Il Trauma Grave nel paziente che assume anticoagulanti

Geminiano Bandiera

Responsabile del Pronto Soccorso NOCSAE

ASL Modena

Preinjury warfarin does not impact outcome in trauma patients

J Trauma. 2001 Dec; 51(6):1147-51; discussion 1151-2

The objective of this study was to determine whether the preinjury condition of anticoagulation had an adverse impact on patients sustaining injury.

CONCLUSION: Our data suggest that the PIC of anticoagulation with warfarin does not adversely impact mortality or LOS outcomes in both head and non-head injured patients. In non-head injured patients, however, the occurrence rates and discharge destination were different. More research needs to be done to determine whether this is related to anticoagulation or other reasons (i.e., number of PICs). These data should be used when weighing risk/benefit ratios of prescribing chronic anticoagulation.

La mortalità non peggiora

Mountain D, Sistenich V, Jacobs IG

Characteristics, management and outcomes of adults with major trauma taking pre-injury warfarin in a Western Australian population from 2000 to 2005: a population-based cohort study

MJA. 2010 Aug 16; 193(4): 202-06

Conclusions: Patients with major trauma taking warfarin at the time of injury have high mortality rates, poor functional outcomes and long delays to initiation and completion of anticoagulation reversal. Rapid, appropriate warfarin reversal was rarely performed and was not independently associated with survival. Age, low on-scene GCS and progressive ICH were strongly associated with mortality, but presenting INR, ICH v no ICH, and sex were not.

L'outcome peggiora!

A meta-analysis to determine the effect of pre-injury warfarin on mortality in trauma patients

John S Batchelor and Shariq Ahmed

Trauma 2014, Vol. 16(2) 108–113

Conclusions

The results of this meta-analysis have shown that pre- injury warfarin does increase mortality in trauma patients by an odds ratio of nearly two.

Eccome se peggiora!!

Registro Regionale Trauma Grave
Emilia Romagna

Classi di età	Sesso	N. pazienti	TAO	
			N.	%
0-14	Femmina	39	0	**0**
	Maschio	98	0	**0**
	Totale	**137**	**0**	**0**
15-40	Femmina	285	0	**0**
	Maschio	1.088	1	**0,1**
	Totale	**1.373**	**1**	**0,1**
41-64	Femmina	315	2	**0,6**
	Maschio	1.083	8	**0,7**
	Totale	**1.398**	**10**	**0,7**
65-74	Femmina	152	7	**4,6**
	Maschio	381	21	**5,5**
	Totale	**533**	**28**	**5,3**
>=75	Femmina	344	36	**10,5**
	Maschio	493	64	**13,0**
	Totale	**837**	**100**	**11,9**
Totale		**4.278**	**139**	**3,2**

Registro Regionale Trauma Grave
Emilia Romagna

Pazienti in TAO	N. pazienti	Trasfusioni di sangue			Trasfusioni di plasma		
		N.	%	Media ml	N.	%	Media ml
No	4.139	1.098	26,5	10.686,1	840	20,3	8.593,4
Si	139	38	27,3	17.924,8	35	25,2	18.212,9
Totale	**4.278**	**1.136**	**26,6**	**10.928,3**	**875**	**20,5**	**8.978,2**

Pazienti in TAO	N. pazienti	Intervento chirurgico		Embolizzazione	
		N.	%	N.	%
No	4.139	2.066	49,9	184	4,4
Si	139	61	43,9	4	2,9
Totale	**4.278**	**2.127**	**49,7**	**188**	**4,4**

Registro Regionale Trauma Grave
Emilia Romagna

Pazienti in TAO	N. pazienti	Degenza totale		Degenza TI	
		Media	Mediana	Media	Mediana
No	4.139	23,5	12	8,7	4
Si	139	21,2	12	9,8	5
Totale	**4.278**	**23,4**	**12**	**8,8**	**4**

Pazienti in TAO	N. pazienti	Decesso 30 gg	
		N.	%
No	4.139	469	11,3
Si	139	42	30,2
Totale	**4.278**	**511**	**11,9**

Complications of Preinjury Warfarin Use in the Trauma Patient

Alfred A. Mina, MD, Holly A. Bair, MSN, Greg A. Howells, MD, and Phillip J. Bendick, PhD

Background: The frequency of use of warfarin anticoagulation increases significantly in the elderly population. It remains controversial whether this puts these patients at increased risk for hemorrhagic complications after trauma.

Methods: We prospectively evaluated consecutive trauma patients who were taking warfarin and compared their outcomes to a group of age-matched patients with head injuries but not taking warfarin.

Results: One hundred fifty-nine trauma patients on warfarin were evaluated, 94 (59%) with some type of head trauma; 25 of these 94 patients (27%) had documented intracranial trauma. Fifteen patients died (9.4%); they had an international normalized ratio of 3.3 ± 1.6 versus 3.0 ± 2.1 for survivors in the warfarin group ($p = 0.585$). Twelve deaths were in the group of 25 patients with intracranial injuries (48%). Three patients without head injury died (5%) of other causes not related to warfarin or hemorrhage at a mean of 13 days after admission. Ten of 12 patients on warfarin with intracranial injuries who died had documented loss of consciousness (LOC); two patients who died secondary to an isolated intracranial injury had no LOC. Of 70 age-matched patients with head trauma not taking warfarin, 47 (67%) had intracranial injury and 5 of these died (10%) ($p < 0.001$ for both values compared with study patients). There were no significant differences for patients with intracranial injury comparing those on warfarin and those who were not in terms of age, gender, mechanism of injury, Injury Severity Score, or Glasgow Come Scale score.

Conclusion: We conclude that the preinjury use of warfarin does not place the trauma patient at increased risk for fatal hemorrhagic complications in the absence of head trauma. Furthermore, the presence of a head trauma alone is not predictive of mortality. However, the presence of intracranial injury is strongly associated with a mortality rate that is significantly higher than patients with head trauma who are not taking warfarin. LOC is also associated with mortality, but the absence of loss of consciousness does not reliably indicate the absence of intracranial injury or risk of death.

Key Words: Warfarin, Anticoagulation, Preinjury, Head injury, Loss of consciousness.

J Trauma. 2003;54:842–847.

Peggior outcome in caso di emorragia cerebrale traumatica

Il Trauma Cranico, di per sé, non si associa ad outcome peggiori

Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma

Franko J, Kish KJ, O'Connell BG, Subramanian, S Yuschak JV

J Trauma 2006 Jul;61(1):107-10

BACKGROUND:A large population of patients on oral anticoagulants is exposed to the risk of traumatic brain injury (TBI). Effects of age and anticoagulation on TBI outcomes need to be assessed separately.
METHODS:Retrospective analysis of consecutive series of TBI patients (age 18 years and older) in a suburban teaching.
CONCLUSIONS: Both age and warfarin anticoagulation are independent predictors of mortality after blunt TBI. Warfarin anticoagulation carries a six-fold increase in TBI mortality. Age over 70 years and excessive anticoagulation are associated with higher mortality, as well.

Età ed INR sono variabili indipendenti nel peggiorare l'outcome dei pazienti in TAO con Trauma Cranico Grave

Mountain D, Sistenich V, Jacobs IG.

Characteristics, management and outcomes of adults with major trauma taking pre-injury warfarin in a Western Australian population from 2000 to 2005: a population-based cohort study.

MJA. 2010 Aug 16; 193(4): 202-06

Conclusions: Patients with major trauma taking warfarin at the time of injury have high mortality rates, poor functional outcomes and long delays to initiation and completion of anticoagulation reversal. Rapid, appropriate warfarin reversal was rarely performed and was not independently associated with survival. Age, low on-scene GCS and progressive ICH were strongly associated with mortality, but presenting INR, ICH v no ICH, and sex were not.

Età e GCS iniziale, nel paziente con ICH, sono variabili indipendenti in grado di influenzare l'outcome

Coagulopathy as a risk factor in warfarinised head injury patients

Simon Rendell, Laith Sultan

*Emerg Med J*2014;**31:**331-337

There is good evidence here to demonstrate the **deleterious effects of a supra-therapeutic INR** (Menditto *et al*, 2012; Major and Reed, 2009; Pieracci *et al*, 2007; Cohen *et al*, 2006; Franko *et al*, 2006) **In tutti i traumi gravi!**

There is much to suggest, though, that **there is not a great causal significance in the level of coagulopathy in the low-risk WHI patient** (Rendell and Batchelor, 2013; Nishijima *et al*, 2012). Nishijima *et al* (2013), Nishijima *et al* (2012), Gittleman *et al* (2005) and Li *et al* (2001) demonstrate the **high incidence of ICH in anticoagulated patients following seemingly trivial injury without high-risk features**.

Rendell and Batchelor (2013) and Ivascu *et al (2005) conclude that* ***neither the GCS nor the level of anticoagulation can reliably predict the presence of ICH****, even that a sub-therapeutic INR appears to offer no protection, and that* ***urgent scanning combined with prompt reversal can reduce ICH progression and improve mortality.***

The Eastern Association for the Surgery of Trauma

east

Geriatric Trauma, Evaluation and Management of

J Trauma 73(5):S345-S350, November 2012

Question 2

How should medication-induced coagulopathy be addressed during the early postinjury period?

Recommendations

Level 3 **Hot Water**

- Controllo precoce INR in tutti gli anziani in TAO
- Precoce TC encefalo nei pazienti con Trauma Cranico importante
- Reversal della terapia anticoagulante entro 2 ore con target di INR <1.6

Treatment of trauma patients with intracranial hemorrhage on preinjury warfarin

Ivascu FA, Janczyk RJ, Junn FS, Bair HA, Bendick PJ, Howells GA

J Trauma 2006 Aug;61(2):318-21

BACKGROUND: Preinjury warfarin anticoagulation has been shown to increase the mortality of traumatic intracranial hemorrhage. We have evaluated the impact on patient mortality of the rapid triage of patients at risk for warfarin associated traumatic intracranial hemorrhage. METHODS: A "Coumadin Protocol" was implemented in January, 2001 in the Emergency Department that expedited triage of anticoagulated trauma patients to immediate physician evaluation. Patient outcomes during a 2 year period were compared with a matched control group of similarly injured, anticoagulated patients who were treated before protocol initiation. RESULTS: Thirty-five patients were treated after implementation of the Coumadin Protocol. Mean time until warfarin reversal was 4.3 +/- 4.4 hours, and there was a 37% mortality. Twenty-two control patients had a mean time to reversal of 4.2 +/- 2.9 hours, with a 45% mortality ($p = 0.610$). Ten protocol patients were shown to have intracranial hemorrhage progression by computed tomography (CT) scan, with a 60% mortality rate. Seventeen patients had follow-up CT scan and showed no progression; only one of these patients (6%) died ($p = 0.004$). Hemorrhage severity based on the initial CT scan did not predict mortality or hemorrhagic progression. **CONCLUSIONS:** We conclude from these data that a *trauma center protocol for rapid identification of intracranial bleeding without a concomitant therapeutic protocol* ***does not improve survival in head injured patients on preinjury warfarin.***

ACS TQIP GERIATRIC TRAUMA MANAGEMENT GUIDELINES

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- Anticoagulation reversal:

  This field and the availability of products for reversal are also changing rapidly. A protocol to rapid anticoagulation reversal is associated with improved outcomes in injured patients.

  - It is suggested that a rapid anticoagulation reversal protocol be developed in each center based on the availability of products, local costs, and preferences. In general, the following principles should be applied:
    - Warfarin reversal: While reversal of warfarin was typically managed using a combination of vitamin K and plasma in the past, the availability and assessment of newer prothrombin complex concentrates (PCC) have provided other options. PCCs available as four-factor concentrates (II, VII, IX, and X) can reverse the effects of warfarin rapidly and are considered the standard in most countries other than the U.S. At this time, only three-factor concentrates are available in the U.S. These PCCs lack factor VII and must either be given with plasma or rVIIa.

AHA, ACEP, FCSA … Guidelines

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Parachutes reduce the risk of injury after gravitatio not been proved with randomised controlled trials

Controversy

Parachute approach to evidence based medicine

Malcolm Potts, Ndola Prata, Julia Walsh, Amy Grossman

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done

BMJ VOLUME 333 30 SEPTEMBER 2006 bmj.com

PHOTOS.COM

Sometimes it's best just to jump in

Regione Emilia-Romagna

Direzione Generale Sanità e Politiche Sociali
Commissione Regionale del Farmaco
(D.G.R. 1540/2006, 2129/2010 e 490/2011)

Documento PTR n. 170 relativo a:

COMPLESSO PROTROMBINICO UMANO A 4 FATTORI E SCHEDA DI ESITO

Dicembre 2012

Regione Emilia-Romagna

Assessorato Politiche per la salute – Commissione Regionale del Farmaco

COMPLESSO PROTROMBINICO UMANO
(Fattori II, VII, IX, X della coagulazione in combinazione)

Indicazioni registrate

- Trattamento e profilassi perioperatoria degli episodi emorragici nei casi di carenza acquisita dei fattori della coagulazione del complesso protrombinico, come la carenza causata da una terapia con antagonisti della vitamina K oppure in caso di sovradosaggio di antagonisti della vitamina K, quando è richiesta una rapida correzione della carenza stessa.
- Trattamento e profilassi perioperatoria degli episodi emorragici nei casi di carenza congenita di uno o più fattori della coagulazione dipendenti dalla vitamina K quando non sia disponibile un prodotto a base dello specifico fattore della coagulazione

Complesso protrombinico	Unità per confezione	Prezzo ex-factory CODIFA 12/12/12	Costo UI	UI necessarie (INR iniziale 4-6) in pazienti di 70 kg	Costo posologico per paziente 70 kg con 4<INR>6
4 fattori	500 UI	230 €	0,46 €	2450 U I =5 flaconi	1150 €
3 fattori	500 UI	155,11 €	0,31 €	2450 UI - 5 flaconi	775,55 €
	SCAMBIO PLASMA 500UI	129 €	0,26 €	2450 UI - 5 flaconi	645 €
	600 UI	155,11 €	0,26 €	2450 UI 4 flaconi	620 €
Plasma fresco congelato	250UI	20 €	0,08 €	1400 UI 6 flaconi	120 €

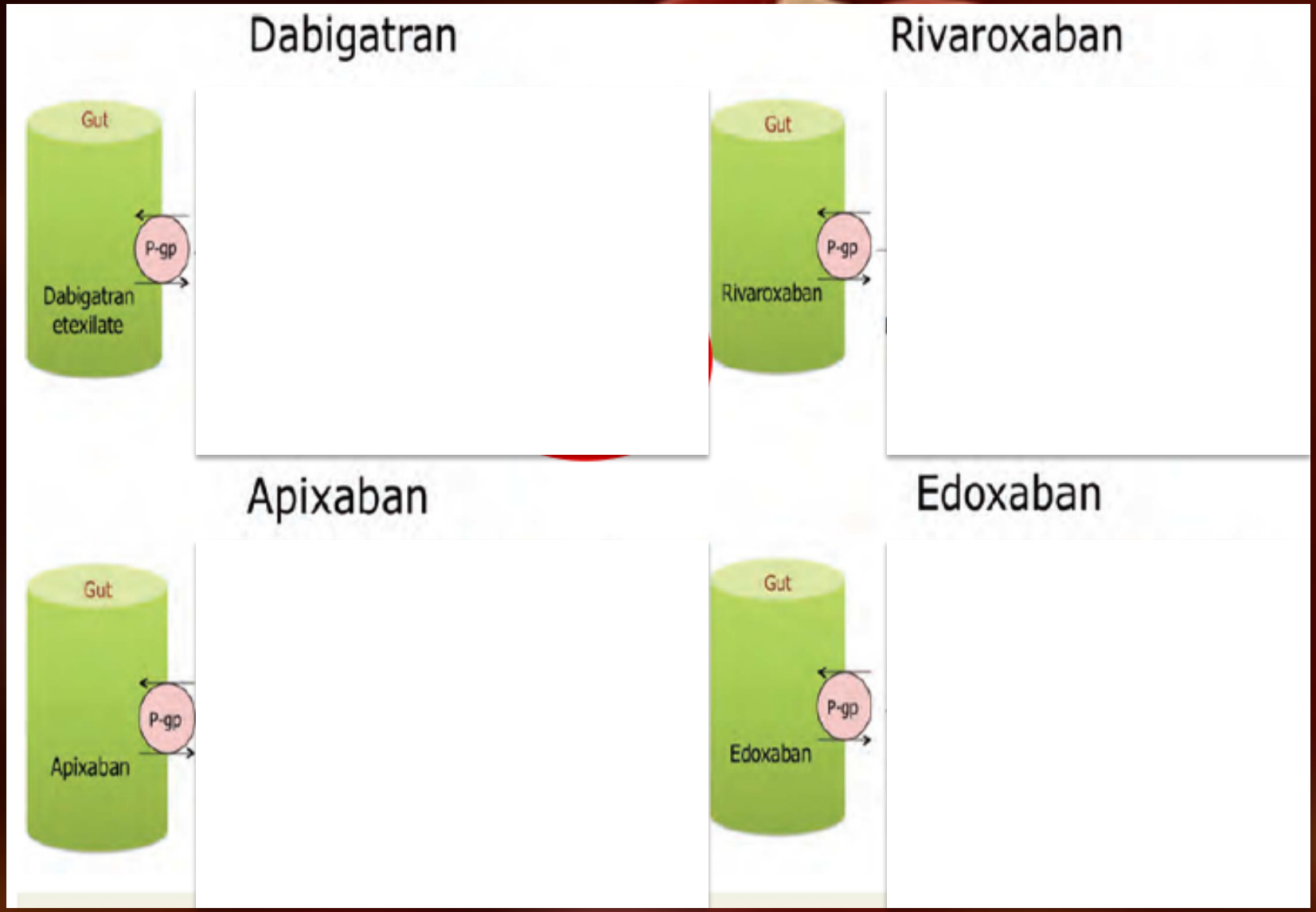
Warfarin-associated intracerebral hemorrhage is inadequately treated at community emergency departments

Liotta EM, Garg RK, Temes RE, John S, Lee VH, Bleck TP, Prabhakaran S

Stroke. 2012 Sep;43(9):2503-5

CONCLUSIONS: Treatment of warfarin-associated intracerebral hemorrhage in community emergency departments **is often suboptima**l and does not adhere to published guidelines. Treating coagulopathy aggressively before interhospital transfer may improve outcomes and warrants further investigation.

Nuovi Anticoagulanti Orali



Quanto tempo è passato dall'ultima somminstrazione?

	Tempo di Picco	Tempo di Valle
Dabigatran	*2h*	*12-24h*
Apixaban	*1-4h*	*12-24h*
Endoxaban	*1-2h*	*12-24h*
Rivaroxaban	*2-4h*	*16-24h*

Funzione Renale e normalizzazione della coagulazione dopo somministrazione di Dabigatran

	Tempo di Valle
Cl. Creat. normale	*12-24h*
Cl. Creat. 50-80 ml/min	*24-36h*
Cl. Creat. 30-50 ml/min	*36-48h*
Cl. Creat. <30 ml/min	*> 48h*

Drug-drug interactions

Table I Effect on new oral anticoagulant plasma levels ('area under the curve, AUC') from drug–drug interactions and recommendations towards new oral anticoagulant dosing

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[39]	no data yet	no effect[40]	no effect[41, 42]
Digoxin	P-gp competition	no effect [43]	no data yet	no effect[40]	no effect[42, 44]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[45] (reduce dose and take simultaneously)	no data yet	+53% (SR)[40] (Reduce dose by 50%)*	minor effect (use with caution if CrCl 15-50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	no effect[45]	+40%[SmPC]	no data yet	minor effect (use with caution if CrCl 15-50 ml/min)
Quinidine	P-gp competition	+50%	no data yet	+80%[40] (Reduce dose by 50%)§	+50%
Amiodarone	P-gp competition	+12-60%[45]	no data yet	no effect[40]	minor effect (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70-100% (JR: 2 x 75 mg)	no data yet	+85% (Reduce dose by 50%)*	no data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (JR: 2 x 75 mg)	+130%[SmPC]	no data yet	up to +160%[47]
fluconazole	moderate CYP3A4 inhibition	no data yet	no data yet	no data yet	+42% (if systemically administered)[42]
Cyclosporin; tacrolimus	P-gp competition	no data yet	no data yet	no data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15-20%	no data yet	no data yet	+30-54%[42, 46]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	no data yet	Strong increase[SmPC]	no data yet	up to +153%[43]
Rifampicin; St. John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	-66%[47]	-54%[SmPC]	-35%	up to -50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	-12-30%[45, 48, 49]	no data yet	no effect	no effect[50, 51]
Other factors:					
Age ≥ 80 years	Increased plasma level			no data yet	
Age ≥75 years	Increased plasma level			no data yet	
Weight ≤ 60 kg	Increased plasma level			52	
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Red, contraindicated/not recommended; orange, reduce dose (from 150 to 110 mg b.i.d. for dabigatran; from 20 to 15 mg q.d. for rivaroxaban; from 5 to 2.5 mg b.i.d. for apixaban); yellow, consider dose reduction if another 'yellow' factor is present; hatching, no data available; recommendation based on pharmacokinetic considerations.
BCRP, breast cancer resistance protein; NSAID, non-steroidal anti-inflammatory drugs; H2B, H2-blockers; PPI, proton-pump inhibitors; P-gp, P-glycoprotein; NSAID, non-steroidal anti-inflammatory agent; GI, gastro-intestinal.
*No EMA approval yet. Needs update after finalization of SmPC.
§Pre-specified dose reduction has been tested in Phase 3 clinical trial (to be published).

European Heart Journal
doi:10.1093/eurheartj/eht134
2013

EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary

Hein Heidbuchel, Peter Verhamme, Marco Alings, Matthias Antz, Werner Hacke, Jonas Oldgren, Peter Sinnaeve, A. John Camm and Paulus Kirchhof

European Heart Journal, 2013

2. How to measure the anticoagulant effect of new oral anticoagulants?

Quantitative tests for DTI and FXa inhibitors do exist (diluted thrombin-time and chromogenic assays, respective), **but they may not (yet) be routinely available** in most hospitals. Moreover, **there are no data on a cut-off** of these specific tests below which elective or urgent surgery is 'safe', and therefore their use in this respect cannot be recommended at this time. Point of care tests to assess the international normalized ratio 210 (INR) should not be used in patients on NOACs.

Vi sono dati che indicano che *in caso di emergenza sia il tempo di protrombina sia l'aPTT (o il tempo di trombina) possono orientare in modo qualitativo sull'esistenza di un effetto anticoagulante, ma non dare una indicazione certa sulla sua entità.* Ciò è vero per l'**aPTT** nei confronti del **dabigatran** (Douxfils J et al. 2012), mentre gli effetti del **rivaroxaban sul PT**, test in genere più sensibile a questo farmaco, sono meno prevedibili

2013

European Heart Journal
doi:10.1093/eurheartj/eht134
2013

Carbone vegetale per os se assunzione <2h

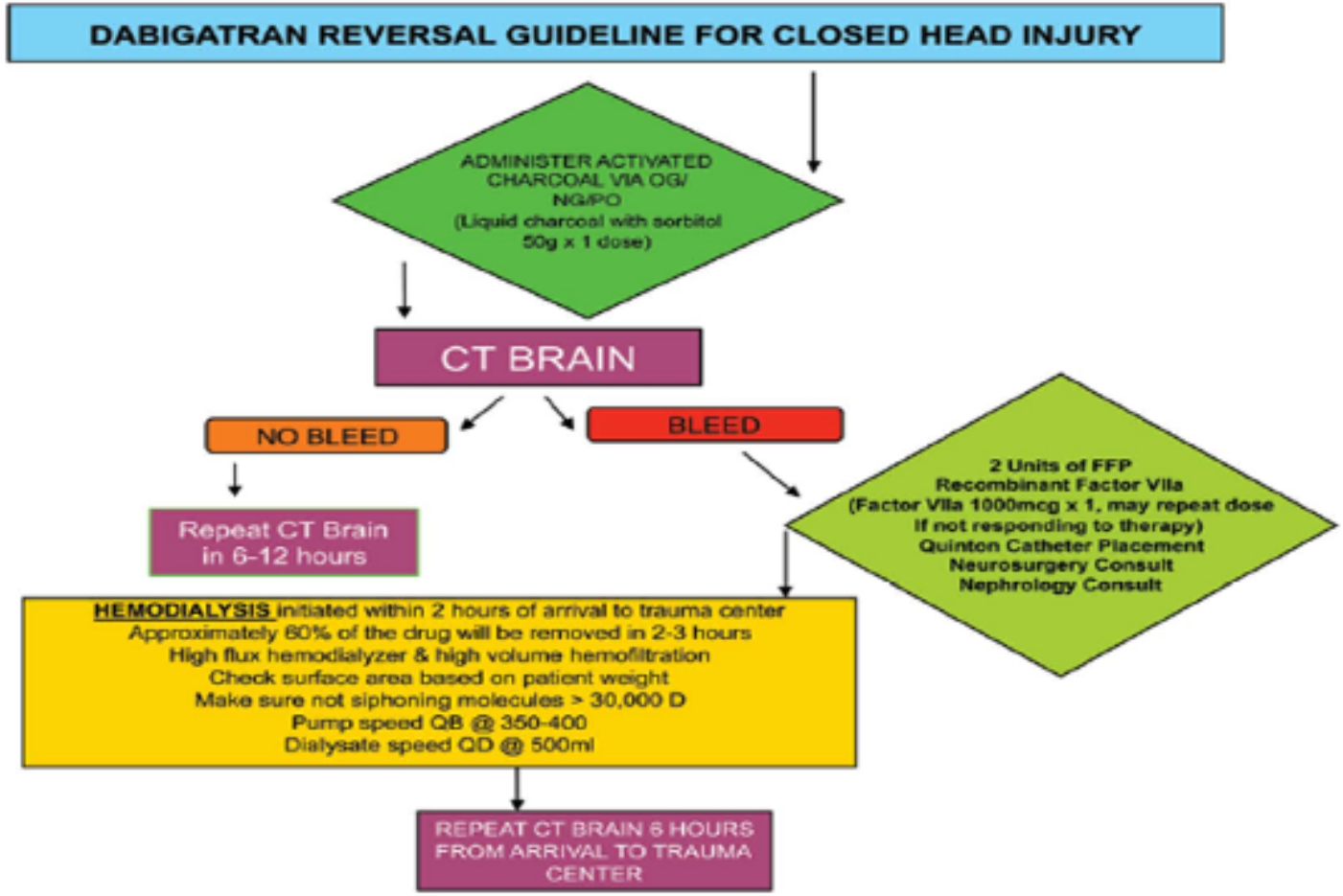
Table 2 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non-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 4h)[53] Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization 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) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/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)	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/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.

Dabigatran bleed risk with closed head injuries: are we prepared?

J Neurosurg 119:760–765, 2013



In fondo nulla di nuovo…

Grazie dell'attenzione!