CONVEGNO

Terapie Anticoagulanti

EVIDENZE ED OPINIONI A CONFRONTO

Cremona, venerdì 4 marzo 2016

Sistema Socio Sanitario
Regione Lombardia
ASST Cremona

La gestione delle complicanze emorragiche Farmaci DOAC

Marco Marietta AOU Modena

marco.marietta@unimore.it

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Regolamento Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, io sottoscritto **Dott. Marco Marietta** dichiaro che negli ultimi due anni ho avuto i seguenti rapporti ricevendo compens individuali con soggetti portatori di interessi commerciali in campo sanitario:

- **Partecipazione ad Advisory Board per l' Azienda Novo-Nordisk**
- **Relazioni a congressi per la ditta Kedrion, Orphan, Novo-Nordisk**

E' sui fianchi delle montagne, e non sulla cima, che si sviluppa la vita.
Ma evidentemente senza la cima non si possono avere i fianchi.
E' la cima che determina i fianchi.
E così saliamo.

Robert Pirsig
Lo zen e l'arte della manutenzione della motocicletta

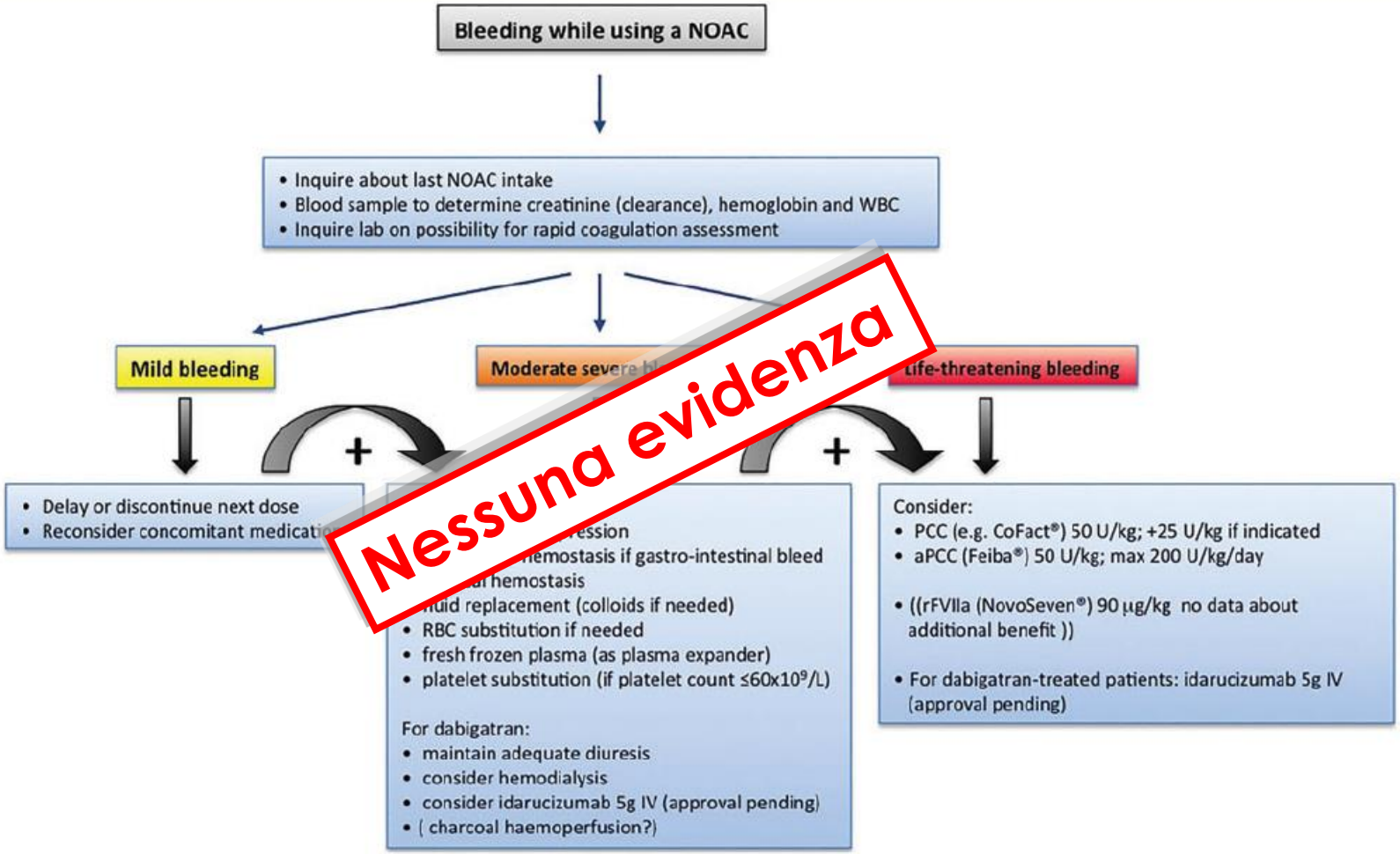
..., e non sulla cima...

Le Linee Guida

Conflict of interest: H.H. is Coordinating Clinical Investigator for the Biotronik-sponsored EuroEco study on health-economics of remote device monitoring. H.H. is a member of the scientific advisory board of Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, and Sanofi-Aventis, received lecturing fees from these same companies and from Merck, Cardiome, Biotronik, St Jude Medical, and received unconditional research grants through the University of Leuven from St Jude Medical, Medtronic, Biotronik, and Boston Scientific Inc. P.V. has received research funding through the University of Leuven from Boehringer Ingelheim, Bayer HealthCare, Daiichi-Sankyo, and ThromboGenics. P.V. has received speaker honoraria from Boehringer Ingelheim, Bayer Healthcare, Daiichi-Sankyo, Pfizer, and Sanofi-Aventis. M.Alings has received advisory board fees from Bayer, Boehringer Ingelheim, Bristol-Meyer-Squib, Pfizer, and Daiichi-Sankyo, fees for development of educational presentations from Boehringer Ingelheim and travel support by St Jude Medical. M.Antz has received consulting fees and speaker honoraria from Biosense Webster, Bayer HealthCare, Boehringer Ingelheim, Sanofi-Aventis, Bristol-Myers-Squibb, Daichii-Sankyo, Pfizer, as well as speaker honoraria from Boston Scientific and Pioneer Medical Devices. H.-C.D. received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, St Jude, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi. Financial support for research projects was provided by AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Talecris. Within the past year H.-C.D. served as editor of Aktuelle Neurologie, Arzneimittelthera-pie, Kopfschmerznews, Stroke News and the Treatment Guidelines of the German Neurological Society, as co-editor of Cephalalgia and on the editorial board of Lancet Neurology, Stroke, European Neurology and Cerebrovascular Disorders. The Department of Neurology at the University Duisburg-Essen re-ceived research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertelsmann Foundation and Heinz-Nixdorf Foundation. H.-C.D. has no ownership interest and does not own stocks of any pharmaceutical company. W.H. received grants for clinical research from Boehringer Ingelheim Pharmaceuticals. J.O. received institutional research grant from Boehringer Ingelheim; and has received consulting and speaker fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. P.S. has received research funding through the University of Leuven from Astra Zeneca and GSK. P.S. has received speaker and/or consulting honoraria from Boehringer Ingelheim, Bayer Healthcare, Daiichi-Sankyo, Pfizer, Sanofi-Aventis, Bristol-Meyer-Squib, and Abbott. A.J.C. received grants for clinical research from Bristol-Myers Squibb, Daiichi-Sankyo, Sanofi-Aventis, and Servier. A.J.C. served as an advisor, speaker and/or, consultant for Actelion Pharmaceuticals, ARYx Therapeutics, Bristol-Myers Squibb, Cardiome Pharma, CV Therapeutics, Daiichi-Sankyo, Menarini Group, Merck, Novartis Pharmaceuticals, Pfizer, Sanofi-Aventis, Servier, and Xention. He served as a member of the data and safety monitoring board for Bristol-Myers Squibb, Novartis Pharmaceuticals, and Servier. He served as an expert witness for Johnson & Johnson, Sanofi-Aventis, and Servier. P.K. received consulting fees and honoraria from 3M Medica, MEDA Pharma, AstraZeneca, Bayer Healthcare, Biosense Webster, Boehringer Ingelheim, Daiichi-Sankyo, German Cardiac Society, MEDA Pharma, Medtronic, Merck, MSD, Otsuka Pharma, Pfizer/BMS, sanofi, Servier, Siemens, TAKEDA, and support for research from 3M Medica/MEDA Pharma, Cardiovascular Therapeutics, Medtronic, OMRON, SANOFI, St Jude Medical, German Federal Ministry for Education and Research (BMBF), Fondation Leducq, German Research Foundation (DFG), and the European Union (EU).

Martin Van Eickels, M.D. (Bayer Healthcare Pharmaceuticals), and
Isabelle Richard-Lordereau, M.D. (Bristol Myers Squibb/Pfizer)

Europace
doi:10.1093/europace/euv309

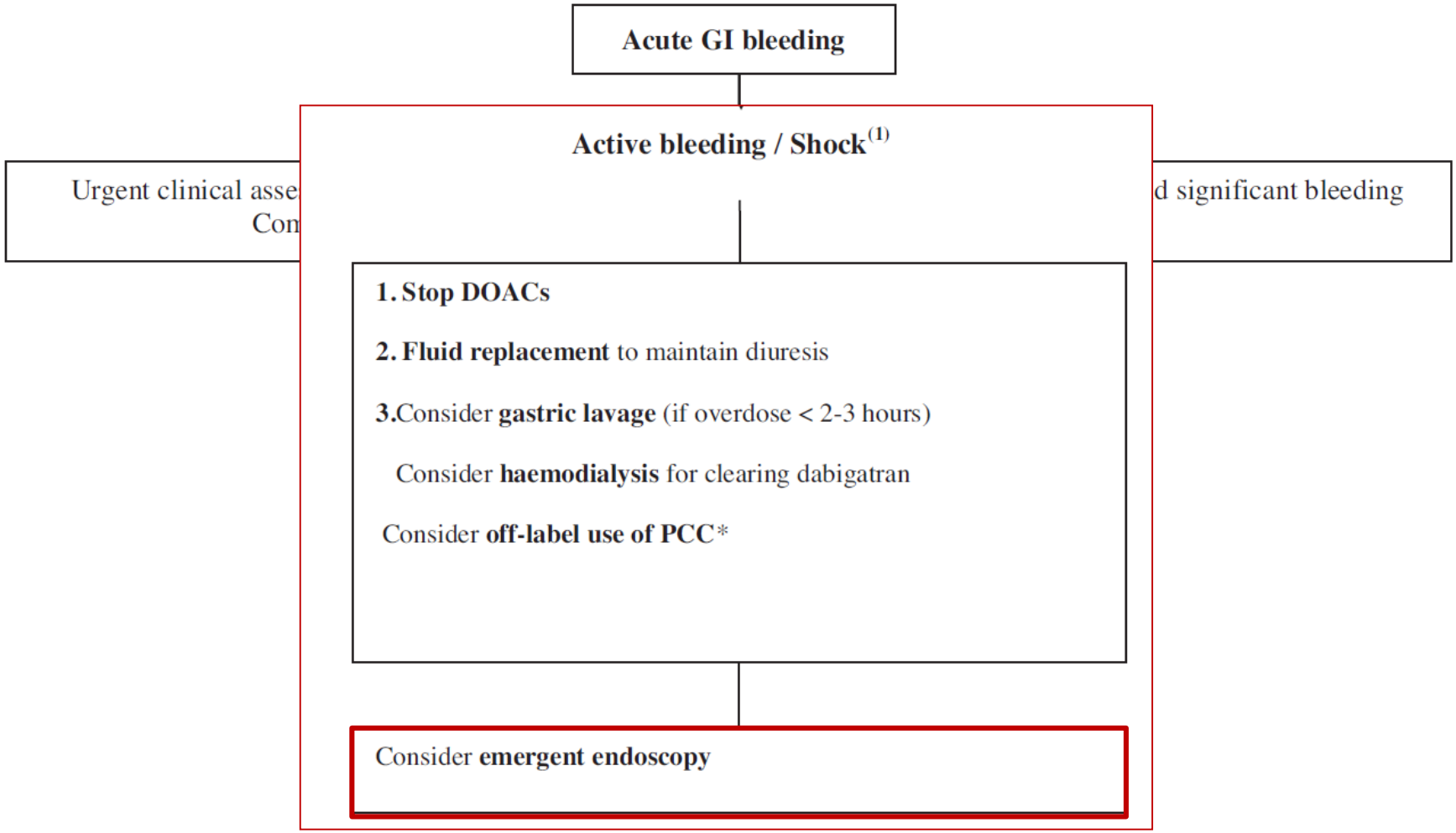


Digestive and Liver Disease 47 (2015) 621–627

Review Article

Management of anticoagulation in patients with acute gastrointestinal bleeding

Franco Radaelli[a,*], Francesco Dentali[b], Alessandro Repici[c], Arnaldo Amato[a], Silvia Paggi[a], Emanuele Rondonotti[a], Jean Marc Dumonceau[d]



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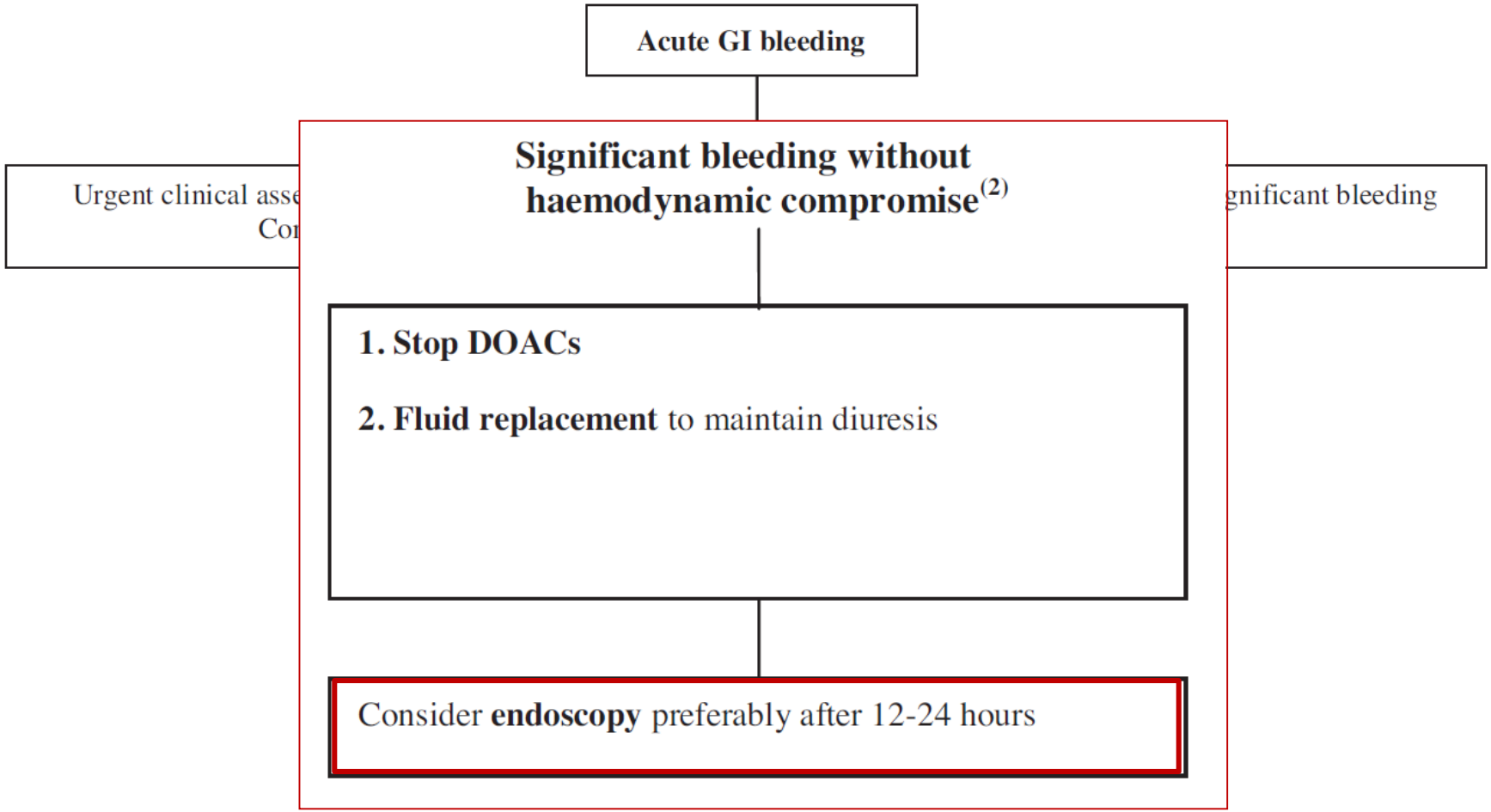

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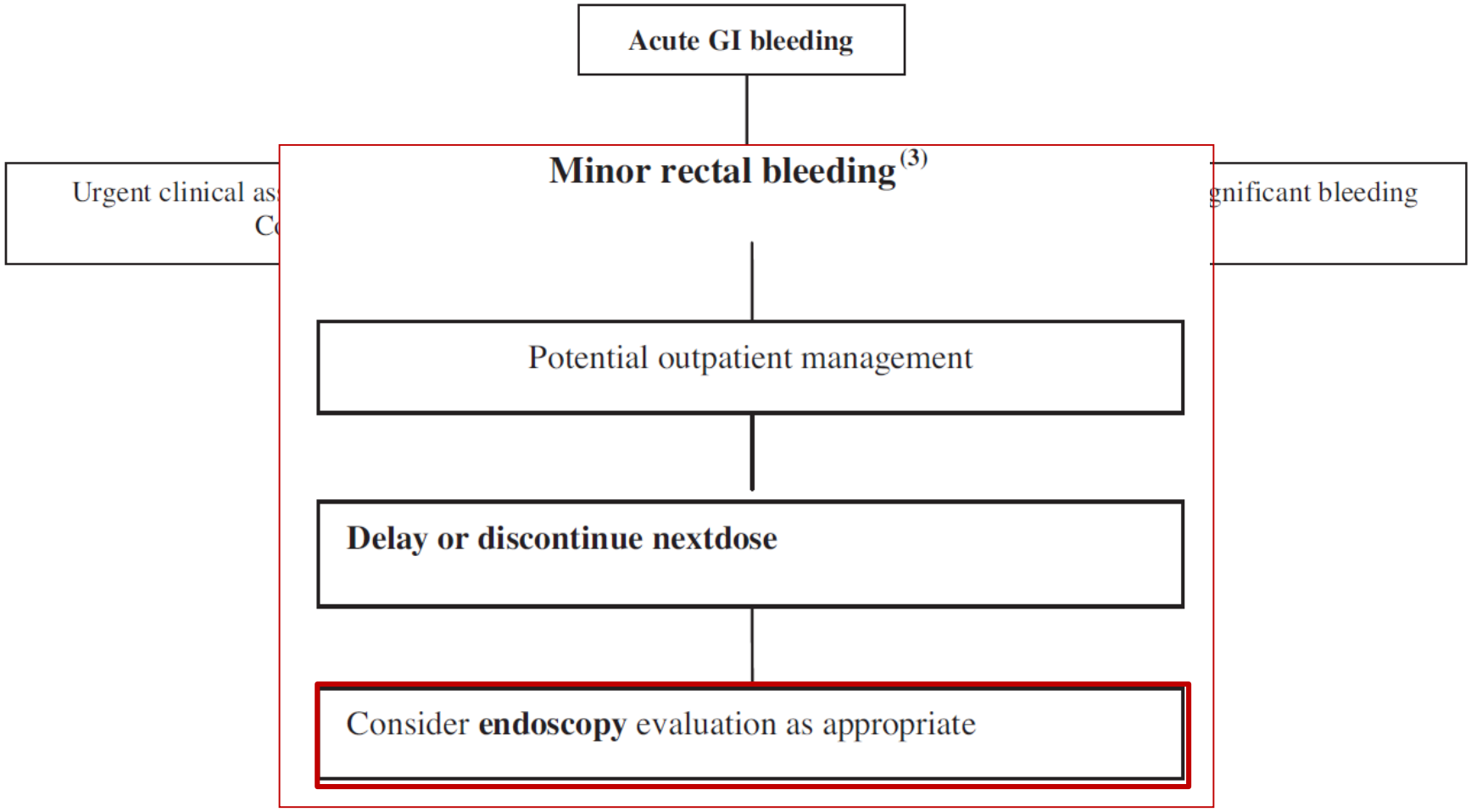


..., e non sulla cima...

Gli antidoti

ORIGINAL ARTICLE

This article was published on June 22, 2015, at NEJM.org.

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S.,

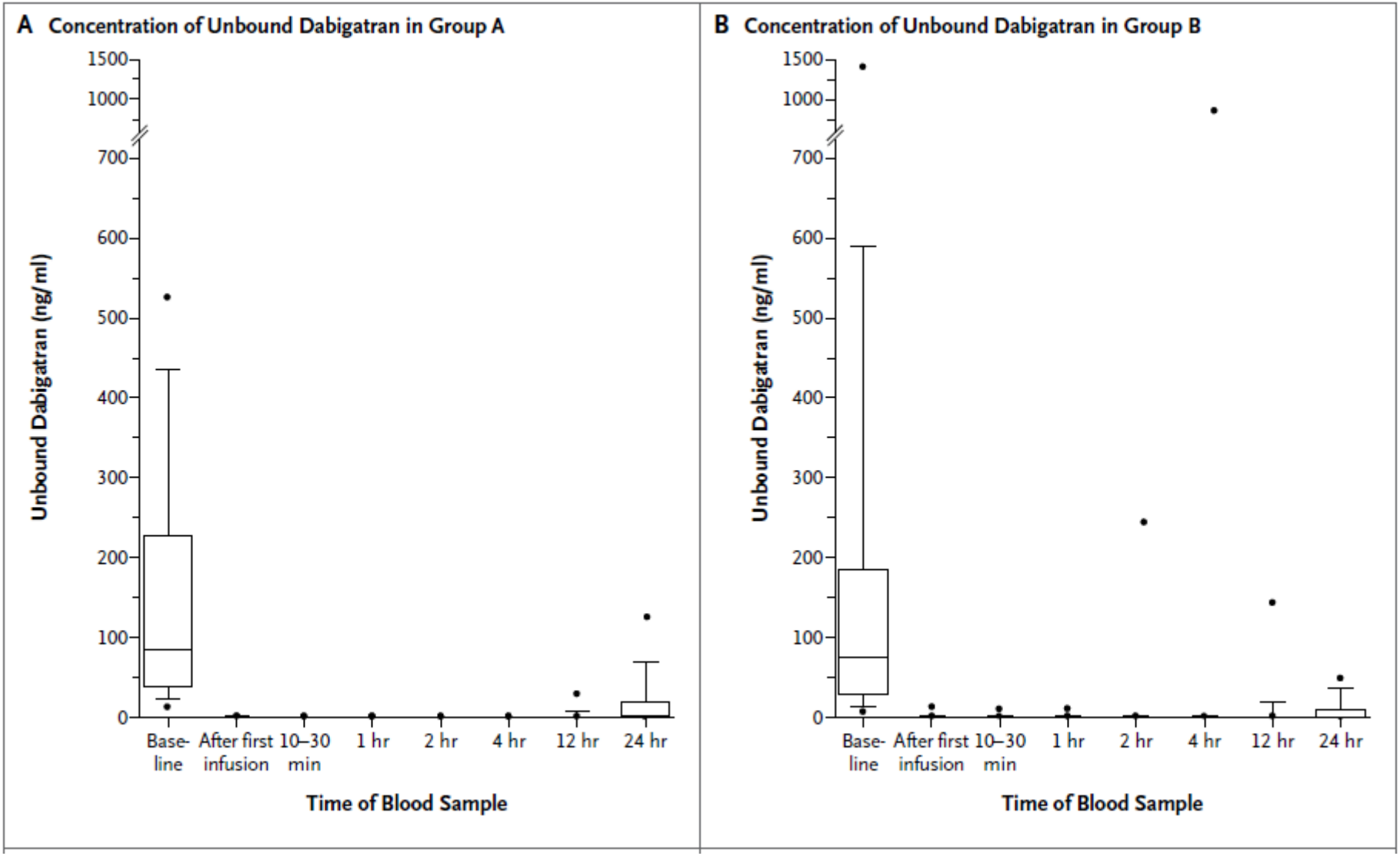
Patients in group A were those with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent.

Patients in group B were those who required surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal hemostasis was required.

The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran

Clinical outcomes, as assessed by the treating clinicians, were secondary end points.

This article was published on June 22, 2015, at NEJM.org.



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Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S.,

The time to the cessation of bleeding could not be ascertained in 13 (26%) patients, of whom 5 had intracranial hemorrhage, 4 had gastrointestinal bleeding, 2 had intramuscular bleeding, 1 had pericardial bleeding, and 1 had retroperitoneal bleeding.

In the remaining patients, the median investigator-reported time to the cessation of bleeding was 11.4 hours.

ORIGINAL ARTICLE

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Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S.,

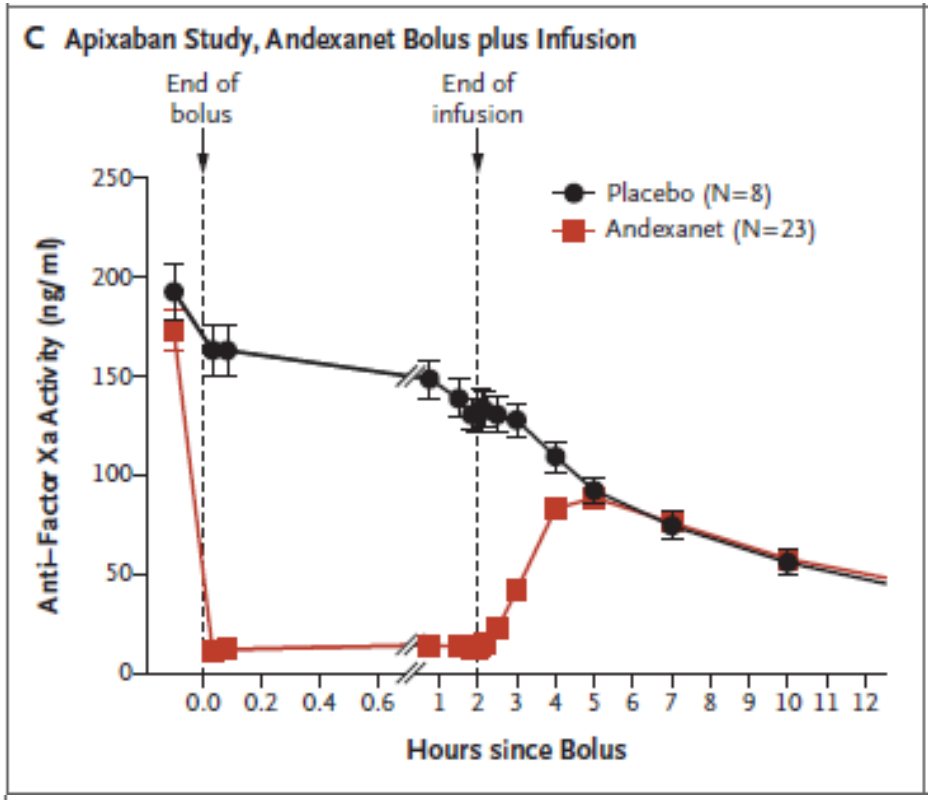
Mortality rate = 20%
Mortality rate bleeding-related ≈ 6%

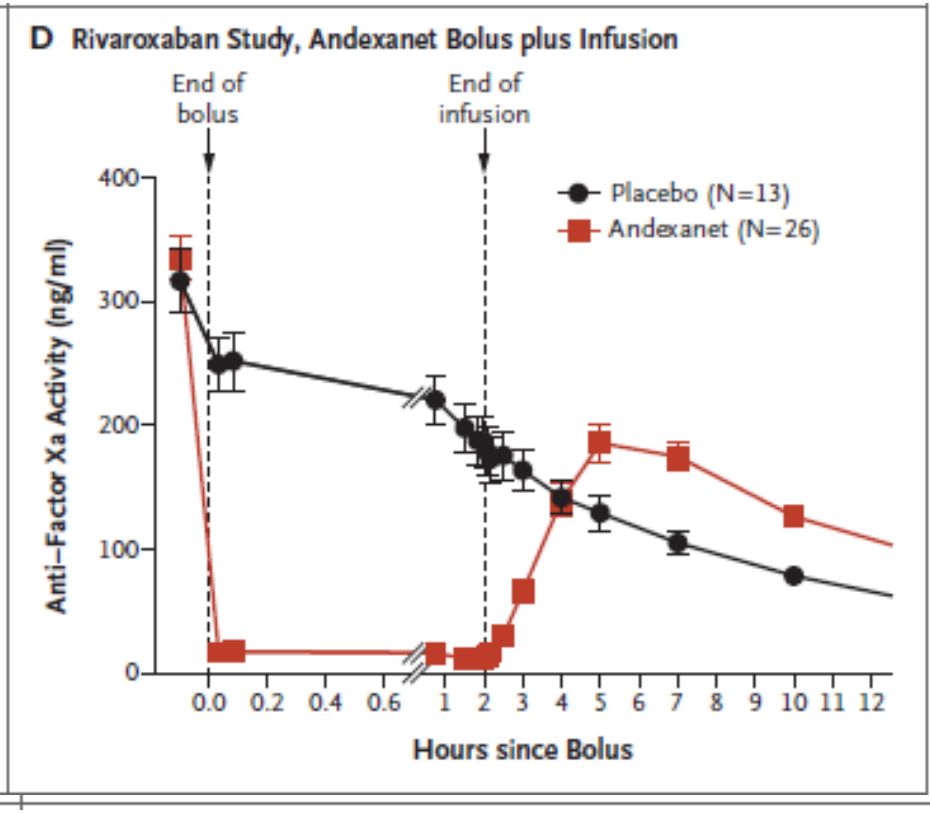
	stics ents		Study Group*	Treatment to Death
	yr	Sex		*days*
Cardiac arrest	82	Female	B	<1
Circulatory collapse	93	Male	B	<1
Hemodynamic collapse	88	Female	B	<1
Septic shock	87	Female	B	1
Sepsis, shock, and gastrointestinal bleeding	60	Male	B	1
Progression of respiratory failure	60	Male	A	1
New intracranial hemorrhage	77	Male	A	1
Progression of intracranial hemorrhage	69	Male	A	2
Multiorgan failure	87	Male	B	2
Progression of intracranial hemorrhage	69	Male	A	4

ORIGINAL ARTICLE

This article was published on November 11, 2015, at NEJM.org.

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity





E' sui fianchi delle montagne che si sviluppa la vita.

I percorsi ed il ruolo del Laboratorio

…e così saliamo….

- ✓ Ore 8 dell'1.11
  - SA, maschio, 77 anni, assume Dabi 150 per FA
- ✓ Ore 12
  - Accesso al PS di un Ospedale della provincia di MO per dolore improvviso fianco dx
  - PA 85/40, addome dolente e con resistenza alla palpazione emiaddome dx
  - Somministrati Tranexamico 2 gr **+ CCP 2000 UI**
  - Centralizzato su un DEA di 2° livello

- ✓ Ore 16:44
  - Arrivo al PS del DEA
  - PA 70/52
- ✓ Ore 17.23
  - TC addome: «*voluminoso ematoma in adiacenza al margine antero-laterale del rene destro con diametro trasverso massimo di 10x6.6 cm, esteso cranio-caudalmente per 14 cm, nel cui contesto è apprezzabile spandimento di mezzo di contrasto in fase arteriosa, e più evidente in fase venosa*»
  - aPTT ratio 1.4, Hb 10.1, eGFR 43 ml/min
  - Trasfonde 2 U EC

- ✓ Ore 19.49
  - «*L'angiografia selettiva dell' arteria renale destra evidenzia spandimento di mdc dell'a. segmentale superiore, che viene embolizzata con spongostan e spirali*»
  - Trasferito in TIPO
- ✓ Ore 21.32
  - aPTT Ratio 1.49, Hb 10.3, eGFR 35 ml/min
  - PAS 80/60

Dabigatranemia (dTT) 314 ng/ml

Quesito 3

Quali sono gli esami di laboratorio che devono essere disponibili in urgenza per la gestione dei NAO?

RACCOMANDAZIONE

In situazioni cliniche di urgenza/emergenza nei pazienti in trattamento certo o presunto con un NAO (dabigratan, rivaroxaban, apixaban) il GdL raccomanda l'esecuzione di specifici test per conoscere la presenza dell'effetto anticoagulante e misurarne l'entità.
Le principali condizioni di urgenza/emergenza in cui è raccomandabile l'esecuzione di tali test sono:

- emorragia in atto
- eventi trombotici acuti
- valutazione degli effetti dei trattamenti somministrati per la neutralizzazione dell'attività anticoagulante dei farmaci
- valutazione preliminare ad interventi chirurgici in urgenza/emergenza
- valutazione preliminare a manovre invasive (diagnostiche o terapeutiche) in urgenza/emergenza

In queste situazioni il GdL raccomanda di utilizzare test specifici per la misurazione dell'effetto anticoagulante dei NAO:

- per i pazienti in trattamento con **dabigatran**:
  ⇒ Tempo di Trombina diluito o dosaggio cromogenico dell'attività anti-IIa
- per i pazienti in trattamento con **rivaroxaban** e **apixaban**
  ⇒ Dosaggio cromogenico dell'attività anti Xa

Il GdL raccomanda che tali test siano eseguibili in urgenza.

(J Am Coll Cardiol 2014;63:321–8)

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Paul A. Reilly, PhD,* Thorsten Lehr, PhD,†‡ Sebastian Haertter, PhD,†

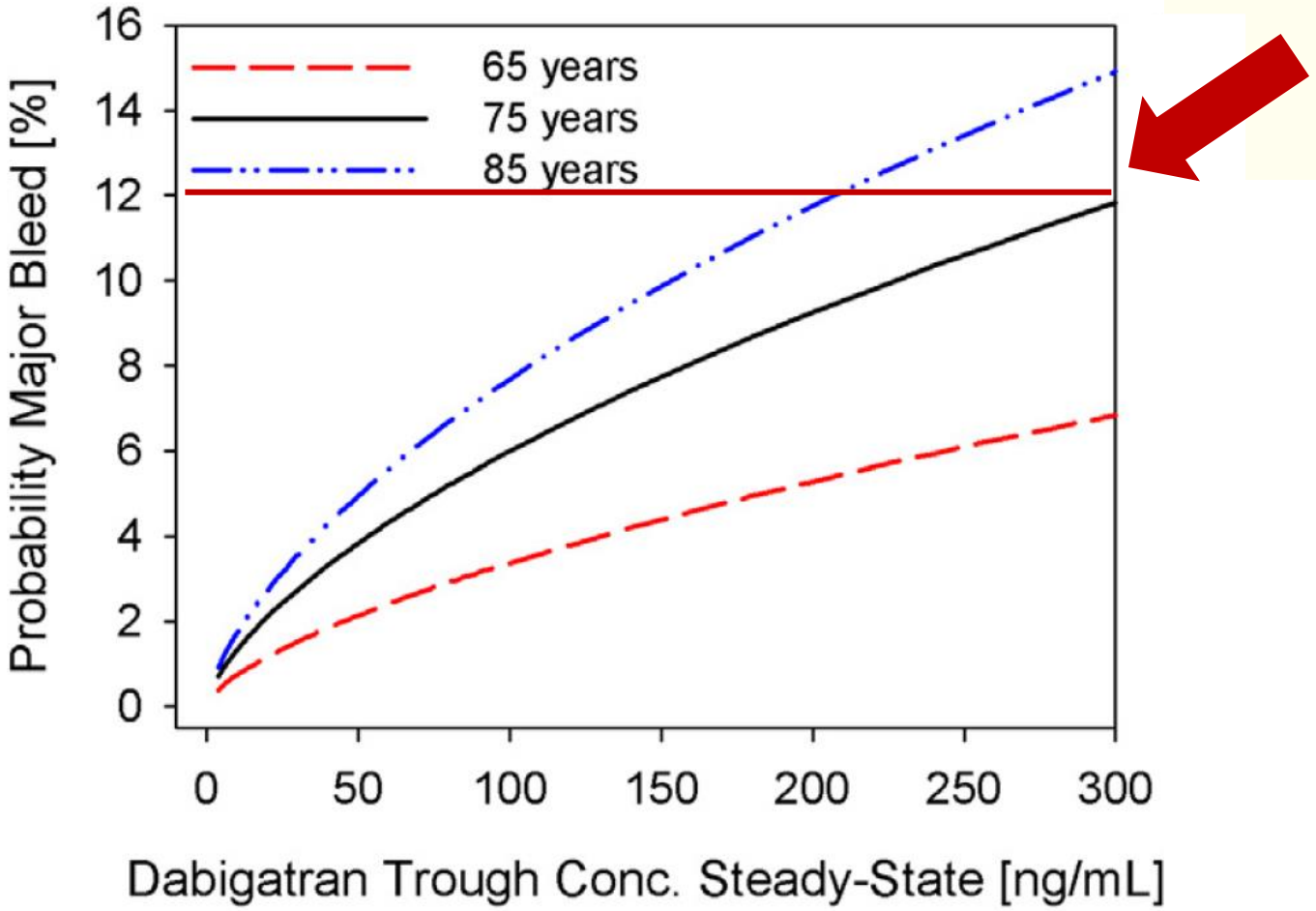
Table 3 Trough Concentrations of Dabigatran (ng/ml/mg) Grouped by Outcome Event Occurrence

	Major Bleed (n = 323)	Any Bleed (n = 2,319)	No Bleed (n = 5,899)	Stroke/SEE (+) (n = 129)	No Stroke/SEE (−) (n = 8,250)	Stroke/SEE/Death (+) (n = 387)	No Stroke/SEE/Death (−) (n = 7,789)	CV Events* (+) (n = 391)	No CV Events (−) (n = 7,865)
gMean	113	86.9	72.8	76.6	76.5	88.5	75.4	87.8	75.6
gCV, %	79.8	81.4	84	84.1	83.9	84.7	83.3	89.5	83.1
Median	116	88.2	75.3	80.6	78.3	91.4	77.6	90.7	77.6
P10	46.7	35.7	30.7	26.4	32.1	33.1	31.8	31.2	32
P90	269	211	175	185	186	226	181	229	182

*Cardiovascular (CV) events include stroke, systemic embolism, pulmonary embolism, myocardial infarction, and vascular deaths.
(+) = with event on-treatment; (−) = without event; other abbreviations as in Table 1.

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

(J Am Coll Cardiol 2014;63:321–8)



Anesthesiology 2013; 118:00-00

David S. Warner, M.D., Editor

Managing New Oral Anticoagulants in the Perioperative and Ir

Jerrold H.
James D.

Table 1. Preoperative Discontinuation of Dabigatran Based on Renal Function

Renal Function (CL_{CR}, ml/min)	Half-life, h	Timing of Last Dose before Surgery: Normal Bleeding Risk	Timing of Last Dose before Surgery: High Bleeding Risk
>80	13 (11–12)	1 d	2–4 d
50–80	15 (12–34)	1 d	2–4 d
30–50	18 (13–23)	>2 d	>4 d
<30	27 (22–35)	2–5 d	>5 d

CL_{CR}, ml/min (creatinine clearance, ml/min); h (hours); d (days).

Ore 0.23 del 2.11

Inizia CVVH in TIPO

ORIGINAL ARTICLE

J Thromb Haemost 2015; 13: 1790–8.

Hemodialysis for the treatment of dabigatran-associated bleeding: a case report and systematic review

C. CHAI-ADISAKSOPHA,*†‡ C. HILLIS,§ W. LIM,† K. BOONYAWAT,† K. MOFFAT† and M. CROWTHER†‡¶**

- ✓ 35 pazienti
  - 23 Intermittent Dyalisis (ID)
  - 10 CCVH
  - 2 entrambi
- ✓ Dabigatran PRE 315 ng/ml (41-2350 ng/ml)
- ✓ Dabigatran POST ridotto dal 33 al 99%
- ✓ In 12 casi con ID, rebound del 33% dopo fine trattamento

Ore 0.23 del 2.11

Inizia CVVH in TIPO

Ore 10

Dabigatranemia (dTT) 150 ng/ml

Ore 8 del 3.11

Dabigatranemia 45 ng/ml

Dimesso in buone condizioni generali una settimana dopo

Poi, quando smetti di pensare alla meta, ogni passo non è soltanto un mezzo, ma un evento fine a se stesso.
Questa foglia ha l'orlo frastagliato. Questa roccia è instabile.
Queste sono cose che dovresti notare comunque.
Vivere soltanto in funzione di una meta futura è sciocco.

Robert Pirsig
Lo zen e l'arte della manutenzione della motocicletta