DALLE ORIGINI AI GIORNI NOSTRI

Gestione delle Complicanze Emorragiche

Flavia Dispensa

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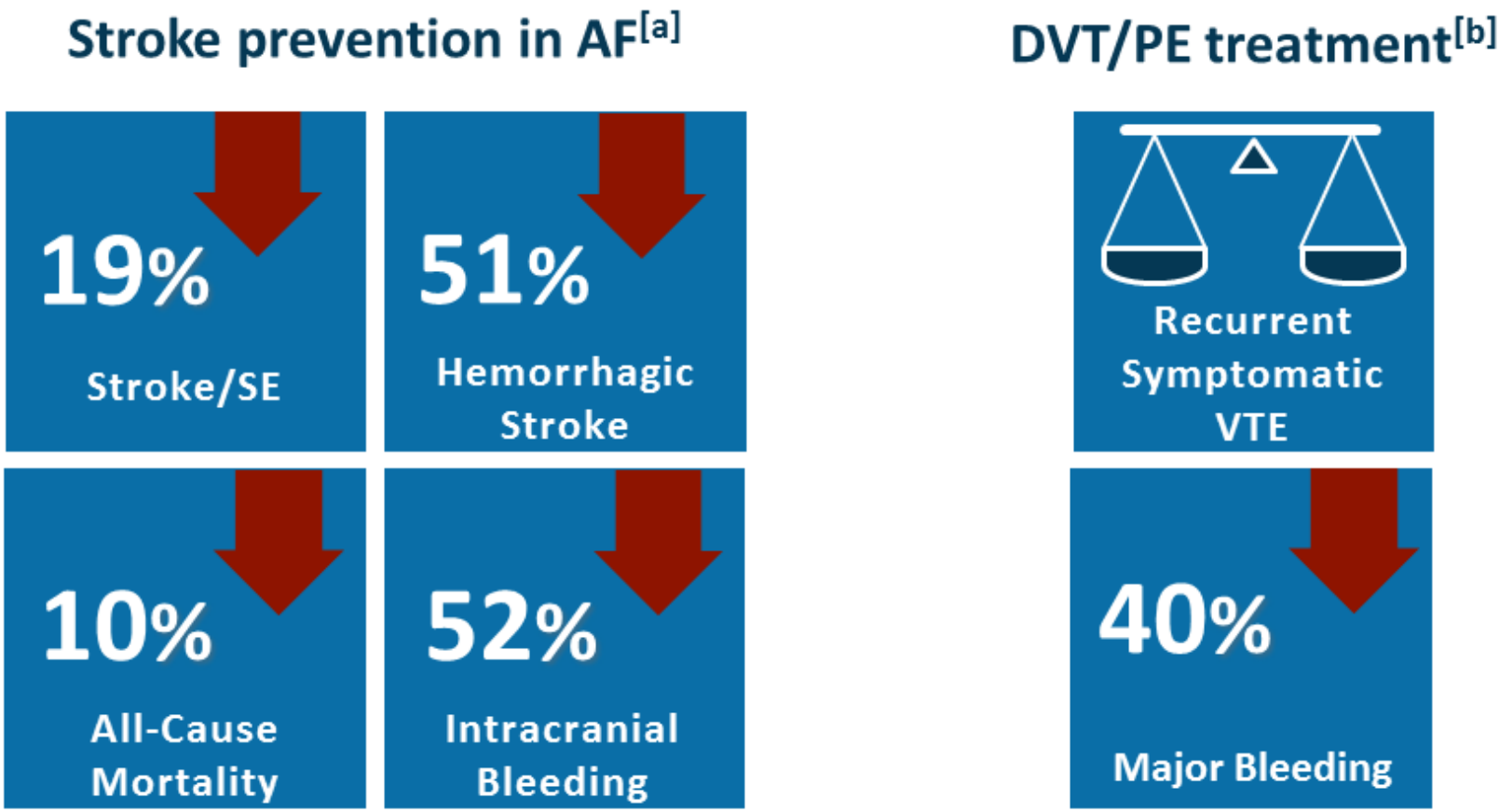
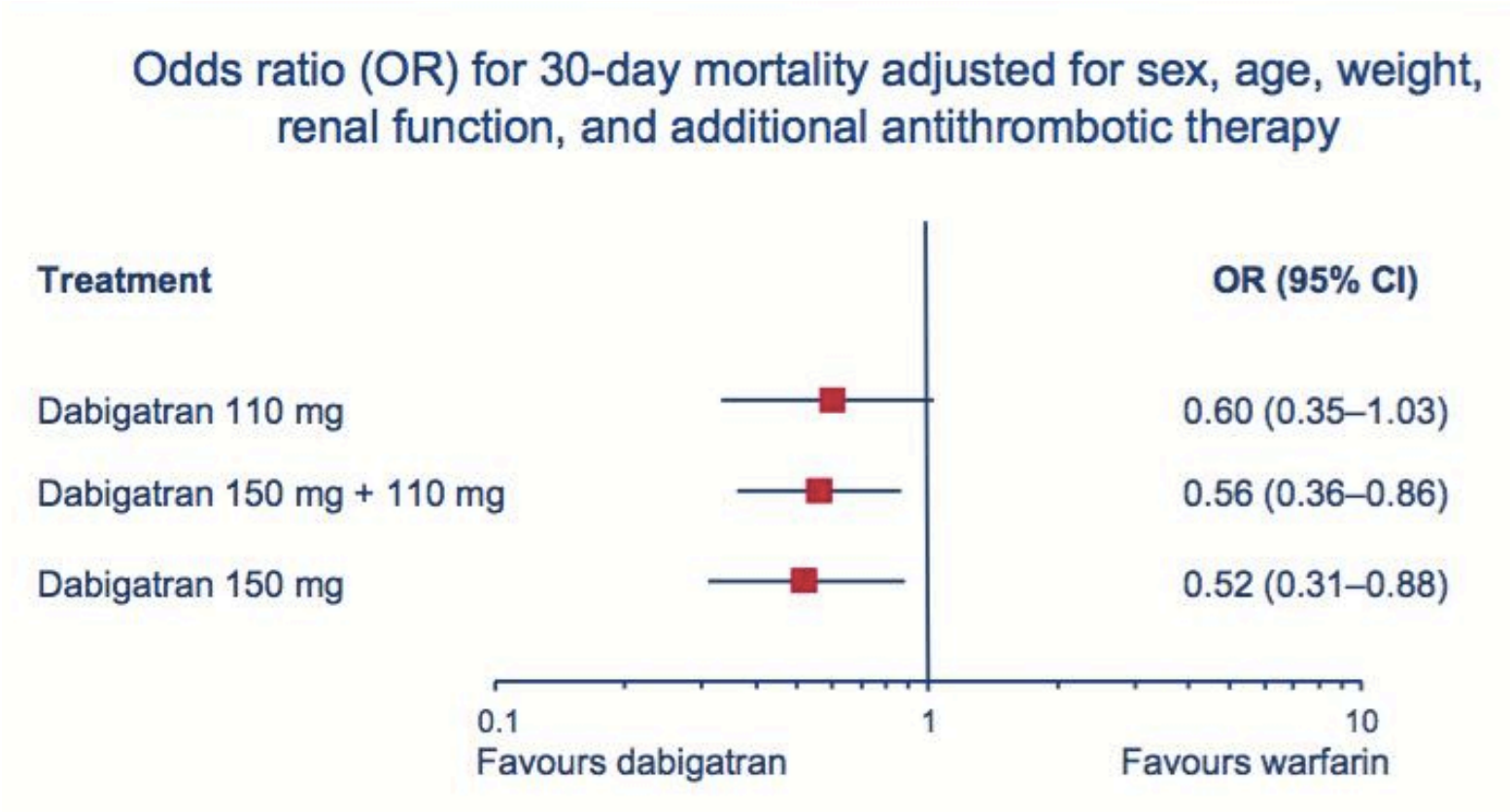
NAO vs VKA:
profilo di efficacia e sicurezza nei trials



Ruff C ed al, Lancet 2014; 383:955-962
Hirschl M Vasa. 2014; 43:353-364

Analisi della mortalità dopo un sanguinamento maggiore in RE-LY trial



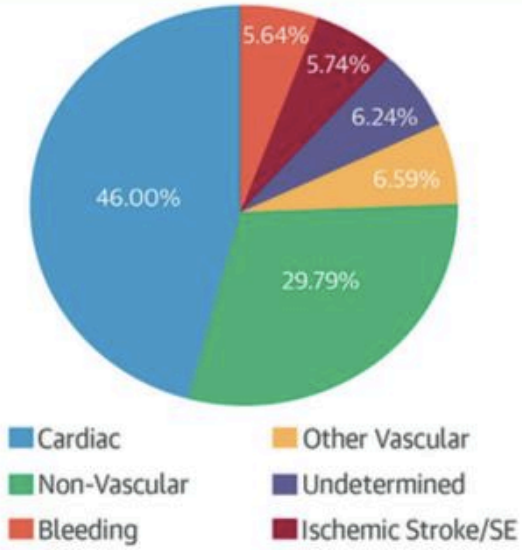
Majeed A et al. Ciculation 2013;128:2325-32

Causes of Death in Anticoagulated Patients With Atrial Fibrillation

Antonio Gómez-Outes, MD, PhD,[a] Julián Lagunar-Ruíz, MD,[b] Ana-Isabel Terleira-Fernández, MD, PhD,[b,c] Gonzalo Calvo-Rojas, MD, PhD,[d] Maria Luisa Suárez-Gea, PharmD, PhD,[a] Emilio Vargas-Castrillón, MD, PhD[b,c]

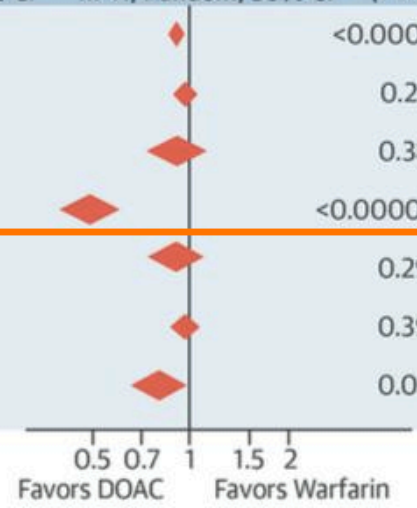
CENTRAL ILLUSTRATION **Causes of Death in AF**

Causes of Death (n = 6,206)



Comparison Between DOACs and Warfarin for Causes of Death

Study or Subgroup	Risk Ratio M-H, Random, 95% CI	p Value
All-Cause Death	0.90	<0.0001
Cardiac Death	0.96	0.23
Ischemic Stroke/SE	0.91	0.38
Fatal Bleeding	0.49	<0.00001
Other Vascular Death	0.90	0.29
Non-Vascular Death	0.96	0.39
Undetermined Death	0.80	0.03



Gómez-Outes, A. et al. J Am Coll Cardiol. 2016;68(23):2508-21.

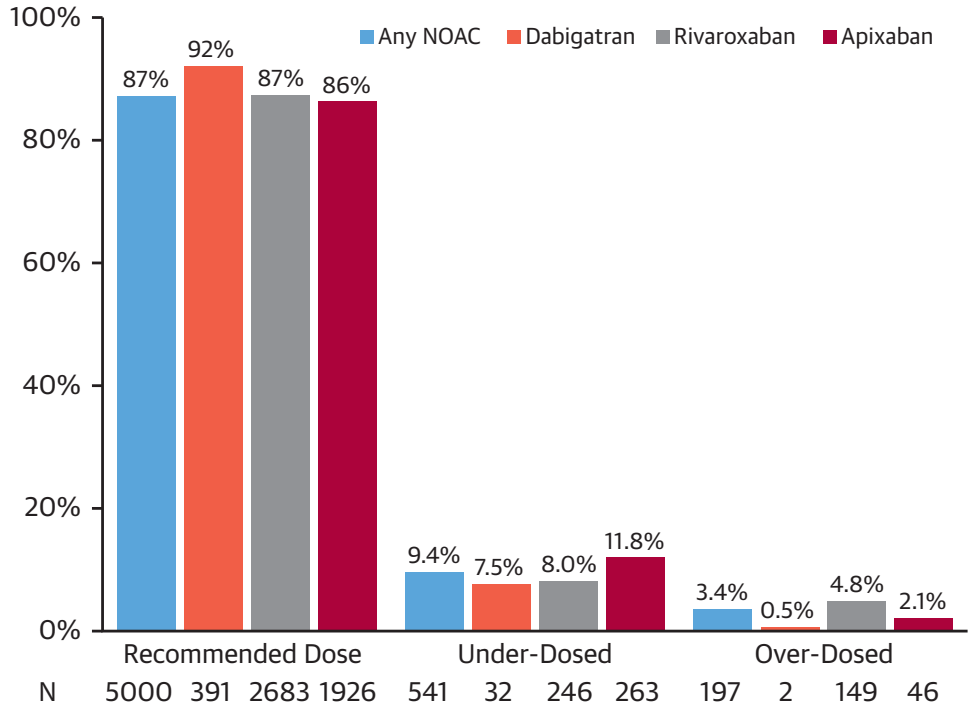
Causes of death in 6,206 of 71,683 total patients who died during ≈1.87 years follow-up (≈134,046 patient-years) treated with DOACs or warfarin in 4 contemporary anticoagulation trials in AF. AF = atrial fibrillation; CI = confidence interval; DOACs = direct oral anticoagulants; M-H = Mantel-Haenszel; SE = systemic embolism.

JACC 2016; vol 68 n.23: 2508-21

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes

The ORBIT-AF II Registry

FIGURE 1 **NOAC Dosing By Drug**

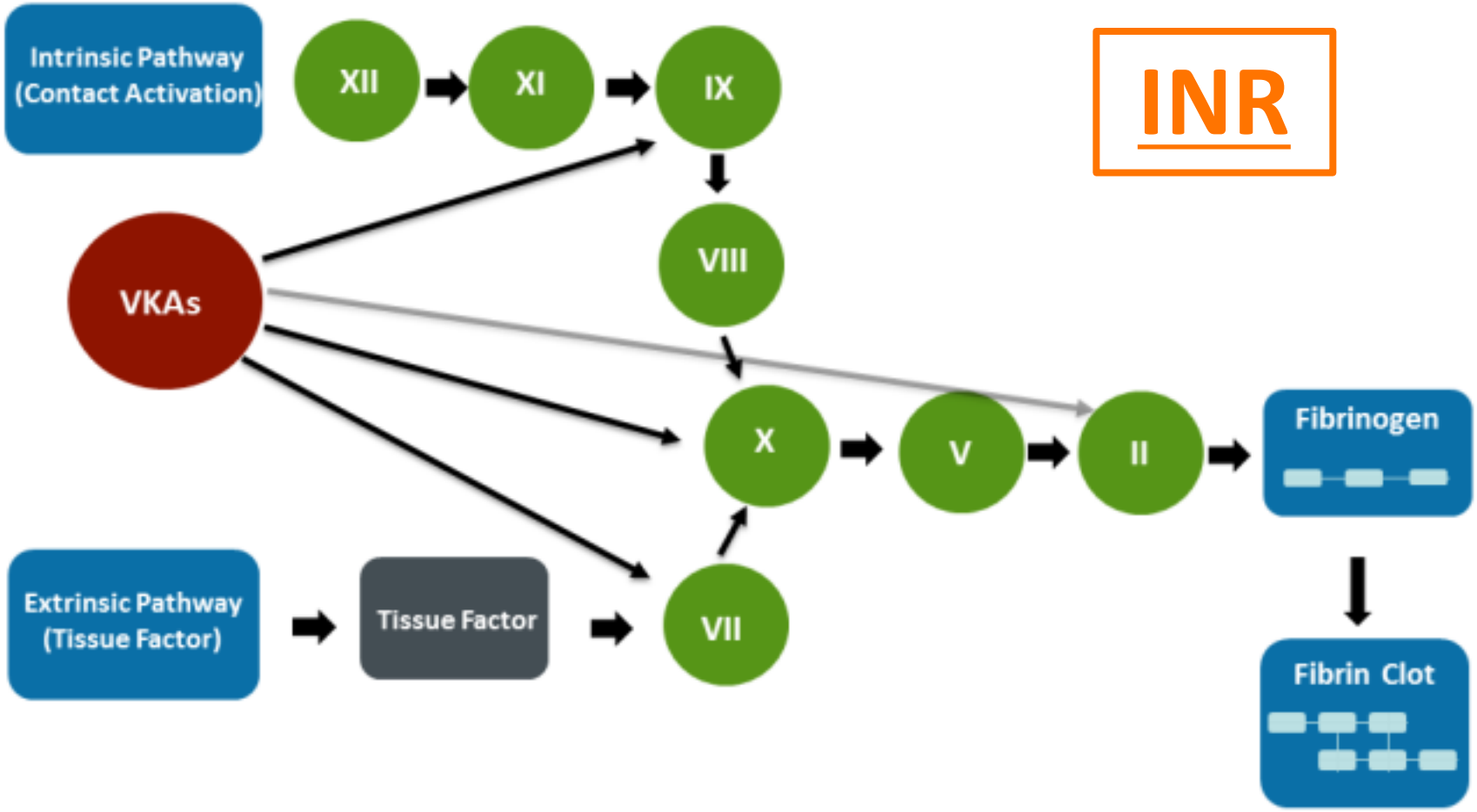


Rates of NOAC prescription, according to the U.S. FDA-approved labeling, using the recommended dose, below the recommended dose (underdosing), and above the recommended dose (overdosing). NOAC = nonvitamin K antagonist oral anticoagulant.

TABLE 1 Demographics, Medical History, and Laboratory Studies

	Overall (N = 5,738)	Recommended Dose (n = 5,000, 87%)	Underdosed (n = 541, 9.4%)	Overdosed (n = 197, 3.4%)	p Value
Age, yrs	71.00 (64.00-79.00)	70.00 (63.00-77.00)	79.00 (72.00-85.00)	80.00 (76.00-84.00)	<0.0001
Female	2,399 (41.81)	2,006 (40.12)	261 (48.24)	132 (67.01)	<0.0001
Race					0.07
White	5,062 (88.22)	4,425 (88.50)	473 (87.43)	164 (83.25)	
Black or African American	232 (4.04)	200 (4.00)	24 (4.44)	8 (4.06)	
Hispanic	250 (4.36)	211 (4.22)	27 (4.99)	12 (6.09)	
Health insurance status					<0.0001
Private health insurance	2,967 (51.71)	2,666 (53.32)	228 (42.14)	73 (37.06)	
Medicaid	230 (4.01)	193 (3.86)	27 (4.99)	10 (5.08)	
Medicare	2,282 (39.77)	1,907 (38.14)	269 (49.72)	106 (53.81)	
Other	206 (3.59)	185 (3.70)	15 (2.77)	6 (3.05)	
None	53 (0.92)	49 (0.98)	2 (0.37)	2 (1.02)	
CHA_2DS_2-VASc score					<0.0001
0	188 (3.28)	181 (3.62)	5 (0.92)	2 (1.02)	
1	556 (9.69)	539 (10.78)	14 (2.59)	3 (1.52)	
≥2	4,994 (87.03)	4,280 (85.60)	522 (96.49)	192 (97.46)	
ORBIT bleeding score					<0.0001
Low: 0-2	4,114 (72.85)	3,737 (75.97)	283 (52.90)	94 (48.70)	
Medium: 3	793 (14.04)	638 (12.97)	117 (21.87)	38 (19.69)	
High: ≥4	740 (13.10)	544 (11.06)	135 (25.23)	61 (31.61)	
History of coronary artery disease	1,626 (28.34)	1,353 (27.06)	210 (38.82)	63 (31.98)	<0.0001
Prior cerebrovascular events	683 (11.90)	573 (11.46)	79 (14.60)	31 (15.74)	0.02
Congestive heart failure	1187 (20.69)	1,001 (20.02)	139 (25.69)	47 (23.86)	0.005
Prior gastrointestinal bleeding	226 (3.94)	186 (3.72)	32 (5.91)	8 (4.06)	0.04
Concomitant aspirin therapy	1,487 (25.91)	1,306 (26.12)	133 (24.58)	48 (24.37)	0.7
Body mass index, kg/m^2	31.35 ± 7.98	31.65 ± 7.99	30.34 ± 7.59	26.32 ± 6.64	<0.0001
Calculated creatinine clearance, ml/min/1.73 m^2*	89.15 ± 42.55	93.24 ± 42.66	66.70 ± 28.41	47.16 ± 27.68	<0.0001
New-onset AF at baseline	2,386 (41.58)	2,066 (41.32)	225 (41.59)	95 (48.22)	0.08
Left ventricular ejection fraction	55.02 ± 11.50	54.89 ± 11.50	55.43 ± 11.23	57.24 ± 11.81	0.005
Physician specialty					<0.0001
Primary care	316 (5.51)	241 (4.82)	52 (9.61)	23 (11.68)	
Cardiology	3,916 (68.25)	3,386 (67.72)	393 (72.64)	137 (69.54)	
Electrophysiology	1,503 (26.19)	1,370 (27.40)	96 (17.74)	37 (18.78)	
Neurology	3 (0.05)	3 (0.06)	0 (0.00)	0 (0.00)	

Warfarin e Cascata Coagulativa



January CT et al, JACC 2014;64:e1-76

Valutazione della coagulazione nei pazienti in terapia con NAO

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

Green = quantitative; orange = qualitative; red = not applicable.

Time of last NOAC dose should always be considered when interpreting test results.

aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; FXa, activated Factor X; PT, prothrombin time; TT, thrombin time

Adapted from Heidbuchel et al. Europace 2013;15:625–51; Pradaxa SPC; Xarelto SPC; Eliquis SPC; Lixiana SPC; Current versions available online at: http://www.medicines.org.uk/emc/

Tempi di normalizzazione dell'emostasi in pazienti trattati con NAO in base alla funzionalità renale

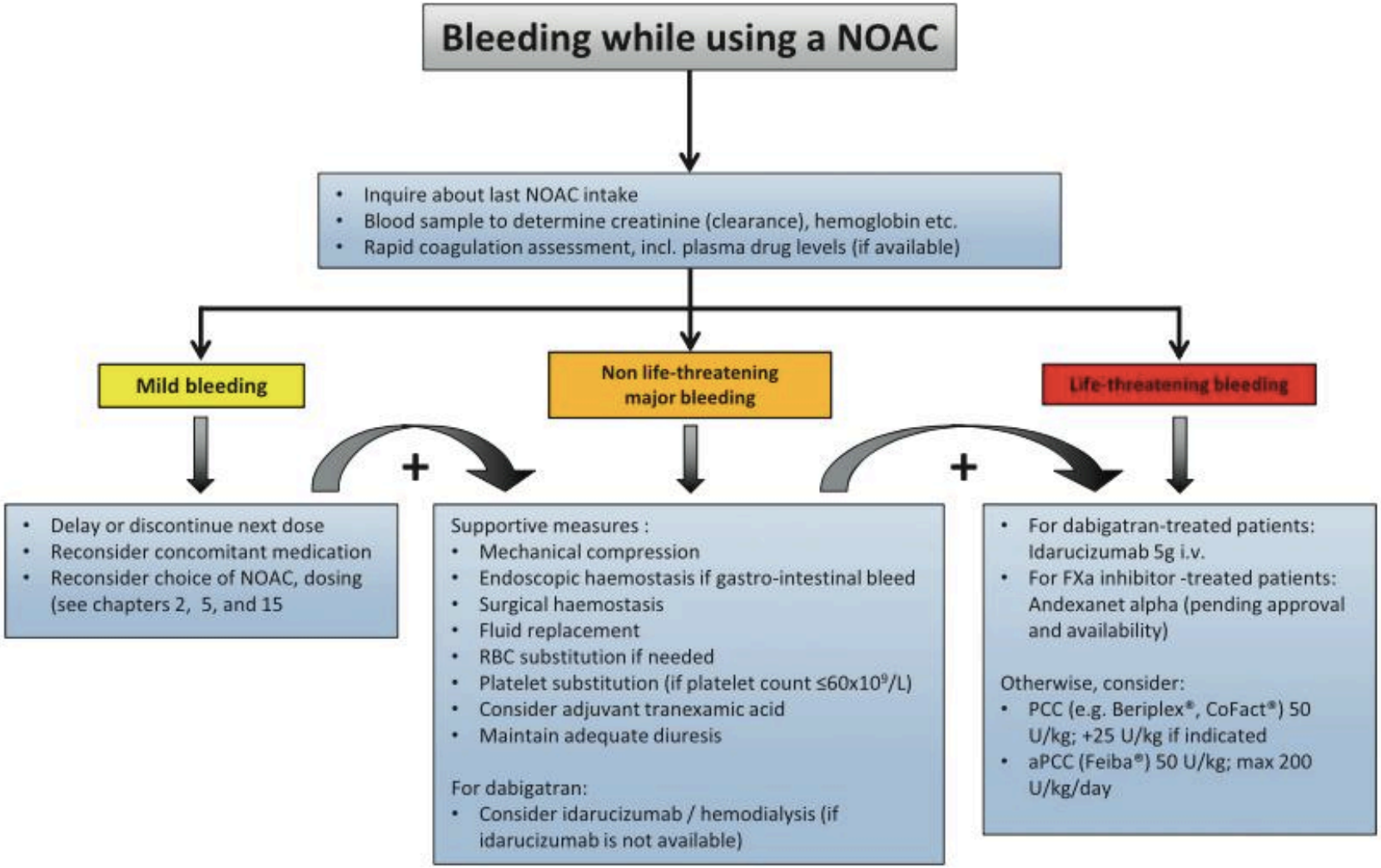
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl >80 mL/min	12–17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)
CrCl 50–80 mL/min CKD Stages I and II	~17 h[122] (+50%)	~14.6 h[123] (+16%)	~8.6 h[124] (+32%)[SmPC]	~8.7 h[125] (+44%)[126]
CrCl 30–50 mL/min CKD Stage III	~19 h[122] (+320%)	~17.6 h (+29%)	~9.4 h[124] (+74%)[SmPC]	~9.0 h (+52%)[126]
CrCl 15–30 mL/min CKD Stage IV	~28 h[122] (+530%)	~17.3 h (+44%)	~16.9 h[124] (72%)[SmPC]	~9.5 h (+64%)[126]
CrCl ≤ 15 mL/min CKD Stage V; off-dialysis	No data	– (+36%)	– (+93%)[SmPC]	– (+70%)[127]

CKD, chronic kidney disease; CrCl, creatinine clearance.

L'effetto anticoagulante dei NAO tende a risolversi rapidamente in rapporto alle loro caratteristiche farmacocinetiche (emivita breve)

"time is the most important antidote of the NOACs"

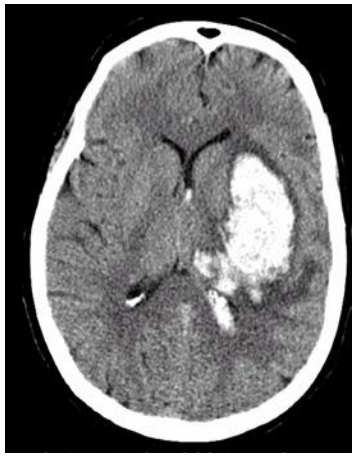
Heidbuchel H et al. Europace (2015)



J.Steffel et al, European Heart Journal (2018) 00, 1–64

Emorragia in corso di terapia con NAO: **quanto è grave?**

- Sede
- Entità (calo di emoglobina)
- Condizioni emodinamiche
- Attività del sanguinamento



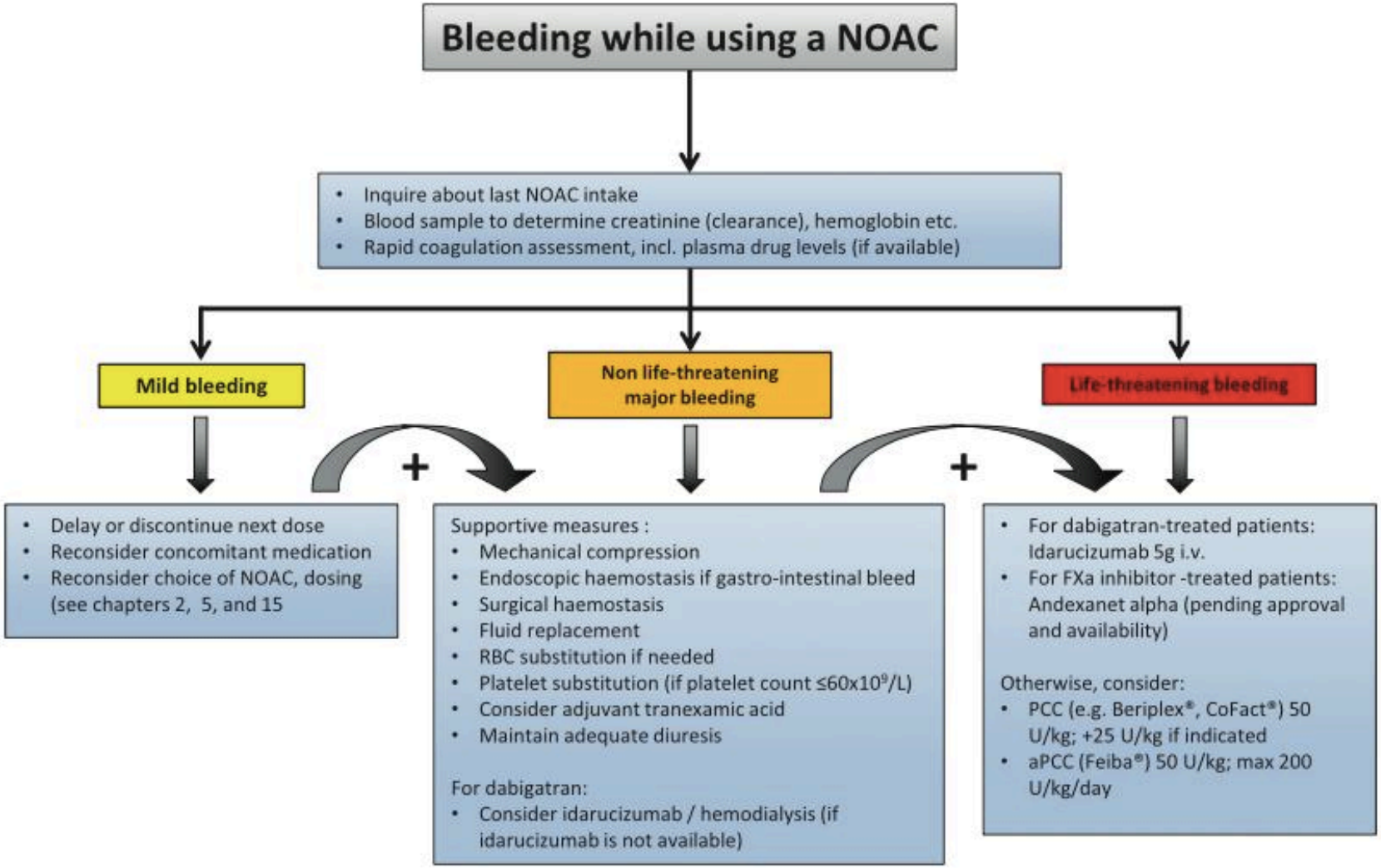
Emorragia in corso di terapia con NAO: **informazioni necessarie**

- Quale NAO ?
  - Dabigatran o inibitore FXa
- Quale dose?
  - Dose corretta per funzione renale, età, peso…
- Terapie associate?
  - DAPT, erronea concomitante somministrazione di eparine
- Patologie associate?
  - insufficienza renale, piastrinopenia, insufficienza epatica/cirrosi, ipertensione arteriosa non controllata
- Ora dell'ultima assunzione?
  - <8 ore
  - >12 ore

Heidbuchel H et al, Europace 2015;17:1467-1507

Carbone attivo

Farmaco	trattamento
DABIGATRAN	Efficace entro le **2** ore da ultima dose
RIVAROXABAN	efficace entro le **8** ore da ultima dose
APIXABAN	Efficace entro le **6** ore da ultima dose



J.Steffel et al, European Heart Journal (2018) 00, 1–64

Definizione di Sanguinamento Maggiore

RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
Major Bleeding: ≥ 1 of:	**Major Bleeding : ≥ 1 of:**	**Major Bleeding : ≥ 1 of:**	**Major Bleeding : ≥ 1 of:**
1. With ↓ Hb ≥ 2.0 g/dl	1. With ↓ Hb ≥ 2.0 g/dl	1. With ↓ Hb ≥ 2.0 g/dl	1. With ↓ Hb ≥ 2.0 g/dl
2. With transfusion ≥ 2 U blood or packed cells	2. With transfusion ≥ 2 U blood or packed cells	2. With transfusion ≥ 2 U blood or packed cells	2. With transfusion ≥ 2 U blood or packed cells
3. Symptomatic ocular, cranial, spinal, intra-muscular with compartment syndome, retroperitoneal, pericardial	3. Symptomatic ocular, cranial, spinal, intra-muscular with compartment syndome, retroperitoneal, pericardial	3. Symptomatic ocular, cranial, spinal, intra-muscular with compartment syndome, retroperitoneal, pericardial	3. Symptomatic ocular, cranial, spinal, intra-muscular with compartment syndome, retroperitoneal, pericardial

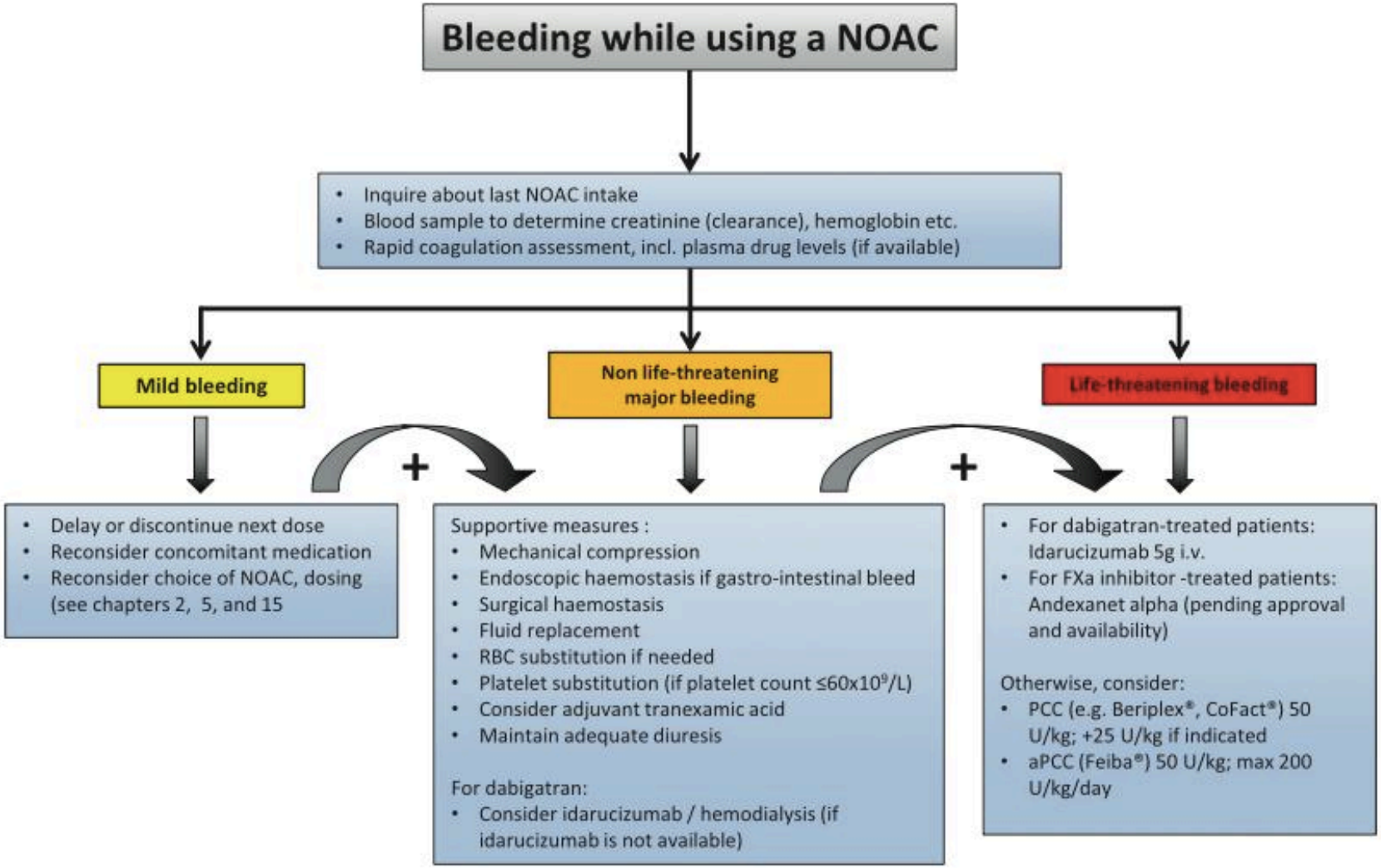
Definizione di Sanguinamento Maggiore

MAGGIORE

- associato a riduzione dell'Hb > 2g/dl o che richiede necessita trasfusione di almeno 2 unità di eritrociti
- sintomatico intraoculare, intracranico, intraspinale o intramuscolare con sindrome compartimentale, retroperitoneale, intra-articolare o pericardico

MINACCIOSO PER LA VITA

- intracranico sintomatico
- associato a riduzione dell'Hb > 5 g/dl o che richiede necessita trasfusione di almeno 4 unità di eritrociti
- associato ad ipotensione che richieda l'uso di agenti inotropi somministrati per via endovenosa
- che richieda intervento chirurgico

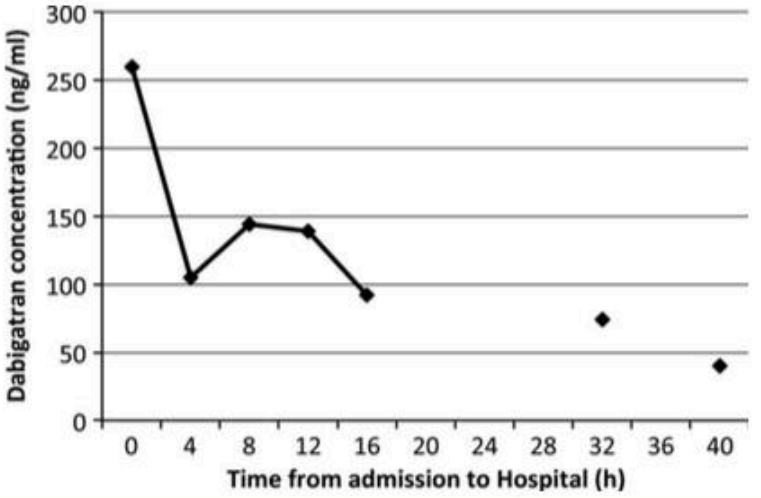


J.Steffel et al, European Heart Journal (2018) 00, 1–64

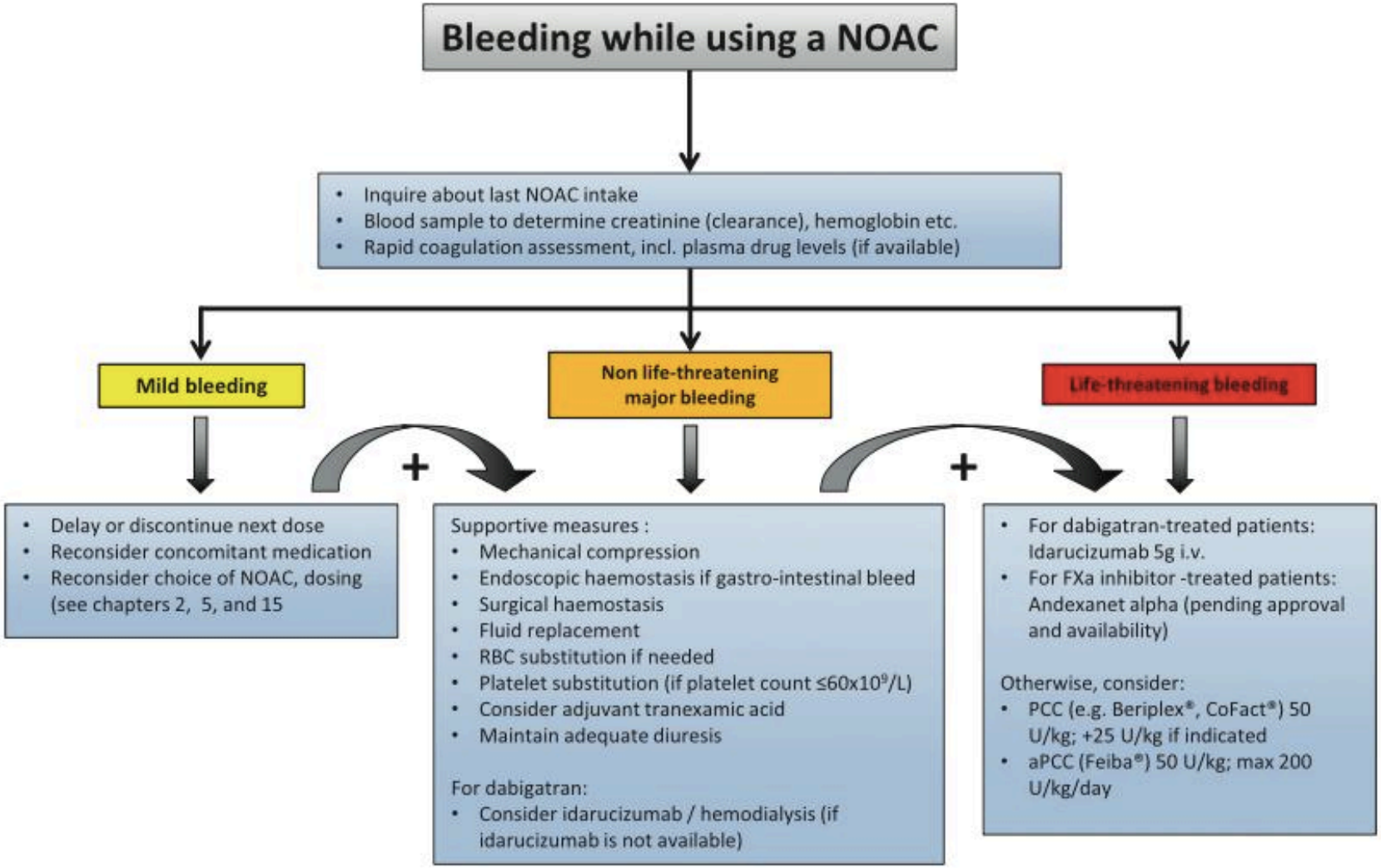
Intermittent haemodialysis and continuous veno-venous dialysis are effective in mitigating major bleeding due to dabigatran

- Possibile solo per Dabigatran poiché solo il 30% si lega alle proteine plasmatiche

- Efficace sia l'emodialisi intermittente che la CVVH



Getta B. British Journal of Haematology 2015, 169,595–604



J.Steffel et al, European Heart Journal (2018) 00, 1–64

Concentrati di complesso protrombinico

Preparati (Fattori)	Dosaggio (EV)
3 FATTORI : Fattore II-IX-X **(Uman Complex®, Protromplex TIM3®)**	50 units/Kg
4 FATTORI non attivati: Fattore II-VII-IX-X **(Confidex®, Pronativ®)**	50- 80 units/Kg
4 FATTORI attivato: Fattore II-VIIa-IX-X **(FEIBA®)**	50-100 units/Kg

Auspicabile la disponibilità in PS

Dickneite et al, Thromb Haemost 2014;111:189

Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study

Ammar Majeed,[1-4] Anna Ågren,[1,3] Margareta Holmström,[1,3] Maria Bruzelius,[1,3] Roza Chaireti,[3,5,6] Jacob Odeberg,[1,3,7] Eva-Lotta Hempel,[1,3] Maria Magnusson,[6,8,9] Tony Frisk,[10] and Sam Schulman[11,12]

- 84 pz con emorragia maggiore in terapia con apixaban o rivaroxaban
- 70% emorragia intracranica, 15% emorragia GI
- 1500-2000 UI in bolo ev
- efficacia nel 69% dei casi
- 2,4% trombosi entro 30 giorni
- 32% morte entro 30 giorni

RECOMMENDATIONS AND GUIDELINES

Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH

N. KHORSAND,*† A. MAJEED,‡ R. SARODE,§ J. BEYER-WESTENDORF,¶ S. SCHULMAN‡** and K. MEIJER,* FOR THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION

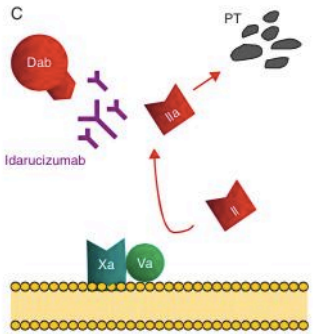
Table 5. Details of deaths within the first week after PCC treatment

Patient	Age, y	Sex	DOAC indication	Anticoagulant	Dose	Bleeding	Death after PCC, d	Cause of death
1	79	Male	SPAF	Apixaban	2.5 mg × 2	ICH	6	ICH
2	80	Male	SPAF	Apixaban	2.5 mg × 2	ICH	1	ICH
3	84	Male	SPAF	Apixaban	5 mg × 2	ICH	1	ICH
4	84	Female	SPAF	Apixaban	5 mg × 2	ICH	0	ICH
5	77	Male	SPAF	Apixaban	5 mg × 2	ICH	4	ICH
6	80	Female	SPAF	Apixaban	5 mg × 2	ICH	3	ICH
7	74	Male	SPAF	Rivaroxaban	20 mg × 1	ICH	0	ICH
8	70	Female	SPAF	Rivaroxaban	20 mg × 1	ICH	2	ICH
9	69	Female	SPAF	Rivaroxaban	20 mg × 1	ICH	2	ICH
10	84	Female	SPAF	Rivaroxaban	5 mg × 2	ICH	2	ICH
11	69	Male	SPAF	Rivaroxaban	20 mg × 1	ICH	2	ICH
12	73	Male	VTE	Rivaroxaban	20 mg × 1	ICH	5	ICH
13	65	Female	VTE	Rivaroxaban	20 mg × 1	ICH	4	ICH
14	85	Male	SPAF	Rivaroxaban	20 mg × 1	GI	1	Multiorgan failure
15	84	Male	SPAF	Rivaroxaban	20 mg × 1	Visceral	0	Cardiogenic shock

•Blood. 2017;130(15):1706-1712

ANTIDOTI

ANTIDOTI per tutti i DOA	→	**PER977; Perosphere**
ANTIDOTI per il DABIGATRAN	→	**aDabi-Fab; Idarucizumab**
ANTIDOTI per INIBITORI DEL Xa	→	**PRT064445; andexanet alfa**



Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D., John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D.,

Table 2. Indications for Dabigatran Reversal.

Indication	Group A (N=301)*
	no. of patients (%)
Bleeding	
Intracranial	98 (32.6)
Subdural	39 (13.0)
Subarachnoid	26 (8.6)
Intracerebral	53 (17.6)
Gastrointestinal	137 (45.5)
Lower	47 (15.6)
Upper	52 (17.3)
Unknown	42 (14.0)
Intramuscular	9 (3.0)
Retroperitoneal	10 (3.3)
Intrapericardial	7 (2.3)
Intraarticular	5 (1.7)
Intraocular	1 (0.3)
Other	52 (17.3)
Not identified	4 (1.3)
Trauma-related	78 (25.9)

	Group B (N=202)†
Reason for procedure‡	
Abdominal condition or infection: hernia, peritoneal infection	49 (24.3)
Fracture or septic arthritis: involvement of the hip or femur	41 (20.3)
Cardiovascular condition: pacemaker implantation, aneurysm repair	37 (18.3)
Central nervous system condition: craniotomy	17 (8.4)
Pancreatic or hepatobiliary disease: cholecystitis, cholangitis	14 (6.9)
Respiratory condition: chest trauma	14 (6.9)
Kidney and urinary tract condition: acute renal failure	11 (5.4)
Septicemia or sepsis	8 (4.0)
Skin condition: abscess, hematoma	6 (3.0)
Postoperative complications	3 (1.5)
Uterine condition	1 (0.5)
Poisoning: deliberate overdose	1 (0.5)

N Engl J Med 2017;377:431-41

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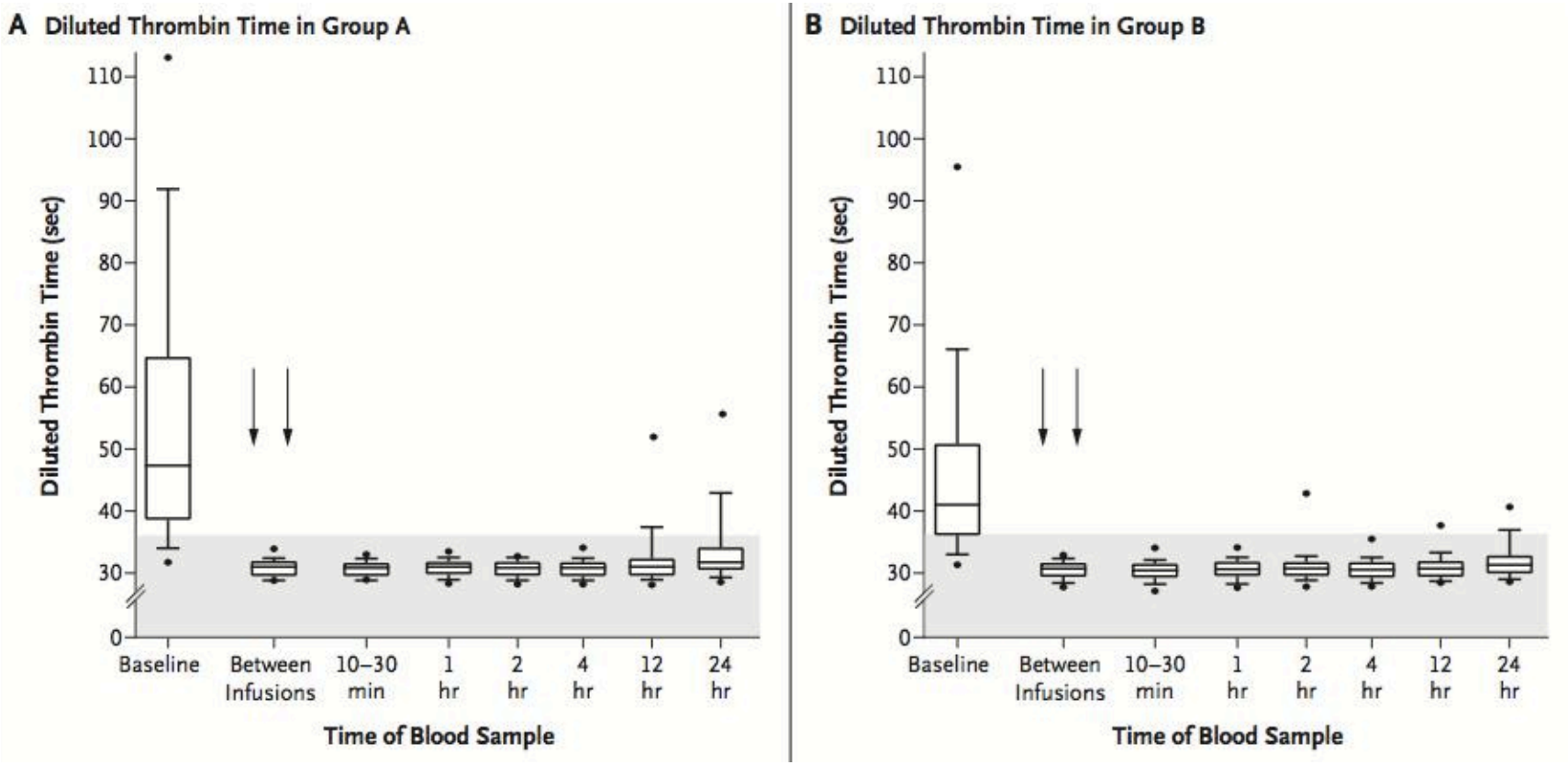


Trombosi/30 gg 4,8%

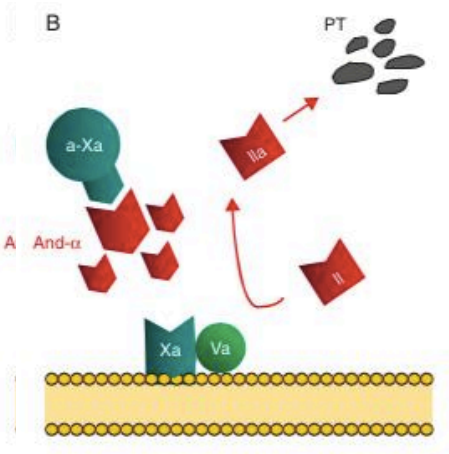
Morte/30 gg 13%

N Engl J Med 2017;377:431-41

IDARUCIZUMAB
indicazioni approvate dall'EMA

- Emergency surgery/urgent procedures

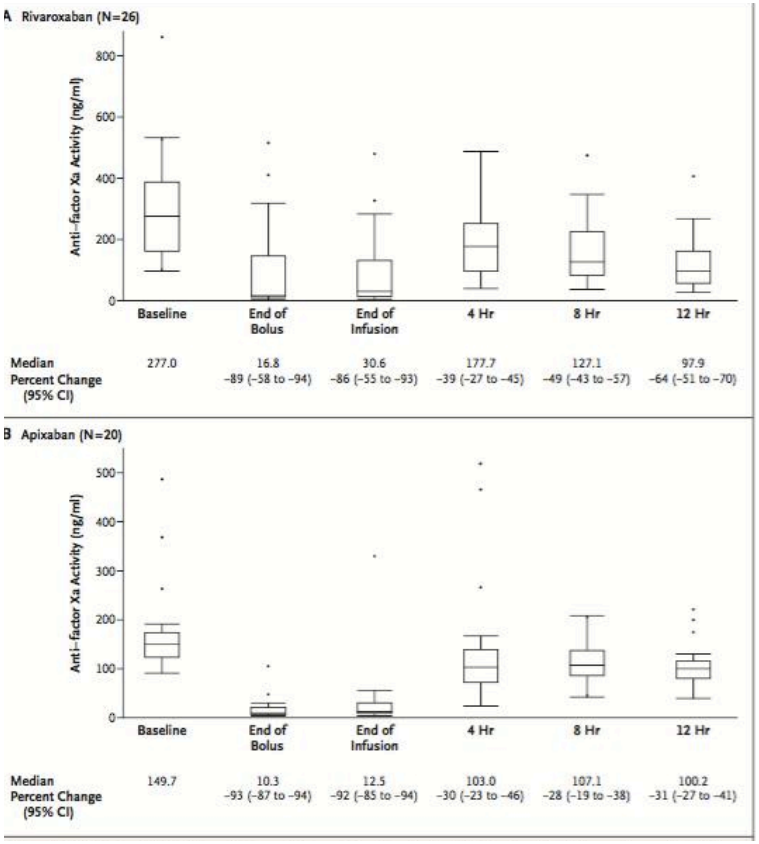
- Life-threatening or uncontrolled bleeding



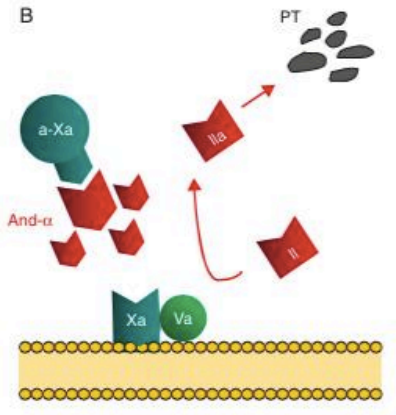
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

-Sanguinamento maggiore <18 ore da anti-FXa
-inizio bolo 4,8 ore dopo l'ingresso



N Engl J Med 2016;375:1131-41.



Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

TERZA ANALISI AD INTERIM OTTOBRE 2017

227 pazienti

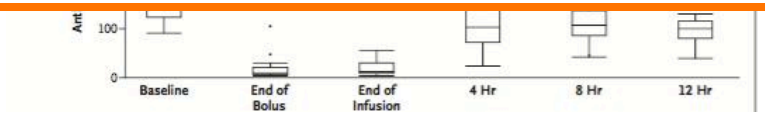
105: apixaban; 75: rivaroxaban; 16: enoxaparina

61% emorragia intracranica; 27% emorragia gastrointestinale

83% buona o eccellente emostasi entro 12 ore

11% eventi trombotici entro 30 giorni

12% mortalità entro 30 giorni

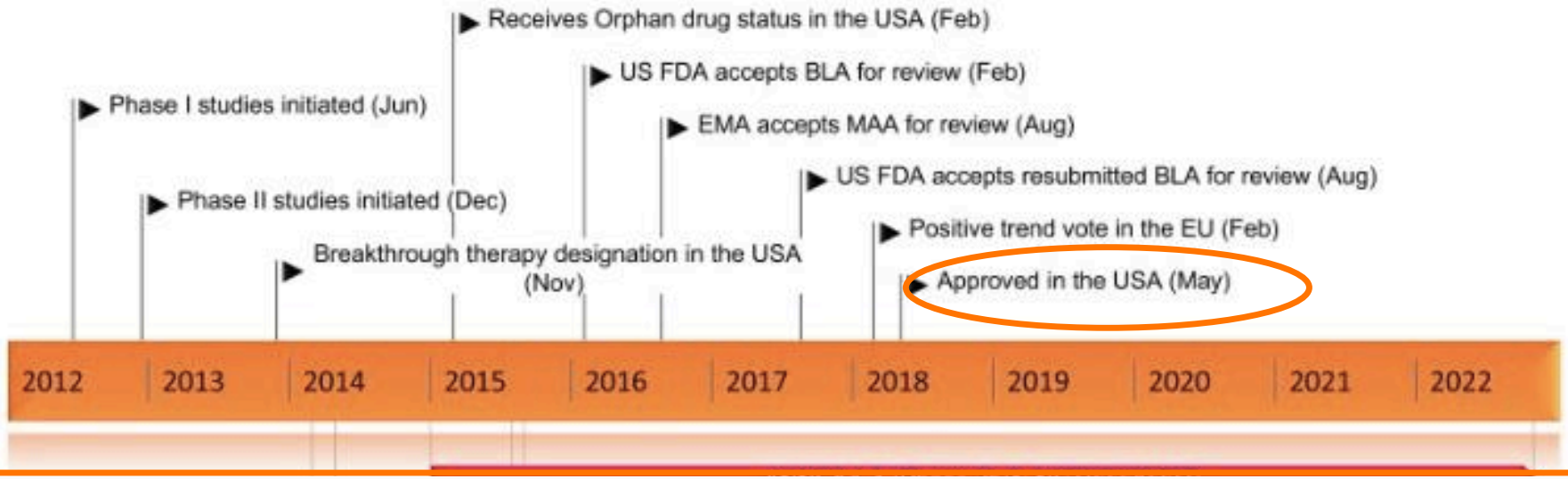


Non valutato l'uso nei pazienti da sottoporre a procedura/chirurgia in emergenza/urgenza

American College of Cardiology's 67th annual scientific session & expo (ACC18). 2018

Andexanet Alfa: First Global Approval

Young-A Heo[1]



Drugs & Therapy Perspectives
November 2018, Volume 34, Issue 11, pp 507–512 | Cite as

Andexanet alfa in the treatment of acute major bleeding related to apixaban and rivaroxaban: a profile of its use in the USA

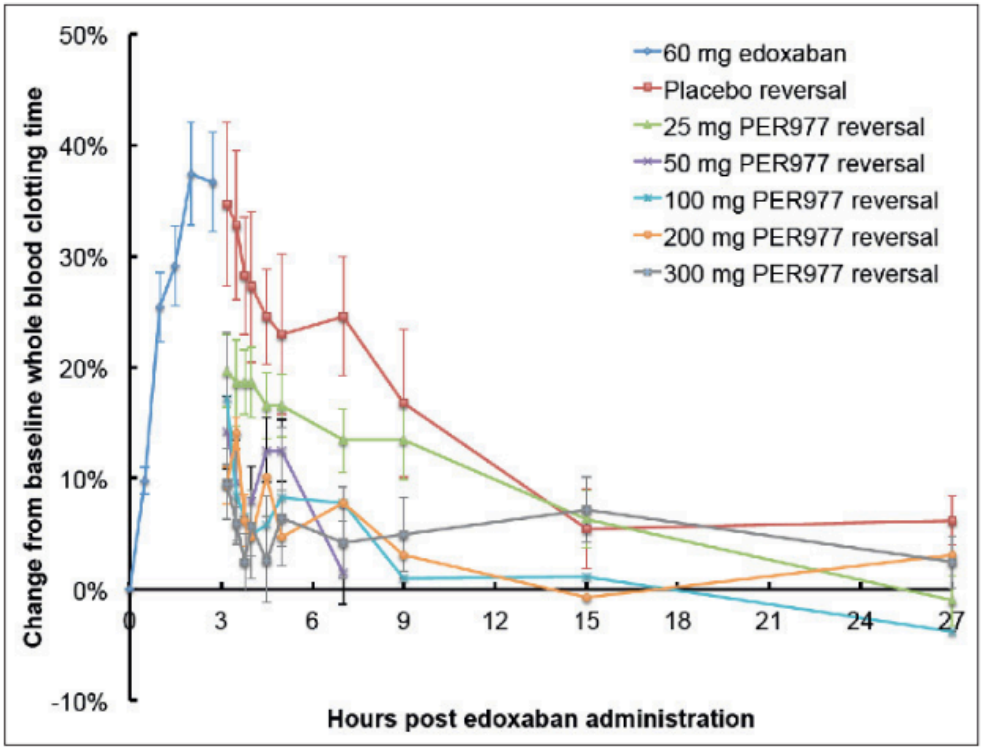
CIRAPARANTAG

Structure	Synthetic small molecule
Target	Direct Xa inhibitors, DTIs, UFH, LMWH (universal antidote)
Mechanism	Noncovalent hydrogen bind (exact mechanism unsure)
Current status	Phase 2 study ongoing

Hu TY. Vasc Health Risk Manag. 2016;12:35-44

Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban

Jack E. Ansell[1]; Sasha H. Bakhru[2]; Bryan E. Laulicht[2]; Solomon S. Steiner[2]; Michael A. Grosso[3]; Karen Brown[3]; Victor Dishy[3]; Hans J. Lanz[3]; Michele F. Mercuri[3]; Robert J. Noveck[4]; James C. Costin[2]



pathway inhibitor levels. In conclusion, ciraparantag in healthy subjects is safe and well tolerated with minor, non-dose limiting adverse events. Baseline haemostasis was restored from the anticoagulated state with doses of 100 to 300 mg ciraparantag within 10–30 minutes of administration and sustained for at least 24 hours.

Thromb Haemost 2017; 117: 238–245

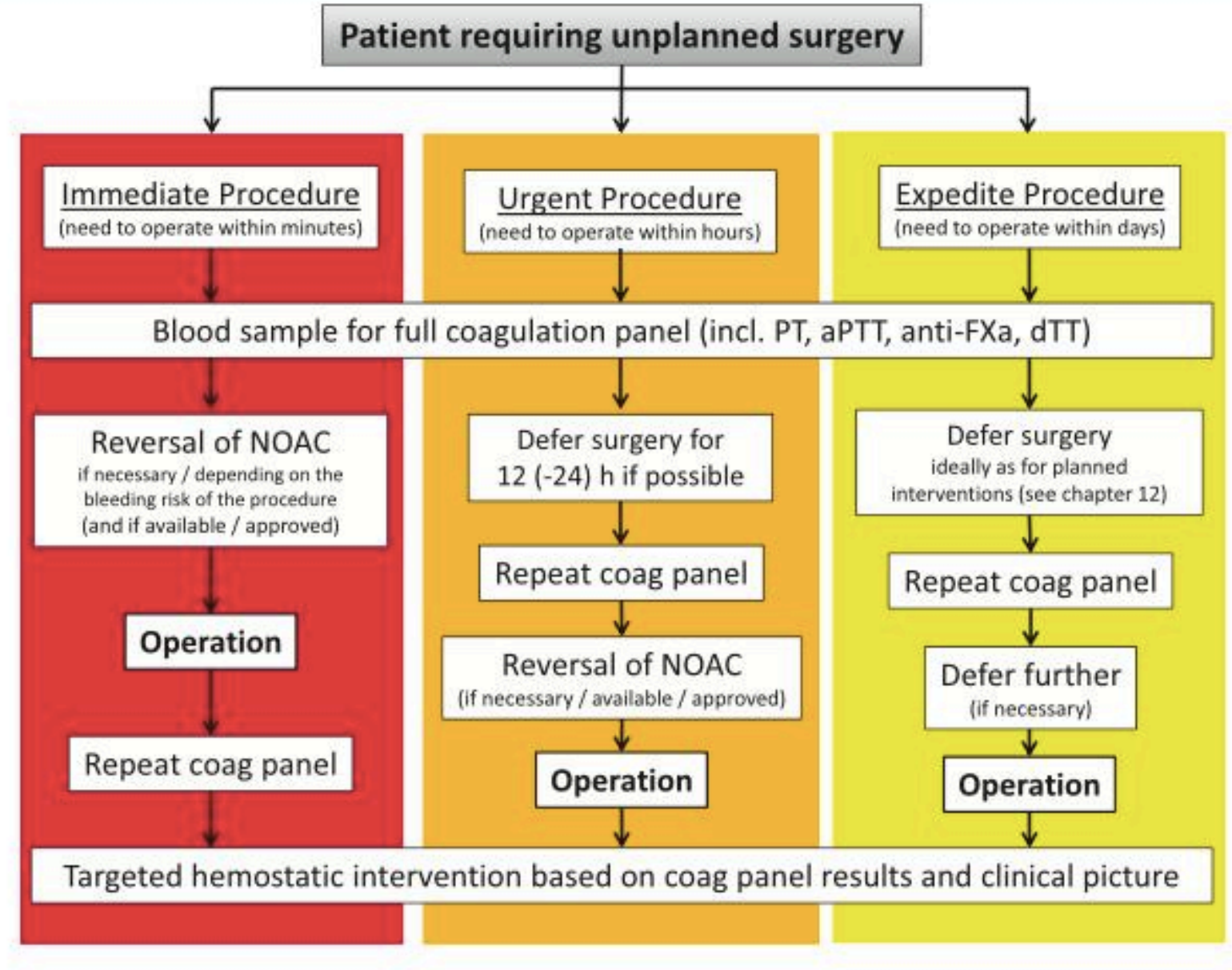
Quando considerare l'uso dell'antidoto?

- **Sanguinamento potenzialmente fatale e/o inarrestabile**
- **Procedura/intervento chirurgico in emergenza-urgenza**

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.



J.Steffel et al, European Heart Journal (2018) 00, 1–64

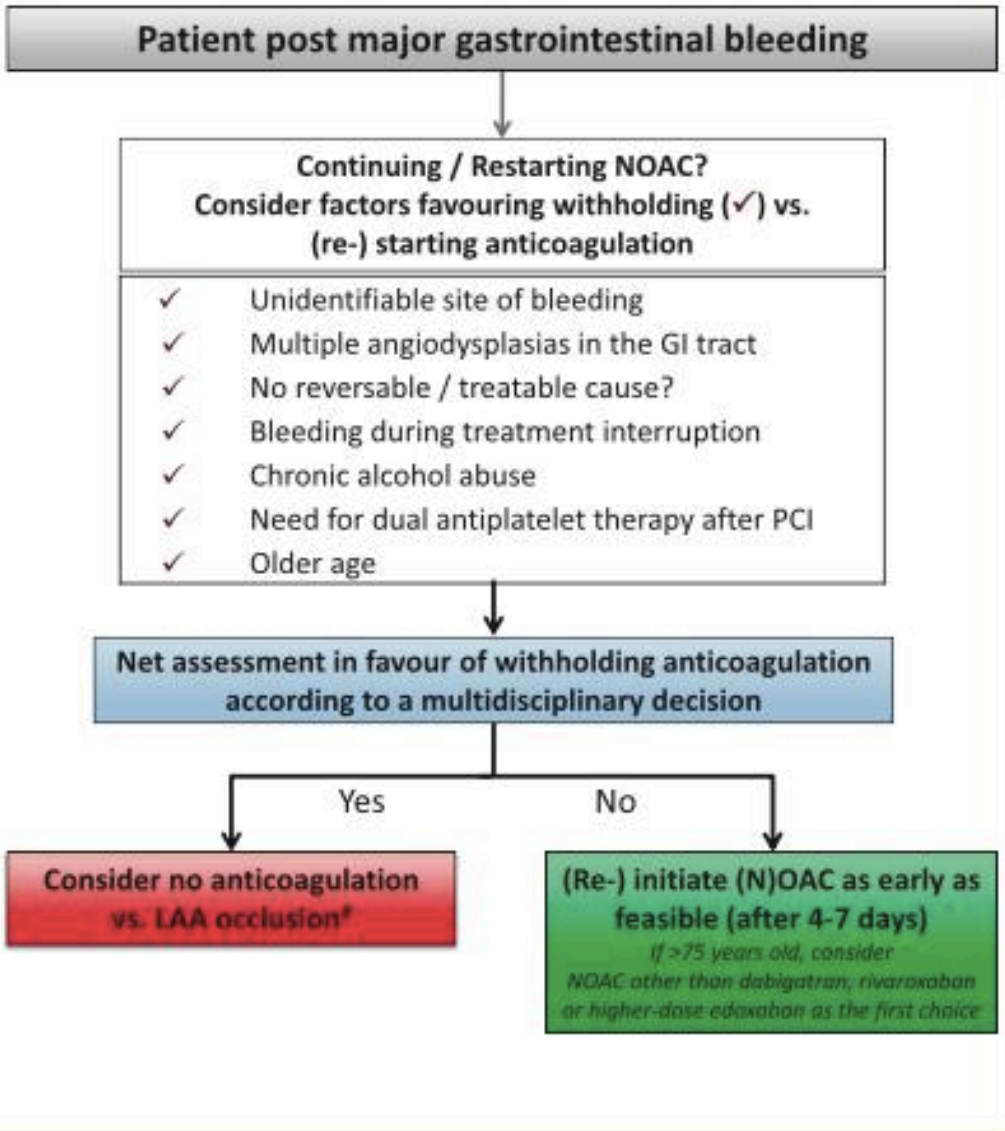


Figure 7 (Re-) initiation of anticoagulation post-gastrointestinal bleeding. #Without evidence; ideally include patient in ongoing trial.

J.Steffel et al, European Heart Journal (2018) 00, 1–64

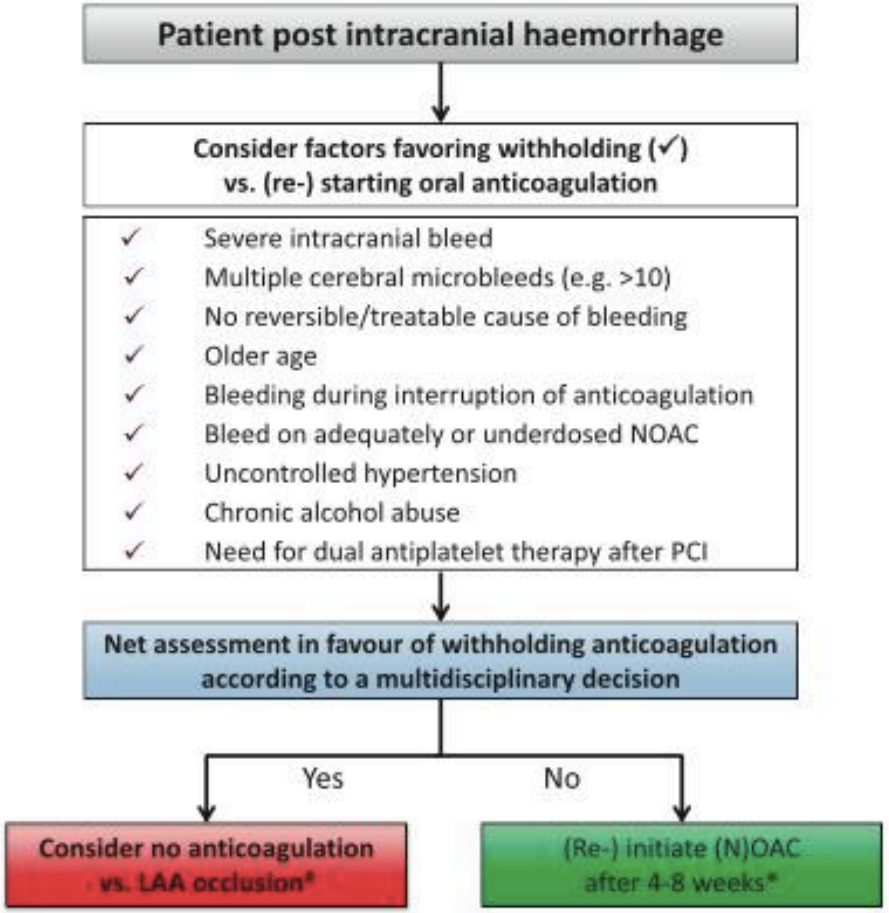
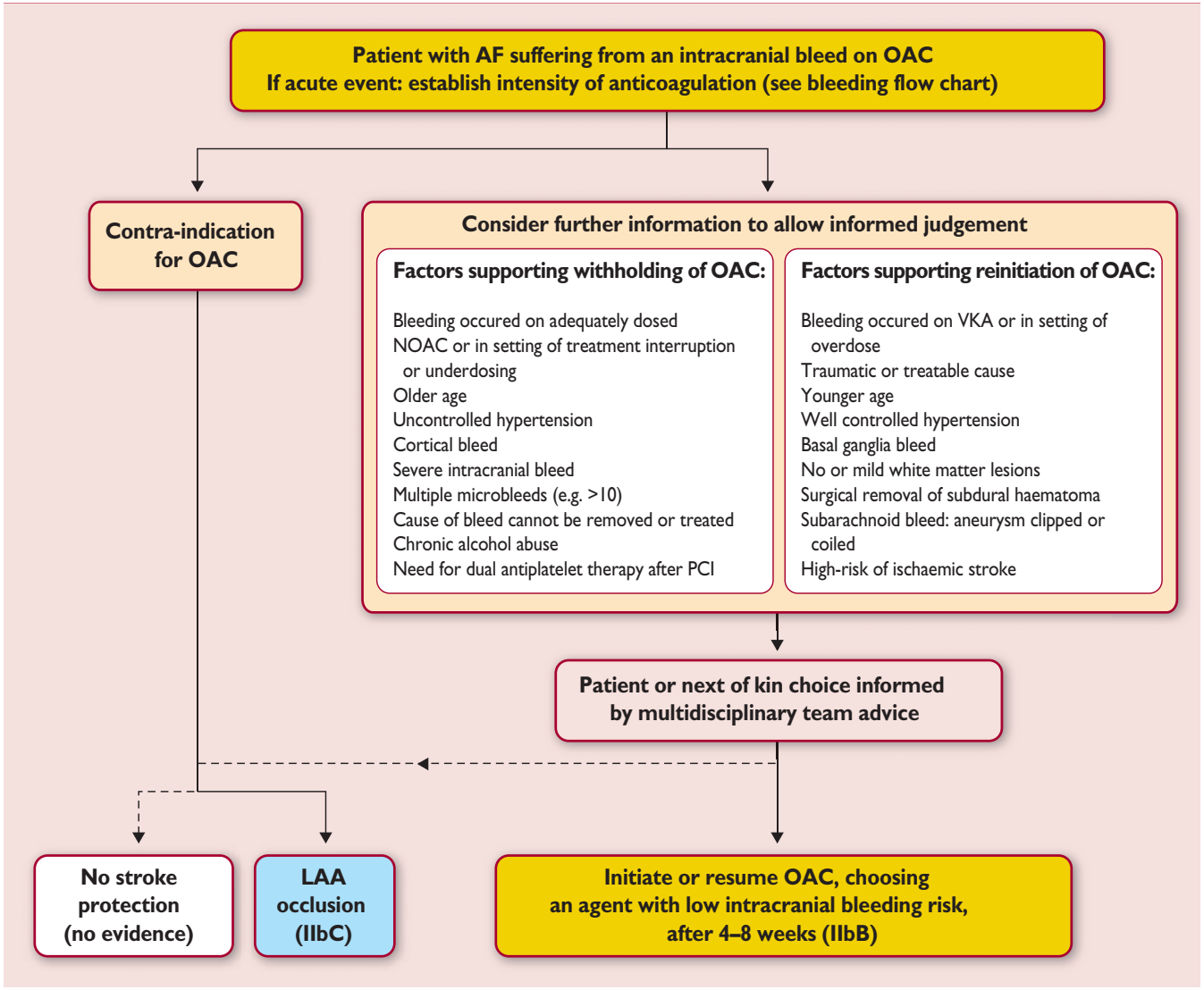


Figure 15 (Re-) initiation of anticoagulation post intracranial bleeding. #Without evidence; ideally include the patient in an ongoing trial. *Brain imaging (CT/MRI) should be considered before (re-)initiation of (non)-vitamin K antagonist oral anticoagulant.

J.Steffel et al, European Heart Journal (2018) 00, 1–64

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



European Heart Journal (2016) 37, 2893–2962

RESEARCH REVIEW

Reversal Agents: What We Have and What We Can Expect

CHRISTIAN T. RUFF, MD, MPH[1]

ited than expected. Patients with serious bleeding often have an anatomic cause for the bleeding due to a compromise in vascular integrity. Although the presence of an anticoagulant may exacerbate the problem, reversing the anticoagulant effect does not address the primary cause of the bleed. This is reflected in the high 30-day mortality rate of
ANNE

"Wait and See Strategy"

The most important impact of the availability of NOAC-specific reversal agents will likely be reassurance, since serious bleeding with NOAC usage is uncommon. The vast majority of bleeds can be managed conservatively with temporary discontinuation of NOACs and supportive measures—time is the only "antidote" required in most cases. Guidelines and institutional pro-

J Inn Card Rhytm Manag 9(2018), 3108-3114

“Ricordati che il miglior medico è la natura: guarisce i due terzi delle malattie e non parla male dei colleghi”.

Galeno 129-216 d.c.