SOCIETÀ MEDICA
DI SANTA MARIA NUOVA

VIII EDIZIONE

Giornate Mediche di
Santa Maria Nuova 2016

L'Ospedale dei Fiorentini

SANTA MARIA NUOVA:
DALL'OSPEDALE DEL CENTRO
DI FIRENZE ALLA
USL TOSCANA CENTRO

Condivisione di percorsi gestionali comuni e di peculiarità assistenziali

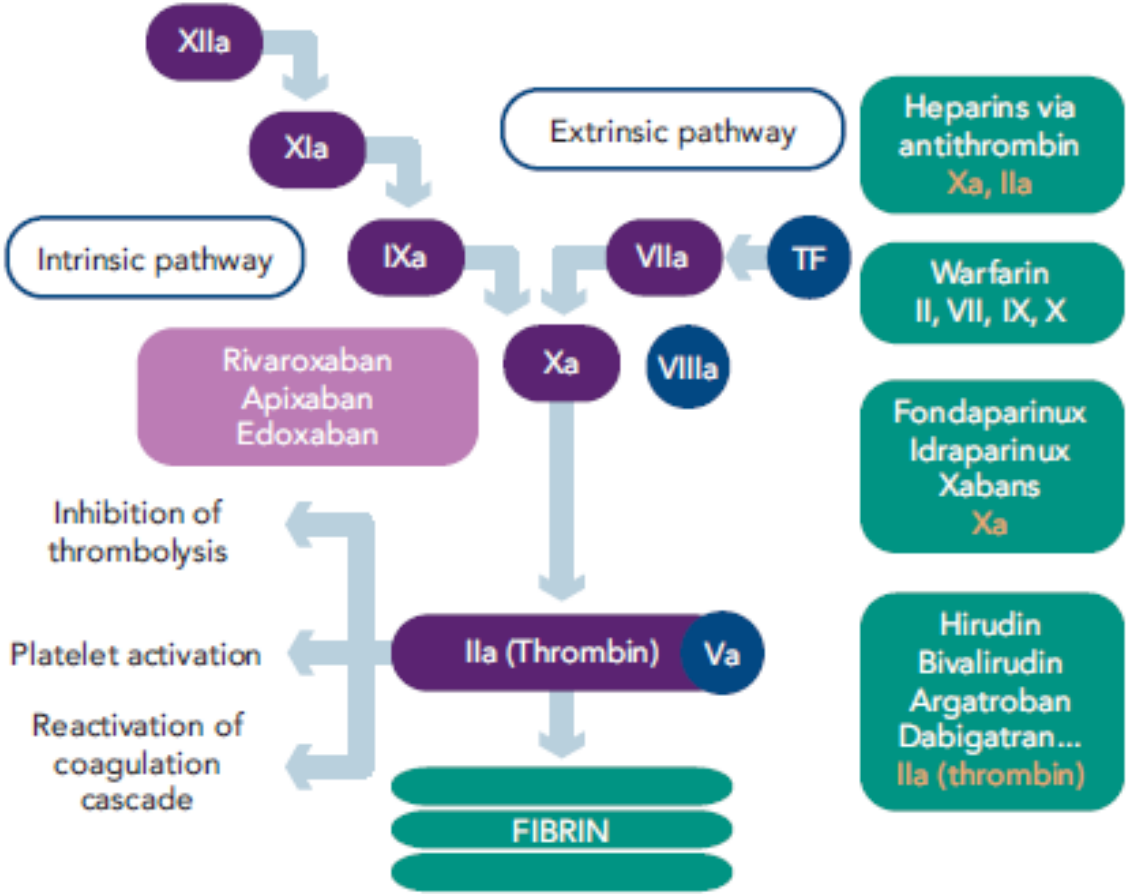
7 - 8 Ottobre 2016

Up-dating sui nuovi anticoagulanti orali

LUCA MASOTTI

MEDICINA INTERNA SMN

Figure 1: Action of Anticoagulants in the Coagulation Cascade



	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Molecular weight	628 KD pro-drug 471 KD drug	460 KD	538 KD	436 KD
Hours to Cmax	1.25-3	3-4	1-2	2-4
CYP metabolism	None	Minimal	<4%	32%
Bioavailability	6%	60%	62%	80%
Volume distribution	60-70 L	0.3 L/Kg	90 L	0.6-1.5 L/Kg
Transporters	P-gp	P-gp	P-gp	P-gp
Protein binding	35%	87%	50%	93%
Half-life	12-14 h	10-12 h	10-14 h	7-13 h
Renal elimination	80%	25%	35%	33%
Daily oral intake	Twice	Twice	Once	Once

FA non valvolare: caratteristiche die pazienti inclusi nei trials clinici di fase III

		ROCKET AF (n=14,264)	ARISTOTLE (n=18,201)	ENGAGE AF (n=21,105)	RE-LY (n=18,113)
Mean $CHADS_2$-Score		3.5	2.1	2.8	2.1
C	CHF	64%	35%	57%	32%
H	Hypertension	91%	87%	94%	79%
A	Age ≥75 years	44%	31%	40%	40%
D	Diabetes mellitus	40%	25%	36%	23%
S_2	Prior stroke or TIA	52%	19%	28%	20%
Moderate renal impairment		21%	15%	19%	19%

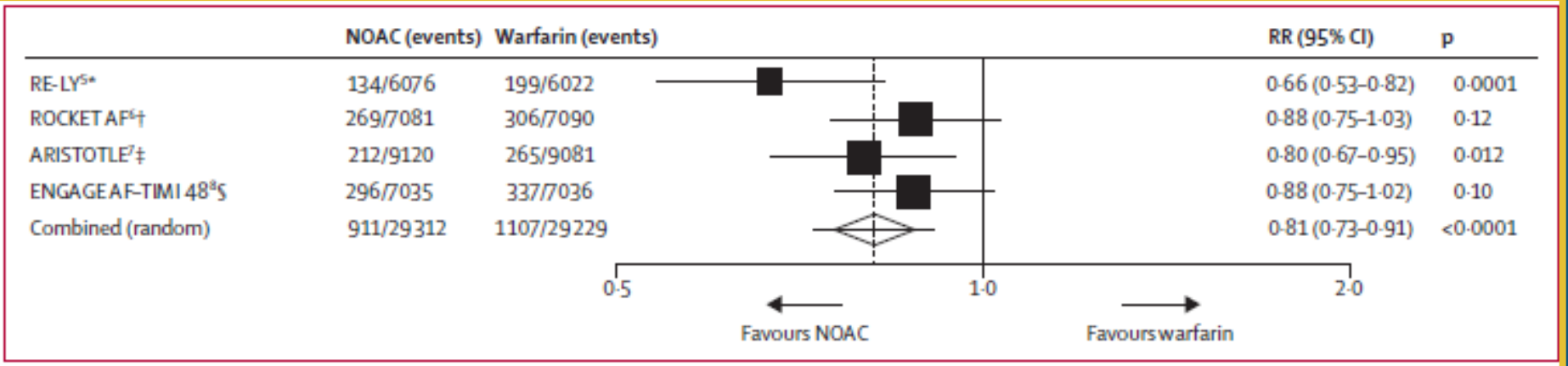


Figure 1: Stroke or systemic embolic events

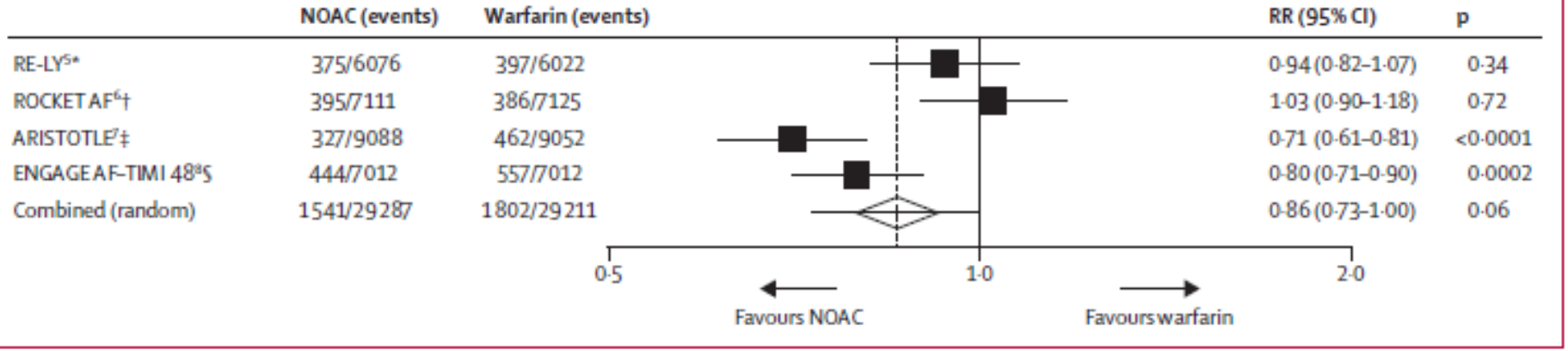


Figure 3: Major bleeding

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

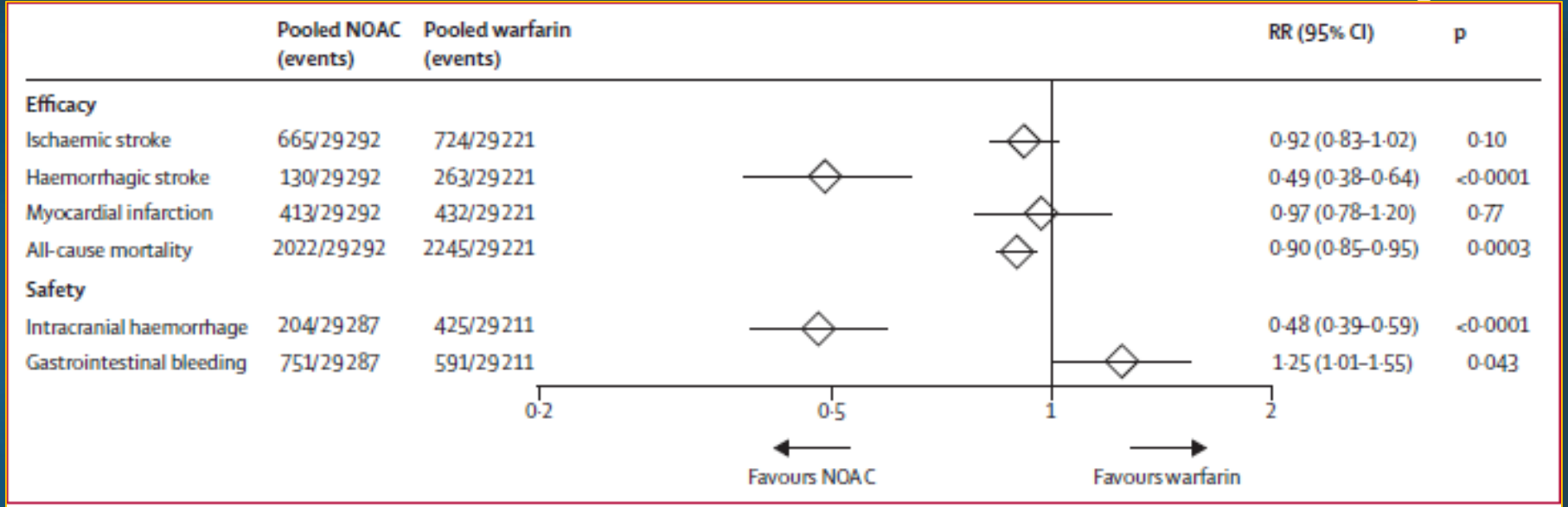
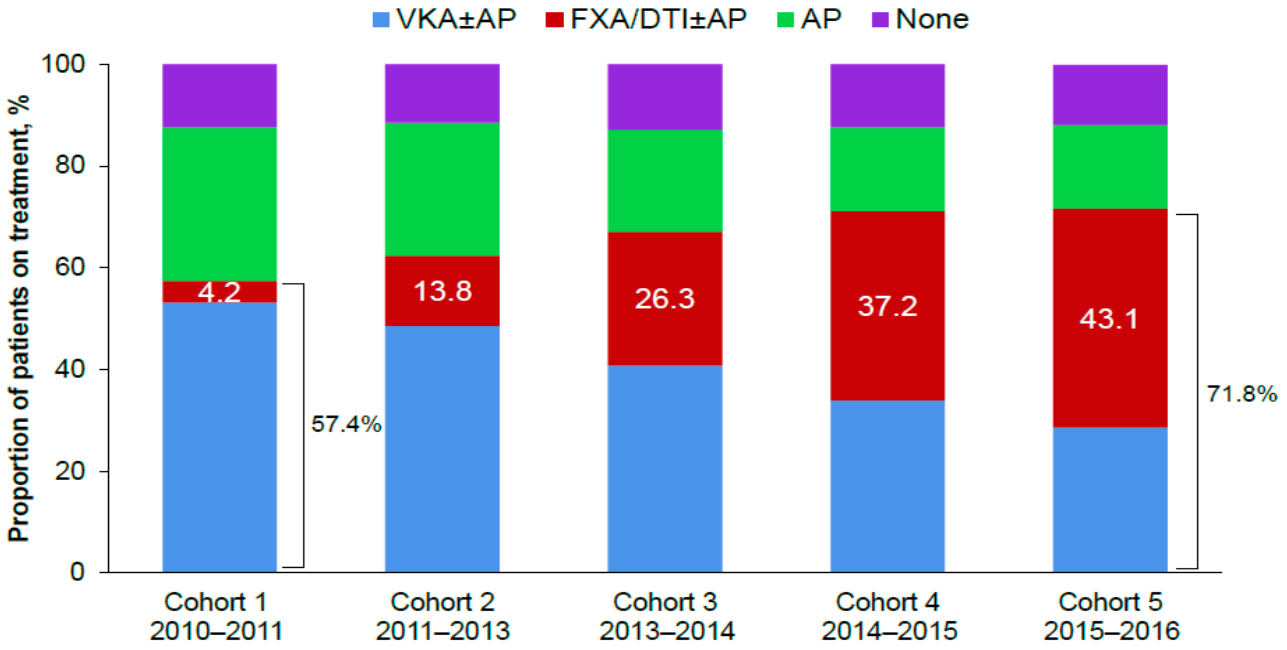


Figure 2: **Secondary efficacy and safety outcomes**
Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal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

Evolution in baseline treatment for patients enrolled in sequential cohorts of GARFIELD-AF

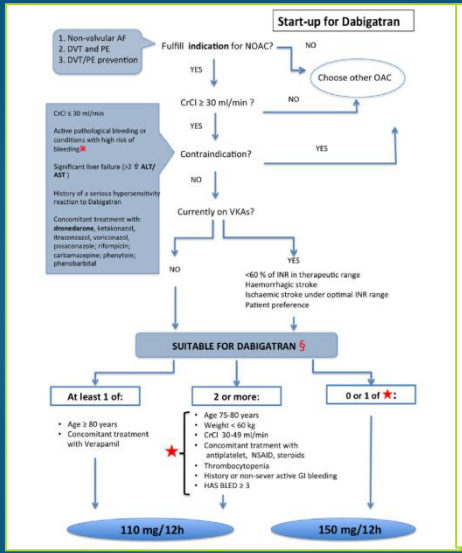


European Heart Journal – Cardiovascular Pharmacotherapy (2015) 1, 134–145
doi:10.1093/ehjcvp/pvv002

REVIEW

New oral anticoagulants: a practical guide for physicians

Rocio Hinojar*, Jose Julio Jiménez-Natcher, Covadonga Fernández-Golfín, and Jose Luis Zamorano

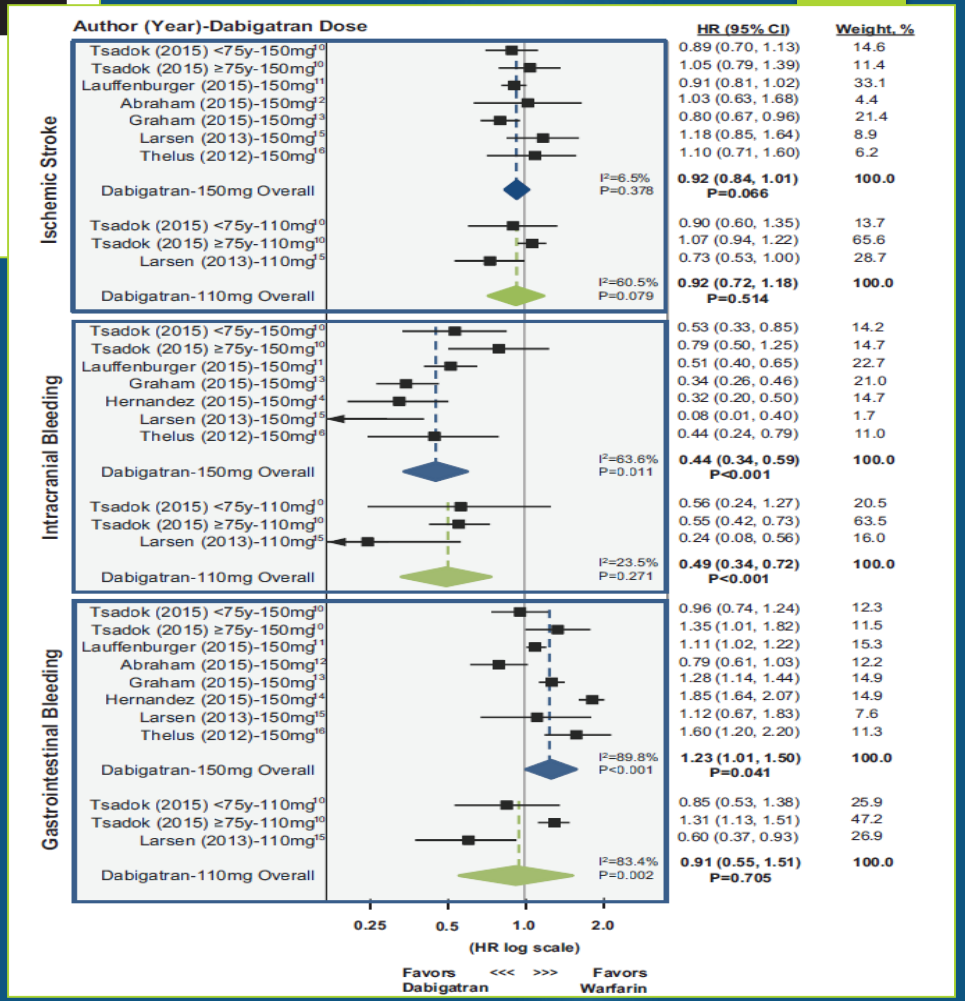


Original Article

Dabigatran Versus Warfarin for Atrial Fibrillation in Real-World Clinical Practice

A Systematic Review and Meta-Analysis

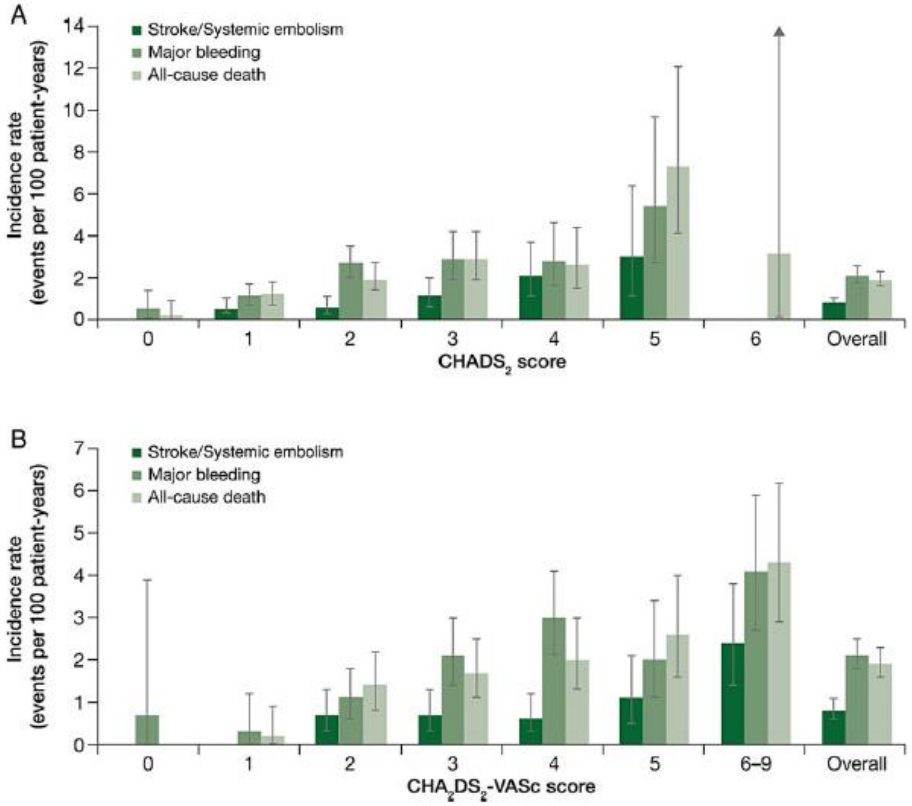
Robert J. Romanelli, PhD, MPH; Laura Nolting, BS; Marina Dolginsky, BS; Eunice Kym, PharmD; Kathleen B. Orrico, PharmD



European Heart Journal
doi:10.1093/eurheartj/ehv466

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

A. John Camm[1]*, Pierre Amarenco[2], Sylvia Haas[3], Susanne Hess[4], Pau
Silvia Kuhls[7], Martin van Eickels[4], and Alexander G.G. Turpie[8], on bel
XANTUS Investigators



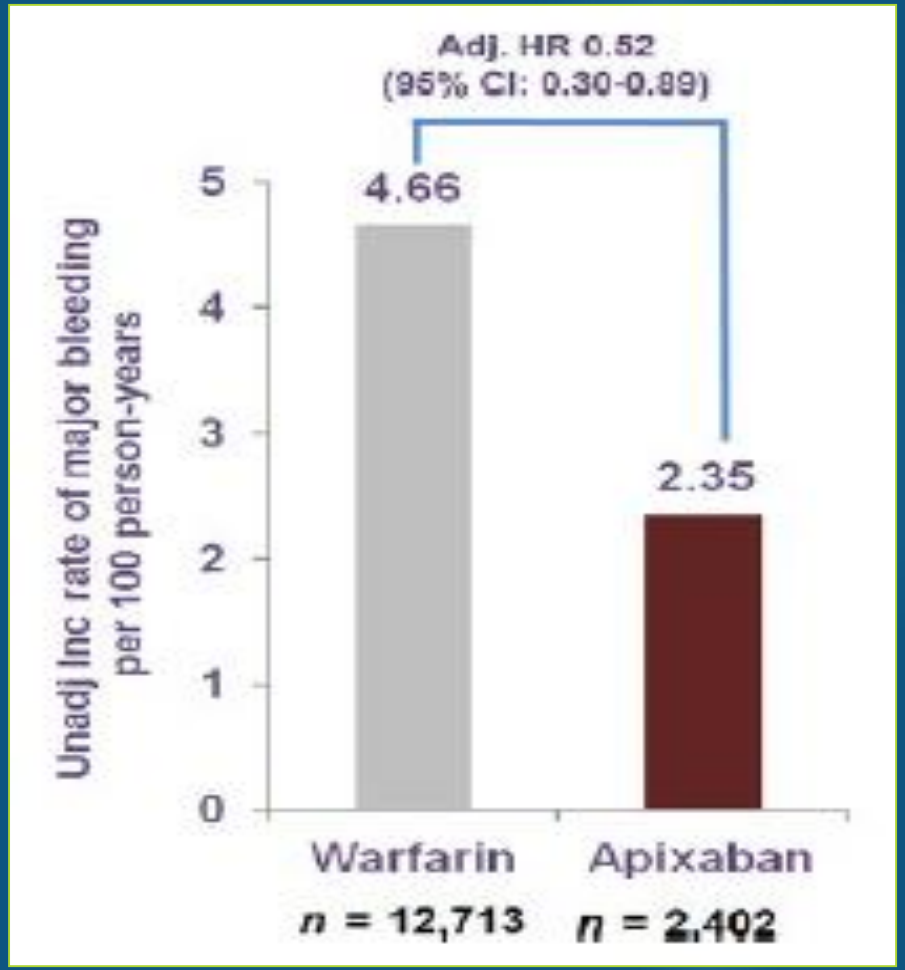
Received: 16 May 2016 | Accepted: 1 July 2016
DOI: 10.1111/ijcp.12863

ORIGINAL ARTICLE

WILEY THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States

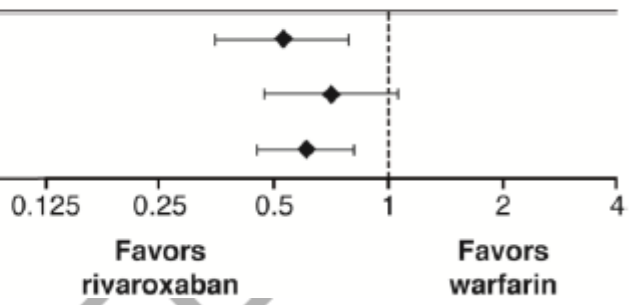
Gregory Y. H. Lip[1,2] | Xianying Pan[3] | Shital Kamble[3] | Hugh Kawabata[3] | Jack Mardekian[4] | Cristina Masseria[4] | Amanda Bruno[3] | Hemant Phatak[3]



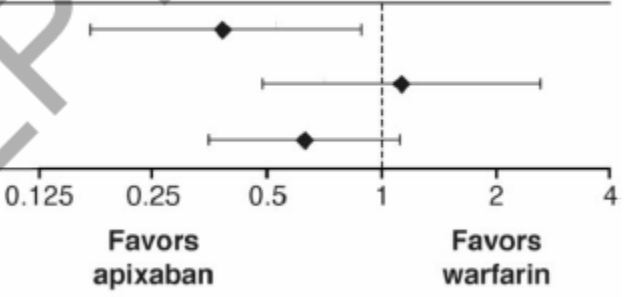
Real-World Evidence of Stroke Prevention in Patients with Nonvalvular Atrial Fibrillation in the United States: the REVISIT-US Study

Craig I. Coleman, Matthias Antz, Kevin Bowrin, Thomas Evers, Edgar P. Simard, Hendrik Bonnemeier & Riccardo Cappato

	Rivaroxaban Rate (%/year)	Warfarin Rate (%/year)	HR (95% CI) rivaroxaban vs. warfarin
ICH	0.49	0.96	0.53 (0.35–0.79)
Ischemic stroke	0.54	0.83	0.71 (0.47–1.07)
Combined	0.95	1.60	0.61 (0.45–0.82)



	Apixaban Rate (%/year)	Warfarin Rate (%/year)	HR (95% CI) apixaban vs. warfarin
ICH	0.38	0.97	0.38 (0.17–0.88)
Ischemic stroke	0.56	0.51	1.13 (0.49–2.63)
Combined	0.89	1.44	0.63 (0.35–1.12)



Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; G. Caleb Alexander, MD, MS; William Crown, PhD; Victor M. Montori, MD, MSc; Lindsey R. Sangaralingham, MPH; Bernard J. Gersh, MB, ChB, DPhil, FRCP; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

American Heart Association | American Stroke Association

Table 7. Adherence to OACs (PDC ≥80%) Within First 6 Months of Follow-up, Stratified by Index Medication (N=64 661)

	Apixaban (n=3900)	Dabigatran (n=10 235)	Rivaroxaban (n=12 336)	All NOACs (n=26 471)	Warfarin (n=38 190)	*P* Value (All NOACs Pooled vs Warfarin)
Unadjusted adherence*						
All	64.5%	51.2%	58.4%	56.5%	51.6%	<0.001
CHA_2DS_2-VASc score 0 or 1	53.2%	37.1%	45.8%	42.6%	40.3%	0.06
CHA_2DS_2-VASc score 2 or 3	64.6%	53.3%	60.1%	58.0%	49.8%	<0.001
CHA_2DS_2-VASc score ≥4	66.7%	55.0%	61.0%	59.8%	53.4%	<0.001
Adjusted adherence, 95% CI†						
All	62.5% (60.8–64.2)	57.3% (56.2–58.4)	59.5% (58.5–60.5)	58.9% (58.2–59.7)	49.9% (49.3–50.5)	<0.001
CHA_2DS_2-VASc score 0 or 1	51.2% (46.3–56.1)	41.4% (39.0–43.7)	44.4% (42.1–46.7)	43.7% (42.1–45.2)	37.8% (35.9–39.7)	<0.001
CHA_2DS_2-VASc score 2 or 3	62.4% (59.5–65.2)	58.3% (56.6–60.0)	60.1% (58.6–61.6)	59.6% (58.5–60.6)	48.3% (47.3–49.4)	<0.001
CHA_2DS_2-VASc score ≥4	64.4% (62.2–66.5)	59.5% (58.0–61.0)	61.7% (60.3–63.0)	61.1% (60.2–62.1)	52.8% (52.1–53.5)	<0.001

J Am Heart Assoc. 2016

European Heart Journal
doi:10.1093/eurheartj/ehw210

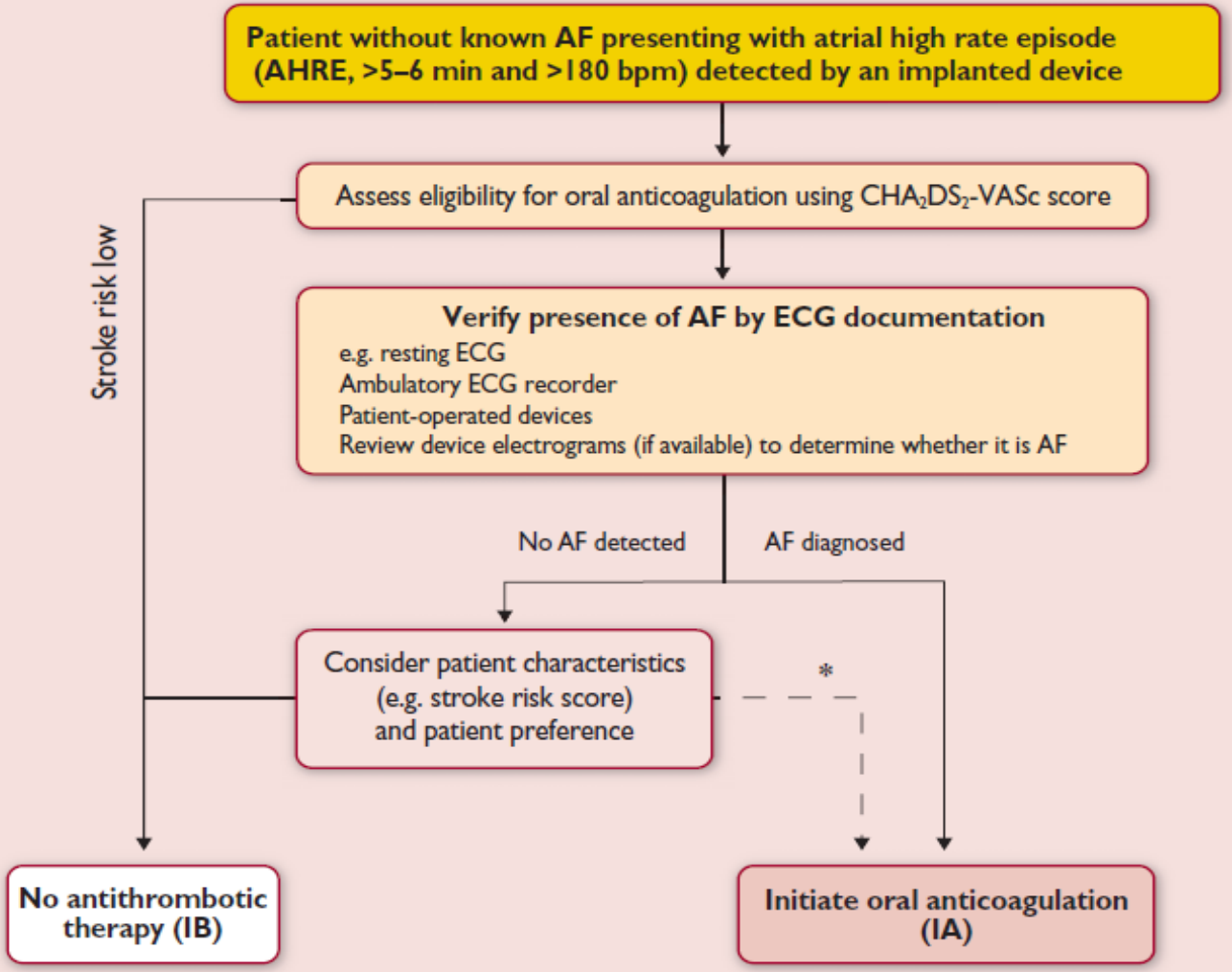
ESC GUIDELINES

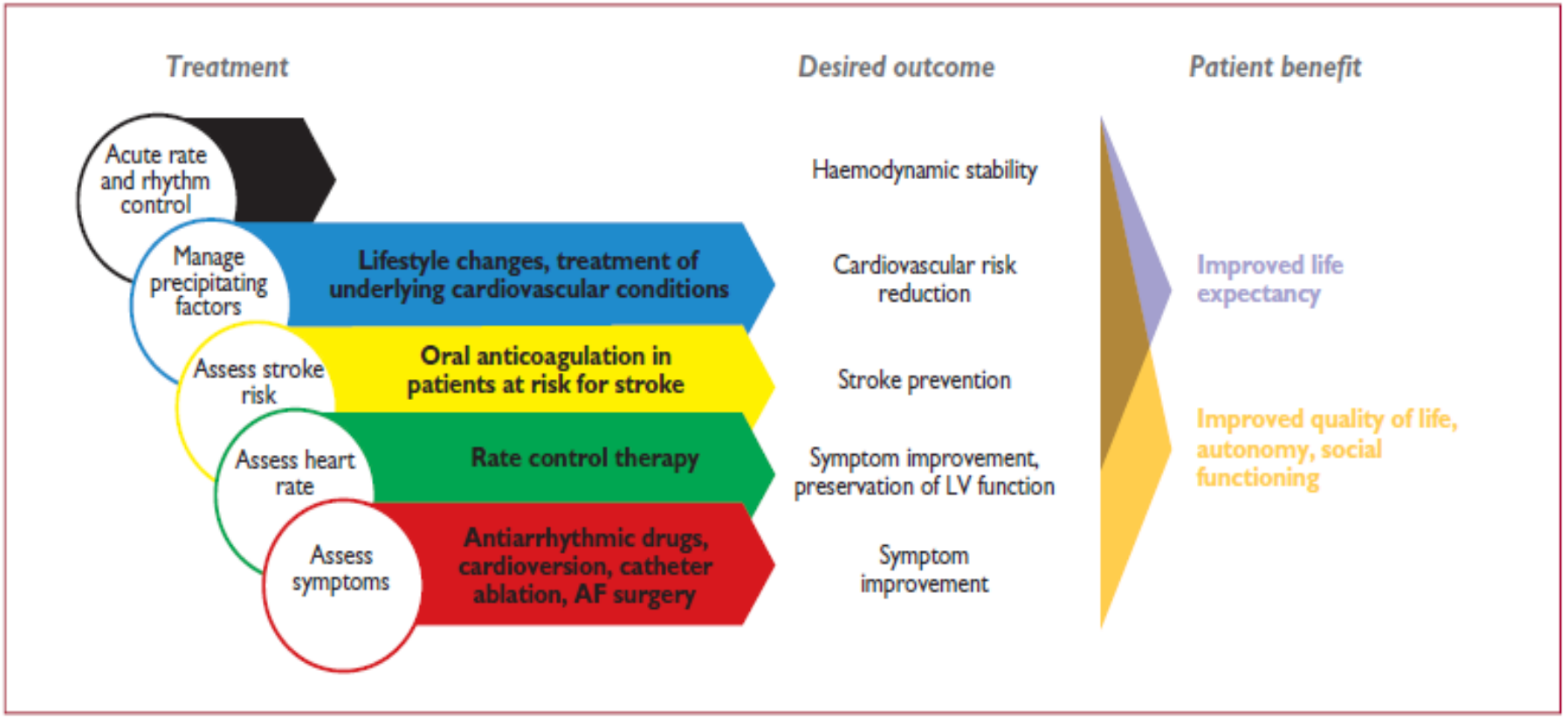
2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

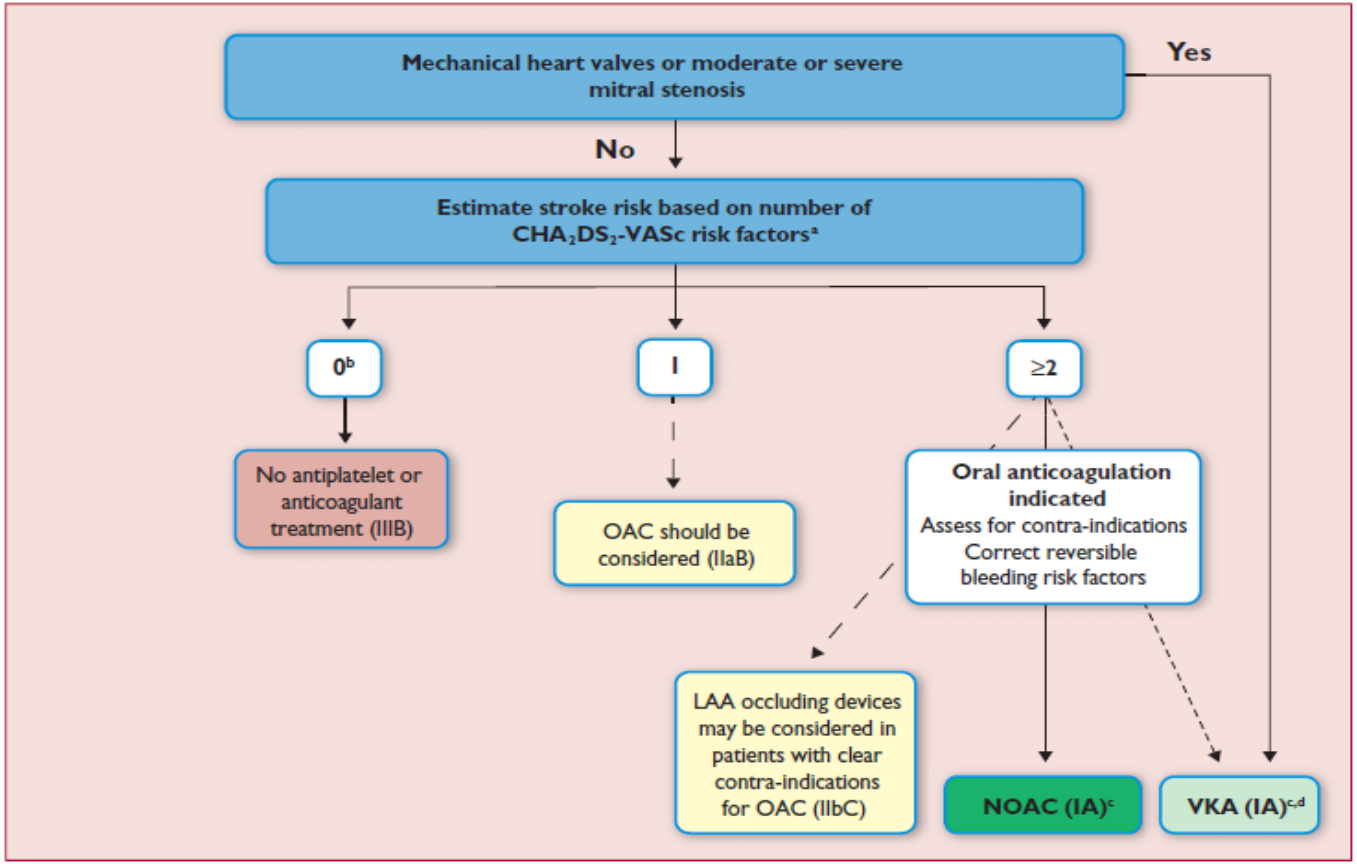
Endorsed by the European Stroke Organisation (ESO)


Patient without known AF presenting with atrial high rate episode (AHRE, >5–6 min and >180 bpm) detected by an implanted device
Assess eligibility for oral anticoagulation using CHA_2DS_2-VASc score
Stroke risk low
Verify presence of AF by ECG documentation
e.g. resting ECG
Ambulatory ECG recorder
Patient-operated devices
Review device electrograms (if available) to determine whether it is AF
No AF detected
AF diagnosed
Consider patient characteristics (e.g. stroke risk score) and patient preference
*
No antithrombotic therapy (IB)
Initiate oral anticoagulation (IA)



AF = atrial fibrillation; LV = left ventricular.

Figure 5 Acute and chronic management of atrial fibrillation patients, desired cardiovascular outcomes, and patient benefits. Adapted from the report on the 4th AFNET/EHRA consensus conference.[76]



AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.
[a]Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Sstroke/TIA/embolus (2 points), Vascular disease, age 65–74 years, female Sex.
[b]Includes women without other stroke risk factors.
[c]IIaB for women with only one additional stroke risk factor.
[d]IB for patients with mechanical heart valves or mitral stenosis.

Figure 8 Stroke prevention in atrial fibrillation.

Recommendations for stroke prevention in patients with atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B	371, 375–377
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B	371, 376, 377
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B	274, 435–440
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A	39, 318–321, 404
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	395, 432, 441-444
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A	39, 318, 319, 404, 408
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B	429, 445
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B	368, 371, 376, 377
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A	38, 429, 430
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C	318–321, 400, 404

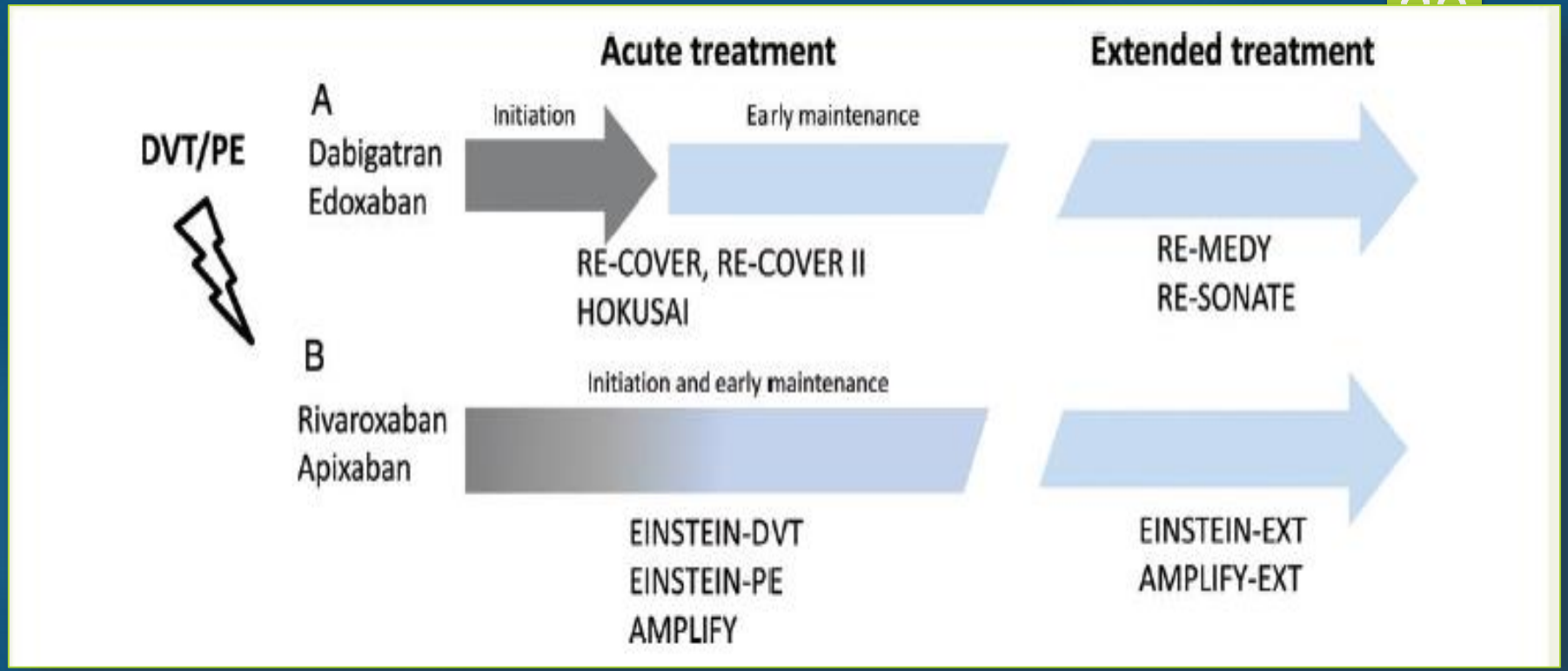
Farmaci per il trattamento della fibrillazione atriale

Non c'è sovra-trattamento:

- solo il **6,1%** dei pazienti trattati con NAO hanno una storia di terapia ben controllata con warfarin (TTR ≥70%) e hanno rischio trombotico o emorragico basso (CHA2DS2-VASc <1 o HAS-BLED <3).

C'è un importante sotto-trattamento:

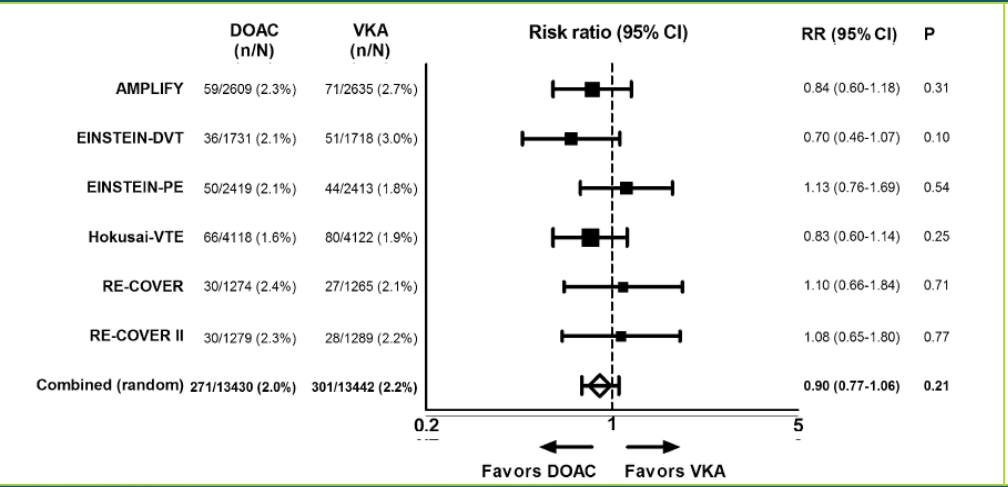
- Il **59,0%**, dei pazienti con FA senza un adeguato controllo dell'INR in warfarin (TTR <70%) o con un'alterazione del rischio trombotico o emorragico (CHA2DS2-VASc ≥1 e HAS-BLED >3) è risultata non in trattamento con NAO

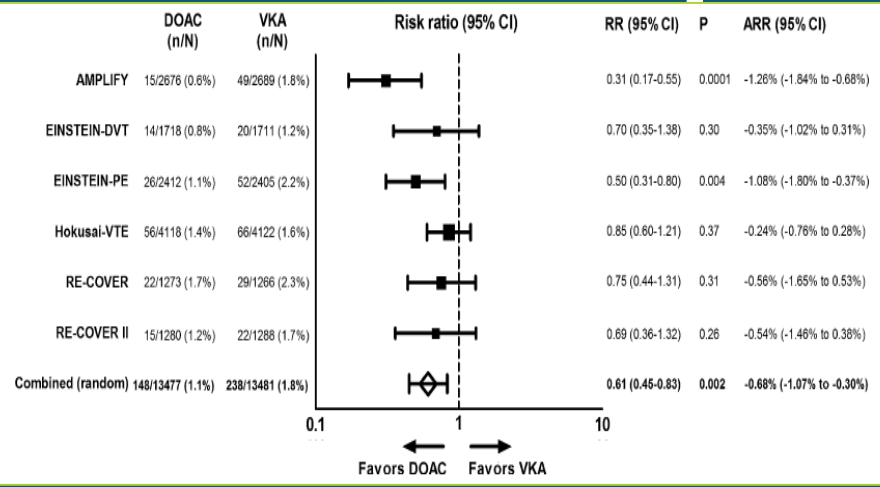


Fontana et al Eur Heart J 2014

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials

Nick van Es,[1] Michiel Coppens,[1] Sam Schulman,[2] Saskia Middeldorp,[1] and Harry R. Büller[1]





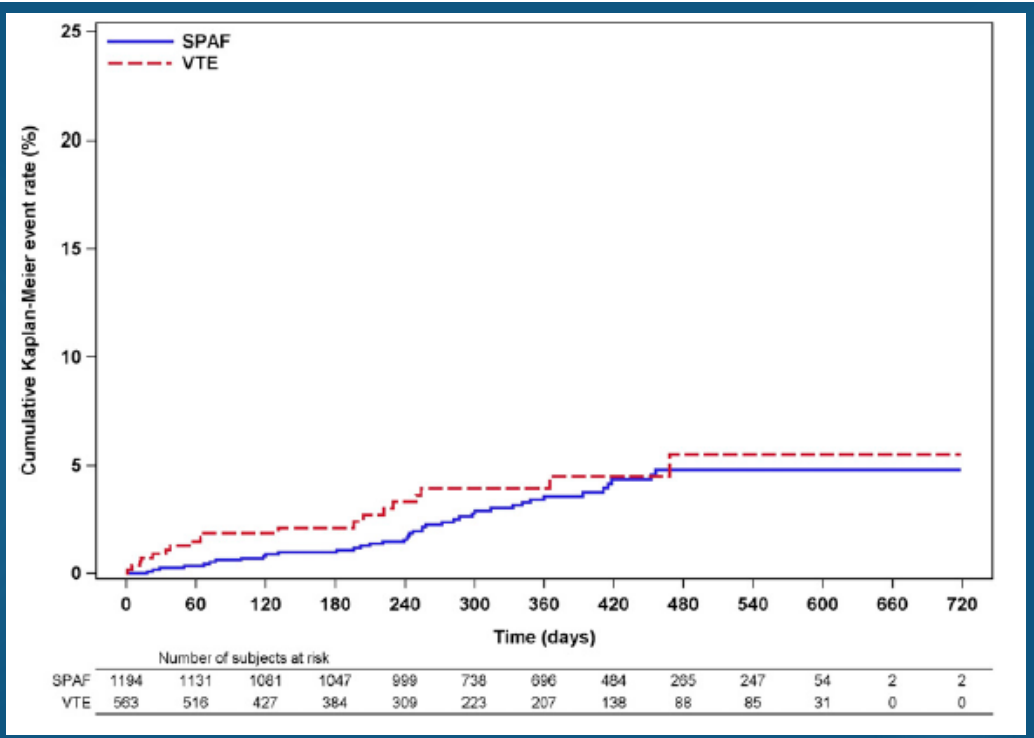
THROMBOSIS AND HEMOSTASIS

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

Jan Beyer-Westendorf,[1] Kati Förster,[1] Sven Pannach,[2] Franziska Ebertz,[1] Vera Gelbricht,[1] Christoph Thieme,[1] Franziska Michalski,[1] Christina Köhler,[1] Sebastian Werth,[1] Kurtulus Sahin,[3] Luise Tittl,[1] Ulrike Hänsel,[1] and Norbert Weiss[1]

Table 2. Bleeding rates per 100 patient-years in valid-for-safety analysis set

	All patients	SPAF	VTE	*P* value: SPAF vs VTE
n (%)	1775 (100)	1200 (67.6)	575 (32.4)	
Any bleeding, % (95% CI)	59.4 (55.2-63.9)	59.3 (54.4-64.6)	59.6 (51.7-68.4)	.4989
Minor bleeding, % (95% CI)	36.3 (33.2-39.7)	35.8 (32.2-39.7)	37.8 (31.8-44.6)	.4199
NMCR bleeding, % (95% CI)	19.7 (17.6-22.1)	20.7 (18.1-23.5)	17.2 (13.5-21.6)	.1585
Major bleeding, % (95% CI)	3.4 (2.6-4.4)	3.1 (2.2-4.3)	4.1 (2.5-6.4)	.2849



nasotti 7 ottobre 2016

XALIA: Treatment-Emergent Clinical Outcomes (Propensity-Score Adjusted Comparison)

	Rivaroxaban (n=2505) n (%)	Standard anticoagulation (n=2010) n (%)	Hazard ratio (95% CI)	*p*-value
Major bleeding	19 (0.8)	43 (2.1)	**0.77 (0.40–1.50)**	0.44
Recurrent VTE	36 (1.4)	47 (2.3)	**0.91 (0.54–1.54)**	0.72
All-cause mortality	11 (0.4)	69 (3.4)	**0.51 (0.24–1.07)**	0.07

Propensity score-adjusted population

CHEST

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Summary of Recommendations

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulant

1. In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).

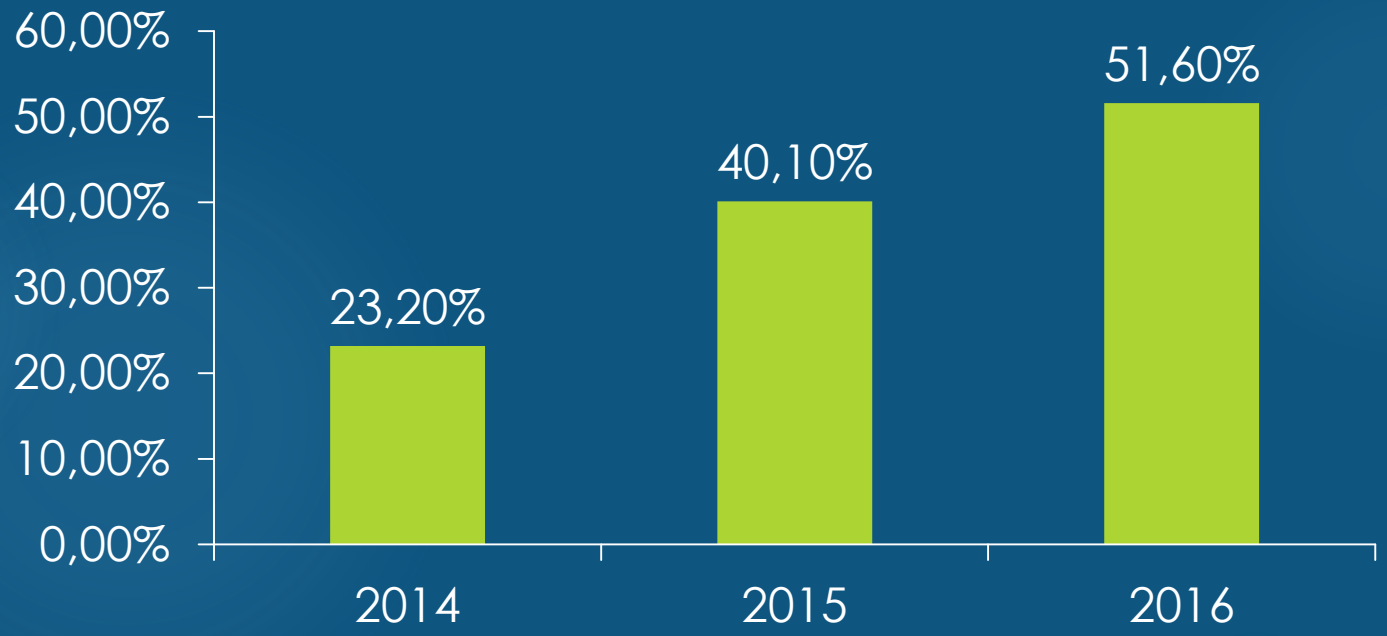
***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).**

For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban, or edoxaban, we suggest VKA therapy over low-molecular weight heparin (LMWH) (Grade 2C).

***3. In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).**

CHEST 2016; 149(2):315-352

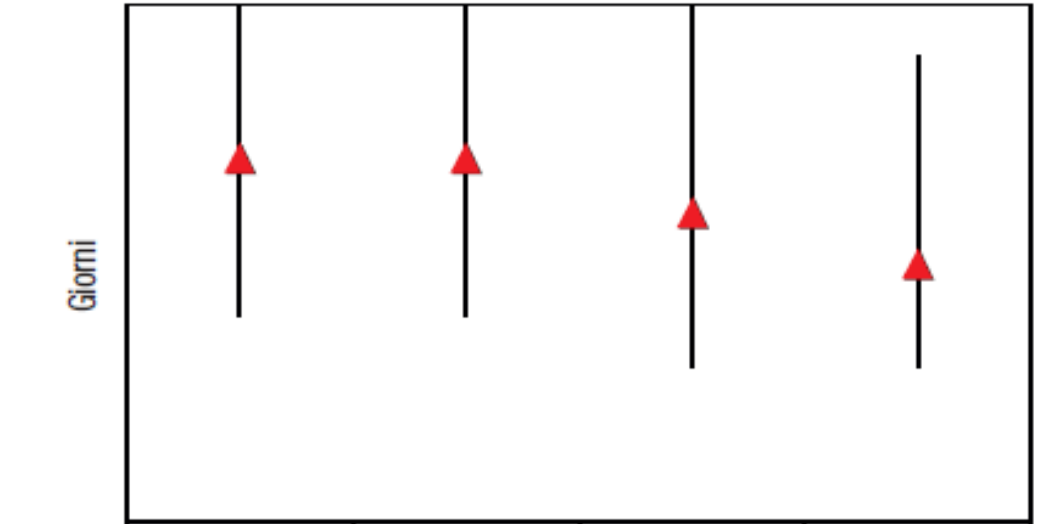
Trend di prescrizione dei NAO nel paziente dimesso con diagnosi di EP acuta nella ASF



Masotti L et al Farmaci 2016

Andamento della degenza ospedaliera nei pazienti dimessi con diagnosi di EP acuta nel corso degli anni

Figura 3. *Andamento della DO nei pazienti dimessi con diagnosi di EP acuta nel corso degli anni.*

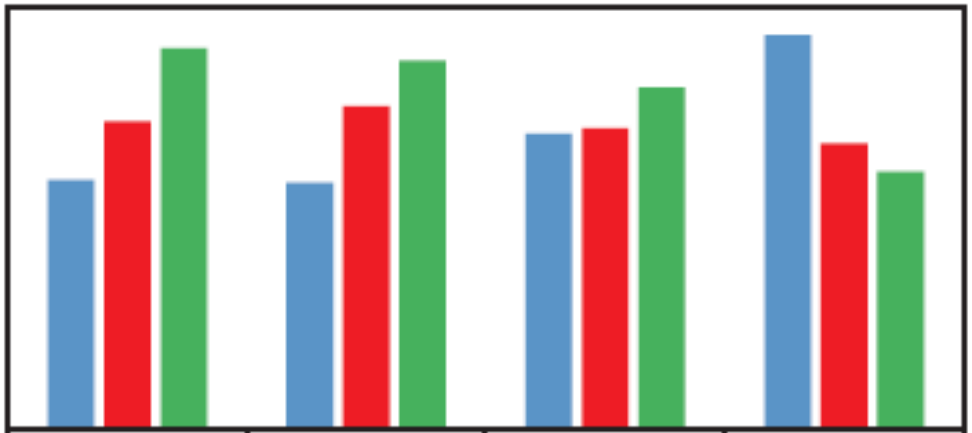


	2010	2012	Gennaio 2014 Agosto 2015	Settembre 2015 Agosto 2016
IQR max	13	13	12	11
IQR min	6	6	5	5
▲Mediana	9	9	8	7

Masotti L et al Farmaci 2016

Variazioni percentuali della degenza ospedaliera nei pazienti dimessi con diagnosi di EP acuta nel corso degli anni

Figura 4. *Variazioni percentuali della DO nei pazienti dimessi con diagnosi di EP acuta nel corso degli anni.*



	2010	2012	Gennaio 2014 Agosto 2015	Settembre 2015 Agosto 2016
≤6 gg	26,60%	26,30%	31,50%	42%
≥7 ≤10 gg	32,80%	34,40%	32,10%	30,50%
≥11 gg	40,60%	39,30%	36,40%	27,50

Masotti L et al Farmaci 2016

	Anti Xa (rivaroxaban, apixaban)	Altra terapia anticoagulante alla dimissione (eparine a basso peso molecolare, fondaparinux, AVK)	p
Numero	184 (Rivaroxaban 163, Apixaban 21)	320	-
M/F	41%/59%	45%/55%	ns
Età media ± DS(anni)	76 ± 13	75 ± 13	ns
Età mediana (IQR) (anni)	78 (70-84)	77 (68-84)	ns
DO media ± DS (giorni)	**8 ± 5**	**10 ± 6**	<0.005
DO mediana (IQR) (giorni)	**7 (5-9)**	**9 (6-13)**	<0.001
Dimissioni entro 48 ore	5.4%	2.4%	ns
Dimissioni entro 5 giorni	**30.9%**	**23.1%**	<0.005

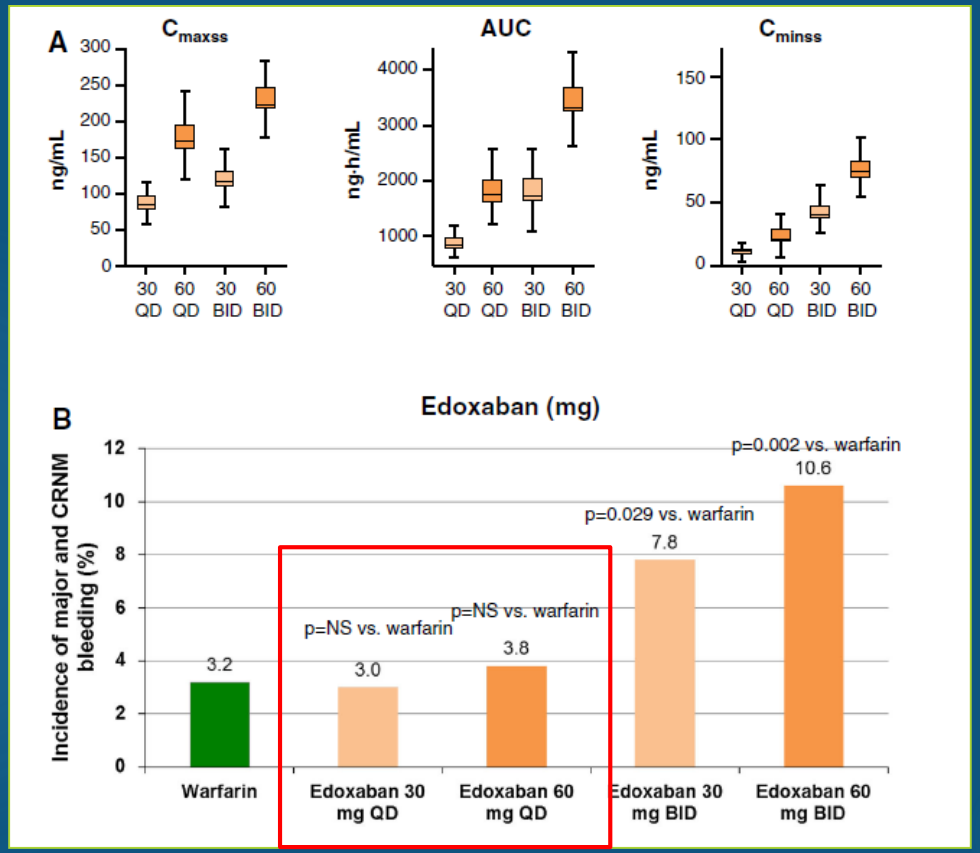
Masotti L et dati non pubblicati

Drugs (2014) 74:1209–1231
DOI 10.1007/s40265-014-0261-1

REVIEW ARTICLE

Edoxaban: An Update on the New Oral Direct Factor Xa Inhibitor

Henri Bounameaux · A. John Camm



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Warfarin (N=7036)	High-Dose Edoxaban (N=7035)	Low-Dose Edoxaban (N=7034)
Age ≥75 yr	2820 (40.1)	2848 (40.5)	2806 (39.9)
Prior stroke or transient ischemic attack	1991 (28.3)	1976 (28.1)	2006 (28.5)
Congestive heart failure	4048 (57.5)	4097 (58.2)	3979 (56.6)
Diabetes mellitus	2521 (35.8)	2559 (36.4)	2544 (36.2)
Hypertension requiring treatment	6588 (93.6)	6591 (93.7)	6575 (93.5)
$CHADS_2$ score†	2.8±1.0	2.8±1.0	2.8±1.0
≤3 — no. (%)	5445 (77.4)	5422 (77.1)	5470 (77.8)
4–6 — no. (%)	1591 (22.6)	1613 (22.9)	1564 (22.2)

Table 2 Results of the ENGAGE AF-TIMI 48 trial

	Warfarin event rate	High-dose edoxaban event rate	Low-dose edoxaban event rate	High-dose edoxaban versus warfarin	
				Hazard ratio (95% CI)	*P*-value
Efficacy outcomes					
Stroke or systemic embolic event (primary) (noninferiority)	1.50	1.18	1.61	0.79 (0.63–0.99)	<0.001
Stroke	1.69	1.49	1.91	0.88 (0.75–1.03)	0.11
Hemorrhagic stroke	0.47	0.26	0.16	0.54 (0.38–0.77)	<0.001
Stroke, systemic embolism or death from cardiovascular cause	4.43	3.85	4.23	0.87 (0.78–0.96)	0.005
Death from any cause	4.35	3.99	3.80	0.92 (0.83–1.01)	0.08
Death from cardiovascular cause	3.17	2.74	2.71	0.86 (0.77–0.97)	0.013
Safety outcomes					
ISTH major bleeding (primary)	3.43	2.75	1.61	0.80 (0.71–0.91)	<0.001
Fatal	0.38	0.21	0.13	0.55 (0.36–0.84)	0.006
Intracranial	0.85	0.39	0.26	0.47 (0.34–0.63)	<0.001
Gastrointestinal	1.23	1.51	0.82	1.23 (1.02–1.50)	0.03

Note: *From N Engl J Med*, Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. 369:2093 with permission from Massachusetts Medical Society.[1]

Abbreviations: CI, confidence interval; ISTH, International Society on Thrombosis and Haemostasis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators*

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	All Patients		Patients with Deep-Vein Thrombosis Only		Patients with Pulmonary Embolism	
	Edoxaban (N=4118)	Warfarin (N=4122)	Edoxaban (N=2468)	Warfarin (N=2453)	Edoxaban (N=1650)	Warfarin (N=1669)

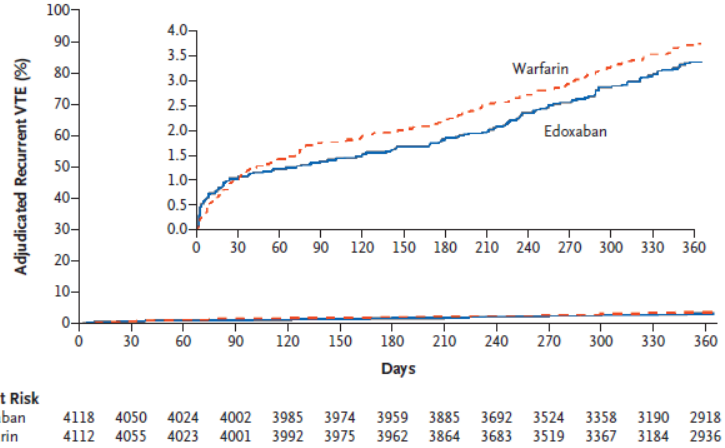


Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome.

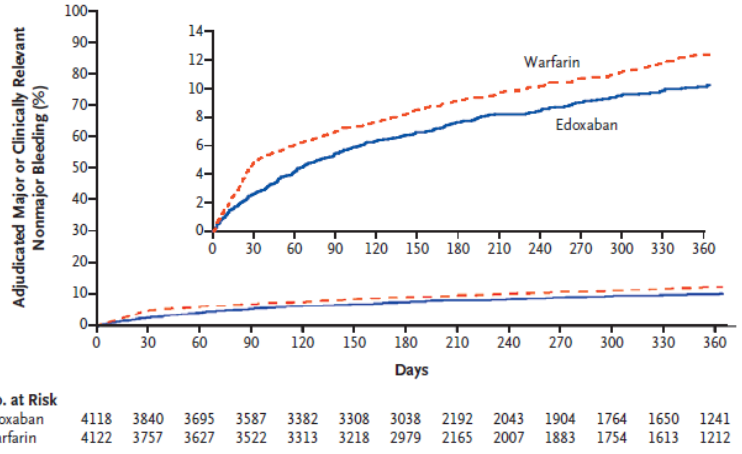


Figure 3. Kaplan–Meier Cumulative Event Rates for the Principal Safety Outcome.

Levi *Critical Care* (2016) 20:249
DOI 10.1186/s13054-016-1413-3

Critical Care

REVIEW Open Access

Management of bleeding in patients treated with direct oral anticoagulants

Marcel Levi[1,2]

Managing reversal of direct oral anticoagulants in emergency situations

Anticoagulation Education Task Force White Paper

Walter Ageno[1]; Harry R. Büller[2]; Anna Falanga[3]; Werner Hacke[4]; Jeroen Hendriks[5,6]; Trudie Lobban[7]; Jose Merino[8]; Ivan S. Milojevic[2]; Francisco Moya[10]; H. Bart van der Worp[11]; Gary Randall[12]; Konstantinos Tsioufis[13]; Peter Verhamme[14]; A. John Camm[15,16]

Table 2: Situations in which to consider use of a reversal agent.

Clinical situation	Definite need for a reversal agent	Reversal agent possibly helpful (patient-dependent)	Reversal agent generally not needed
Life-threatening bleeding (e.g., intracranial haemorrhage, symptomatic or expanding extradural haemorrhage, or uncontrollable haemorrhage)	X		
Bleeding in a closed space or critical organ (e.g., intracranial, intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome)	X		
Persistent major bleeding despite local haemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose	X		
Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance	X		
Emergency surgery or intervention in patients at high risk for procedural bleeding: neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac, or vascular surgery (aortic dissection/aneurysm repair), hepatic, or other major organ surgery	X		
Need for urgent surgery or intervention in patients with acute renal failure		X	
Elective surgery			X
Gastrointestinal bleeds that respond to supportive measures			X
High drug levels or excessive anticoagulation without associated bleeding			X
Need for surgery or intervention that can be delayed long enough to permit drug clearance			X

DOACs, non-Vitamin K oral anticoagulants. Adapted from Levy et al. 2015 (31).

Thromb Haemost 2016;

Managing reversal of direct oral anticoagulants in emergency situations

Anticoagulation Education Task Force White Paper

Walter Ageno[1]; Harry R. Büller[2]; Anna Falanga[3]; Werner Hacke[4]; Jeroen Hendriks[5,6]; Trudie Lobban[7]; Jose Merino[8]; Ivan S. Milojevic[9]; Francisco Moya[10]; H. Bart van der Worp[11]; Gary Randall[12]; Konstantinos Tsioufis[13]; Peter Verhamme[14]; A. John Camm[15,16]

Bleeding or Need for Surgery in Anticoagulated Patients

Mild Bleeding

- Delay or omit the next dose
- Evaluate concomitant medication
- Check renal function
- Consider any possible underlying source of bleeding

- Reassure the patient
- Ensure anticoagulation continued

+

Moderate to Severe Bleeding

Source Control:

- Mechanical compression
- Endoscopic, surgical hemostasis
- Interventional radiological hemostasis

Supportive Measures:

- Fluid replacement
- Transfusional support
- Maintain diuresis

+

Life-threatening Bleeding

Consider:

- PCC (4 factor) 50U/kg + 25 U/kg
- aPCC – 50U/kg, up to 200 U/kg

- For dabigatran: idarucizumab 5g*

Emergency Surgery

- Proceed to surgery when necessary – wait if possible
- Check anticoagulation status if time available
- Cross-match blood; packed RBC stand-by
- PCC (4 factor) stand-by

- For dabigatran: idarucizumab 5g

Resume anticoagulant as soon as hemostasis satisfactory and patient stabilized

Thromb Haemost 2016;

Idarucizumab is a humanized monoclonal antibody fragment

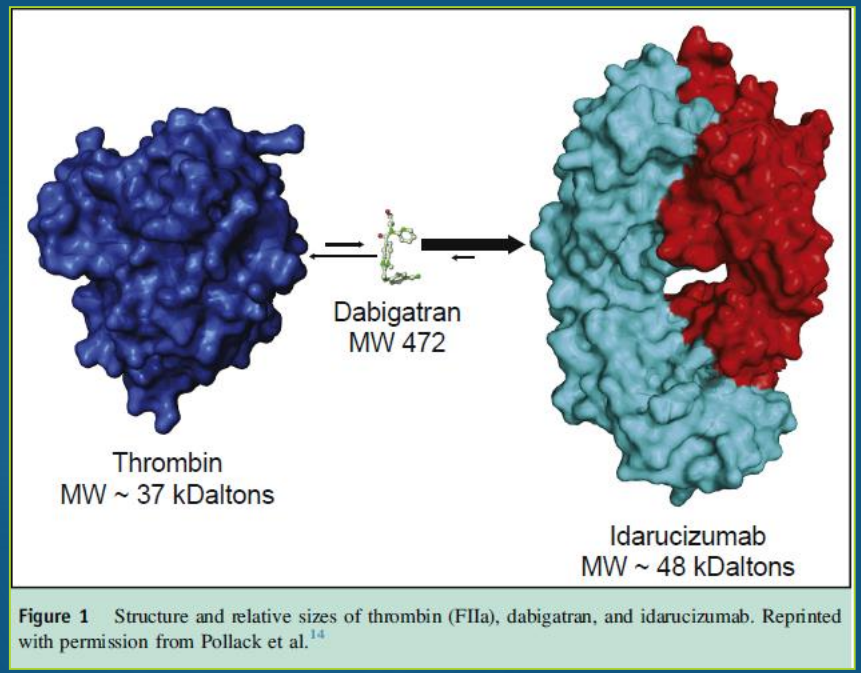


Figure 1 Structure and relative sizes of thrombin (FIIa), dabigatran, and idarucizumab. Reprinted with permission from Pollack et al.[14]

- Humanized Fab fragment
- Binding affinity **around 350 times higher** than dabigatran to thrombin
- No intrinsic pro-coagulant or anticoagulant activity
- IV dosing by bolus or rapid infusion (2 x 2.5 g in 50 mL in 15 minutes); immediate onset of action (in minutes)
- Short half-life (45 minutes-4h)

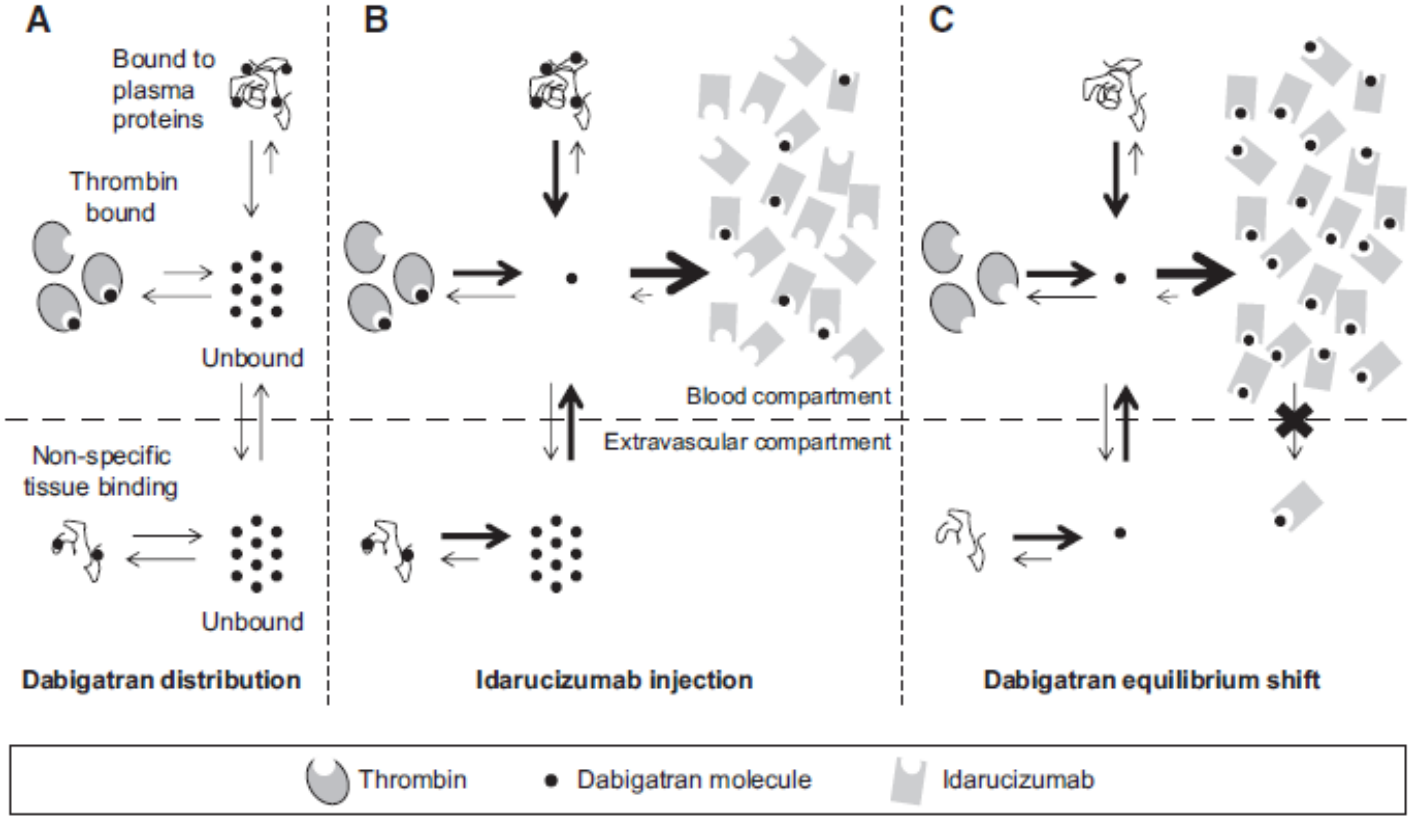


Figure 3. Changes in the distribution of dabigatran after idarucizumab administration. **A**, Circulating dabigatran exists in a state of equilibrium between the plasma and the extravascular compartments. Only unbound dabigatran in the plasma is able to bind thrombin and to inhibit coagulation. **B**, Idarucizumab rapidly binds dabigatran in the plasma. This alters the equilibrium, causing dabigatran in the extravascular compartment to move into the plasma and to potentially dissociate from thrombin (larger arrows). **C**, Because of the high affinity of idarucizumab for dabigatran, thrombin is no longer inhibited, and it regains its capacity to trigger clotting.

Table 1. Clinical Characteristics of the Patients.*

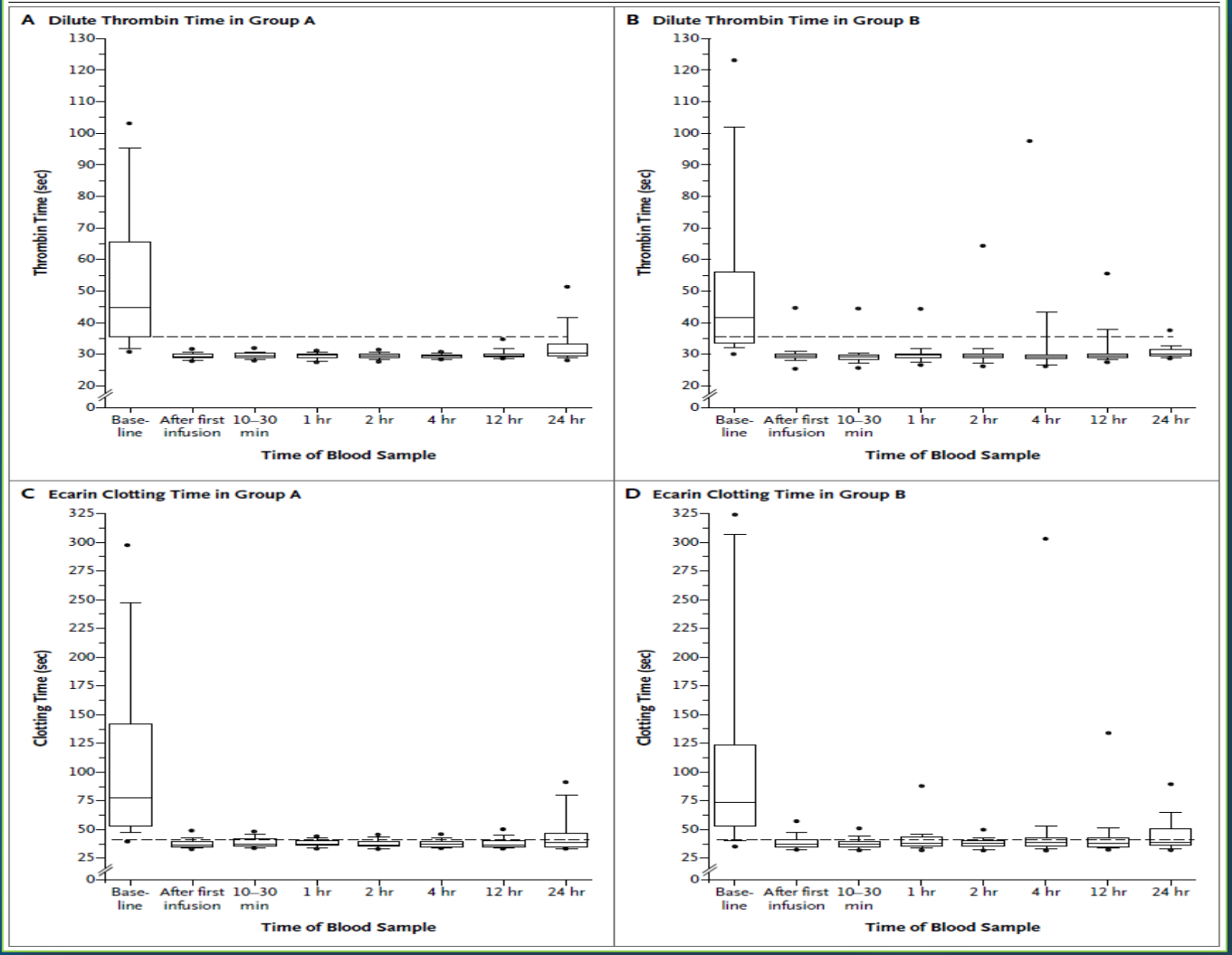
Characteristic	Group A (N=51)	Group B (N=39)	Total (N=90)
Age — yr			
Median	77.0	76.0	76.5
Range	48–93	56–93	48–93
Male sex — no. (%)	32 (63)	18 (46)	50 (56)
Race or ethnic group — no. (%)†			
Asian	5 (10)	1 (3)	6 (7)
Hawaiian or Pacific Islander	3 (6)	3 (8)	6 (7)
White	43 (84)	35 (90)	78 (87)
Weight — kg			
Median	70.5	73.0	71.9
Range	42.4–127.5	49.5–116.0	42.4–127.5
Creatinine clearance‡			
Value — ml/min			
Mean	59±33	65±36	62±35
Median	54	60	58
Range	16–187	11–171	11–187
Distribution — no. (%)			
<30 ml/min	5 (10)	7 (18)	12 (13)
30 to <50 ml/min	14 (27)	6 (15)	20 (22)
50 to <80 ml/min	16 (31)	11 (28)	27 (30)
≥80 ml/min	6 (12)	9 (23)	15 (17)
Missing data	10 (20)	6 (15)	16 (18)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

and were not used to guide therapy. After administration of idarucizumab, the median maximum reduction in these assays within 4 hours was 100% (95% confidence interval, 100–100;



Idarucizumab

The Antidote for Reversal of Dabigatran

John W. Eikelboom, MBBS, FRCPC; Daniel J. Quinlan, MBBS; Joanne van Ryn, PhD; Jeffrey I. Weitz, MD, FRCPC

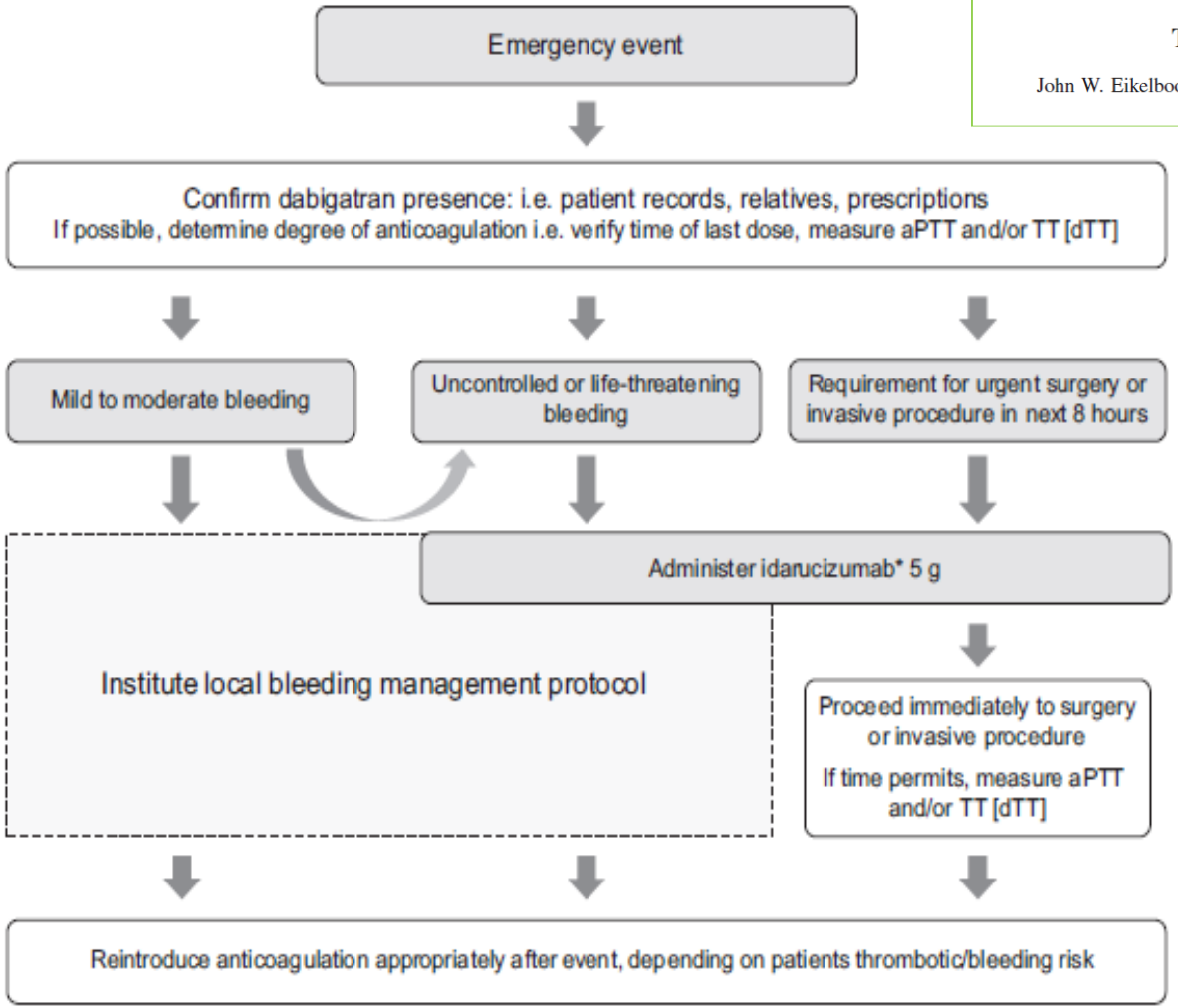
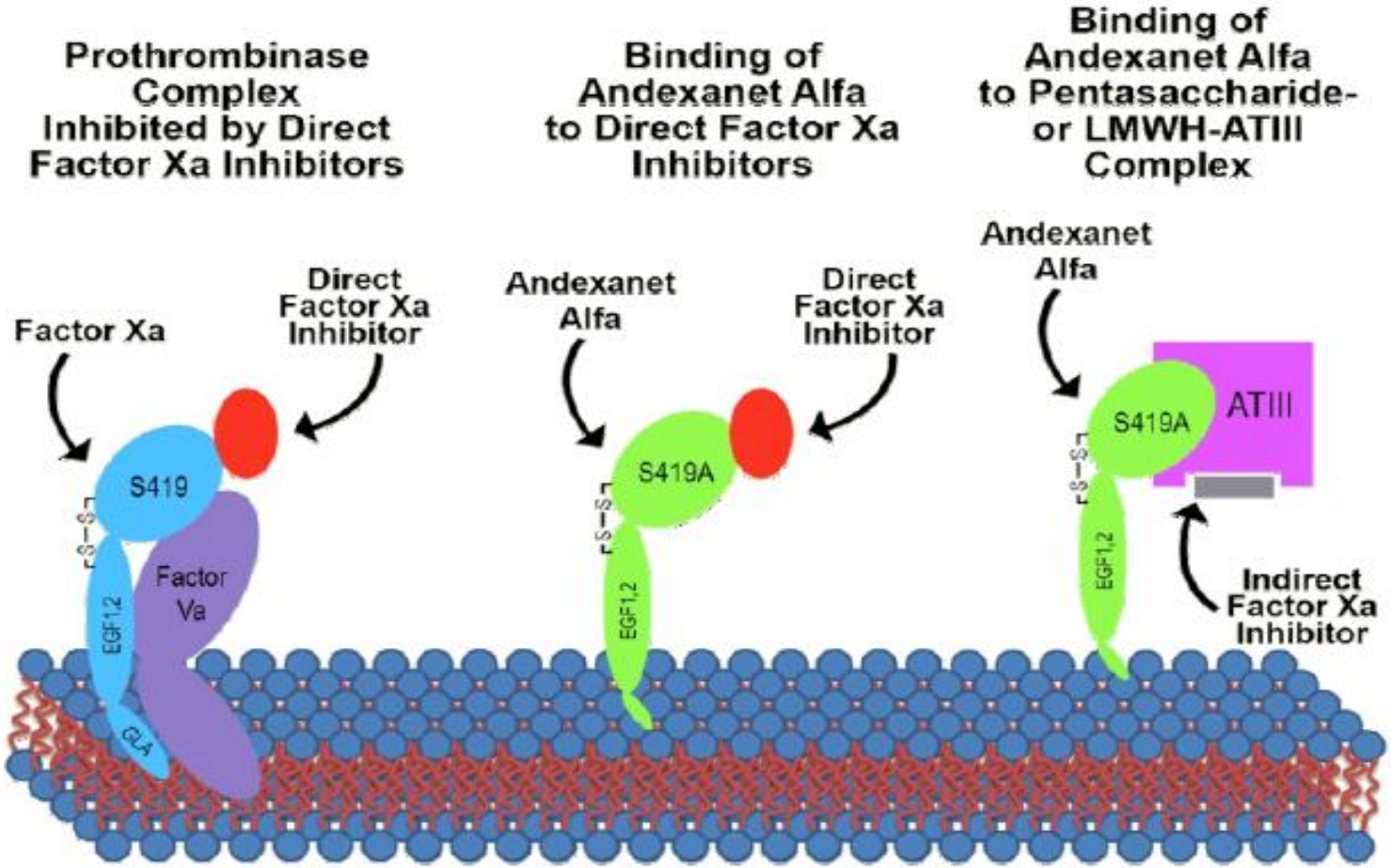


Figure 7. Proposed algorithm for management of patients treated with dabigatran who present with bleeding episodes or require urgent surgery/invasive procedures. *Administer two 50-mL vials of idarucizumab (each containing 2.5 g) intravenously. In rare cases when dabigatran anticoagulation remains present after idarucizumab and bleeding continues in the patient, a second 5-g dose of idarucizumab may be considered. aPTT indicates activated partial thromboplastin time; dTT, diluted thrombin time; and TT, thrombin time.

Circulation. 2015;132:2412-2422



Original artwork by: Mohammad A. Rattu, PharmD

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

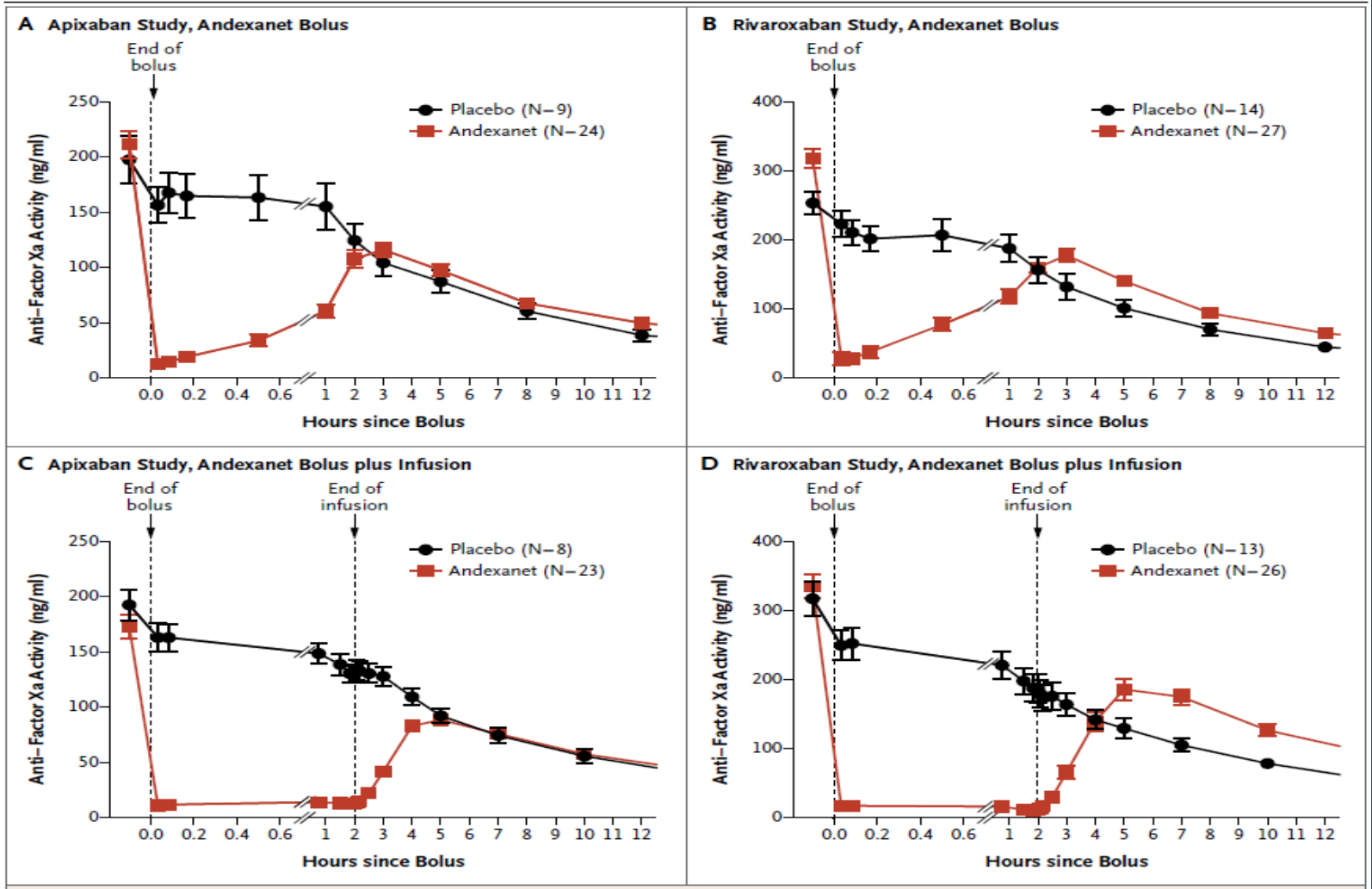


Figure 1. Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet.

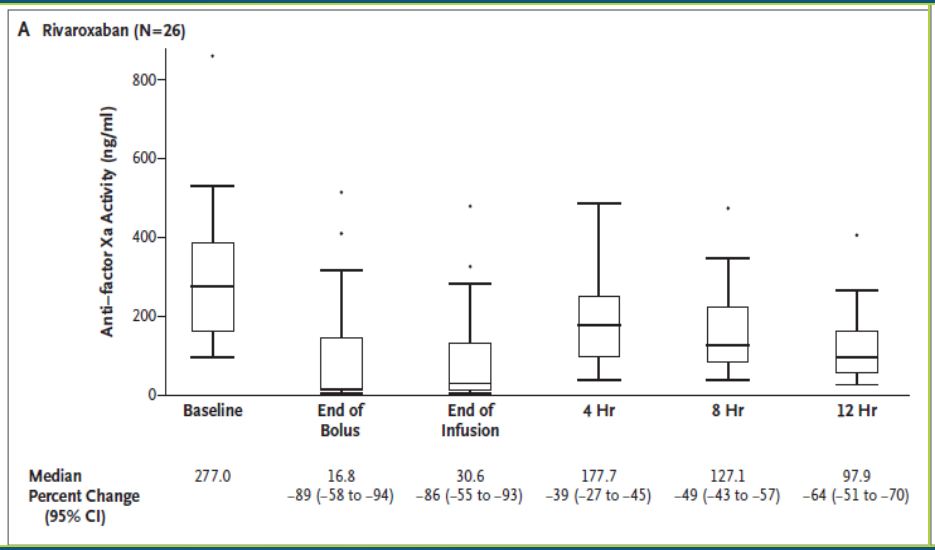
The NEW ENGLAND JOURNAL of MEDICINE

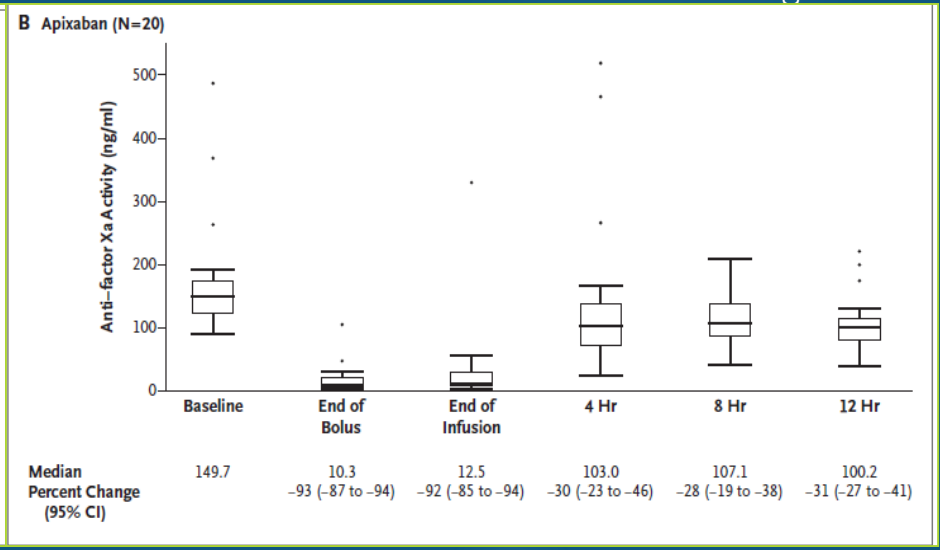
ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Safety Population (N=67)	Efficacy Population (N=47)





Conclusioni

- I risultati dei trials clinici di fase III con i NAO sono stati confermati nella vita reale
- I NAO sono ormai entrati nell'uso comune e rappresentano una realtà terapeutica ormai ben consolidata con evidenti vantaggi nella pratica clinica
- Le LLGG su FA e TEV riconoscono ai NAO un ruolo di primo piano
- Da poco abbiamo a disposizione anche una quarta molecola NAO
- Oggi è già disponibile un antidoto specifico per dabigatran e successivamente lo sarà anche per gli antiXa che ci permettono di superare uno dei maggiori gap rappresentato dal reverse urgente di questi farmaci