XI congresso nazionale

simeu

ROMA 24-26 MAGGIO 2018

Le complicanze tromboemboliche nella fibrillazione atriale trattata con cardioversione elettrica

Dott.ssa Ernesta Dores

Documento ANMCO su prevenzione del tromboembolismo nella fibrillazione atriale e ruolo dei nuovi anticoagulanti orali

Paolo Colonna[1], Maurizio G. Abrignani[2], Furio Colivicchi[3], Paolo Verdecchia[4], Gianfranco Alunni[5], Angelo S. Bongo[6], Roberto Ceravolo[7], Fabrizio Oliva[8], Serena Rakar[9], Carmine Riccio[10], Marino Scherillo[11], Roberto Valle[12], Francesco Bovenzi[13], a nome dell'Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)

La maggior parte degli ictus cerebrali che insorgono in pazienti con fibrillazione atriale (FA) sono attribuibili ad emboli distaccati da trombi originati all'interno dell'atrio sinistro

Va tuttavia segnalato che i pazienti con FA presentano, in oltre il 50% dei casi, diverse fonti emboligene (placche aterosclerotiche aortiche complesse o ulcerate, forame ovale pervio, aneurisma del setto interatriale, ecc.) che potrebbero contribuire alla patogenesi degli eventi tromboembolici indipendentemente dalla trombosi in atrio sinistro.

La FA induce una progressiva dilatazione dell'atrio sinistro. La dilatazione è in grado di aumentare ulteriormente la stasi ematica e la tendenza alla trombosi

L'incidenza media dell'ictus cerebrale invalidante nei pazienti con FA è di circa il 2.5% per anno, che aumenta ad oltre il 7% se includiamo anche gli attacchi ischemici transitori (TIA) e gli ictus silenti.

Circa una persona su 3 affetta da FA va incontro, nel corso della vita, ad ictus cerebrale, e circa un ictus su 5 è attribuito a questa aritmia.

I nuovi farmaci anticoagulanti orali (NAO) inibiscono un solo fattore della coagulazione (Figura 1), presentando quindi un meccanismo d'azione più selettivo rispetto agli antagonisti della vitamina K (AVK).

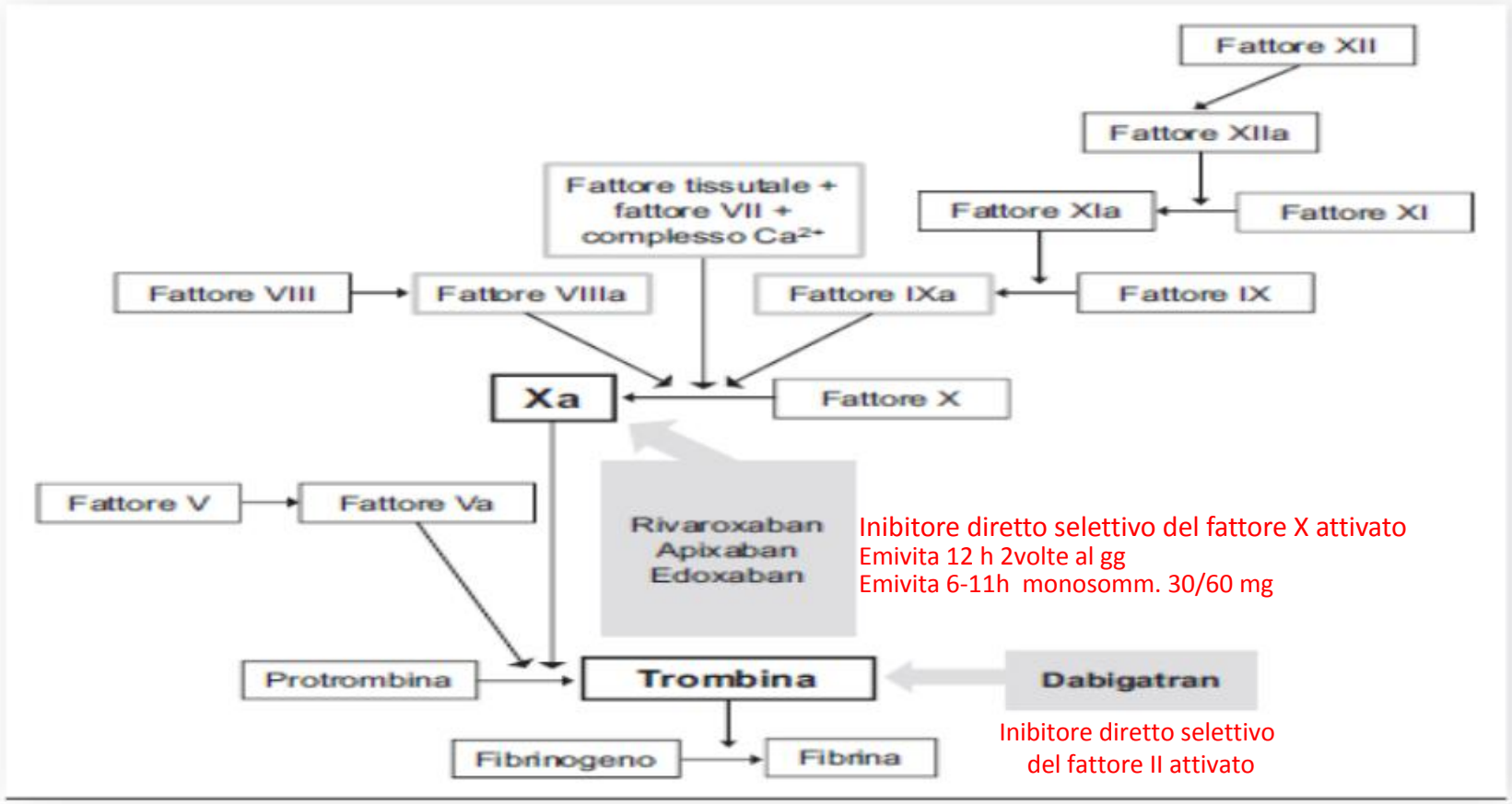


Figura 1. Punti d'azione dei nuovi anticoagulanti orali all'interno della cascata della coagulazione.

Tabella 1. Farmacologia e farmacocinetica dei nuovi anticoagulanti orali utilizzati nei trial clinici per la prevenzione del tromboembolismo nella fibrillazione atriale non valvolare.

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET AF)	Apixaban (ARISTOTLE)
Meccanismo	Inibitore orale diretto della trombina	Inibitore orale diretto del fattore X attivato	Inibitore orale diretto del fattore X attivato
Tempo al picco (h)	3	3	3
Biodisponibilità (%)	6	60-80	50
Metabolismo (citocromo P450)	No	Sì	Sì
Emivita (h)	12-17	5-13	9-14
Profarmaco	Sì	No	No
Eliminazione	80% renale	2/3 epatica, 1/3 renale	25% renale, 75% fecale
Interazioni farmacologiche	Glicoproteina-P	Glicoproteina-P, CYP3A4	Glicoproteina-P, CYP3A4
Monitoraggio (routine)	No	No	No
Dose utilizzata nei trial	Randomizzazione a 150 o 110 mg bid	20 mg/die	5 mg bid
Dose in pazienti con insufficienza renale moderata	Invariata	15 mg/die	2.5 mg bid

Il rivaroxaban è stato il primo farmaco anticoagulante orale approvato, dopo il warfarin, per la profilassi tromboembolica nei pazienti sottoposti a chirurgia ortopedica. Gli studi RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) 1, 2, 3 e 4 hanno infatti dimostrato la superiorità del rivaroxaban rispetto all'enoxaparina nella prevenzione della trombosi venosa profonda e dell'embolia polmonare, in assenza di aumento del rischio di emorragie.

L'apixaban è stato testato nello studio AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes) che ha coinvolto 5599 pazienti affetti da FA associata ad almeno un fattore di rischio per ictus, intolleranti o non adatti al trattamento con warfarin. Rispetto all'ASA, l'apixaban si è dimostrato superiore ($p<0.001$) per l'endpoint primario di efficacia (compositon di ictus ed embolia sistemica). I sanguinamenti maggiori, le emorragie fatali ed i sanguinamenti intracranici non hanno mostrato differenze statisticamente significative tra il gruppo apixaban ed il gruppo ASA.

I risultati incoraggianti di questi studi hanno portato allo sviluppo dei trial di fase III RE-LY18, ROCKET AF19 e ARISTOTLE20 al fine di valutare l'efficacia e la sicurezza, rispettivamente,del dabigatran, del rivaroxaban e dell'apixaban nella prevenzione dell'ictus cardioembolico e dell'embolia sistemica nei pazienti con FA.

Tabella 6. Nuovi anticoagulanti orali: confronto tra trial di fase III.

	RE-LY	ROCKET AF	ARISTOTLE
Farmaco	Dabigatran	Rivaroxaban	Apixaban
Dose	150 mg, 110 mg bid	20 mg/die (15 mg/die)	5 mg (2.5 mg) bid
Disegno dello studio	Randomizzato, aperto (probe)	Randomizzato, doppio cieco	Randomizzato, doppio cieco
N. pazienti	18 111	14 264	18 201
Età media (anni)	71	70	73
Warfarin-naive (%)	50	37.5	43
$CHADS_2$ medio	2.1	3.5	2.1
TTR medio (%)	64	55	62

TR, tempo nel range terapeutico.

Tabella 7. Nuovi anticoagulanti orali: endpoint primario composito di ictus ed embolia sistemica.

	%/anno	Hazard ratio	p
RE-LY			
Dabigatran 110 mg	1.53	0.91	<0.001 per non inferiorità
Dabigatran 150 mg	1.11	0.66	<0.001 per superiorità
Warfa			
ROCKET			
Rivaro			
Warfa			
ARISTOT			
Apixa			
Warfa			

Tabella 10. Nuovi anticoagulanti orali: mortalità per tutte le cause.

	%/anno	Hazard ratio	p
RE-LY			
Dabigatran 110 mg	3.75	0.91	0.13
Dabigatran 150 mg	3.64	0.88	0.05
Warfarin	4.13		
ROCKET AF			
Rivaroxaban 20 mg	4.52	0.92	0.152
Warfarin	4.91		
ARISTOTLE			
Apixaban 5 mg	3.52	0.89	0.047
Warfarin	3.94		

Tabella 8

RE-LY			
Dabig			03
Dabig			32
Warfa			
ROCKET			
Rivaroxaban 20 mg	0.26	0.59	0.024
Warfarin	0.44		
ARISTOTLE			
Apixaban 5 mg	0.24	0.51	<0.001
Warfarin	0.47		

Rivaroxaban 20 mg	3.60	0.92	0.58
Warfarin	3.45		
ARISTOTLE			
Apixaban 5 mg	2.13	0.69	<0.001
Warfarin	3.09		

Lo studio ENGAGE AF-TIMI 48

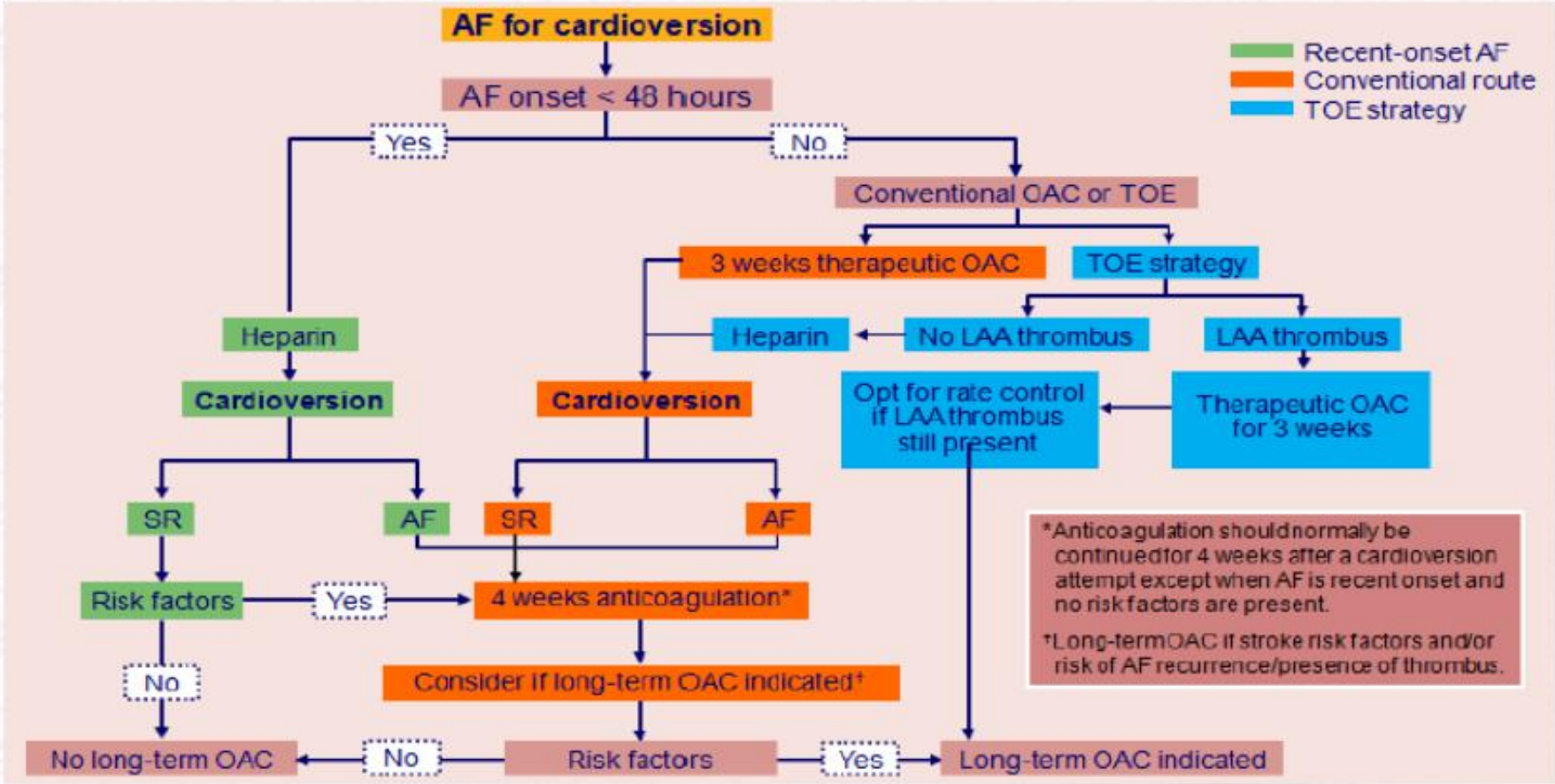
Andrea Rubboli1, Paolo Colonna21
U.O. Cardiologia, Laboratorio di Cardiologia Interventistica, Ospedale Maggiore, Bologna
2U.O. Cardiologia Ospedaliera, Azienda Ospedaliero-Universitaria Consorziale Policlinico, Bari

Tabella 1. Rischio relativo (intervalli di confidenza 95%) dei più importanti endpoint di efficacia e sicurezza vs warfarin.

	Ictus/embolia sistemica	Emorragia maggiore	Emorragia intracranica
ENGAGE AF-TIMI 48[2]			
Edoxaban 30 mg/die	1.07 (0.87-1.31)[a,b]	0.47 (0.41-0.55)[d]	0.30 (0.21-0.43)[d]
Edoxaban 60 mg/die	0.79 (0.63-0.99)[a,b]	0.80 (0.71-0.91)[d]	0.47 (0.34-0.63)[d]
RE-LY[3]			
Dabigatran 110 mg bid	0.91 (0.74-1.11)[b]	0.80 (0.69-0.93)[d]	0.31 (0.20-0.47)[d]
Dabigatran 150 mg bid	0.66 (0.53-0.82)[c]	0.93 (0.81-1.07)	0.40 (0.27-0.60)[d]
ROCKET AF[4]			
Rivaroxaban 20 mg/die	0.88 (0.75-1.03)[b]	1.04 (0.90-1.20)	0.67 (0.47-0.93)[d]
ARISTOTLE[5]			
Apixaban 5 mg bid	0.79 (0.66-0.95)[c]	0.69 (0.60-0.80)[d]	0.42 (0.30-0.58)[d]

[a]impiegato intervallo di confidenza 97.5%; [b]significativo per non inferiorità; [c]significativo per superiorità; [d]statistically significativo.

Sanguinamento maggiore ridotto del 20 % per il 60 mg e del 50% per il 30 mg



AF = atrial fibrillation; DCC = direct current cardioversion; LA = left atrium; LAA = left atrial appendage; OAC = oral anticoagulant
SR= sinus rhythm; TOE= transoesophageal echocardiography.

www.escardio.org/guidelines

European Heart Journal (2010) 31, 2369-2429

EUROPEAN SOCIETY OF CARDIOLOGY®

Profilassi tromboembolica in corso di CVE/farmacologica

	Terapia antitrombotica raccomandata	Classe di raccomandazione e livello di evidenza
Fa insorta <48h	Cardioversione senza anticoagulazione	IIaC
FA insorta >48h o non databile per insorgenza	Terapia anticoagulante orale per 3 settimane pre-cardioversione e per 4 settimane post-cardioversione (indefinitamente in caso di CHADS2 o CHAD2 DS2-VASc >2)	IB
FA insorta >48h o non databile per insorgenza	Strategia eco-guidata seguita da terapia anticoagulante orale per 4 settimane post-cardioversione (indefinitamente in caso di CHADS2 o CHAD2 DS2-VASc >2)	IB

www.escardio.org/guidelines

EUROPEAN SOCIETY OF CARDIOLOGY

I trombi atriali si formano ed ebolizzano nelle prime 72 ore dalla cardioversione per un meccanismo di disfunzione contrattile atriale.

X-VeRT

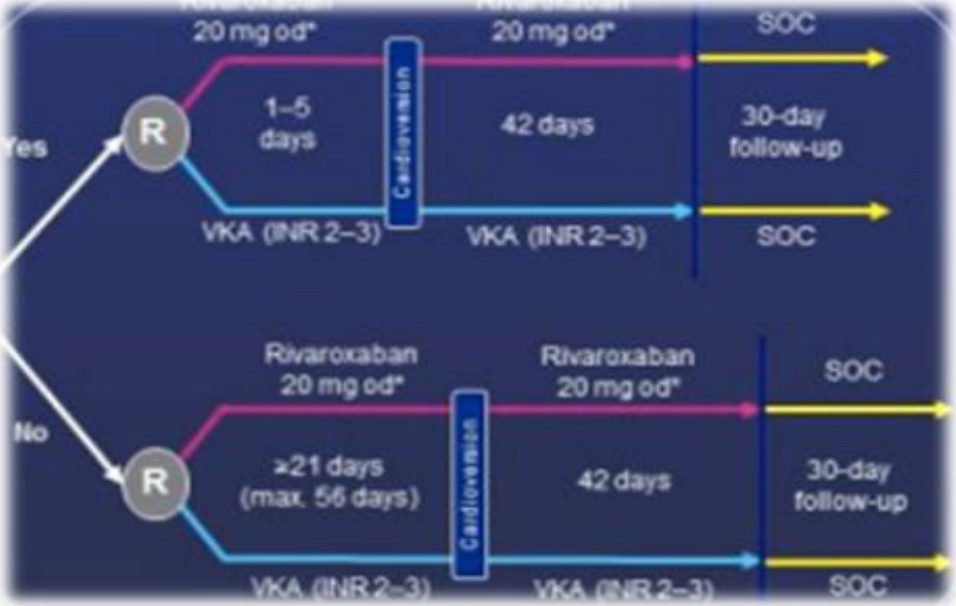
EX plore the efficacy and safety of once-daily oral ri**V**aroxaban for the p**r**evention of ca**R**diovascular events in subjects with non-valvular a**T**rial fibrillation scheduled for cardioversion

- Studio prospettico, randomizzato, in aperto, a gruppi paralleli
- Fase III b, Multicentrico (16 paesi del mondo)

Precoce

Tardiva

Sufficient anti-coagulation or Immediate TEE



Primary endpoints:

Efficacy: Thromboembolic events

Safety: major bleeding

Tabella 1. Numero di pazienti con eventi nello studio X-VeRT[17].

	Totale		Precoce		Convenzionale	
	RIVA	AVK	RIVA	AVK	RIVA	AVK
N. pazienti	978	492	567	277	411	215
Ictus ischemico	0	2 (0.40%)	0	1 (0.36%)	0	1 (0.46%)
TIA	0	0	0	0	0	0
Embolia sistemica	0	1 (0.20%)	0	1 (0.36%)	0	0
Endpoint primario parziale[a]	0	3 (0.60%)	0	2 (0.72%)	0	(0.46%)

AVK, antagonisti della vitamina K; RIVA, rivaroxaban; TIA, attacco ischemico transitorio.
[a]sono stati esclusi dall'endpoint primario eventi correlati a ictus emorragico, infarto miocardico o morte cardiovascolare in quanto indipendenti dalla strategia di cardioversione precoce mediante ecocardiografia transesofagea o convenzionale.

L'outcome primario di efficacia era costituito da un composito di ictus, attacco ischemico transitorio, embolia periferica, infarto miocardico e morte cardiovascolare.

Il gruppo RIVA mostrava un rischio inferiore di eventi cardiovascolari(0,51% VS1,02%) rispetto agli AVK ed un minor richio di emorraggia maggiore 0,6% VS 0,8%

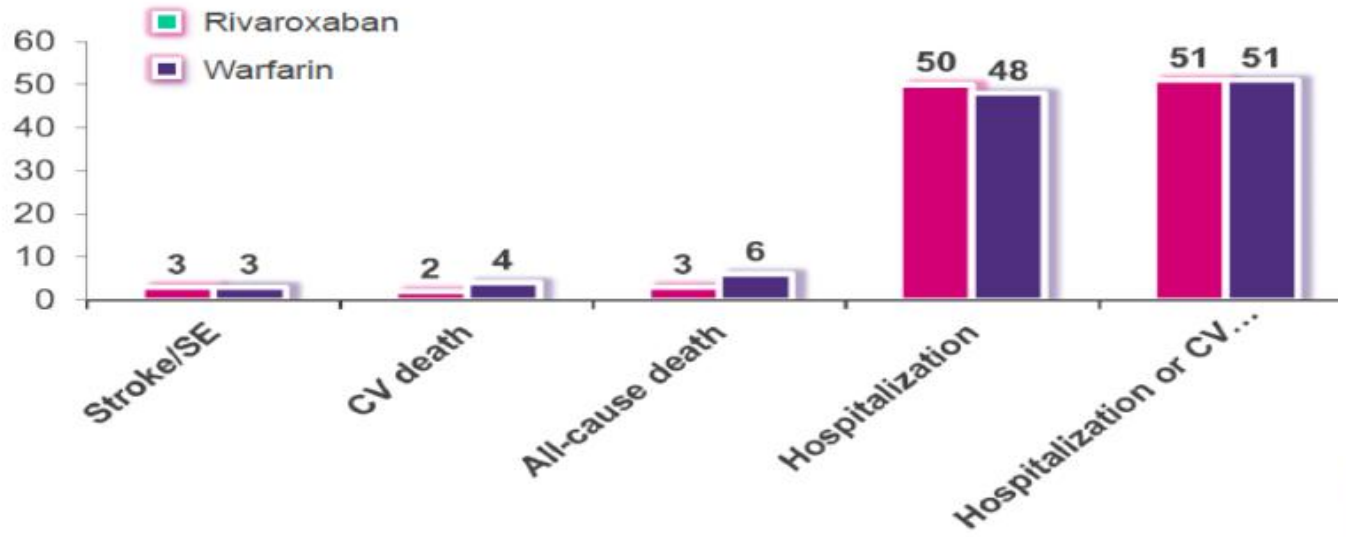
Evidenze dallo studio ROCKET AF - Rivaroxaban

Durante lo studio 321 CVE pz :

181 CVE
194 CVF
85 procedure ablative

Totale 480 riconversione a RS

Risultati dei pazienti sottoposti a CVE/CVF/Ablazione nello studio ROCKET AF



1983 cardioversions were performed in 1270 patients during RE-LY®

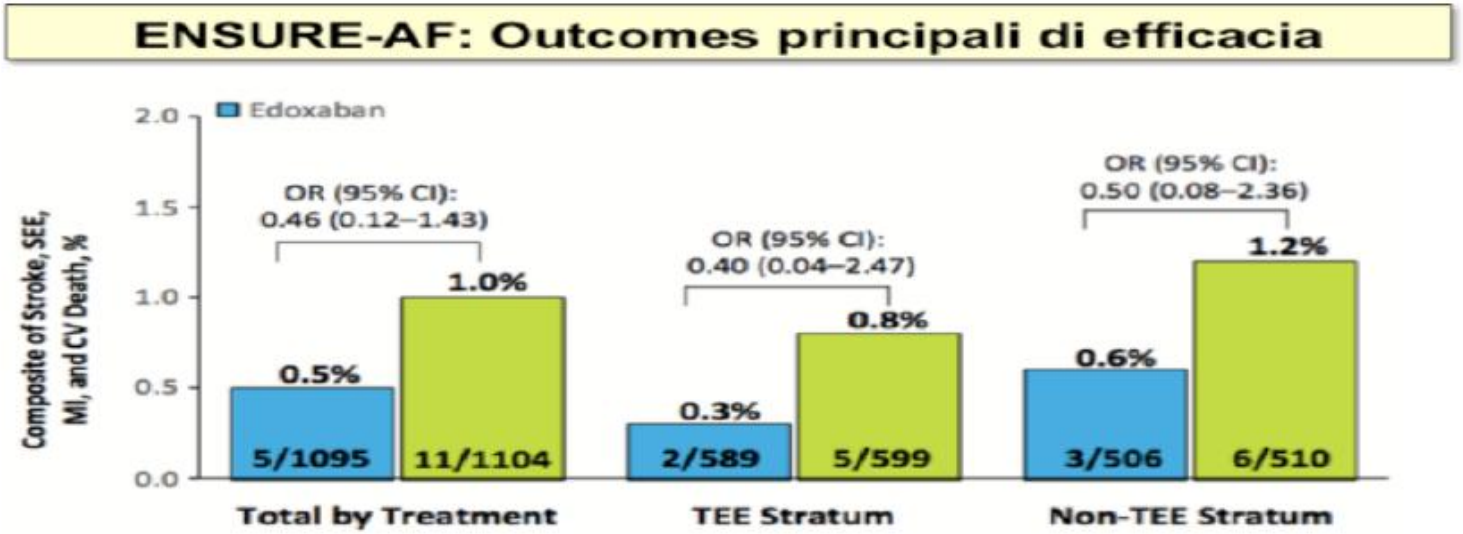
	Dabigatran 110 mg BID		Dabigatran 150 mg BID		Warfarin	
	n	%	n	%	n	%
Total randomized	6015		6076		6022	
Cardioversions performed						
Electrical	554	85.6	550	81.9	553	83.3
Pharmacological	91	14.1	122	18.2	111	16.7
TEE	165	25.5	162	24.1	88	13.3
Normal sinus rhythm at discharge	566	87.5	596	88.7	595	89.6

- >75% of patients received study drug for ≥3 weeks before cardioversion
- >85% of patients continued on randomized treatment within 30 days after cardioversion

TEE = transoesophageal echocardiography
Nagarakanti R et al. Circulation 2011;123:131–6

1270 pz ictus	DAB 110mg 0,77%	DAB 150 0,30%	AVK 0,60%
Sanguinamento maggiori	1,7%	0,6%	0,60%

Ensure af



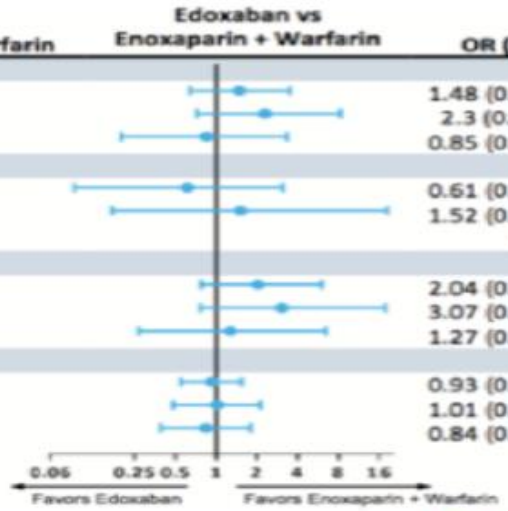
Goette A. et al. Lancet 2016 Oct 22;388(10055):1995-2003

PZ = 2199	Dose 30 mg	Dose 60 mg	Follow up 28 gg + 30 gg

Per l'*endpoint composito primario di efficacia* (ictus, eventi embolici sistemici, infarto miocardico e mortalità cardiovascolare), edoxaban ha dimostrato un'incidenza simile rispetto a enoxaparina/warfarin (0,5% vs. 1,0% rispettivamente, OR 0,46). La principale differenza tra i gruppi di trattamento è stata determinata dalla mortalità cardiovascolare, con un evento nel gruppo edoxaban e cinque eventi nel gruppo enoxaparina/warfarin (0,1% vs. 0,5%,Rispettivamente).

ENSURE-AF: Outcomes principali di sicurezza

	Event Rate, % (n/N)		OR (95% CI)
	Edoxaban	Enoxaparin + Warfarin	
First Major or CRNM Bleeding			
Total by Treatment	1.5 (16/1067)	1.0 (11/1082)	1.48 (0.64–3.55)
TEE Stratum	1.9 (11/570)	0.9 (5/577)	2.3 (0.72–8.31)
Non-TEE Stratum	1.0 (5/497)	1.2 (6/505)	0.85 (0.20–3.35)
Major Bleeding			
Total by Treatment	0.3 (3/1067)	0.5 (5/1082)	0.61 (0.09–3.13)
TEE Stratum	0.5 (3/570)	0.3 (2/577)	1.52 (0.17–18.27)
Non-TEE Stratum	0	0.6 (3/505)	NC
CRNM Bleeding			
Total by Treatment	1.3 (14/1067)	0.6 (7/1082)	2.04 (0.77–6.00)
TEE Stratum	1.6 (9/570)	0.5 (3/577)	3.07 (0.76–17.70)
Non-TEE Stratum	1.0 (5/497)	0.8 (4/505)	1.27 (0.27–6.45)
Any Bleeding			
Total by Treatment	3.0 (32/1067)	3.2 (35/1082)	0.93 (0.55–1.55)
TEE Stratum	3.0 (17/570)	2.9 (17/577)	1.01 (0.48–2.13)
Non-TEE Stratum	3.0 (15/497)	3.6 (18/505)	0.84 (0.39–1.79)



Goette A. et al. Lancet 2016 Oct 22;388(10055):1995-2003

Per quanto riguarda l'*endpoint composito principale di sicurezza* (incidenza di emorragie maggiori ed emorragie non maggiori clinicamente rilevanti), gli eventi si sono verificati nell'1,5% dei pazienti nel gruppo edoxaban e nell'1,0% del gruppo enoxaparina/warfarin (OR 1,48). L'incidenza di emorragia maggiore è stata numericamente inferiore nel gruppo edoxaban rispetto al gruppo enoxaparina/warfarin (0,3% vs. 0,5%, rispettivamente; OR 0,61). Nello studio non sono stati segnalati casi di emorragia intracranica per nessuno dei due gruppi di trattamento. Nessuna emorragia fatale è stata segnalata nel gruppo edoxaban, mentre si è verificato un caso nel gruppo enoxaparina/warfarin.

Già nello studio ARISTOTELE 553 pz (272 apixaban e 281 AVK) sono stati sottoposti a CVE ed a 90 gg non si è verificato alcun ictus o embolia in nessuno dei due gruppi.

ESC European Society of Cardiology

European Heart Journal (2018) 00, 1–13
doi:10.1093/eurheartj/ehy148

FASTTRACK CLINICAL RESEARCH
Atrial fibrillation

Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial

Michael D. Ezekowitz[1,2,3]*, Charles V. Pollack Jr[4], Jonathan L. Halperin[5], Richard D. England[6], Sandra VanPelt Nguyen[6], Judith Spahr[4], Maria Sudworth[7], Nilo B. Cater[8], Andrei Breazna[8], Jonas Oldgren[9], and Paulus Kirchhof[10]

[1]Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA; [2]Lankenau Heart Center, Wynnewood, PA, USA; [3]Bryn Mawr Hospital, Bryn Mawr, PA, USA; [4]Thomas Jefferson University, Philadelphia, PA, USA; [5]Icahn School of Medicine, New York, NY, USA; [6]Pfizer, Groton, CT, USA; [7]Pfizer, London, UK; [8]Pfizer, New York, NY, USA; [9]Uppsala Clinical Research Centre and Department of Medical Sciences, Uppsala University, Uppsala, Sweden; and [10]University of Birmingham Institute of Cardiovascular Sciences, SWBH and UHB NHS Trusts, Birmingham, UK

Received 27 July 2017; revised 14 August 2017; editorial decision 30 January 2018; accepted 22 March 2018

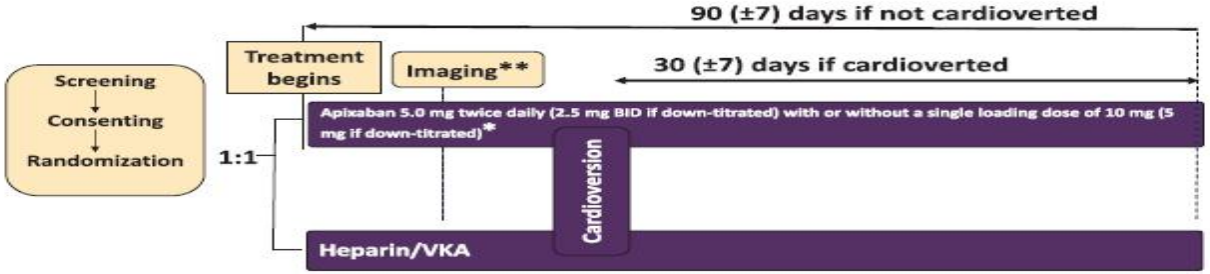


Figure 1 Study design. *The protocol encouraged a single loading dose of apixaban either 10 mg or 5 mg and image-guided at the discretion of the investigator, to allow more rapid transition to cardioversion. *Dosage was reduced to 2.5 mg b.i.d. or a single loading dose of 5 mg when two of the following were present: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 μmol/L). **Imaging guidance (transoesophageal echocardiography or computer tomography) was at the discretion of the investigator. b.i.d., twice daily; VKA, vitamin K antagonist.

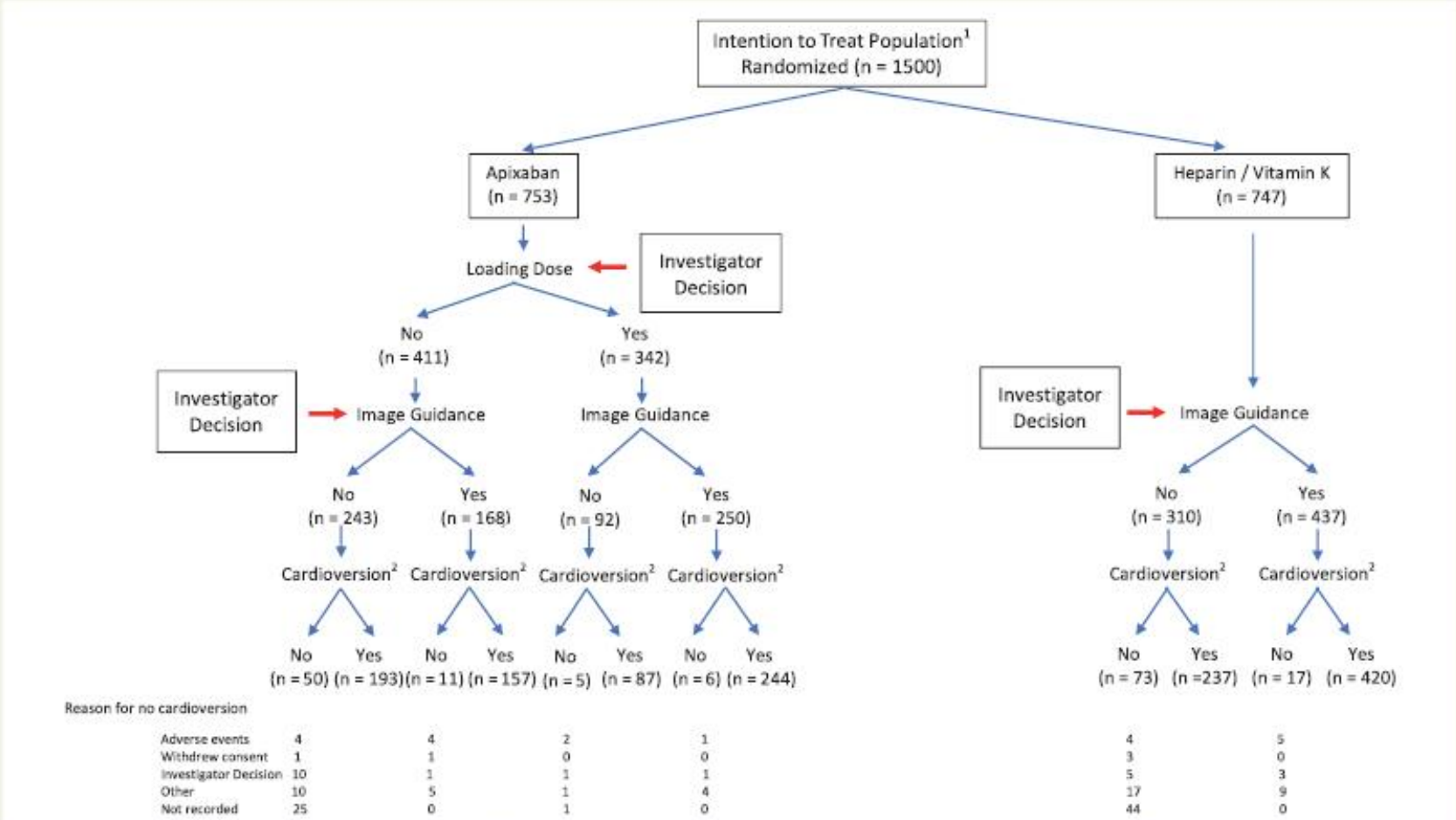


Figure 2 Patient disposition (ITT population). [1]≤48h of anticoagulation for current episode of atrial fibrillation. [2]Includes active and first spontaneous cardioversions.

Stroke/SE

Morte

Sangiunamenti Maggiori

Sangiunamenti non Maggiori

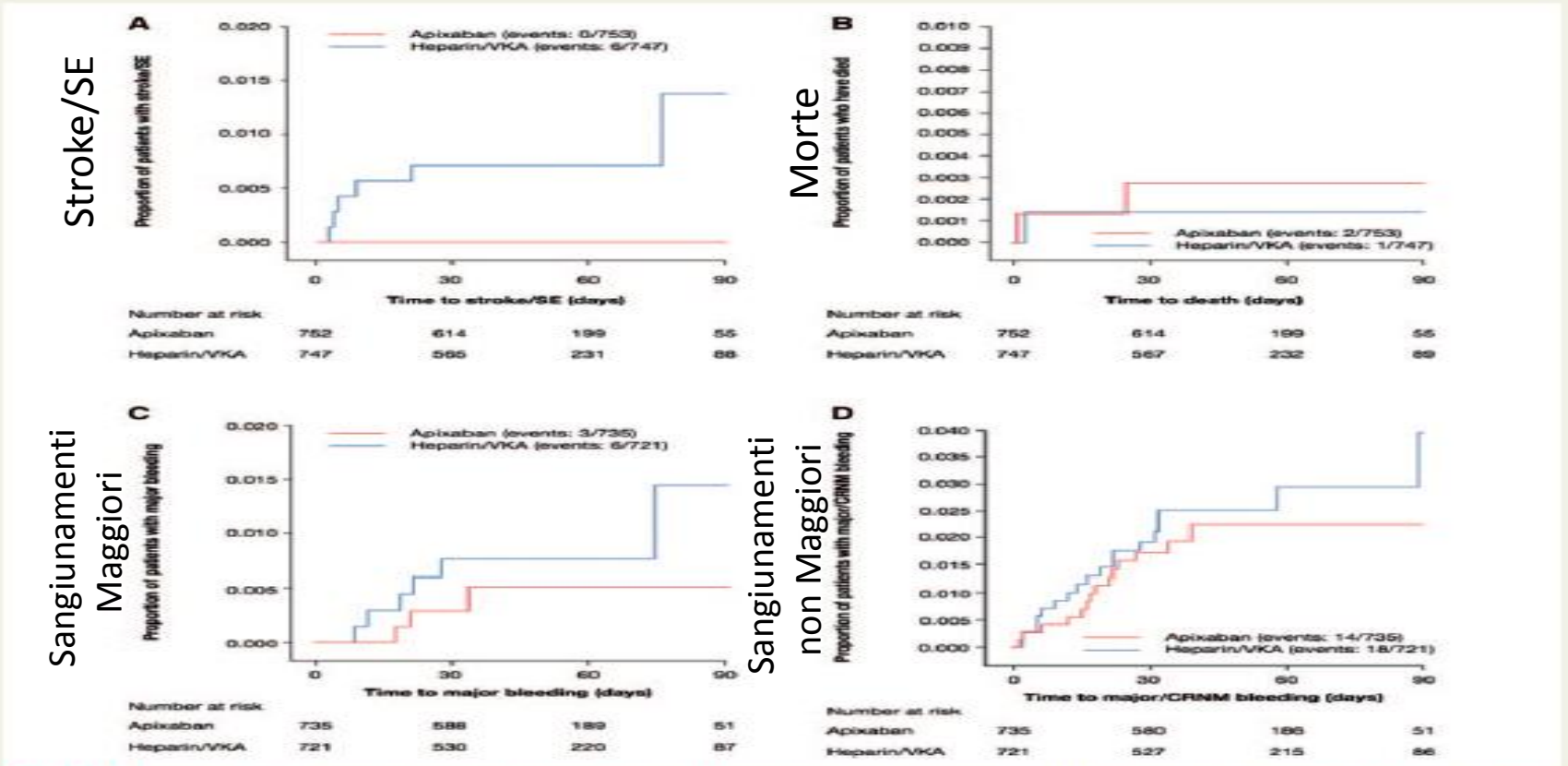


Figure 3 The Kaplan–Meier curve for time to first event for (A) stroke/SE, (B) death, (C) major bleeding, and (D) major/CRNM bleeding from randomization. CRNM, clinically relevant non-major; SE, systemic embolism; VKA, vitamin K antagonist.

I risultati hanno dimostrato che nel gruppo Eliquis della popolazione intent-to-treat (ITT) (n = 1500, Eliquis n = 753, Eparina / VKA n = 747) non si sono verificati ictus o embolie sistemiche, rispetto a sei ictus (uno emorragico e cinque ischemici) e nessuna embolia sistemica nel gruppo con terapia standard.

European Heart Journal Advance Access published August 27, 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

9. Stroke prevention therapy in atrial fibrillation patients

OAC therapy can prevent the majority of ischaemic strokes in AF patients and can prolong life.[38,39,42,194,201,329,350–352] It is superior to no treatment or aspirin in patients with different profiles for stroke risk.[353,354] The net clinical benefit is almost universal, with the exception of patients at very low stroke risk, and OAC should therefore be used in most patients with AF (*Figure 8*). Des-

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

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

ESC European Society of Cardiology

European Heart Journal (2018) **00**, 1–64
doi:10.1093/eurheartj/ehy136

SPECIAL ARTICLE

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Jan Steffel[1]*, Peter Verhamme[2], Tatjana S. Potpara[3], Pierre Albaladejo[4], Matthias Antz[5], Lien Desteghe[6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[2], Ronan Collins[12], A. John Camm[13], and Hein Heidbüchel[6,14]

Advisors: Martin van Eickels, M.D. (Bayer Healthcare), Jutta Heinrich-Nols, M.D. (Boehringer Ingelheim), Markus Müller, M.D., Ph.D. (Pfizer), Wolfgang Zierhut M.D. (Daiichi-Sankyo) and Poushali Mukherjea, Ph.D. (Bristol-Myers Squibb)

Document reviewers (ESC scientific document group): Gregory YH Lip (EHRA Review Coordintaor; UK, Denmark), Jeffrey Weitz (Canada), Laurent Fauchier (France), Deirdre Lane (UK), Giuseppe Boriani (Italy), Andreas Goette (Germany), Roberto Keegan (Argentina), Robert MacFadyen (Australia), Chern-En Chiang (Taiwan), Boyoung Joung (Korea), and Wataru Shimizu (Japan)

Criteri di Eligibilità

Table I Selected indications and contraindications for non-vitamin K antagonist oral anticoagulant therapy in atrial fibrillation patients

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Severe aortic stenosis	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post operatively)	Not advised if for rheumatic mitral stenosis Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post operatively)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

Hatched—limited data.
PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.

Switching tra NOAC e VKA

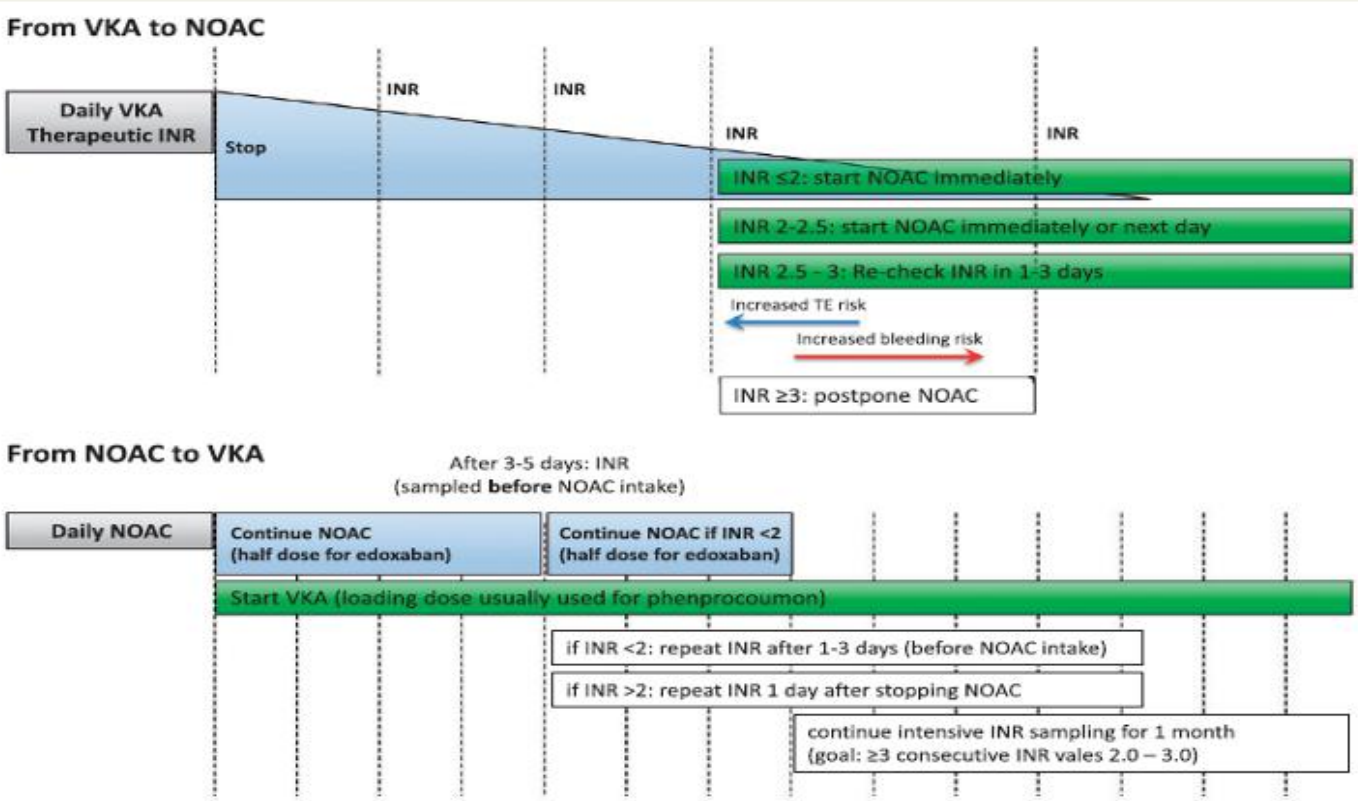


Figure 2 Switching between vitamin K antagonists and non-vitamin K antagonist oral anticoagulants and vice versa. TE, thromboembolic.

Interazioni Farmacologiche

Table 3 Effect of drug–drug interactions and clinical factors on NOAC plasma levels ("area under the curve")

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (≈4%)	Yes (≈18%)[77]
Antiarrhythmic drugs					
Amiodarone	moderate P-gp competition	↑12 to 60%[3mPC]	No PK data[a]	↑40%[130,131,134]	Minor effect[a]
Digoxin	P-gp competition	No effect[3mPC]	No effect[135]	No effect	No effect[3mPC]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[3mPC]	↑40%[134]	No data yet	No effect
Dronedarone	P-gp competition and CYP3A4 inhibition	↑70 to 100% (200 mg bid; CrCl 30–50 mL/min)	No PK or PD data available	↑85%[a]	Moderate effect, should be avoided
Quinidine	P-gp competition	↑53%[89mPC]	No data yet	↑77%[131] (no dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	↑12 to 180%[3mPC] (if taken simultaneously)	No PK data	↑53% (SR)[131,134] (no dose reduction required by label)	No effect
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	No relevant interaction	No data yet	No effect	No effect
Ticagrelor	P-gp competition	↑25%[3mPC] (given loading dose 2h after dabigatran)[a]	No data	No data	No data
Antibiotics					
Clarithromycin; Erythromycin	Moderate P-gp competition and strong CYP3A4 inhibition	↑15 to 20%	↑60% AUC ↑30% C_{max}	↑90%[3mPC]	↑34% (Erythromycin) ↑54% (Clarithromycin)[3mPC][77]
Rifampicin	P-gp/BCRP and CYP3A4/CYP2J2 inducers	Minus 66%[3mPC]	Minus 54%[136]	Minus 35%, but with compensatory increase of active metabolites	Up to minus 50%[3mPC]
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	No data yet	No data yet	Up to ↑153%[77]

Fungistatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	↑42% (if systemically administered)[3mPC]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	↑140 to 150% (Lit: 3 x 75 mg/d CrCl 30–50 mL/min)	↑160%[135]	↑87 to 95%[135] (reduce NOAC dose by 50%)	Up to ↑160%[3mPC]
Posaconazole	Mild to moderate P-gp inhibition	See PC	See PC		See PC
Others					
Naproxen	P-gp competition; pharmacodynamically increased bleeding time	No data yet	↑55%[139]	No effect	No data yet
HGB; PPI; Al-mg-hydroxide	GI absorption	Minus 12–30%	No effect	No effect[3mPC]	No effect[140]
St. John's wort	P-gp/BCRP and CYP3A4/CYP2J2 inducers				
Other factors					
Age ≥80 years	Potential for increased plasma levels		b	c	
Age ≥75 years	Potential for increased plasma levels			c	
Weight ≤60 kg	Potential for increased plasma levels		b	b	
Renal function	Increased plasma level	See figure 4			
Other increased bleeding risk		• Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • History of GI bleeding • Recent surgery on critical organ (brain; eye) • Frail/fall risk • Skin bleeding or predisposition (anaemia, thrombocytopenia)			

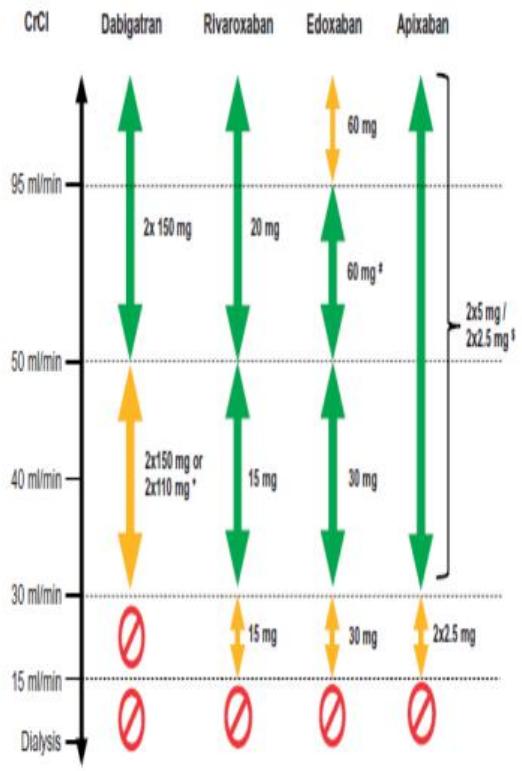


Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). ‡2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

Table 8 Calculation of the Child-Turcotte-Pugh score and use of NOACs in hepatic insufficiency

Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory/chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate-severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
	<34 µmol/L	34–50 µmol/L	>50 µmol/L
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
	>35 g/L	28–35 g/L	<28 g/dL
INR	<1.7	1.71–2.30	>2.30

Child-Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

Monitoraggio livelli plasmatici

Table 9 Plasma levels and coagulation assays in patients treated with non-vitamin K antagonist oral anticoagulants

	Dabigatran[229,230]	Apixaban[231], SmPc	Edoxaban[184,232]	Rivaroxaban[131,186]
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)				
Expected range of plasma levels *at peak* for standard dose (ng/mL)[a]	64–443	69–321	91–321	184–343
Expected range of plasma levels *at trough* for standard dose (ng/mL)[a]	31–225	34–230	31–230	12–137
Expected impact of NOACs on routine coagulation tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

Ranges indicate the P5/95 percentiles for dabigatran, rivaroxaban, and apixaban, and the interquartile ranges for edoxaban.
The reagents influence the sensitivity of the PT for FXa inhibitors and of the aPTT for dabigatran. When a sensitive assay is used, normal aPTT excludes above on-therapy levels in dabigatran-treated patients, and normal PT excludes above on-therapy levels in rivaroxaban and edoxaban, but not apixaban treated patients. Point-of-care INR devices developed to monitor vitamin K antagonists do not accurately reflect the anticoagulant status of NOAC treated patients.
ACT, activated clotting time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECA, ecarin clotting assay; INR, international normalized ratio; PT, prothrombin time.

Gestione del pz con sanguinamenti maggiori

Table 10 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening major bleeding	• Inquire about last intake + dosing regimen • Local haemostatic measures • Fluid replacement • RBC substitution, if necessary • Platelet substitution (in case of thrombocytopenia ≤60 × 109/L or thrombopathy) • Fresh frozen plasma not as reversal agent (may be considered as plasma expander) • Tranexamic acid can be considered as adjuvant (1 g i.v., repeat every 6 h, if necessary) • Desmopressin can be considered in special cases such as coagulopathy or thrombopathy; 0.3 μg/kg i.v. infusion (max dose 20 μg)	

	• Estimate normalization of plasma levels:
	  • Normal renal function: 12–24 h
	  • CrCl 50–80 mL/min: 24–36 h
	  • CrCl 30–50 mL/min: 36–48 h
	  • CrCl <30 mL/min: ≥48 h
	• Maintain diuresis
	• Consider idarucizumab (see below)
		• Normalization of plasma levels: 12–24 h

Life-threatening bleeding	• All of the above
	• Direct reversal: Idarucizumab 5 g i.v. in two doses a 2.5 g i.v. no more than 15 min apart
		• All of the above
		• Direct reversal: Andexanet alpha (if available and approved)*
		  • Bolus over 15–30 min, followed by 2-h infusion
		  • Rivaroxaban (last intake >7 h before) or apixaban: 400 mg bolus, 480 mg infusion @ 4 mg/min
		  • Rivaroxaban (last intake <7 h before or unknown) or enoxaparin or edoxaban: 800 mg bolus, 960 mg infusion @ 8 mg/min

	• Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) • Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC, if available	

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.
*Andexanet alpha is currently neither approved nor available and final results of the ANNEXA-4 study are pending.

Gestione del pz che necessita di chirurgia elettiva

Table 11 Timing of last non-vitamin K antagonist oral anticoagulant intake before start of an elective intervention

	Dabigatran		Apixaban – Edoxaban – Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. 12 h or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 mL/min	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–49 mL/min	≥48 h	≥96 h	≥24 h	≥48 h
CrCl 15–29 mL/min	Not indicated	Not indicated	≥36 h	≥48 h
CrCl <15 mL/min	No official indication for use			
No bridging with LMWH/UFH				
Resume full dose of NOAC ≥24 h post-low bleeding risk interventions and 48 (–72) h post-high-bleeding risk interventions (see also *Figure 8*)				
Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention, and the date and time of the last intake of their NOAC (and any other medication)				

Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk: with a high frequency of bleeding and/or important clinical impact. See also *Table 12*.
CrCl, creatinine clearance; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

Gestione del pz che necessita di chirurgia d'urgenza

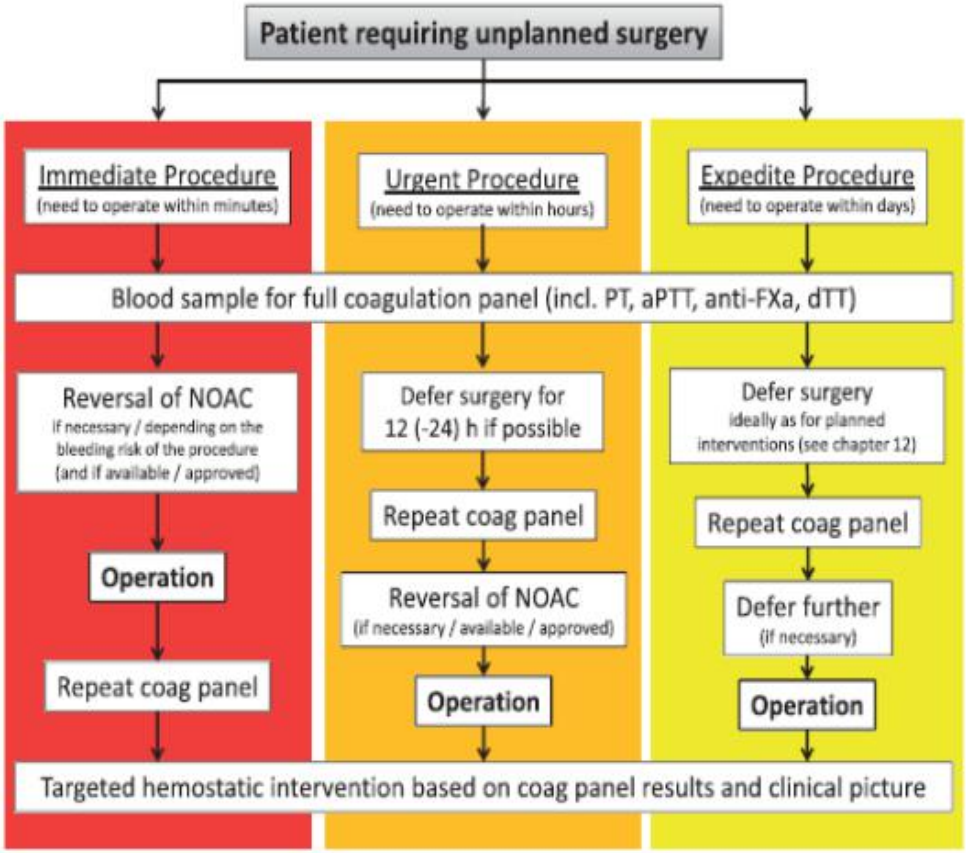


Figure 9 Non-vitamin K antagonist oral anticoagulant management in the setting of unplanned surgery.

Gestione del pz con SCA

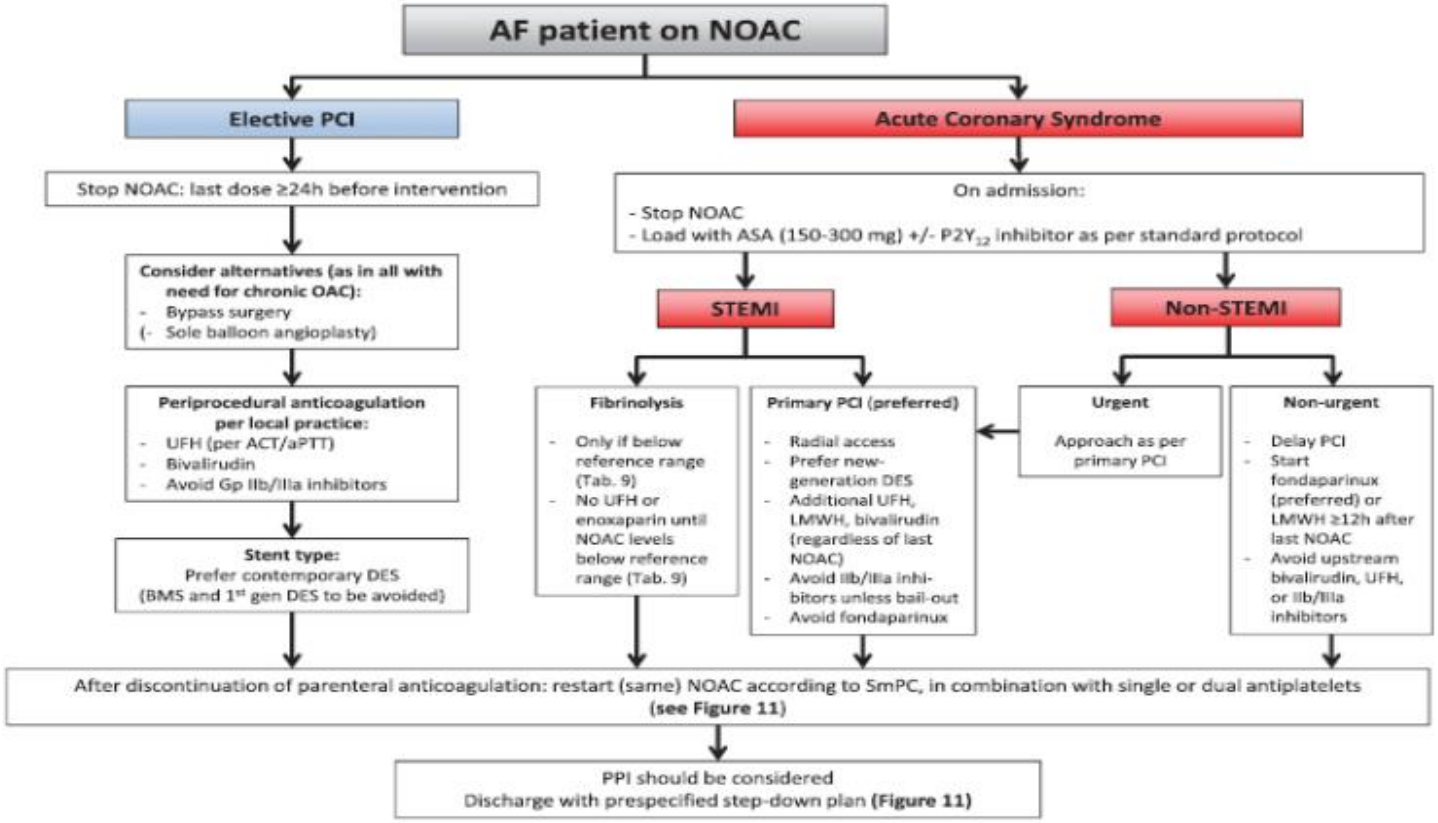


Figure 10 Acute management of elective percutaneous coronary intervention or acute coronary syndrome in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulant.

Gestione del pz con stroke

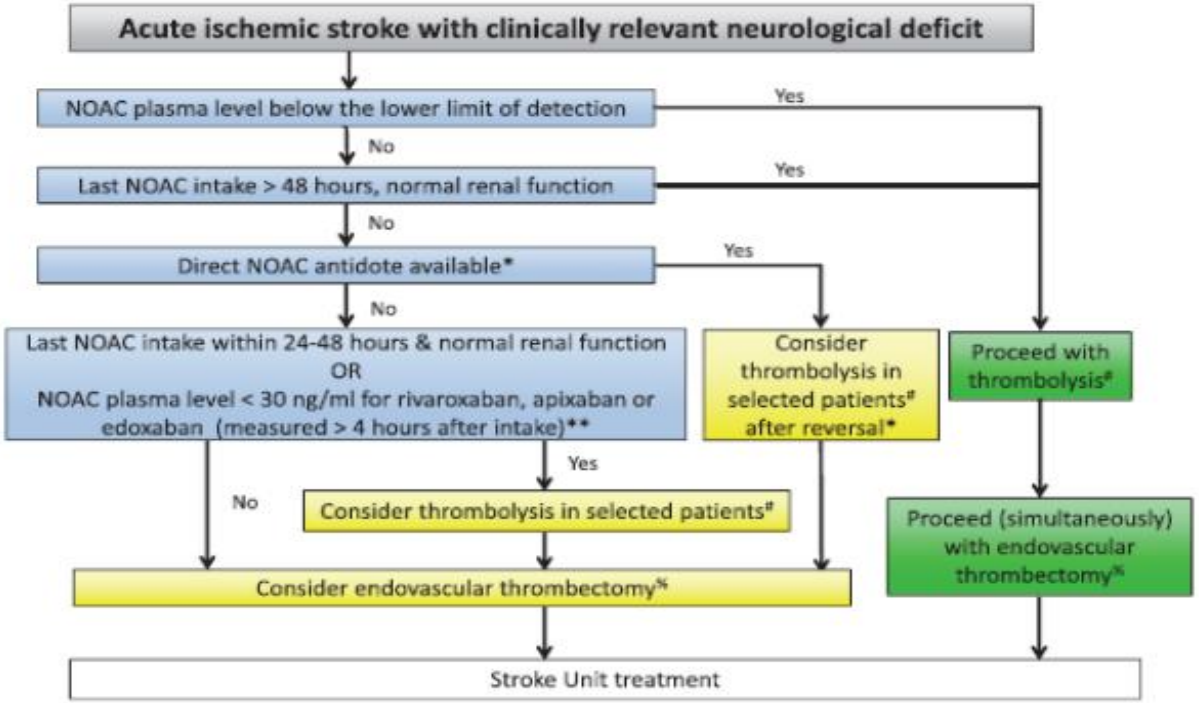
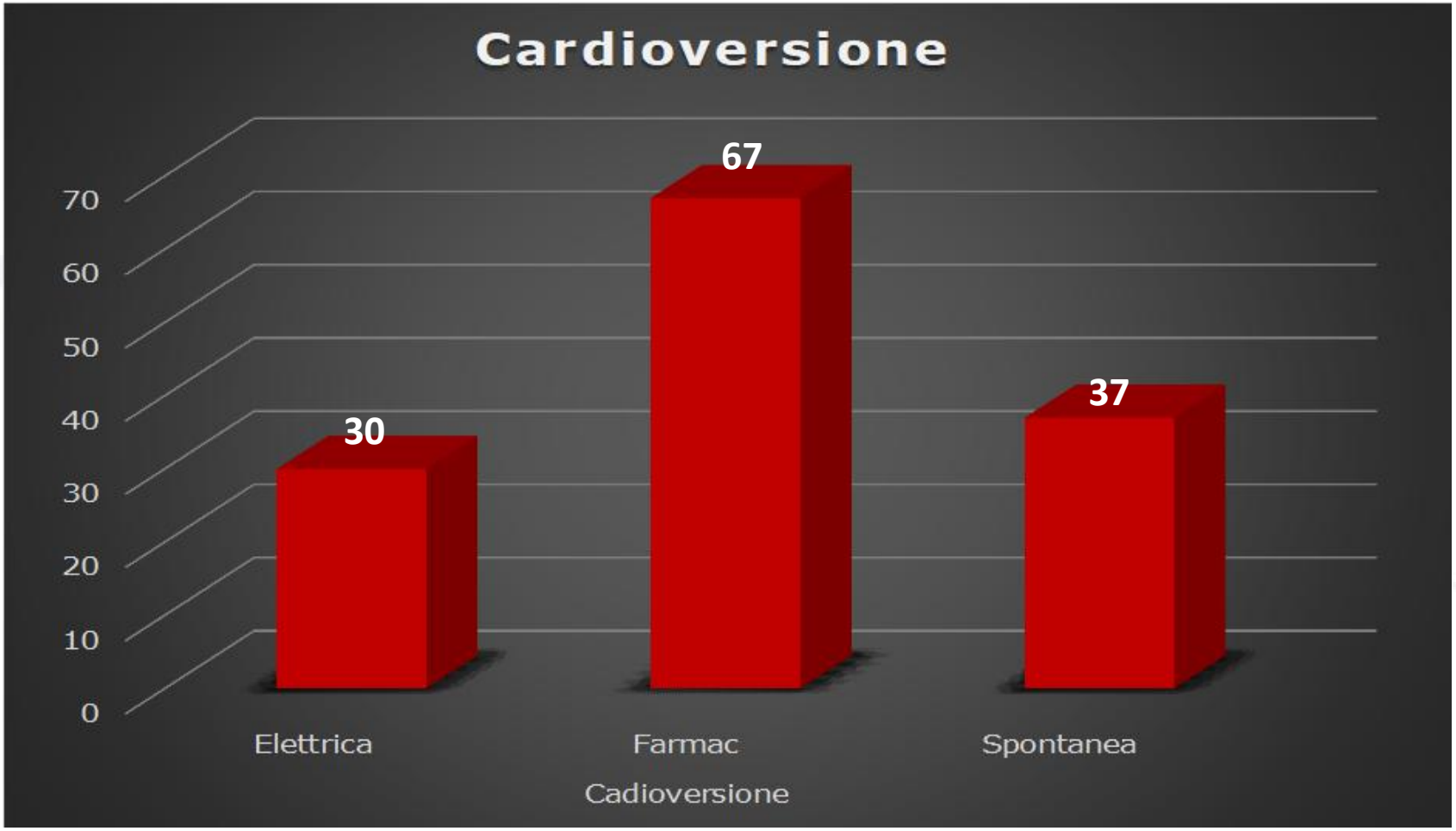


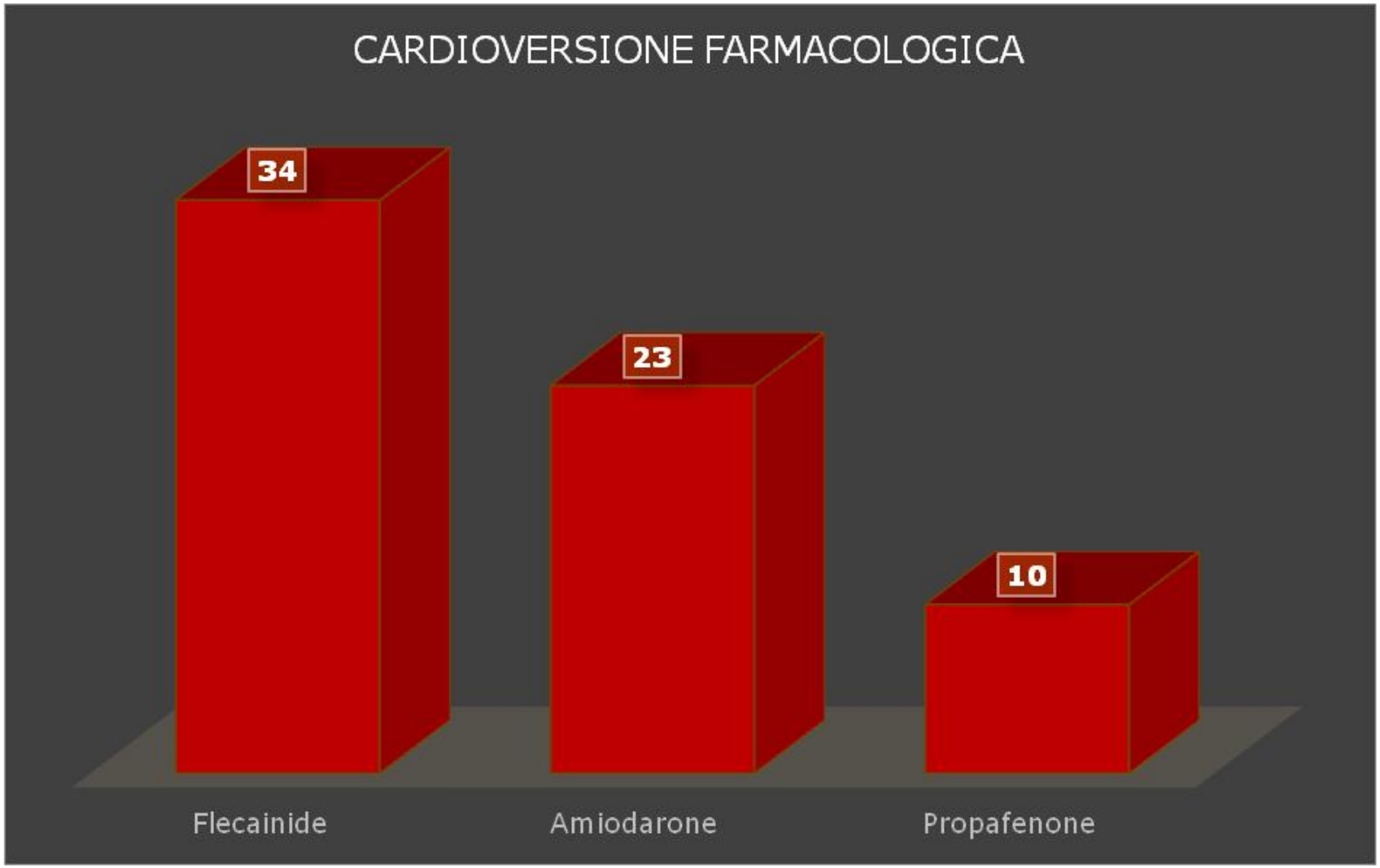
Figure 13 Acute management of acute ischaemic stroke in a patient on non-vitamin K antagonist oral anticoagulant. *Currently only available for dabigatran (idarucizumab). #Perform systemic thrombolysis only if there are no (other) contraindications for intravenous application of recombinant tissue plasminogen activator according to its label. %Perform endovascular thrombectomy only if there is a target vessel occlusion and procedure is indicated and feasible according to present evidence. **According to expert consensus.[370]

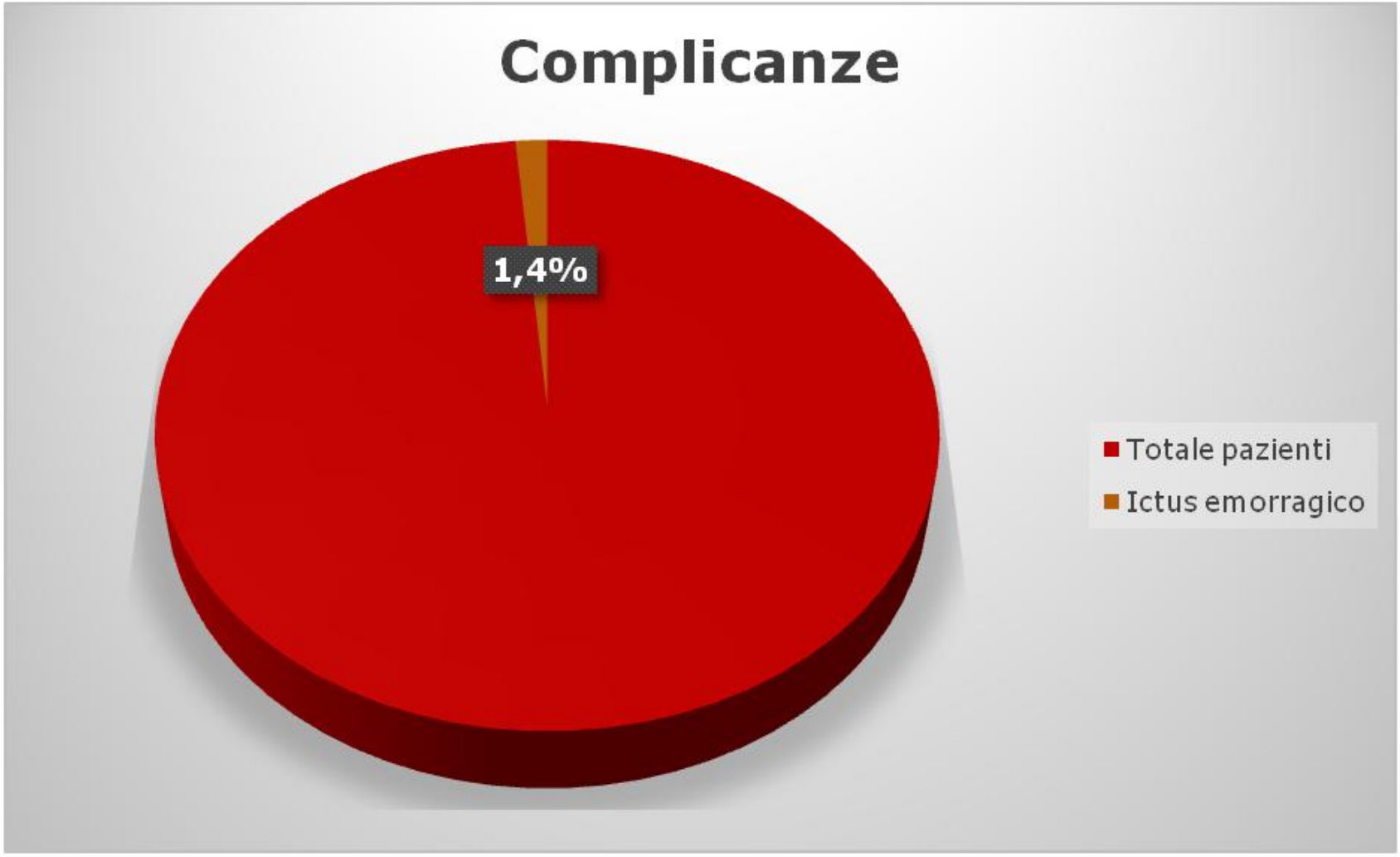
La cardioversione farmacologica del elettrica della FA parossistica nel Pronto Soccorso di Potenza nell'anno 2017 (Gennaio - Ottobre)

- Pazienti n. 138
- Età media 68,2 (24 - 92)
- M/F = 58/80
- CHA2DS2-VASC medio = 2,36

San Carlo
Azienda Ospedaliera
Regionale


Cardioversione
70
60
50
40
30
20
10
0
30
67
37
Elettrica
Farmac
Spontanea
Cadioversione


CARDIOVERSIONE FARMACOLOGICA
34
23
10
Flecainide
Amiodarone
Propafenone


Complicanze
1,4%
Totale pazienti
Ictus emorragico

Segreteria Nazionale:
Via Valprato, 68 - 10155 Torino
c.f. 91206690371
p.i. 02272091204

Contatti:
tel +39 02 67077483
fax +39 02 89959799
segreteria@simeu.it

Grazie per l'attenzione

Dott.ssa Ernesta Dores
Unità Operativa complessa di Pronto Soccorso, Accettazione e Medicina d'urgenza
San Carlo
Azienda Ospedaliera Regionale