucizumab administration in healthy volunteers and endogenous thrombin potential

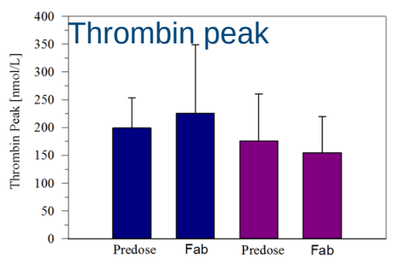
- Endogenous thrombin potential in plasma
- Measured before and 15 min after idarucizumab in volunteers <u>not</u> receiving dabigatran
- Idarucizumab plasma concentrations at 15 min were ~20 µmol/L

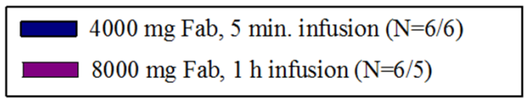
Endogenous thrombin potential (ETP)





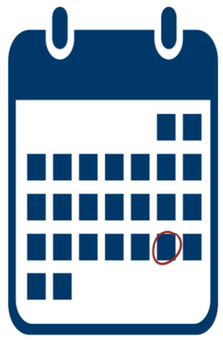




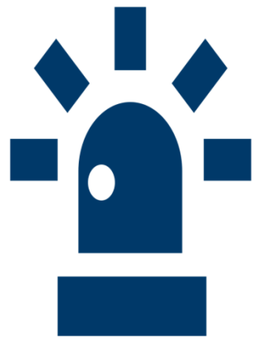


Glund et al. Circulation 2013

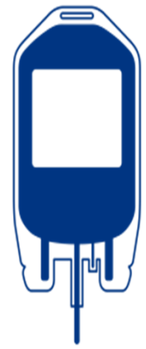
Interruption or reversal of anticoagulation can be planned or in response to an emergency



Elective surgery



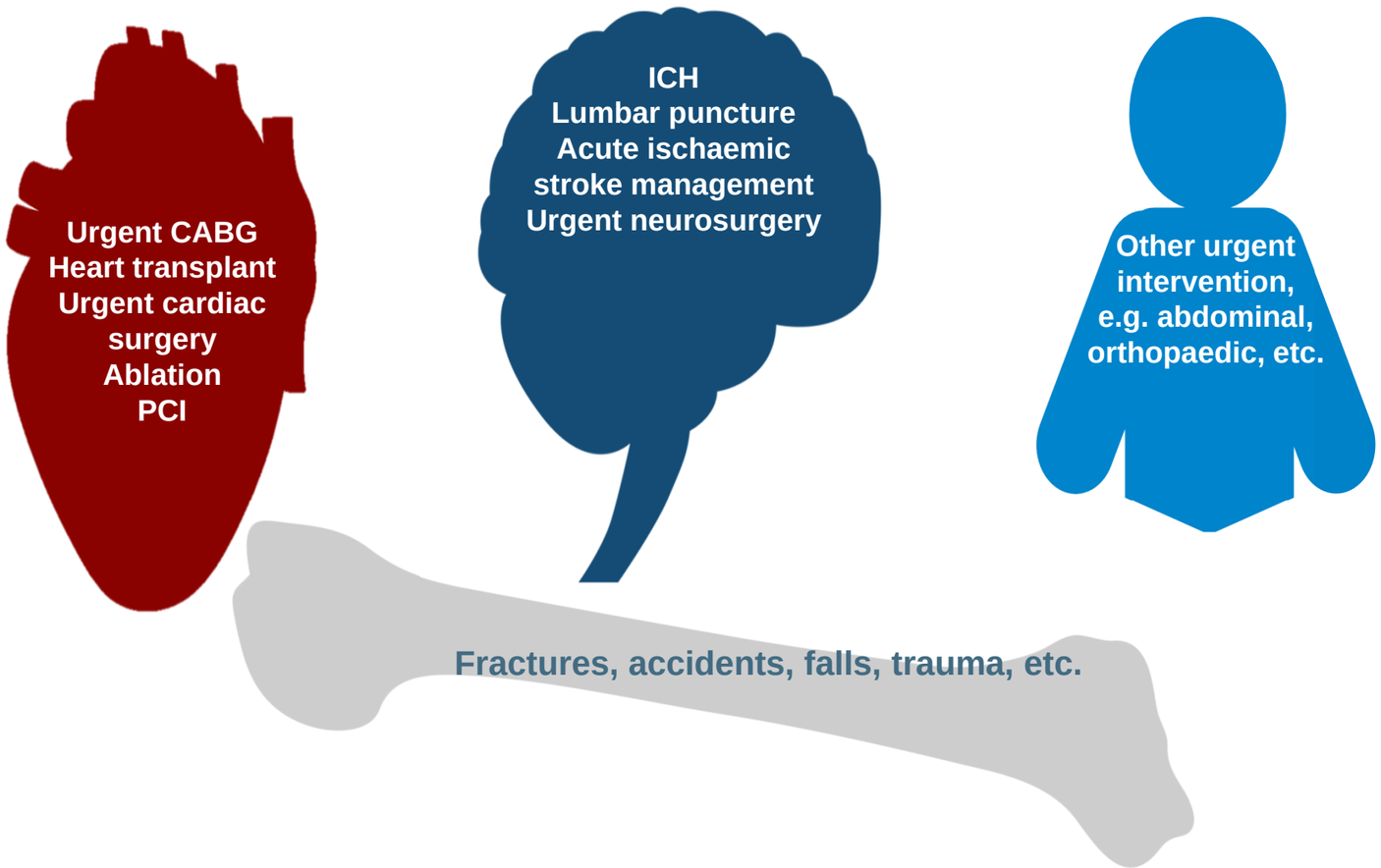
Emergency surgery



Uncontrolled bleeding

Emergency management

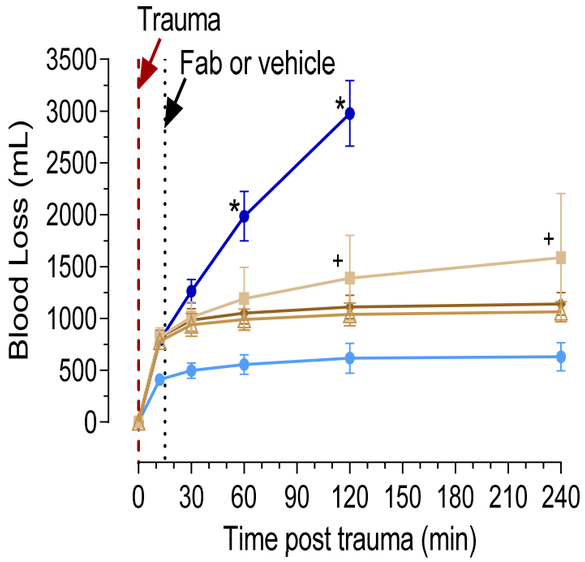
What is the relevance of a specific reversal agent for cardiologists and neurologists?



CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention

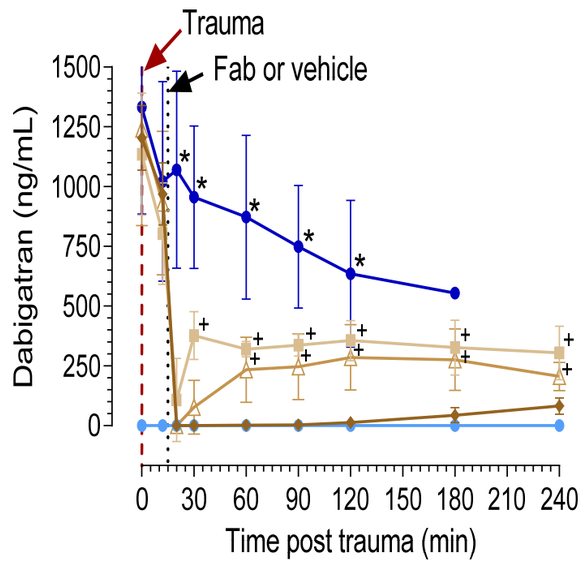
Reduced blood loss and increased survival with idarucizumab after liver trauma

Cumulative blood loss



*p<0.001 vs Fab treatment, +p<0.01 vs control

Diluted thrombin time

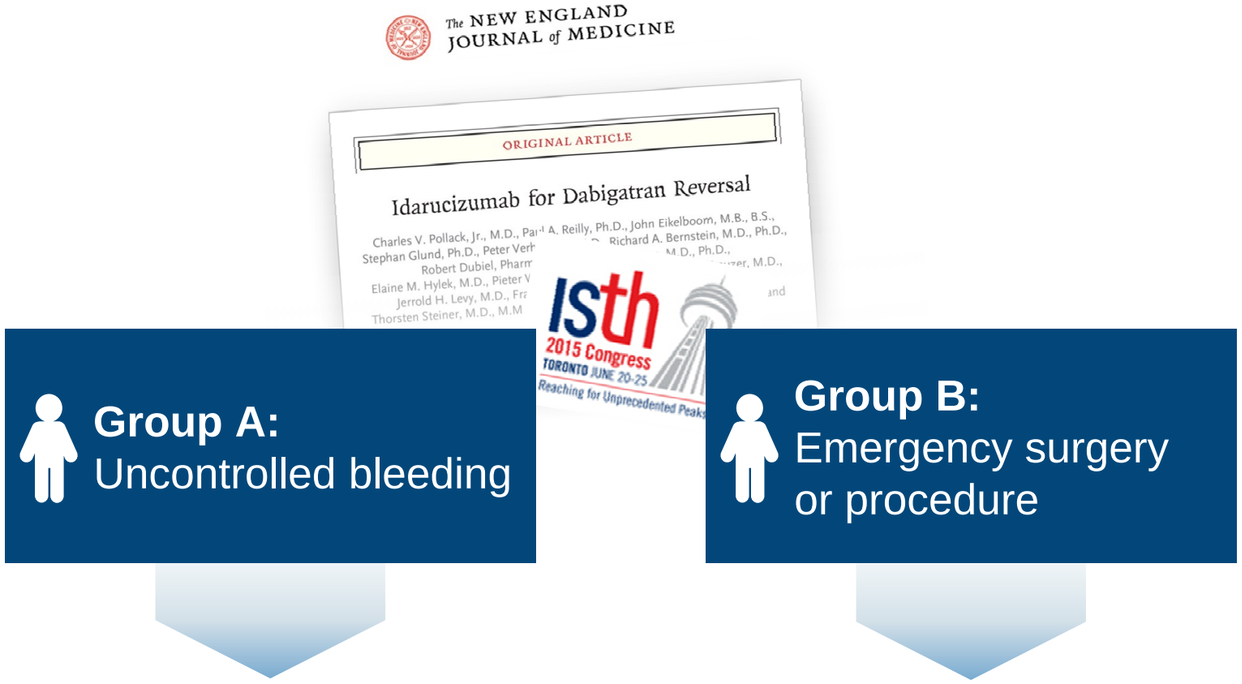


*p<0.001 vs Fab treatment, +p<0.01 vs control

Data represent mean ± SD, n=6

Reversal was measured with all assays tested:
dTT, ECT, Activated Clotting Time , aPTT, PT, Thromboelastometry, ROTEM (Extem and Intem)

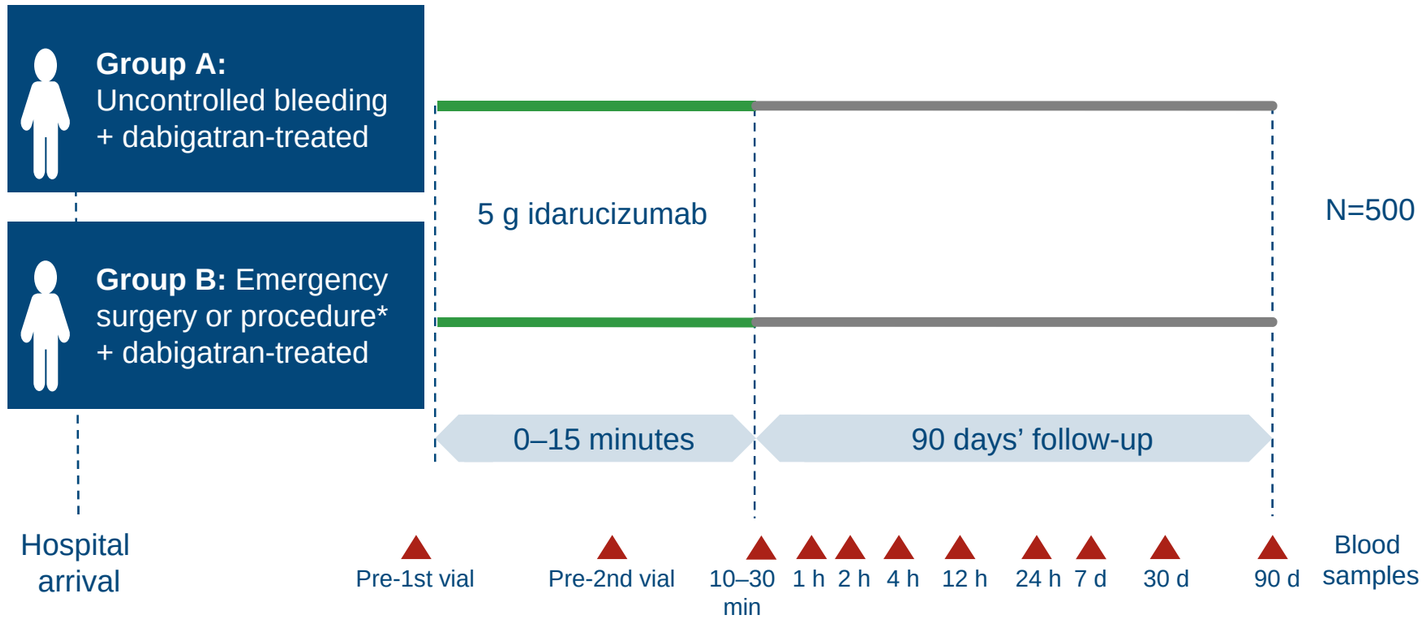
Honickel et al. J Am Coll Cardiol 2015



Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

Pollack et al. Presented at ISTH 2015; Pollack et al. N Engl J Med 2015

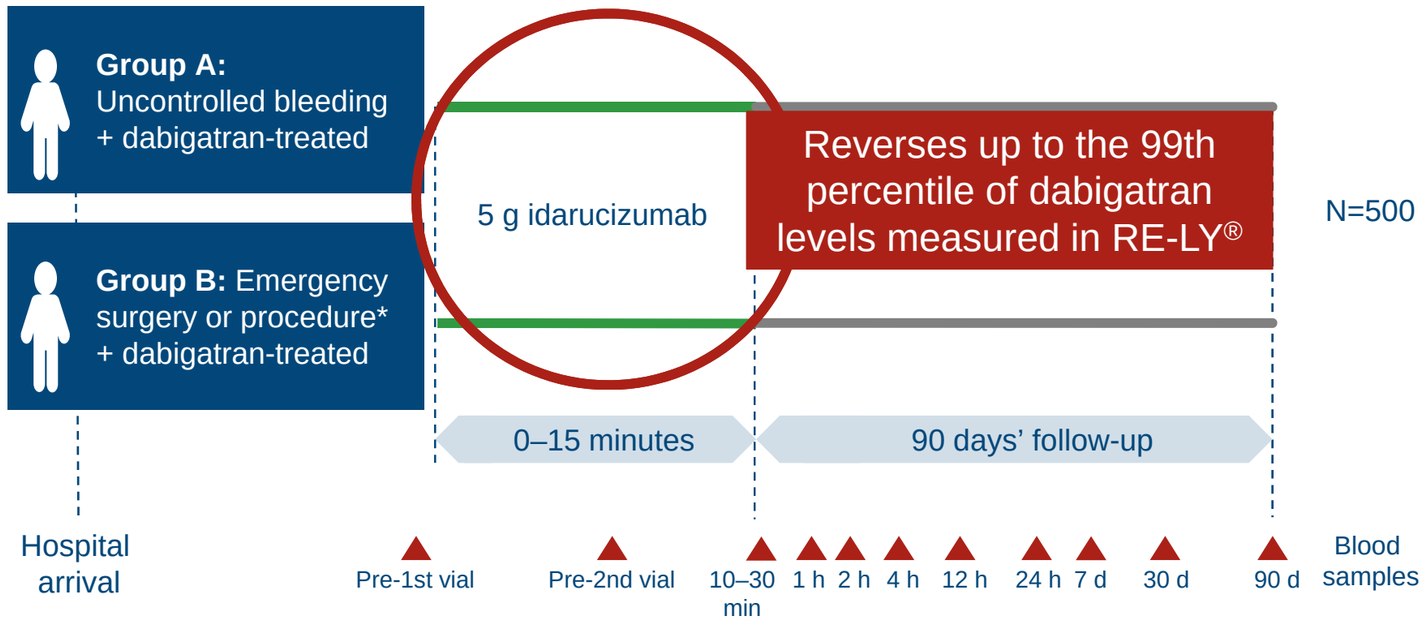
RE-VERSE AD™: multicentre, ongoing, single-arm, open-label Phase III study



*Other than bleeding. dTT, diluted thrombin time; ECT, ecarin clotting time

Pollack et al. Thromb Haemost 2015

RE-VERSE AD™: multicentre, single-arm, open-label Phase III study

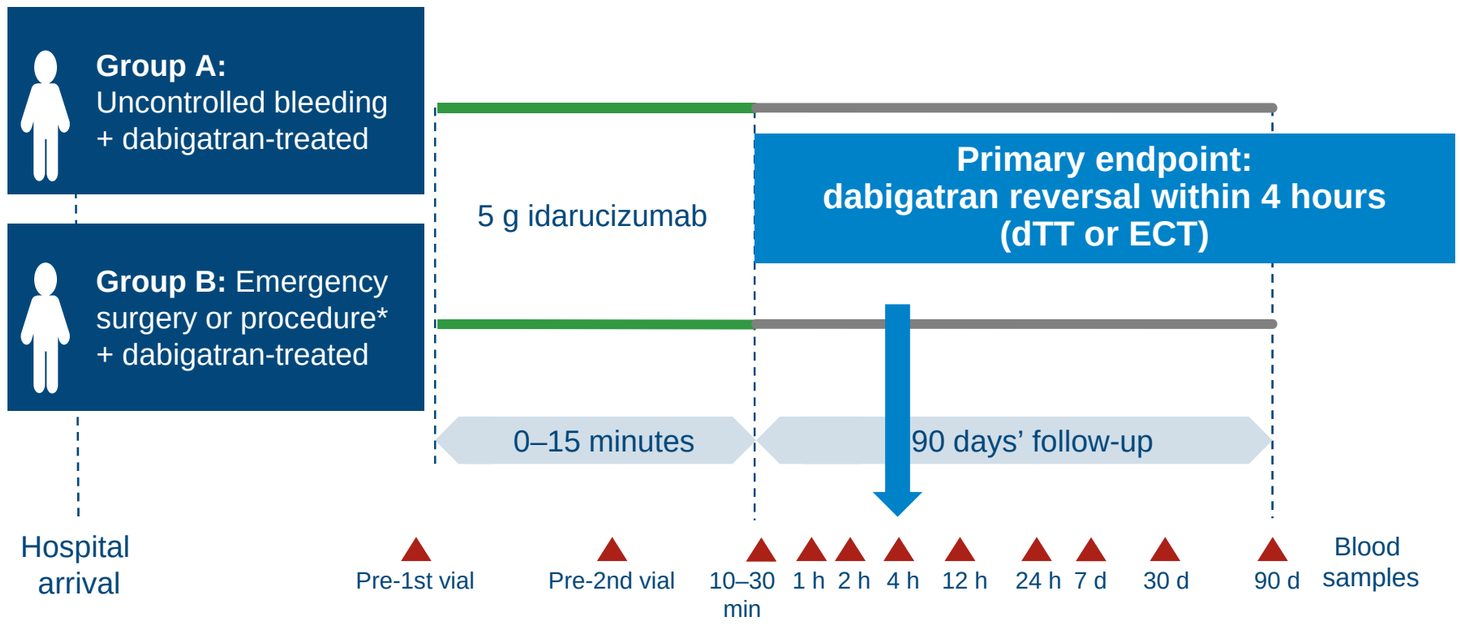


Idarucizumab is not approved in all countries. Please check your local prescribing information for details.
This information is presented for medical education purposes only

*Other than bleeding. dTT, diluted thrombin time; ECT, ecarin clotting time

Pollack et al. Thromb Haemost 2015

RE-VERSE AD™: multicentre, ongoing, single-arm, open-label Phase III study



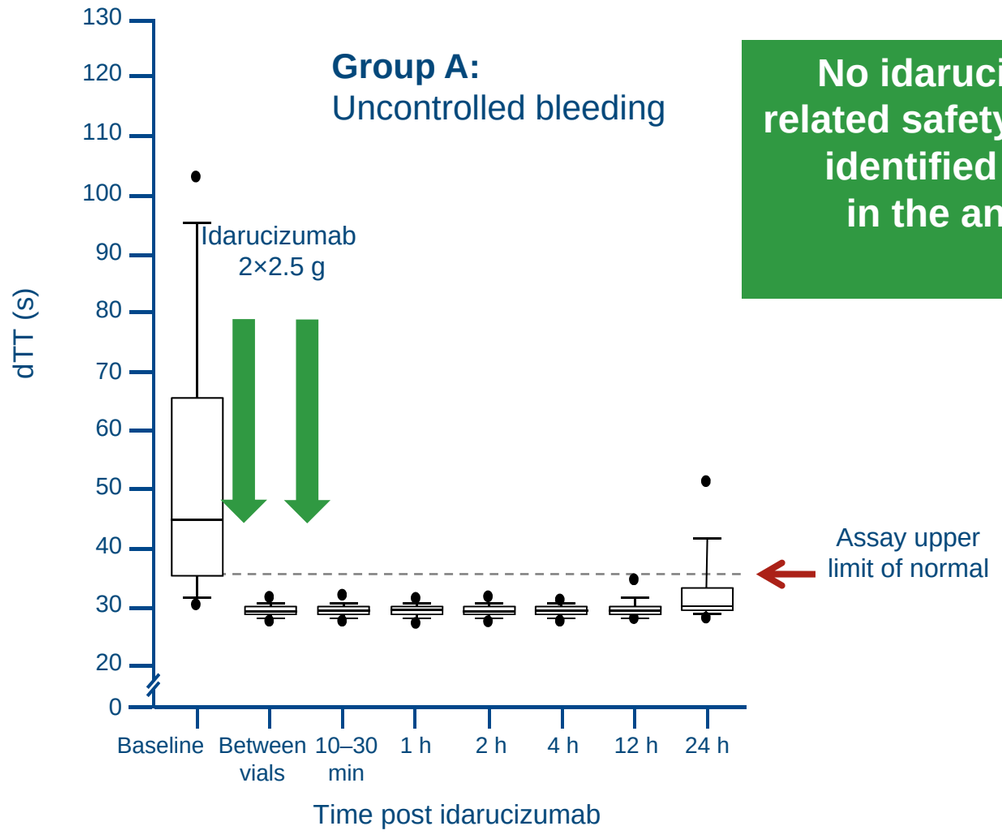
Idarucizumab is not approved in all countries. Please check your local prescribing information for details.
This information is presented for medical education purposes only

*Other than bleeding. dTT, diluted thrombin time; ECT, ecarin clotting time

Pollack et al. Thromb Haemost 2015

RE-VERSE AD™ Group B interim results: reasons for inclusion

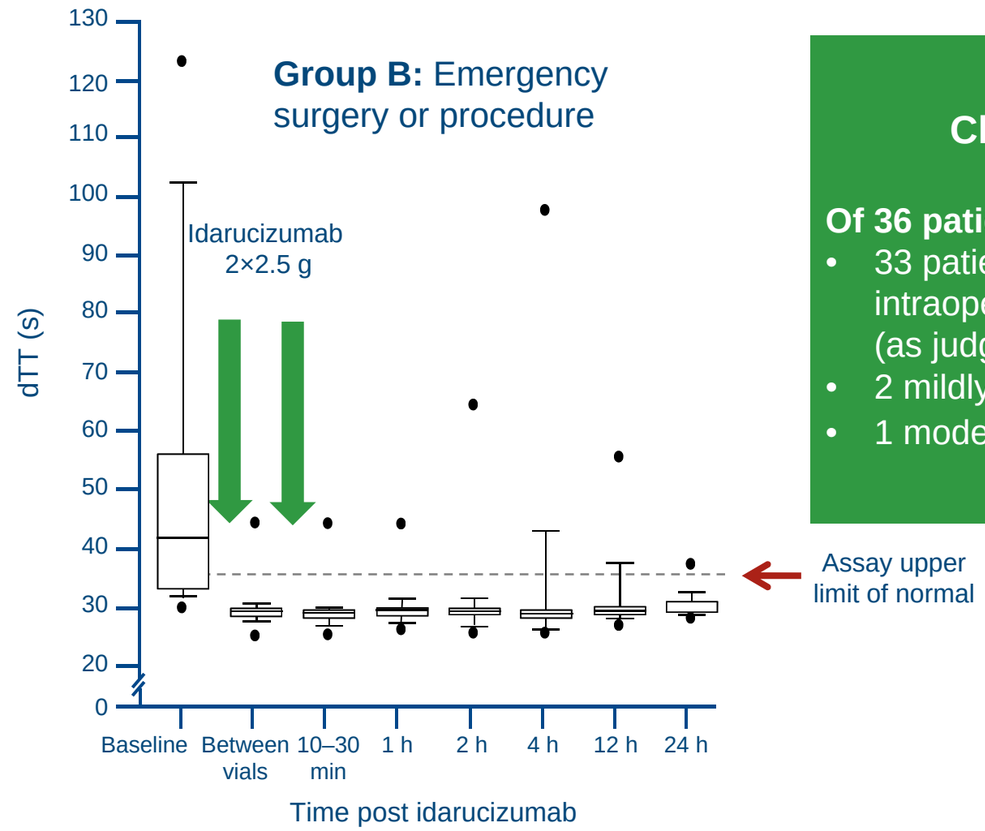
Group A interim results: reversal of dabigatran anticoagulation with idarucizumab based on dTT



No idarucizumab-related safety concerns identified to date in the analysis

Adapted from: Pollack et al. N Engl J Med 2015

Group B interim results: reversal of dabigatran anticoagulation with idarucizumab based on dTT



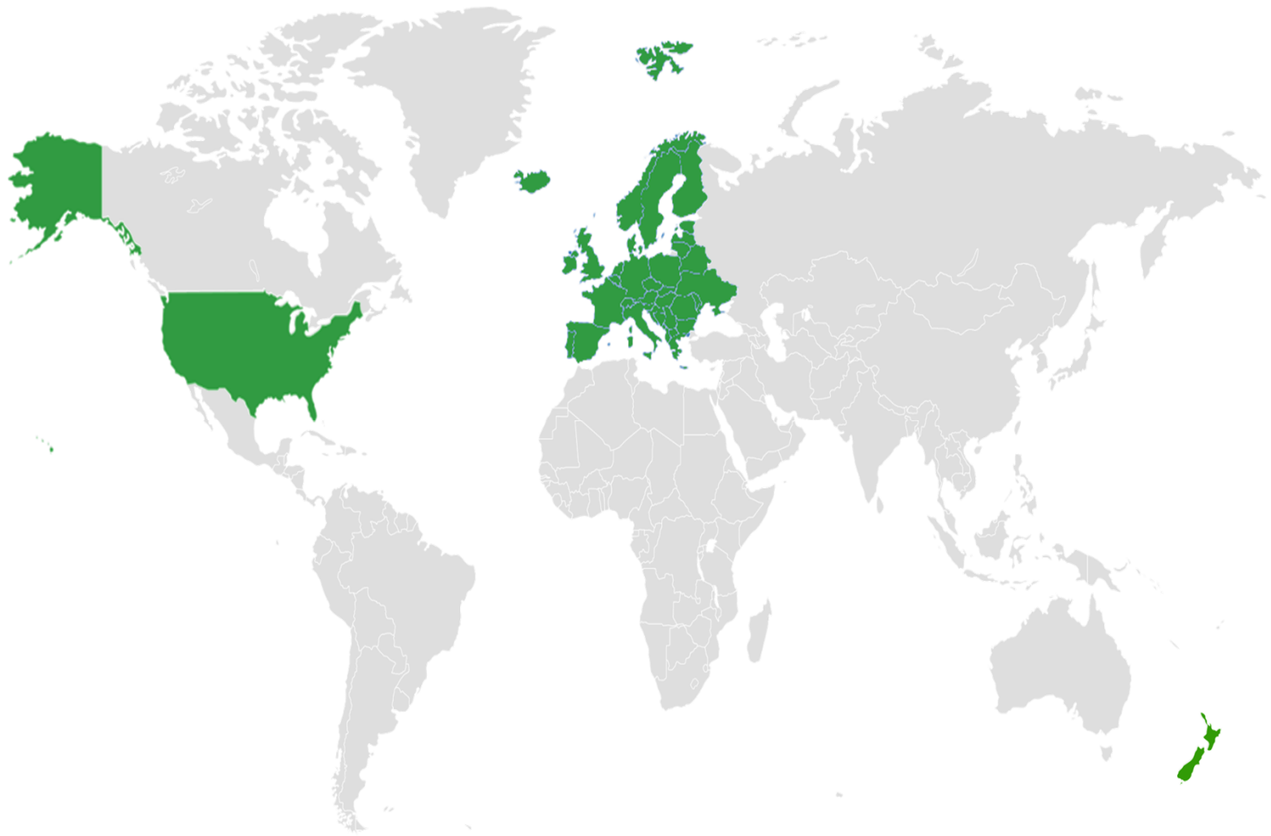
Clinical outcomes

Of 36 patients undergoing surgery:

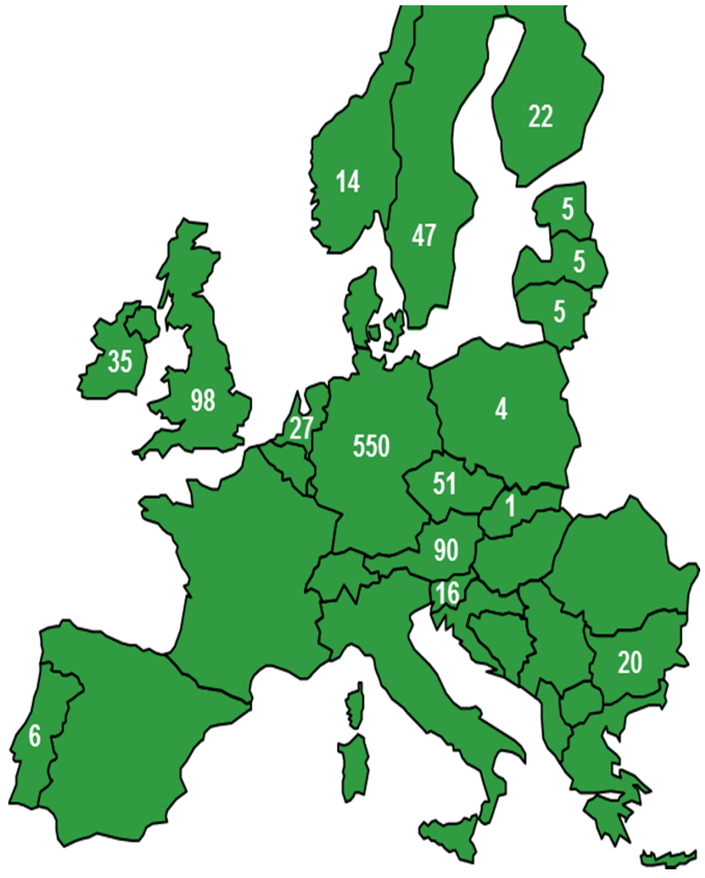
- 33 patients (92%) had normal intraoperative haemostasis (as judged by the physician)
- 2 mildly abnormal
- 1 moderately abnormal

Adapted from: Pollack et al. N Engl J Med 2015

Idarucizumab is now approved

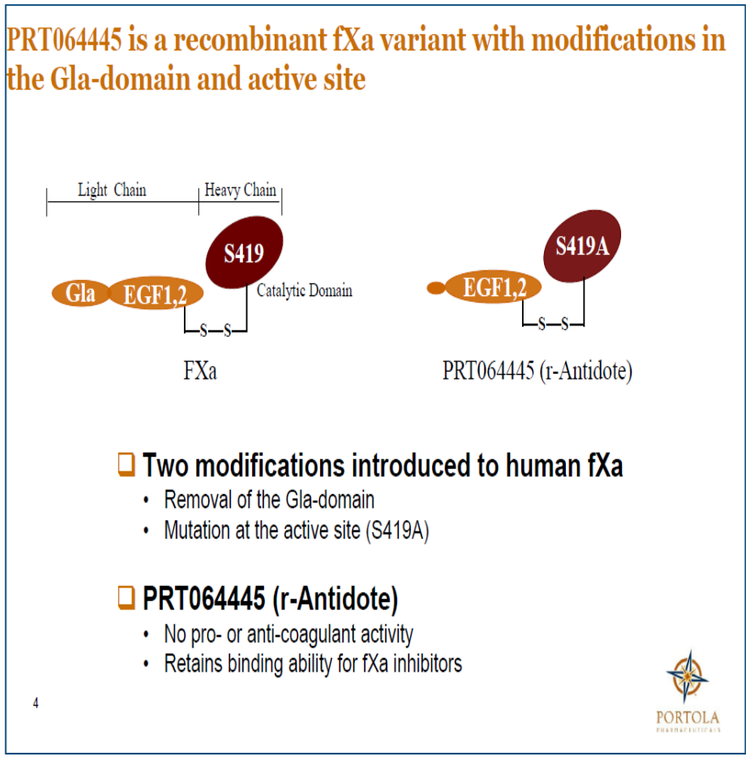


Praxbind® availability in Europe



- Numbers of hospitals where Praxbind® is commerically available
- Additional availability via early access schemes in certain countries (e.g. in ~200 hospitals in France)
- Continued availability at RE-VERSE AD™ centres

Reversal: Andexanet alfa



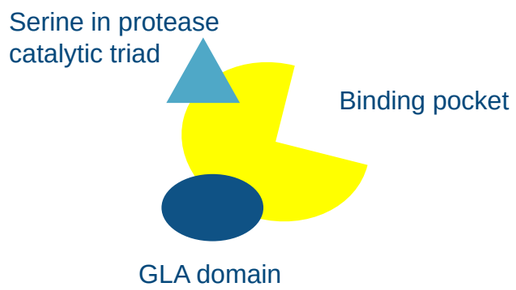
• Andexanat alfa (PRT4445) è un fattore Xa ricombinante che ha la potenzialità di essere il primo antidoto universale per rendere reversibili gli effetti degli inibitori del fattore Xa.

•La molecola è simile al fattore Xa nativo, ma è stato modificato per limitarne l'attività biologica, come la capacità di scindere la trombina.

•Agisce come un finto fattore Xa che lega e sequestra direttamente gli inibitori del fattore Xa nel sangue. Una volta legati ad andexanet alfa, questi farmaci non sono più in grado di legare e inibire il fattore Xa nativo, che può partecipare nuovamente al processo di coagulazione e restaurare l'emostasi.

Andexanet alfa (PRT064445) – universal Factor Xa inhibitor reversal agent

Normal Factor Xa molecule



PRT064445

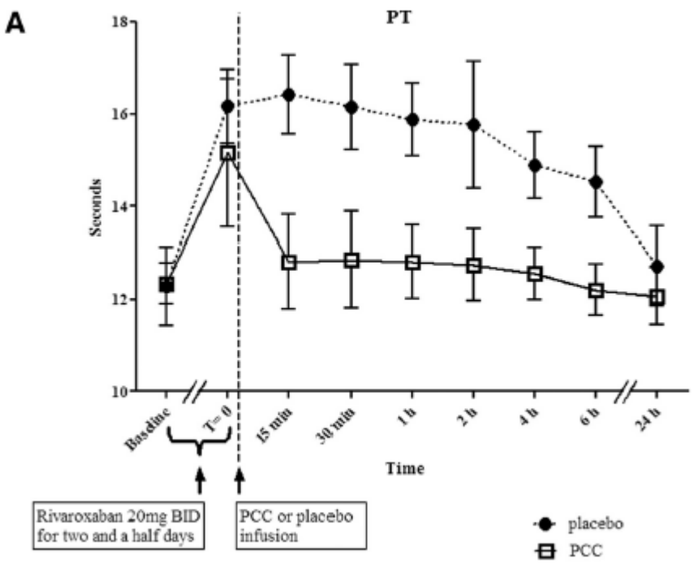
- Andexanet alfa reduces the non-protein-bound free fraction of the Factor Xa inhibitor ⇨ anticoagulant effect caused by a direct Factor Xa inhibitor is rapidly neutralized by administration of andexanet alfa
- Andexanet alfa is inactivated Factor Xa
  - Lower molecular weight owing to truncated chain
  - No GLA domain
  - Mutated serine
  - Active binding site to Factor Xa substrates
- The molecule has no catalytic activity and does not bind to the protaminase complex
- Intact binding site allows binding to:
  - Direct Factor Xa inhibitors, e.g. rivaroxaban
  - ATIII activated by LMWH or fondaparinux

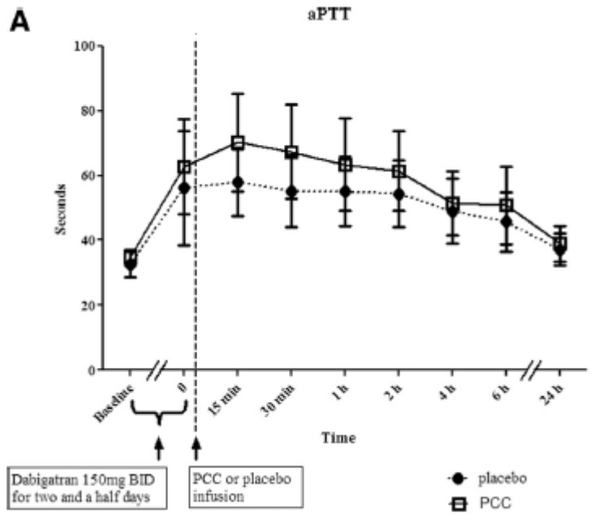
Lu *et al*, 2013

Ciraparantag

- PER977 is under development by Perosphere[1]
  - Potential for universal reversal agent (unfractionated heparin, LMWH, fondaparinux, and Factor Xa and IIa inhibitors)
  - Synthetic small molecule that binds competitively to the anticoagulant
- *In vitro* in animal models and *ex vivo* in human blood: PER977 successfully reversed anticoagulant activity for various anticoagulants[1]
- Phase I clinical trial initially testing the ability of PER977 to reverse the anticoagulant activity of edoxaban has been completed[2]

Dato particolarmente significativo per rivaroxan con netta riduzione del tempo di trombina



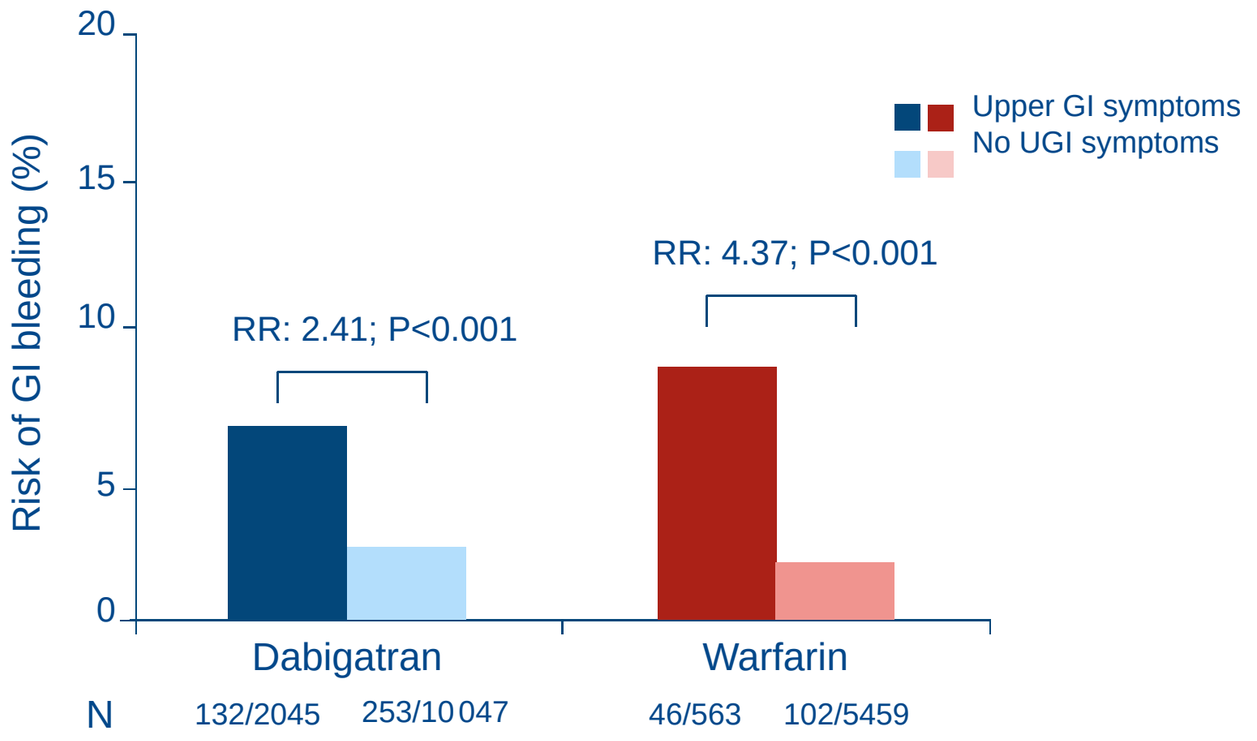


Lo studio non ha mostrato efficacia nei pazienti in trattamento con dabigatran

Circulation. 2011;124:1573-1579.

Practical guidance for reducing the risk of bleeding in anticoagulated patients

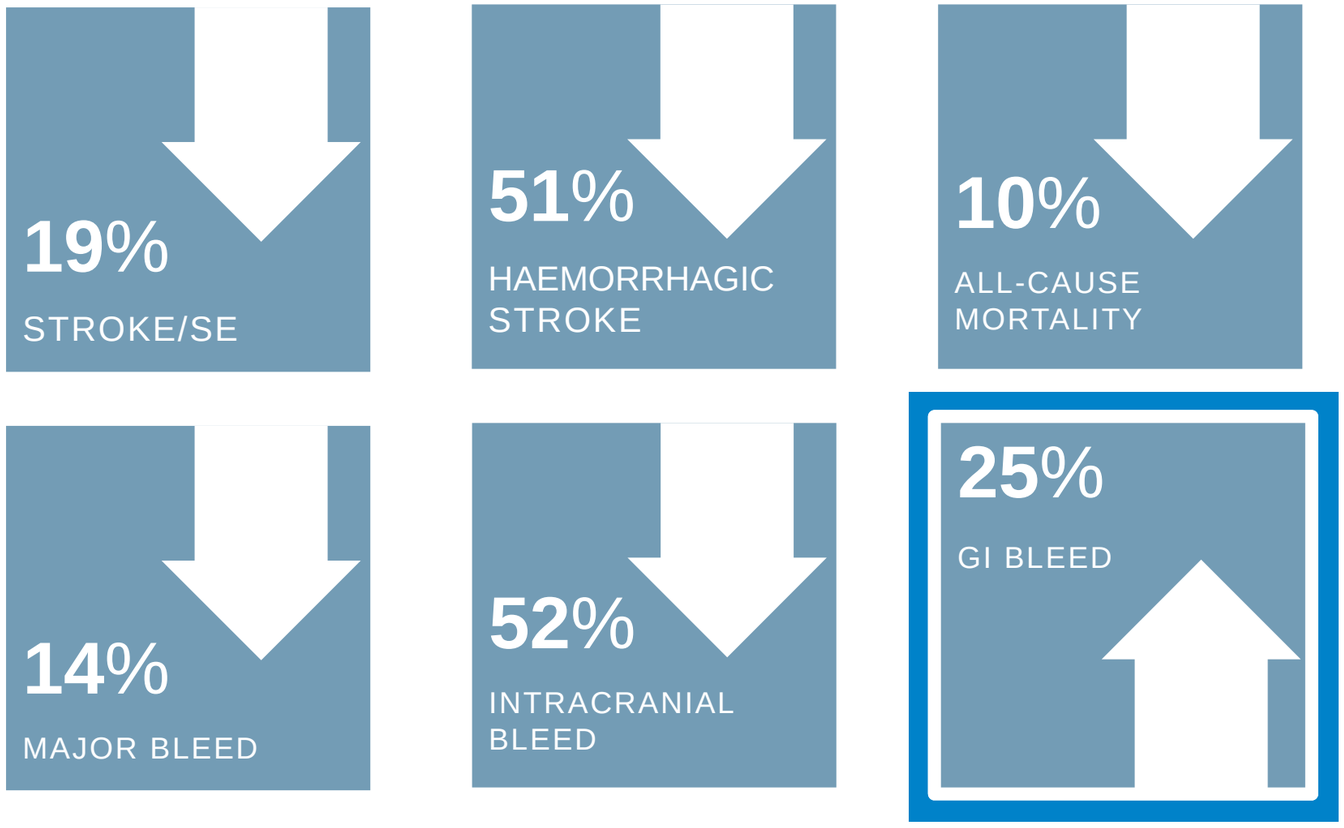
Patients with upper GI symptoms do have an increased risk of GI bleeding vs those without GI symptoms



Upper GI symptoms associated with a 2× increased risk of major GI bleeding with dabigatran and a 4× increased risk with warfarin

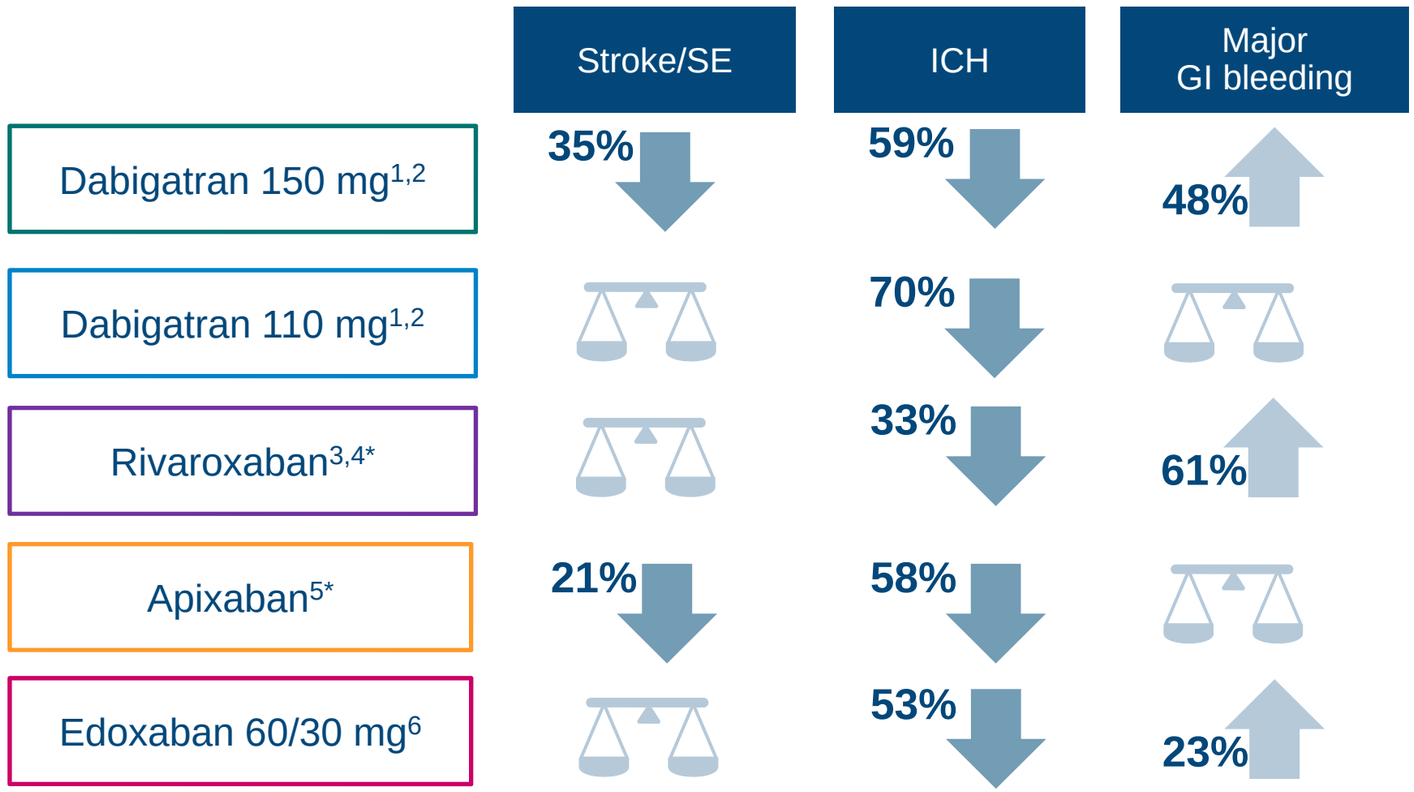
Bytzer et al. Clin Gastroenterol Hepatol 2013

When assessing GI bleeding risk, it is imperative to consider the context of improved outcomes with NOACs vs warfarin



Meta-analysis of data from RE-LY®, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48; Ruff et al. Lancet 2014

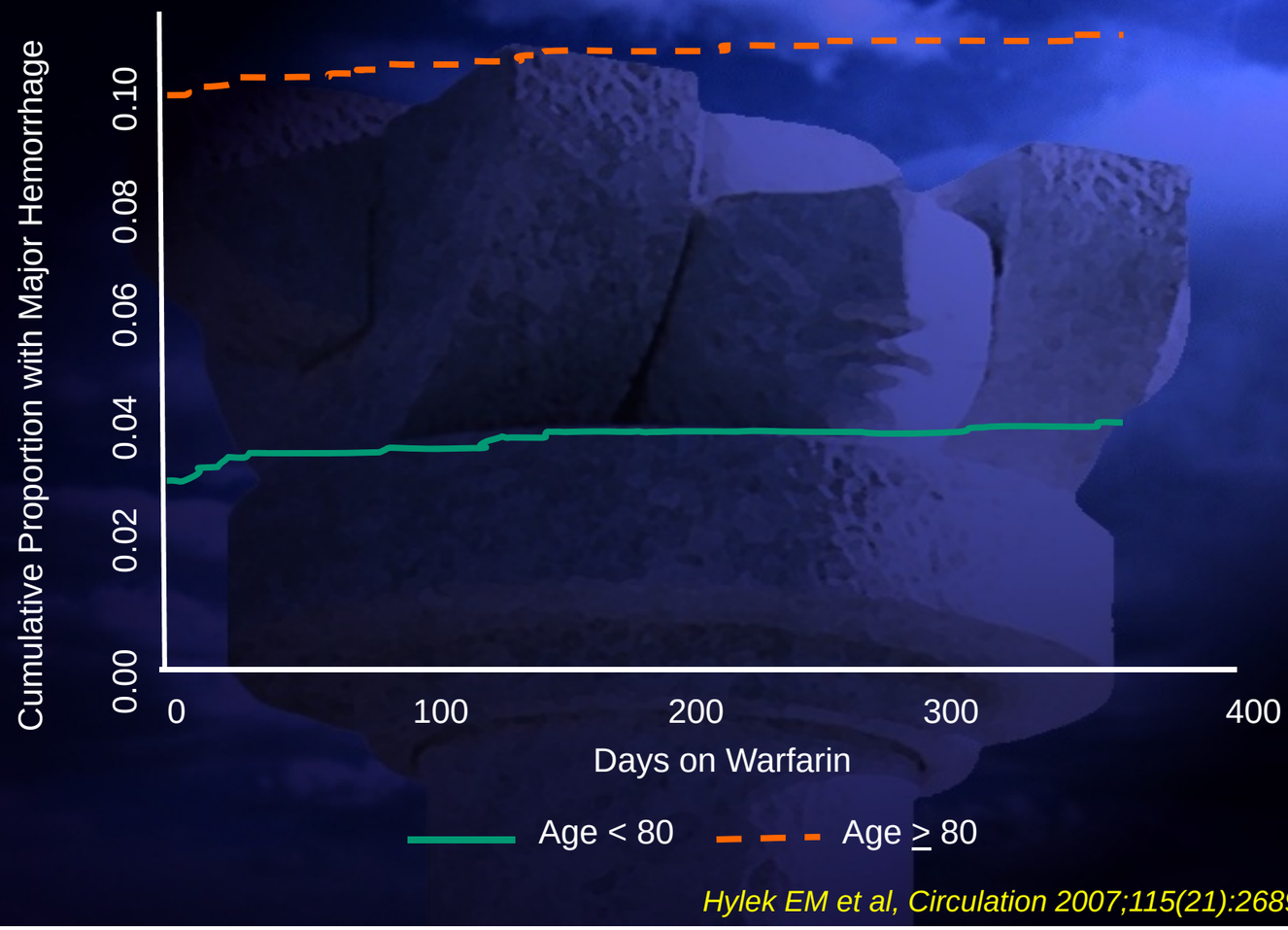
Overall, it is important to balance GI bleeding risk against reduction in stroke and ICH risk with NOACs vs warfarin



*Reduced dose regimen specified for certain populations

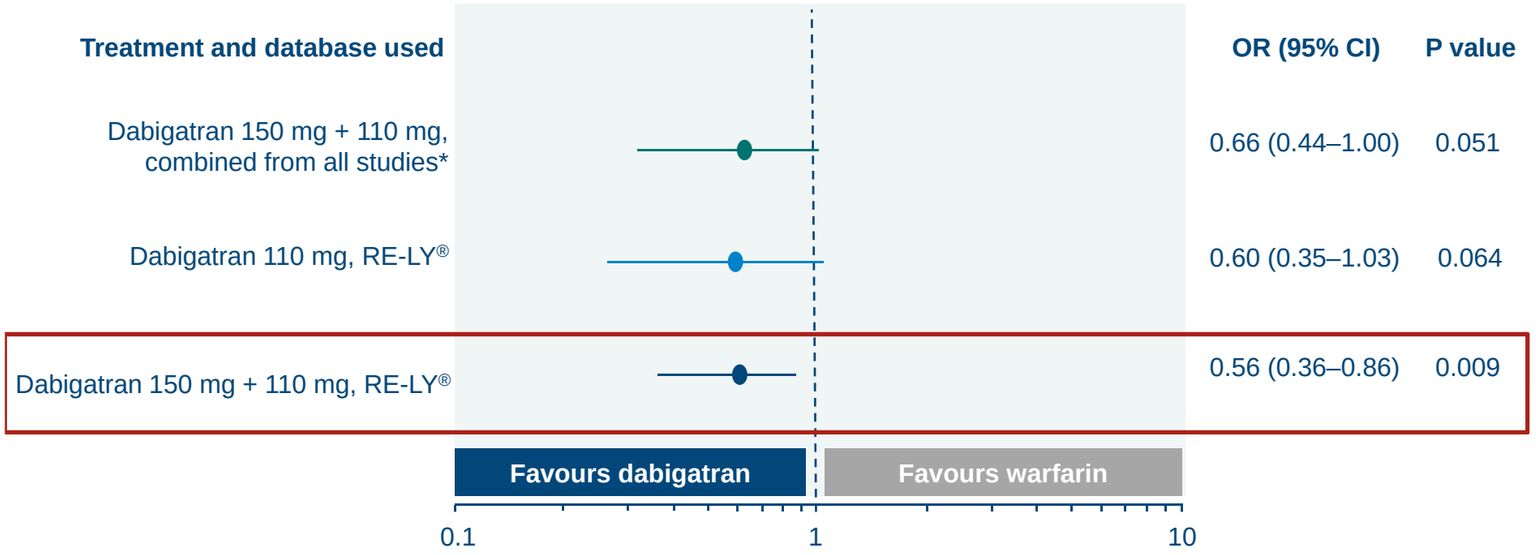
1. Connolly et al. N Engl J Med 2014; **2.** Connolly et al. N Engl J Med 2010; **3.** Patel et al. N Engl J Med 2011; **4.** Nessel et al. Chest 2012; **5.** Granger et al. N Engl J Med 2011; **6.** Giugliano et al. N Engl J Med 2013

Cumulative Incidence of Major Bleeding in the First Year Among Patients Newly Starting Warfarin by Age



Hylek EM et al, Circulation 2007;115(21):2689-2696.

Dabigatran is associated with improved mortality outcomes during 30 days after major bleeds vs warfarin



This was in the **absence** of a specific reversal agent

*Combined data from dabigatran 150 mg and 110 mg BID treatment groups in RE-LY®, RE-COVER™, RE-COVER™ II, RE-MEDY™, and RE-SONATE™. Only first major bleed included; analysis not adjusted for covariates
Majeed et al. Circulation 2013

Practical guidance for patients undergoing surgery and options to manage emergency bleeding

Beneficial pharmacological profile of NOACs compared with warfarin may facilitate perioperative management

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Time to peak, hrs	<4	2	2–4	3–4	1–2
Terminal half-life	~1 week	12–14 hrs	11–13 hrs	~12 hrs	10–14 hrs
Renal excretion, %	<1	85	~33	27	50

Pradaxa®: EU SPC, 2015; Xarelto: EU SPC, 2015; Eliquis: EU SPC, 2014; Warfarin sodium: EU SPC, 2014; Lixiana: EU SPC, 2015

Guidance on perioperative management of NOACs is available

CrCl, mL/min	Dabigatran		Apixaban, edoxaban, rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 hrs after last intake)			
	Low risk	High risk	Low risk	High risk
≥80	≥24 hrs	≥48 hrs	≥24 hrs	≥48 hrs
50–80	≥36 hrs	≥72 hrs	≥24 hrs	≥48 hrs
30–50	≥48 hrs	≥96 hrs	≥24 hrs	≥48 hrs
18–30	Not indicated	Not indicated	≥36 hrs	≥48 hrs
<15	No official indication for use			

CrCl, creatinine clearance
Heidbuchel et al. Europace 2015

Perioperative bridging sub-analysis of RE-LY®

Warfarin	1424 patients; treatment interruption for elective surgery/procedure Heparin bridging vs no bridging • **Increased major bleeding** **6.8% vs 1.6% (P<0.001)** • **Any thromboembolism** **1.8% vs 0.3% (P=0.007)**
Dabigatran	2709 patients; treatment interruption for elective surgery/procedure Heparin bridging vs no bridging • **Increased major bleeding** **6.5% vs 1.8% (P<0.001)** • **Any thromboembolism** **1.2% vs 0.6% (P=0.16)**

Douketis et al. Thromb Haemost 2015

Bridging anticoagulation associated with higher risk of bleeding and adverse events in ORBIT-AF

7372 patients with AF treated with OAC

- 2803 interruptions (in 2200 patients; 30%)

Bridging used in 665 interruptions (24%)

Unadjusted, % (n)	No bridging (N=1724) †	Bridging (N=503)†	P value
Bleeding events*	1.3 (22)	5.0 (25)	<0.0001

*Bleeding events = major bleeding or bleeding hospitalization

†Excluding interruptions, missing date, or those that occurred within 30 days of a previous interruption

Steinberg et al. Circulation 2015

“Bridging with LMWH or heparin, as was proposed in AF patients with higher thrombo-embolic risk treated with VKAs, **is not necessary in NOAC-treated patients**”

Heidbuchel et al. Europace 2015

Assessment of renal function and coagulation tests can support decision-making for all NOACs

Renal function assessment	Coagulation tests
Estimate time of elimination	Determine if OAC is present and may be contributing to bleeding
Renal impairment may reduce capacity of elimination of NOAC	Timing and NOAC dose influence coagulation tests

Pradaxa®: EU SPC, 2015; Huisman et al. Thromb Haemost 2012; Heidbuchel et al. Europace 2015

Standard assays can be used to determine anticoagulation status in patients treated with dabigatran

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
aPTT	✓	✗	✗	✗
TT	✓	✗	✗	✗
dTT, ECT	✓	✗	✗	✗
Anti-FXa assays	✗	✓	✓	✓
PT	✗	✓	✗	✗
INR	✗	✗	✗	✗

Time of last NOAC dose should always be considered when interpreting test results
Green = quantitative; orange = qualitative only; red = not applicable
FXa, activated Factor X
Adapted from: Heidbuchel et al. Europace 2015; Pradaxa®: EU SPC, 2015; Xarelto: EU SPC, 2015; Eliquis: EU SPC, 2015; Lixiana: EU SPC, 2015

Practical guidance for treatment of anticoagulated patients experiencing bleeding

Bleeding management strategies for NOACs are similar to those for VKAs

Apply same measures as for patients treated with VKAs
(apart from Vitamin K)

Discontinue NOAC and investigate the source of bleeding
Consider oral charcoal administration if NOAC ingested <2 hours earlier*

Maintain adequate diuresis
Before initiation of standard treatments

This information is not intended and must not be considered as a specific recommendation from Boehringer Ingelheim
Each treating physician should determine what medical treatment and/or bleeding management measures should be taken on a case by case basis, based on his/her medical experience and judgment

*Statement based only on limited clinical data

Heidbuchel et al. Europace 2015; Pradaxa®: EU SPC, 2015

GI bleeding and NOAC reversal

Most GI bleeds will NOT require administration of a specific reversal agent

But…GI bleeding and/or the need for emergency GI surgery will be the most common indication for administration of a specific reversal agent (30–50%)

Pollack et al. New Engl J Med 2015

Management of GI bleeding depends on severity

Occult GI bleeding	Endoscopy within 1–2 weeks Continue NOAC
Clinically overt GI bleeding	Withhold NOAC Initiate standard resuscitation measures and coagulation tests Endoscopy after 24 hours
Rapid GI bleeding or clinically unstable patient	Emergency endoscopy Thermal, mechanical, injection, arteriographic, or surgical intervention Pro-coagulant factors Idarucizumab for dabigatran-treated patients

Desai et al. Thromb Haemost 2013; Heidbuchel et al. Europace 2015

Bleeding while using a NOAC

- Inquire about last NOAC intake
- Blood sample to determine CrCl, haemoglobin, white blood cells
- Inquire with lab about possibility of rapid coagulation assessment

Mild bleeding

- Delay or discontinue next dose
- Reconsider concomitant medication

Moderate/severe bleeding

Supportive measures

- Mechanical compression
- Endoscopic haemostasis if GI bleed
- Surgical haemostasis
- Fluid replacement (colloids if needed)
- RBC transfusion if needed
- FFP (as plasma expander)
- Platelet transfusion (if platelet count ≤60×10^9/L)

For dabigatran-treated patients

- **Idarucizumab 5 g IV (when available)**
- *Maintain adequate diuresis*
- *Consider haemodialysis*

Life-threatening bleeding

For dabigatran-treated patients

- **Idarucizumab 5 g IV (when available)**

For all NOACs, consider:

- PCC 50 U/kg + 25 U/kg if indicated
- aPCC 50 U/kg; max 200 U/kg/day
- rFVIIa 90 µg/kg

FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; RBC, red blood cell; rFVIIa, activated Factor VII; Figure adapted from Heidbuchel et al. Europace 2015

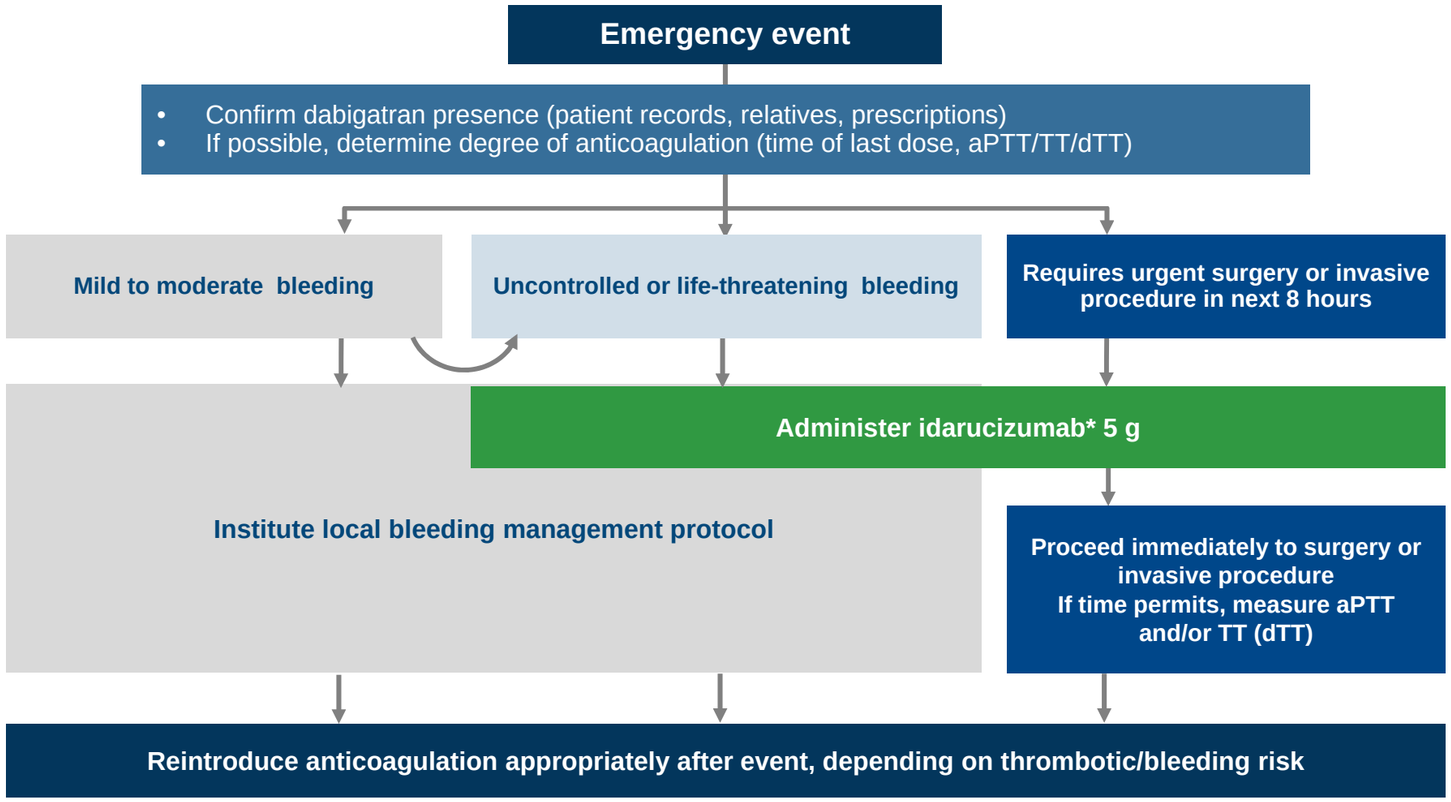
Bleeding and NOAC reversal

Factors favouring the use of reversal agent

- Moderate or severe, on-going haemorrhage
- High likelihood of on-going anticoagulant effect
  - Last NOAC dose < 12 hours
  - Impaired NOAC clearance
  - Laboratory evidence of on-going anticoagulant effect
- Emergency endoscopic or surgical therapy planned

Heidbuchel et al. Europace 2015

Proposed algorithm for management of dabigatran-treated patients with bleeding or requiring urgent surgery



Idarucizumab is not approved in all countries. Please check your local prescribing information for details. This information is presented for medical education purposes only. *Administer two 50 mL vials of idarucizumab (each containing 2.5 g) intravenously. In rare cases where dabigatran anticoagulation remains present after idarucizumab and bleeding continues in the patient, a second 5 g dose of idarucizumab may be considered. Figure adapted from Eikelboom et al. Circulation 2015

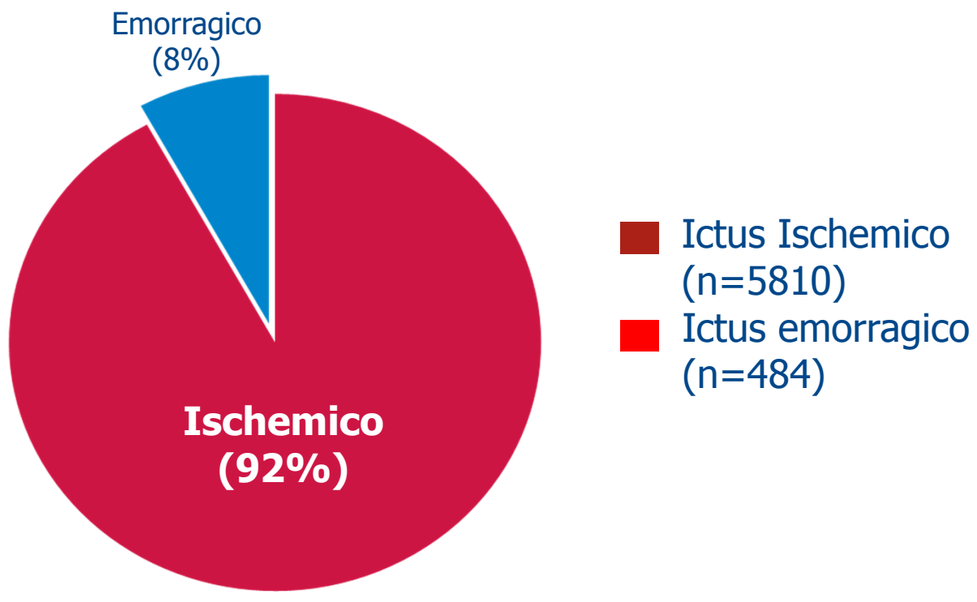
NOAC management: What to do after a GI bleed

- Too often the NOAC is NOT resumed after a GI bleed is controlled
- In order to minimize risk of thrombosis, NOAC should be resumed once secure haemostasis has been obtained

Sengupta et al. Am J Gastroenterol 2015

NOAC management: What to do after a GI bleed

- Too often the NOAC is NOT resumed after a GI bleed is controlled
- In order to minimize risk of thrombosis, NOAC should be resumed once secure haemostasis has been obtained



NOAC management: What is still to do

Italia, dati 2015:

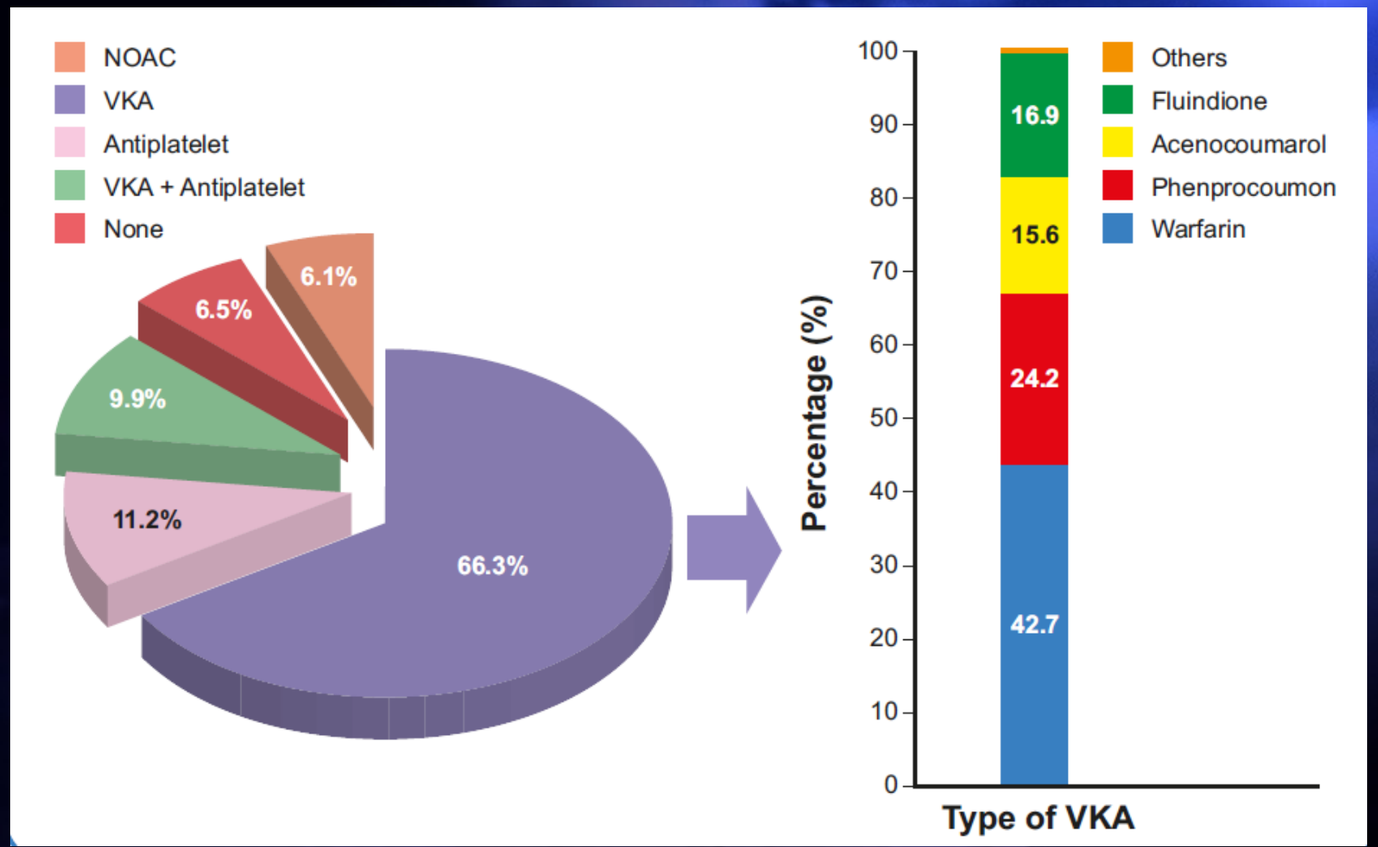
Il 37% dei pazienti con FA permanente è in trattamento cronico con ASA.

Il 17% non riceve alcuna terapia antiaggregante o anticoagulante.

Il 54% dei pz è trattato impropriamente sia sotto l'aspetto scientifico che <u>medico-legale</u>!


Grazie
“Quando penso ad una malattia, non è per trovarvi rimedio, ma, invece, per prevenirla”
L. Pasteur

EU: Treatment used for the prevention of thromboembolic events



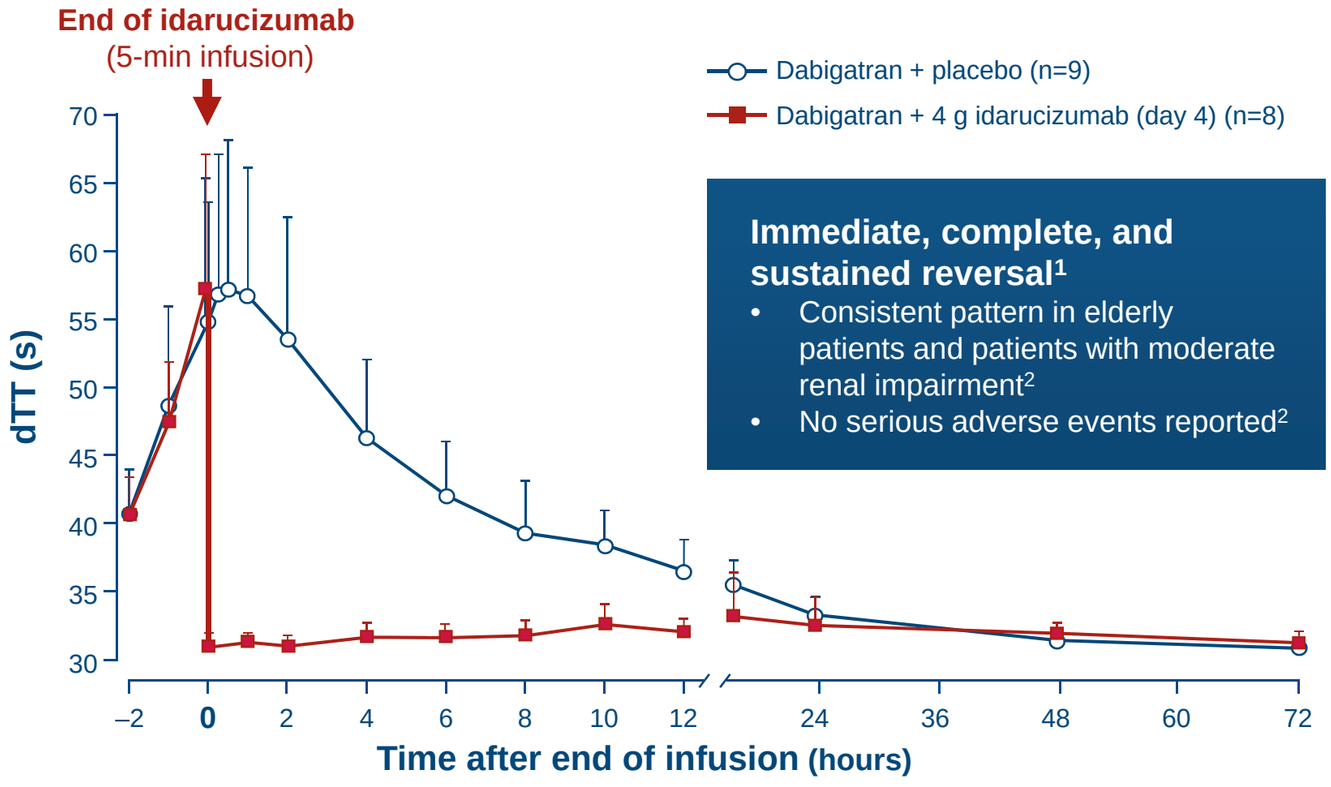
PREFER in AF registry: Presented at ESC Congress 2013 in Amsterdam

Summary: RE-VERSE AD™ is providing insights into innovation in anticoagulation care

1. **RE-VERSE AD™ showed that idarucizumab reverses the anticoagulant effects of dabigatran within minutes**

2. **A rapid onset of action and short half-life support its use in emergency situationsA rapid onset of action and short half-life support its use in emergency situations**

3. **Idarucizumab will add a specific treatment option for patients on dabigatran requiring emergency management**

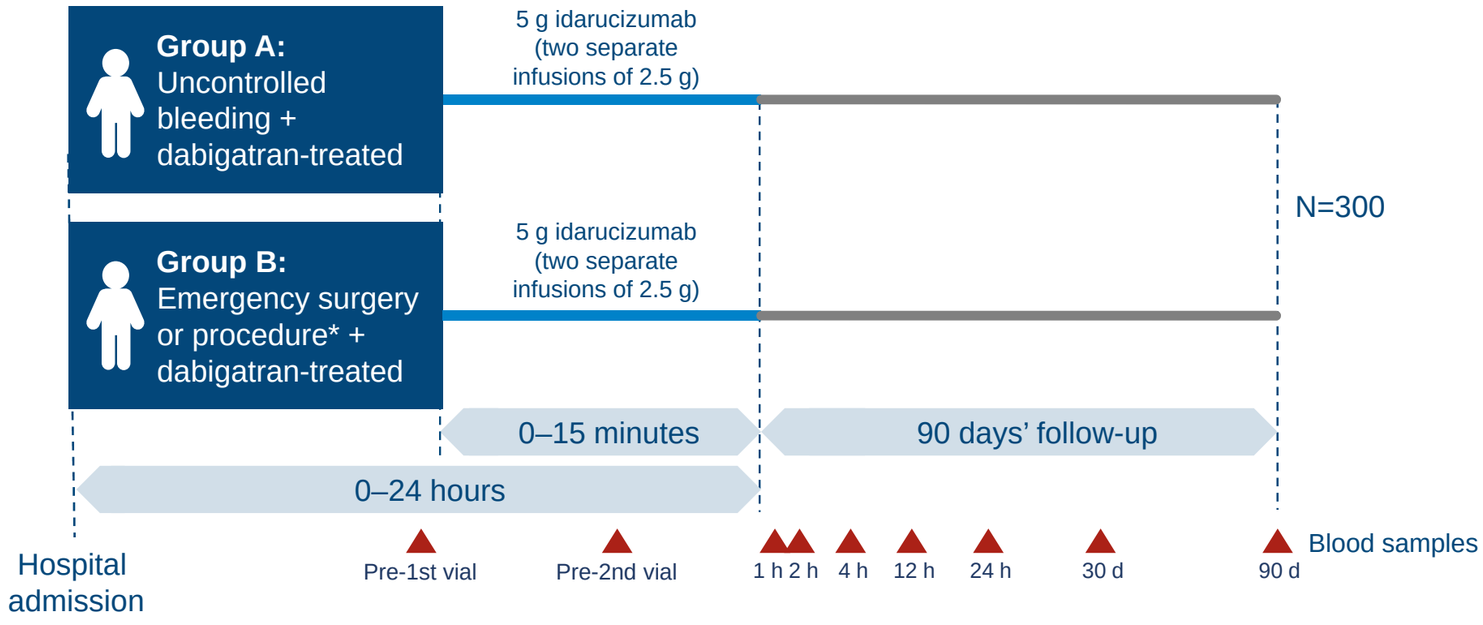


Immediate, complete, and sustained reversal[1]

- Consistent pattern in elderly patients and patients with moderate renal impairment[2]
- No serious adverse events reported[2]

Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

1. Glund et al. Lancet 2015; **2.** Glund et al. abstr. 344; presented at ASH 2014

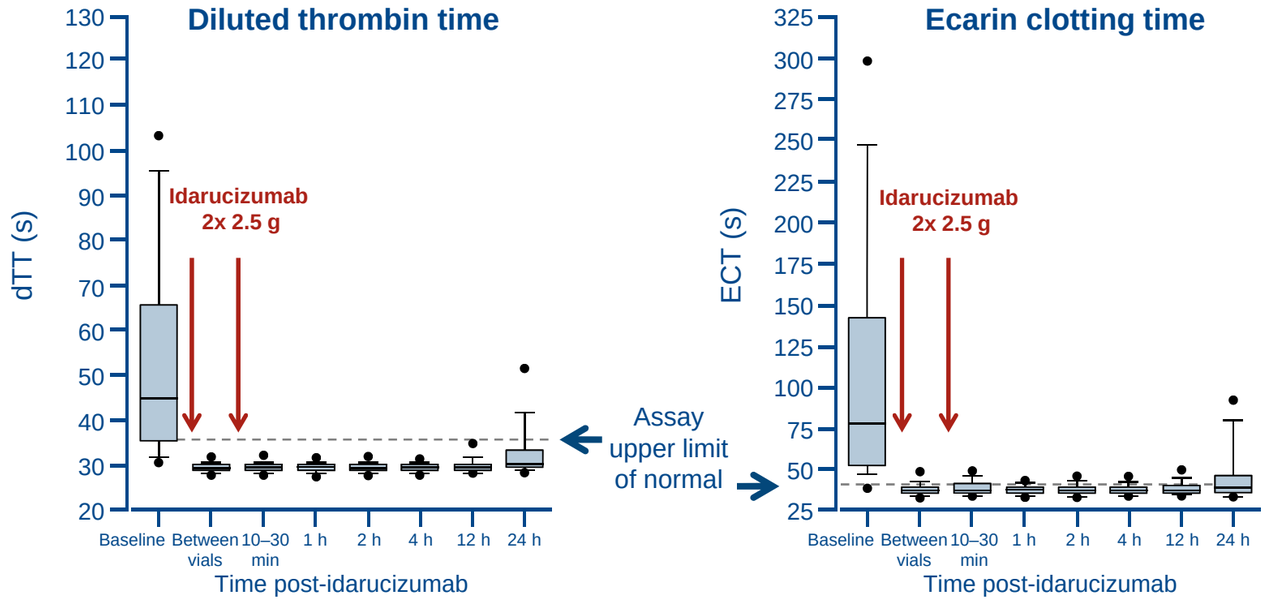


Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

*Other than bleeding

Pollack et al. Thromb Haemost 2015

Patients with uncontrolled bleeding



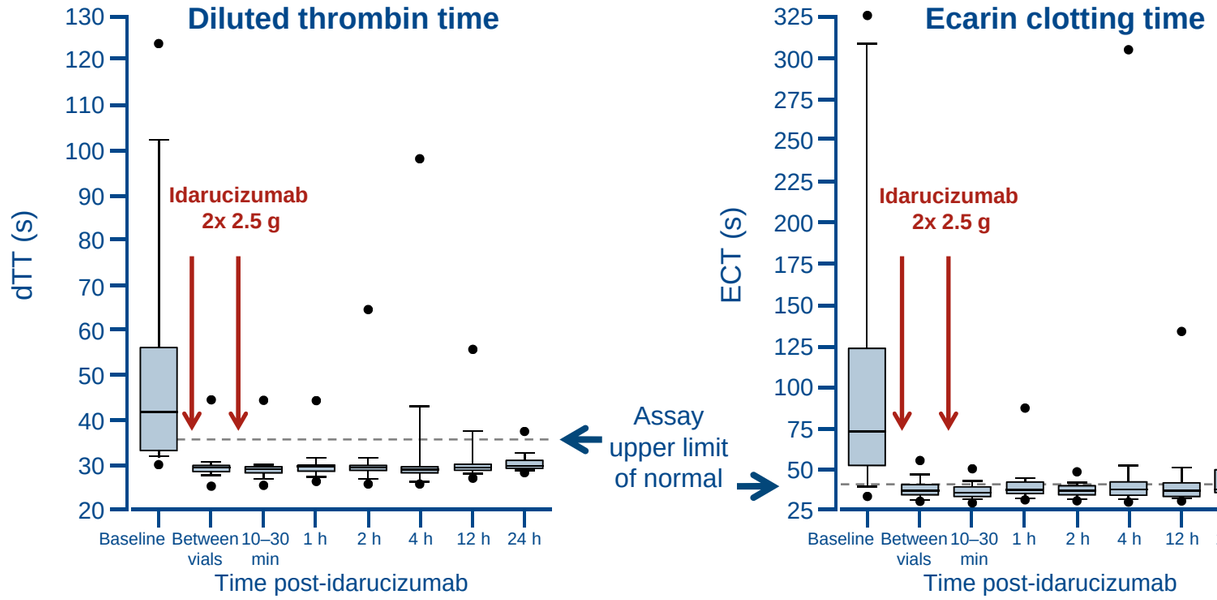
Median maximum reversal within 4 hours was 100% (95% CI: 100–100)

dTT normalized in 98% and ECT in 89% of patients with elevated values at baseline*

Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

*Calculated in 40/51 for dTT and 47/51 for ECT. Pollack et al. N Engl J Med 2015

Patients undergoing emergency procedures

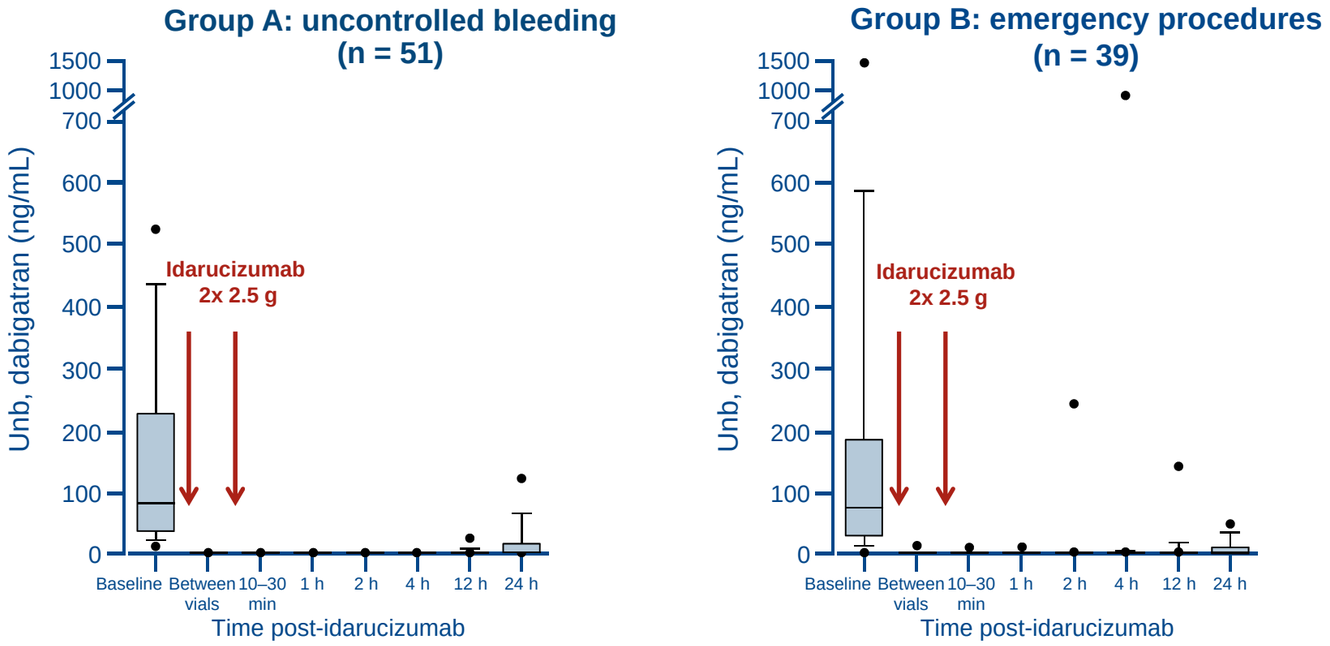


Median maximum reversal within 4 hours was 100% (95% CI: 100–100)

dTT normalized in 93% and ECT in 88% of patients with elevated values at baseline*

Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

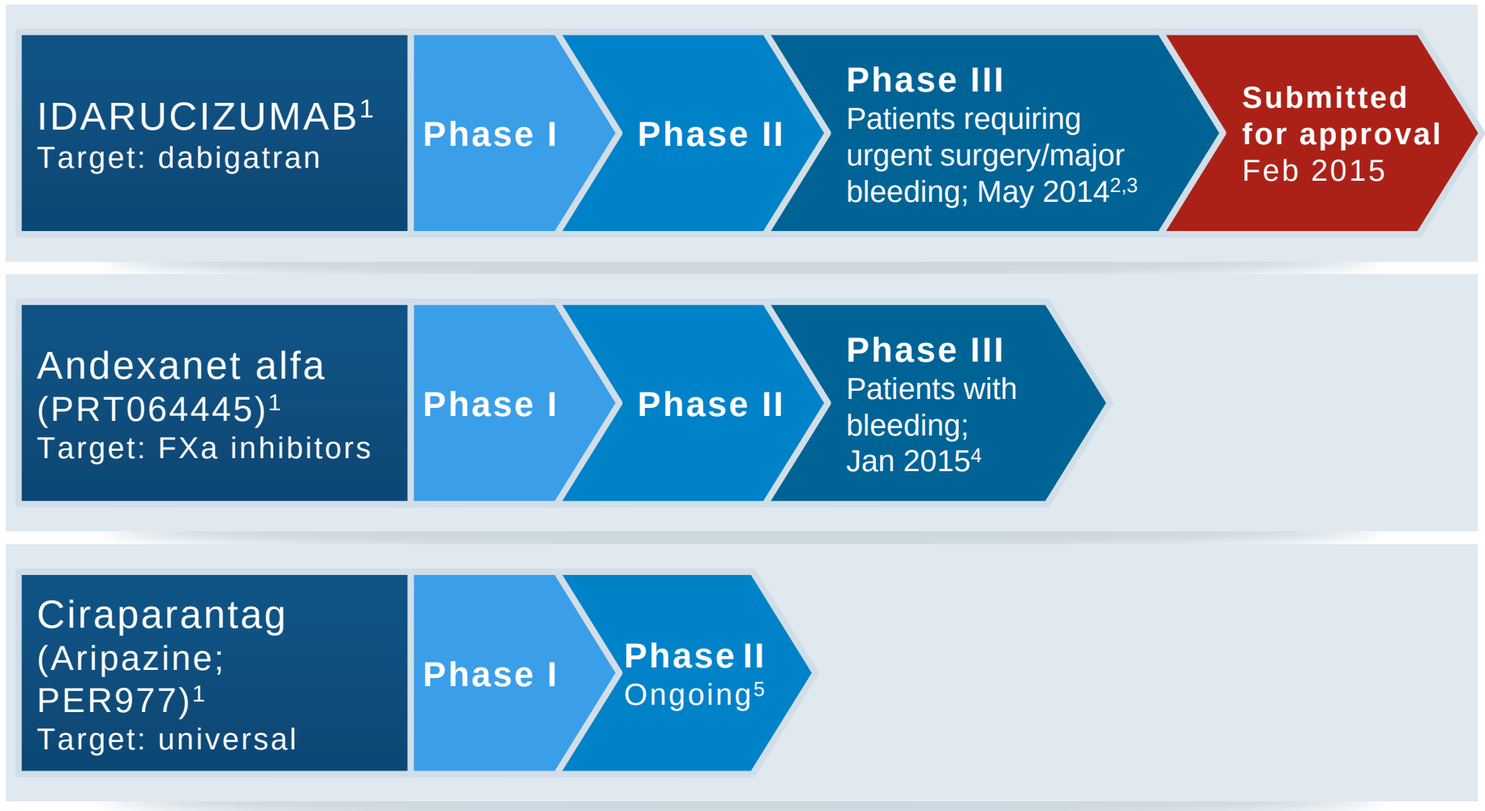
*Calculated in 28/39 for dTT and 34/39 for ECT. Pollack et al. N Engl J Med 2015



Dabigatran levels were <20 ng/mL* in 89/90 patients after infusion of first vial, in 77/83 at 12 hours and 62/78 patients at 24 hours

Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

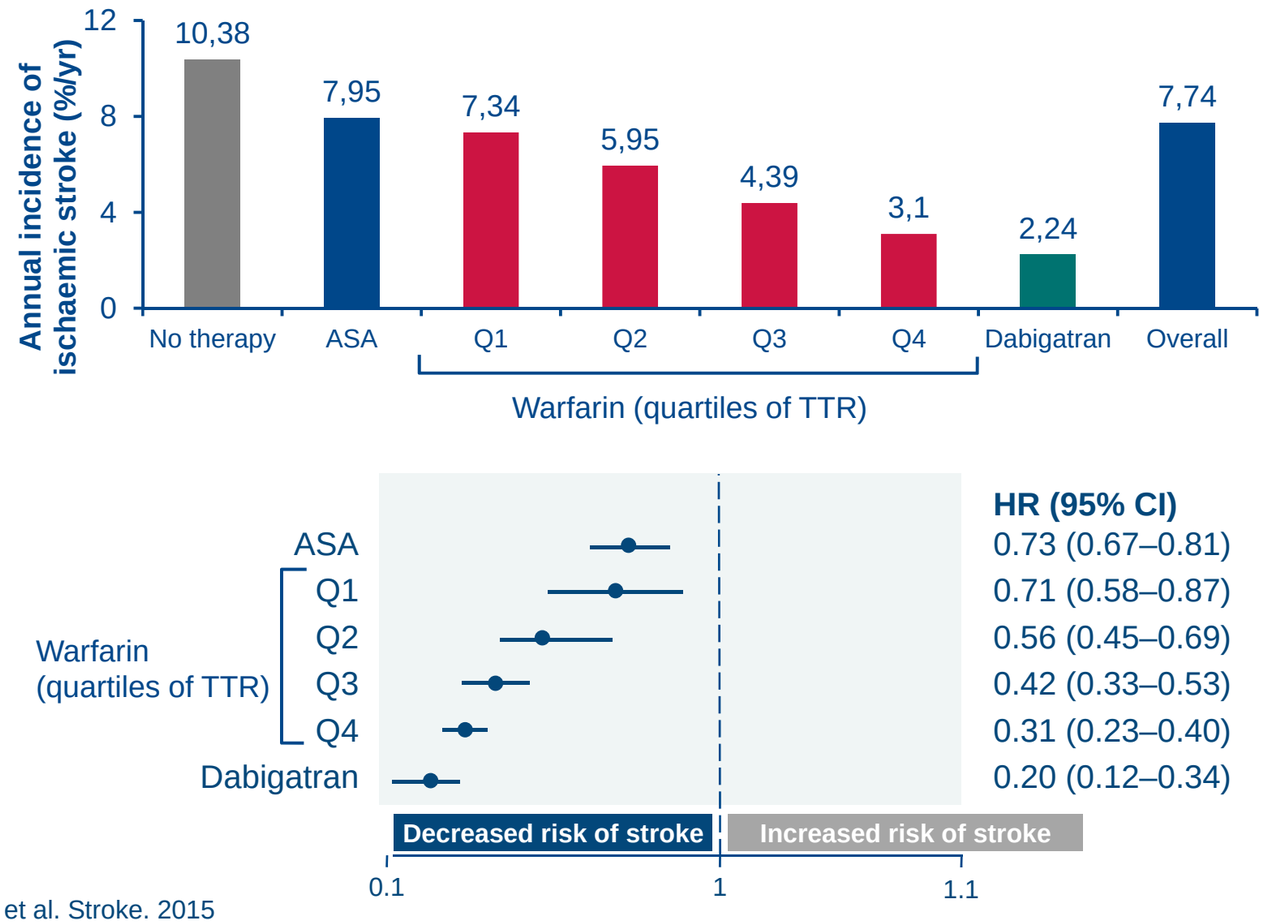
*A level that produces little or no anticoagulant effect. Pollack et al. N Engl J Med 2015



Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

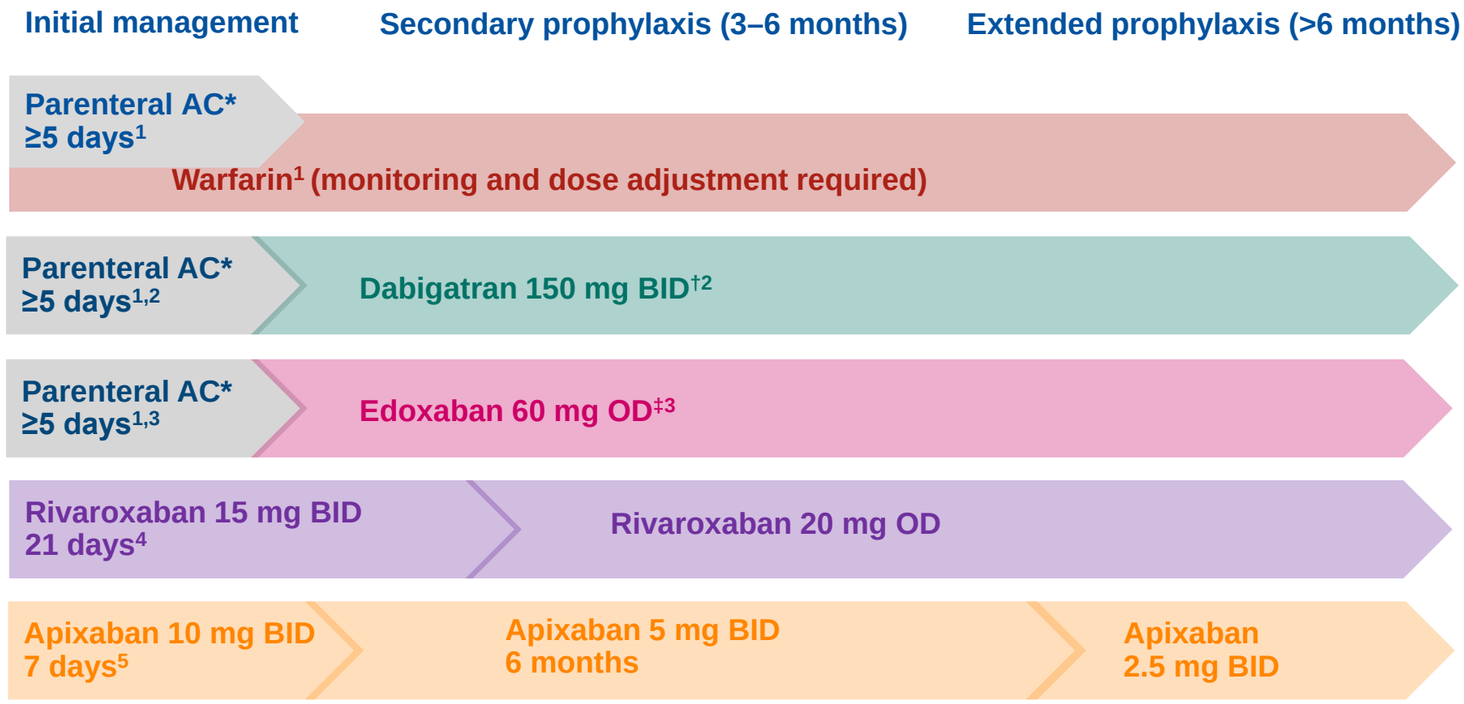
1. Adapted from Greinacher et al. Thromb Haemost 2015; **2.** Pollack et al. N Engl J Med 2015; **3.** Pollack et al. Thromb Haemost 2015; **4.** ClinicalTrials.gov Identifier: NCT02329327; **5.** ClinicalTrials.gov Identifier: NCT02207257

Dabigatran was associated with the lowest incidence of ischaemic stroke



Ho et al. Stroke. 2015

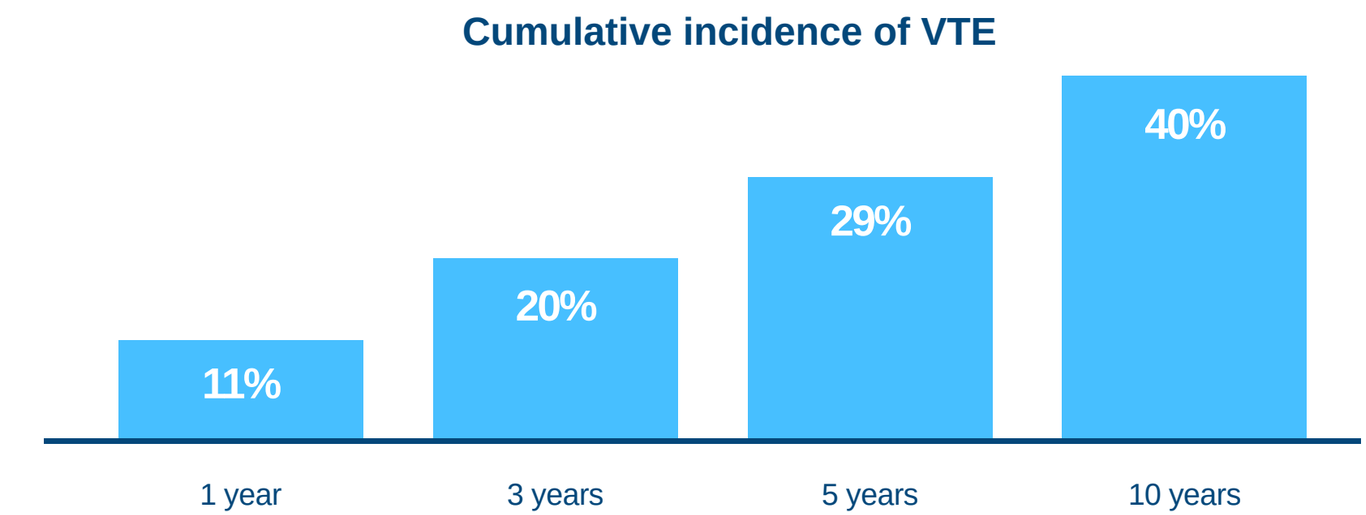
VTE requires acute and extended treatment for prevention of recurrence



*LMWH, fondaparinux, or UFH; †Dabigatran 110 mg BID for aged ≥80 years, concomitant verapamil, or based on individual assessment of thromboembolic/bleeding risk (110 mg BID is not approved in all countries); ‡Edoxaban 30 mg OD for CrCl 15–50 mL/min, weight ≤60 kg, certain concomitant P-glycoprotein inhibitors

1. Kearon et al. Chest 2012; **2.** Pradaxa® SPC, 2016; **3.** Lixiana SPC, 2016; **4.** Xarelto SPC, 2015; **5.** Eliquis SPC, 2016. Current versions available online at: http://www.medicines.org.uk/emc/

Patients remain at risk of recurrent VTE years after treatment for an initial event[1]*



For some patients with VTE, extended or indefinite anticoagulation is recommended[2,3]

*10-year follow-up of 1626 patients who discontinued anticoagulation after a first episode of clinically symptomatic proximal DVT and/or PE

1. Prandoni et al. Haematologica 2007; **2**. Kearon et al. Chest 2012; **3**. Konstantinides et al. Eur Heart J 2014

Subgroup analyses stratified by age and gender showed that risk of major gastrointestinal bleeding with dabigatran was increased for women age 75 years and older and for men age 85 years and older compared with warfarin (Table 3 and Supplemental Tables 4 and 5). Below these ages, gastrointestinal bleeding risk was comparable for both anticoagulants. The point estimate for the risk of death with dabigatran compared with warfarin was reduced in all strata except women age 85 years and older, where it was increased compared with lower aged women (P (interaction) = 0.004). There were no interactions for ischemic stroke or intracranial hemorrhage. Results in other subgroups defined by chronic kidney disease, use of prescription antiplatelet agents or SSRI antidepressants, or in patients hospitalized in the 30 days before starting anticoagulant use were similar to the main analysis.

DOI: 10.1161/CIRCULATIONAHA.114.012061

RE-LY® – Disegno dello studio

RELY®
Study of stroke prevention
in atrial fibrillation

Fibrillazione atriale
con ≥1 fattore di rischio
Assenza di controindicazioni

R

Dabigatran etexilato
150 mg bid
N=6.000

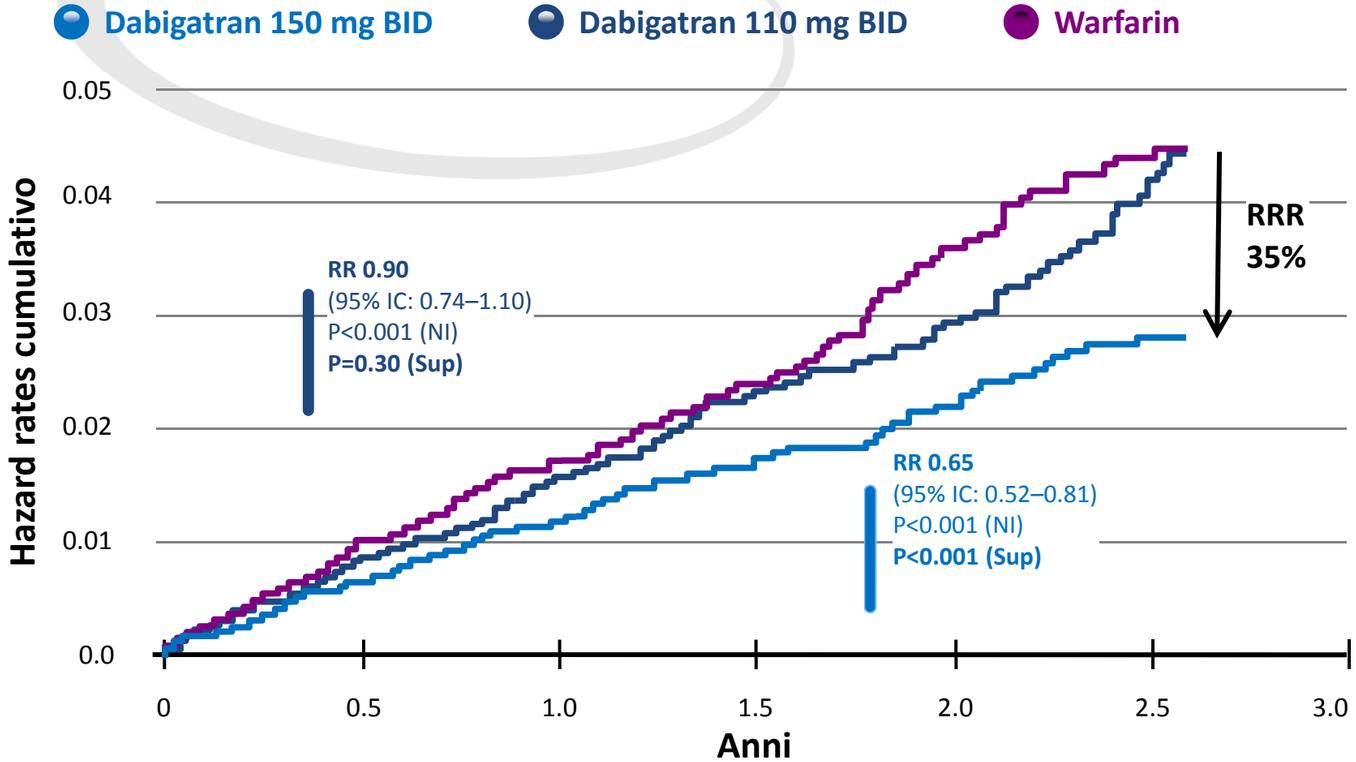
Dabigatran etexilato
110 mg bid
N=6.000

Warfarin
1 mg, 3 mg, 5 mg
(INR 2,0–3,0) N=6000

Obiettivo primario: stabilire la non-inferiorità di dabigatran etexilato vs warfarin;
(tutti gli ictus (ischemico + emorragico) e embolia sistemica)
Minimo 1 anno di follow-up, massimo 3 anni e in media 2 anni di follow-up

Ezekowitz MD, et al. *Am Heart J* 2009;157:805-810.
Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.

Tempo al primo ictus/ embolismo sistemico



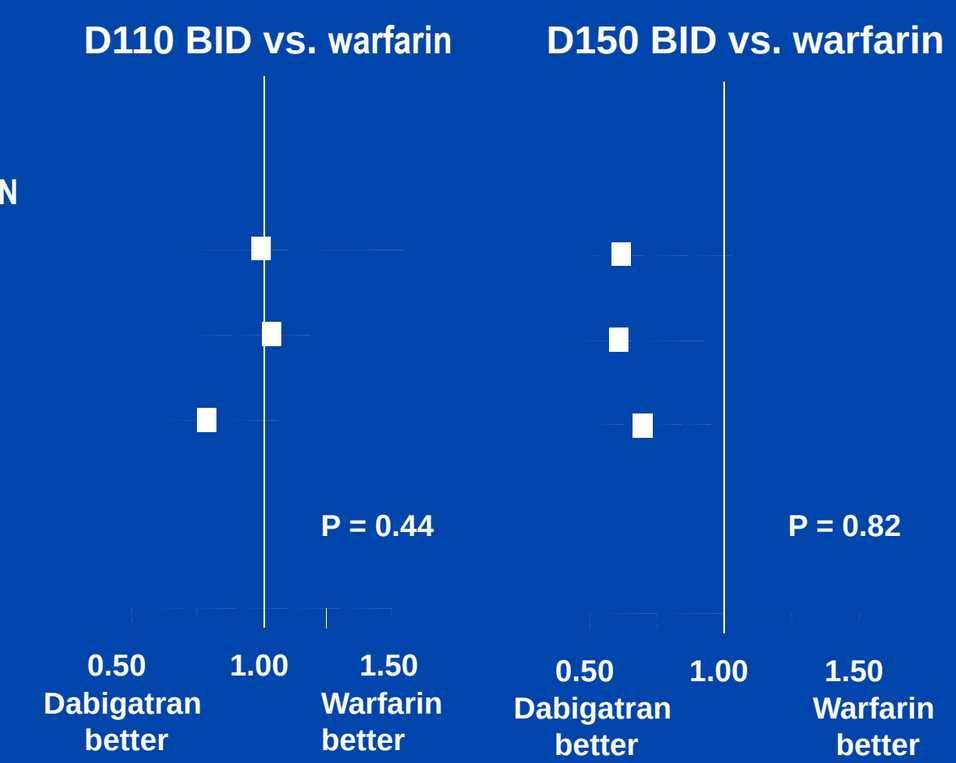
D = dabigatran; RR = rischio relativo; RRR = riduzione rischio relativo ; SSE= embolismo sistemico
Dabigatran etexilato è in sviluppo clinico e non è approvato per l'uso nella pratica clinica nella prevenzione dell'ictus nei pazienti con FA

Connolly SJ. *N Engl J Med* 2010;369(19):1876-5.

Stroke and systemic embolism (SE)

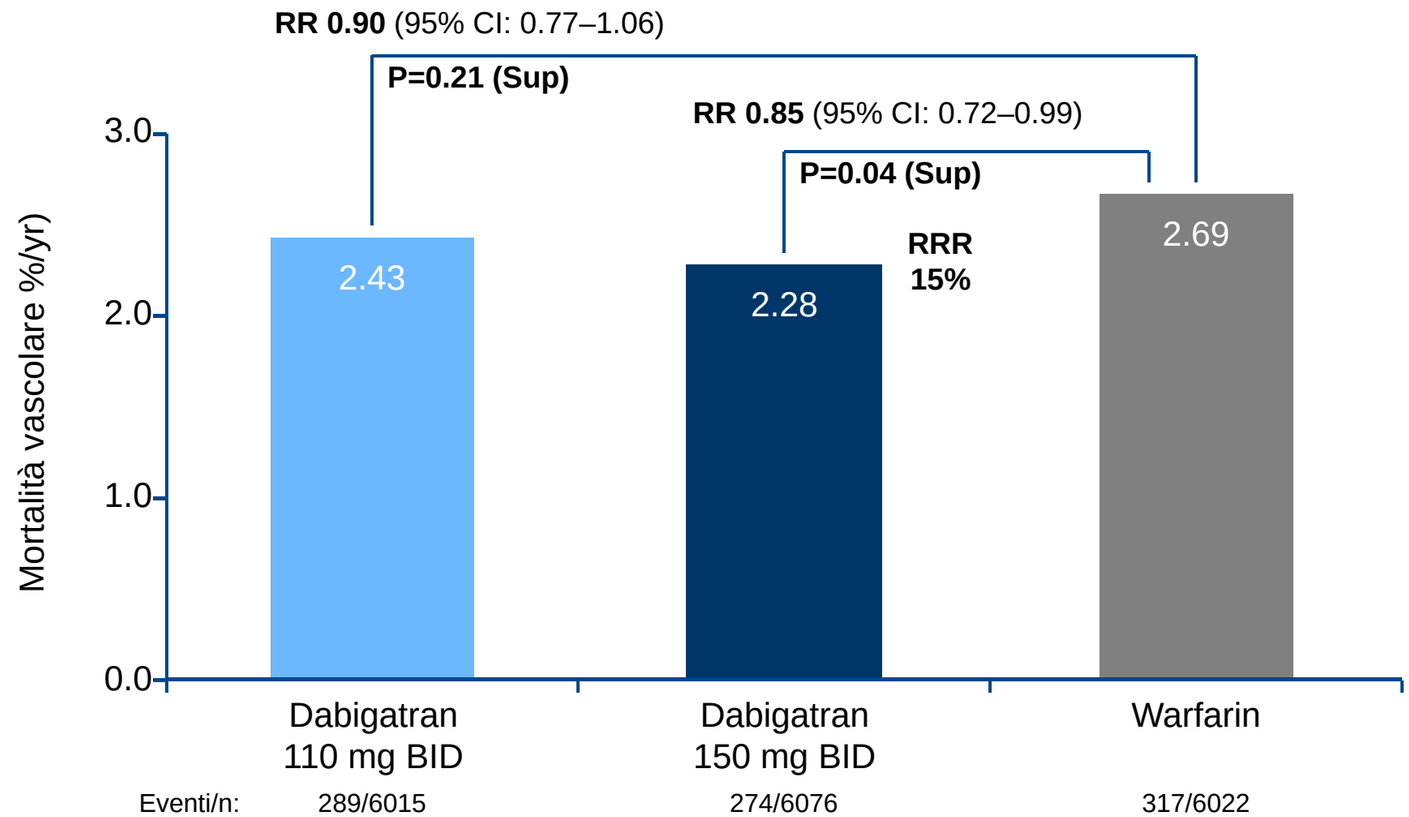
RELY®
Study of stroke prevention in atrial fibrillation

CHADS2	Annual rate, % D110	D150	WARFARIN
0-1	1.06	0.65	1.05
2	1.43	0.84	1.38
3-6	2.12	1.88	2.68



Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

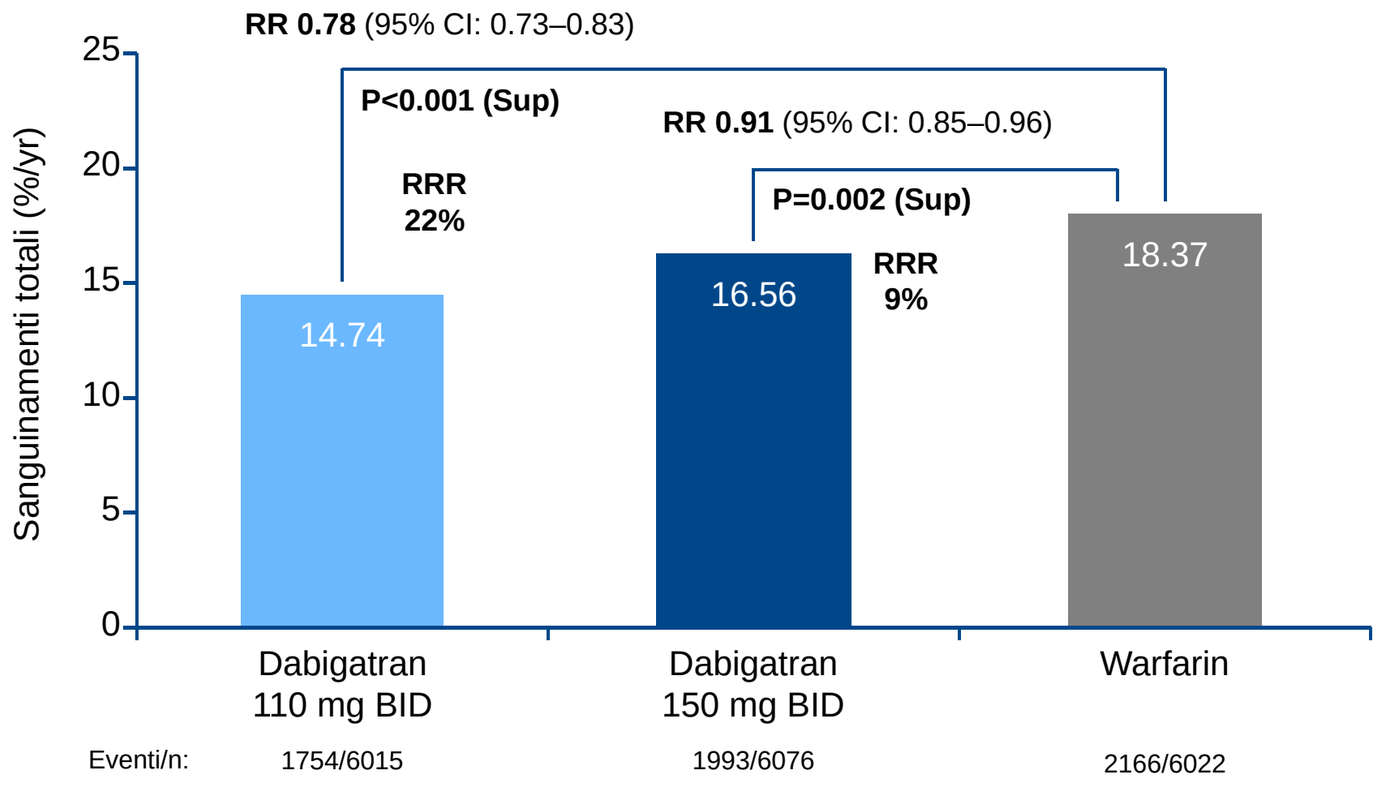
RE-LY®: mortalità per cause vascolari



BID = due volte al giorno; RR = rischio relativo; RRR = riduzione del rischio relativo; Sup = superiorità

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6

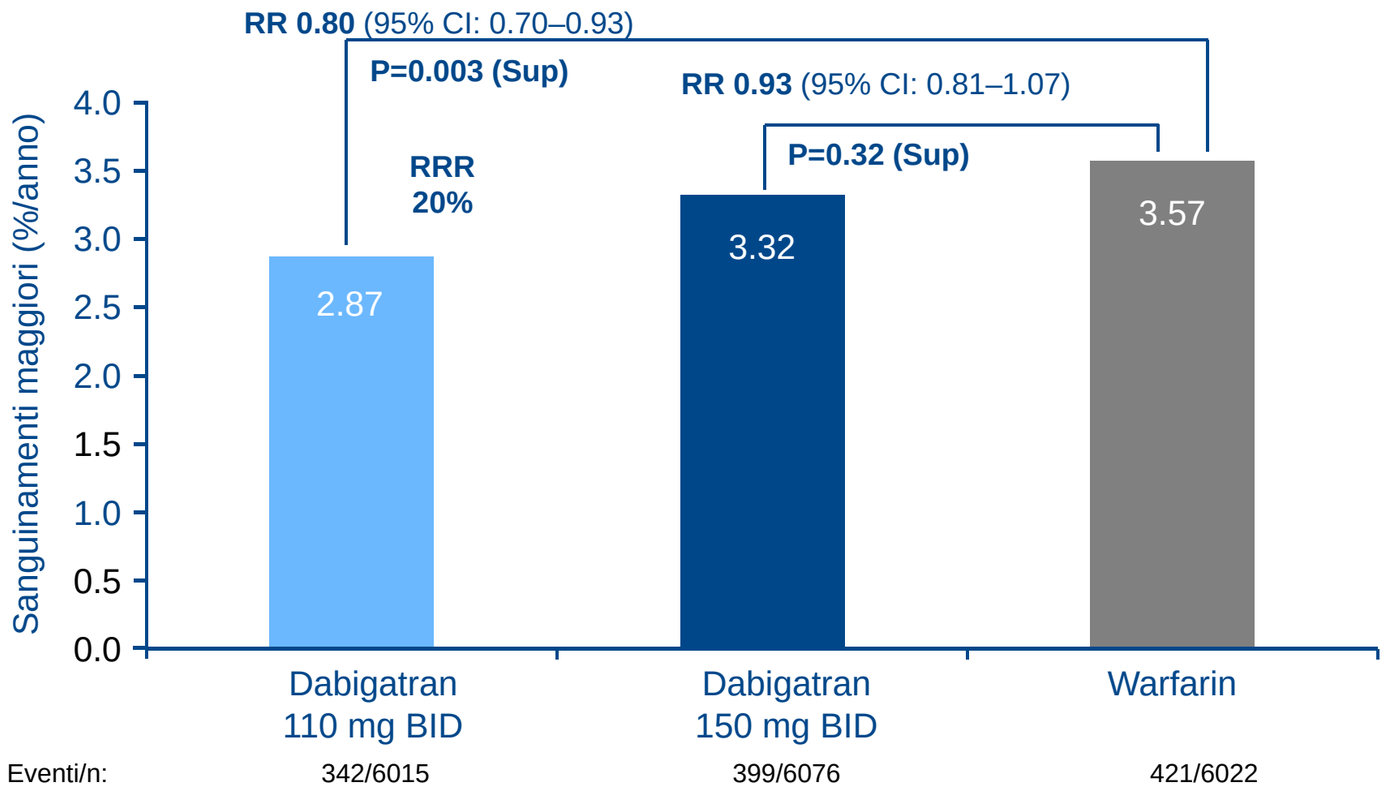
RE-LY®: sanguinamenti totali



BID = due volte al giorno; RR = rischio relativo; RRR = riduzione del rischio relativo; Sup = superiorità

Connolly SJ et al. N Engl J Med 2010;363:1875–6

Endpoint primario di sicurezza: sanguinamenti maggiori



BID = due volte al giorno; NI = non inferiorità; RR = rischio relativo; RRR = riduzione del rischio relativo; Sup = superiorità

Connolly SJ et al. N Engl J Med 2010;363:1875–6

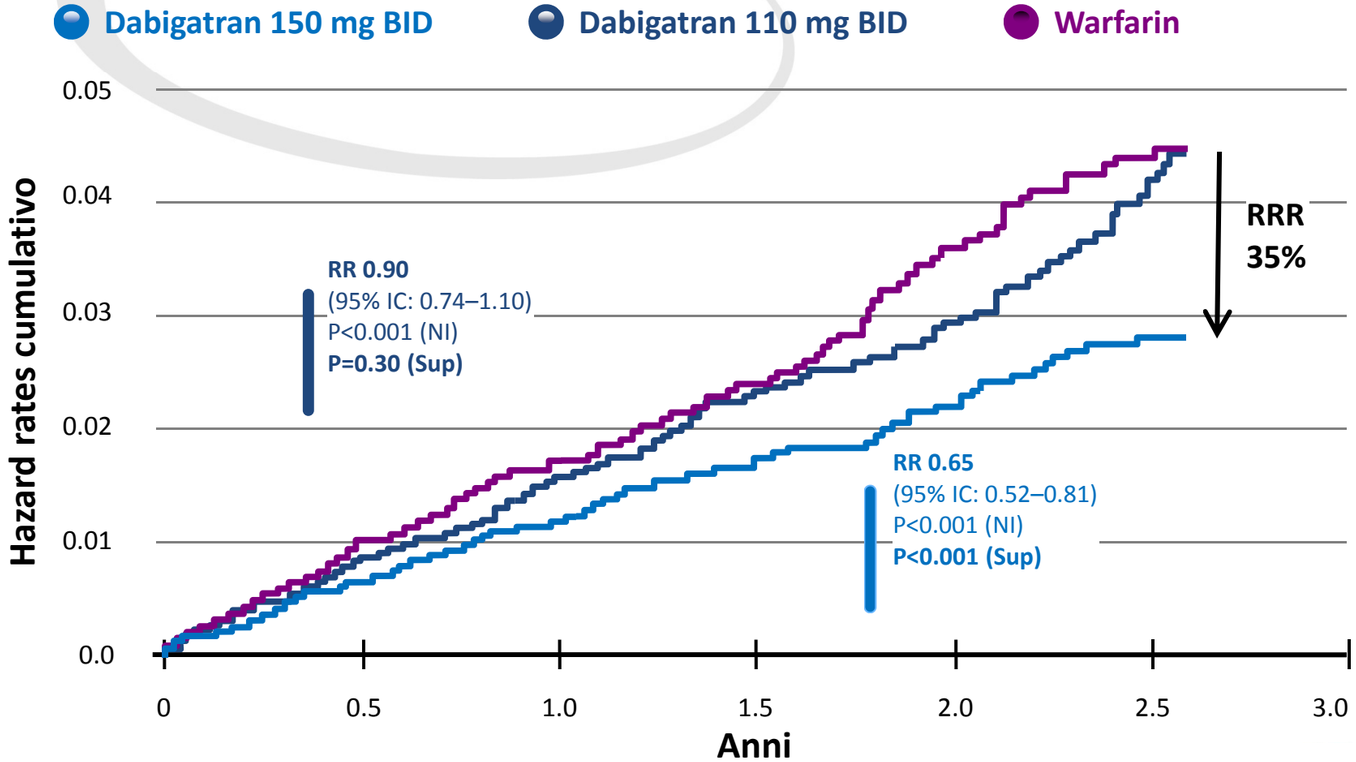
The NEW ENGLAND JOURNAL of MEDICINE

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 Steering Committee and Investigators*

Tempo al primo ictus/ embolismo sistemico



D = dabigatran; RR = rischio relativo; RRR = riduzione rischio relativo ; SSE= embolismo sistemico
Dabigatran etexilato è in sviluppo clinico e non è approvato per l'uso nella pratica clinica nella prevenzione dell'ictus nei pazienti con FA

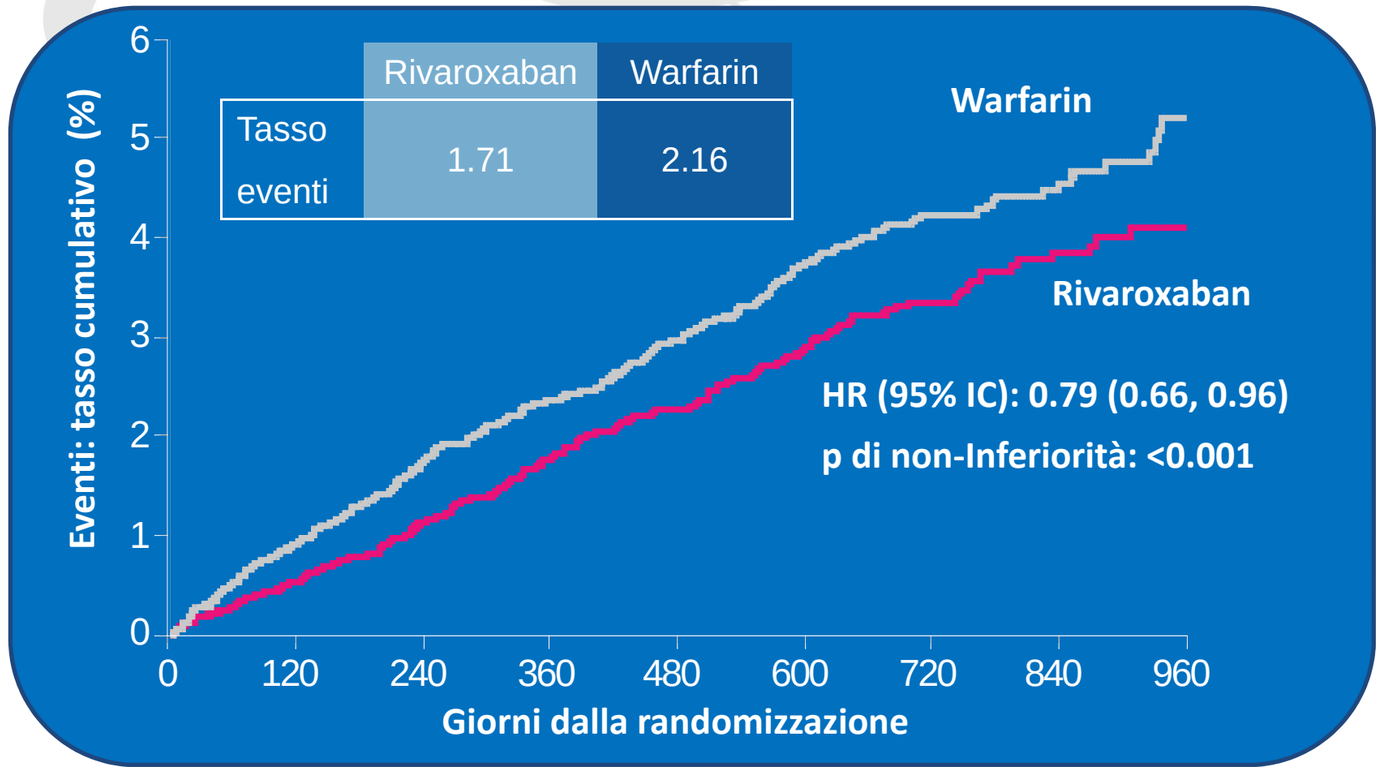
Connolly SJ. *N Engl J Med* 2010;369(19):1876-5.

ROCKET AF

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

Outcome primario di efficacia

Ictus ed embolismo non-CNS

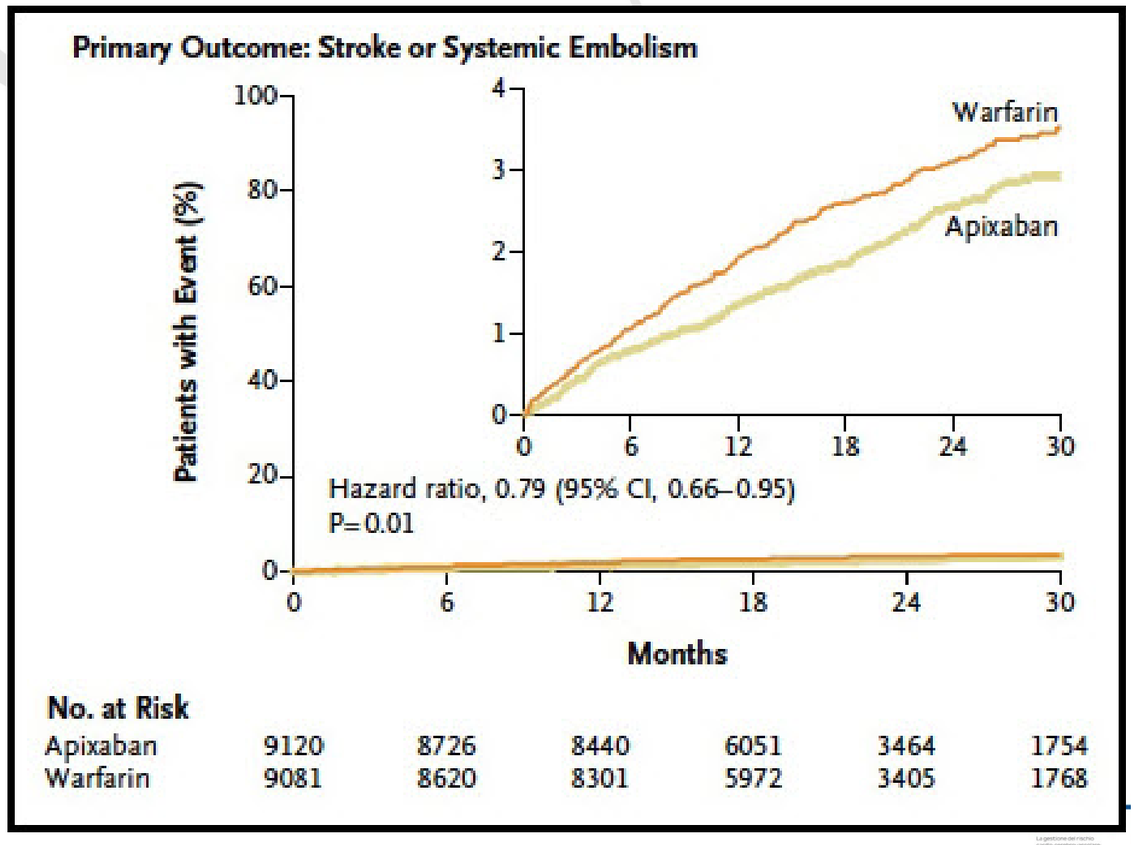


Tasso di eventi per 100 anni-paziente
Basato sul protocollo della popolazione in trattamento
ROCKET AF Study investigators: Am Heart J. 2010 Mar;159(3):340-347

ARISTOTLES

(apixaban)

ARISTOTLES: primary end point



The Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation

ENGAGE AF-TIMI 48

La nuova generazione di anticoagulanti efficaci con il fattore Xa nella FA

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

ENGAGE AF-TIMI 48 N Engl J Med 2013; 369:2093-2104
November 28, 2013

Both once-daily regimens of **edoxaban were noninferior to warfarin** with respect to the prevention of stroke or systemic embolism and were associated with **significantly lower rates of bleeding and death from cardiovascular causes**.


In conclusione,
il messaggio dei trials
(evidence-based medicine)

Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27.467 patients taking rivaroxaban

Objective

To provide longitudinal safety data by obtaining information associated with MB among rivaroxaban users with NVAF

Design

5-year observational, post-marketing safety surveillance study using fully integrated electronic medical records (EMRs)

Patient Characteristics

Characteristic	MB, n = 478	No MB, n = 26 989
Age, y, mean (SD)[a]	78.4 (7.7)	75.7 (9.7)
Comorbid condition, %[b]	100.0	87.0
HF	48.5	23.7
Hypertension	95.6	75.8
CHD	64.2	36.7
Renal disease	38.7	16.7
$CHADS_2$ score, mean (SD)	3.0 (1.2)	2.2 (1.3)
CHA_2DS_2-VASc score, mean (SD)	4.8 (1.5)	3.7 (1.7)

Tamayo et al., *Clin Cardiol* 2015

Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27.467 patients taking rivaroxaban

Objective

To provide longitudinal safety data by obtaining information associated with MB among rivaroxaban users with NVAF

Design

5-year observational, post-marketing safety surveillance study using fully integrated electronic medical records (EMRs)

Major Bleed Characteristics*

	MB Cases (N = 478)
MB cases with fatal outcome	14
Patients with multiple MB events	16
MB incidence rate per 100 person-years (95% CI)[b]	2.86 (2.61-3.13)
Bleeding cases with fatal outcome (95% CI)	0.08 (0.05-0.14)
MB location, n	
GI hemorrhage	423
ICH	36
Genitourinary hemorrhage	2
Other	12
Length of hospitalization, d, mean (SD)[c]	3.8 (3.0)
Blood transfusion received, %	46.7
Transferred to ICU, %	43.3
Surgical intervention needed, %	25.1

*MB classified using the Cunningham et al. defintion including: GI bleeding, hemorragic Strokes and other intracranial bleeds, genitourinarybleeding and bleeding at other sites.

Tamayo et al., *Clin Cardiol* 2015

Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27.467 patients taking rivaroxaban

Objective

To provide longitudinal safety data by obtaining information associated with MB among rivaroxaban users with NVAF

Design

5-year observational, post-marketing safety surveillance study using fully integrated electronic medical records (EMRs)

Fatal Outcomes

	MB Cases, N = 478
Fatal outcomes in rivaroxaban users who experienced a MB event, n[a]	14
Primary hospital admission diagnosis of those who experienced a fatal outcome, %	
Intracerebral hemorrhage	50.0
GI hemorrhage NOS	21.4
Blood in the stool	14.3
Subdural hemorrhage	7.1
ICH NOS	7.1

Tamayo et al., *Clin Cardiol* 2015

Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27.467 patients taking rivaroxaban

Objective

To provide longitudinal safety data by obtaining information associated with MB among rivaroxaban users with NVAF

Design

5-year observational, post-marketing safety surveillance study using fully integrated electronic medical records (EMRs)

Conclusions

- Observational post-marketing study of 27.467 patients with NVAF followed for 455 days in real life
- Rate of MB 2.86% person/y
- Rate of MB in ROCKET AF trial: 3.6% person/y for rivaroxaban and 3.5 for warfarin*
- Patients who experienced MB were older and more likely to have comorbidity
- The most common bleeding site is GI
- Of the 478 patients who suffered a MB, 14 died (fatal bleeding rate 0.08% person/y)
- The MB rate was generally consistent with the registration trial results and fatal bleeds were rare.

*MB classified using the International Society on Thrombosis and Haemostasis defintion

Tamayo et al., *Clin Cardiol* 2015

Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27.467 patients taking rivaroxaban

Conclusions

- **Rate of MB 2.86% person/y**
- **Rate of MB in ROCKET AF trial:**
  - **3.6% person/y for rivaroxaban**
  - **3.5 for warfarin***

*MB classified using the International Society on Thrombosis and Haemostasis defintion

Tamayo et al., *Clin Cardiol* 2015

2014

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

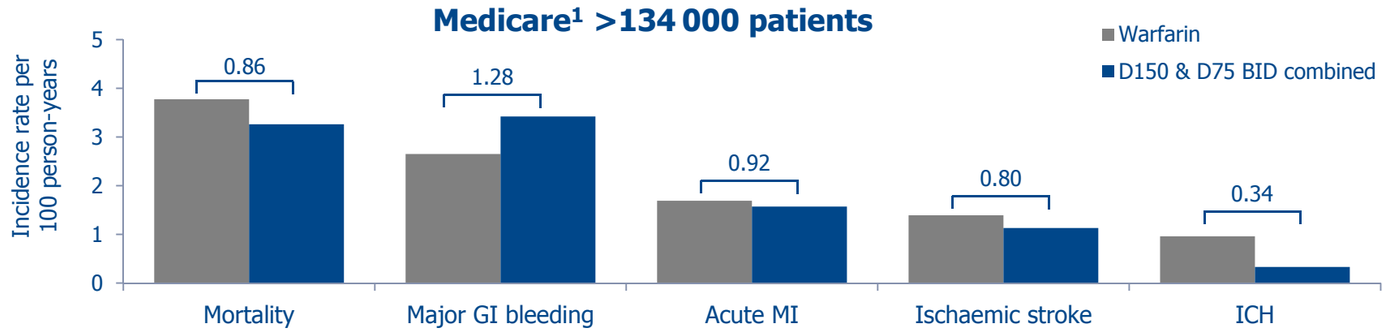
Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated with Dabigatran or Warfarin for Non-Valvular Atrial Fibrillation

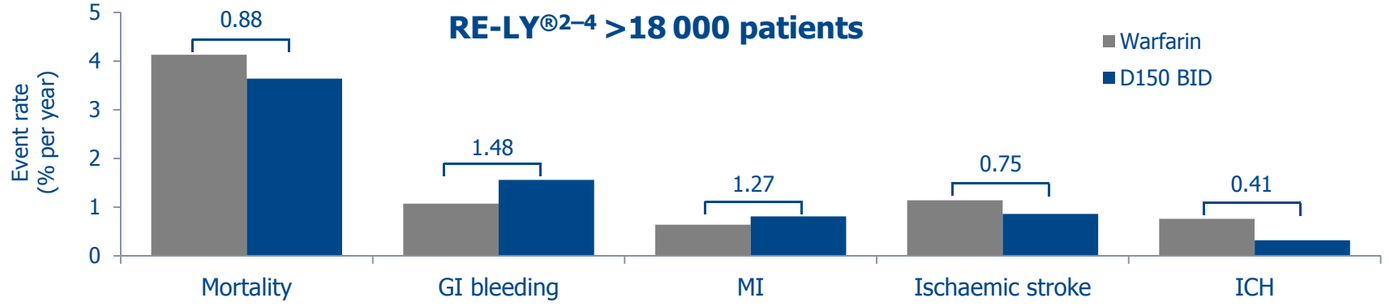
David J. Graham, Marsha E. Reichman, Michael Wernecke, Rongmei Zhang, Mary Ross Southworth, Mark Levenson, Ting-Chang Sheu, Katrina Mott, Margie R. Goulding, Monika Houstoun, Thomas E. MaCurdy, Chris Worrall and Jeffrey A. Kelman

Circulation. published online October 30, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Independent FDA Medicare analysis findings are consistent with findings from RE-LY®





Independent FDA analysis confirmed the favourable benefit–risk profile of dabigatran in clinical practice

In the USA, the licensed doses for Pradaxa ® are: Pradaxa® 150 mg BID and Pradaxa ® 75 mg BID for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF

Numbers on bars denote HRs vs warfarin. D75 = dabigatran 75 mg; D150 = dabigatran 150 mg

1. Available at http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm; accessed September 2014; **2.** Connolly SJ et al. N Engl J Med 2009;361:1139–51; **3.** Connolly SJ et al. N Engl J Med 2010;363:1875–6; **4.** Pradaxa®: EU SPC, 2014

Table 2. Outcome event counts, incidence rates, and adjusted hazard ratios with 95% confidence intervals comparing propensity score matched new user cohorts of dabigatran and warfarin treated for non-valvular atrial fibrillation. Warfarin served as the reference group.

	No. events		Incidence rate per 1000 person-years		Adjusted hazard ratio (95% CI)	P-value
	Dabigatran	Warfarin	Dabigatran	Warfarin		
Primary outcomes						
Ischemic stroke	205	270	11.3	13.9	0.80 (0.67-0.96)	0.02
Major hemorrhage	777	851	42.7	43.9	0.97 (0.88-1.07)	0.50
Gastrointestinal	623	513	34.2	26.5	1.28 (1.14-1.44)	< 0.001
Intracranial	60	186	3.3	9.6	0.34 (0.26-0.46)	< 0.001
Intracerebral	44	142	2.4	7.3	0.33 (0.24-0.47)	< 0.001
Acute myocardial infarction	285	327	15.7	16.9	0.92 (0.78-1.08)	0.29
Secondary outcomes						
All hospitalized bleeds	1079	1139	59.3	58.8	1.00 (0.92-1.09)	0.97
Mortality*	603	744	32.6	37.8	0.86 (0.77-0.96)	0.006

* For 1,064 deaths not preceded by a primary study outcome, the adjusted hazard ratio (95% CI) was 0.89 (0.79-1.00), p=0.051, while for 283 deaths occurring within 30 days after a primary outcome, the adjusted hazard ratio (95% CI) was 0.77 (0.61-0.98), p=0.03.

In our study, the increased risk of major gastrointestinal bleeding with dabigatran appeared to be restricted to women aged ≥75 years and to men aged ≥85 years. The beneficial

DOI: 10.1161/CIRCULATIONAHA.114.012061

Conclusions

- **The risk of major GI bleedings was increased in women aged >75y and men aged >85y compared with warfarin.**
- **Below these ages, the risk was comparable for both anticoagulants.**

*MB classified using the International Society on Thrombosis and Haemostasis defintion

Tamayo et al., *Clin Cardiol* 2015

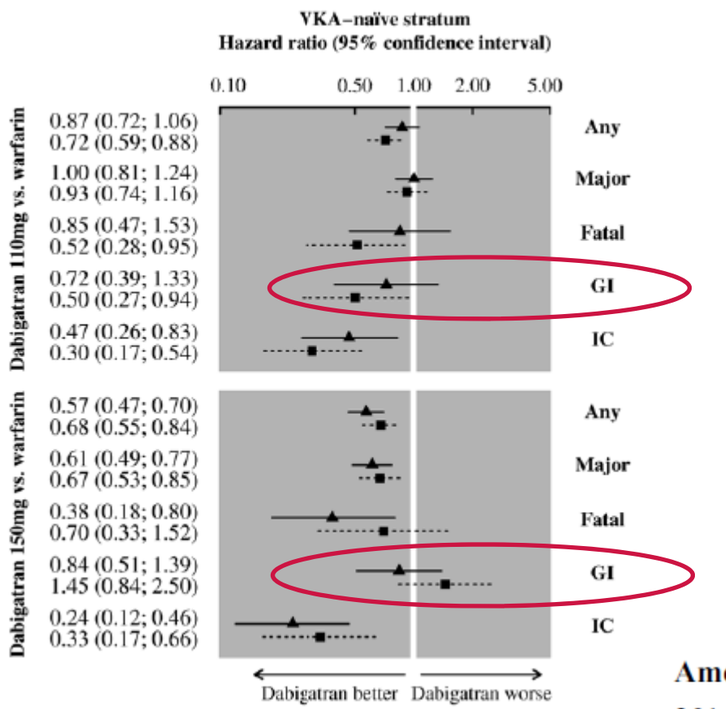
CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

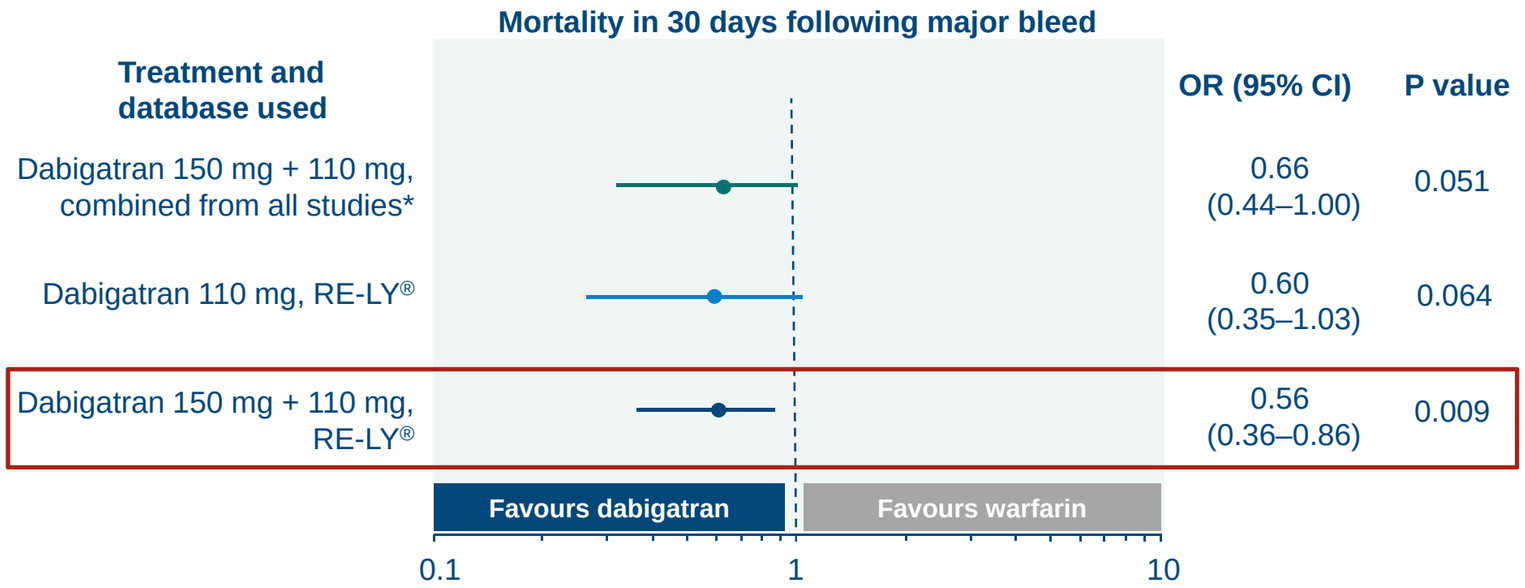
Bleeding Events Among New Starters and Switchers to Dabigatran Compared with Warfarin in Atrial Fibrillation

Torben Bjerregaard Larsen, MD, PhD,[a,b] Anders Gorst-Rasmussen, MSc, PhD,[a,b] Lars Hvilsted Rasmussen, MD, PhD,[b] Flemming Skjøth, MSc, PhD,[a,b] Mary Rosenzweig, MSc,[c] Gregory Y.H. Lip, MD[b,d]

[a]Department of Cardiology, Atrial Fibrillation Study Group, Aalborg University Hospital, Aalborg, Denmark; [b]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark; [c]Division of Pharmacovigilance and Medical Devices, Danish Health and Medicines Authority, Copenhagen, Denmark; [d]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom.



American Journal of Medicine
2014, 127 : 7 650-656

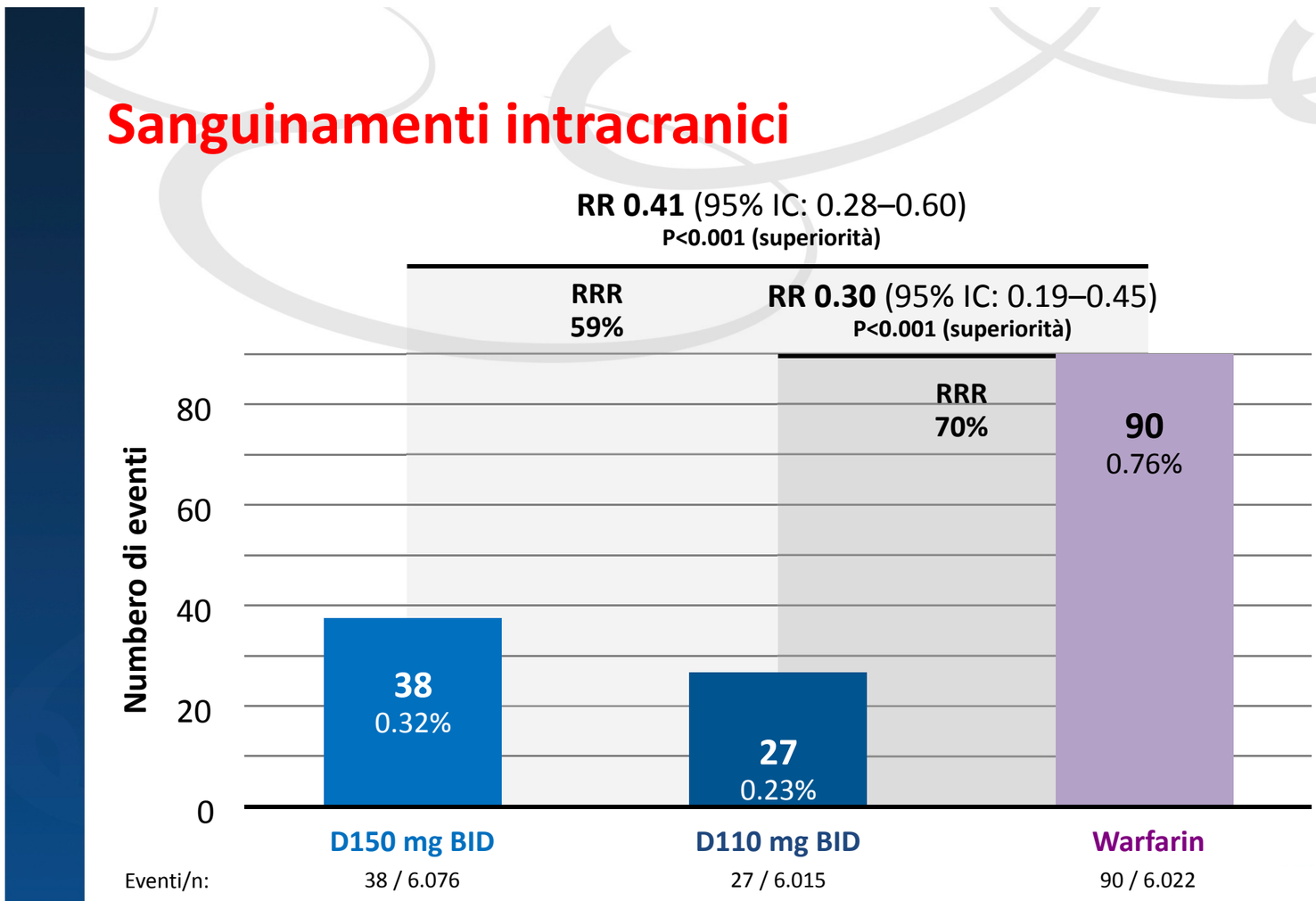


This is in the absence of a specific reversal agent

*Combined data from dabigatran 150 mg BID and 110 mg BID treatment groups in RE-LY®, RE-COVER™, RE-COVER™ II, RE-MEDY™ and RE-SONATE™. Only first major bleed included; analysis not adjusted for covariates

Majeed et al. Circulation 2013

Sanguinamenti intracranici



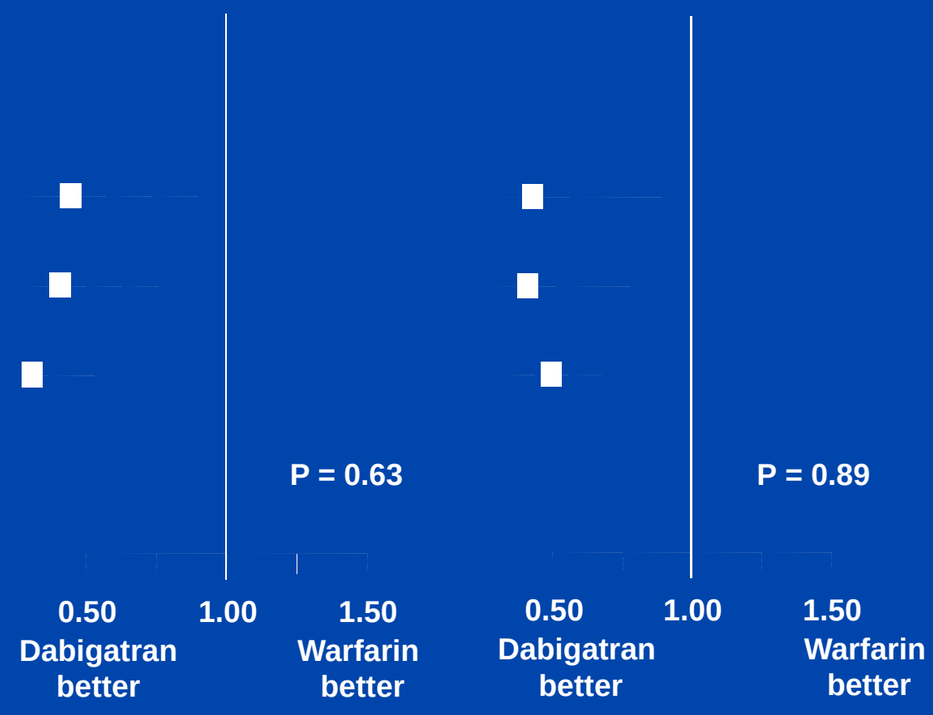
D = dabigatran; RR = rischio relativo; RRR = riduzione del rischio relativo. Le percentuali sulle barre rappresentano il tasso annuo.
Dabigatran etexilato è in sviluppo clinico e non è approvato per l'uso nella pratica clinica nella prevenzione dell'ictus nei pazienti con FA.

Connolly SJ, et al. *N Engl J Med* 2010;363:1875-1876.

Intracranial bleeding

RELY®
Study of stroke prevention in atrial fibrillation

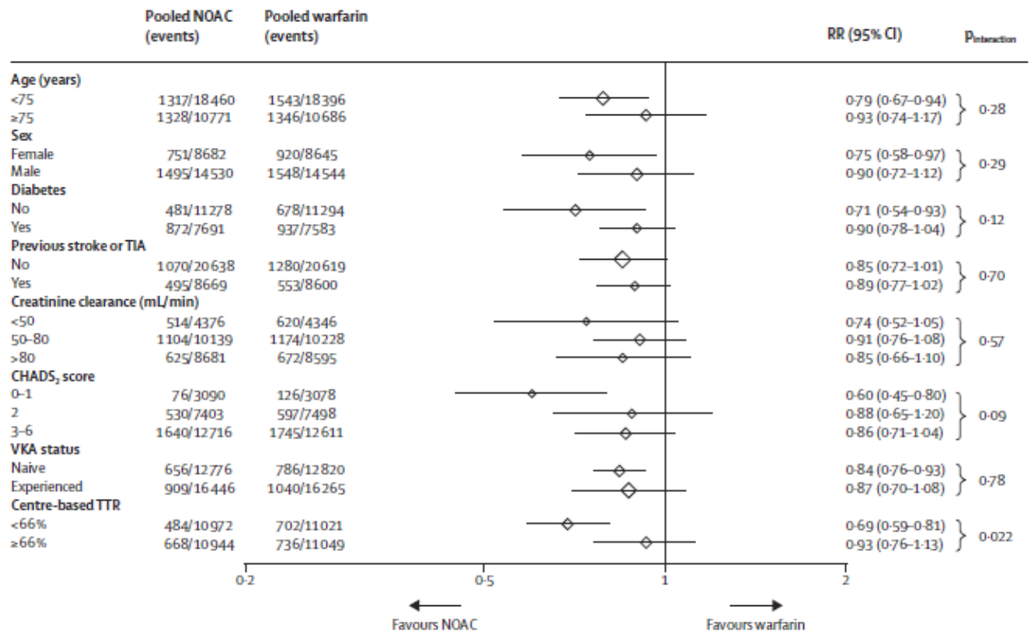
	Annual rate, %		
CHADS2	D110	D150	WARFARIN
0-1	0.20	0.20	0.51
2	0.22	0.24	0.64
3-6	0.26	0.49	1.07



Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

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

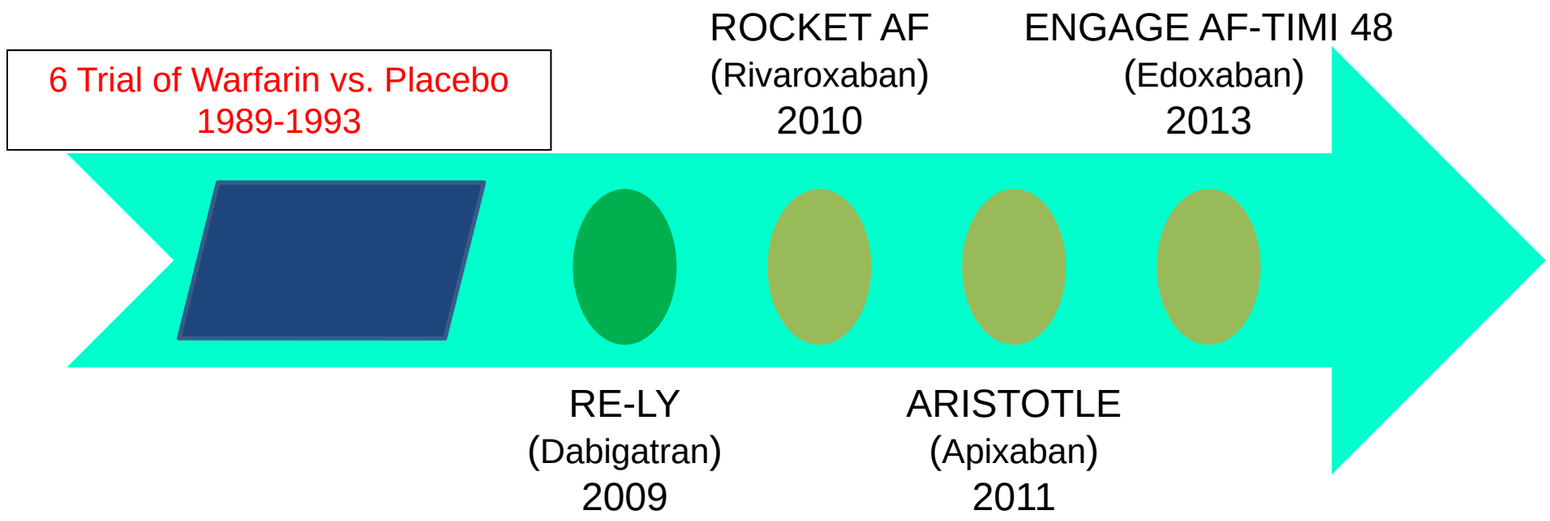


The safety of NOACs compared with warfarin was generally consistent for the reduction of major bleeding across subgroups, with the exception of a significant interaction for centre-based time in therapeutic range: greater relative reduction in bleeding with NOACs at centres that achieved a centre-based time in therapeutic range of less than 66% than at those achieving a time in therapeutic range of 66% or more.

Pivotal Warfarin-Controlled Trials
Stroke Prevention in AF

Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients



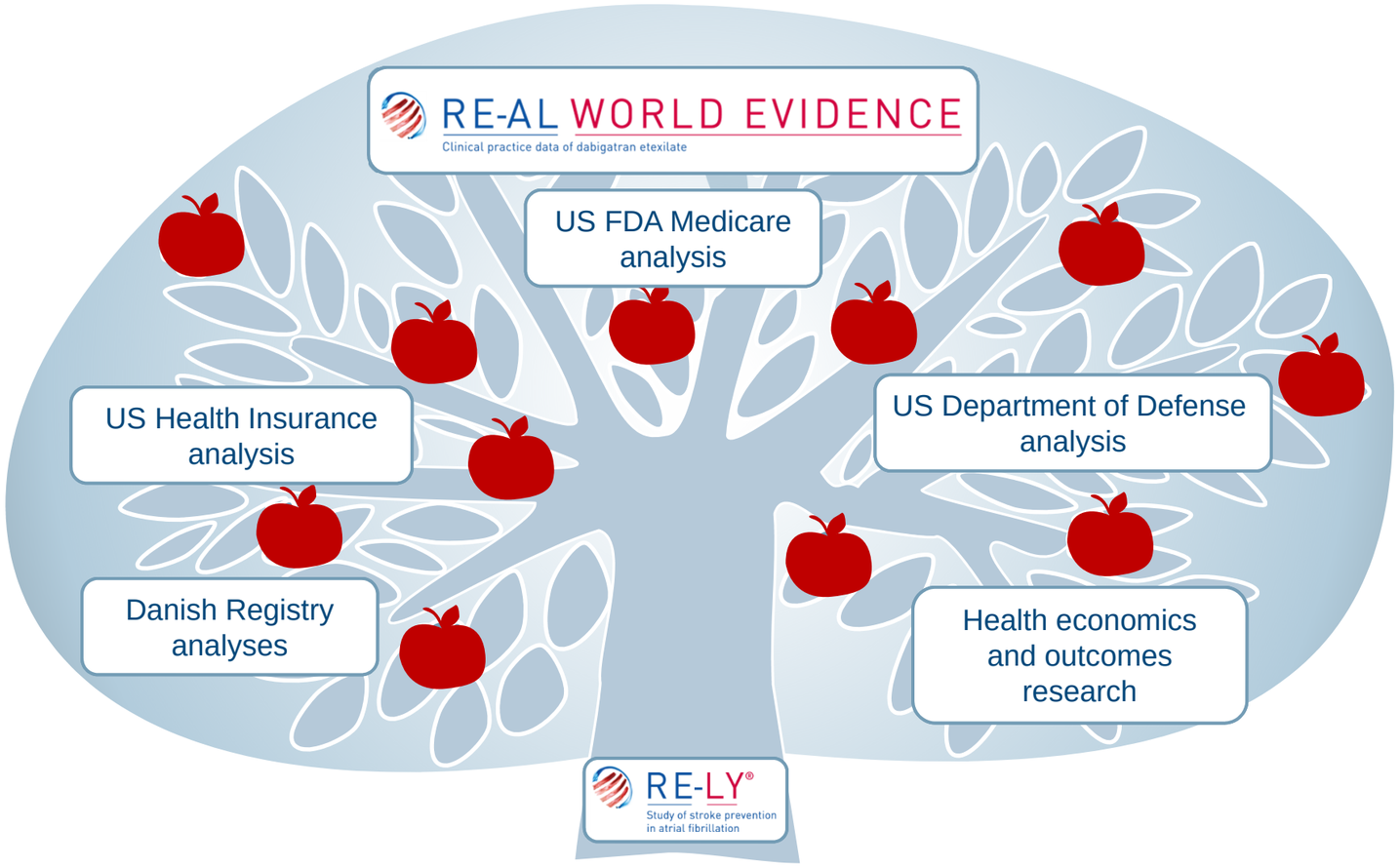
RCTs are the gold standard for evidence-based medicine but RWE is important to confirm safety and effectiveness in everyday practice

	Randomized controlled trial	Real-world evidence (non-interventional studies)
Objective	Determine if it works under **HIGHLY CONTROLLED** circumstances	Determine if it works under **USUAL** circumstances
Patients	**Predefined population** (stringent inclusion/exclusion criteria)	**Varied medical settings with diverse patient populations**
Intervention or treatment	**Randomized, defined regimens**	**Non-randomized regimen** (according to label and physician judgement)
Adherence to regimen	**Usually high**	**Can vary from low to high**
Follow-up	**Limited**	**Long-term** follow-up possible
Purpose	Regulatory approval	Drug performance in real world

Both sources of information are **VALUABLE** but have limitations

They should be viewed as **COMPLEMENTARY** to confirm the validity of safety and efficacy data for new agents and to answer different physician questions

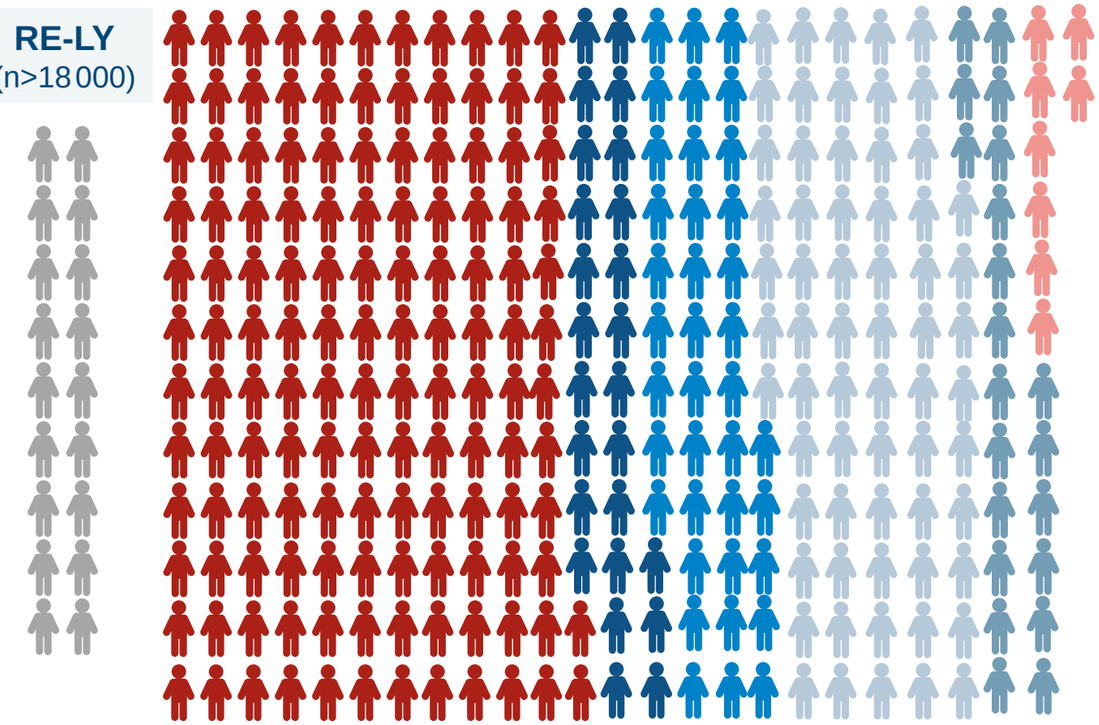
Real-world evidence confirms and extends the favourable clinical profile of dabigatran established in RE-LY® and RELY-ABLE®



Growing body of real-world experience from >250 000 patients confirms safety and efficacy profile of dabigatran

Real-world: (n>250 000 OAC-naïve patients)

RE-LY
(n>18 000)



- FDA Medicare study (n>134 000)[1]
- US Dept of Defense database (n>25 000)[2]
- 2 US insurance databases (n>38 000)[3]
- US insurance database (n>64 000)[6]
- Danish observational studies (n>21 000)[4,5]
- Hong-Kong hospital study (n>8 000)[7]

In the USA, the licensed doses for Pradaxa® are: 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAF

1. Graham et al. Circulation 2015; **2.** Villines et al. Presented at AHA 2014; **3.** Seeger et al. Presented at AHA 2014; **4.** Larsen et al. Am J Med 2014a; **5.** Larsen et al. Am J Med 2014b; **6.** Lauffenburger JC et al. J Am Heart Assoc. 2015; **7.** Ho CW et al. Stroke. 2015

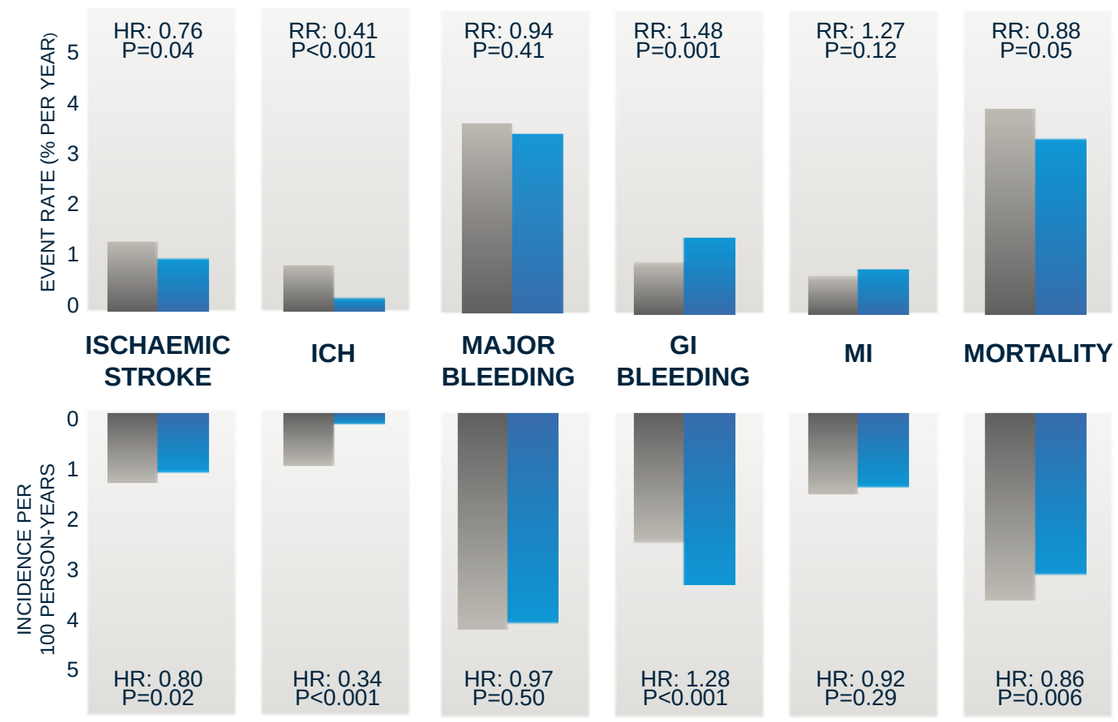
Independent FDA study of Medicare patients **mirrors** the favourable benefit–risk profile of dabigatran established in RE-LY®

RE-LY®1–4

N>18 000
Warfarin
D150 BID

MEDICARE*5

N>134 000
Warfarin
D150 & D75 BID combined



In the USA, the licensed doses for Pradaxa® are: 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAF. RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

*Primary findings for dabigatran are based on analysis of both 75 mg and 150 mg together without stratification by dose. **1.** Connolly et al. NEJM 2009; **2.** Connolly et al. NEJM 2010; **3.** Pradaxa®: EU SPC, 2015; **4.** Connolly et al. NEJM 2014; **5.** Graham et al. Circulation 2015

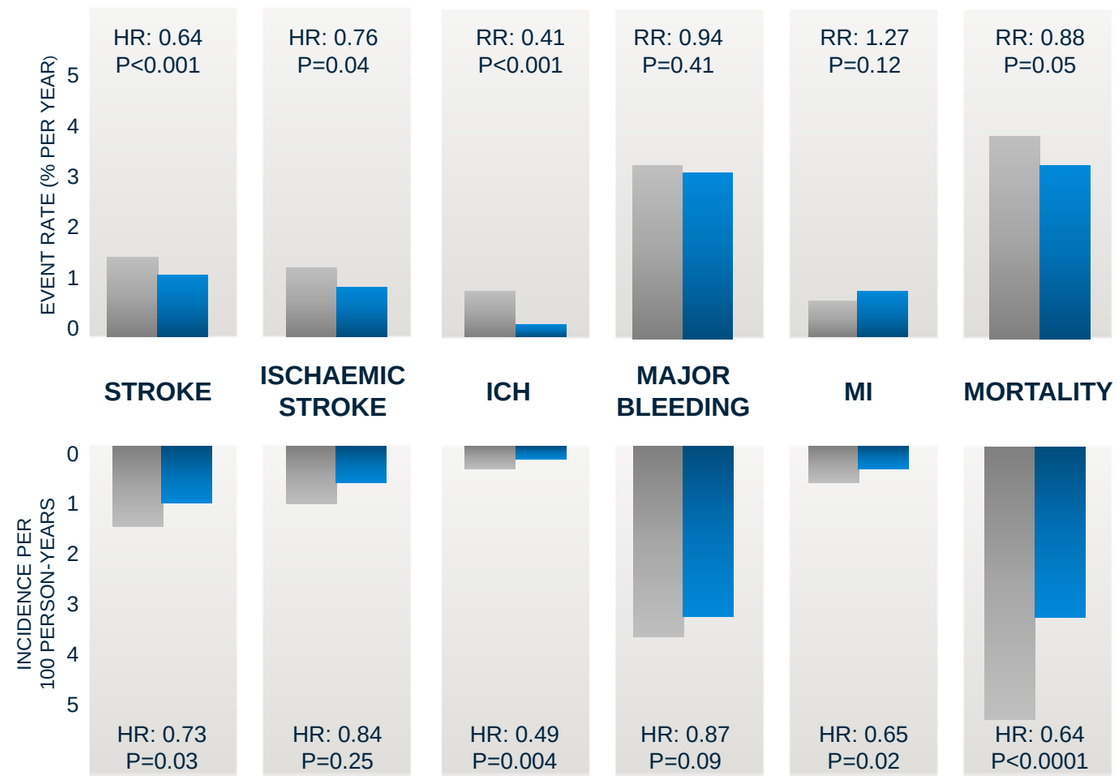
US DoD database showed clear consistency in outcomes with data from RE-LY® and FDA Medicare study

RE-LY®1–4

N>18 000
Warfarin
D150 BID

DoD*5

N>25 000
Warfarin
D150 & D75 BID combined



In the USA, the licensed doses for Pradaxa® are: 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAF. RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

*Primary findings for dabigatran are based on analysis of both 75 mg and150 mg together without stratification by dose. **1.** Connolly et al. NEJM 2009; **2.** Connolly et al. NEJM 2010; **3.** Pradaxa®: EU SPC, 2015; **4.** Connolly et al. NEJM 2014; **5.** Villines et al. Circulation 2014

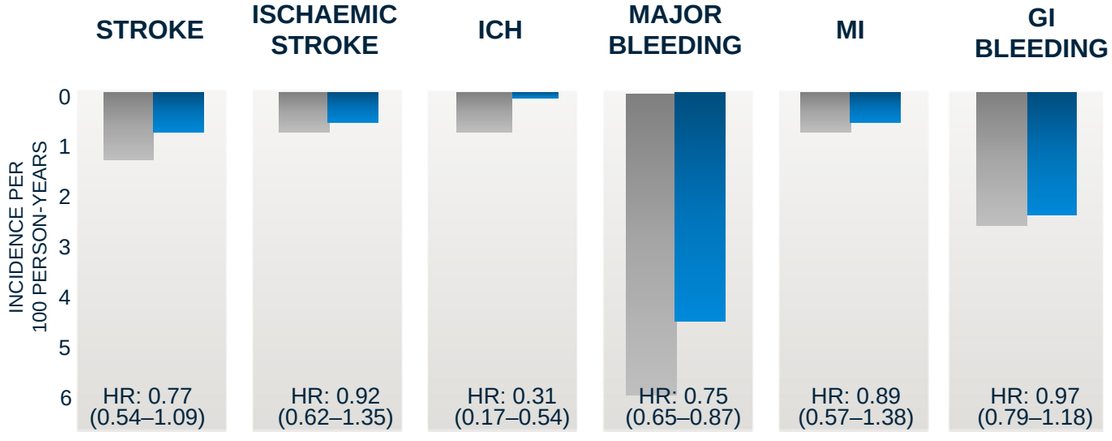
US Health Insurance interim analysis data are consistent with RE-LY® and additional real-world data

RE-LY®1–4

N>18 000
Warfarin
D150 BID

US Health Insurance*5

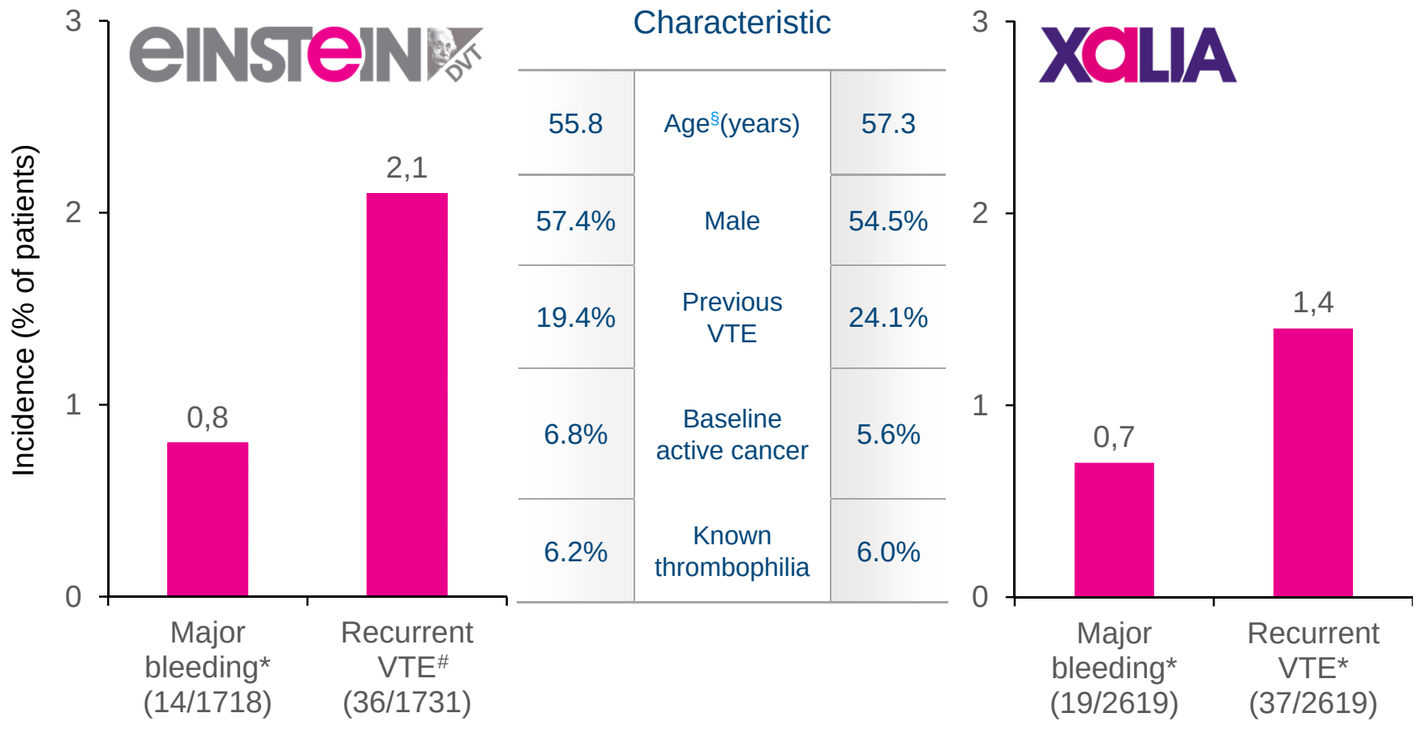
N>38 000
Warfarin
D150 & D75 BID combined



In the USA, the licensed doses for Pradaxa® are: 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAF. RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

*Primary findings for dabigatran are based on analysis of both 75 mg and 150 mg together without stratification by dose. **1.** Connolly et al. NEJM 2009; **2.** Connolly et al. NEJM 2010; **3.** Pradaxa®: EU SPC, 2015; **4.** Connolly et al. NEJM 2014; **5.** Seeger et al. Circulation 2014

EINSTEIN DVT and XALIA: Rivaroxaban Outcomes

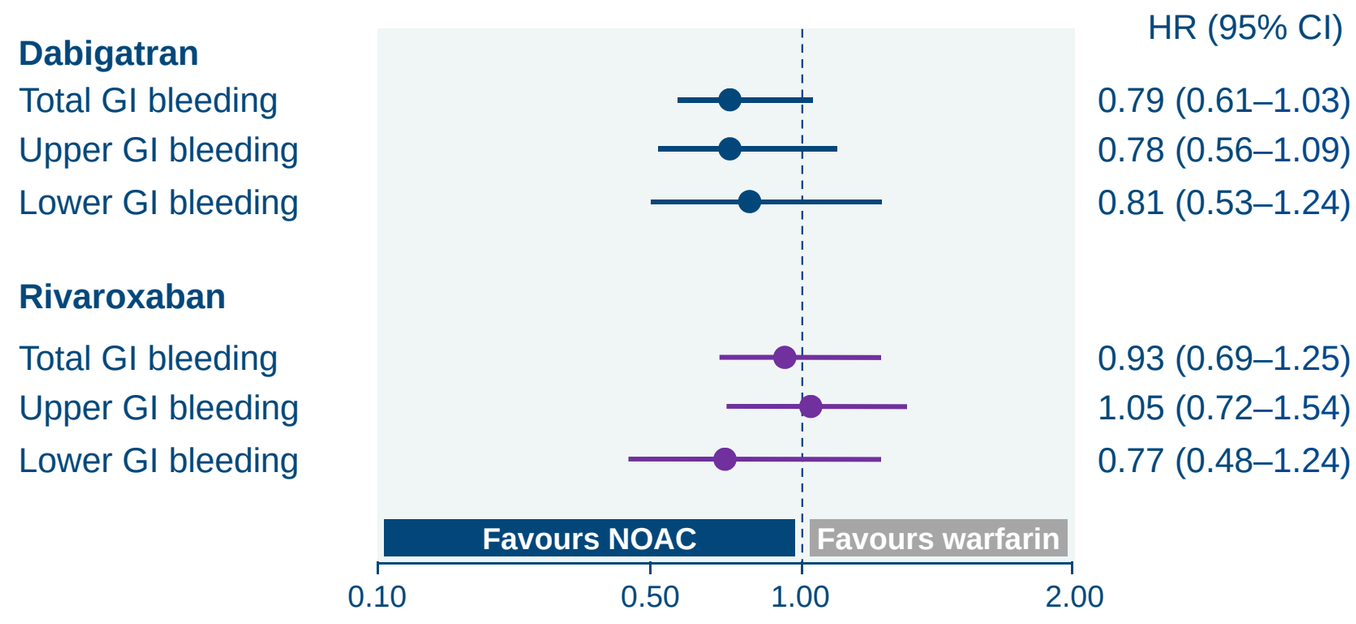


#ITT analysis; *Safety population (patients taking ≥1 dose of study drug); §mean

The EINSTEIN Investigators, *N Engl J Med* 2010;363:2499–2510

US health insurance study showed similar GI bleeding rates with rivaroxaban and dabigatran vs warfarin

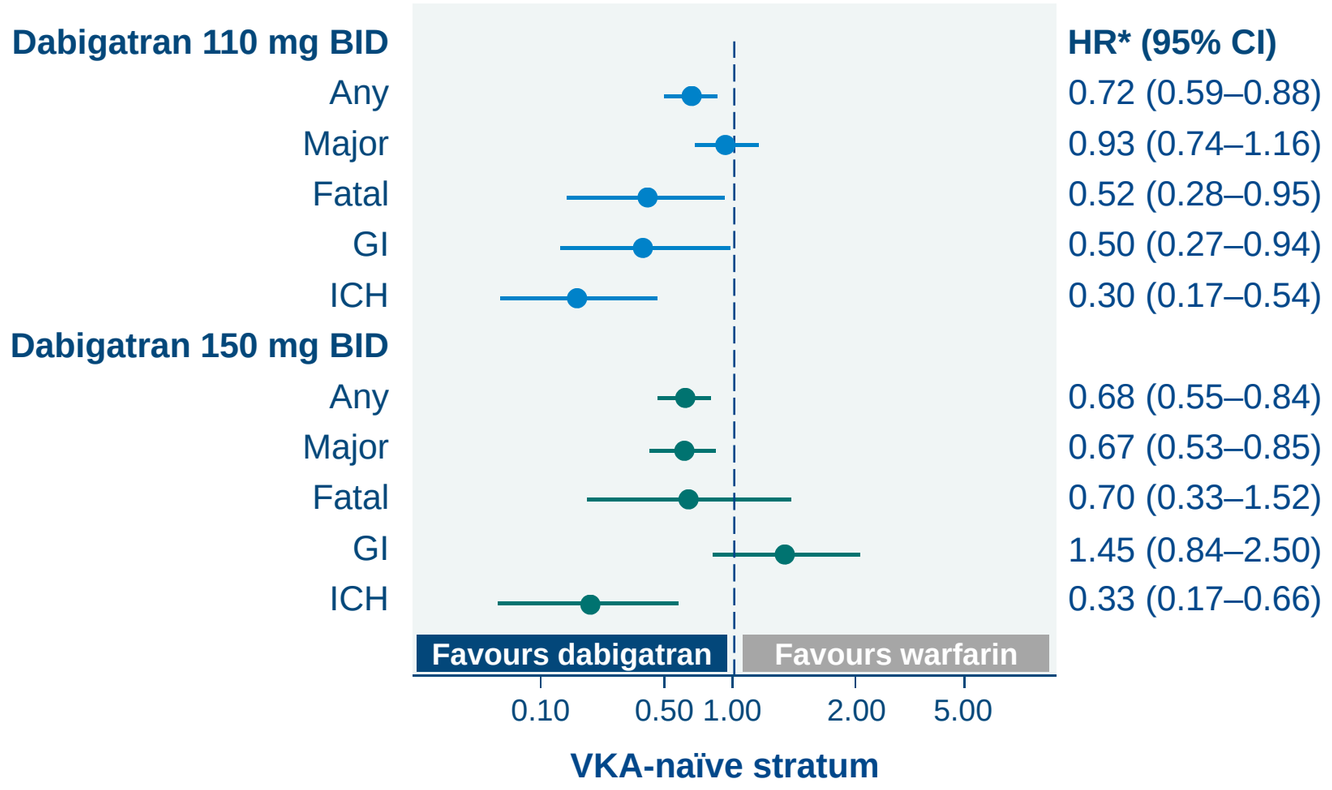
New users of dabigatran (n=7846), rivaroxaban (n=5434) or warfarin (n= 22 787) with AF



Propensity-score matched cohort: dabigatran, n=7749; rivaroxaban, n = 5166

Abraham et al. BMJ 2015

Reduced risk of ICH and any bleeding with both doses of dabigatran vs warfarin



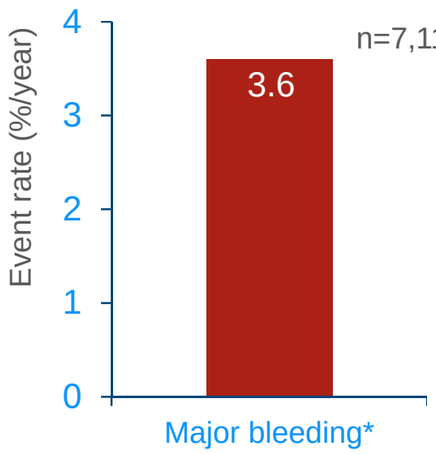
*HR adjusted for: age, components of CHA_2DS_2-VASc, HAS-BLED, months since August 2011

Larsen et al. Am J Med 2014a

Major Bleeding Rates with Rivaroxaban in Real Life Studies are Consistent with Findings from ROCKET AF

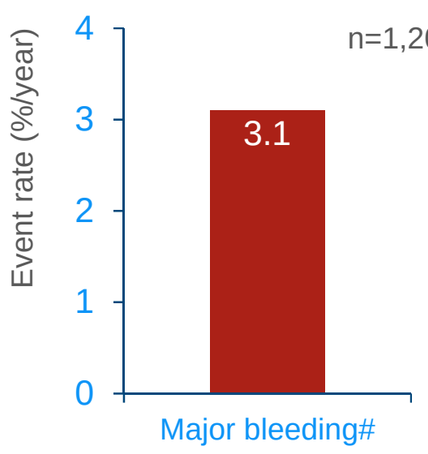
ROCKET AF[1]

mean $CHADS_2$-Score 3.5



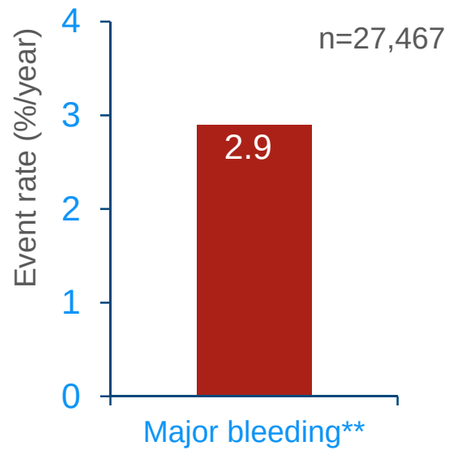
Dresden NOAC Registry[2]

mean $CHADS_2$-Score 2.4[#]



US DoD PMSS[3]

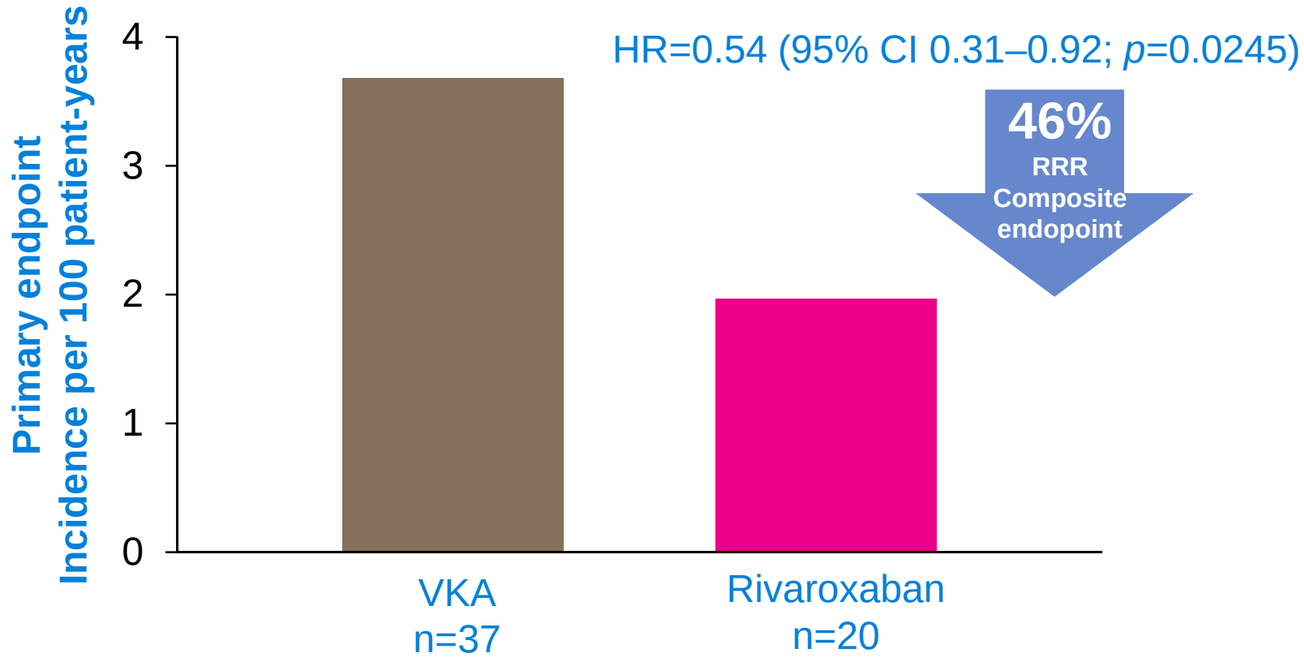
mean $CHADS_2$-Score 2.2



*Major bleeding definitions according to ISTH; [#] modified ISTH definition (additionally included surgical revision from bleeding)
**Major bleeding was defined by the Cunningham algorithm[3]
[#]55th ASH Meeting 2013, Oral presentation, Abstract 213, https://ash.confex.com/ash/2013/webprogram/Paper58333.html

1. Patel MR et al. *N Engl J Med* 2011; 365(10):883–891; 2. Beyer—Westendorf et al. Blood 2014;124(6); 955-962; 3. Tamayo S et al. Clin Cardiol. 2015;38(2):63–68

Lower Rates of Clinically Relevant CV Events* Compared with VKA Treatment

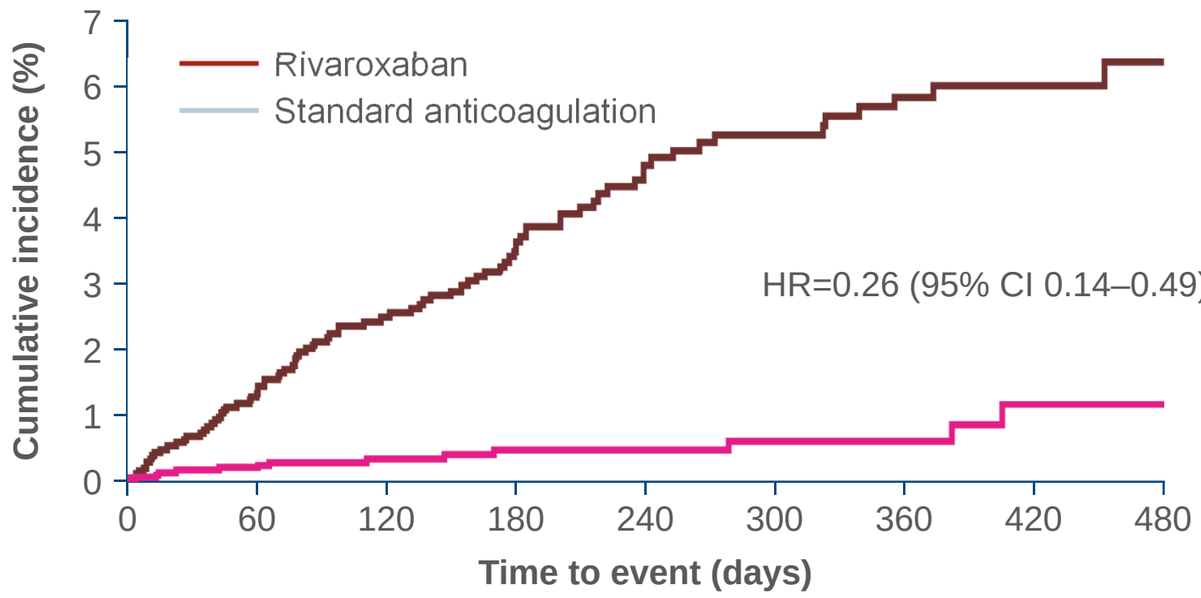


Rates of most individual endpoints of the composite were numerically less frequent with Rivaroxaban

* CV events include ischemic stroke, TIA, ICH, MI

Coleman CI et al., Int J Cardiol 2015

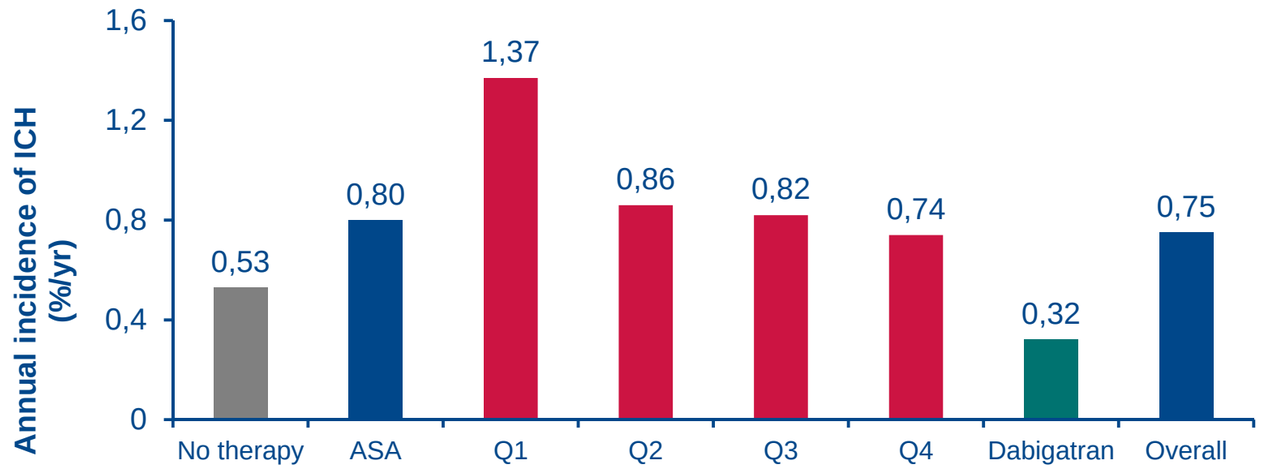
Cumulative Incidence of All-Cause Mortality (Before Propensity Adjustment)

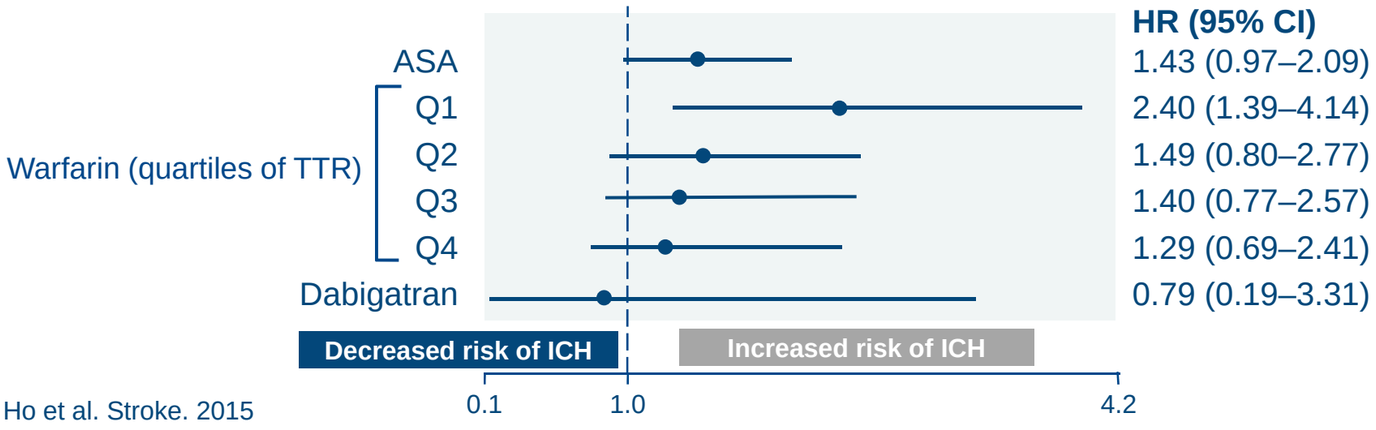


Rivaroxaban									
Patients at risk	2619	2389	1652	1349	797	664	566	263	174
Patients with events	0	4	7	9	9	10	10	12	12
Standard anticoagulation									
Patients at risk	2419	1878	1467	1232	847	716	619	322	200
Patients with events	0	26	47	63	75	79	83	84	85

Safety population; stratified for cancer at baseline

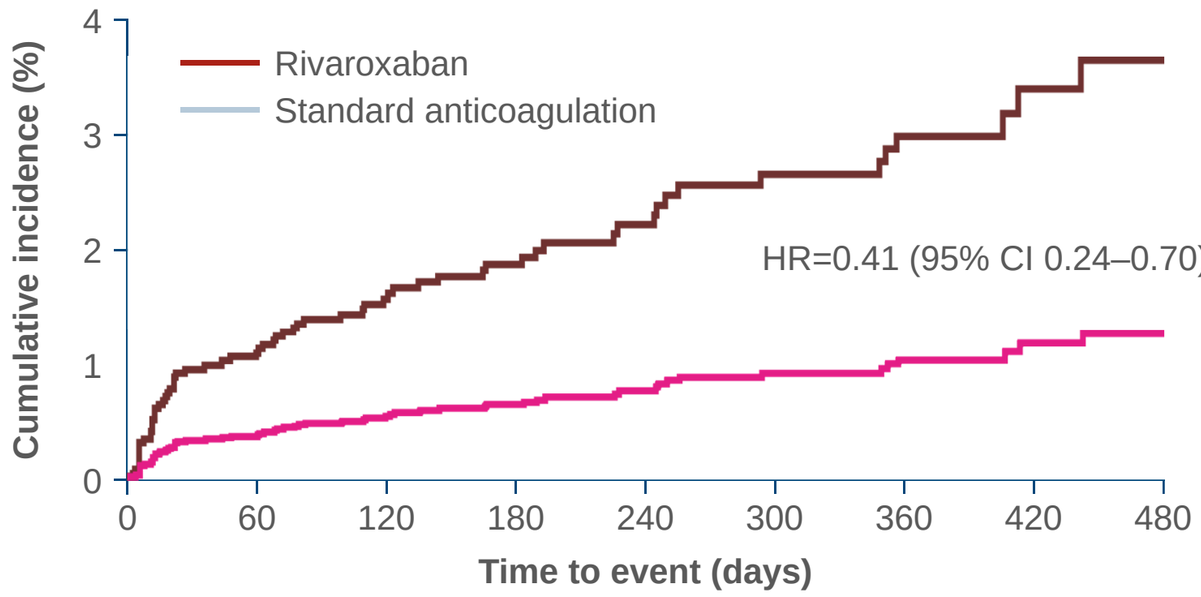
Dabigatran was associated with the lowest incidence of ICH





Ho et al. Stroke. 2015

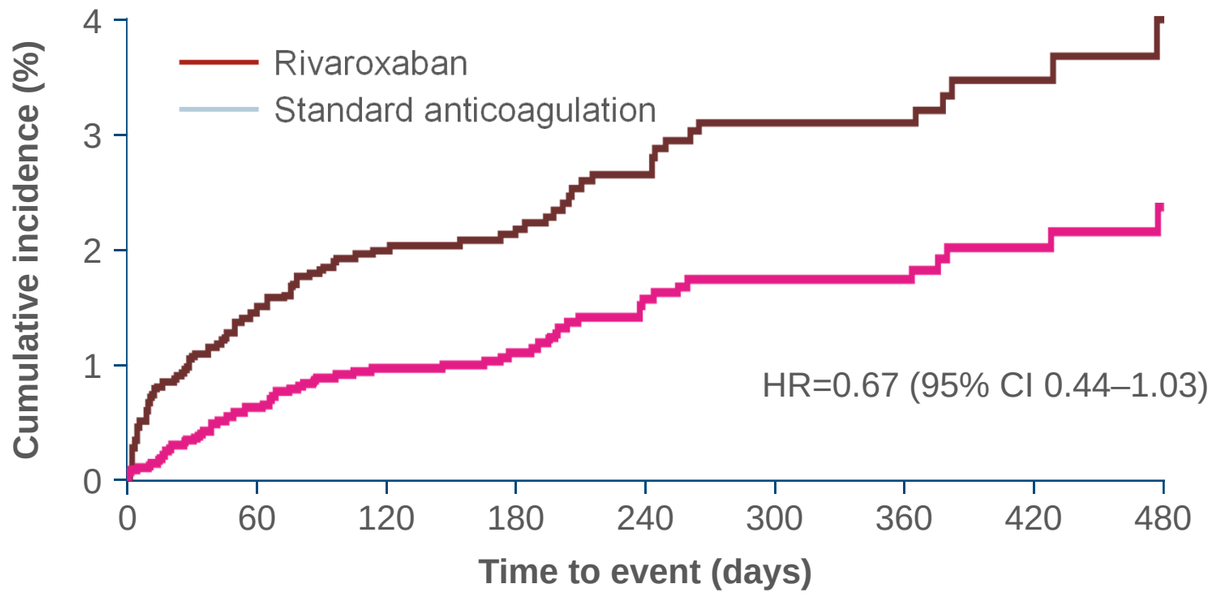
Cumulative Incidence of Major Bleeding (Before Propensity Adjustment)



Rivaroxaban									
Patients at risk	2619	2386	1650	1348	797	664	566	262	173
Patients with events	0	10	14	17	18	18	18	19	19
Standard anticoagulation									
Patients at risk	2419	1870	1458	1226	842	710	612	317	197
Patients with events	0	22	30	33	37	42	45	46	47

Safety population; adjusted for cancer at baseline

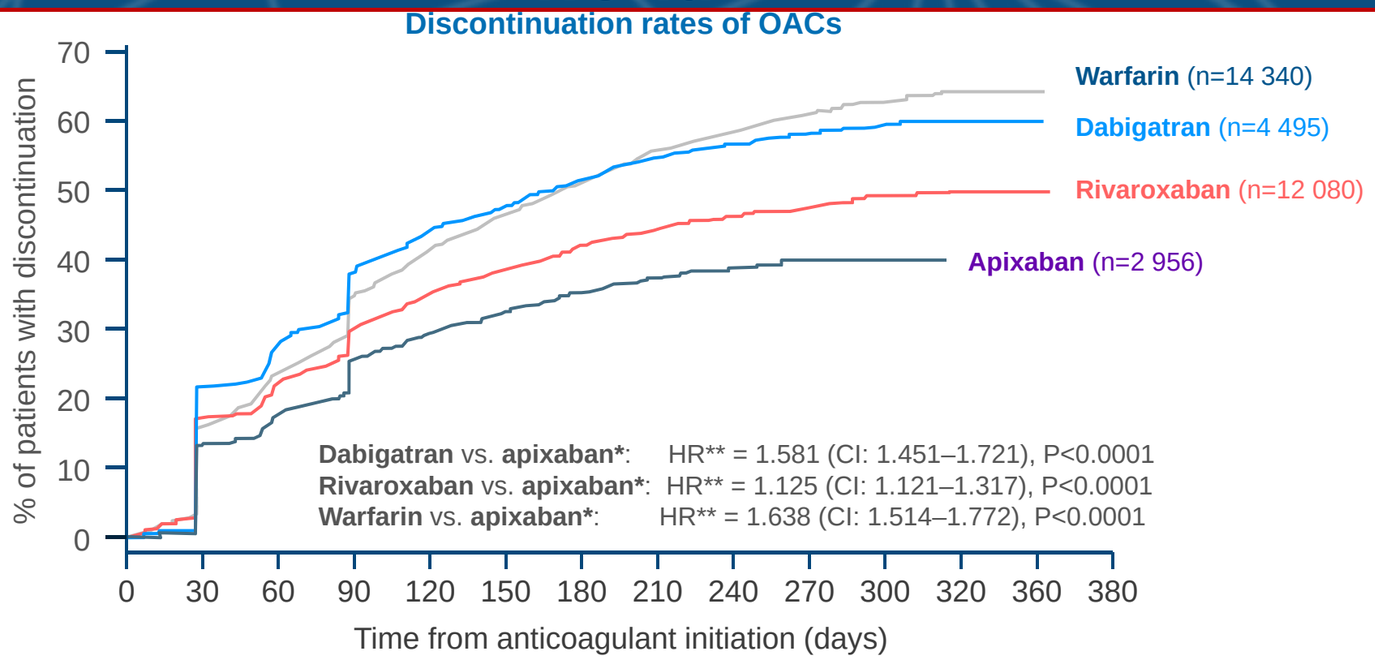
Cumulative Incidence of Recurrent VTE (Before Propensity Adjustment)



Rivaroxaban									
Patients at risk	2619	2380	1642	1340	789	658	560	263	174
Patients with events	0	23	31	32	34	34	34	36	37
Standard anticoagulation									
Patients at risk	2419	1858	1444	1212	828	695	603	313	193
Patients with events	0	30	37	40	46	52	52	53	54

Safety population; adjusted for cancer at baseline

Discontinuation rates of NOACs in real world



* Effect size is versus apixaban which acts as a reference category.

** Analysis controlled for other variables including age, gender, onset of embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of TIA or stroke and history of bleeding.

Retrospective cohort study NVAF patients newly prescribed a NOAC or newly prescribed warfarin without knee/hip replacement surgeries in the time period of Jan 1 – Dec 31, 2013

Pan *et al.* Presented at the ESC Congress 2014. Abstract #5112.

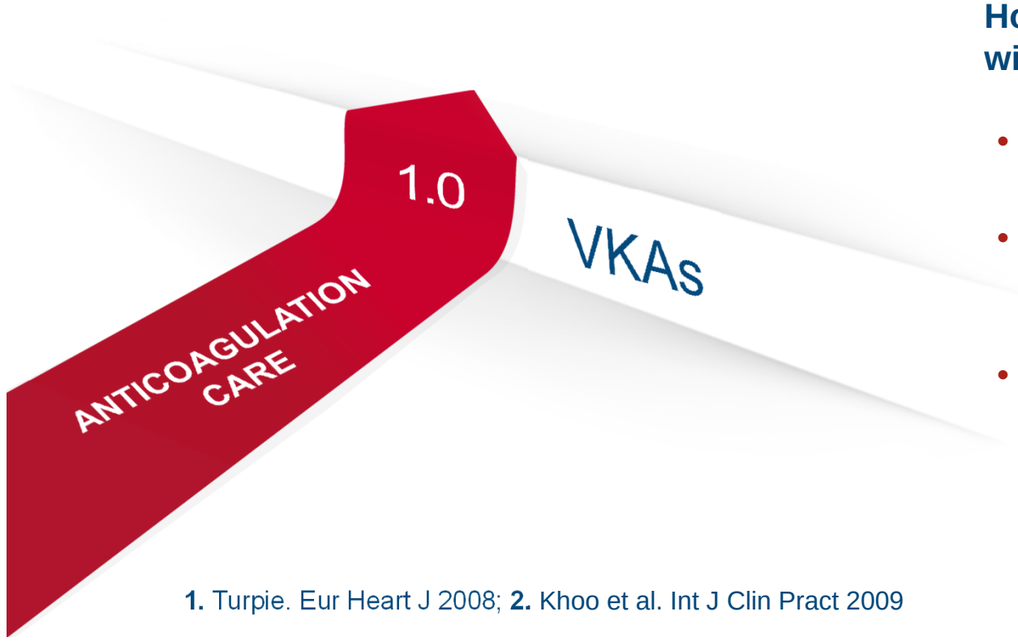
L’unico rischio da evitare

Trasformare la facilità d’impiego dei NOACs (pregio) in una banalizzazione d’impiego (difetto).

Introduction of oral anticoagulation marked the beginning of the first phase of anticoagulation care

1.0 The first oral anticoagulants

VKAs offered much-needed protection from thromboembolic events



However, VKAs are associated with major limitations:[1,2]

- Variable and unpredictable PK/PD
- Need for regular anticoagulation monitoring and dose adjustments
- Slow onset and offset of action

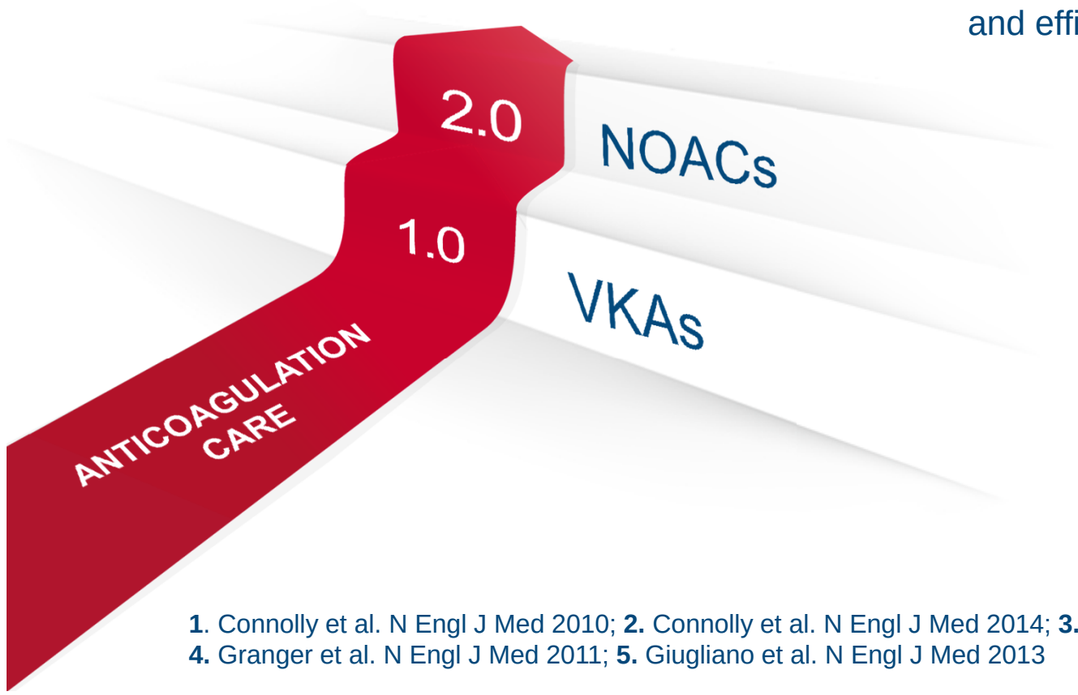
1. Turpie. Eur Heart J 2008; **2.** Khoo et al. Int J Clin Pract 2009

50 years later, NOACs revolutionized protection from thromboembolic disease

2.0

50 years later

NOACs address many of the limitations of traditional therapies

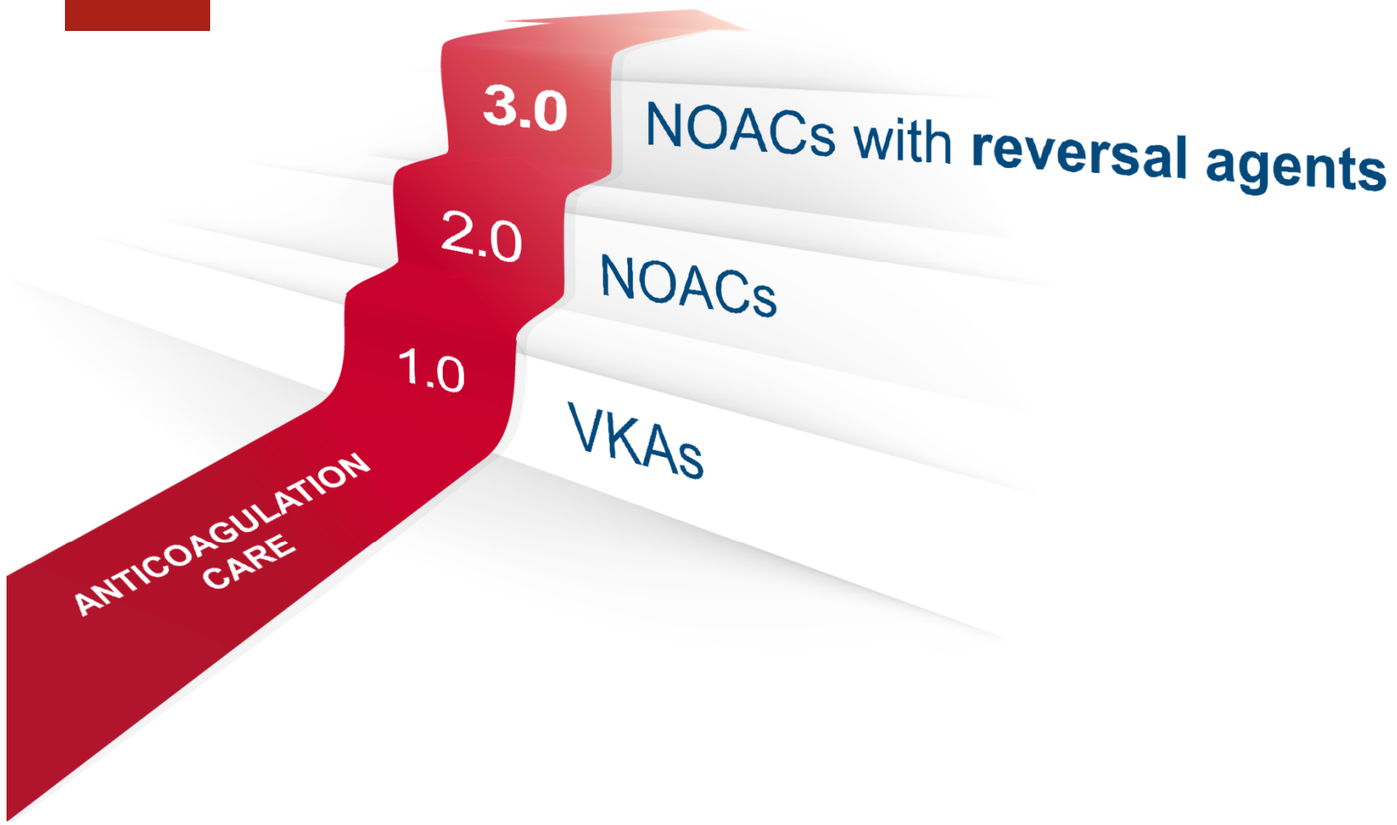


- In clinical trials, NOACs have demonstrated favourable safety and efficacy profiles vs warfarin[1–5]

1. Connolly et al. N Engl J Med 2010; **2.** Connolly et al. N Engl J Med 2014; **3.** Patel et al. N Engl J Med 2011; **4.** Granger et al. N Engl J Med 2011; **5.** Giugliano et al. N Engl J Med 2013

The Future: availability of specific reversal agents marks the next phase in anticoagulation care

3.0 **The Future**
Specific reversal agents mark the next phase in anticoagulation care



Idarucizumab now gives the option of immediate specific reversal in dabigatran patients requiring urgent surgery/procedure

Patient on dabigatran requires emergency surgery/urgent procedure

Give idarucizumab

Patient proceeds to surgery without delay
and with NOAC anticoagulation immediately reversed

Dabigatran can be re-started 24 hrs after idarucizumab administration
(earlier re-start with LMWH also possible)

Time without anticoagulation is minimized

Praxbind®: EU SPC, 2015

RE-VERSE AD™ interim results: GI bleeding/GI surgery

GI bleeding	• 20/51 (39%) of all bleeds requiring idarucizumab were into the GI tract • No patient death was directly attributable to GI bleeding
GI surgery	• 14/39 (36%) of all emergency surgeries requiring idarucizumab involved surgery on the GI tract (e.g. acute appendicitis or cholecystitis)

Pollack et al. N Engl J Med 2015

Idarucizumab is not approved in all countries. Please check your local prescribing information for details. This information is presented for medical education purposes only

Key message

- **FA: aritmia estremamente frequente (in Italia da 600.000 a 1.200.000 persone affette + 120.000 nuovi casi ogni anno)**