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I NAO NELLA PRATICA CLINICA

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RASSEGNA

Efficacia e sicurezza dei nuovi farmaci anticoagulanti orali rispetto al warfarin nella profilassi cardioembolica del paziente con fibrillazione atriale non valvolare. Più luci che ombre

Efficacy and safety of new oral anticoagulants compared with warfarin in cardioembolic prophylaxis of patients with non valvular atrial fibrillation. More lights than shadows

Luca Masotti [a,*], Mario Di Napoli [b], Walter Ageno [c], Davide Imberti [d], Daniel Godoy [e], Grazia Panigada [f], Niccolò Napoli [f], Giancarlo Landini [g], Roberto Cappelli [h], Ido Iori [i], Domenico Prisco [j], Giancarlo Agnelli [k]

Punti di forza NAO derivanti dai grandi trials sulla FA

- Efficacia superiore o quanto meno non inferiore ai VKA
- Sicurezza non inferiore
  - Riduzione del rischio di emorragie intracranica
- Tollerabilità alla terapia non inferiore ai farmaci comparati (bassa percentuale di drop-outs, comunque non superiore ai farmaci comparati)
- Efficacia e sicurezza mantenute in molti sottogruppi:
  - profilassi secondaria
  - pazienti in warfarin con TTR ≥ 60%
  - insufficienza renale moderata
  - età > 75 anni
  - concomitante terapia con antiaggreganti
  - in pazienti con CHADS2 ≥ 2
  - pazienti da sottoporre a ablazione o cardioversione
  - ecc.

Punti di debolezza dei NAO

- Utilizzo non possibile nei pazienti con insufficienza renale severa (ClCr < 30 ml/min per dabigatran, ClCr < 15 ml/min per gli antiXa) e nei pazienti con insufficienza epatica classe C Child-Pugh o in trattamento con alcuni farmaci interferenti con glicoproteina P e/o citocromo P3A4

- Difficoltà nel valutare l'aderenza dei pazienti alla terapia (monitoraggio)

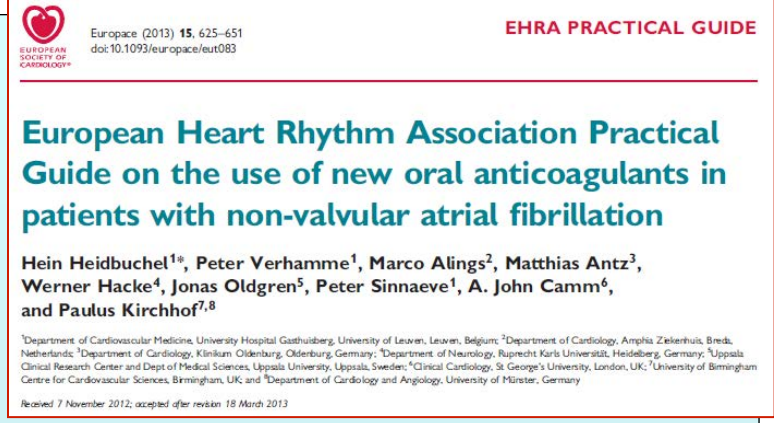
- Difficoltà nel valutare l'attività anticoagulante in particolari situazioni di emergenza (eventi ischemici o emorragici)

- Alcuni risultati da rivalutare nella pratica reale (dabigatran-SCA, dabigatran-dispepsia, dabigatran e rivaroxaban emorragie gastro-intestinali)

- Mancanza di un antidoto specifico

Management pratico

- Quali dosaggi per quali pazienti
  - Insufficienze d'organo
  - Età avanzata
  - Pesi corporei estremi
  - Interferenze farmacologiche
  - Paziente in concomitante terapia antiaggregante
- Gestione del peri-operatorio in elezione
- Gestione del paziente da sottoporre a cardioversione
- Gestione dello switch
- Test di laboratorio e "monitoraggio"
- Gestione del paziente con eventi trombotici
  - Gestione del paziente candidato alla trombolisi
  - Gestione del paziente con ictus ischemico cardioembolico in fase acuta
  - Gestione del paziente con SCA
- Gestione del reverse in urgenza: come e quando
- ……



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EHRA PRACTICAL GUIDE

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

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	CRITERI DI INCLUSIONE	CRITERI DI ESCLUSIONE
RE-LY (Dabigatran)	FA documentata a ECG di screening o nei precedenti 6 mesi + almeno uno di: pregresso ictus o TIA, FE < 40%, scompenso cardiaco classe NYHA ≥ 2 entro 6 mesi prima dello screening, età ≥ 75 anni o, età 65-74 anni se associata ad almeno uno di diabete mellito, ipertensione arteriosa o malattia coronarica	Età < 18 anni, valvulopatia di grado severo, ictus nelle precedenti 2 settimane o ictus severo entro 6 mesi (mRS 4-5), condizioni predisponenti eventi emorragici, insufficienza renale severa (clearance della creatinina < 30 ml/min), malattia epatica attiva, gravidanza
ROCKET-AF (Rivaroxaban)	FA documentata all'ECG + almeno uno di: pregresso ictus o TIA o embolia sistemica od almeno due di: scompenso cardiaco o FE ≤ 35%, ipertensione arteriosa, diabete mellito, età ≥ 75 anni	Età < 18 anni, stenosi mitralica significativa, FA parossistica da causa reversibile, sanguinamento interno attivo, ictus con severa disabilità nei tre mesi precedenti (mRS 4-5) o ictus nelle due settimane precedenti, TIa nei 3 giorni precedenti, anamnesi di emorragia intracranica, patologie emorragiche, insufficienza renale severa (clearance della creatinina < 30 ml/min)
ARISTOTLE (Apixaban)	FA documentata all'ECG in 2 settimane non consecutive nei 12 mesi precedenti + almeno uno di: età ≥ 75 anni, pregresso ictus o TIA o embolia sistemica, scompenso cardiaco nei precedenti 3 mesi o FE ≤ 40%,, diabete mellito, ipertensione arteriosa	Età < 18 anni , FA da cause reversibili, stenosi mitralica moderato-severa, condizioni in cui anticoagulazione necessaria (esempio protesi valvolari), ictus nella settimana precedente, condizioni richiedenti un dosaggio di ASA > 165 mg oppure richiedenti ASA + clopidogrel, insufficienza renale severa (creatinina > 2.5 mg/dl o clearance creatinina < 25 ml/min)
ENGAGE-AF (Edoxaban)	FA documentata all'ECG nei 12 mesi precedenti + almeno uno di: età ≥ 75 anni, pregresso ictus o TIA o embolia sistemica, scompenso cardiaco nei precedenti 3 mesi o FE ≤ 40%,, diabete mellito, ipertensione arteriosa, CHADS2 ≥ 2.	Età < 21 anni, FA da cause reversibili, stenosi mitralica moderato-severa, alto rischio di doppia antiaggregazione piastrinica concomitante, insufficienza renale severa (clearance creatinina < 30 ml/min), sanguinamento, CHADS2 ≤ 1, altre cause richiedenti l'anticoagulazione, SCA o rivascolarizzazione coronarica o stroke nei 30 giorni precedenti, incapacità ad aderire alle procedure dello studio

Quali dosaggi per quali pazienti?

	DOSE STANDARD	DOSE RIDOTTA
DABIGATRAN	150 mg x 2 volte/die	110 x 2/die: Età > 80 anni Peso inferiore 50 Kg Concomitante uso di verapamil o antiaggreganti **ClCr 30-50 ml/min** o età 75-80 anni se alto rischio emorragico
RIVAROXABAN	20 mg x 1	15 mg: **ClCr 15-50 mlmin** Considerare nel paziente con età > 80 anni se alto rischio emorragico
APIXABAN	5 mg x 2 volte/die	2,5 mg x 2/die: **ClCr 15-50 ml/min** Età > 80 anni Peso < 60 Kg

Recommendations for prevention of thromboembolism in non-valvular AF—NOACs			
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[a] … is recommended.	I	B	2, 28, 65, 107
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[a] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A	3, 4, 70, 82
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • concomitant use of interacting drugs (e.g. verapamil) • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	B	85, 96
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	C	3, 108
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa	B	85
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A	3, 24, 70

Monitoraggio clinico raccomandato

Importanti istruzioni per il paziente

Prendere il farmaco esattamente come prescritto (una o due volte al giorno). Se non si prende il farmaco si perde la protezione!

Non interrompere mai il farmaco senza consultare il tuo medico.

Non aggiungere mai altri farmaci senza consultare il tuo medico, anche nel caso di farmaci antidolorifici disponibili senza prescrizione medica.

Avverti il tuo dentista o i chrirurghi prima di un intervento chirurgico.

Farmaci concomitanti

Nome:	Dose:

N.B.: In Emergenza i test standard non danno una valutazione quantitativa del livello di scoagulazione!

Nome e telefono dei famigliari da contattare in caso di emergenza:

Gruppo sanguigno del paziente (+ firma del medico):

Terapia Anticoagulante Orale nella Fibrillazione atriale

Per gli anticoagulanti non inibitori della Vitamina K

Cognome e nome paziente: Data di nascita:

Indirizzo paziente:

Dosaggio anticoagulante orale, orario, assunzione a digiuno o dopo cibo:

Indicazione al trattamento anticoagulante:

Data inizio trattamento:

Nome e indirizzo del medico che coordina il trattamento anticoagulante:

Numero di telefono del medico o del centro che coordinano il trattamento anticoagulante:

EUROPEAN Heart Rhythm ASSOCIATION

EUROPEAN SOCIETY OF CARDIOLOGY®

Ulteriori informazioni:
www.NOACforAF.eu
www.noacforaf.eu

Controlli pianificati o non pianificati

Data (o data approssimativa):	Sede (medico di famiglia,cardio-logo, ...):	Finalità/rilievi:

Controlli raccomandati

(vedi EHRA at **www.NOACforAF.eu** per informazioni e consigli pratici)

Controllare a ogni visita:

1. Compliance (il pz. assume I farmaci?)
2. Eventi trombo-embolici?
3. Sanguinamenti?
4. Altri eventi avversi?
5. Altri farmaci e farmaci da banco.

Prelievi di sangue:

- **il monitoraggio del livello di anticoagulazione non è richiesto!**
- **ogni anno:** Hb, funzione epatica e renale
- **se CrCl 30-60 ml/min, età >75aa, o fragilità:** controllo funzione renale ogni 6 mesi
- **se CrCl 15-30 ml/min:** controllo funzione renale ogni 3 mesi
- **se condizioni intercorrenti a potenziale impatto:** renal and/or liver function

Data	Creatinina Sierica	Clearance creatinina	Emo-globina	Funzione epatica

Bleeding Risk with Dabigatran in the Frail Elderly

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Table 1. (Continued.)

Patient No.	Age	Sex	Weight	Daily Dose†	Site of Bleeding	Degree of Renal Impairment‡	Required Blood Products§
	yr		kg	mg			
10‖	67	M	69	220	Subdural hematoma	None	Yes
11¶	70	M	82	300	Rectal	None	No
12	70	F	70	NA	Hemarthrosis	None	No
13	71	M	74	300	Hematuria	None	No
14	73	F	67	300	Rectal	None	No
32	92	M	NA	300	Hemoptysis	Moderate	No
33	80	F	NA	300	Mucosal	Mild	No
34	80	M	93	220	Rectal	Mild	No
35	82	M	78	300	Rectal	Mild	No
36	84	M	120	220	Rectal	Mild	No
37	88	M	NA	220	Rectal	Mild	Yes
38‖	89	F	57	NA	Hip fracture	Mild	Yes
39¶	80	F	NA	NA	Hematuria	None	No
40	80	M	NA	220	Rectal	None	No
41	85	F	NA	220	Rectal	None	No
42	87	M	NA	220	Hematemesis	None	No
43	87	M	NA	220	Hematuria	None	No
44	89	F	NA	NA	Rectal	None	No

Table 1. Detail

Patient No.	Age
	yr
1	65
2¶	71
3‖	77
4	78
5‖	40
6	65
7	71
8	74
9	75

A review of these cases identified four major factors that contributed to the episode: prescriber error, impaired renal function, patient age, and complications arising from the lack of a reversal agent. Prescriber errors contributed to bleeding in approximately 25% of the patients, including

44 p

13,6% con insuff renale severa
11,3% > 80 anni dose piena

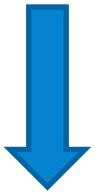
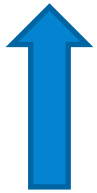
Table 2: Factors identified in clinical trials which may increase the bleeding risk[a].

Demographic	Age ≥75 years
Factors increasing dabigatran plasma levels	Major: Moderate renal impairment (CrCL 30–50 ml/min) P-gp inhibitor co-medication Minor: Low body weight (<50 kg)
Pharmacodynamic interactions	ASA NSAID Clopidogrel
Diseases/procedures with special haemorrhagic risks	Congenital or acquired coagulation disorders Thrombocytopenia or functional platelet defects Active ulcerative GI disease Recent GI bleeding Recent biopsy or major trauma Recent ICH Brain, spinal, or ophthalmic surgery Bacterial endocarditis

[a]For special patient populations requiring a reduced 110 mg bid dose, see Figure 1. ASA, acetylsalicylic acid; CrCL, Creatinine clearance; P-gp, P-glycoprotein; GI, gastrointestinal; ICH, intracranial haemorrhage; NSAID, non-steroidal anti-inflammatory drug.

Interferenze farmacologiche ed aggiustamento posologico dei NAO

Dabigatran			
Caution but use possible at standard dose	**Caution** Reduce dose to 110 mg bid	Not recommended	Contraindicated
Atorvastatine, Diclofenac, pantoprazole, clopidogrel, digoxin, amiodarone, chinidine, clarhytromicine	**Verapamil**	**Dronedarone, carbamazepine, rifampicine, phenitoine, anti-retroviral drugs**	**Azoles, tracolimus, ciclosporine**

AntiXa			
Caution but use possible at standard dose	**Caution** The anticoagulant effect could be reduced because inducers of P-glycoprotein or cytocrome 3A4	**Caution** The anticoagulant effect could be increased because inhibitors of P-glycoprotein or cytocrome 3A4	Contraindicated
Digoxin, atorvastatine, midazolam	Rifampicine, fenobarbital, phenitoine, carbamazepine, ipericum 	Fluconazole, erhytromicine, clarhytromicine, amiodarone, verapamil 	**Azoles, anti-retroviral drugs**

Consensus Document

Management of Antithrombotic Therapy in Atrial Fibrillation Patients Presenting with Acute Coronary Syndrome and/or Undergoing Percutaneous Coronary Intervention/ Stenting

A Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association [EHRA] and the European Association of Percutaneous Cardiovascular Interventions [EAPCI]

Gregory Y. H. Lip[1]*; Kurt Huber[2]**; Felicita Andreotti[3]***; Harald Arnesen[4]***; K. Juhani Airaksinen[5]***; Thomas Cuisset[6]***; Paulus Kirchhof[7]***; Francisco Marín[8]***

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- FA a moderato-alto rischio
- Protesi valvolari meccaniche
- Anamnesi di stroke cardioembolico
- Anamnesi di recente tromboembolismo venoso

Lip G et al. Thromb Haemost 2010

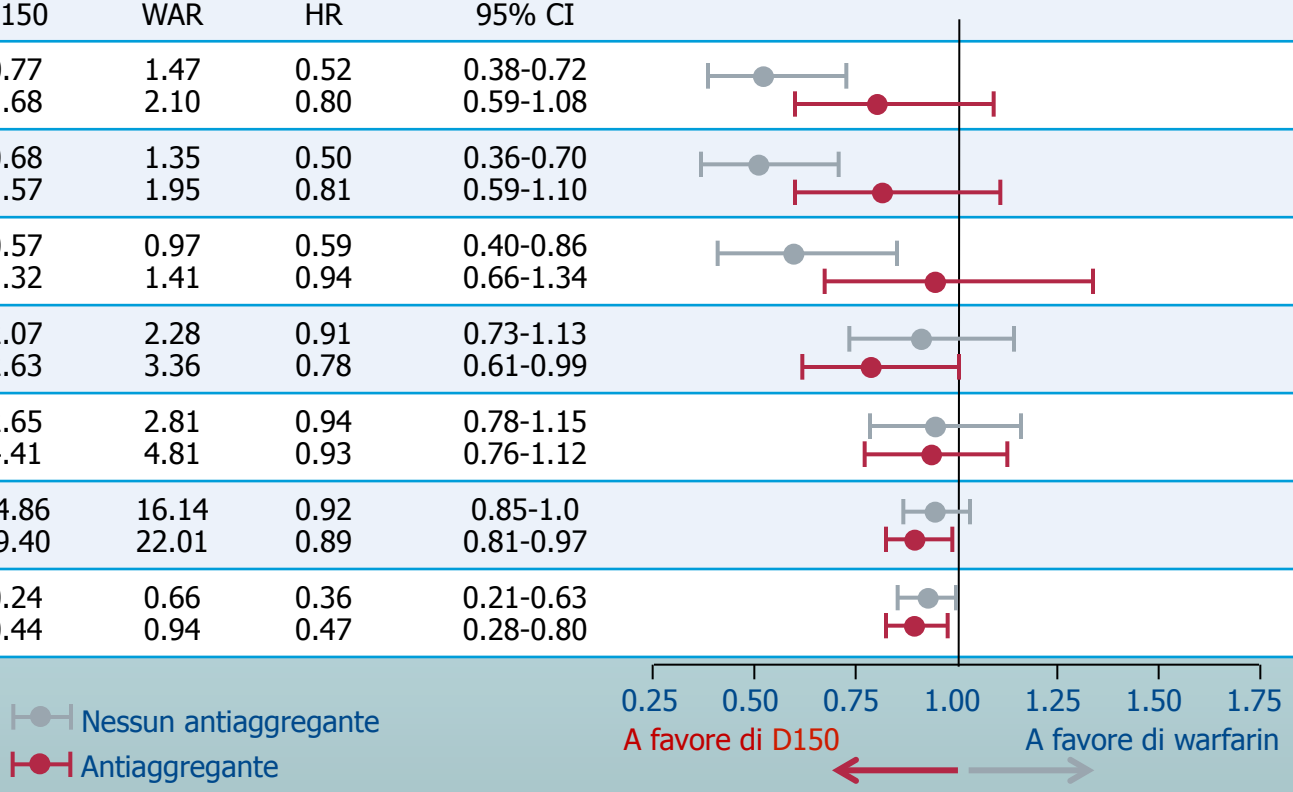
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY®) Trial

Antonio L. Dans, Stuart J. Connolly, Lars Wallentin, Sean Yang, Juliet Nakamya, Martina Brueckmann, Michael Ezekowitz, Jonas Oldgren, John W. Eikelboom, Paul A. Reilly and Salim Yusuf

	Rate (%/year)				
	D150	WAR	HR	95% CI	P(INTER)
Ictus/embolia sistemica	0.77 1.68	1.47 2.10	0.52 0.80	0.38-0.72 0.59-1.08	0.06
Ictus	0.68 1.57	1.35 1.95	0.50 0.81	0.36-0.70 0.59-1.10	0.04
Ictus ischemico	0.57 1.32	0.97 1.41	0.59 0.94	0.40-0.86 0.66-1.34	0.08
Mortalità CV	2.07 2.63	2.28 3.36	0.91 0.78	0.73-1.13 0.61-0.99	0.36
Sanguinamenti maggiori	2.65 4.41	2.81 4.81	0.94 0.93	0.78-1.15 0.76-1.12	0.87
Sanguinamenti totali	14.86 19.40	16.14 22.01	0.92 0.89	0.85-1.0 0.81-0.97	0.5
Sanguinamenti intracranici	0.24 0.44	0.66 0.94	0.36 0.47	0.21-0.63 0.28-0.80	0.53



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Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY®) Trial

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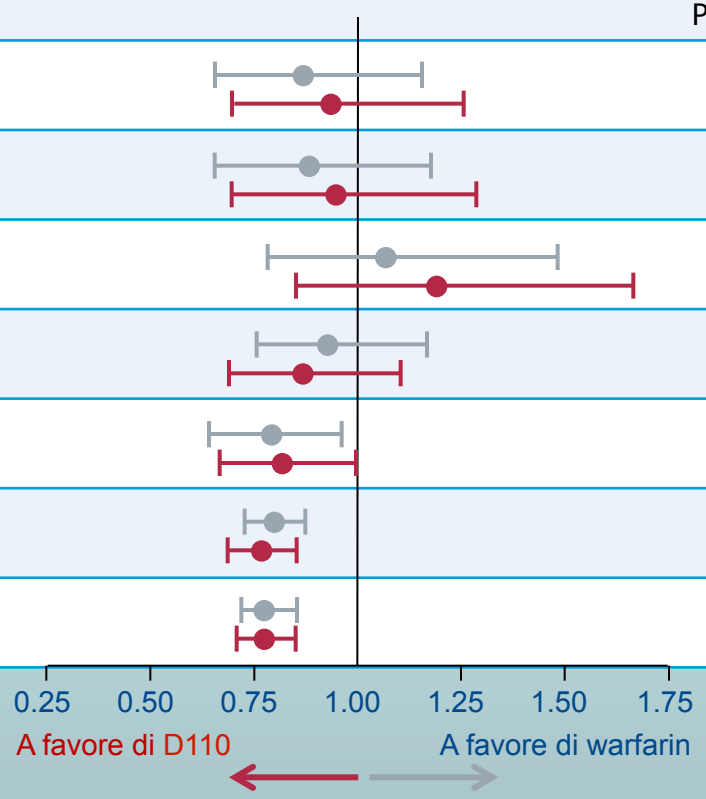
	Rate (%/year)				
	D110	WAR	HR	95% CI	P(INTER)
Ictus/embolia sistemica	1.29 1.95	1.47 2.10	0.87 0.93	0.65-1.15 0.7-1.25	0.74
Ictus	1.19 1.84	1.35 1.95	0.88 0.95	0.66-1.17 0.7-1.28	0.72
Ictus ischemico	1.04 1.66	0.97 1.41	1.07 1.19	0.78-1.48 0.85-1.66	0.67
Mortalità CV	2.13 2.92	2.28 3.36	0.93 0.87	0.75-1.16 0.69-1.1	0.67
Sanguinamenti maggiori	2.22 3.94	2.81 4.81	0.79 0.82	0.64-0.96 0.67-1.0	0.79
Sanguinamenti totali	12.94 17.71	16.14 22.01	0.78 0.78	0.72-0.85 0.71-0.85	0.85
Sanguinamenti intracranici	0.23 0.22	0.66 0.94	0.35 0.23	0.20-0.61 0.12-0.47	0.37



Nessun antiaggregante
Antiaggregante

The NEW ENGLAND JOURNAL of MEDICINE

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Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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

European Heart Journal
doi:10.1093/eurheartj/eht445

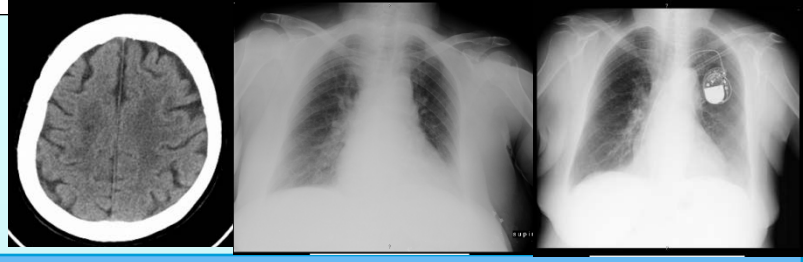
CLINICAL RESEARCH
Atrial fibrillation

Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial

John H. Alexander[1]*, Renato D. Lopes[1], Laine Thomas[1], Marco Alings[2], Dan Atar[3], Philip Aylward[4], Shinya Goto[5], Michael Hanna[6], Kurt Huber[7], Steen Husted[8], Basil S. Lewis[9], John J.V. McMurray[10], Prem Pais[11], Hubert Pouleur[12], Philippe Gabriel Steg[13], Freek W.A. Verheugt[14], Daniel M. Wojdyla[1],

APIXABAN + ASA	eventi versus warfarin + ASA	p interaction
EFFICACIA (stroke o embolismo sistemico)	0.58 (0.39 - 0.85)	0.10
SICUREZZA (sanguinamenti maggiori)	0.77 (0.56 - 0.99)	0.29
RIVAROXABAN + ASA	**HR (95% CI) versus warfarin +ASA**	**p interaction**
EFFICACIA (stroke o embolismo sistemico)	0.87 (0.57-1.13)	0.905
SICUREZZA (sanguinamenti maggiori)	0.78 (0.57-1.07)	0.941

Raccomandazioni per il corretto management peri-operatorio in elezione dei pazienti in trattamento con NOA



ClCr	Timing della sospensione dei DOAC	
DABIGATRAN		
	Rischio di sanguinamento standard	Rischio di sanguinamento elevato
≥80 ml/min	Almeno 24 ore prima	Almeno 24-48 ore prima
80-50 ml/min	Almeno 24-48 ore prima	Almeno 48-72 ore prima
50-30 ml/min	Almeno >48 ore prima	Almeno >72 ore prima
<30 ml/min	Controindicazione all'impiego	
RIVAROXABAN E APIXABAN		
≥80 ml/min	Almeno 24 ore prima	Almeno 48 ore prima
80-50 ml/min	Almeno 24 ore prima	Almeno 48 ore prima
50-30 ml/min	Almeno 24 ore prima	Almeno 48 ore prima
30-15 ml/min	Almeno 36 prima	Almeno 48 ore prima
<30 ml/min	Controindicazione all'impiego	

Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: Resolving uncertainties in routine practice

Menno V. Huisman[1]; Gregory Y. H. Lip[2]; Hans-Christoph Diener[3]; Martina Brueckmann[4]; Joanne van Ryn[5]; Andreas Clemens[4]

[1]Departments of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands; [2]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [3]Department of Neurology, University Hospital Essen, Essen, Germany; [4]Global Clinical Development and Medical Affairs, Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany, [5]Department of CardioMetabolic Disease Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany

Conversion	Start times recommenced
From VKAs to dabigatran	Discontinue VKA and start dabigatran when INR <2
From dabigatran to VKAs[a]	Start times for VKAs are based on renal function: – If CrCL ≥50 ml/min, start VKA 3 days before stopping dabigatran – If CrCL ≥30 to <50 ml/min, start VKA 2 days before stopping dabigatran – If CrCL 15–30 ml/min, start VKA 1 day before stopping dabigatran[b]
From dabigatran to parenteral	Start parenteral anticoagulant 12 h after last dose of dabigatran
From parenteral to dabigatran	Start dabigatran at the same time or up to 2 hours before the next parenteral drug dose. For continuous infusions of parenteral drugs, start dabigatran at the time of discontinuation of the continuous infusion.

[a]Because dabigatran may contribute to an elevated INR, the INR will better reflect the effect of the VKA after dabigatran has been stopped for at least 2 days; [b]Applies to patients treated in the US and for patients in whom the CrCL drops below 30 mL/min. CrCL, Creatinine clearance; h, hours; INR, International normalised ratio; VKA, vitamin K antagonists.

Management consensus guidance for the use of rivaroxaban – an oral, direct factor Xa inhibitor

Alexander G. G. Turpie[1]; Reinhold Kreutz[2]; Juan Llau[3]; Bo Norrving[4]; Sylvia Haas[5]

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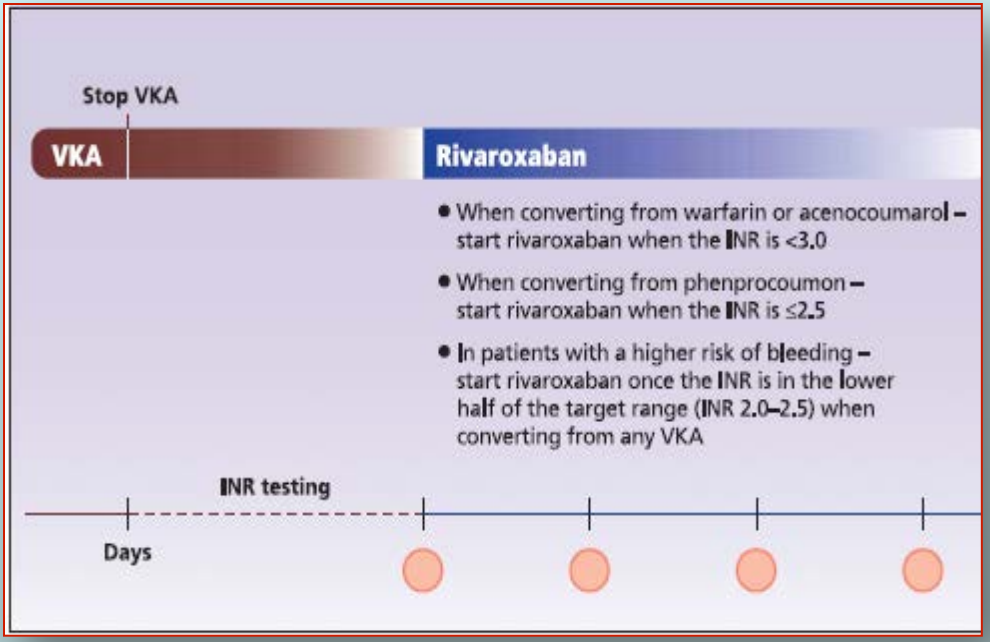

Converting patients from rivaroxaban to VKAs

- In patients converting from rivaroxaban to VKAs, VKA therapy should be given concurrently until the INR is ≥2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both rivaroxaban and VKA the INR should be measured 24 h after the previous dose of rivaroxaban but before the next dose because of its influence on the INR. Once rivaroxaban is discontinued, INR testing may be done reliably at least 24 h after the last dose.

Switching from and to parenteral anticoagulants

- For patients currently receiving a parenteral anticoagulant, rivaroxaban should be started at the time of the next scheduled administration of the parenteral anticoagulant, such as subcutaneous LMWH, or at the time of discontinuation of continuous intravenously administered unfractionated heparin.

Ward et al. Thrombosis Journal 2013, 11:27
http://www.thrombosisjournal.com/content/11/1/27

THROMBOSIS JOURNAL

REVIEW Open Access

Practical management of patients on apixaban: a consensus guide

Christopher Ward[1*], Greg Conner[2], Geoffrey Donnan[3], Alexander Gallus[4] and Simon McRae[5]

Switching from low molecular weight heparin (LMWH) to apixaban

As both agents have a similar rapid onset of FXa inhibition and effective half-life, switching anticoagulation from LMWH (e.g. enoxaparin) to apixaban, (and vice versa), can simply be done at the time of the next scheduled dose [5].

Apixaban to low molecular weight heparin (LMWH)

As both agents have a similar rapid onset of FXa inhibition and effective half-life, switching anticoagulation from apixaban to LMWH (e.g. enoxaparin) and vice versa, can simply be done at the time of the next scheduled dose [5].

Switching from apixaban

An increased risk of stroke was observed during the transition from apixaban to warfarin in clinical trials in patients with non-valvular atrial fibrillation [16]. Discontinuation of apixaban prior to the onset of an effective antithrombotic effect of VKA could result in an increased risk of thrombosis. If anticoagulation with apixaban must be discontinued for any reason other than pathological bleeding, consider coverage with another anticoagulant.

Apixaban to warfarin

When converting from apixaban to warfarin, continue apixaban for 48 hours after the first dose of warfarin. After 2 days of co-administration of apixaban with warfarin, obtain an INR prior to the next scheduled dose of apixaban. Continue co-administration of apixaban and warfarin until the INR is ≥ 2.0.

Indicazioni al monitoraggio clinico e di laboratorio

- Emorragia o embolia
- Prima di chirurgia o manovre invasive
- Possibile sovradosaggio o condizioni a rischio di sanguinamento
- Assunzione di farmaci interferenti
- Pesi corporei estremi (obesità severa e magrezza)
- Alterazione o deterioramento della funzione renale o della funzione epatica
- Verifica della compliance (?)

Quali test di laboratorio?

DABIGATRAN	aPTT	PT	ECT	dTT
Disponibilità	++	++	-+	++
Linearità	-	+	+	+
Standardizzazione	-	-	+	-
Responsività	+	-	++	+++

RIVAROXABAN	antiXa	PT	aPTT	HepTEST	dRWt
Disponibilità	-+	++	++	+	+
Linearità	+	+	+	-	-
Standardizzazione	-?	+	-	?	?
Responsività	++	+	+	++	++

Modificato da Tripodi A, Blood 2013

Journal of Thrombosis and Haemostasis, 11: 756–760 DOI: 10.1111/jth.12149

OFFICIAL COMMUNICATION OF THE SSC

Measuring oral direct inhibitors of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis

T. BAGLIN,* A. HILLARP,† A. TRIPODI,‡ I. ELALAMY,§ H. BULLER¶ and W. AGENO**

- dabigatran

Recommendation

1 The APTT, with most available reagents, can be used to determine the relative intensity of anticoagulation caused by dabigatran, e.g. in an emergency or urgent clinical situation. The APTT should not be used to quantify the drug plasma concentration. Further studies are required to determine the relative sensitivity of APTT reagents to dabigatran, in order to give more specific recommendations regarding the choice of APTT reagent.
2 Each laboratory should be aware of the sensitivity of their APTT assays to dabigataran, and this can be achieved by the use of commercially available dabigatran plasma calibrants.
3 A normal TT indicates a very low or undetectable level of dabigatran.
4 The dilute TT in combination with dabigatran calibrant plasmas can be used to determine the drug level.

- rivaroxaban

Recommendation

1 A PT assay with a plain thromboplastin can be used to determine the relative intensity of anticoagulation caused by rivaroxaban, e.g. in an emergency or urgent clinical scenario. Further studies are required to determine the relative sensitivity of PT reagents to rivaroxaban, in order to give more specific recommendations regarding the choice of PT reagent.
2 Each laboratory should be aware of the sensitivity of their PT assay to rivaroxaban, and this can be achieved by the use of commercially available rivaroxaban plasma calibrants.
3 Anti-FXa assays (without exogenous antithrombin) and specific PT assays can be used with rivaroxaban plasma calibrants to determine the drug level.

Stroke, Trombolisi e NOA

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Guidelines for the Early Management of Patients With Acute Ischemic Stroke : A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Edward C. Jauch, Jeffrey L. Saver, Harold P. Adams, Jr, Askiel Bruno, J.J. (Buddy) Connors, Bart M. Demaerschalk, Pooja Khatri, Paul W. McMullan, Jr, Adnan I. Qureshi, Kenneth Rosenfield, Phillip A. Scott, Debbie R. Summers, David Z. Wang, Max Wintermark and Howard Yonas

Stroke. published online January 31, 2013;

Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)

2. The use of intravenous rtPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended unless sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for >2 days (assuming normal renal metabolizing function). Similar consideration should be given to patients being considered for intra-arterial rtPA *(Class III; Level of Evidence C)*. (New recommendation) Further study is required.

Europace (2013) **15**, 625–651
doi:10.1093/europace/eut083

EHRA PRACTICAL GUIDE

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

14.1.2 Patients with acute ischaemic stroke

According to current guidelines and official labelling, thrombolytic therapy with recombinant tissue plasminogen activator (rtPA), which is approved within a 4.5 h time window from onset of stroke symptoms, is not recommended in patients under therapy with anticoagulants. As plasma half-life of NOACs ranges between 8 and 17 h, thrombolytic therapy cannot be given within 48 h after the last administration of NOAC (corresponding to four plasma half lives). This is an arbitrary recommendation, which has yet to be tested. In case of uncertainty concerning last NOAC administration, a prolonged aPTT (for dabigatran) or PT (for Fxa inhibitors) indicates that the patient is anticoagulated (see Section 3) and thrombolysis should not be administered. Until there are reliable and sensitive rapid (point-of-care) tests for the individual NOAC, we would discourage the use of thrombolytics in situations with uncertainty about the anticoagulaton

Case Reports in Neurology

Case Rep Neurol 2013;5:56–61
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Published online: March 25, 2013

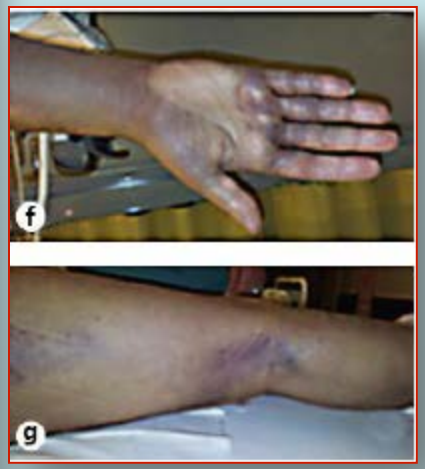
1662–680X/13/0051–0056$38.00/0
www.karger.com/crn

Thrombolysis in a Stroke Patient on Dabigatran Anticoagulation: Case Report and Synopsis of Published Cases

Table 1. Synopsis of the seven published cases of stroke under dabigatran in the therapeutic time window

Reference	Age years, sex	Dabigatran indication and dose	Interval last dose to thrombolysis	NIHSS upon admission	aPTT s	INR	Therapeutic decision	Outcome (NIHSS)	Future OAC therapy
De Smedt et al. [8]	46, f	AF (RELY-ABLE extension study), dose not indicated, b.i.d.	7 h	19	35	1.2	thrombolysis	improvement (12 at discharge)	warfarin
Chong and Chiu [6]	75, f	AF (RE-LY-trial), dose unknown, b.i.d., off dabigatran for 3 days in preparation for surgery	i.n.a.	8	34	1.1	no thrombolysis	improvement (2 at discharge)	n.i.
Matute et al. [9]	76, f	DVT prophylaxis after surgery, 220 mg o.d.	15 h	4	31	1.0	thrombolysis	improvement (0 at discharge)	n.i.
Casado Naranjo et al. [7]	62, m	AF, 110 mg b.i.d., patient not in steady state prior to stroke (3 doses)	6 h	18	37	1.3	thrombolysis	fatal intracerebral hemorrhage	–
Sangha et al. [10]	51, m	AF, 150 mg b.i.d.	18 h	6	31	1.1	thrombolysis	improvement (2 at 6 months)	warfarin
Marrone and Marrone [11]	73, m	AF, 110 mg b.i.d.	7 h	14	38	1.1	thrombolysis	improvement (7 next day)	dabigatran 110 mg b.i.d.
Lee et al. [12]	64, m	AF, i.n.a.	i.n.a.	i.n.a.	38	1.1	thrombolysis	i.n.a., CCT: no hemorrhage	i.n.a.

o.d. = Once daily; b.i.d. = twice daily; i.n.a. = information not available; n.i. = not indicated.



Il corretto timing dell'anticoagulazione con VKA nella fase acuta di uno stroke cardioembolico

• <4,5 h	trombolisi se non controindicata, INR < 1.7
• <48 h	ASA
• 48h-14 giorni	inizio VKA valutando sul singolo paziente: Severità del quadro clinico Ampiezza della lesione ischemica evidenziata al controllo TC Comorbidità cardiaca
• >14 giorni	inizio VKA in pazienti con severo danno neurologico, che hanno un'ampia lesione ischemica, che non presentano evidenti fattori di rischio di embolismo dimostrati da ETT o ETE

Quando iniziare un NAO nella fase acuta di uno stroke cardioembolico e quale è il rischio di trasformazione emorragica?

Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: Resolving uncertainties in routine practice

Menno V. Huisman[1]; Gregory Y. H. Lip[2]; Hans-Christoph Diener[3]; Martina Brueckmann[4]; Joanne van Ryn[5]; Andreas Clemens[4]

[1]Departments of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands; [2]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [3]Department of Neurology, University Hospital Essen, Essen, Germany; [4]Global Clinical Development and Medical Affairs, Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany, [5]Department of CardioMetabolic Disease Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany

Stroke Severity	Restart dabigatran
TIA	As soon as imaging has excluded a cerebral haemorrhage
Mild Stroke	3–5 days after symptom onset
Moderate Stroke	5–7 days after stroke onset
Severe Stroke	2 weeks after stroke onset

ARISTOTLE	Stroke nella settimana precedente (44 pazienti con TIA/stroke tra 7-14 giorni prima dell'arruolamento randomizzati ad apixaban, 21, o warfarin, 23 187 pazienti tra 14-30 giorni)

Italian Journal of Medicine 2013; volume 7(s8):8-21

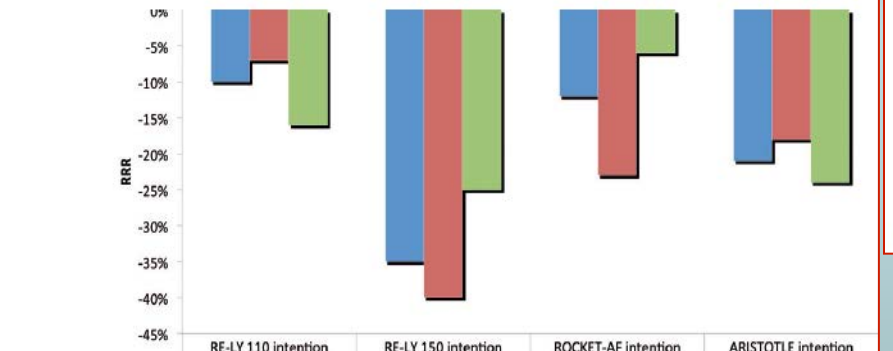
Direct oral anticoagulants for secondary prevention in patients with non-valvular atrial fibrillation

Luca Masotti,[1] Mario Di Napoli,[2] Walter Ageno,[3] Davide Imberti,[4] Cecilia Becattini,[5] Maurizio Paciaroni,[5] Daniel Augustin Godoy,[6] Roberto Cappelli,[7] Giancarlo Landini,[8] Grazia Panigada,[9] Ido Iori,[10] Domenico Prisco,[11] Giancarlo Agnelli[5]

Masotti et al. Ital J Med 2013

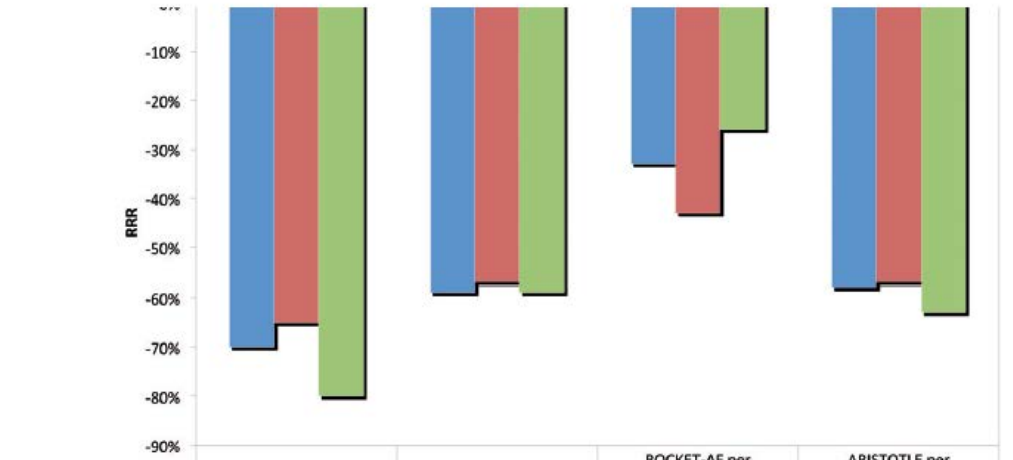
	RE-LY 110 intention to treat	RE-LY 150 intention to treat	ROCKET-AF per protocol RRR total, intention to treat RRR primary and secondary prevention	ARISTOTLE intention to treat
overall	-9%	-12%	-8%	-11%
primary prevention	-4%	-14%	-12%	-10%
secondary prevention	-30%	-5%	-3%	-11%

Figure 3. Relative risk reduction (RRR) of all causes mortality with DOACs compared to warfarin.



	RE-LY 110 intention to treat	RE-LY 150 intention to treat	ROCKET-AF intention to treat	ARISTOTLE intention to treat
overall	-10%	-35%	-12%	-21%
primary prevention	-7%	-40%	-23%	-18%
secondary prevention	-16%	-25%	-6%	-24%

Figure 4. Relative risk reduction (RRR) of strokes and systemic embolism with DOACs compared to warfarin.



	RE-LY 110 intention to treat	RE-LY 150 intention to treat	ROCKET-AF per protocol, on treatment	ARISTOTLE per protocol, on treatment
overall	-70%	-59%	-33%	-58%
primary prevention	-65%	-57%	-43%	-57%
secondary prevention	-80%	-59%	-26%	-63%

Figure 5. Relative risk reduction (RRR) of intracranial bleedings with DOACs compared to warfarin.

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

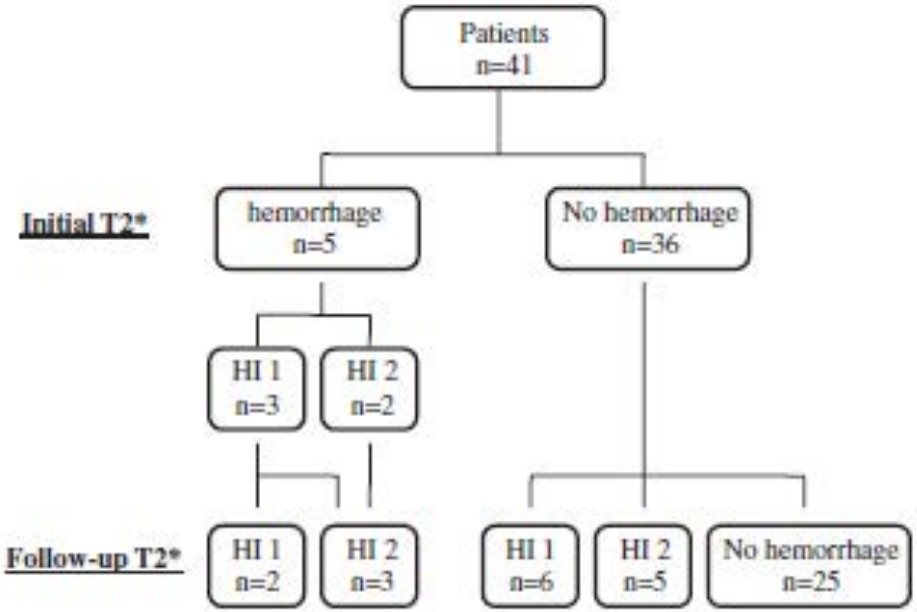
Early initiation of new oral anticoagulants in acute stroke and TIA patients with nonvalvular atrial fibrillation

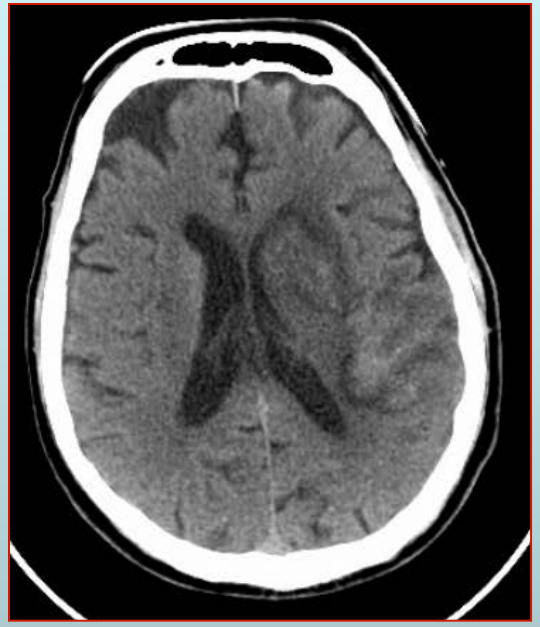
Kensaku Shibazaki *, Kazumi Kimura, Junya Aoki, Naoki Saji, Kenichiro Sakai

Department of Stroke Medicine, Kawasaki Medical School, Japan

3. Results

A total of 113 patients (58 males; mean age 79.0 years) with acute stroke or TIA and NVAF who started anticoagulant therapy within 2 weeks after onset were enrolled retrospectively. Thirty nine (36%) of 108 patients with stroke and two (40%) of five patients with TIA were treated NOAC. The median (interquartile range) interval from onset to treatment with NOAC was 2 (1–6) days. Dabigatran was used





Indicazioni al reverse urgente

- Emorragia maggiore in atto
- Alto rischio di eventi emorragici
- Sovradosaggio con elevato rischio di sanguinamento
- Interventi chirurgici d'urgenza

DEFINIZIONE DI EMORRAGIA IN CORSO DI FARMACI ANTITROMBOTICI

INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

MAGGIORE

- **Emorragia intracranica** ed altro sanguinamento in organi critici (midollo spinale, peritoneo, retroperitoneo, tratto gastro-enterico, torace, articolazioni, occhio)
- Emorragie che determinano un calo di 2 g/dl di Hb o che richiedono almeno 2 sacche di GR per trattarle
- Emorragie che richiedono l'intervento chirurgico o manovre invasive per arrestarle
- Emorragie fatali

MINORE

- Ecchimosi e petecchie
- Ematomi sottocutanei e muscolari
- Epistassi
- Emorragia congiuntivale e palpebrale
- Gengivorragie
- Emoftoe
- Otorragia
- Ematuria
- Meno-metrorragie

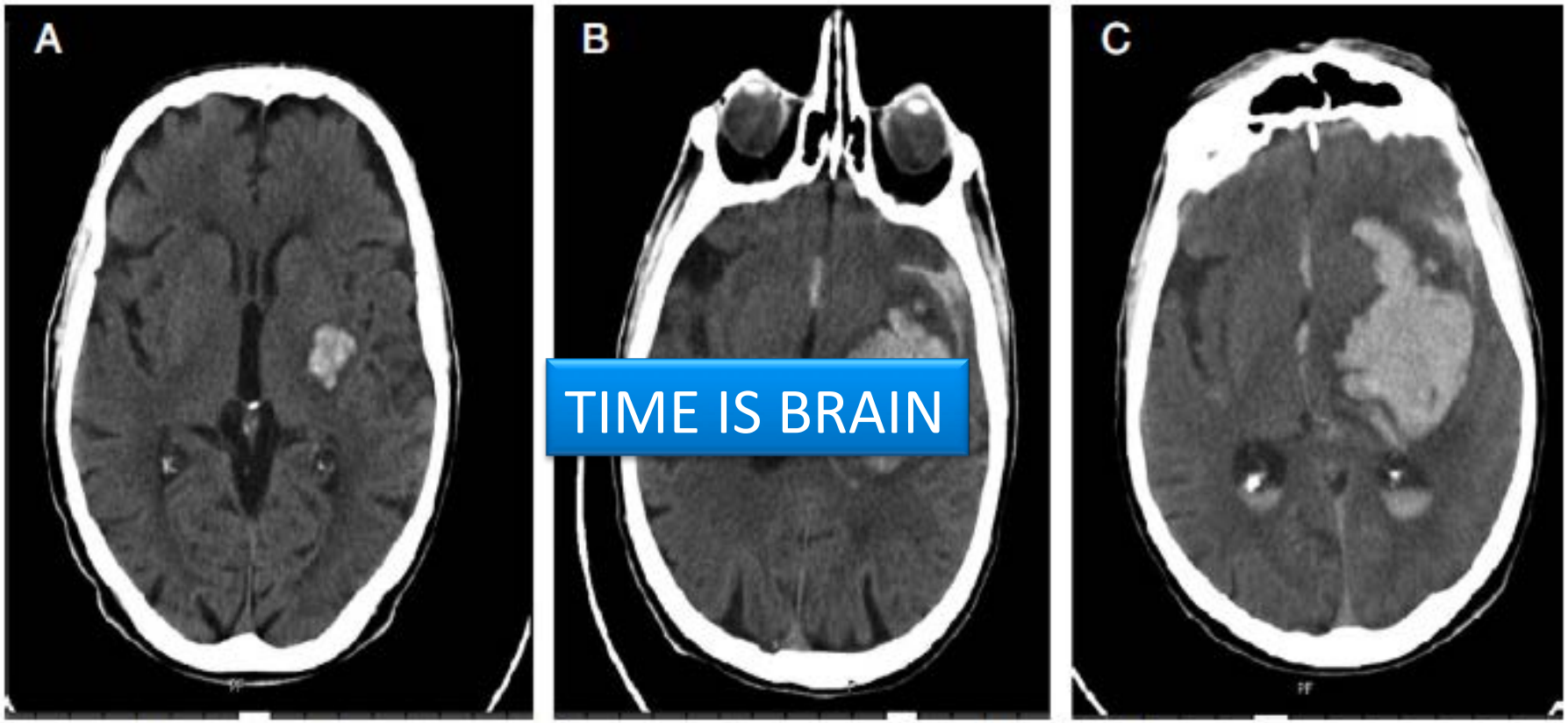


Figure 2. Hematoma enlargement in a delayed reversal of a warfarin-related intracranial hemorrhage. A) Hospital admission: international normalized ratio (INR) 3.1., Glasgow coma scale (GCS): 15/15, treatment: i.v. vitamin K; B) Three hours after admission: GCS 4/15, started treatment with prothrombin complex concentrates INR 1.1 after infusion; C) Eighteen hours after admission: GCS 3/15, INR 0.7. 72 hours after hospital admission death occurred.

EMORRAGIE MAGGIORI VKA-ASSOCIATE
TEMPI DI SOMMINISTRAZIONE E NEUTRALIZZAZIONE

Agente	Dosaggio	Tempo di somministrazione	Tempo di neutralizzazione
CCP*	INR < 2.0 20UI/kg INR 2.0-3.0 30 UI/Kg INR 3.0-4.0 40 UI/Kg INR >4.0 50UI/kg	10-15'	15-30'
PFC	15-30 ml/Kg	2-6 h	6-12 h
FVIIra	10-120 microg/kg 80-90 microg/Kg	5'	15'
VK1 ev	10 mg in sol. Fisiol. 250 cc ripetibile	1mg/min	Inizio dopo 2 h Max effetto dopo 12-16 ore
Sola sospensione della TAO	/	/	3-5 giorni

*variabile a seconda del CCP utilizzato
Lo schema sopra si riferisce a UMAN COMPLEX

Da Masotti et al. Aggiornamento Medico 2010; 34:11-6

Reviews in Health Care 2011; 2(1): 9-28

DRUGS
Narrative review

Emorragia cerebrale intraparenchimale associata a terapia anticoagulante orale: gestione pratica della terapia di neutralizzazione in urgenza

The intracerebral haemorrhage associated to oral anticoagulant therapy: the practical management of urgent reversal therapy

Luca Masotti[1], Mario Di Napoli[2], Daniel Godoy[3], Daniela Rafanelli[4], Giancarlo Liumbruno[5], Domenico Prisco[6], Daniela Poli[6], Giancarlo Landini[7], Nicholas Koumpouros[8], Paolo Pennati[9], Alessandro Pampana[1], Roberto Cappelli[10]

CCP	Numero di fattori presenti	Tipo di fattori presenti	Altri fattori presenti	Contenuto	Dose raccomandata
Uman Complex® (Kedrion, Castelvecchio Pascoli, Lucca, Italia)	3	II,IX,X	Proteina C, proteina S, antitrombina, eparina	Fattore II 25 UI/ml Fattore IX 25 UI/ml Fattore X 20 UI/ml	INR < 2,0; 20 UI/kg INR 2,0-3,0; 30 UI/kg INR 3,0-4,0; 40 UI/kg INR > 4,0; 50 UI/kg
Protromplex TIM 3® (Baxter, Vienna, Austria)	3	II,IX,X	Proteina C, antitrombina	Fattore II 30 UI/ml Fattore IX 30 UI/ml Fattore X 30 UI/ml	INR < 2,0; 20 UI/kg INR 2,0-3,0; 30 UI/kg INR 3,0-4,0; 40 UI/kg INR > 4,0; 50 UI/kg
Pronativ® (Octapharma, Pisa, Italia)	4	II,VII,IX,X	Proteina C, proteina S, eparina	Fattore II 11-38 UI/ml Fattore VII 9-24 UI/ml Fattore IX 25 UI/ml Fattore X 18-30 UI/ml	INR 2,0-2,5; 0,9-1,3 ml/kg INR 2,5-3,0; 1,3-1,6 ml/kg INR 3,0-3,5; 1,6-1,9 ml/kg INR > 3,5; > 1,9 ml/kg
Confidex® (CSL Behring, Marburg, Germania)	4	II,VII,IX,X	Proteina C, proteina S, antitrombina, eparina	Fattore II 20-48 UI/ml Fattore VII 10-25 UI/ml Fattore IX 20-31 UI/ml Fattore X 22-60 UI/ml	INR 2,0-3,9; 1 ml/kg INR 4,0-5,9; 1,4 ml/kg INR ≥ 6,0; 2,0 ml/kg

Tabella III. Concentrati protrombinici disponibili in Italia, composizione e dosaggi

Intracerebral haemorrhage associated with antithrombotic treatment: translational insights from experimental studies

Arne Lauer, Waltraud Pfeilschifter, Chris B Schaffer, Eng H Lo, Christian Foerch

Little is known about the pathophysiology of intracerebral haemorrhage that occurs during anticoagulant treatment.

Lancet Neurol 2013; 12: 394–405

	Experimental model	Animal, strain	Anticoagulant	Dose	Haemostatic agent	Effect on haemorrhage volumes relative to controls*
Vitamin K antagonists: anticoagulation						
Foerch et al,[11] (2008)	Collagenase injection	Mice, CD-1	Warfarin	Dose 1: 2 mg/kg per 24 h; dose 2: 2 mg/kg/24 h for 30 h	None	Dose 1: increase; dose 2: large increase
Illanes et al,[12] (2010)	Collagenase injection	Mice, C57BL/6	Warfarin	0·4 mg/kg/24 h for 72 h	None	Increase
Lauer et al,[13] (2011)	Laser-induced haemorrhage	Mice, CD-1	Warfarin	2 mg/kg/24 h for 30 h	None	Increase
Vitamin K antagonists: reversal of anticoagulation						
Foerch et al,[14] (2009)	Collagenase injection	Mice, CD-1	Warfarin	2 mg/kg per 24 h	PCC 100 U/kg	Decrease
Illanes et al,[12] (2011)	Collagenase injection	Mice, C57BL/6	Warfarin	0·4 mg/kg/24 h for 72 h	FFP 200 µL; PCC 100 U/kg; rFVIIa 3·5 mg/kg; rFVIIa 10 mg/kg; TA 400 mg/kg	FFP: large decrease; PCC: large decrease; rFVIIa (both doses): decrease; TA: decrease
Schlunk et al,[15] (2012)	Collagenase injection	Mice, CD-1	Warfarin	2 mg/kg per 24 h	PCC 100 U/kg; rFVIIa 1 mg/kg	PCC: decrease; rFVIIa: decrease
New oral anticoagulants: anticoagulation						
Lauer et al,[13] (2011)	Collagenase injection	Mice, CD-1	Dabigatran	Dose 1: 37·5 mg/kg p.o.; dose 2: 112·5 mg/kg p.o.	None	No change at either dose
Lauer et al,[13] (2011)	Laser-induced haemorrhage	Mice, CD-1	Dabigatran	75 mg/kg p.o.	None	No change
Zhou et al,[17] (2011)	Collagenase injection	Mice, C57BL/6	Dabigatran	Dose 1: 2·25 mg/kg i.p.; dose 2: 4·5 mg/kg i.p.; dose 3: 9 mg/kg i.p.	None	Dose 1: no change; dose 2: increase; dose 3: large increase
Zhou et al,[18] (2013)	Collagenase injection	Mice, C57BL/6	Rivaroxaban	Dose 1: 10 mg/kg p.o.; dose 2: 30 mg/kg p.o.	None	Dose 1: no change; dose 2: increase
New oral anticoagulants: reversal of anticoagulation						
Zhou et al,[17] (2011)	Collagenase injection	Mice, C57BL/6	Dabigatran	Dose 1: 4·5 mg/kg i.p.; dose 2: 9 mg/kg i.p.	FFP 200 µL; PCC 100 U/kg; rFVIIa 8 mg/kg	Dose 1 and FFP: decrease; dose 1 and PCC: large decrease; dose 1 and rFVIIa: no change. Dose 2 and FFP: no change; dose 2 and PCC: decrease; dose 2 and rFVIIa: no change
Zhou et al,[18] (2013)	Collagenase injection	Mice, C57BL/6	Rivaroxaban	30 mg/kg p.o.	FFP 200 µL; PCC 100 U/kg; rFVIIa 8 mg/kg	Decrease
Antiplatelet drugs: antithrombotic treatment						
Mihara et al,[40] (2005)	Collagenase injection	Guineapigs	Aspirin or FK419	Aspirin 1 mg/kg, 3 mg/kg, or 3·2 mg/kg; FK419 0·03 mg/kg, 0·06 mg/kg, or 0·12 mg/kg	None	No change for all doses
Lauer et al,[41] (2011)	Collagenase injection	Mice, CD-1	Aspirin, clopidogrel, and both combined	Aspirin 60 mg/kg; clopidogrel 22·5 mg/kg; or aspirin 60 mg/kg plus clopidrogrel 22·5 mg/kg	None	No change for all doses

PCC=prothrombin complex concentrate. FFP=fresh frozen plasma. rFVIIa=recombinant factor VIIa. TA=tranexamic acid. p.o.=per os. i.p.=intraperitoneal. *Controls were either non-anticoagulated (sham-treated) animals or anticoagulated animals that received sham treatment for anticoagulation reversal.

Table 2: Effects on haematoma volumes of experimental anticoagulation and anticoagulation reversal

NAO: sintesi delle raccomandazioni per il reverse urgente

	Dabigatran	Rivaroxaban	Apixaban
Carbone attivo	si	si	si
Emodialisi	si	no	no
PFC	no	no	no
FVIIra	Non chiaro possibile	Non chiaro possibile	Non chiaro possibile
CCP 3 fattori	No dati	No dati	No dati
CCP 4 fattori	possibile	possibile	possibile
FEIBA	possibile	Non chiaro possibile	Non chiaro possibile

Modificato da Kaatz S et al Am J Hematol. 2012; 87(suppl 1):S141–S145.

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European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

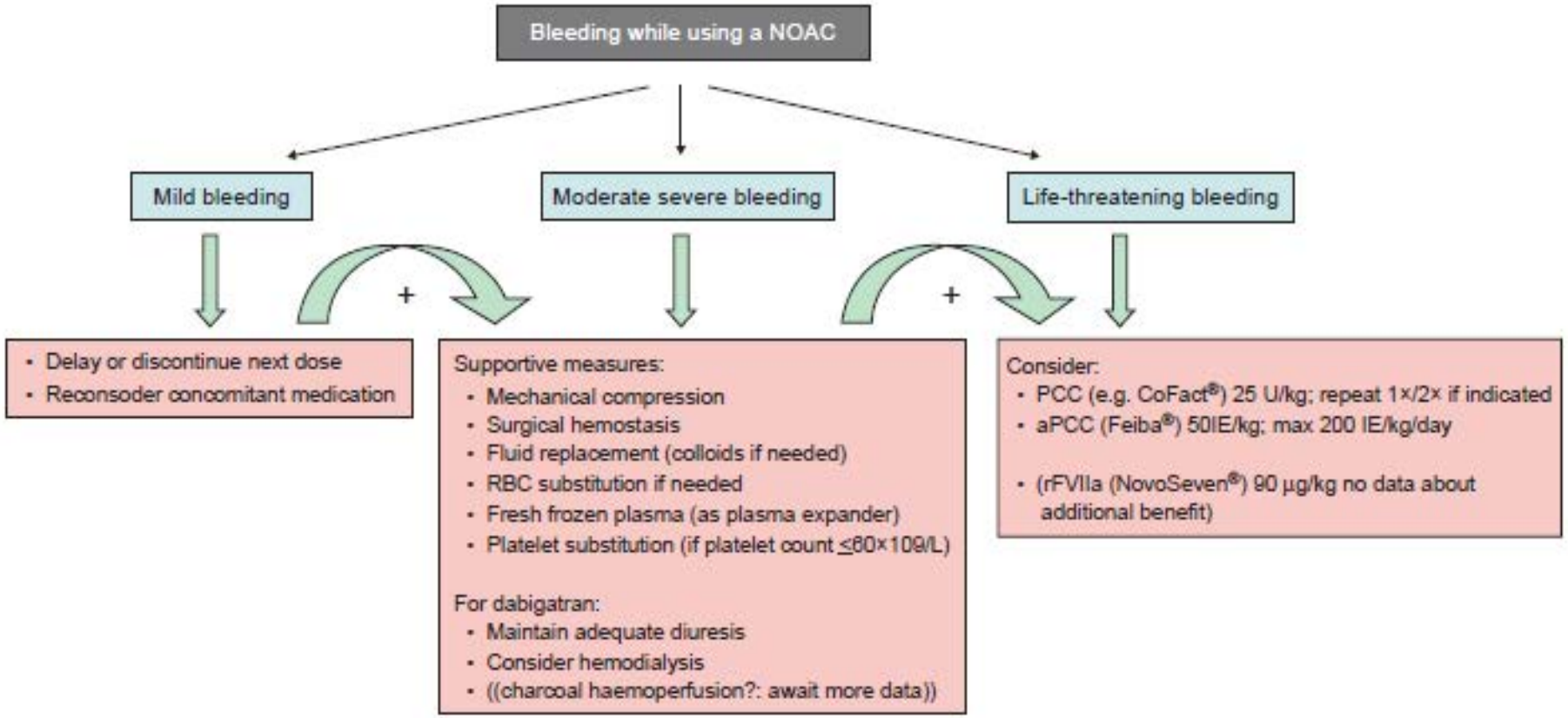


Figure 6 Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy. Based on van Ryn *et al.*[12]

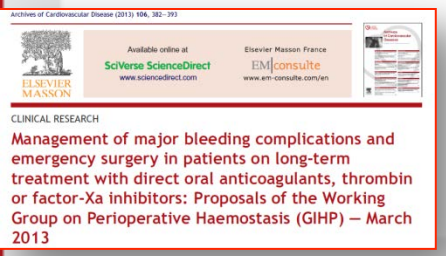
Haemorrage and DABIGATRAN (PRADAXA®) or RIVAROXABAN (XARELTO®)

Bleeding into a critical organ (intracranial, acute subdural, intraocular…)

1) FEIBA® 30-50 UI / kg* or
2) PCC 50 UI / kg*

Serious bleeding according to the French Health Authority (2008) (excluding previous cases)

- If ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2: no reversal
- Prefer haemostatic procedure if feasible
- If no haemostatic procedure is appropriate and if ratio aPTT > 1.2 (isolated) or ratio PT > 1.2
- ▶ Discuss reversal** (not always necessary) and obtain specific dosage



* Depending on availability. No data available on the thrombotic risk of high doses of PCC or FEIBA in these patients
** PCC=25-50 UI/kg or FEIBA=30-50 UI/Kg
rFVIIa is not considered first-line

Hemorrhagic Complications in Emergency Department Patients Who Are Receiving Dabigatran Compared With Warfarin

Russell Berger, MD; Steven D. Salhanick, MD; Maureen Chase, MD, MPH; Michael Ganetsky, MD

Annals of Emergency Medicine 475

Table 3. Details of patients under treatment with dabigatran who were admitted with bleeding.

Patient No.	Age, Years	Sex	Bleeding Site	Daily Dose, mg	Length of Stay, Days	Hematocrit Level Decrease	Creatinine Level Change, % From Baseline	Blood Products Transfused, Units	Outcome
1	59	Male	GI bleed	300	4	3.3	8		Survival
2	59	Male	Pericardium	300	1	6.5	25	PRBC 1; FFP 3	Death
3	61	Male	GI bleed	300	2	4.1	0		Survival
4	65	Male	GI bleed	300	2	0	60	PRBC 2	Survival
5	66	Male	GI bleed	150	7	6.9	67	PRBC 4	Survival
6	75	Female	Scalp	300	1	0	20		Survival
7	76	Male	GI bleed	300	2	0	50		Survival
8	79	Female	Hemorrhoid	150	3	2.7	19		Survival
9	81	Female	GI bleed	300	4	6.9	0	PRBC 2	Survival
10	82	Female	Vaginal	300	1	0	100		Survival
11	84	Female	GI bleed	150	4	5.4	−4	PRBC 1	Survival
12	84	Female	GI bleed	300	3	6.7	92		Survival
13	89	Female	GI bleed	300	3	6.5	0	PRBC 1	Survival
14	93	Female	GI bleed	300	11	8.9	106	PRBC 1	Survival
15	104	Male	GI bleed	150	4	20.6	56	PRBC 4; FFP 2	Death

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Treatment of Dabigatran-Associated Bleeding: Case Report and Review of the Literature

Lisa M. Harinstein, PharmD, BCPS[1], Joseph W. Morgan, MD[2], and Nicholas Russo, MD[2]

Table 1. Published Cases of Dabigatran-Induced Bleeding and Supportive Treatments Received[a]

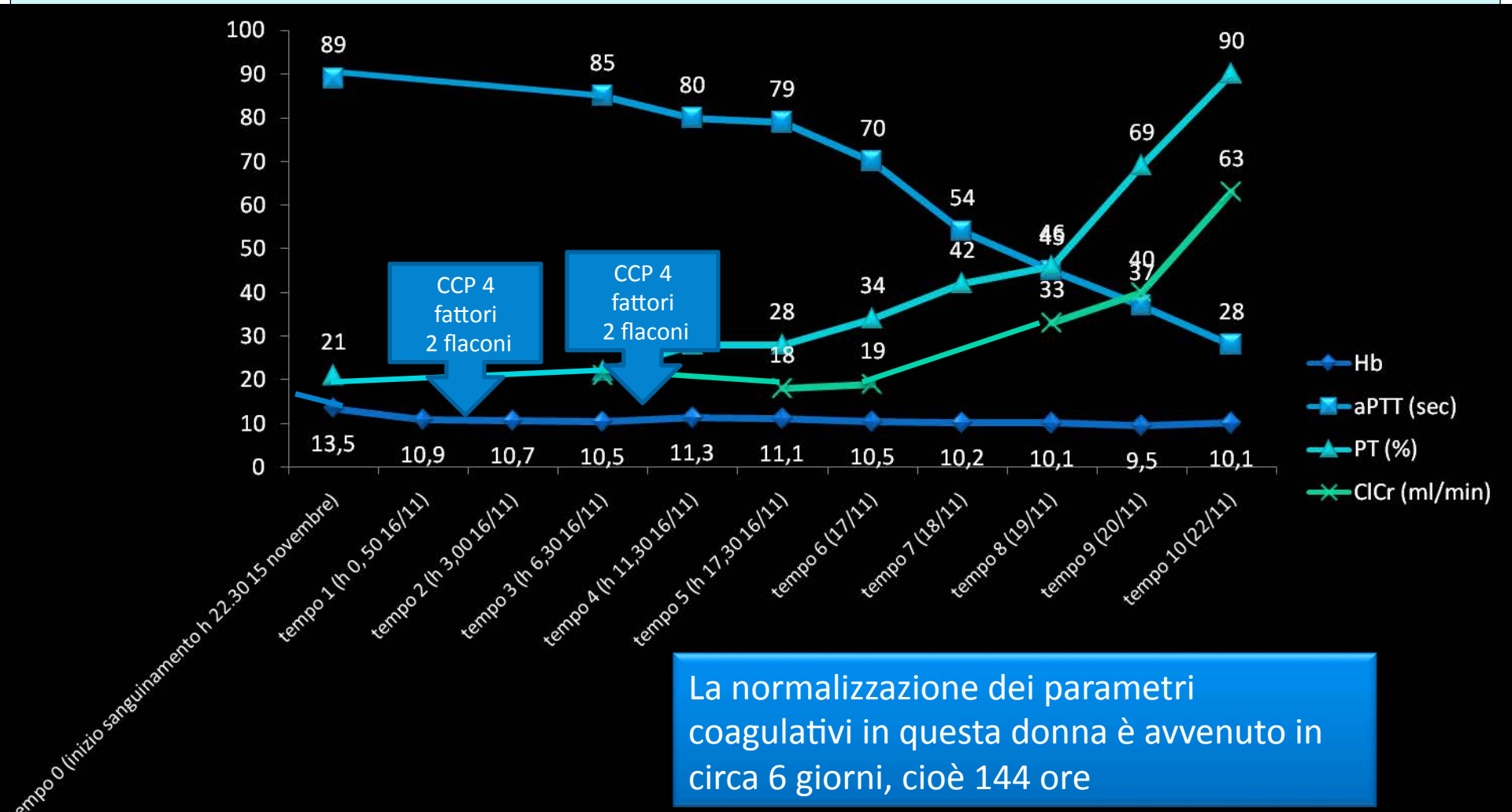
Ref	Age	Bleed site/type	Admission CrCl (mL/min)	Vit K	FFP	CP	rFVIIa	PCC	Dialysis	Surgical	Outcome
5	84	Rectal	32		Yes						Death
5	89	Epistaxis	29							Nasal cauterization	Recovery
8	79	Surgical site (cardiac surgery)	36			Yes	3 doses of 2.4 mg (30 mcg/kg), 2 doses of 7.2 mg (90 mcg/kg)		IHD		Recovery
9	62	Lobar hemorrhage after rTPA									Death
10	72	Traumatic epidural hematoma, intraoperative bleeding			Yes		2 doses of 1 mg			Spine decompression	Recovery
11	67	Transeptal perforation during cardiac ablation			Yes			FEIBA 26 units/kg			Recovery
6	78	RP, GI, abdominal and pleural cavity	15	10 mg	Yes	Yes		Profilnine 50 units/kg	CVVHD		Death
7	66	Upper GI	30.5-43.2	5 mg				Profilnine 25 and 50 units/kg doses	IHD		Recovery
12	79	Rectal	20.7	10 mg	Yes						Recovery
12	84	Rectal	33.5	3 mg							Recovery
13	66	Mucosal, puncture site	11.8		Yes	Yes					Death
14	92	Gastric ulcer	24.2	10 mg	Yes						Death
—	84	GI bleed, surgical site	25		Yes	Yes	3 mg (30 mcg/kg)		CVVHD		Recovery

Abbreviations: Ref, reference; CrCl, creatinine clearance; Vit K, vitamin K; FFP, fresh frozen plasma; CP, cryoprecipitate; rFVIIa, recombinant coagulation factor VIIa; PCC, prothombin complex concentrates; IHD, intermittent hemodialysis; rTPA, recombinant tissue plasminogen activator; FEIBA, factor eight bypassing activity; RP, retroperitoneal; GI, gastrointestinal; CVVHD, continuous venovenous hemodialysis.
[a]No patient received activated charcoal.

Caso clinico

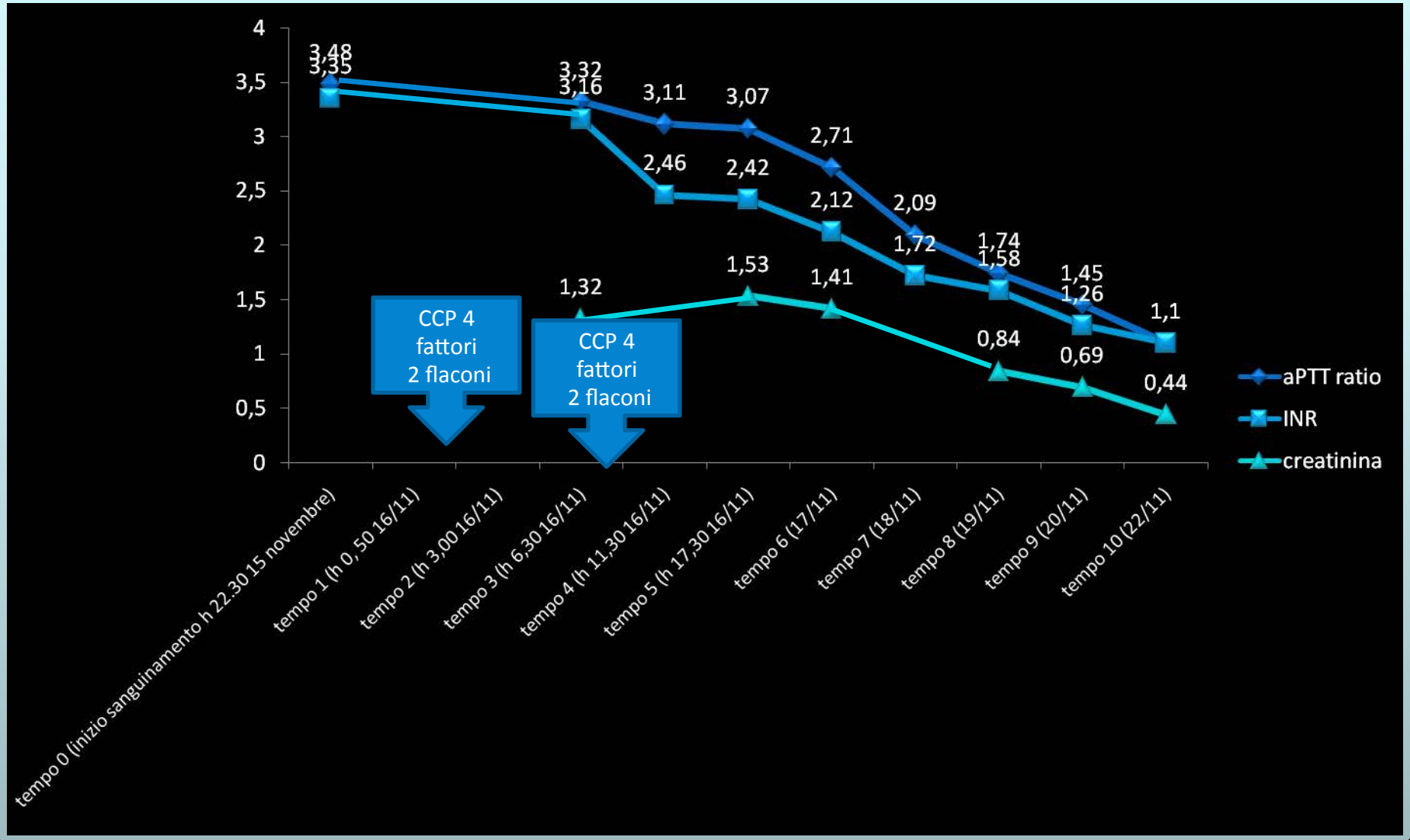
- Donna 93 anni
- Dal 31/10 dabigatran 110 x 2 per occlusione arteriosa acuta in FA permanente
- Peso 50 Kg circa
- Creatinina all'inizio trattamento 0,67 mg/dl (ClCr 41 ml/min)
- Il 15/11 alle 12 circa accesso in PS per dolore addominale. Ricoverata per sub-occlusione intestinale da fecaloma. Parametri coagulativi emolisati. Hb **15,3** g/dl. Creatina 0,98 mg/dl (ClCr 28 ml/min)
- Alle 22.30 15/11 rettorragia massiva: paziente in stato di shock (PA 60/40 mmHg), tachicardica, sudata
- Somministrato:
  - Tranex in fisiologica 100 cc x 2 volte, quindi messo x 3 in terapia
  - Emagel 500 cc + 500 cc
  - Omeprazolo 40 mg in fisiologica 100 cc, poi messo in infusione 5 fiale
  - Somatostatina 6 mg in fisiologica 500 cc 21 ml/h
  - Posizionato SNG

Caso clinico: andamento dei parametri coagulativi



La normalizzazione dei parametri coagulativi in questa donna è avvenuto in circa 6 giorni, cioè 144 ore

Caso clinico: andamento dei parametri coagulativi



Use of prothrombin complex concentrates for urgent reversal of dabigatran in the Emergency Department

and the types of hemorrhagic complications are summarized in Table 1. The reason for dabigratan treatment in these 5 patients was atrial fibrillation. Patients had a median age of 82 years (range 76-88 years), were predominant-

Table 1. Demographic and clinical characteristics, bleeding complications.

ID	Age (years)	Gender	Weight (kg)	HAS-BLED Score	Creatinine clearance (mL/min)	Bleeding complications	Hours from last dose to admission	PCC Dose (IU)	Dose/ weight (IU/kg)	Vitamin K	RBC (N. of units)	Time from admission to bleeding cessation	Death
1	83	Male	57	3	36.5	rectal bleeding	1.5	1000	17	No	No	<6 hours	No
2	82	Male	67	3	73.3	melena	1	1000	15	Yes	Yes (2)	–	No
3	88	Male	51	5	53.7	rectal bleeding	1.1	1000	20	No	Yes (2)	<12 hours	Yes
4	76	Male	54	5	113	rectal bleeding	2	1000	19	No	Yes (1)	<12 hours	No
5	82	Female	60	4	35.5	rectal bleeding	2	1500	25	No	No	<6 hours	No

boplastin (aPTT) ratios. We found no significant differences in the coagulation tests performed before and after the bleeding episode, although a tendency was noted in the INR values (1.8±1.2 *vs.* 1.2±0.2) and in the aPTT ratio (2.4±1.5 *vs.* 1.5±0.6). All patients received treatment with a prothrombin complex concentrate (Octaplex®, Octapharma, Vienna, Austria). Table 1 lists the

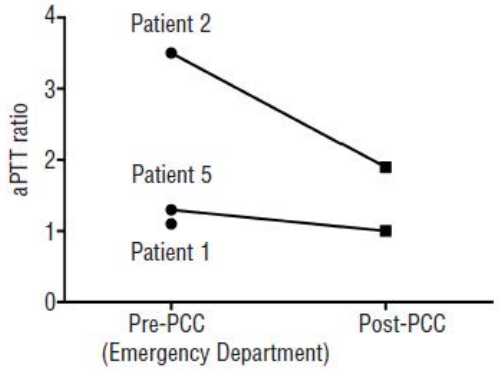


Figure 1. Coagulation tests before and after the bleeding episode. Activated partial thromboplastin (aPTT) ratio at the emergency department during the bleeding episode (before PCC administration) and after the treatment of the hemorrhage (post-PCC administration).

Life-threatening bleeding in four patients with an unusual excessive response to dabigatran: Implications for emergency surgery and resuscitation

Agnès Lillo-Le Louët[1]; Martine Wolf[2]; Lilia Soufir[3]; Arnaud Galbois[4,5,6]; Anne-Sylvie Dumenil[2]; Georges Offenstadt[4,5,7]; Meyer-Michel Samama[8, 9]

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Coagulation tests [units] (normal values)	Hours after Dabigatran withdrawal						
Case 1	**26 h**	**28 h**	**32 h**	**34 h**	**36 h**	**38 h**	**-**
Prothrombin time (12.6–14.6 sec)	> 60	> 60	31	58	20.9	24.3	N.A
aPTT ratio (0.9–1.2)	>4.5	>4.5	>4.5	>4.5	>4.5	>4.5	N.A
Fibrinogen [g/l] (2–4 g/L)	6.4	4.9	4.2	2.4	2.1	2.3	N.A
Platelets [G/l] (150–400)	124	92	80	105	36	11	N.A
Haemoglobin [g/dl] (12.0–16.0)	9.3	6.9	8	9.3	4.3	8.7	N.A
Dabigatran plasma concentration [µg/ml] (Ctrough 0.05 –0.15)	N.A.	N.A.	420–480	N.A.	N.A.	340–420	N.A
Case 2	**24 h**	**-**	**46 h**	**51 h**	**55 h**	**72 h**	**96 h**
Prothrombin time (12.6–14.6 sec)	> 60	N.A	> 60	> 60	40	39	26
aPTT ratio (0.9–1.2)	3.2	N.A	4	5.2	3.9	3.7	2.8
Fibrinogen [g/l] (2–4 g/L)	4.2	N.A	3.4	3.1	3	3.2	3
Platelets [G/l] (150–400)	249	N.A	224	187	137	96	40
Haemoglobin [g/dl] (12.0–16.0)	14.8	N.A	13	11.7	8.1	9.9	11.6
Case 3	**25 h**	**-**	**48 h**	**51 h**	**55 h**	**72 h**	**96 h**
Prothrombin time [sec] (11.3 13.6)	33	N.A	> 70	> 70	> 70	> 70	54
aPTT ratio (0.9–1.2)	3.33	N.A	> 5	> 5	> 5	> 5	4.7
Fibrinogen [g/l] (2–4 g/L)	4.2	N.A	3.4	3.1	3.0	3.2	3.0
Platelets [G/l] (150–400)	737	N.A	354	250	250	124	80
Haemoglobin [g/dl] (12.0–16.0)	7.8	N.A	6.5	N.A.	N.A.	N.A.	5.3
Dabigatran plasma concentration [µg/ml] (Ctrough 0.05 –0.15)	1300	N.A	N.A.	N.A.	N.A.	N.A.	N.A.
Case 4	**0**	**6 h**	**24 h**	**32 h**	**46 h**	**64 h**	**85 h**
Prothrombin time [sec] (12.6–14.6)	> 60	50	20.8	19.1	17.1	15.7	17.1
aPTT ratio (0.9–1.2)	> 4.5	4.15	2.15	2.03	1.82	1.39	1.30
Fibrinogen [g/l] (2–4 g/L)	5.4	2.8	2.7	2.7	3.3	3.5	3.1
Platelets [G/l] (150–400)	294	130	113	108	107	113	108
Haemoglobin [g/dl] (13.0–18.0)	7.6	8.9	8.7	10.2	9.8	11.6	10.9
Dabigatran plasma concentration [µg/ml] (Ctrough 0.05 to 0.15)	2350	920	270	160	60	10	0

Case 1: Transfusion was restarted 22 hours after Dabigatran withdrawal. RBC, FFP, recombinant F VIIa, fibrinogen were transfused during surgery, from 31 h to 38 h after dabigatran withdrawal. N.A. for not available. Case 2: during the following days, progressive shortening of PT and aPTT, reaching moderately increased values at the end of 18 days of hospitalization. N.A for not available.

Correspondence

Activated prothrombin complex concentrate for dabigatran-associated bleeding

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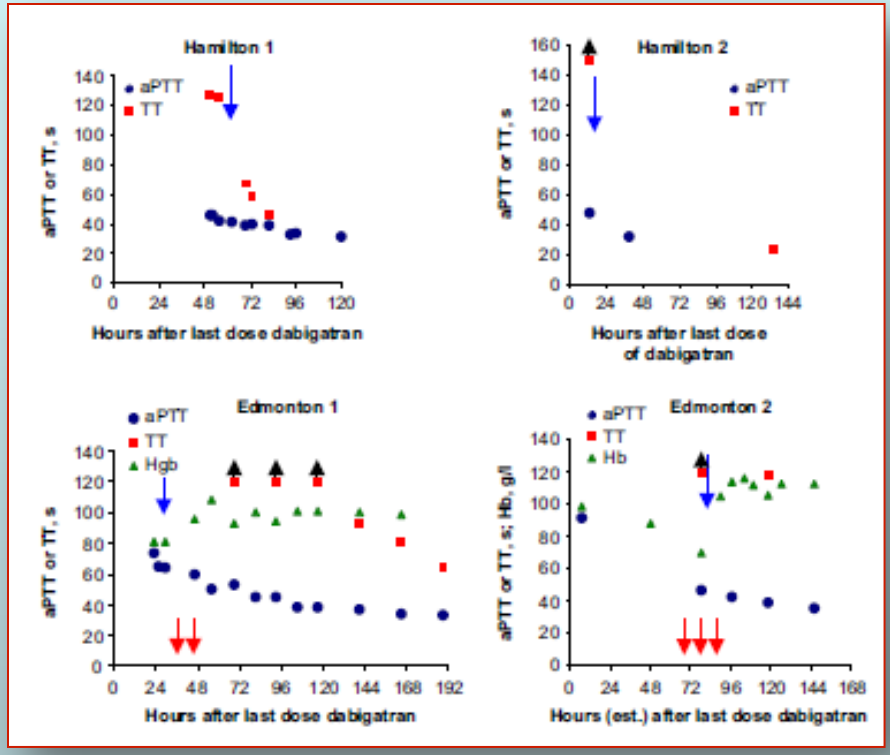

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Conclusioni

- I NOA rappresentano una reale novità nel management della FA
- I grandi trials hanno dimostrato che sono almeno efficaci e sicuri quanto i farmaci comparati e, su molti aspetti, anche superiori ad essi (riduzione del rischio emorragico cerebrale)
- I primi dati di real life confermano i risultati dei trials di fase III
- I NOA presentano problematiche gestionali che devono essere attentamente conosciute dal clinico
- Tra queste, la gestione del reverse urgente dei NAO è ancora controversa perché non sono disponibili antidoti, ma solo prodotti emostatici e non è ancora chiaro come monitorare l'effetto pro-emostatico