DOACs: La sicurezza del paziente anche nella gestione elle urgenze in PS, tra evidenze scientifiche e mondo reale

- La sicurezza del paziente nel Peri-procedurale

Each year, ≈10% of patients on any long-term oral anticoagulation require surgery or other invasive procedures

The limited data available pertaining to patients on NOAC therapy who require surgery suggest that the perioperative bleeding risk is low for nonurgent surgery.

The Dresden NOAC registry prospectively evaluated 2179 patients taking NOACs, of which 595 patients (27.3%) underwent 863 invasive procedures;

most were not urgent.

Beyer-Westendorf J, et al Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014;35:1888–1896

Of the entire cohort, only 46 patients (5.3%)

experienced any bleeding complication up to 30±5 days after the procedure. Major bleeding occurred in 10 of 863 (1.2%) procedures.

Clinically relevant nonmajor bleeding occurred in 29 patients (3.4%) and minor bleeding occurred in only 7 patients (0.8%).

PATIENTS UNDERGOING A PLANNED SURGICAL INTERVENTION OR ABLATION

Table 11 Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of one to three teeth
Paradontal surgery
Incision of abscess
Implant positioning
Ophthalmology
Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)
Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation for right-sided supraventricular tachycardia
Non-coronary angiography (for coronary angiography and ACS: see 'Patient with atrial fibrillation and coronary artery disease' section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with major bleeding risk (i.e. frequent and/or with high impact)
Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with major bleeding risk AND increased thrombo-embolic risk[a]
Complex left-sided ablation (PVI; some VT ablations)

For each patient, individual factors relating to bleeding and thrombo-embolic risk need to be taken into account, and be discussed with the intervening physician.
[a]Last intake can vary from ≥24 to 1 h before intervention: see text.

Europace Advance Access published August 31, 2015
Europace
doi:10.1093/europace/euv309
EHRA PRACTICAL GUIDE

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

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Manovre Invasive/Interventi Chirurgici

Interventi a basso rischio emorragico	Interventi a moderato rischio emorragico	Interventi ad elevato rischio emorragico
• Estrazioni dentali • Incisioni di ascessi • Cataratta/glaucoma • Endoscopie senza chirurgia • Chirurgia superficiale (dermatologica)	• Endoscopia con biopsia • Studio elettrofisiologico/ablazione • Angiografia • Impianto di pacemaker	• Interventi con anestesia spinale o epidurale • Chirurgia toracica • Chirurgia addominale • Chirurgia ortopedica maggiore • Biopsia del fegato/reni • Resezione della prostata

EHRA Practical Guide, Europace 2013

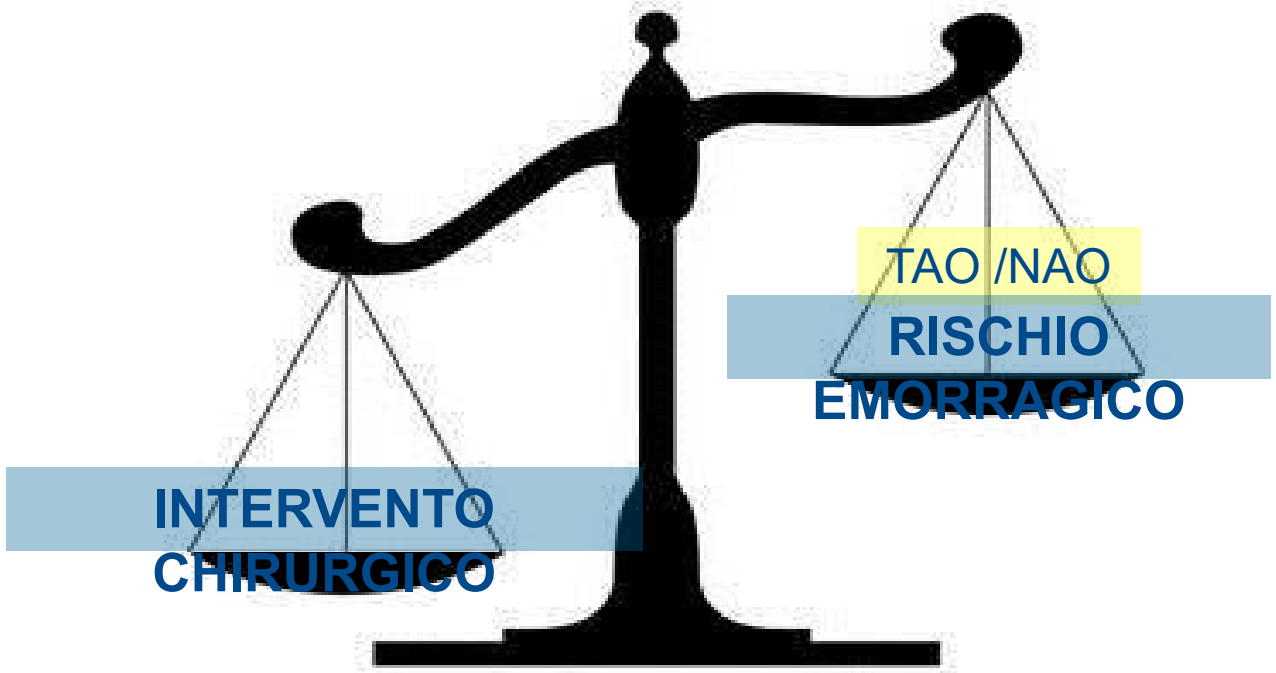
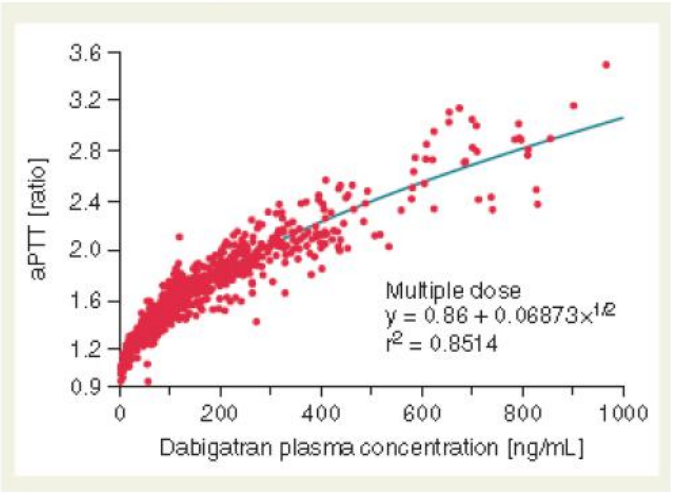

TAO /NAO
RISCHIO
EMORRAGICO
INTERVENTO
CHIRURGICO

Table 1. Continued

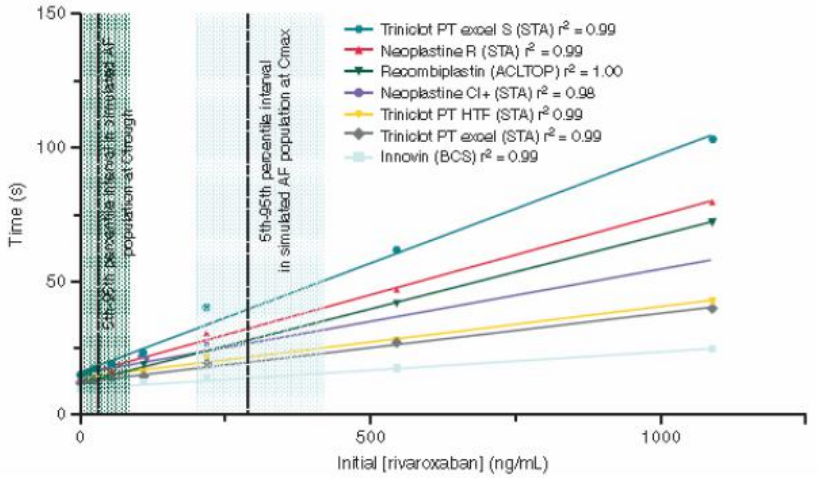
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Therapeutic measurement	Routine not required	Routine not required	Routine not required	Routine not required
	To detect presence: aPTT, ECT (if available), TT	To detect presence: PT, aPTT, antifactor Xa activity	To detect presence: PT, aPTT, antifactor Xa activity	Prolongs PT, aPTT, antifactor Xa activity
	aPTT >2.5 times control may indicate overanticoagulation	Renal function, CBC periodically, at least annually; hepatic function	Renal function, CBC periodically, at least annually	Renal function, CBC periodically, at least annually
	Renal function, CBC periodically, at least annually			

AC indicates anticoagulant; AF, atrial fibrillation; aPTT, activated partial thromboplastin time; BID, twice daily; CBC, complete blood count; CrCl, creatinine clearance; DVT, deep vein thrombosis; ECT, ecarin clotting time; IV, intravenous; NOACs, non–vitamin K antagonist oral anticoagulants; PE, pulmonary embolism; P-gp, P-glycoprotein; PT, prothrombin time; and TT, thrombin time.

Dabigatran e aPTT



Rivaroxaban e PT



- Unlike the PT/INR for warfarin, routine coagulation tests have not been validated for ensuring that dabigatran effect has resolved.
- A normal or near-normal aPTT may be used in selected patients to evaluate whether dabigatran has been adequately cleared from the circulation prior to surgery (eg, patients at high risk of surgical bleeding)
- Importantly, the reliability of aPTT testing may depend on the specific assay used; if available, a diluted plasma thrombin time may be preferable

RE-LY® Peri-procedural outcomes subgroup analysis

- Compared with warfarin, both doses of dabigatran associated with similar rates of:
  - Peri-procedural* bleeding (including major and fatal bleeding)
  - Thrombotic complications
- Trend towards a lower rate of major bleeding in patients who underwent urgent surgery
- For patients who underwent procedure within 48 hours of stopping anticoagulation:
  - Dabigatran significantly reduced bleeding risk vs warfarin
- Bridging therapy is not recommended during NOAC therapy interruption for patients undergoing surgery. The dabigatran RE-LY study demonstrated an increased risk for major bleeding with bridging therapy

*Peri-procedural period defined as 7 days before to day 30 post-procedure

Healey JS et al. Circulation 2012;126:343–8

Peri-procedural outcomes subgroup analysis: background

- Aim:
  - To assess outcomes in patients undergoing surgery/invasive procedure during RE-LY®
- Approach:
  - Bleeding and thromboembolic events assessed
  - Primary analysis limited to the first surgery/procedure per patient
  - Peri-procedural period: 7 days before to day 30 post-procedure
- 4591 patients included in the subanalysis
  - Even distribution of patients and surgery types across treatment arms
  - Common surgeries/procedures included dental, pacemaker/ICD, cataract removal (all ~10%)

ICD = implantable cardioverter defibrillator

Healey JS et al. Circulation 2012;126:343–8

Peri-procedural outcomes subgroup analysis: anticoagulation management

- Warfarin managed according to local practice
- Dabigatran withheld prior to procedure:
  - Dec 2005 – Aug 2008: 24 hours for all patients
  - Aug 2008 – Mar 2009: 2–5 days (based on CrCl) for high-risk procedures
- Dabigatran restarted post-procedure after achieving adequate haemostasis
- Time from last anticoagulant dose to procedure:
  - Dabigatran: 49 (35–85) hours
  - Warfarin: 114 (87–144) hours
- Peri-procedural bridging with heparin used in 15.3% (D110), 17.0% (D150), and 28.5% (warfarin) of patients (P<0.001)

CrCl = creatinine clearance; D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 twice daily

Healey JS et al. Circulation 2012;126:343–8

Peri-procedural outcomes subgroup analysis: bleeding outcomes

No significant difference in risk of bleeding for either dose vs warfarin

	% patients			D110 vs warfarin		D150 vs warfarin	
	D110 n=1487	D150 n=1546	Warfarin n=1558	RR (95% CI)	P value	RR (95% CI)	P value
Major bleeding	3.8	5.1	4.6	0.83 (0.59–1.17)	0.28	1.09 (0.80–1.49)	0.58
Fatal bleeding	0.2	0.1	0.1	1.57 (0.26–9.39)	0.62	1.01 (0.14–7.15)	0.99
Re-operation	0.6	1.4	1.0	0.59 (0.26–1.33)	0.20	1.39 (0.73–2.63)	0.32
RBC transfusion	3.3	3.5	4.0	0.81 (0.56–1.18)	0.27	0.86 (0.60–1.23)	0.42
Minor bleeding	8.1	9.0	7.8	1.03 (0.81–1.31)	0.81	1.15 (0.91–1.45)	0.24

D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily;
RBC = red blood cell; RR = relative risk

Healey JS et al. Circulation 2012;126:343–8

Peri-procedural outcomes subgroup analysis: thromboembolic events

Low incidence of thromboembolic events across all treatment groups

	% patients			D110 vs warfarin		D150 vs warfarin	
	D110 n=1487	D150 n=1546	Warfarin n=1558	RR (95% CI)	P value	RR (95% CI)	P value
Ischaemic stroke or SE	0.5	0.5	0.5	1.05 (0.55–2.01)	0.89	1.01 (0.35–2.87)	0.99
Stroke (all cause)	0.5	0.5	0.6	0.73 (0.28–1.92)	0.53	0.71 (0.27–1.85)	0.48
SE	0.1	0.1	0.1	1.05 (0.07–16.7)	0.97	1.01 (0.06–16.1)	1.00
CV death	0.6	0.5	0.5	1.35 (0.50–3.61)	0.55	1.01 (0.35–2.96)	0.99

CV cardiovascular; D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily; RR = relative risk; SE =systemic embolism

Healey JS et al. Circulation 2012;126:343–8

Peri-procedural outcomes subgroup analysis: major bleeding by type of surgery

Similar risk of bleeding within each surgery type; no significant interaction between surgery type and treatment

	% patients (n/N)			D110 vs warfarin		D150 vs warfarin	
	D110	D150	Warfarin	RR (95% CI)	P value	RR (95% CI)	P value
Urgent surgery	17.8 (19/107)	17.7 (25/141)	21.6 (24/111)	0.82 (0.48–1.41)	0.47	0.82 (0.50–1.35)	0.43
Elective surgery	2.8 (38/1380)	3.8 (53/1405)	3.3 (48/1447)	0.83 (0.55–1.26)	0.38	1.14 (0.77–1.67)	0.51
P (interaction)					0.90		0.31
Major surgery	6.1 (29/473)	6.5 (33/511)	7.8 (39/498)	0.78 (0.49–1.24)	0.30	0.82 (0.53–1.29)	0.40
Minor surgery	1.9 (8/424)	3.2 (14/435)	1.8 (8/436)	1.03 (0.39–2.71)	0.96	1.75 (0.74–4.14)	0.19
P (interaction)					0.61		0.13

D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily; RR = relative risk

Healey JS et al. Circulation 2012;126:343–8

Peri-procedural outcomes subgroup analysis: major bleeding by timing of anticoagulation interruption

Significantly lower rate of bleeding with dabigatran (both doses) for patients undergoing surgery within 48 hours of anticoagulation interruption

	% patients (n/N)			D110 vs warfarin		D150 vs warfarin	
	D110	D150	Warfarin	RR (95% CI)	P value	RR (95% CI)	P value
<24 hrs	2.8 (5/180)	6.8 (13/192)	15.4 (12/78)	0.18 (0.07–0.50)	<0.001	0.44 (0.21–0.92)	0.027
24–48 hrs	3.2 (16/505)	3.3 (17/520)	9.0 (8/89)	0.35 (0.16–0.80)	0.01	0.36 (0.16–0.82)	0.01
48–72 hrs	4.5 (14/310)	4.5 (14/309)	5.7 (7/122)	0.79 (0.33–1.90)	0.60	0.79 (0.33–1.91)	0.60
>72 hrs	4.7 (21/451)	6.2 (29/468)	3.6 (45/1237)	1.28 (0.77–2.12)	0.34	1.70 (1.08–2.68)	0.02
P-trend				0.002		0.001	

D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily; RR = relative risk

Healey JS et al. Circulation 2012;126:343–8

Europace Advance Access published March 26, 2015

Europace
doi:10.1093/europace/euv030

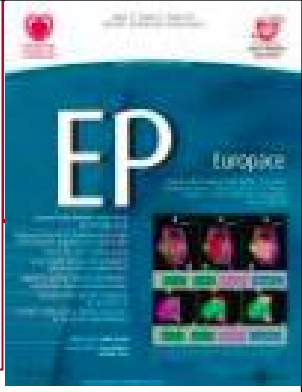
REVIEW

Anticoagulation reversal in the era of the non-vitamin K oral anticoagulants

Andres Enriquez[1]*, Gregory Y.H. Lip[2,3], and Adrian Baranchuk[1]

[1]Division of Cardiology, Queen's University, Kingston, ON, Canada; [2]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; and [3]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Received 14 October 2014; accepted after revision 29 January 2015

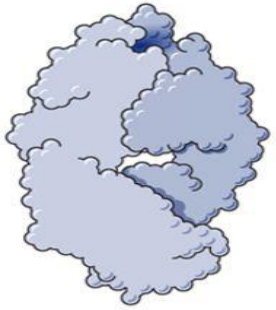
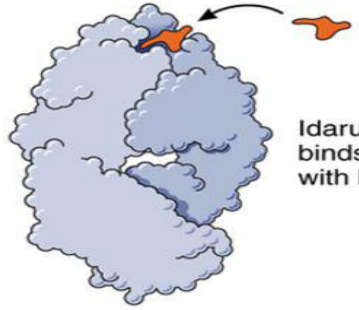
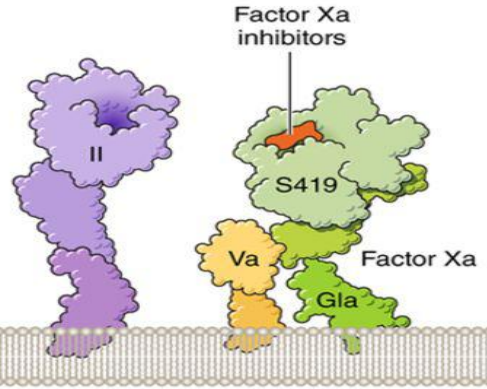
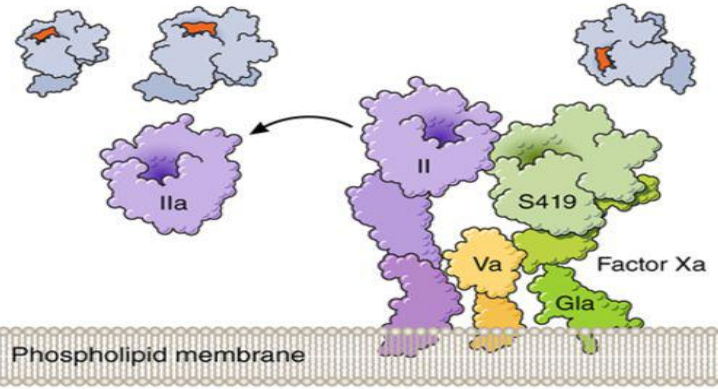
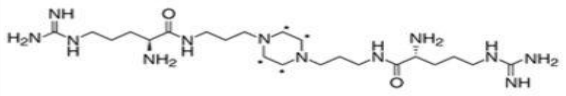
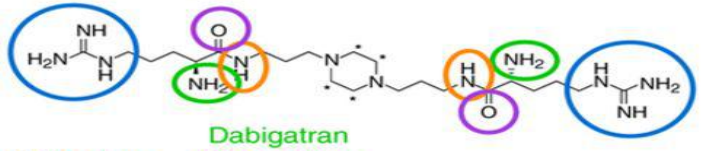


Quando?

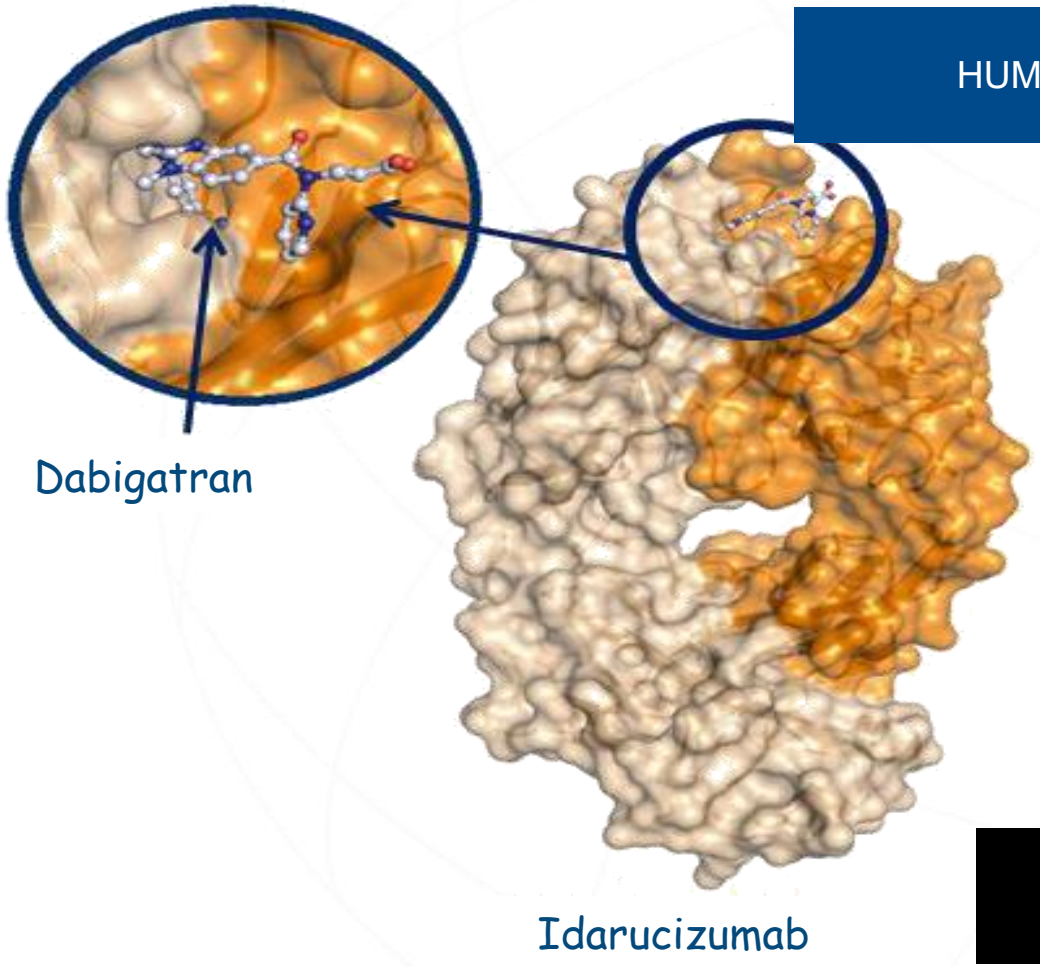
- emorragia maggiore
- emergenze chirurgiche
- procedure diagnostiche invasive in urgenza

DOACs: Antidoti

Christian T. Ruff et al. Circulation. 2016;134:248-261

NOAC reversal agent	Target	Mechanism
 Idarucizumab	 Dabigatran	 Idarucizumab binds Dabigatran with high affinity
 Andexanet alpha	 Factor Xa inhibitors; II; S419; Va; Factor Xa; Gla	 II; IIa; S419; Va; Factor Xa; Gla; Phospholipid membrane
 Ciraparantag (PER977)	Apixaban Argatroban Edoxaban Dabigatran Rivaroxaban UFH LMWH Fondaparinux	 Edoxaban Dabigatran Rivaroxaban UFH/LMWH Fondaparinux; Dabigatran Rivaroxaban Apixaban Argatroban UFH/LMWH Fondaparinux; Dabigatran Rivaroxaban UFH/LMWH Fondaparinux; Edoxaban Apixaban Computer-aided energy minimization modeling predicts 8 non-covalent binding sites on ciraparantag for NOACs or heparins

IDARUCIZUMAB



HUMANIZED FAB FRAGMENT

BINDING AFFINITY ~350× HIGHER THAN DABIGATRAN TO THROMBIN

NO INTRINSIC PROCOAGULANT OR ANTICOAGULANT ACTIVITY

IV DOSING BY BOLUS OR RAPID INFUSION, IMMEDIATE ONSET OF ACTION

SHORT HALF-LIFE

RE-VERSE trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N Engl J Med 2015; 373:511-520

- Studio prospettico, ha indagato la capacità di 5 gr ev di Idarucizumab di ripristinare la coagulazione in pazienti in trattamento con Dabigatran, che presentavano sanguinamenti pericolosi per la vita (gruppo A) o che dovevano essere sottoposti a procedure urgenti (gruppo B).

- Endopoint primario: la percentuale di antagonizzazione dell'attività anticoagulante di Dabigatran entro 4 ore dalla somministrazione dell'antidoto sulla base della misurazione del tempo di trombina diluito e dell'ecarin clotting time.
- Endopoint secondario: tempo di cessazione al sanguinamento, emostasi intraoperatoria normale.

Idarucizumab reverses the anticoagulant effects of dabigatran in patients in an emergency setting of major bleeding, urgent surgery, or interventions

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/776490/2015
EMEA/H/C/003986

20 novembre 2015

EPAR summary for the public

What is Praxbind and what is it used for?

Praxbind is a medicine used to neutralise the effects of dabigatran (the active substance of Pradaxa), a medicine that treats and prevents blood clots. Praxbind is used to rapidly stop the anticlotting effect of dabigatran, before emergency surgery or in case of life-threatening bleeding.

Praxbind contains the active substance idarucizumab.

Infuse intravenously

The complete 5 g dose should be given as two consecutive intravenous **infusions** over 5–10 minutes each

Su 36 pazienti nel gruppo B, sottoposti a procedure, una normale emostasi intraoperatoria era riportata in 33 soggetti.

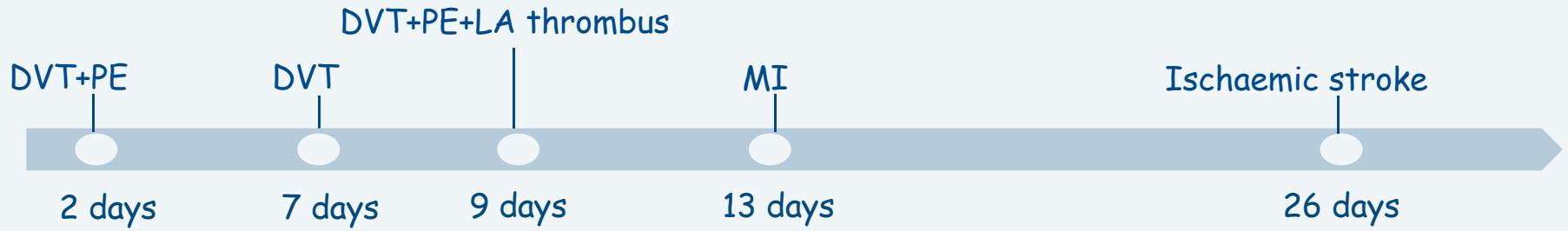
In pratica, dopo 4 e 12 ore, gli esami di laboratorio hanno riportato livelli normali di coagulazione in quasi il 90% dei pazienti.

RE-VERSE AD™: SAFETY

No cases of hypersensitivity observed

5 thrombotic events

- 1 early event (DVT+PE) 2 days after idarucizumab administration
- 4 events after >6 days of idarucizumab administration



- None of these 5 patients were receiving any antithrombotic therapy when the events occurred

18 deaths (9 in each Group)

- RE-VERSE AD™ allows even severely ill patients into the study
- All deaths related to presenting index event and comorbidities

Pollack et al; NEJM 2016

PATIENTS UNDERGOING A PLANNED SURGICAL INTERVENTION OR ABLATION

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 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 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
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 clincial impact. See also *Table 11*.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

2018 EHRA Practical Guide to NOAC Use in AF
Mar 22, 2018 | Geoffrey D. Barnes, MD, MSc, FACC

- Most patients taking NOACs can safely undergo surgical procedures with a 24- to 48-hour pre-procedure hold.
- Longer hold times may be necessary for patients taking dabigatran who have chronic kidney disease. No bridging heparin is needed for NOAC-treated patients.
- Resume full-dose NOAC within 72 hours post-procedure, once the bleeding risk is appropriate

PATIENTS UNDERGOING A PLANNED SURGICAL INTERVENTION OR ABLATION

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 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 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
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 clincial impact. See also *Table 11*.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

https://noacguide.com/procedure-advisor/

Overall recommendations:

- For procedures with low bleeding risk, stop 2-3 half-lives before procedure (1-2 days)
- For procedures with high bleeding risk, stop 4-5 half-lives before procedure (2-3 days, longer with dabigatran and CrCl <50)
- Consider checking coagulation level (aPTT for dabigatran, PT for rivaroxaban) prior to procedure
- For procedures with complete immediate hemostasis, anticoagulation can be resumed 6-8 hours after intervention. For many interventions, full dose anticoagulation within 48-72 hours may increase bleeding complications.
- For each patient assess the risk and benefit of bleed vs. stroke from atrial fibrillation

- **Specific Procedure recommendations**
- **Cardioversion:** Each of three trials of novel drugs had several hundred patients undergoing electric cardioversion on novel drugs with comparable outcome compared to warfarin. More data would be helpful, and in meantime same guidelines as with warfarin reasonable – three weeks pretreatment with ≤ 1 missed dose, TEE if concerned over high risk of thromboembolism. Continue for 4 weeks post cardioversion.
- **Cardiac Catheterization:** These are general recommendations however prior to a cardiac catheterization, the recommendations of the physician performing the procedure which will take patient specific considerations into account, should be confirmed.
- Femoral Cases: For daily and BID drugs, skip 2 doses
  (this can be modified depending on stroke and bleeding risk)
  Post-procedure:
  * If no hematoma, start medications the day after your procedure
  * If hematoma, start medication 48 hours after
- Radial Cases: Hold dose day of procedure
- Restart day after the procedure

Pacemaker/Defibrillator Implantation: (reference: Birnie DH, Healey JS et al. Circulation 2014)

Table. Suggested Period of NOAC Interruption Before Device Surgery

Renal Function (CrCl), mL/min	Dabigatran, h	Apixaban, h	Rivaroxaban, h
≥80	>24	>24	>24
≥50–<80	>36	>24	>24
≥30–<50	>48	>24	>24

CrCl indicates creatinine clearance; and NOAC, new oral anticoagulant.

- **Atrial fibrillation ablation:** (reference: Knight BP, Estes NA et al 2014)
- *Pre-procedure:* 3 weeks of oral anticoagulation prior to the procedure. When 3 weeks cannot be completed, consider TEE prior to ablation.

- *Peri-procedure:* For patients taking warfarin, continuous warfarin is recommended with goal INR 2.0-3.0. For novel agents, switching the patient to warfarin is not necessary as dabigatran and rivaroxaban have been compared to warfarin in this setting with most (but not all) studies showing comparable outcomes. Until more data are available, we suggest stopping the drug 24 to 36 hours prior to the procedure depending on drug half-life and patient risk.

- *Post-procedure:* For warfarin, continuous warfarin is recommended. For novel anticoagulants, wait to restart for at least 6 hours after sheath removal. The time of restart will depend on complications during the procedure and the risk of the patient.

- **Surgery**
- **Spinal/Epidural anesthesia and surgical procedures**: Heidbuchel 2013
- Dabigatran should be discontinued for 1-2 days (CrCl ≥ 50 ml/min) or 3-5 days (CrCl < 50 ml/min) before invasive or surgical procedures. Consider longer times (>5 days) for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port in whom complete hemostasis may be required, and CrCl < 30 ml/min.
- If anticoagulation must be discontinued to reduce the risk of bleeding with surgical procedures, rivaroxaban should be stopped at least 24 hours before the procedure. Rivaroxaban should be restarted after the surgical procedure as soon as adequate hemostasis has been established.
- The next rivaroxaban dose is not to be administered earlier than 48 hours after the removal of an epidural catheter.
- Colonoscopy
- Medium risk procedure: stop drug 24 hours prior to procedure, have colonoscopy, and resume that night if no polypectomy and 24-48 hours after hemostasis if polypectomy.

EXAMPLE of a "Serious Bleeding on NOAC PROTOCOL"

General Measures

- mechanical compression if possible
- two sites of IV access
- determine timing of last NOAC dose
- CBC, BUN, Creatinine, liver enzymes
- plasma expanders/PRBC's as necessary
- consider activated charcoal if NOAC ingestion <2hours
- notify on-call hematologist
- Refer to chart below for specific measures

NOAC	Blood tests for NOAC presence or effect	Specific Antidote	Alternative Treatments Options
Dabigatran	PTT , TT	Idarucizumab 5 grams IV (2 infusions of 2.5 grams)	4 Factor PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV Hemodialysis
Rivaroxaban	Anti-Factor Xa	Unavailable in the U.S.	4 Factor PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV
Apixaban	Anti-Factor Xa	Unavailable in the U.S.	PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV
Edoxaban	Anti-Factor Xa	Unavailable in the U.S.	PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV

TT = thrombin time, PTT = partial thromboplastin time, PCC = prothrombin complex concentrate

AHA SCIENTIFIC STATEMENT

Management of Patients on Non–Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting

A Scientific Statement From the American Heart Association

Circulation. 2017;135:00–00. DOI: 10.1161/CIR.0000000000000477

Amish N. Raval, MD, FAHA, Chair
Joaquin E. Cigarroa, MD
Mina K. Chung, MD, FAHA
Larry J. Diaz-Sandoval, MD, FAHA
Deborah Diercks, MD
Jonathan P. Piccini, MD, MHS, FAHA
Hee Soo Jung, MD
Jeffrey B. Washam, PharmD, FAHA
Babu G. Welch, MD
Allyson R. Zazulia, MD
Sean P. Collins, MD, MSc, FAHA, Co-Chair
On behalf of the American Heart Association Clinical Pharmacology Subcommittee of the Acute Cardiac Care and General Cardiology Committee of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Quality of Care and Outcomes Research

ACIDO TRANEXAMICO

15 mg/kg x 3 volte al giorno fino al controllo dell'emorragia

Riduce la mortalità in pz con emorragia da trauma

[CRASH-2 trial collaborators 2010] CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with signifi cant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; 376: 23–32

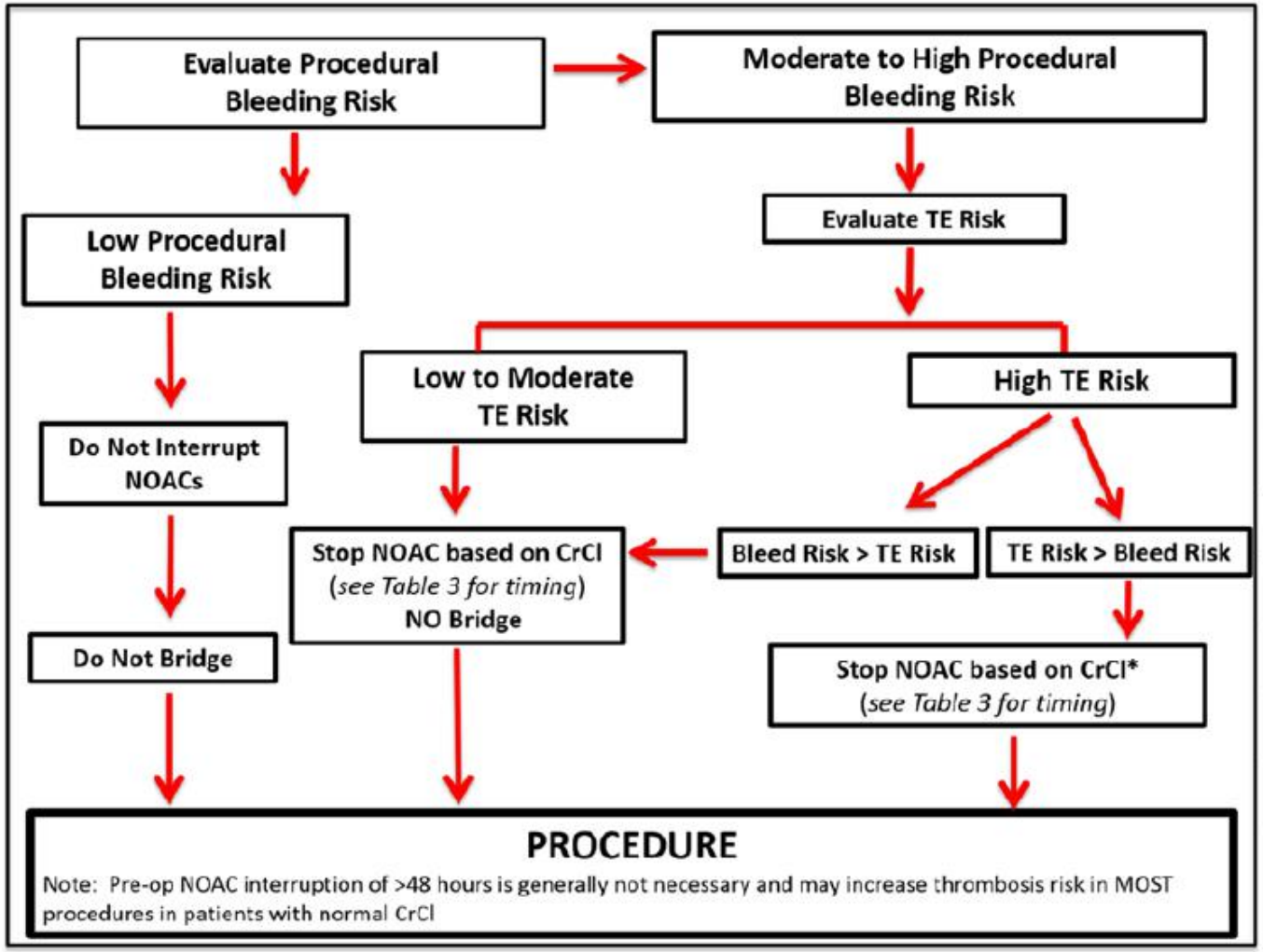
Riduce le perdite ematiche in pz sottoposti ad interventi chirurgici

[Ker K 2013] Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *Br J Surg* 2013;100:1271–9

Sconsigliato in

- *Ematuria (idronefrosi da ostruzione ureterale per coaguli)*
- *Emorragia cerebrale*
- *(possibile incremento di eventi ischemici*

[Baharoglu MI 2013]. Baharoglu MI et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD001245



Peri-Procedural Bleeding Risk

Low	Moderate	High
Minor Dental	SVT ablation	Cardiovascular/Thoracic Surgery
Minor Dermatologic	ICD Implant	Intra-abdominal/Pelvic surgery
Opthalmologic	Endoscopy with Biopsy	Major Orthopedic Surgery
Endoscopy without Biopsy	Prostate Biopsy	Neurosurgery
	Cardiac catheterization via radial artery	Cardiac catheterization via femoral artery

Peri-Procedural Thromboembolic Risk

Low	Moderate to High
$CHA_2DS_2VASc \leq 1$	$CHA_2DS_2VASc > 2$
No Stroke/TIA, VTE within 3 months	Stroke/TIA, VTE within 3 months
Heterozygous Factor V Leiden Heterozygous PT gene mutation	Protein C or S Deficiency Antithrombin Deficiency Antiphospholipid Syndrome

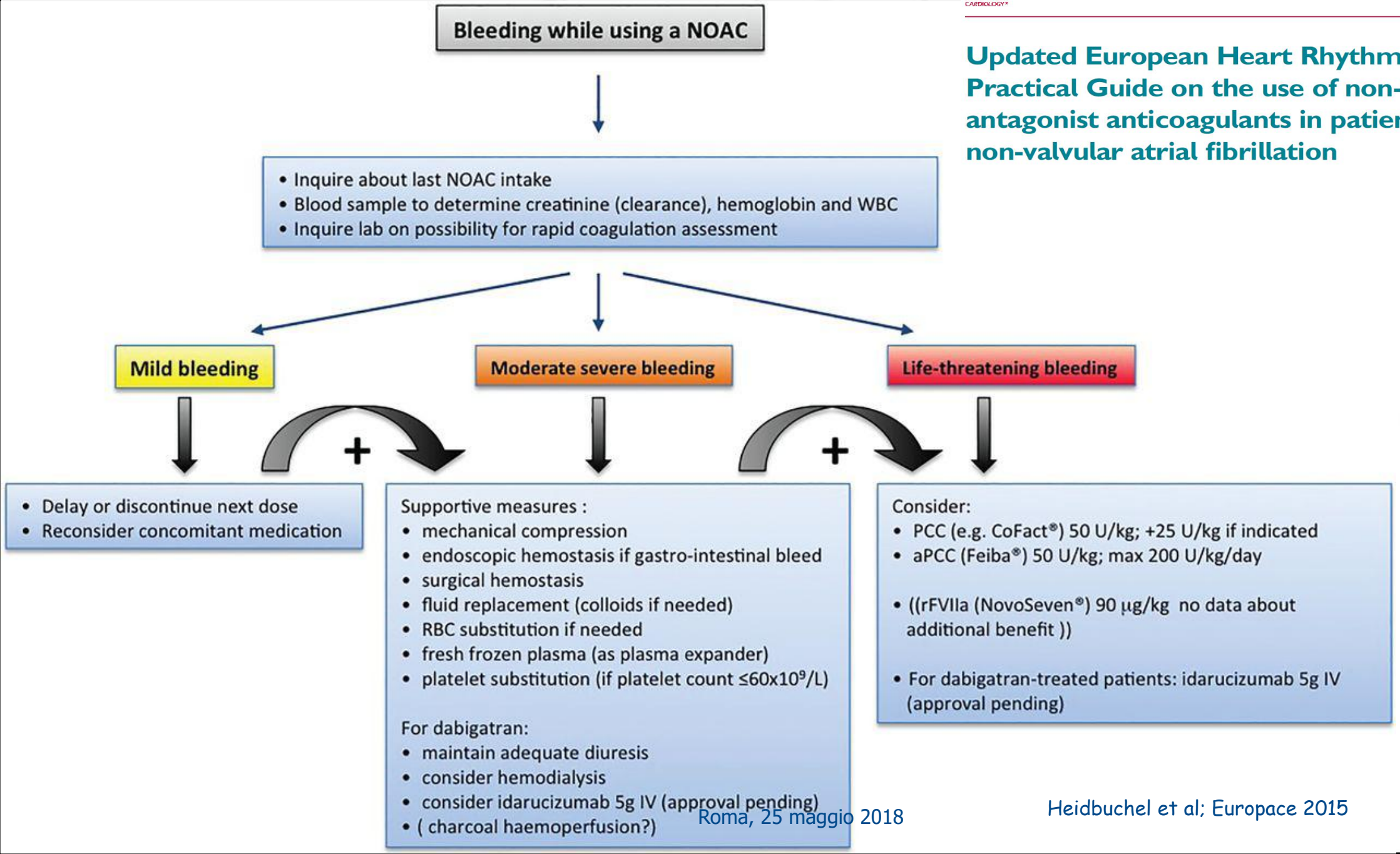
Figure 3. Periprocedural management of patients on NOACs (non–vitamin K antagonist oral anticoagulants).

CrCl indicates creatinine clearance; ICD, implantable cardioverter-defibrillator; PT, prothrombin time; SVT, supraventricular tachycardia; TE, thromboembolic event; TIA, transient ischemic attack; and VTE, venous thromboembolism.

*Bridging may be considered in patients with a history of systemic embolus in the last 6 weeks.[110a]

Europace (2015) 17, 1467–1507
doi:10.1093/europace/euv309

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



Heidbuchel et al; Europace 2015

GESTIONE SANGUINAMENTO IN NAO

•Sospettare sanguinamento anche se non evidente
• VALUTARE SEDE

SANGUINAM- IN SEDE CRITICA (es. Intracranica e intraspinale, intraoculare, pericardica, retroperit., s. compartim...)

APPARATO GE, TRAUMA (considerare aspetti specifici nella gestione emorr.)

•NAO: vedi
•**Valutazione clinica** (ABCD, parametri vitali, Caratteristiche del pz, Età, comorbidità,
•**ES LABORATORIO** (coagulazione, funzione renale, EGA, Hb,..) ev. Attività NAO

Evoluzione emorr : Andamento emorr, efficacia compenso, possibilità controllo emostasi
Monitorare e PREVEDERE evoluzione emorr (Ecografia, parametri, clinica)

SANGUINAMENTO MINORE(*)
•Sospendere/ritardare NAO
•(Compressione meccanica)
•monitorare condiz.emodinamiche
•Valutare terapie concomitanti

(*) No trasfusione, stabilità emodinamica

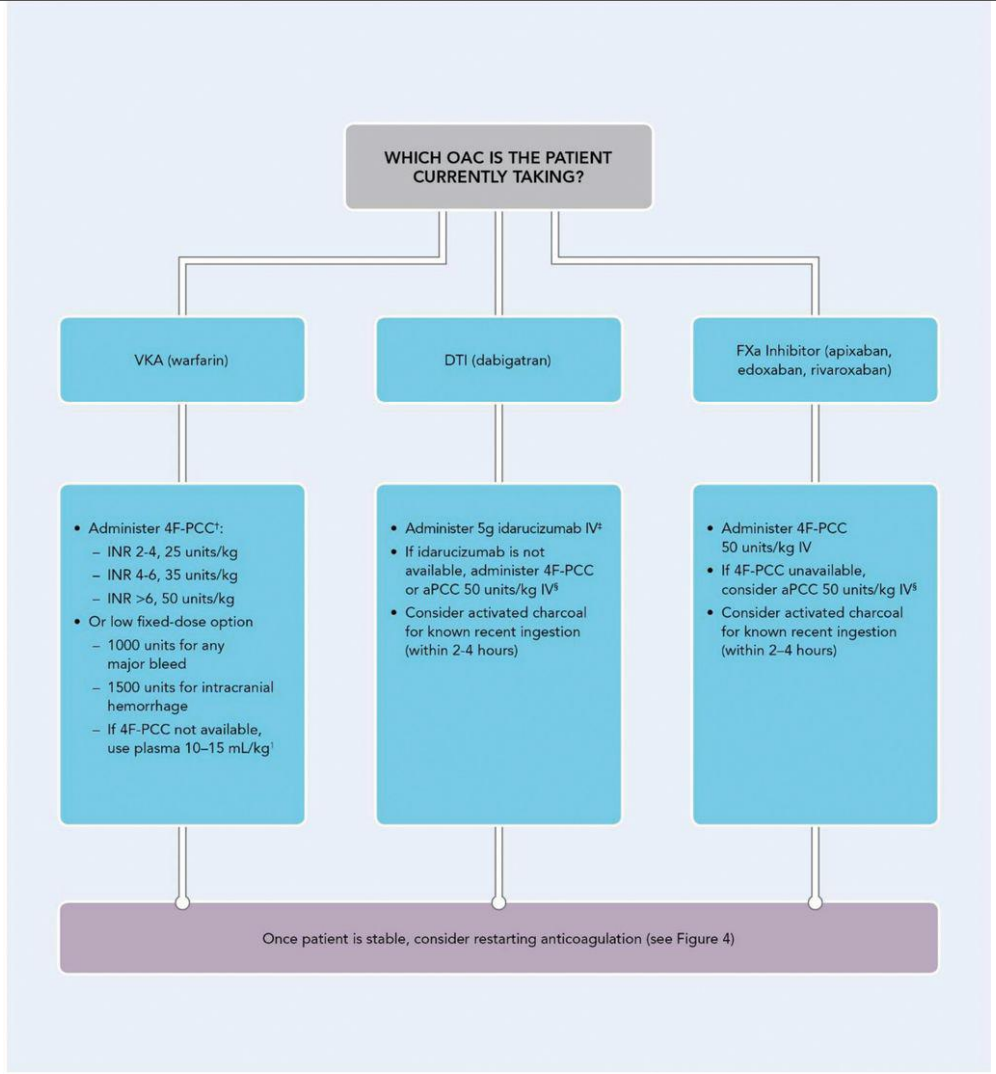
SANGUINAM MODERATO/SEVERO O CLINICAM. SIGNIFICATIVO (**)
•Carbone vegetale se ingest< 2h
- Adeguata idratazione
- Misure emostatiche locali
- Interventi (emostasi endoscopica, o chirurgica trattamento endoscopico, radiol interventistica,..)
- Somministraz liquidi
- Trasfusione GR se necessario
  PP se ≤60×109/L,
- Ac. Tranexamico

Pazienti trattati con DABIGATRAN
- Idarucizumab 5 g IV (se disponibile)
- Idratazione e mantenimento adeguata diuresi
- Eventuale emodialisi

SANGUINAMENTO MAGGIORE (°)
Per tutti i NAO considerare:
•PCC III o IV 50 U/kg
+ 25 U/kg se indicato
•aPCC 50 U/kg; max 200U/kg/day
•Ac. Tranexamico

(**) _emorr ext non controllabile con procedure convenzionali;< 4 concentrati emazie stabilità emodin. / aum. f.c./ valutazione volemica con eco, lattati,..

(°) ≥ 4 concentrati emazie instabilità emodinamica PAS< 90 mmHg o riduz >40 mmHg rispetto all'usuale o PAM < 65 mmHg



4F-PCC = four-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; DOAC = direct oral anticoagulant; DTI = direct thrombin inhibitor; FXa = Factor Xa; INR = international normalized ratio; IV = intravenous; OAC = oral anticoagulant, including DOACs and VKAs; PCCs = prothrombin complex concentrates; VitK = vitamin K; VKA = Vitamin K antagonist.

*Reversal agents include repletion strategies such as PCCs, plasma, VitK, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran).

† When PCCs are used to reverse VKAs, VitK should also always be given (see Figure 2 for dosing guidance).

‡ If bleeding persists after reversal and there is laboratory evidence of a persistent dabigatran effect, or if there is concern for a persistent anticoagulant effect before a second invasive procedure, a second dose of idarucizumab may be reasonable.

§ Refer to prescribing information for max units.

1. Sarode R, Milling TJ, Jr., Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013; 128:1234-43.

Writing Committee et al. JACC 2017;j.jacc.2017.09.1085

©2017 by American College of Cardiology