Anestesia e coagulazione

Dr Luca Torri

Sion, 6 ottobre 2018

Coagulopatie e diatesi emorragiche…

- Malattia di Von Willebrand
- Emofilia A
- Emofilia B
- Déficit di altri fattori dell[illegible]ulazione
- Tromboastenia di Gl[illegible]in
- Trombocitopeni[illegible]
- Déficit in vi[illegible] K
- CIVD
- HI[illegible]
- E[illegible]opatie
- …

DIATESI EMORRAGICA MEDICAMENTOSA

Qualche cifra…

- Anticoagulanti:
  - Prevalenza in Italia nel 2008: 1,58% (source FCSA)
  - In France, 13.7% delle personne >65 anni sono state esposte almeno une volta a un anticoagulante nel 2013 (source ANSM)
- Antiaggreganti:
  - Ancora più diffusi
  - Aspirina è il 7° farmaco più venduto in Francia nel 2013 (source ANSM)

Una popolazione in forte espansione…

…and counting…

Le sfide per l'anestesista

- Detezione
- Arresto
- Bilancio d'emostasi
- Switch tra anticoagulanti
- Anestesia neurassiale
- Presa in carico dell'emorragia ←
- Ripresa dell'anticoagulazione
- …

Presa in carico: primo bilancio

- Tipo di farmaco
- Indicazione
- Ultima assunzione
- Assunzione di altri farmaci che potrebbero interferire farmacologicamente o clinicamente
- Comorbidità che potrebbero influenzare l'effeto o la durata (insufficienza epatica, insufficienza renale)
- Interpretazione dei risultati di laboratorio

Presa in carico: valutazione clinica

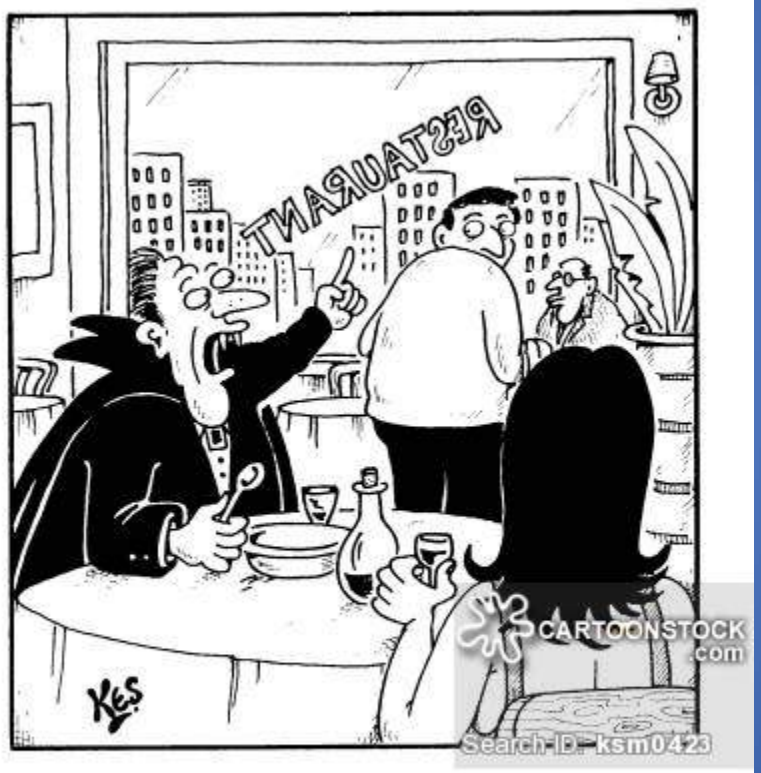
- Il paziente è emodinamicamente stabile?
- L'emorragia è da considerarsi maggiore (es. perdita di >20 g/L d'hemoglobina, 2 o più CE transfusi)?
- Un sito critico è coinvolto?

TABLE 1 Critical Site Bleeds

Type of Bleed	Initial Signs and Symptoms	Potential Consequences of Bleed
Intracranial hemorrhage: Includes intraparenchymal, subdural, epidural, and subarachnoid hemorrhages	**Unusually intense headache, emesis** **Neurological signs:** e.g., reduced LOC, vision changes, numbness, weakness, aphasia, ataxia, vertigo, seizures	Stupor or coma Permanent neurological deficit Death
Other central nervous system hemorrhage: Includes Intraocular, intra- or extra-axial spinal hemorrhages	**Intraocular:** monocular eye pain, vision changes, blindness **Spinal:** back pain, bilateral extremity weakness or numbness, bowel or bladder dysfunction, respiratory failure	**Intraocular:** permanent vision loss **Spinal:** permanent disability, paraplegia, quadriplegia, death
Pericardial tamponade	Shortness of breath, tachypnea Hypotension, jugular venous distension Tachycardia, muffled heart sounds, rub	Cardiogenic shock Death
Airway, including posterior epistaxis	**Airway:** hemoptysis, shortness of breath, hypoxia **Posterior epistaxis:** profuse epistaxis, hemoptysis, hypoxia, shortness of breath	Hypoxemic respiratory failure, Death
Hemothorax, intra-abdominal bleeding, and RPH	**Hemothorax:** tachypnea, tachycardia, hypotension **Intra-abdominal (nongastrointestinal):** abdominal pain, distension, hypotension, tachycardia **RPH:** Back/flank/hip pain, tachycardia, hypotension	**Hemothorax:** respiratory failure **RPH:** femoral neuropathy **All:** hypovolemic shock, death
Extremity bleeds: includes intramuscular and intra-articular bleeding	**Intramuscular:** pain, swelling, pallor, paresthesia, weakness, diminished pulse **Intra-articular:** joint pain, swelling, decreased range of motion	**Intramuscular:** compartment syndrome, paralysis, limb loss **Intra-articular:** irreversible joint damage

LOC = loss of consciousness; RPH = retroperitoneal hematoma.

Emorragia e anticoagulanti



"Oh waiter! Will you pass me the anticoagulant please?"

Principaul anticoagulanti

Orali	**Parenterali**
Antivitamina K • Sintrom, Marcoumar, Warfarin	Eparine non frazionate Eparine a basso peso molecolare
Anticoagulanti diretti orali • Dabigatran (Pradaxa) • Rivaroxaban (Xarelto), Apixaban (Eliquis), Edoxaban (Lixiana)	Fondaparinux (Arixtra) Altri (bivalirudine, danaparoïde,…)

Farmacodinamica

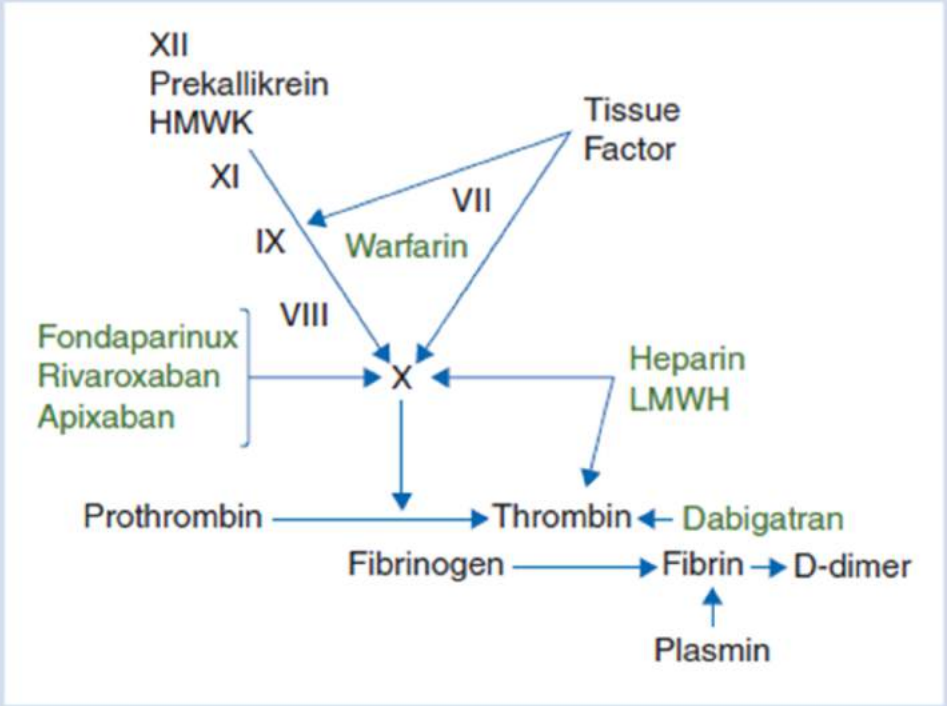


Fig 1 Sites of action of anticoagulant drugs. Clotting factors are indicated by Roman numerals. Warfarin reduces production of factors VII, IX, X, and prothrombin. Heparin and LMWH inhibit factor Xa and thrombin. Fondaparinux, rivaroxaban, and apixaban are direct factor Xa inhibitors. Dabigatran is a DTI. HMWK, high molecular weight kininogen; LMWH, low molecular weight heparin.

Benzon et al, New oral anticoagulants and regional anesthesia, Br J Anaesth. 2013 Dec;111 Suppl 1:i96-113

Emorragia: misure generali

- Arresto dell'anticoagulante
- Se possibile, arresto degli antiaggreganti
- Trattamento locale/compressione manuale
- Supporto emodinamico
- Trattamento delle comorbidità che possono favorire l'emorragia (es. trombopenia, uremia, insufficienza epatica,…)
- Trattamenti adiuvanti: considerare ac. tranexamique
- Presa in carico chirurgica/interventistica del sanguinamento

Anti-vitamina K

- Bilancio di laboratorio utile alla presa in carico: TP, INR
- Trattamento «etiologico»: vitamina K 5-10mg
  - Preferire la via IV (inizio azione più corto: 4-6h vs 18-24h per la via orale)
- Trattamento di prima linea: concentrato del complesso protrombinico (Prothromplex, Beriplex, etc.)
- Trattamento di seconda linea: plasma fresco congelato

Dosi

Diversi schemi…

- Administer 4F-PCC†:
  - INR 2-4, 25 units/kg
  - INR 4-6, 35 units/kg
  - INR >6, 50 units/kg
- Or low fixed-dose option
  - 1000 units for any major bleed
  - 1500 units for intracranial hemorrhage
  - If 4F-PCC not available, use plasma 10–15 mL/kg[1]

Tomaselli *et al.*

2017 ACC ECDP on Management of Bleeding in Patients on Oral Anticoagulants

In VKA-treated patients undergoing an emergency procedure, we recommend that INR must be measured on the patient's admission to the hospital, with the administration of four-factor PCC to reverse VKA anticoagulant effects (e.g. at an initial dose of 25 IU factor IX kg^{-1} at an INR of 4) rather than the transfusion of plasma. **1B**

If PCC is not available, then in bleeding patients where VKA-induced coagulopathy is considered a contributing factor, we recommend the transfusion of plasma (15 to 20 ml kg^{-1} plus 5 to 10 mg IV vitamin K. **1C**

Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology

•Posologie en cas de déficits acquis en facteurs du complexe prothrombinique
La formule suivante peut être utilisée pour le calcul de la dose:
Dose (en U.I.) = augmentation souhaitée du temps de Quick (en %) × kg de poids corporel × 1,2.

compendium.ch, Prothromplex

Anticoagulanti diretti orali

Inibizione diretta trombina (fattore IIa)

- Dabigatran (Pradaxa®)

Inibizione fattore Xa

- Rivaroxaban (Xarelto®)
- Edoxaban (Lixiana®)
- Apixaban (Eliquis®)

L'avantage des AOD par rapport aux AVK est surtout leur simplicité d'utilisation:

- posologie standardisée ne nécessitant pas de monitoring sanguin
- moindre interaction médicamenteuse et alimentaire
- absorption rapide par voie orale et action rapide
- Demi-vie plus brève (entre 9 et 15 h) que celle de la warfarine (35 à 45 h), AVK de référence, ce qui peut être un avantage en cas d'intervention chirurgicale urgente, mais aussi un risque en cas d'oubli de prise médicamenteuse
- moins de saignements intracrâniens

Pierard et Sprynger, Rev Med Suisse 2014; 10: 1562-7

Meno semplice la gestione in urgenza…

- Difficulté à en estimer l'effet résiduel
- Prolongation effet en cas d'IRA
- Manque d'antidotes
- Encore relativement peu d'études cliniques

Anticoagulanti diretti orali e laboratorio

TABLE 3 Suggestions for Laboratory Measurement of DOACs When Specialized Assays are not Available

	Clinical Objective			
	Exclude Clinically Relevant* Drug Levels		Determine Whether On-Therapy or Above On-Therapy Levels Are Present	
Drug	**Suggested Test**	**Interpretation**	**Suggested Test**	**Interpretation**
Dabigatran	TT, aPTT	**Normal TT** excludes clinically relevant* levels **Prolonged TT** does not discriminate between clinically important and insignificant levels **Normal aPTT** usually excludes clinically relevant* levels, if a sensitive reagent is used.	aPTT	**Prolonged aPTT** suggests that on-therapy or above on-therapy levels are present **Normal aPTT** may not exclude on-therapy levels, particularly if a relatively insensitive aPTT reagent is used
Apixaban	None	**Normal PT and aPTT** do not exclude clinically relevant* levels	PT	**Prolonged PT** suggests that on-therapy or above on-therapy levels are present **Normal PT** may not exclude on-therapy *or above on-therapy levels*, particularly if a relatively insensitive PT reagent is used
Edoxaban or rivaroxaban	None	**Normal PT and aPTT** do not exclude clinically relevant* levels	PT	**Prolonged PT** suggests that on-therapy or above on-therapy levels are present **Normal PT** may not exclude on-therapy levels, particularly if a relatively insensitive PT reagent is used

*The term "clinically relevant" refers to DOAC levels that may contribute to bleeding or surgical bleeding risk. The minimum DOAC level that may contribute to bleeding or surgical bleeding risk is unknown. The International Society on Thrombosis and Hemostasis recommends consideration of anticoagulant reversal for patients with serious bleeding and a DOAC level >50 ng/mL, and for patients requiring an invasive procedure with high bleeding risk and a DOAC level >30 ng/mL (17).

Anti-Xa = anti-factor Xa; aPTT = activated partial thromboplastin time; DOAC = direct-acting oral anticoagulant; PT = prothrombin time; TT = thrombin time.

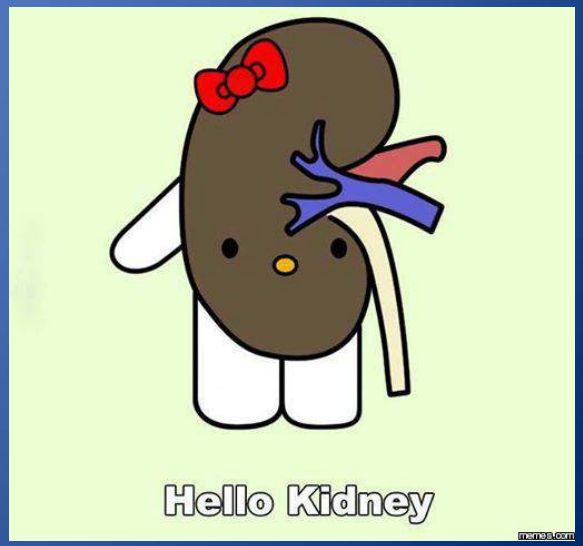
Doherty et al., 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

Anticoagulanti diretti orali et funzione renale

	Dabigatran				
CrCl, mL/min	≥80	50-79	30-49	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)

	Apixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥30	15-29	<15
Estimated drug half-life, h	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)

Doherty et al., 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation



In caso d'emorragia maggiore

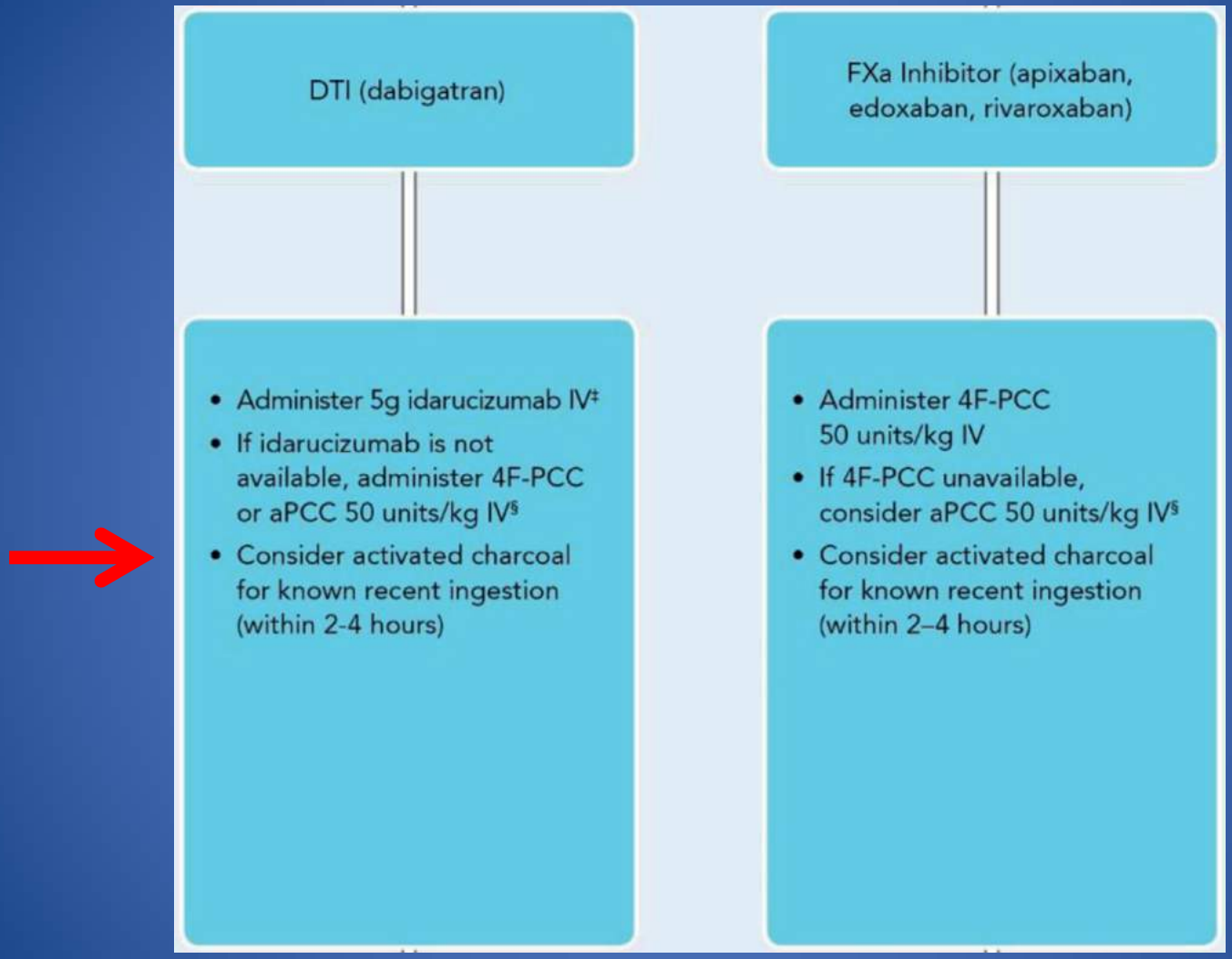
Table 9 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, and rivaroxaban)
None life-threatening bleeding	Inquire last intake + dosing regimen. Estimate normalization of haemostasis: Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl < 30 mL/min: ≥48 h Maintain diuresis. Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy). Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: −65% after 4 h).[122] Charcoal haemoperfusion can be considered (based on preclinical data)	Inquire last intake + dosing regimen. Normalisation of haemostasis: 12–24 h Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy). Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above. Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical ata). Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence) Idarucizumab 5 g IV (approval waiting)	All of the above. Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (healthy volunteer data) Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.

H. Heidbuchel et al., Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation, Europace (2015) 17, 1467–1507

Al di là dell'Atlantico…



Tomaselli *et al.*

2017 ACC ECDP on Management of Bleeding in Patients on Oral Anticoagulants

Per riassumere

TABLE 5 Available Reversal Agents and Suggested Use

Reversal Agent	Vitamin K Antagonists (Warfarin)	Factor IIa Inhibitor (Dabigatran)	Factor Xa Inhibitor (Apixaban, Edoxaban and Rivaroxaban)
4F-PCC (56)	First line	Second line	First line
aPCC	Not indicated	Second line	Second line
Idarucizumab	Not indicated	First line	Not indicated
Plasma	If 4-PCC is unavailable	Not indicated	Not indicated

4F-PCC = 4-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate.

1 flacon ampoule de Prothromplex NF 600 contient respectivement:

Protéines totales	300-750 mg
Facteur II	600 U.I.
Facteur VII	500 U.I.
Facteur IX	600 U.I.
Facteur X	600 U.I.
Protéine C	≥400 U.I.
Antithrombine III	15-30 U.I.
Héparine	≤ 0,5 U.I. / U.I. de facteur IX

PFC:

- Facteur II: 0,7-1,5 U/ml
- Facteur VII: 0,6-1,6 U/ml
- Facteur IX: 0,6-1,5 U/ml
- Facteur X: 0,8-0,9 U/ml
- Protéine C: 0,7-1,4 U/ml

Adapté de «Perioperative hemostasis – Coagulation for anesthesiologist», C.E. Marcucci, P. Schoettker editors, 2015

Eparine

- Non frazionate
  - Liquemine, calciparina,…
- Basso peso molecolare
  - Enoxaparina
  - Fraxiparina
  - …
- Fondaparinux (Arixtra)

La protamina

- Proteina basica, che si lega all'eparina (acida) formando un compleso stabile con essa
- Le eparine non frazionate e a basso peso molecolare rispondono alla protamina, che le lega e le inattiva. La risposta delle HBPM è solamente parziale
- Il Fondaparinux non risponde alla protamina

Dosi

Eparina non frazionata:

- 1 mg per 100 UI d'eparina ricevute nelle ultime 2-3h (es. perfusioni continue)
- In caso di eparina s.c. che non risponde alla dose di 1 mg/100 UI, una perfusione continua può essere utilizzata, controllando il PTT

Eparina a bassp peso molecolare

- 1 mg pour 100 UI antifacteur Xa
- Se nessuna risposta, 0,5 mg pour 100 UI antifacteur Xa
- Se dose ricevuta da più che 8h, delle dosi più basse possono essere considerate

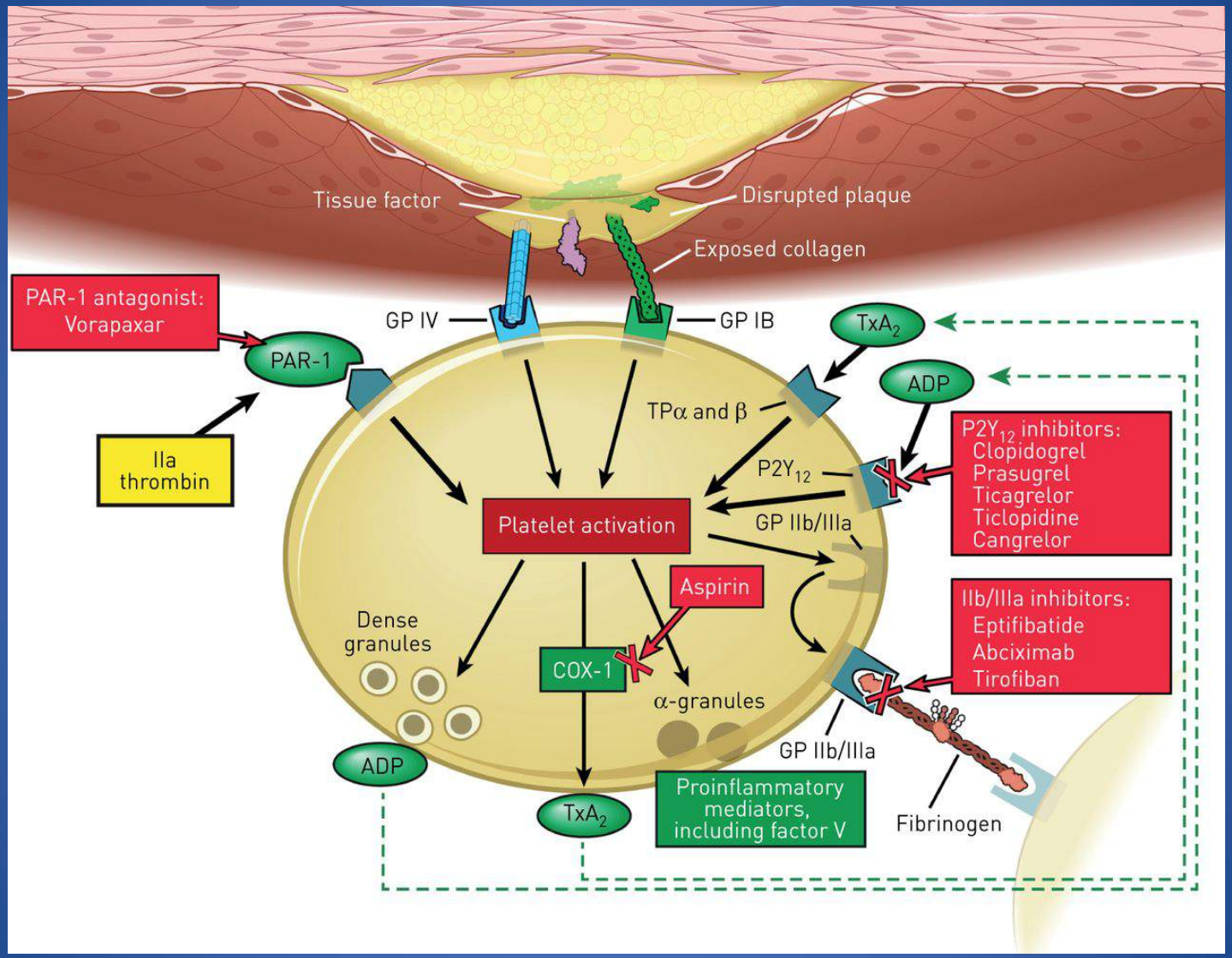
Perfusione lenta (>5 minutes) et attenzione al calcolo delle dosi: in caso di sovradosaggio, la protamina esercita un effeto anticoagulante

Fondaparinux

- Polisaccaride sintetico, si lega all'antitrombina III con un effeto anti-Xa ma senza effetto sulla trombina. Non provoca HIT.
- Lunga emivita (17-20h), eliminazione renale
- Nessuna risposta alla protamina
- Nessun antidoto
- In caso di emorragia a rischio vitale, l'utilizzazione di fattore VIIa ricombinante (Novoseven) è stato proposto (off-label et dose non établie: 90 mcg/Kg?)

Gli antiaggreganti

Larousse.fr



Abuqayyas S, Raju S, Bartholomew JR, et al. Management of antithrombotic agents in patients undergoing flexible bronchoscopy. Eur Respir Rev 2017; 26: 170001

- Corta emivita ma lungo effetto biologico
- Nessun antidoto o antagonista esistente
- Spesso pazienti a alto rischio trombotico: ogni intervento pro-emostatico deve essere soppesato con il rischio trombotico

Drug	Time to normal platelet function/ coagulation activity after drug discontinuation
Antiplatelet drugs	
NSAIDs	24 h
Aspirin	5–7 d
Clopidogrel	5–7 d
Prasugrel	5–7 d
Ticagrelor	3–5 d
Tirofiban	4–8 h
Eptifibatide	4–8 h
Abciximab	24–48 h

Makris et al, British Journal of Haematology, 2012, 160, 35-46

Emorragia: misure generali

- Arresto dell'antiaggregante secondo il rischio emorragico E trombotico
- Arresto degli altri farmaci pro-emorragici
- Trattamento locale/compressione manuale
- Supporto emodinamico
- Trattamento delle comorbidità che possono favorire l'emorragia
- Presa in carico chirurgica/interventistica del sanguinamento

- Trattamenti adiuvanti: desmopressina
  - Effetto: aumento dei livelli di fattore di von Willebrand et di fattore VIII nel sangue; possibile aumento adesione piastrinica
  - Indicazioni «classiche»: certi tipi di malattia di Von Willebrand, emofilia A minore
  - Dose: 0,3 mcg/Kg in NaCl 0,9%, passare su 30’
  - Efficacia: dati contrastanti, potrebbe avere un ruolo nelle emorragie più severe, in particolare nei pazienti trattati con aspirina o in caso d’uremia
  - Rari episodi di trombosi arteriosa

Trasfusione piastrinica

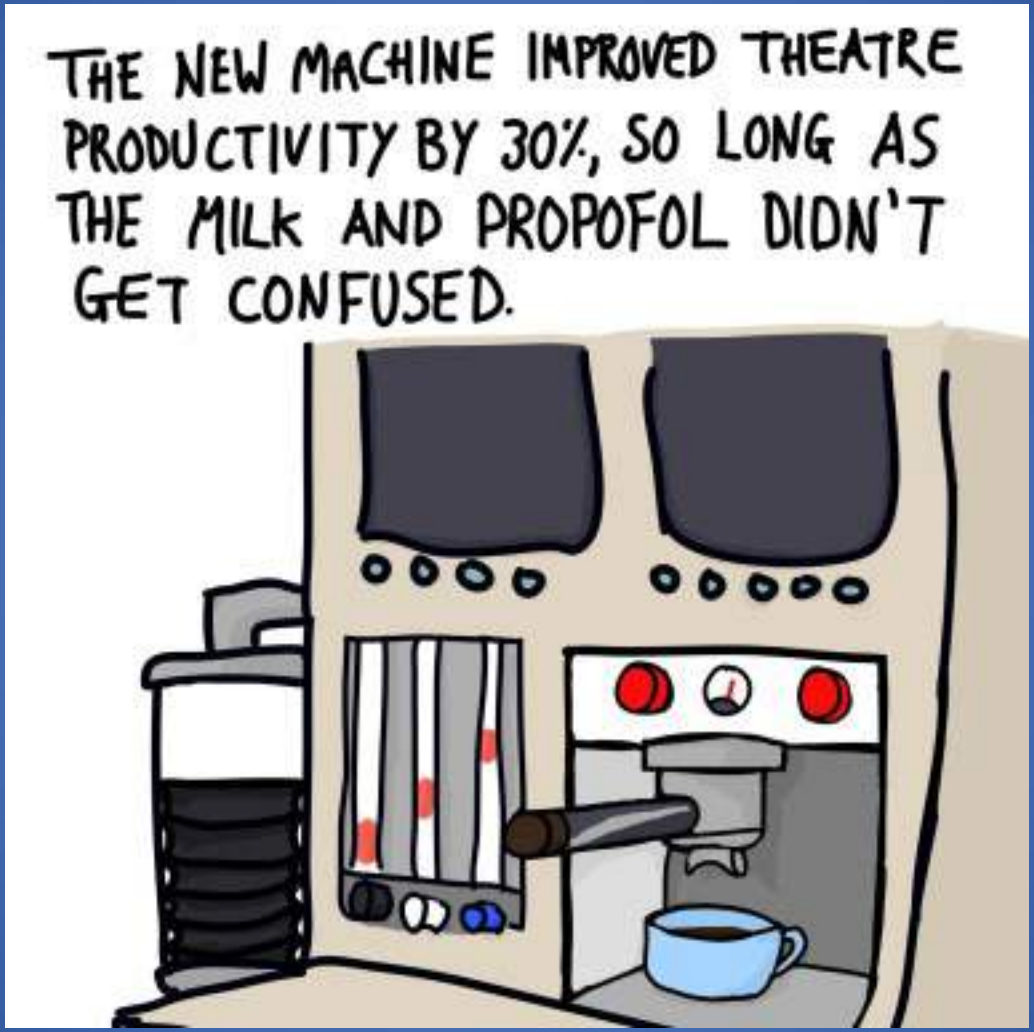
- Solo modo di annullare l'effetto anti-aggregante
- Manca accordo sulla dose
  - 0,7 x 10^{11} per 10Kg di peso (ESA)
  - 2-3 dosi adulte (British Commitee for Standards in Haematology)
- Prodotto sanguigno «raro», tasso di effetti secondari più elevato che gli autri prodotti sanguigni
- La trasfusione piastrinica potrebbe essere inefficace nei pazienti su Ticagrelor (Brilique), soprattutto se ricevuto da meno che 12h

Conclusioni

- Sempre più pazienti hanno un disturbo medicamentoso della coagulazione/aggregazione, e alcuni sanguineranno
- L'attesa è una buona strategia nei casi non urgenti
- Nell'urgenza, un bilancio mirato e delle misure generali restano primordiali
- Negli anticoaguli, i concentrati del complesso protrombinico sono più efficaci del PFC (e più rapidamente disponibili)

Conclusions

- Gli antidoti dei nuovi anticoagulanti sono ancora pochi e cari, ma potrebbero essere la soluzione del futuro
- Per gli antiaggreganti, le piastrine restano il solo trattamento riconosciuto in caso di emorragie massive
- I trattamenti adiuvanti possono essere un’opzione interessante
- Il ticagrelor rappresenta una sfida nella presa in carico dell’emorragia


THE NEW MACHINE IMPROVED THEATRE PRODUCTIVITY BY 30%, SO LONG AS THE MILK AND PROPOFOL DIDN'T GET CONFUSED.

Merci

Referenze principali

- Kozek-Langenecker et al, Management of severe perioperative bleeding: guidelines from the European Society of Anesthesiology. First update 2016, Eur J Anesthesiol 2017; 34:332-395
- Tomaselli et al, 2017 ACC ECDP on Management of Bleeding in Patients on Oral Anticoagulants
- Doherty et al., 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation
- H. Heidbuchel et al., Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation, Europace (2015) 17, 1467–1507
- Makris et al, Guideline on the Management of Bleeding in Patients on Antithrombotic Agents, British Journal of Haematology, 2012, 160, 35-46
- «Perioperative hemostasis – Coagulation for anesthesiologist», C.E. Marcucci, P. Schoettker editors, 2015