XI congresso nazionale

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Il paziente con sanguinamento gastroenterico in terapia con NAO...al PS

Alessandro Cipriano
U.O. Medicina d'Urgenza e Pronto Soccorso - Azienda Ospedaliero-Universitaria Pisana

DOACs vs Warfarin: alcune Certezze!

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Ictus ed Embolismo Sistemico

DOACs **vs** Warfarin

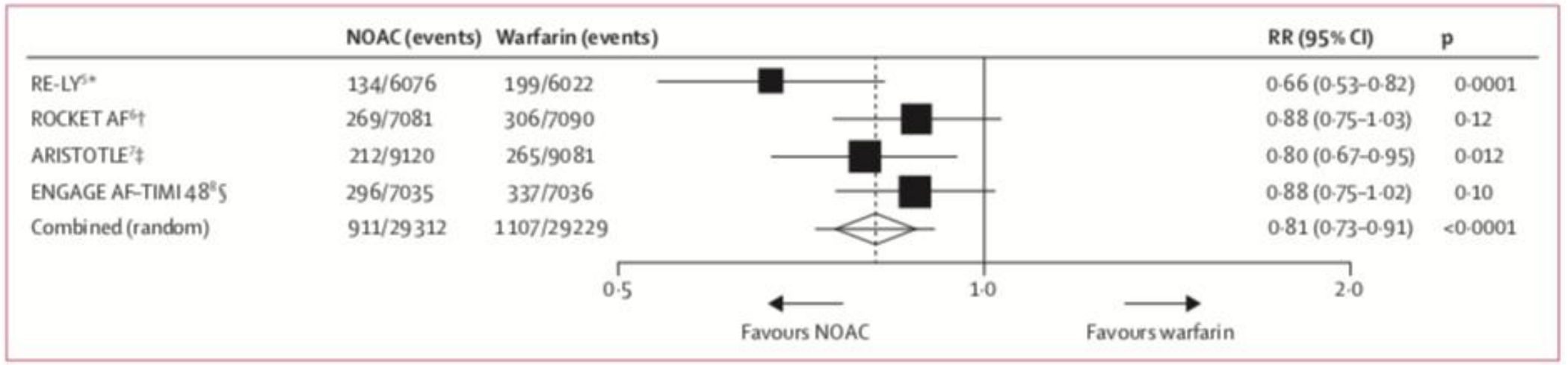


***Figure 1*: Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Ruff CT et al. Lancet. 2014 Mar 15;383(9921):955-62

Sanguinamenti Maggiori

DOACs **vs** Warfarin

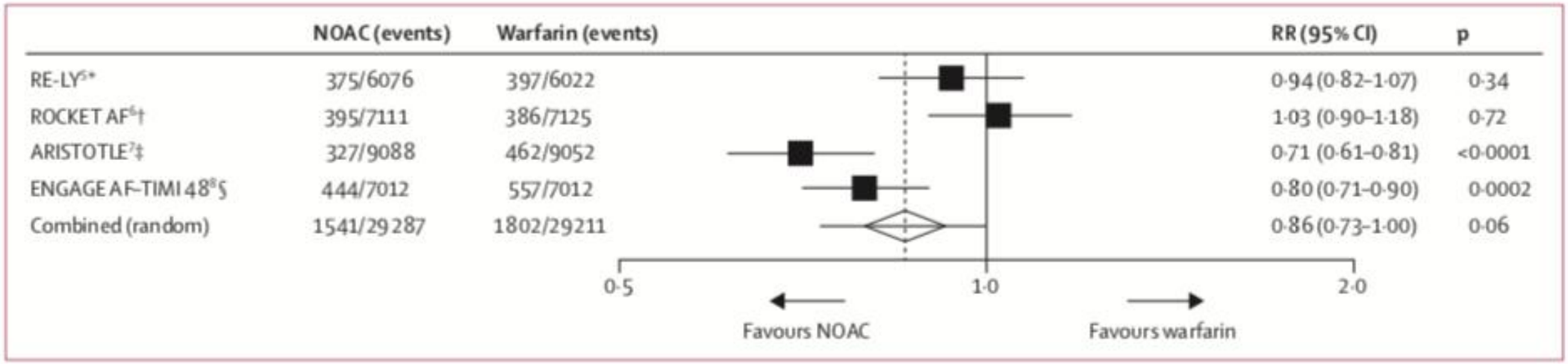


***Figure 3*: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

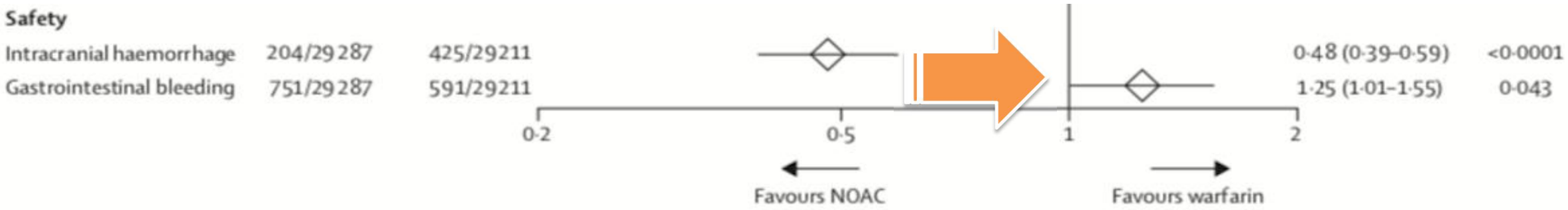
Ruff CT et al. Lancet. 2014 Mar 15;383(9921):955-62

Il Tallone di Achille...

Morte di Achille, particolare, G. Hamilton, olio su tela, 1785

Sanguinamenti Gastrointestinali

DOACs **vs**Warfarin



Sanguinamenti Gastrointestinali

DOACs **vs**Warfarin

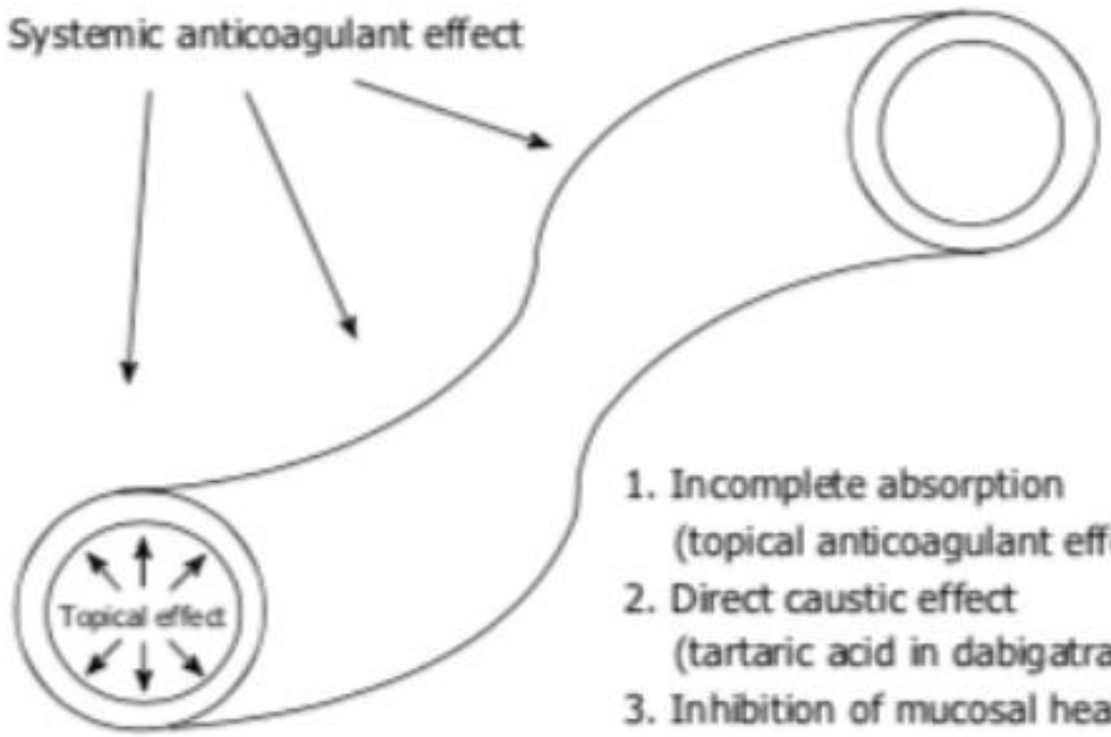


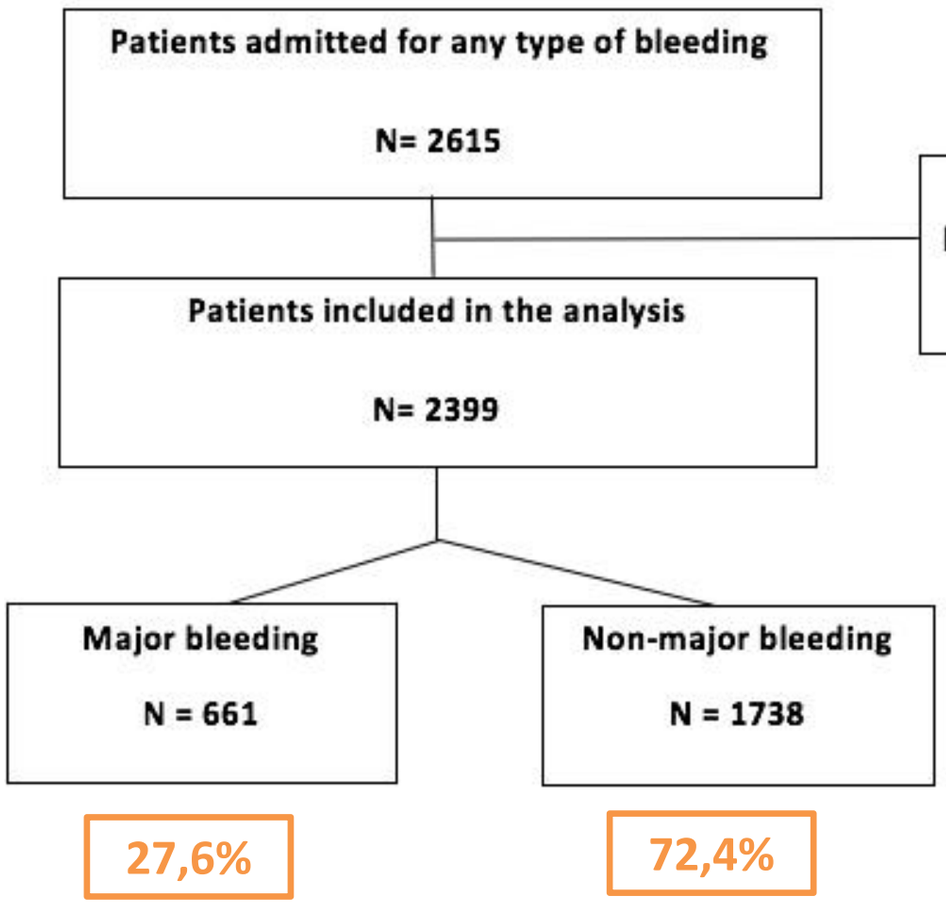
Figure 1 Pathogenesis of novel oral anticoagulant-related gastrointestinal bleeding. NOAC: Novel oral anticoagulant; GIB: Gastrointestinal bleeding.

Cheung KS et al. World J Gastr. 2017 March 21; 23(11): 1954-1963

Sanguinamenti Gastrointestinali

Le dimensioni del problema?

1 Jan 2016 - 31 Dec 2016



ISTH major bleeding in non-surgical patients#:

1. **Fatal** bleeding, and/or
2. Bleeding in a **critical area or organ** (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome) and/or
3. Bleeding causing a **fall in hemoglobin level of 2 g/dl** or more, or leading t transfusion of **2 or more units of whole blood or red cells.**

Cipriano A. et al. in press

#Schulman S, Kearon C, J Thromb Haemost 2005; 3: 692–4.

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Sanguinamenti in PS

Le dimensioni del problema

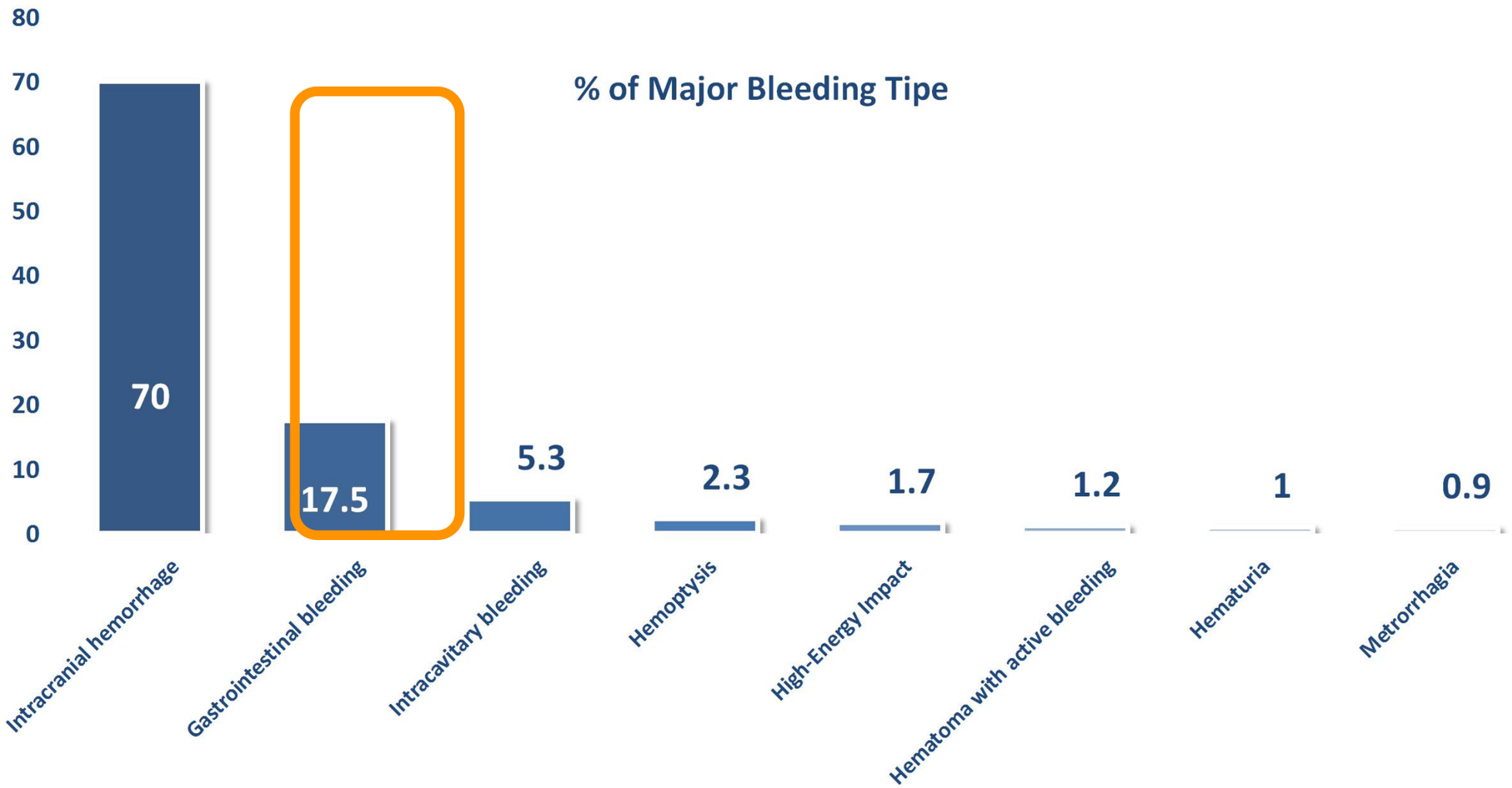
Population and Outcome

- Mean Age **70 yr**
- **ER Mortality**: **1,2%** (8 pts on a total of 661 [95% CI 0,3 %- 2%])
- Mortality was significantly associated with **multiple trauma** ($p < 0,001$)
- Mortality **during hospital stay was of 15,9%**
  (99 pts on a total of 621 admitted patients [95% CI 13 %- 18,8 %]
- Not significantly associated with the **site of bleeding.**

Cipriano A. et al. in press

Sanguinamenti Gastrointestinali

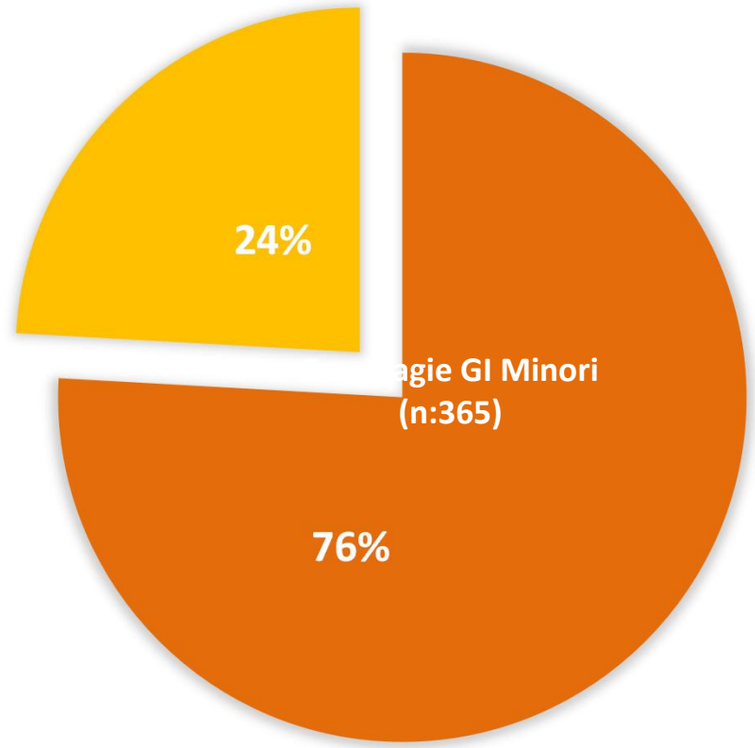
Davvero un problema?



Cipriano A. et al. in press

Sanguinamenti Gastrointestinali in PS

Le dimensioni del problema



n: 481 total GI Bleeding

Cipriano A. et al. in press

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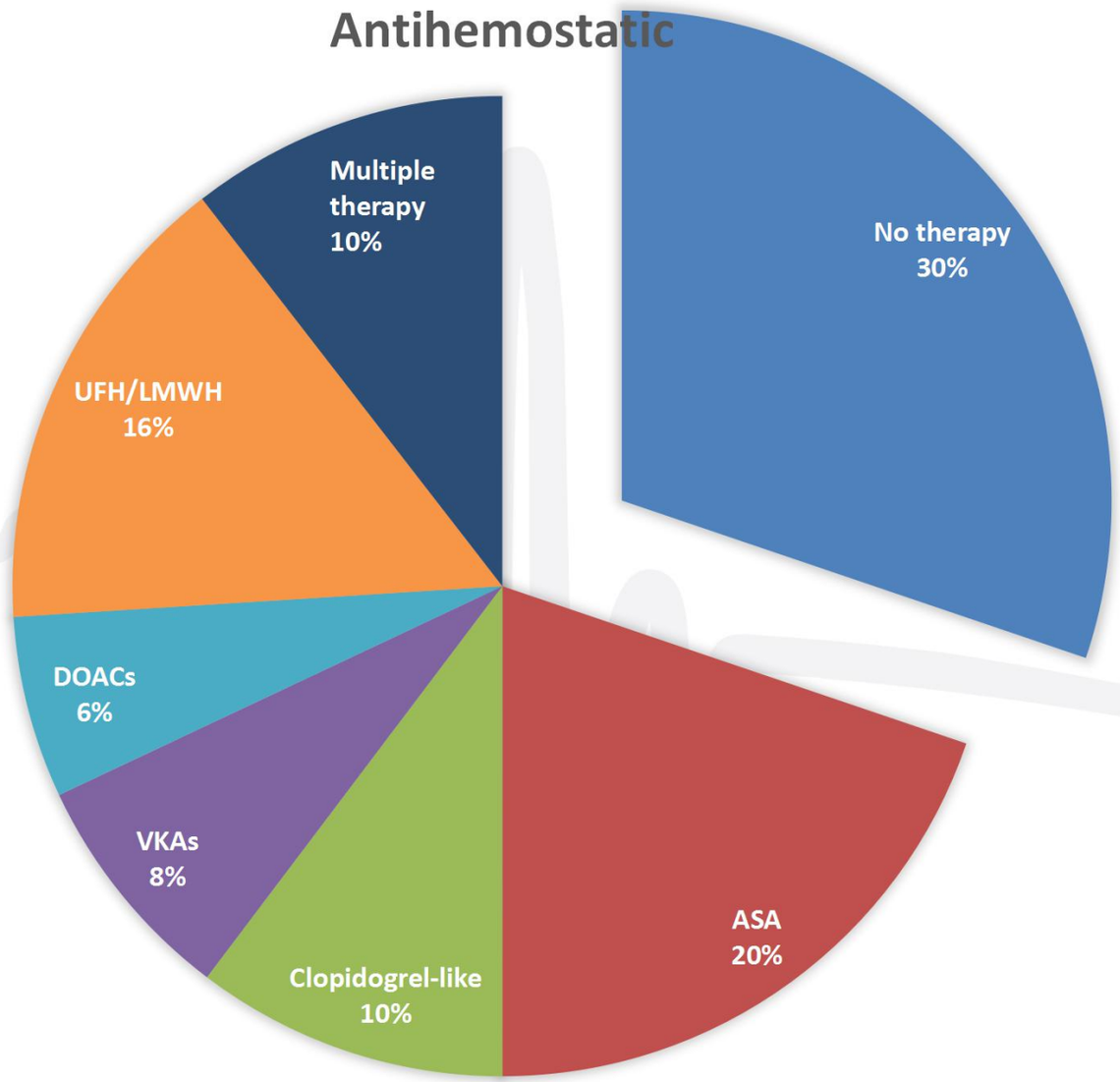
Sanguinamenti Gastrointestinali

Ruolo dei Farmaci Antiemostatici

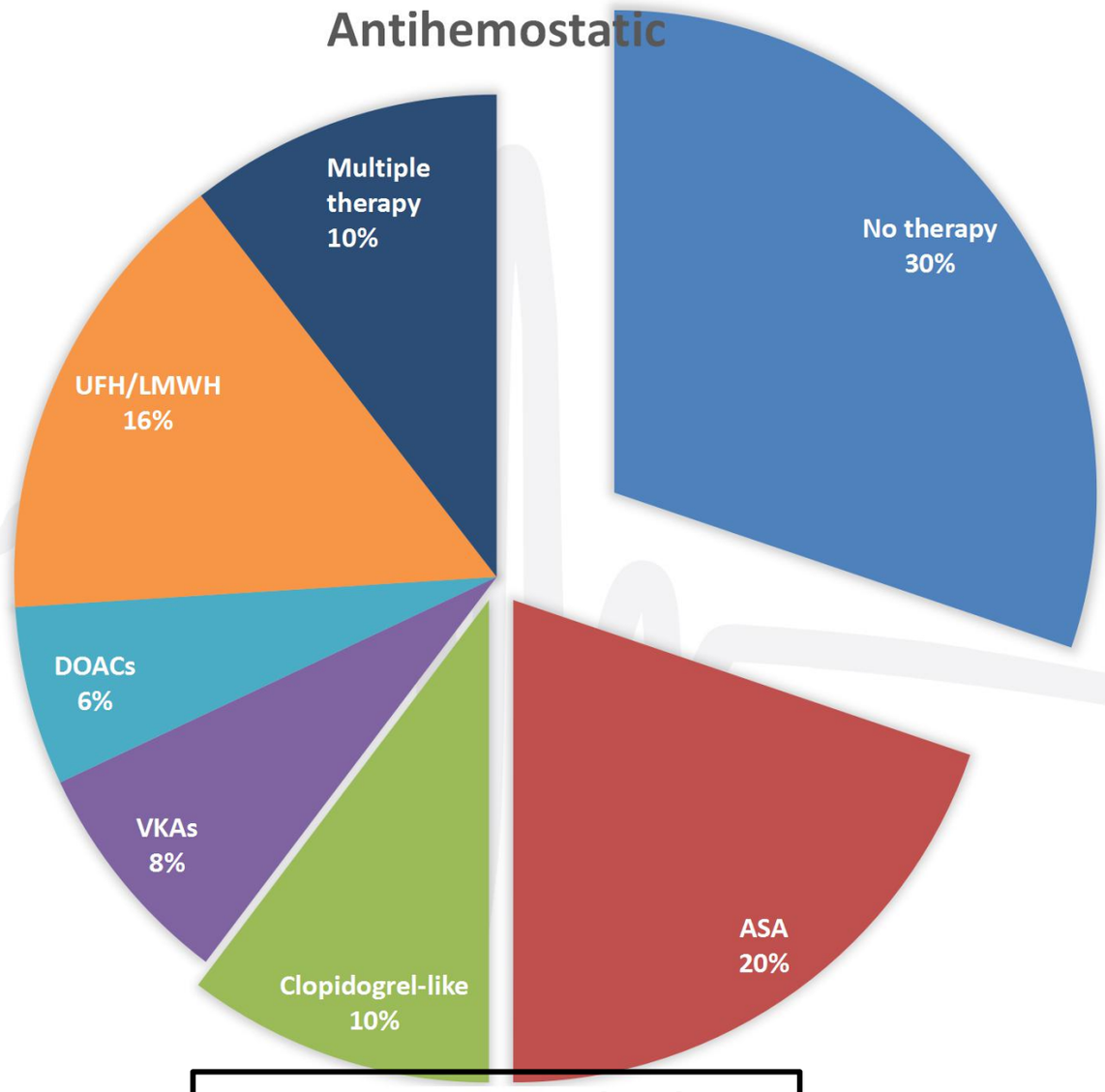


n: 116 GI Major Bleeding

Cipriano A. et al. in press

Sanguinamenti Gastrointestinali

Ruolo dei Farmaci Antiemostatici

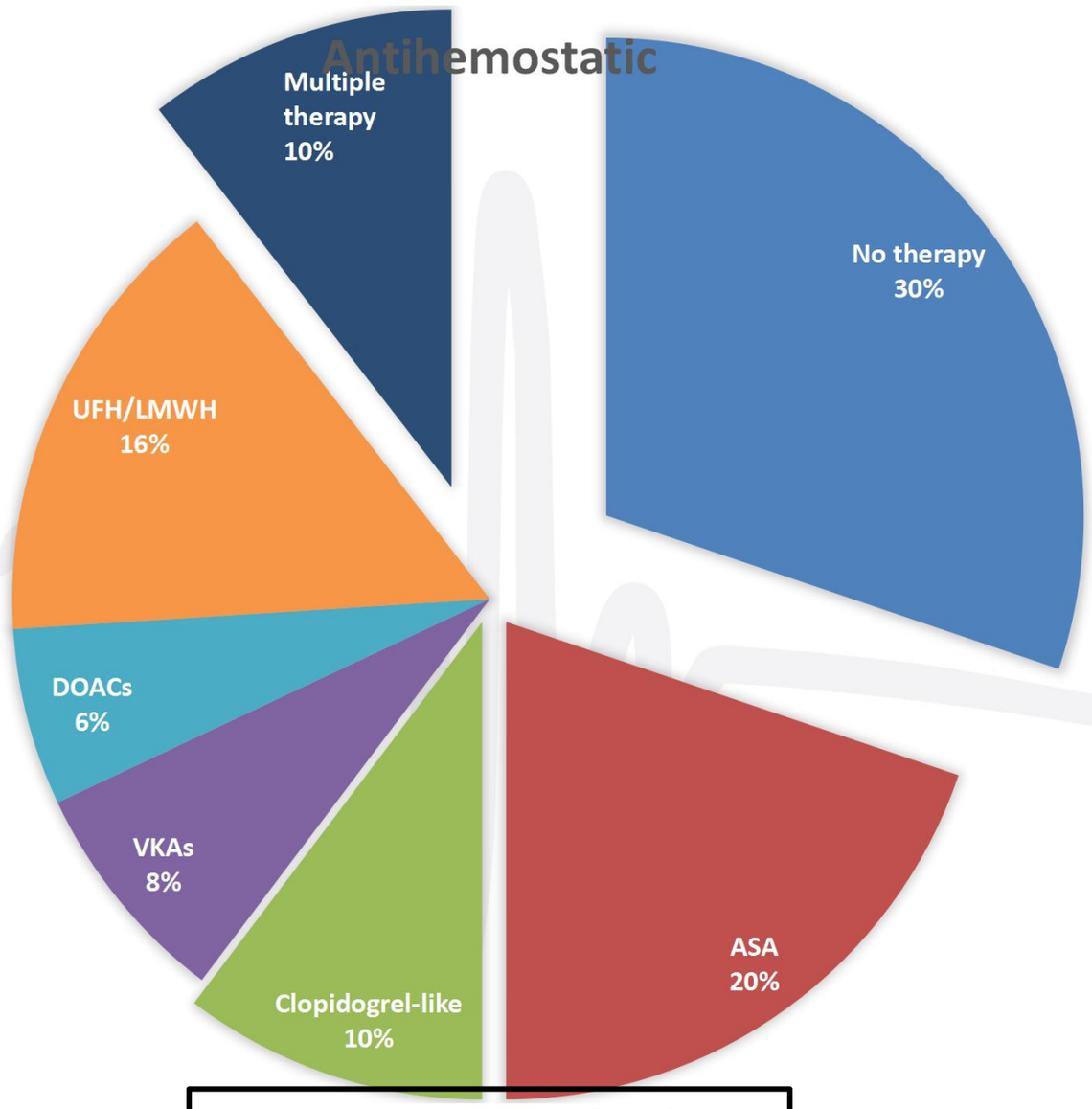


n: 116 GI Major Bleeding

Cipriano A. et al. in press

Sanguinamenti Gastrointestinali

Ruolo dei Farmaci Antiemostatici

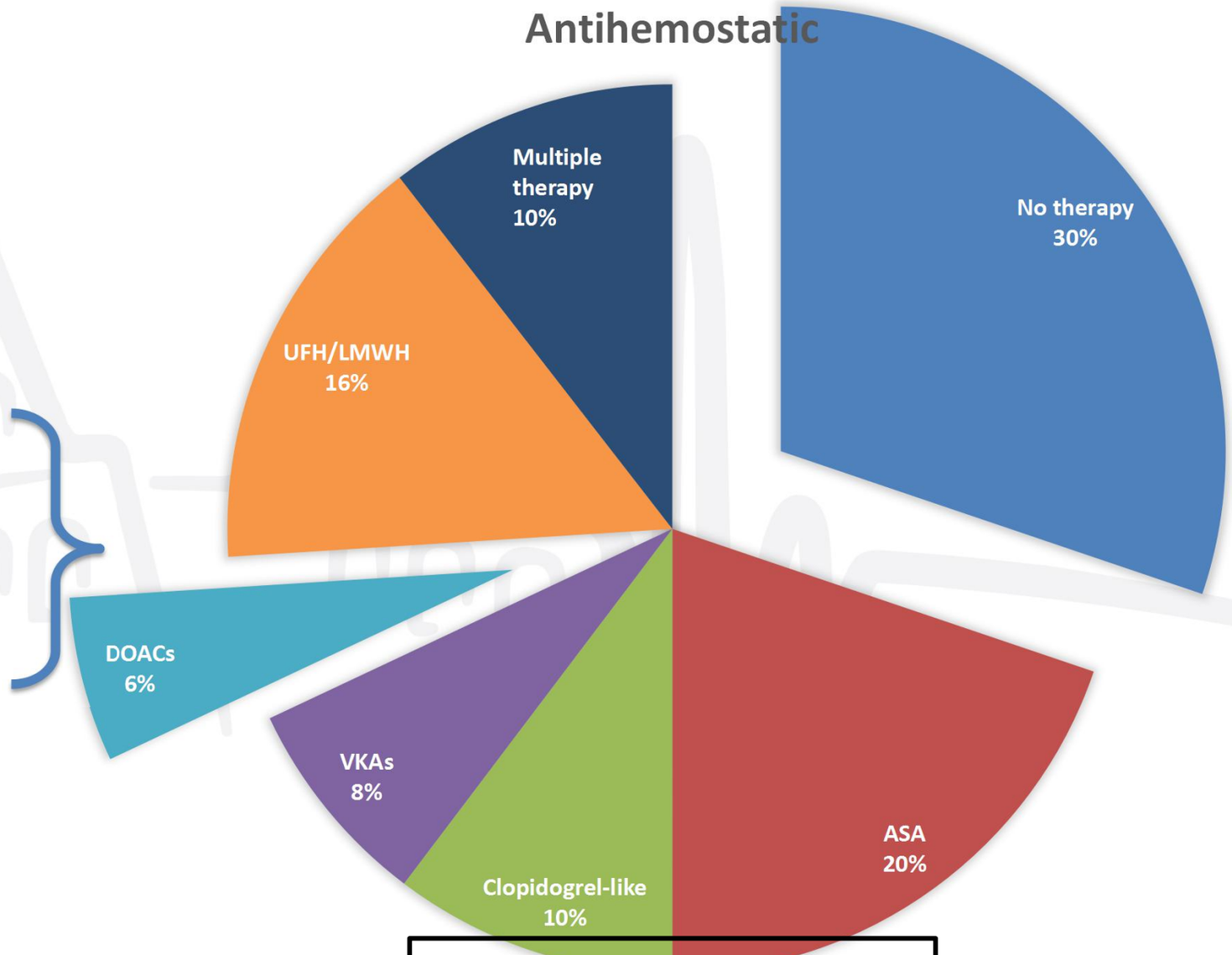


n: 116 GI Major Bleeding

Cipriano A. et al. in press

Sanguinamenti Gastrointestinali

Ruolo dei Farmaci Antiemostatici

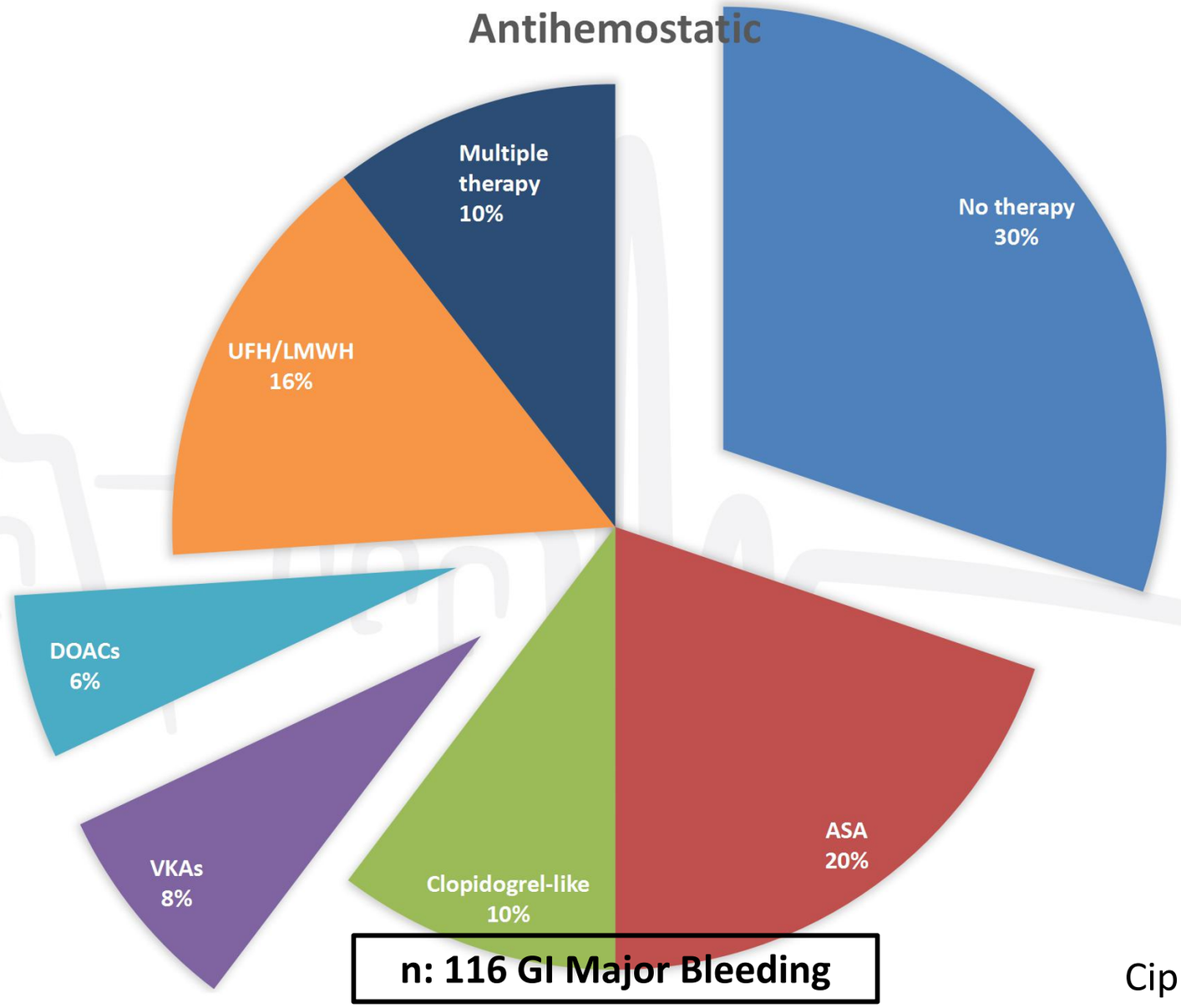


n: 116 GI Major Bleeding

Cipriano A. et al. in press

Sanguinamenti Gastrointestinali

Ruolo dei Farmaci Antiemostatici

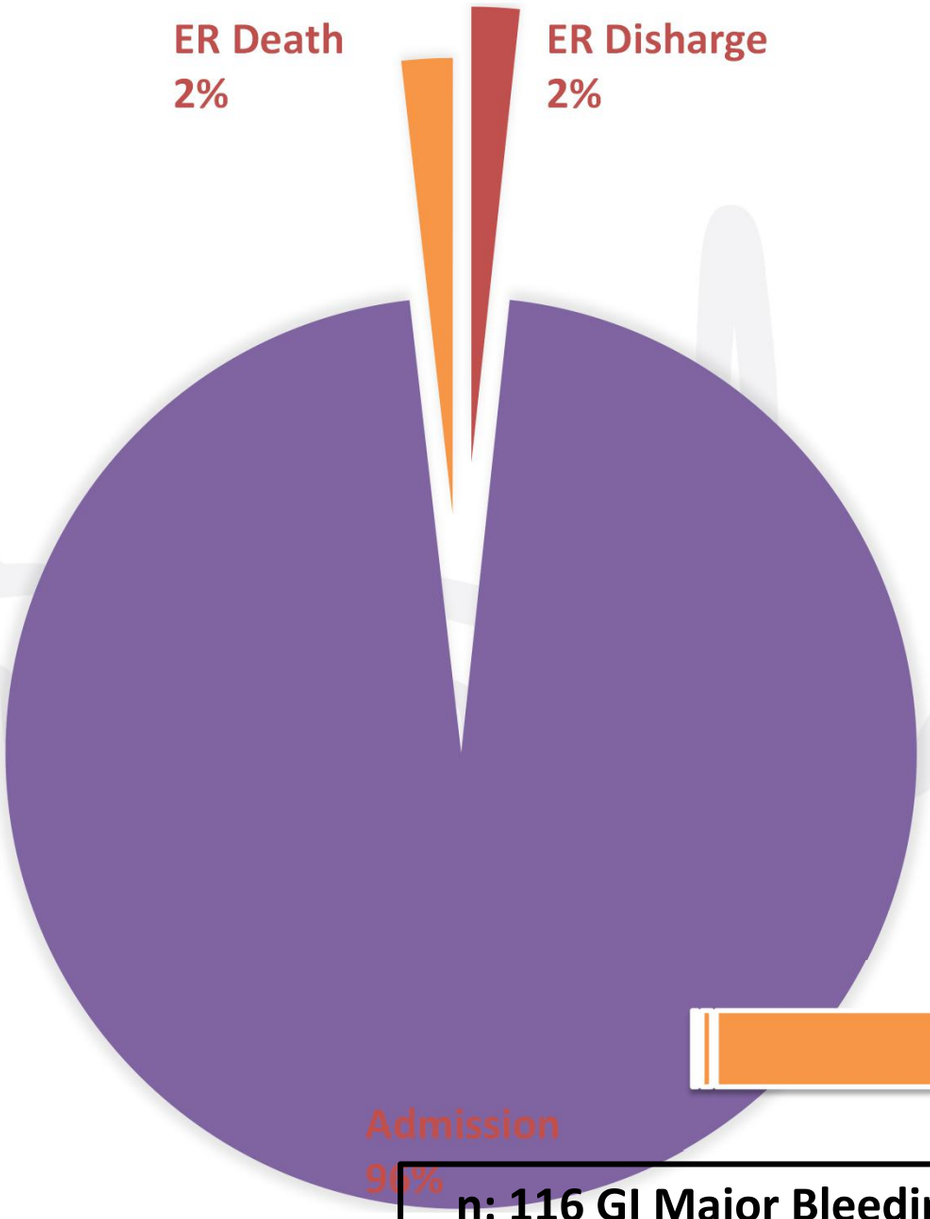


n: 116 GI Major Bleeding

Cipriano A. et al. in press

Sanguinamenti Gastrointestinali

Mortalità



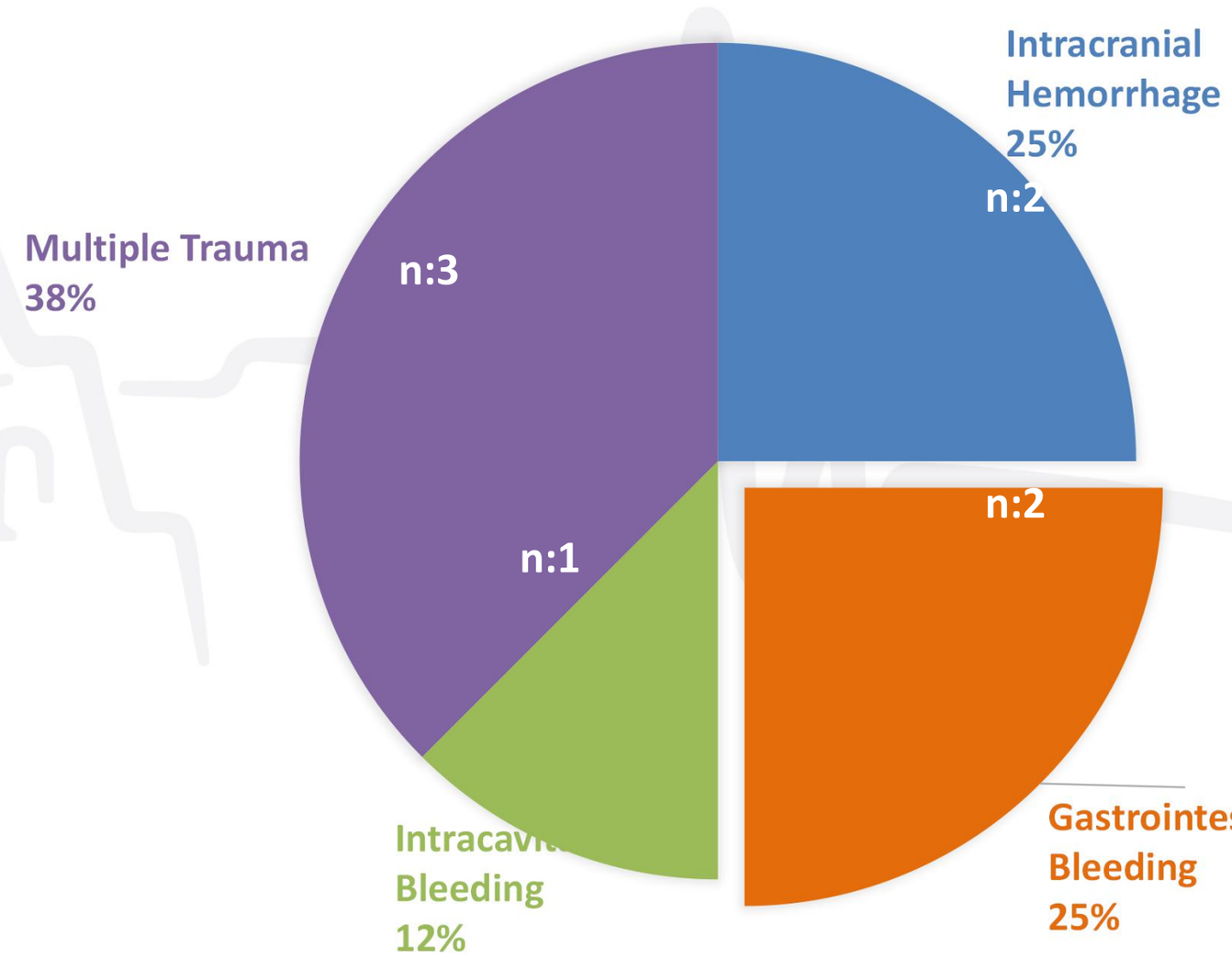
n: 116 GI Major Bleeding

10,7% died (n: 12)

Cipriano A. et al. in press

Sanguinamenti & Sanguinamenti

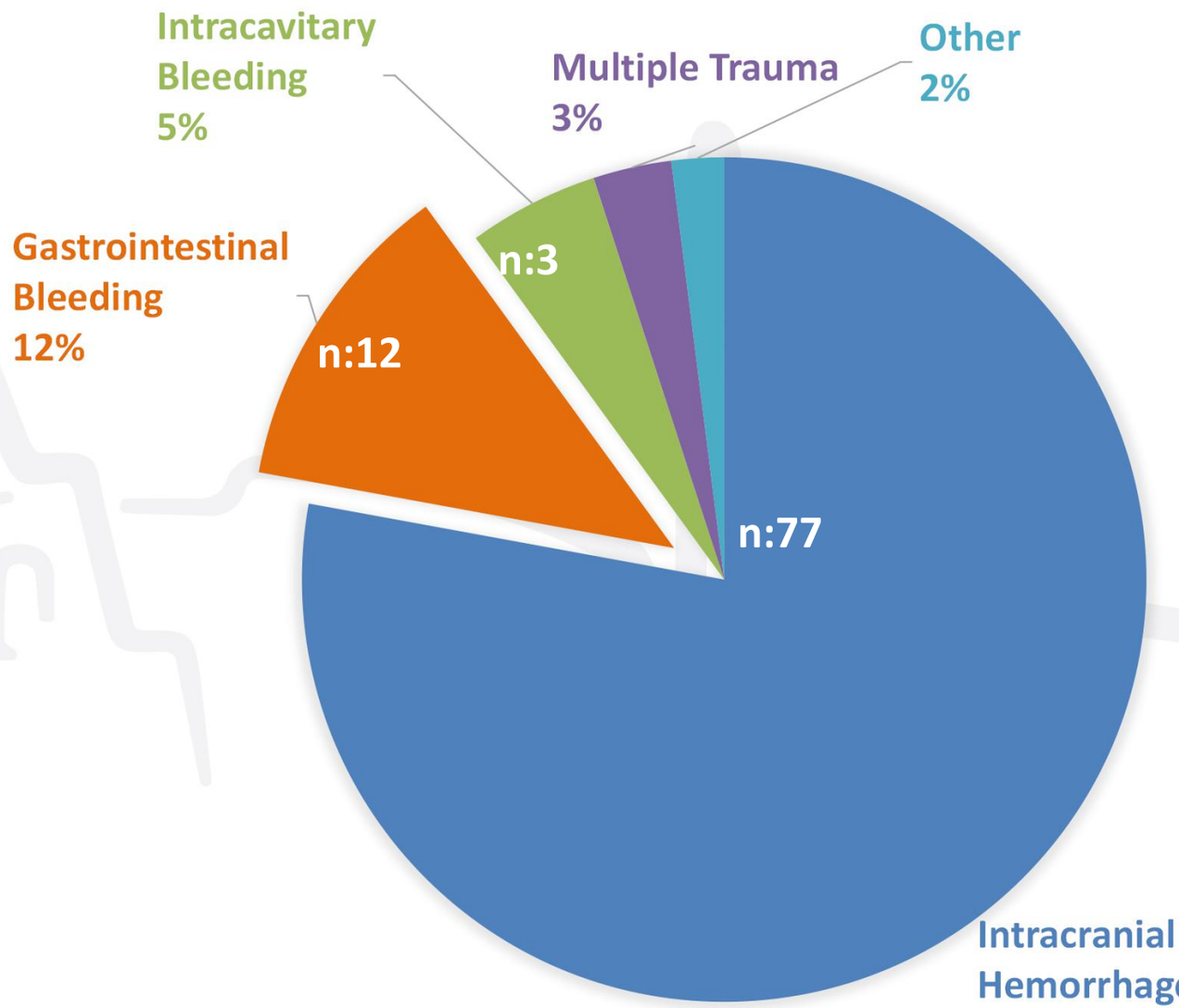
Pochi ma buoni!



Cipriano A. et al. in press

Sanguinamenti & Sanguinamenti

Pochi ma buoni!

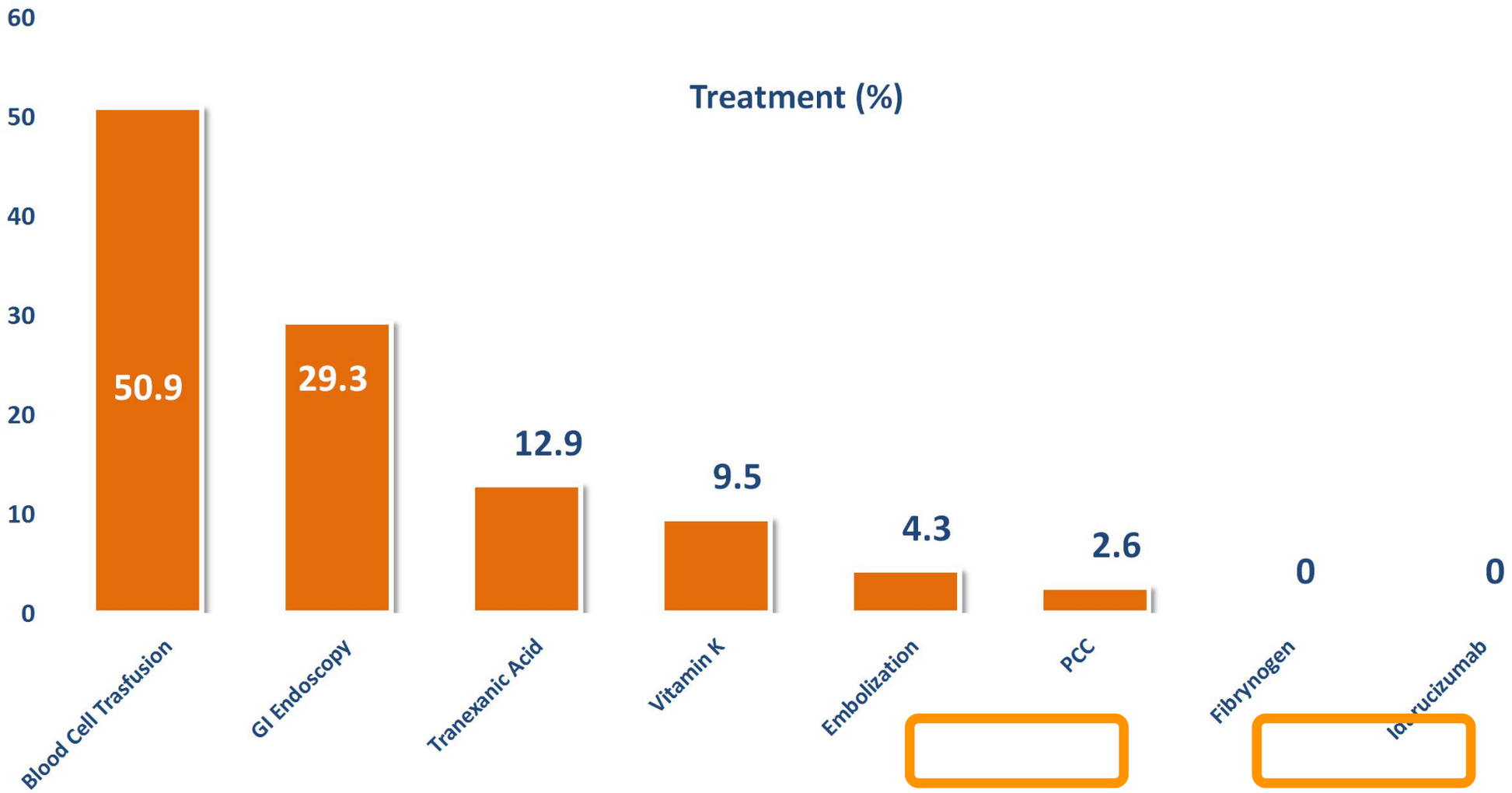


99 Decessi Totali durante il ricovero

Cipriano A. et al. in press

Sanguinamenti Gastrointestinali

Trattamento



n: 116 GI Major Bleeding

Cipriano A. et al. in press

Sanguinamenti Gastrointestinali

Le dimensioni del problema

- Between **September 2013 and September 2015**
- 1019 patients with bleeding, **806 were adjudicated as having a MB**
- 615 patients were on VKAs (76%) and 191 (24%) on DOACs

Table 2
Sites of MB.

MBs	TOT (N = 806)	DOAC (N = 191)	VKA (N = 615)	OR 95% CI	p
Intracranial, n (%)	354 (44)	41 (21)	313 (51)	0.26 0.18–0.39	<0.001
Gastrointestinal, n (%)	239 (30)	88 (46)	151 (25)	2.62 1.87–3.68	<0.001
Soft/muscle, n (%)	80 (10)	11 (6)	69 (11)	0.48 0.25–0.93	0.027
Retroperitoneal, n (%)	33 (4)	2 (1)	31 (5)	0.20 0.05–0.84	0.015
Genito-urinary, n (%)	27 (3)	15 (8)	12 (2)	4.28 1.97–9.32	<0.001
Pleural/pericardial/ peritoneal, n (%)	21 (3)	5 (3)	16 (3)	1.01 0.36–2.78	ns
Articular, n (%)	18 (2)	9 (5)	9 (1)	3.33 1.30–8.51	0.008
Upper airways, n (%)	15 (2)	9 (5)	6 (1)	5.02 1.76–14.29	0.001
Ocular, n (%)	9 (1)	9 (5)	0	–	<0.001
Spinal, n (%)	5 (1)	0	5 (1)	–	ns
Other, n (%)	5 (1)				

Becattini C. et al. International Journal of Cardiology 227 (2017) 261–266

GI Bleeding and DOACs: sappiamo che fare?

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Sanguinamenti Gastrointestinali

Gli assi nella manica del medico d'urgenza

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 pa… non-valvular atrial fibrillation

EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

RESEARCH

The European guideline on management … major bleeding and coagulopathy following trauma: fourth edition

Rolf Rossaint[1], Bertil Bouillon[2], Vladimir Cerny[3,4,5,6], Timothy J. Coats[7], Jacques Duranteau[8], Enrique Fernández-Mondéjar[9], Daniela Filipescu[10], Beverley J. Hunt[11], Radko Komadina[12], Giusep… Edmund A. M. Neugebauer[14], Yves Ozier[15], Louis Riddez[16], Arthur Schultz[17], Jean-Louis Vincent[18] and Donat R. Spahn[19*]

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 1330–1393
doi:10.1093/eurheartj/ehy136

SPECIAL ARTICLE

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

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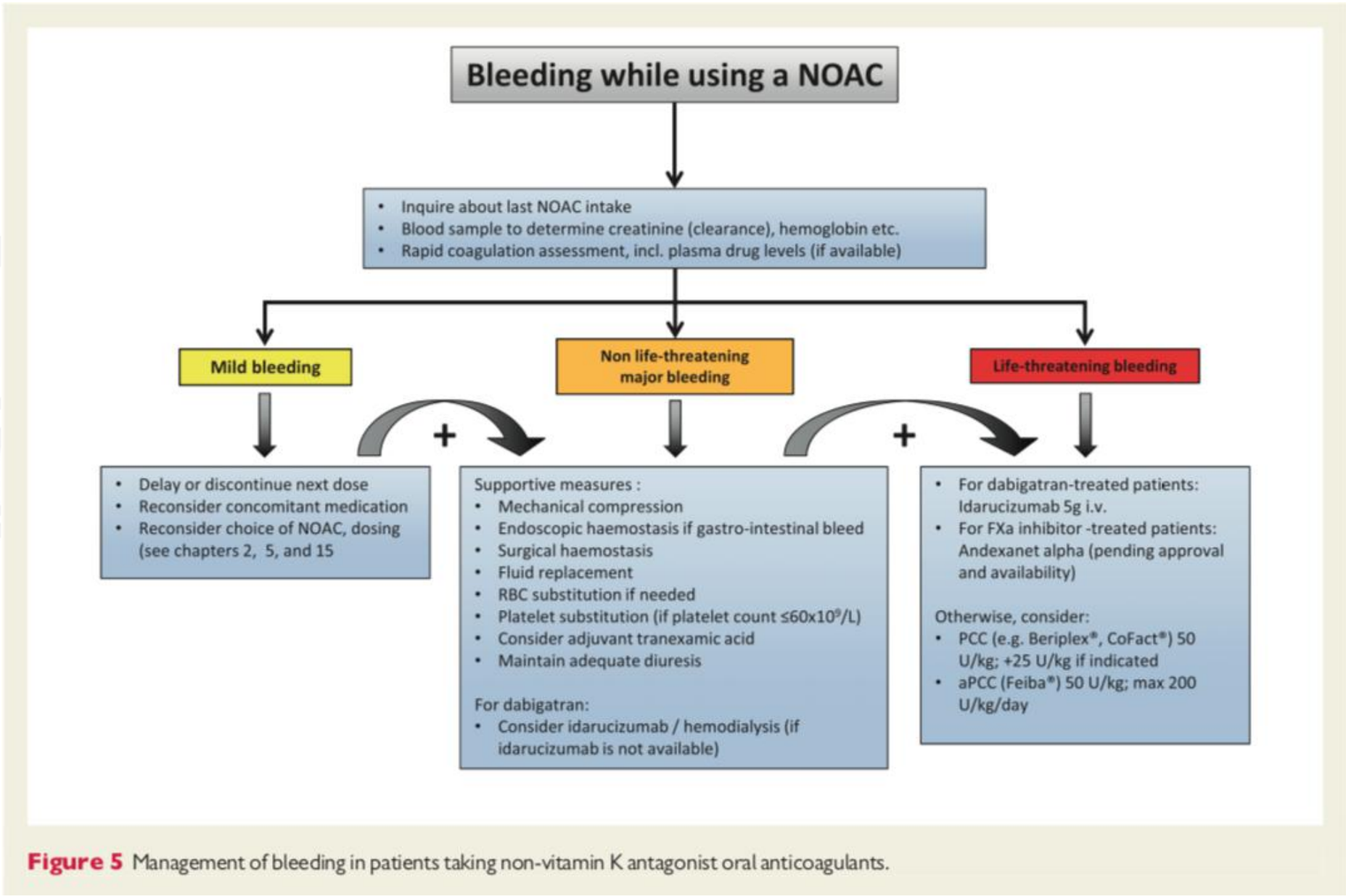

Figure 5 Management of bleeding in patients taking non-vitamin K antagonist oral anticoagulants.

Steffel J et al. ESC Scientific Document Group .
Eur Heart J. 2018 Apr 21;39(16):1330-1393

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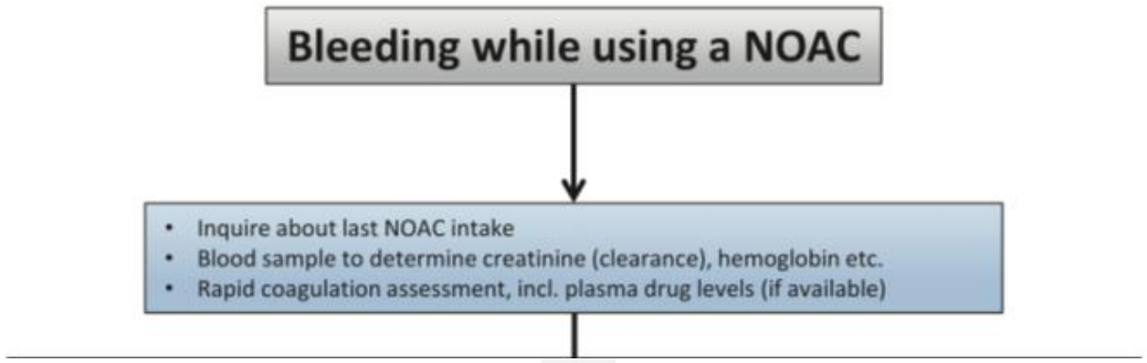

Coagulation normalized:

Dabigatran

Normal:	12–24h
CrCl 50–80 ml/min:	24–36h
CrCl 30–50 ml/min:	36–48h
CrCl < 30 mL/min:	≥48 h

Anti-Xa

12-24 h form last intake

Steffel J et al. ESC Scientific Document Group .
Eur Heart J. 2018 Apr 21;39(16):1330-1393

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	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
aPTT	✓ (1)	✗	✗	✗
TT	✓ (2)	✗	✗	✗
Diluited Trombin Time (dTT) Ecarin Clotting Time (ECT)	✓ (3)	✗	✗	✗
Anti-FXa assays (calibrated)	✗	✓	✓	✓
PT	✗	✓ (4)	✗ (5)	✓ (4)
INR	✗	✗	✗	✗
ACT	✓ (6)	✗	✗	✗

1. Indagine Qualitativa, nei valori normali non esclude la presenza di Dabigatran, anche se con test sensibili, se >2-3 volte UNL a valle, ↑rischio sang.
2. **Ottimo qualitativo per escluderne la presenza**, non quantitativo
   Valori normali escludono l'effetto di Dabigatran, **valori alti NON stimano la diatesi emorragica**
3. Correlazione quantitativa, **ottimo per escluderne la presenza**
4. Corr. in maniera lineare, Neoplastin Plus® or Neoplastin ® ok per Rivaroxaban, Innovin® (EU) non correlato a Rivaroxaban, **valori normali NON escludono la presenza del farmaco**
5. Insensibile ad Apixaban, **valori normali NON eslcudono la presenza del farmaco**
6. Correlazione Lineare, non studi clinici al momento, correlato a dose ENF

Steffel J et al. ESC Scientific Document Group . Eur Heart J. 2018 Apr 21;39(16):1330-1393

Partiamo dalle Linee Guida

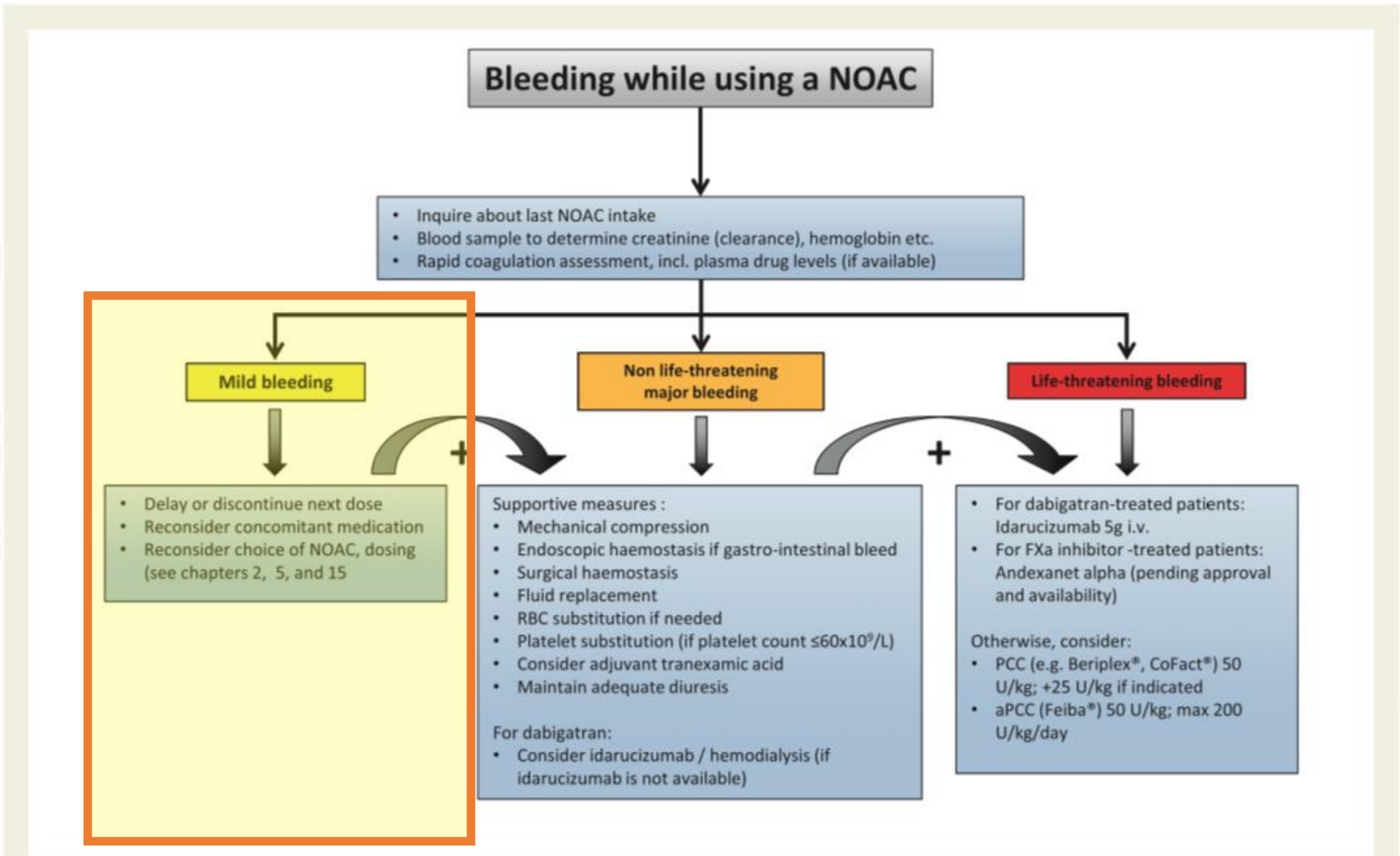

Figure 5 Management of bleeding in patients taking non-vitamin K antagonist oral anticoagulants.

Steffel J et al. ESC Scientific Document Group .
Eur Heart J. 2018 Apr 21;39(16):1330-1393

Partiamo dalle Linee Guida

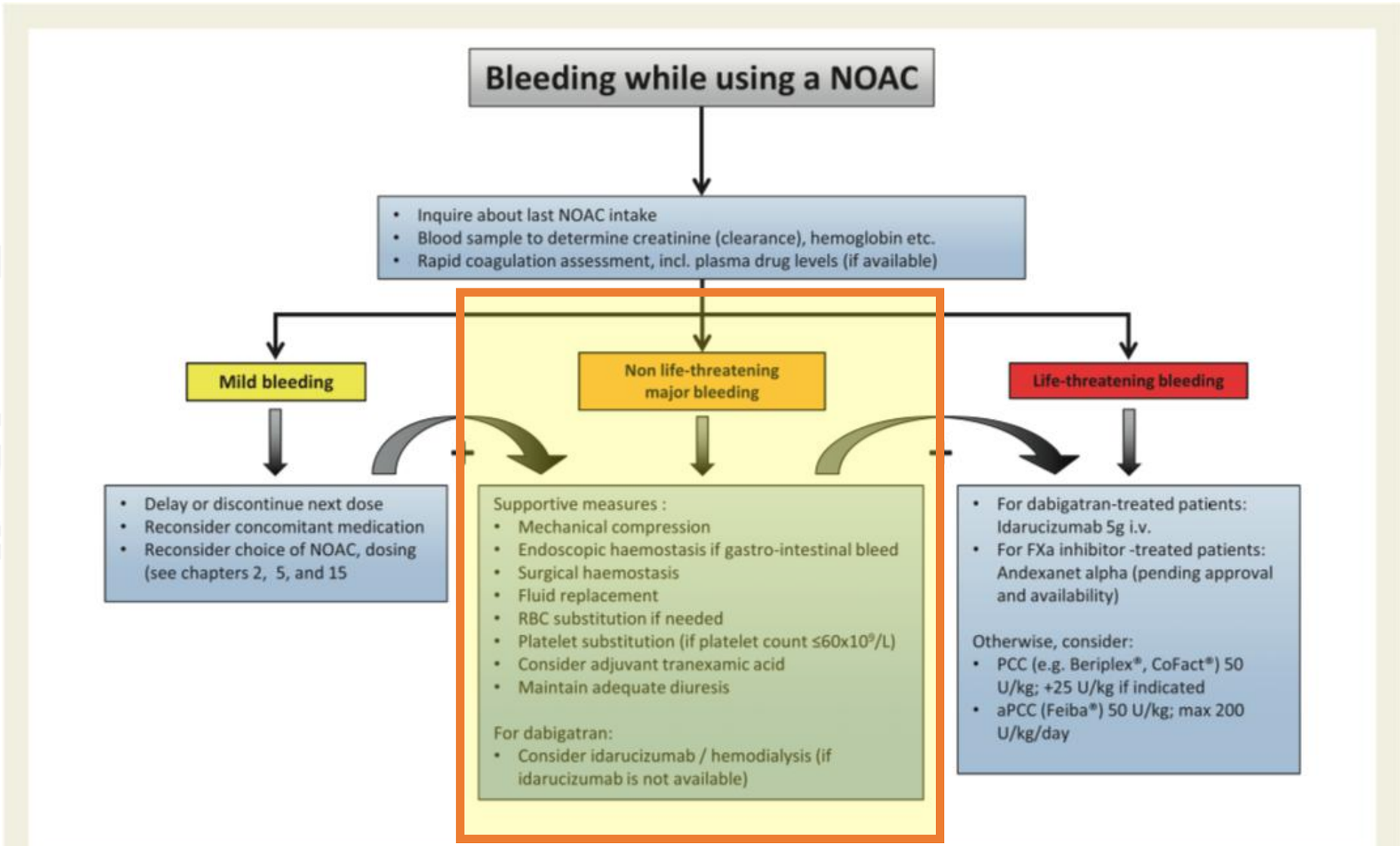

Figure 5 Management of bleeding in patients taking non-vitamin K antagonist oral anticoagulants.

Steffel J et al. ESC Scientific Document Group .
Eur Heart J. 2018 Apr 21;39(16):1330-1393

Il Miglior **ANTIDOTO**
è il **TEMPO**!

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Il Tempo Conta

Events	Time
First onset of bleeding and arrival at the ER	33 ± 42 h
Arrival in the ER and **Endoscopy**	14 ± 16 h

Deutsh D. et al. Ther Adv Gastroenterol 2017, Vol. 10(6) 495–505

Partiamo dalle Linee Guida

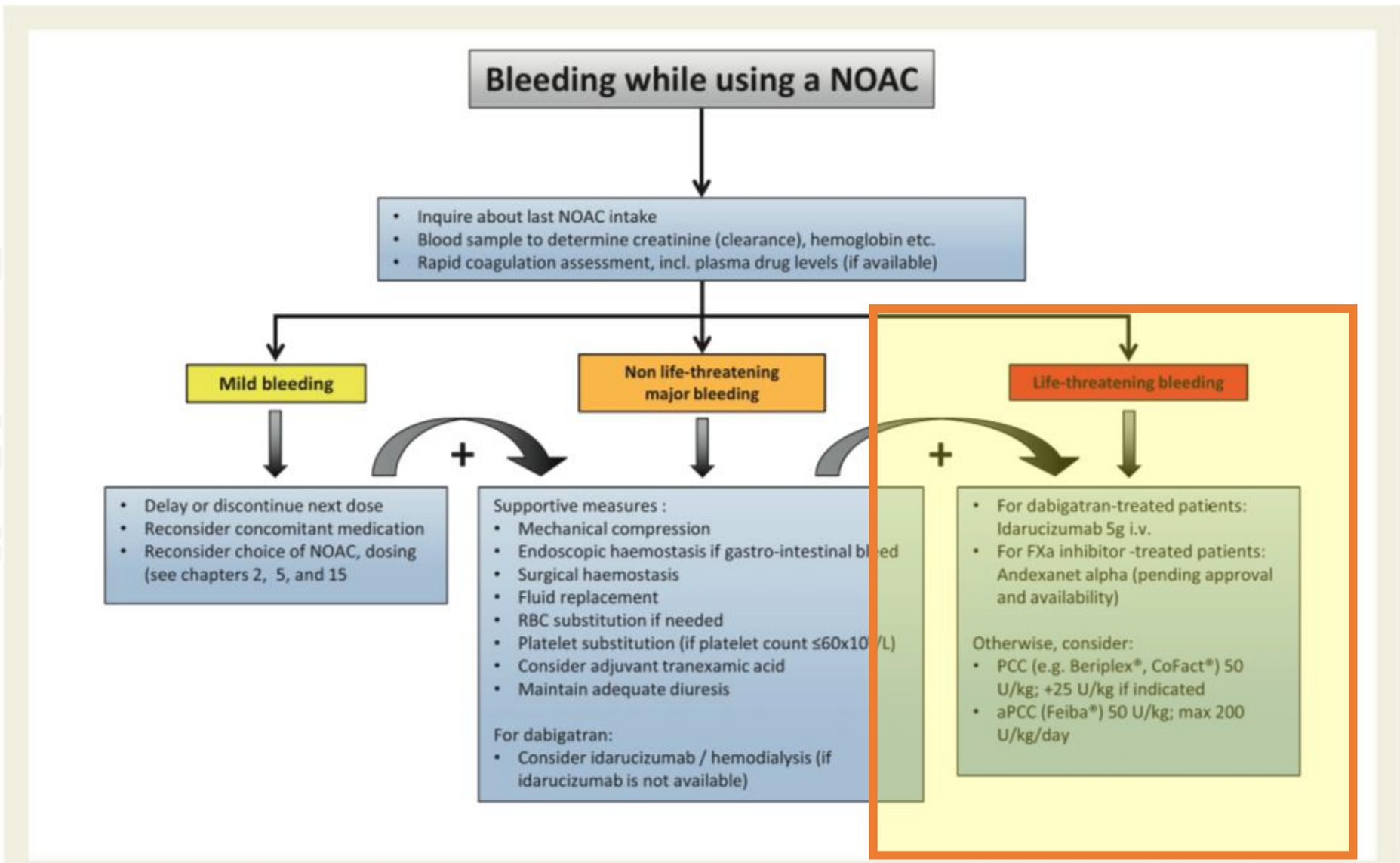
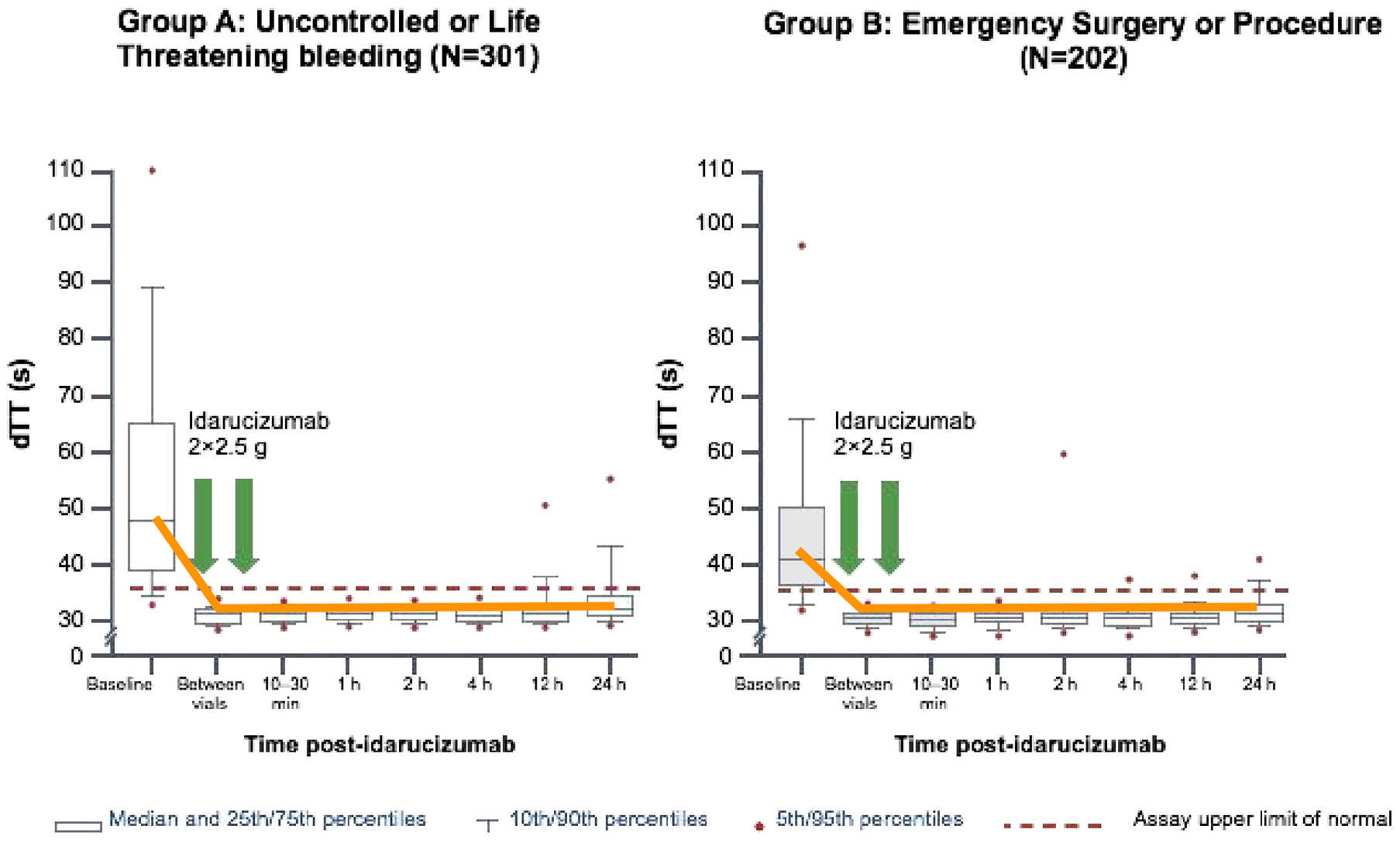


Figure 5 Management of bleeding in patients taking non-vitamin K antagonist oral anticoagulants.

Paulus Kirchhof et al. ESC Guidelines 2016, European Heart Journal (2016) 37, 2893–2962

Dab-Antidote: Idarucizumab



aPTT, activated partial thromboplastin time; dTT, dilute thrombin time

Pollack C et al. N Engl J Med. 2017 Aug 3;377(5):431-441

A.Xa-Antidote: Andexanet alfa

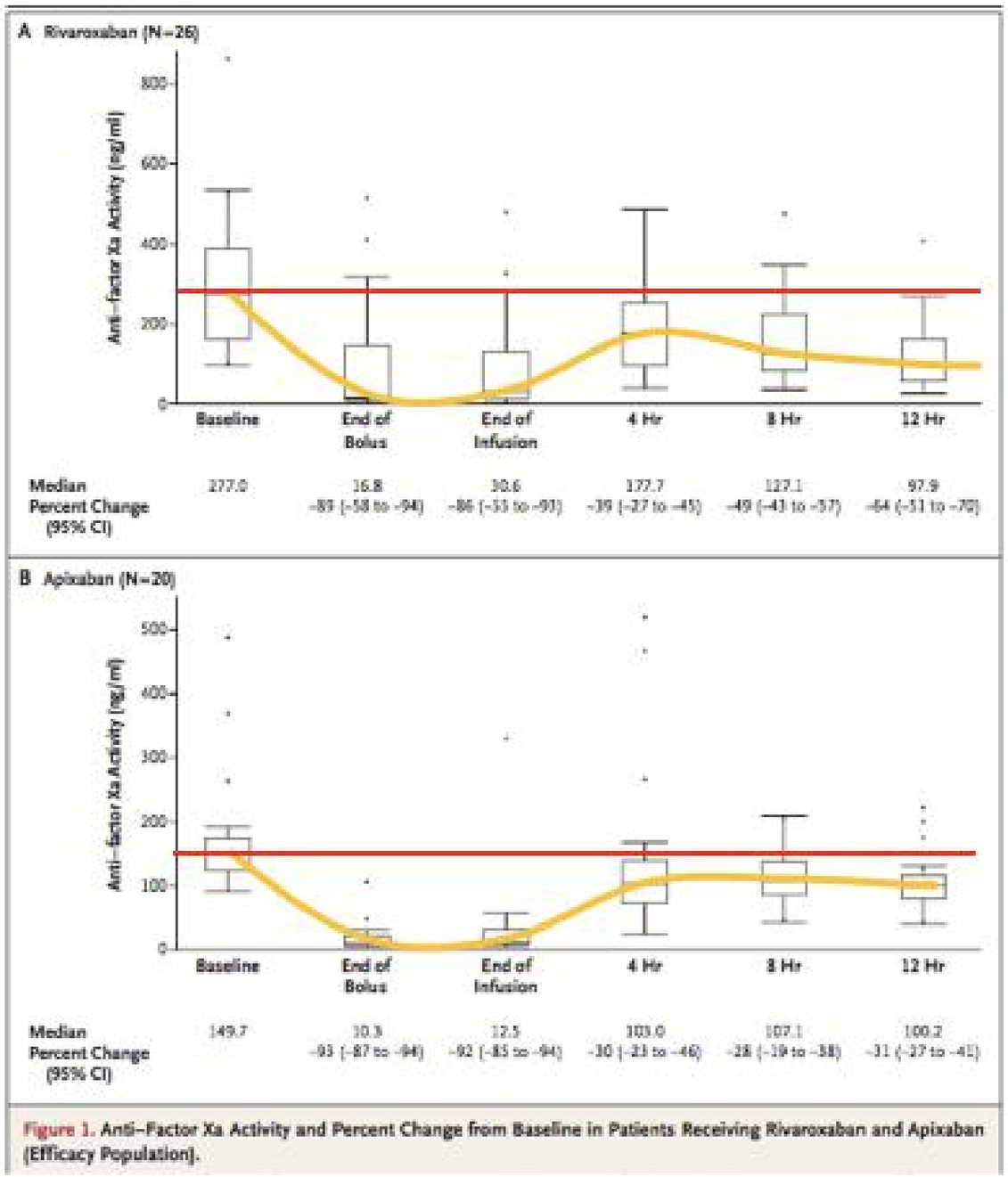


Figure 1. Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population).

Pts on apixaban or
>7 h from last rivaroxaban dose

Bolus 400 mg
+
Infusion 480 mg @ 4 mg/min

Pts on enoxaparin, edoxaban or
≤7 h from last rivaroxaban dose

Bolus 800 mg
+
Infusion 960 mg @ 8 mg/min

Stuart J. Connolly et al. N Engl J Med. 2016 Sep 22;375(12):1131-41

Pessimismo?

Association of prothrombin complex concentrates administration and hematoma enlargement in NOAC-related intracerebral hemorrhage

"...among patients with NOAC-related ICH, **there were no significant differences** between those with PCC-treatment compared to those without regarding rate of **hematoma enlargement**, **mortality** or **functional outcome** at 3 months.In this study."

Gerner St et al. Ann Neurol. 2018 Jan 3

Pessimismo?

CLINICAL TRIALS AND OBSERVATIONS

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

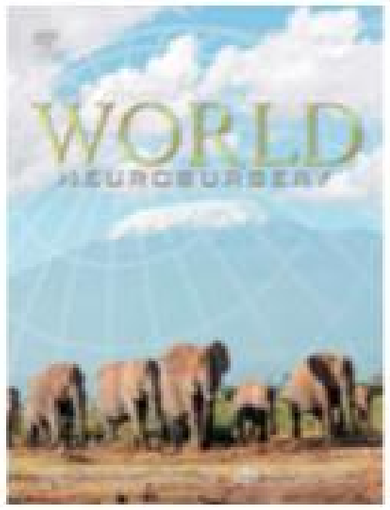
Ammar Majeed,[1-4] Anna Ågren,[1,3] Margareta Holmström,[1,3] Maria Bruzelius,[1,3] Roza Chaireti,[3,5,6] Jacob Odeberg,[1,3,7] Eva-Lotta Hempel,[1,3] Maria Magnusson,[6,8,9] Tony Frisk,[10] and Sam Schulman[11,12]

- Prospettico
- 84 pazienti
- Dose media 4FPCC 26,7 U/kg [21,4 – 29,9 UI/kg]
- **30,9% emostasi ineffettiva** (di cui 61,5% ICH)

Majee d et al. Blood. 2017;130(15):1706-1712

Pessimismo?

Accepted Manuscript



Administration of 4-Factor Prothrombin Complex Concentrate as an Antidote for Intracranial Bleeding in Patients taking Direct Factor Xa Inhibitors

Ramesh Grandhi, MD, W. Christopher Newman, MD, Xiaoran Zhang, BS, Gillian Harrison, MD, Colleen Moran, MD, David O. Okonkwo, MD, PhD, Andrew F. Ducruet,

- **Restrospettivo**
- **18 pazienti**
- Dose media 4FPCC 3177 units + 776 (range, 2124-4770 units, for 70kg men 30-68 U/kg)
- 5,4% emostasi ineffettiva

Grandhi et al. B World Neurosurg. 2015 Dec;84(6):1956-61.

Pessimismo?

Vascular Medicine

Edoxaban Effects on Bleeding Following Punch Biopsy and Reversal by a 4-Factor Prothrombin Complex Concentrate

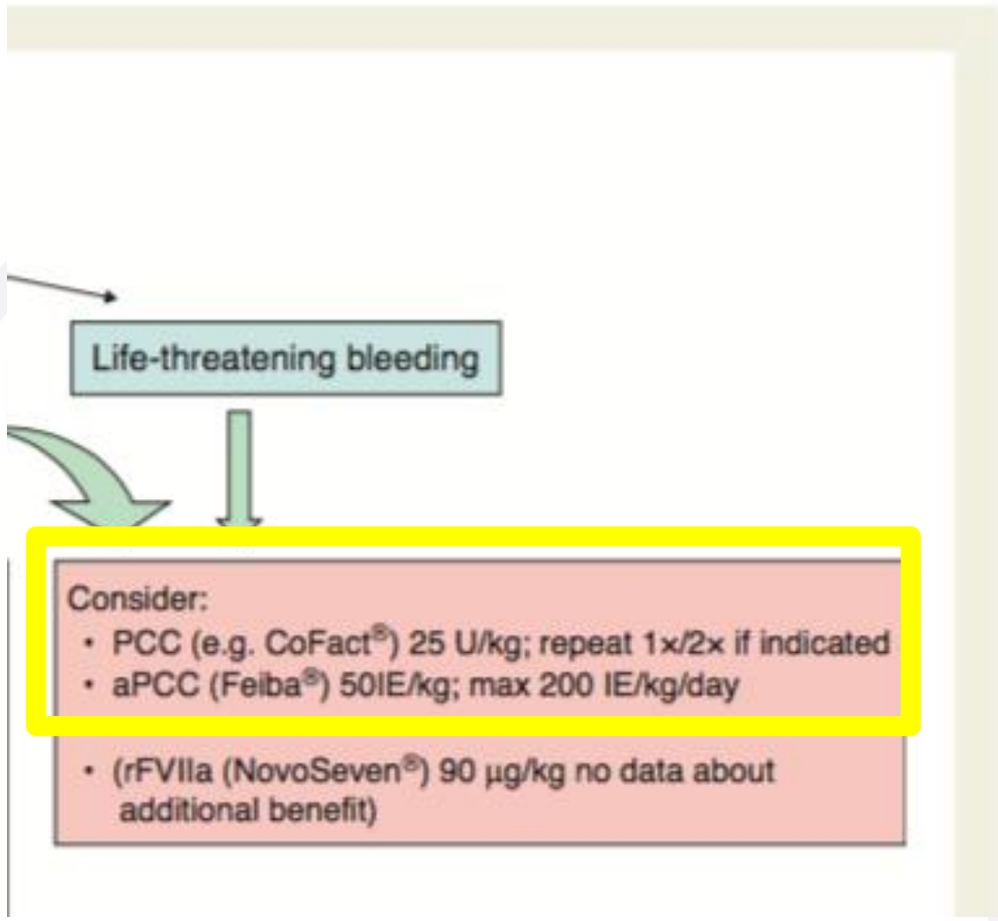
Hamim Zahir, PhD*; Karen S. Brown, PhD*; Alexander G. Vandell, PharmD, PhD; Madhuri Desai, MS; Jen-Fue Maa, PhD; Victor Dishy, MD; Barbara Lomeli, MD; Annette Feussner; Wenqin Feng, PhD; Ling He, PhD; Michael A. Grosso, MD; Hans J. Lanz, MD; Elliott M. Antman, MD

- Prospettico, randomizzato, doppio cieco, cross over
- **110 pazienti**
- Dose scalare di 4FPCC (50, 25, 10 UI/kg) **biopsia pugno**
- Reversal completo con 50 UI/kg

Zahir et al Circulation. 2015;131:82-90

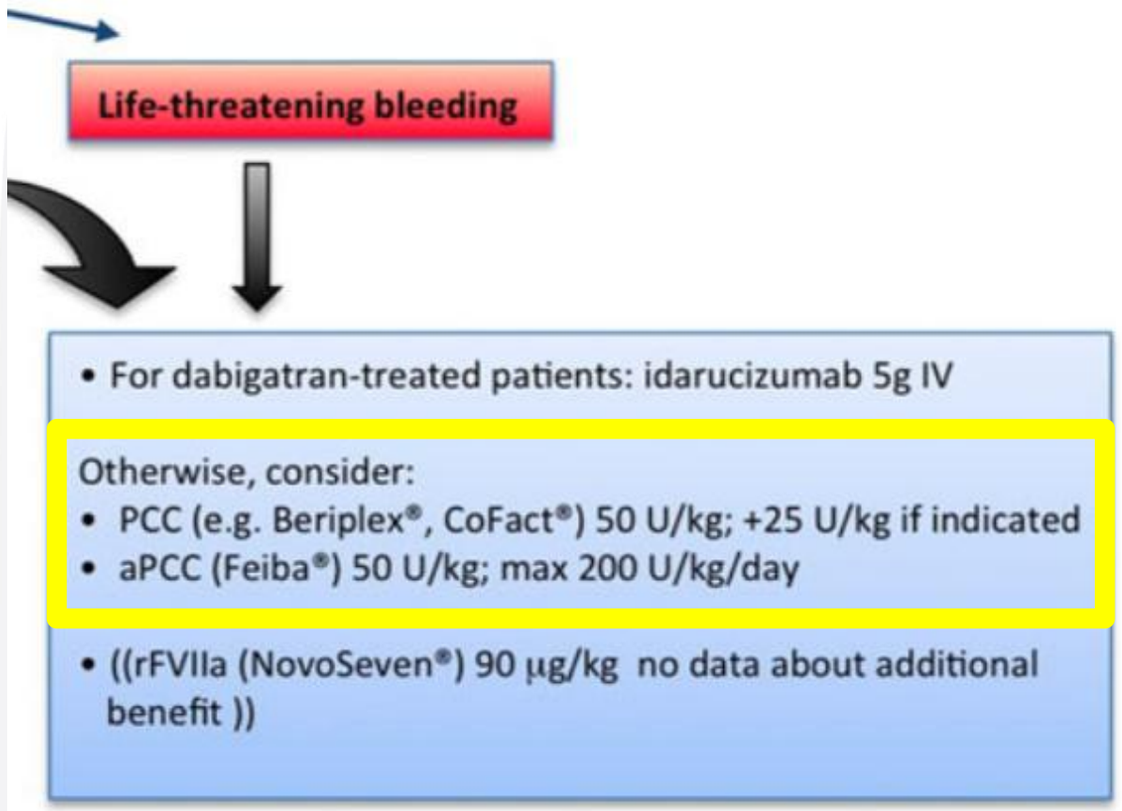
Pessimismo?

2013



Heidbuchel et al. Europace (2013) 15, 625–651

2017



Heidbuchel et al. Eur Heart J. 2017 Jul 14;38(27):2137-2149

Alcune certezze

Facciamo quello che sappiamo

EGDS

Chirurgia

Embol.

Ac- Tranex.

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L’Acido Tranexanico

Una vecchia certezza

Cochrane Library

Cochrane Database of Systematic Reviews

Tranexamic acid for upper gastrointestinal bleeding (Review)

Bennett C, Klingenberg SL, Langholz E, Gluud LL

“This review found that tranexamic acid appears to have a beneficial effect on mortality, but a high dropout rate in some trials means that we cannot be sure of this until the findings of additional research are published”

Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD006640

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SOCIETÀ ITALIANA MEDICINA D’EMERGENZA-URGENZA · SIMEU ·

L'Acido Tranexanico

Una vecchia certezza?

STUDY PROTOCOL Open Access

HALT-IT - tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial

Ian Roberts[1], Timothy Coats[2], Phil Edwards[1], Ian Gilmore[3], Vipul Jairath[4], Katharine Ker[1], Daniela Manno[1*], Haleema Shakur[1], Simon Stanworth[5] and Andrew Veitch[6]

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Riassumendo

1. I Sanguinamenti GI sono **ragionevolmente più frequenti in terapia con DOACs**
2. Sono una causa importante di **accesso e mortalità nei PS**
3. Spesso il **tempo è il vero antidoto**
4. Insieme ai trattamenti di **INTERRUZIONE del SANGUINAMENTO come endocopsia, chirurgia e embolizzazione**
5. Non dimentichiamoci **l'Acido Tranexanico,** se non efficace comunque sicuro
6. **Idarucizumab** prima scelta in caso di Dabigatran
7. **Andexanet alfa**, prima scelta negli Anti-Xa quando disponibile e in attesa di capire come funzionerà
8. Nel'attesa negli Anti-Xa vakutare i **PCC** (**forse meglio 4fPCC**)
9. **aPCC** e Fattore **VIIa** come seconda scelta se non risposta e dopo aver provato tutti i presidi farmacologici e meccanici

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Dialisi e Dabigatran

- 60 pts con 50 mg di Dabigatran
- Emodialisi
- **Rimozione del 63% a 2h e del 68% a 4h**

Stangier J et al Clin Pharmacokinet. 2010 Apr;49(4):259-68

- 28 pts con dosi da 150 a 75 mg di Dabigatran
- Emodialisi
- **Dopo 4 h rimozione de 48.8% e 59.3% di dabigatran (flow rate of 200 and 350-395 ml/minute)**

Khadzhynov D. et al. Thromb Haemost. 2013 Apr;109(4):596-605

IL PROBLEMA DEGLI ACCESSI!

Il Caso dell'Acido Tranexanico

TRANEXAMIC ACID IN UPPER GASTROINTESTINAL HÆMORRHAGE

Fiona Cormack, A.J. Jouhar, R.R. Chakrabarti, G.R. Fearnley

Gloucestershire Royal Hospital, Gloucester, United Kingdom

Published: 02 June 1973

- 1·5 g., eight-hourly
- distal to the gastro-œsophageal junction
- whose barium-meal examination was negative (superficial erosions?)

Il Caso dell'Acido Tranexanico: Riassumendo/1 (1)

- **Few side effects**
- **Inexpensive**
- **Easily** applied
- In orthopaedic surgery, tranexamic acid **reduced the** **blood transfusions by up to 40%** (1).
- In trauma patients, **the overall** 2)
- A small case-contr t of perioperative veno **oral anticoagulant** (3)
- **Equally important wa** **increase of thromboembolic event**
- Based on the availabl reviews suggest that trauma-dose tranexamic acid shoul ministered to patients with anticoagulant-associ- ated bleeding , 3].

DOSE

A. 1 gr ev bolus, 1 gr in 8 hs

B. 10-15 mg/kg bolo

1.Sauter Thomas C et al. Swiss Med Wkly. 2018 Mar 14;148:w14598

2.Henry DA et al. Cochrane Database Syst Rev. 2011

2.CRASH-2 trial collaborators. Lancet. 2010 Jul 3;376(9734):23-32

3.Clavé A et al. Orthop Traumatol Surg Res. 2012;98(5):484–90

4. Levi M. et al. Crit Care. 2016;20(1):249

Il Caso dell'Acido Tranexanico: Riassumendo/2

- The **Tranexamic acid for hyperacute primary IntraCerebral Hemorrhage (TICH-2)** trial is an RCT which will enroll up to 2400 patients with spontaneous ICH presenting within 8 h after symptom onset. Patients are randomized to receive TXA (1 g bolus followed by infusion of 1 g over 8 h) or placebo

- The **CRASH-3** trial, focusing on the effects of TXA in **traumatic brain injury**, is ongoing.

- The ongoing **STOP-AUST trial selects ICH patients for TXA vs placebo.** The trial aims to enroll 100 patients, and results are expected later in 2018.

- TXA in ICH include the **placebo-controlled Tranexamic Acid for Acute ICH Growth prEdicted by Spot Sign trial (TRAIGE**; clinicaltrials.gov NCT02625948)

- the **Tranexamic Acid for Spontaneous Acute Cerebral Hemorrhage Trial (TRANSACT**; NCT03044184),

- **Romanian Emergency Management of Spontaneous Intracerebral Hemorrhage (EsICH) study**.

- **Swiss TICH-NOAC trial** (NCT02866838) specifically focuses on **efficacy of TXA in patients suffering NOAC-related ICH**.

Sauter Thomas C et al. Swiss Med Wkly. 2018 Mar 14;148:w14598

Andexanet Alfa: l'Antidoto per tutti gli Anti-Xa

Acute major bleeding ≤ 18 hours of last dose of apixaban, edoxaban, rivaroxaban, or enoxaparin

Andexanet IV bolus and 2 hour infusion

Pts on apixaban or >7 h from last rivaroxaban dose	Pts on enoxaparin, edoxaban or ≤7 h from last rivaroxaban dose
Bolus 400 mg + Infusion 480 mg @ 4 mg/min	**Bolus 800 mg + Infusion 960 mg @ 8 mg/min**

Lu et al, 2013

Stuart J. Connolly et al. N Engl J Med. 2016 Sep 22;375(12):1131-41

Andexanet Alfa: l'Antidoto per tutti gli Anti-Xa

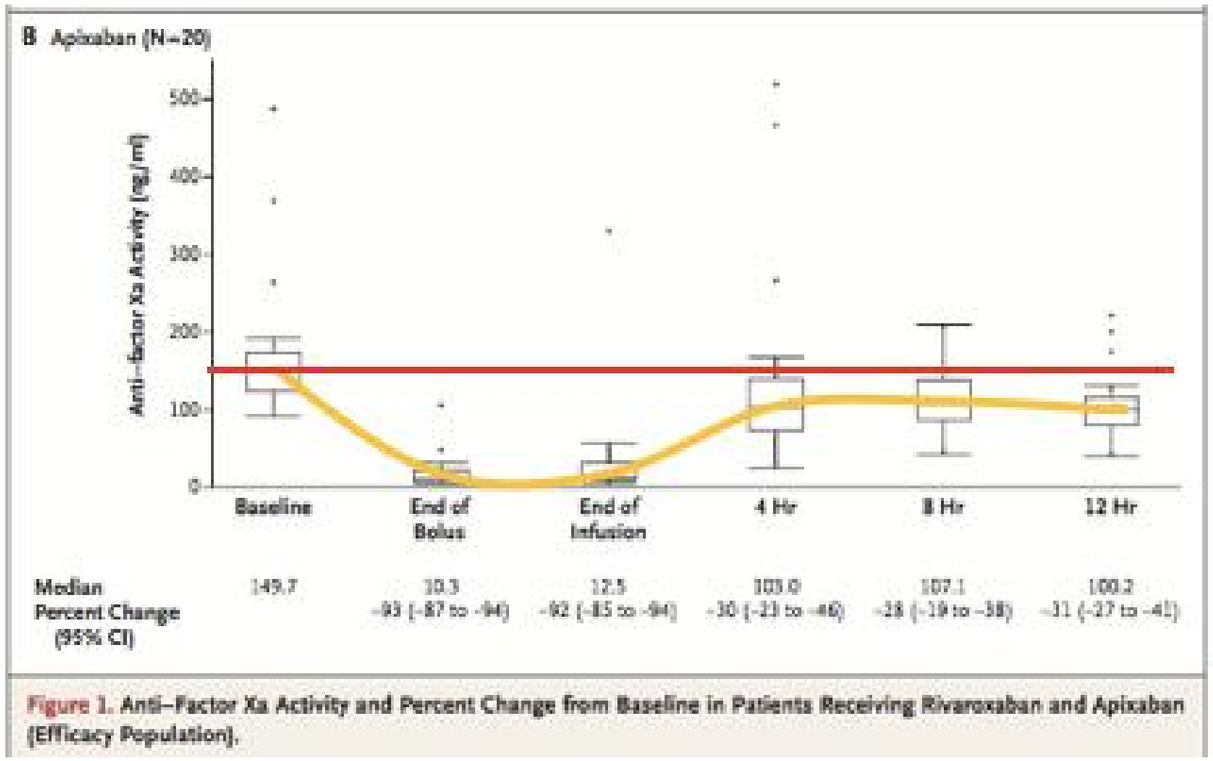

Figure 1. Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population).

- After the bolus median anti–factor Xa ⬇ 89% in rivaroxaban ⬇ 93% apixaban.
- 4h after the end of the infusion ⬇ 39% in rivaroxaban and ⬇ 30% in apixaban
- 12h hemostasis excellent or good in **79%** of patients
- Thrombotic events **18%** during the 30-day follow-up.

Lu et al, 2013

Stuart J. Connolly et al. N Engl J Med. 2016 Sep 22;375(12):1131-41

Riassumendo…

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

"…Therefore, recommendations on bleeding management are still mainly based on **preclinical information** and **experts' opinions**…"

Heidbuchel et al. Europace 2015; Europace; doi:10.1093/europace/euv309

Per non dimenticare…

- **Carbone** Vegetale Attivato (30-50 gr) entro 2 h dall'assunzione[1-2]
- **GASTROLUSI**
- **Vitamina K** nessun razionale nei DOAC e Eparine ma importante nei VKI

1. Green R et al. J Toxicol Clin Toxicol 2001;39:601 – 5
2. Wang X et al. Am J Cardiovasc Drugs

Take Home Message

- Gli Anticoagulanti aumentato il **rischio di emorragia**
- Forse **i DOAC sono meno pericolosi**
- Le evidenze sugli Inibitori della Vitamina K indicano i **PCC come prima scelta nel reversal**
- Forse i **PCC a 4 Fattori** dono migliori di quelli a 3 Fattori
- Per le Eparine non dimenticare il **Solfato di Protamina**
- Oltre **l'Idarucizumab** inizia ad avere solide evidenze nei sanguinamenti da Dabigatran
- i **PCC** sono da considerare la prima scelta nei DOAC prima di altri presidi come Fattore VIIa e FEIBA®
- Anche in questo caso meglio se a **4 Fattori**
- Ricordiamoci che **possono non funzionare** (scarse evidenze)
- Quindi prepariamoci ad utilizzare **soluzioni secondarie**
- Ricordiamoci quello che sappiamo:

  I. **Fermiamo il sanguinamento** (EGDS, Angiografia, chirurgia, ...)

  II. Usiamo l'**acido tranexanico**

  III. Usiamo il **sangue** e le **piastrine** se servono

Reversal Agent and DOAC

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Vitro	✓	✓	✓	?
PCC on Animals	✓	✓	✗	✓
PCC on Coagulation Parameters	✓	✓	✓	✓
3fPCC	✓ Case report	?	?	✓ Healthy Vol.
4fPCC	✗ Vivo ✓ Vivo/Vitro/An.	✓ Vivo e Anim.	✓ Vitro/Vivo	✓ Vivo

Reversal Agent and DOAC

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Vitro	✓	✓	✓	?
PCC on Animals	✓	✓	✗	✓
PCC on Coagulation Parameters	✓	✓	✓	✓
3fPCC	✓ Case report	?	?	✓ Healthy Vol.
4fPCC	✗ Vivo ✓ Vivo/Vitro/An.	✓ Vivo e Anim.	✓ Vitro/Vivo	✓ Vivo
fVIIa (Novoseven®)	✓ Vivo ✓ Vitro e Anim.	✓ Anim. ✓	✓ Vitro	? 2
PCC Prospective Trials of Treatment	✗	✓ 84 pts; 30,9% failure		✓ Punch biopsy
Reversal Healthy Volunteers	✓	✓	✓	✓
Reversal on Bleeding	✓ Coag. Param. Outcome +/-	✓ Pending App.	✓ Pending App.	? Ongoing
Dialysis	✓ 1	✗	✗	?
Feiba®	✓ Vitro ✓ Case Report and Anim.	✓ Vitro and Anim.	✓ Vitro	?

1 62% at 2 h and 68% at 4 h e dopo 4 h rimozione de 48.8% e 59.3%. what about CVC insertion in anticoagulated patient?

2 In a metanalisys on FaVII increased arterial thrombotic risk (not venous) in particular in elderly pts and not in trauma pts. [Levi M et al. N Engl J Med 2010;363:1791–800]

Sanguinamenti Gastrointestinali

Antihemostatic

Demographics	Frequency (%)	ICH	GIB	ICB	Hemoptysis	High-energy impact	Hematoma	Hematuria	Metrorrhagia
N° patients (%)	661 (100%)	463 (70)	116 (17,5)	35 (5,3)	15 (2,3)	11 (1,7)	8 (1,2)	7 (1)	6 (0,9)
Age, median (IQR), y.	75 (23)	76 (22,3)	75 (15,2)	80 (1,1)	67 (14,8)	45,5 (15,6)	55 (20,2)	71,5 (23,2)	77,5 (25,4)
Female sex	305 (46,1)								
Anticoagulant therapy									
DOACs	16 (2,4)	9 (1,9)	7 (6)	0 (0)	1 (6,7)	0 (0)	0 (0)	0 (0)	1 (16,7)
VKAs	24 (3,6)	17 (3,7)	9 (7,7)	1 (2,8)	1 (6,7)	0 (0)	1 (12,5)	1 (14,3)	0 (0)
UFH/LMWH	36 (5,4)	23 (4,9)	18 (15,5)	2 (5,7)	3 (20)	1 (9)	1 (12,5)	0 (0)	0 (0)
Antiplatelet therapy									
ASA	82 (12,4)	71 (15,3)	23 (19,8)	2 (5,7)	4 (26,7)	2 (18)	2 (25)	1 (14,3)	1 (16,7)
Clopidogrel-like drugs	23 (3,5)	25 (5,4)	12 (10,3)	0 (0)	1 (6,7)	0 (0)	0 (0)	1 (14,3)	1 (16,7)
Multiple therapy	28 (4,2)	12 (2,6)	12 (10,3)	1 (2,8)	1 (6,7)	0 (0)	0 (0)	1 (14,3)	1 (16,7)
No therapy	303 (45,8)	306 (66)	35 (30,2)	29 (82,8)	4 (26,7)	8 (72,7)	4 (50)	3 (42,8)	2 (33,3)

Cipriano A. et al. in press

Gli Anticoagulanti e il Sanguinamento
Il **Punto di Vista** del **Medico d'Urgenza**

Major Bleeding site	Frequency (%)	Median Age (median (IQR)) yr.	Traumatic origin n,(%) N=175	ED death n,(%) N = 8	In-hospital death n,(%) N = 99	Admission n,(%) N = 621
Intracranial hemorrhage	463 (70)	76 (22,3)	**151 (32,6) †**	2 (25)	77 (77,8)	438 (70,5)
Gastrointestinal bleeding	116 (17,5)	75 (15,2)	-	2 (25)	12 (12,1)	112 (18)
Intracavitary bleeding	35 (5,3)	80 (1,1)	**14 (38,9) †**	1 (12,5)	5 (5)	34 (5,5)
Hemoptysis	15 (2,3)	67 (14,8)	-	-	1 (1)	13 (2,1)
High-Energy Impact	11 (1,7)	**45,5 (15,6) ***	**11 (100) †**	**3 (37,5) §**	3 (3)	8 (1,3)
Hematoma with active bleeding	8 (1,2)	**55 (20,2) ***	-	-	1 (1)	8 (1,3)
Hematuria	7 (1)	71,5 (23,2)	-	-	-	3 (0,5)
Metrorrhagia	6 (0,9)	77,5 (25,4)	-	-	1 (1)	6 (1)

Age, traumatic origin, mortality and admission rate comparisons among MB sites.
* = p < 0,001 vs. other MB sites: significantly younger.
† = p < 0,001 vs. other MB sites: significantly associated with traumatic origin.
§ = p < 0,001 vs. other MB sites: significantly associated with death in the emergen

Cipriano A. et al.